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REVIEW

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Mechanisms and cross-talk of regulated cell death and their epigenetic modifications in tumor progression

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Abstract

Cell death is a fundamental part of life for metazoans. To maintain the balance between cell proliferation and metabolism of human bodies, a certain number of cells need to be removed regularly. Hence, the mechanisms of cell death have been preserved during the evolution of multicellular organisms. Tumorigenesis is closely related with exceptional inhibition of cell death. Mutations or defects in cell death-related genes block the elimination of abnormal cells and enhance the resistance of malignant cells to chemotherapy. Therefore, the investigation of cell death mechanisms enables the development of drugs that directly induce tumor cell death. In the guidelines updated by the Cell Death Nomenclature Committee (NCCD) in 2018, cell death was classified into 12 types according to morphological, biochemical and functional classification, including intrinsic apoptosis, extrinsic apoptosis, mitochondrial permeability transition (MPT)-driven necrosis, necroptosis, ferroptosis, pyroptosis, PARP-1 parthanatos, entotic cell death, NETotic cell death, lysosome-dependent cell death, autophagy-dependent cell death, immunogenic cell death, cellular senescence and mitotic catastrophe. The mechanistic relationships between epigenetic controls and cell death in cancer progression were previously unclear. In this review, we will summarize the mechanisms of cell death pathways and corresponding epigenetic regulations. Also, we will explore the extensive interactions between these pathways and discuss the mechanisms of cell death in epigenetics which bring benefits to tumor therapy.

Keywords Cancer, Cell death, Epigenetic modifications, Tumor therapy

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Introduction

The process of regulated cell death (RCD) is an irreversible termination of cellular activity and serves as a vital mechanism for maintaining tissue functionality and morphology. The disorder of RCD causes a variety of diseases. Failure of clearing tumor cells or immune cells cause serious results in evoking tumorigenesis and autoimmune diseases respectively. Excessive neural cell apoptosis can lead to neurodegenerative diseases.

Researchers on RCD have been conducted for more than 30 years. Various forms of cell death exhibit distinct morphological characteristics and underlying mechanisms. The apoptotic-cells undergo shrinkage leading to a concentration of the cytoplasm and they are phagocytosed by macrophages without eliciting an inflammatory response [1]. However, both pyroptotic-cells and necroptotic-cells undergo cell swelling, leading to the formation of pores in the cell membrane and subsequent release of cellular contents accompanied by severe inflammatory reactions [2]. What's more, autophagosomes form double-membrane structures within the cytoplasm of cells undergoing autophagy, where they undergo fusion with lysosomes to generate autophagolysosomes, facilitating the degradation of cellular organelles and protein [3]. Ferroptosis has emerged as a prominent research area, characterized by its distinct morphology during RCD [4]. There is an increase in iron ions and lipid peroxides within the cells. Cuproptosis is a form of death that is not yet clear, which is usually caused by protein aggregation and metabolic disorders dependent on copper ions. With the discovery of an increasing number of cell death pathways, there is an imminent need to delve into the molecular mechanisms underlying cell death, given its profound implications for researching treatments for a wide range of diseases. Therefore, while exploring the molecular mechanisms of cell death, we discuss the interaction of various cell death and the decision of cell fate at the fork in various molecular pathways to further understand the role of cell death in tumor progression.

The induction of RCD in tumor cells has emerged as a crucial therapeutic approach for cancer treatment. Such as using apoptosis-inducing agents (such as TRAIL, Bcl-2 inhibitors) to inhibit tumor progression [5], activating Caspase-1 or Gasdermin E to induce tumor pyroptosis [6], Utilizing mTOR inhibitors or autophagy enhancers to promote tumor autophagy, employing ferroptosis inducers to enhance intracellular iron ions and lipid peroxides in tumor cells [7]. Nevertheless, there are certain limitations therapeutic agents targeting cell death mechanisms. For example, Some tumor cells are resistant to apoptosis-inducing agents because of the *p53* mutation and tumor microenvironment may inhibit apoptosis signal transduction [5]. In addition, autophagy plays a complex role in different tumor types, which may promote both survival and death [8]. However, epigenetic regulation enables precise targeting of specific gene expression and enhances therapeutic effects. So, in addition to the conventional induction of tumor cell death, we provide the pivotal role of epigenetics in cancer cells and explores the latest advancements in drug development.

The primary epigenetic regulations include DNA modifications, histone modifications and chromatin remodeling. Epigenetic regulations of cell death-associated proteins with drugs can achieve the purpose of inducing tumor cell death more efficiently and more accurately [9].

Mechanisms of cell death and tumor progression

Apoptosis

The term apoptosis was first used in a 1972 paper by Kerr, Wyllie and Currie to describe a morphologically distinct type of cell death that plays a complementary but opposite role to mitosis in the regulation of animal cell populations without prompting an inflammatory response [10]. Apoptosis is the earliest well-studied programmed cell death with distinct morphological and biochemical features accompanied by apoptotic vesicle formation, which is mediated by several pathways [5]. Mitochondrial apoptotic pathway is directly triggered by the mitochondrial outer membrane permeabilization (MOMP), which later release pro-apoptotic factors (e.g. cytochrome c) from the mitochondria into the cytoplasm and cause cascade of Caspases. Nevertheless, the process of MOMP depends on the interaction of apoptosis-related proteins which sense intracellular stress and regulate intracellular homeostasis. Meanwhile, ER stress sensors can touch off these cascade effects independently by delivering stress signals mainly caused by dysregulation of intracellular nutrient balance. While death receptor pathway induces apoptosis through receiving the extracellular death signals such as Fas, TNF etc. Certainly, these three apoptosis-related pathways enjoy extensive interactions with each other.

Mechanisms of apoptosis

Mitochondrial pathway of apoptosis

The mitochondrial pathway of apoptosis is tightly regulated by a series of pro-apoptotic and anti-apoptotic B-cell lymphoma 2 (BCL-2) family proteins [5]. The BCL-2 family proteins can be categorized into two groups, namely proapoptotic and antiapoptotic proteins, based on their respective roles in the process of apoptosis. The former can be segmented into multidomain proapoptotic proteins (eg. BAX, BAK and BOK) and BH3-only proapoptotic proteins (e.g. BID, BIM, BAD, and NOXA). BAK and BAX are the most important pro-apoptotic protein on the outer membrane of

mitochondria, which can directly commitment to mitochondrial damage and mitochondrial outer membrane permeabilization (MOMP) [11]. BOK located in the endoplasmic reticulum (ER) transfers stimulus-induced calcium from the ER to the mitochondria and improves mitochondrial calcium levels to upregulate apoptosis [12]. It has been widely accepted that BID, BIM, and NOXA triggers the homo-oligomerization of "multidomain" conserved proapoptotic family members BAK or BAX while BAD indirectly activates BAX or BAK by inhibiting the function of BCL-2 antiapoptotic proteins [13]. However, recent studies suggest that all BH3-only proteins primarily target the anti-apoptotic BCL-2 proteins BCL-xL/MCL-1, which suppression enables spontaneous activation of BAX/BAK rather than their direct activation of BAX/BAK [14]. BH3-only proteins constitute the main upstream receptors of the mitochondrial apoptotic pathway and they are one of the nodes that integrate pro-apoptotic and anti-apoptotic signals. Antiapoptotic proteins in BCL-2 families such as BCL-2, BCL-xl and MCL-1can block MOMP and inhibit cell death by interacting with BH3 structure domains of proapoptotic effector proteins in check [15].

BAX/BAK benefits from their pore-forming ability on the outer membrane of mitochondrial to be considered as core effectors of the intrinsic pathway, which release the contents of mitochondrial. Among these released proteins, cytochrome c is the most important which acts on apoptotic peptidase activating factor 1 (APAF-1) and promotes its conformational changes, leading to the recruitment of Caspase9 to form apoptosomes [16]. Once Caspase9 is activated, it cleaves and activates the executioner Caspase3 and Caspase 7 [17]. These amplified signals end up cleaving the proteins and DNA in cells and induce apoptosis ultimately. SMAC and OMI are also released into the cytosol, where they bind and inhibit the X-linked inhibitor of apoptosis (XIAP), to promote activation of Caspases [18] (Fig. 1). Mitochondrial pathway of apoptosis can be triggered by a variety of microenvironmental perturbations, including growth factor withdrawal, DNA damage, endoplasmic reticulum (ER) stress, reactive oxygen species (ROS) overload, replication stress, microtubule alterations and mitotic defects [19–23]. These different stimuli can alter the balance between different groups of BCL-2 proteins, leading to activation of cell death [24]. Remarkably, BCL-2 proteins can be regulated by transcriptional or post-translational modifications [20]. For example, p53 induces PUMA (p53-upregulated apoptosis regulator) and NOXA (pro-apoptotic BH3 protein) transcription in response to DNA damage, thereby initiating apoptosis [25, 26] (Fig. 1).

Endoplasmic reticulum of apoptosis

Endoplasmic reticulum (ER) which contains a large number of chaperone enzymes and redox enzymes plays a major role in maintaining protein homeostasis and is responsible for folding and processing nearly all polypeptides destined for secretion. Nevertheless, cells repeatedly confront a variety of stressors such as starvation and infection that can potentially destroy ER proteostasis. Thus, the unfolded protein response of the endoplasmic reticulum (UPR^{ER}) is initiated to buffer ER stress that orchestrate cell fate to survival or cell death [27]. The onset of UPR relies on stress sensors protein kinase RNA-like ER kinase (PERK), inositol-requiring protein 1α (IRE1α) and activating transcription factor 6 (ATF6) [28]. IRE1, PERK and ATF6 are ER transmembrane proteins that contain an ER luminal stress-sensing domain and a cytoplasmic enzymatic domain [29]. Together, these ER stress sensors disassociate with molecular chaperones upon receipting stress signals and play a role in pro-survival by coordinating a temporal shut down in protein translation. IRE1α which is trans-autophosphorylated upon oligomerization in response to unfolded proteins determines cell fate by processing X box-binding protein 1 (XBP1) and undergoing regulated IRE1-dependent decay (RIDD) of mRNA to evoke the transcription of ER quality control components and degradation of superfluous proteins [30, 31]. Similar to IRE1α, PERK senses the eukaryotic translation initiation factor-2α(eIF2α) upon trans-autophosphorylation by oligomerization in ER-stressed cells and blocks ribosome 80S assembly as well as protein synthesis in the ER [29]. Additionally, activated 50 kDa form of ATF6 (p50ATF6) acts as basic leucine zipper (bZIP) transcription factor for UPR-inducible target genes to trigger the procedure of RIDD and ER-associated degradation (ERAD) which can alleviate the protein load in ER [29] (Fig. 1).

Apoptosis can be triggered when cells fail to resolve ER stress. A key step in the regulation of apoptosis is the crosstalk between the ER and mitochondria through transcriptional and post-translational modifications of members of the BCL-2 family of proteins. Once ER stress intensity reaches its threshold, RIDD initiates apoptosis through repression of anti-apoptotic pre-microRNAs and upregulation of apoptosis executor Caspase2 and Caspase8 which acts on BID to promote the process of MOMP [30]. Meanwhile, PERK-eIF2α-ATF4 branch of the UPR induces the pro-apoptotic transcription factor CHOP, which in turn mediates mitochondrial apoptosis through the upregulation of BH3 only proteins and down regulation of BCL-2 proteins [32]. Also, activated IRE1α combines with TNF receptor-associated factor 2 (TRAF2) to trigger the activation of c-Jun N-terminal kinase (JNK) pathway and mediates apoptosis [33, 34].

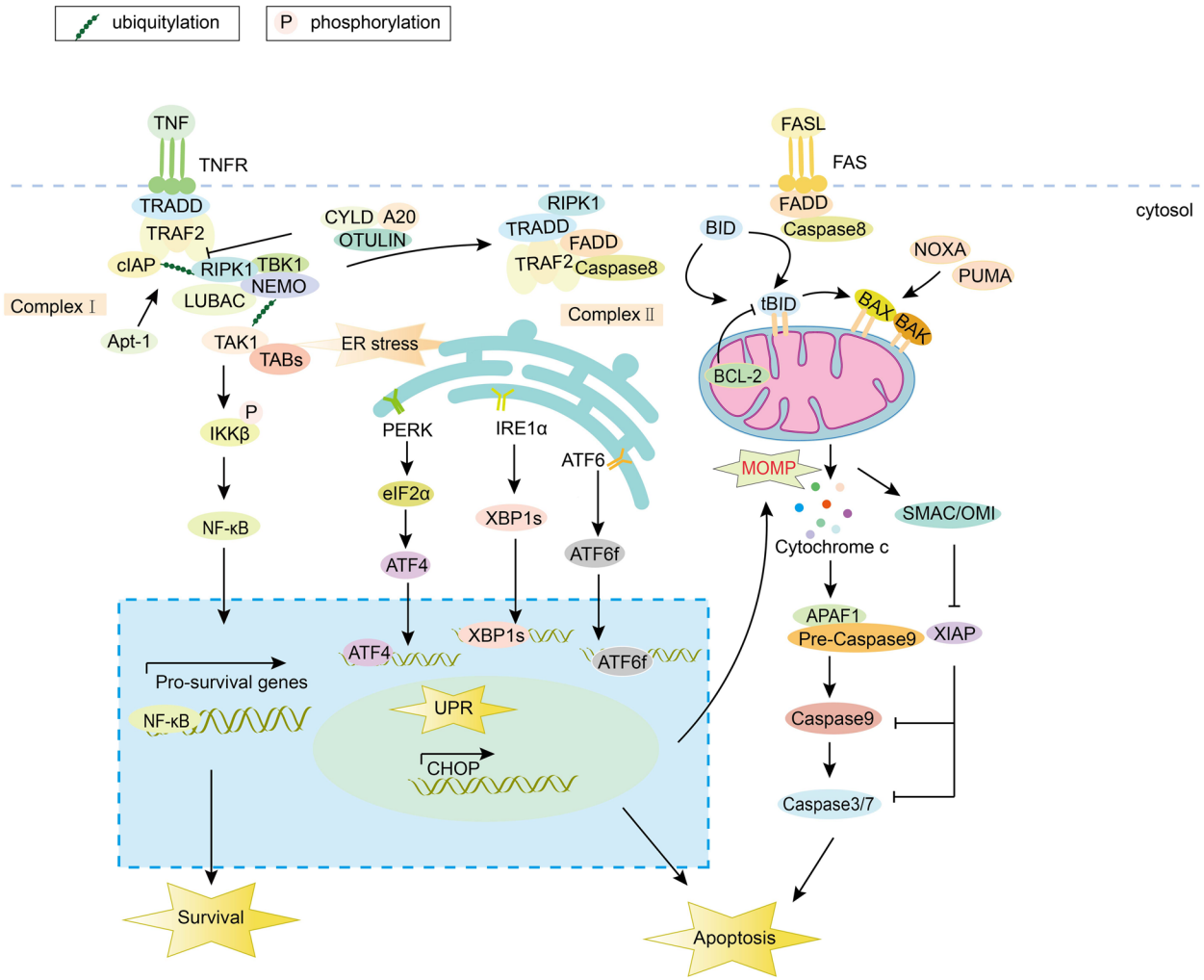

Fig. 1 Crosstalk among mitochondrial pathway, endoplasmic reticulum pathway and death receptor pathway of apoptosis. Internal stresses which cause the imbalance between BH3-only proteins and BCL-2 family can contribute to the mitochondrial pathway of apoptosis through MOMP. Upon MOMP, cytochrome c is released from mitochondria, forming the multimeric apoptosome complex with APAF1 to activate initiator caspase-9. Whereas, death receptor pathway is activated by external death factor ligation. However, cIAP1/2-mediated ubiquitination of RIPK1 drives cells to IKK-mediated cell survival. Once cIAP1/2 is inhibited, activated Caspase8 can directly cleave Caspase 3 /7 or the BH3-only protein BID (tBid) to drive MOMP. Both mitochondrial pathway and death receptor pathway lead to activation of executioner Caspase 3 /7, which cleave essential cellular substrates to implement apoptosis. ER stress can also lead to apoptosis through ER stress-sensing proteins IRE1, PERK and ATF6. ATF6f, the activated form of ATF6 transcription factor, XBP1s, the activated form of XBP1 following splicing

However, the understanding of IRE1 responses and cell death fate remains controversial. It seems that the deficiency of IRE1α in chondrocytes downregulates pro-survival factors XBP1s and BCL-2, which enhances the apoptosis of chondrocytes through increasing proapoptotic factors Caspase3, p-JNK, and CHOP (growth arrest and DNA damage-inducible gene 153/C/EBP homology protein) [33]. Presumably, the exact role of IRE1α in apoptosis may depend on the specific stage of ER stress. Apart from that, PERK promotes the rapid transfer of ROS signals to mitochondria and triggers MOMP by directly crosslinking ER with mitochondria [32] (Fig. 1). Otherwise, inhibition of ATF6 and PERK signaling pathways relieves heat-induced spermatocyte apoptosis in mouse [35]. In general, PERK, ATF6 and IRE1 signaling could promote pro-apoptotic process, but this procedure largely relies on downstream pathways.

Ca2+signaling plays a crucial role in the regulation of cell death and apoptosis. Many studies showed that Ca2+transferred from endoplasmic reticulum to mitochondria is a necessary condition for some chemical substances to induce apoptosis [36]. In HeLa cells upon ceramide treatment, researchers observed Ca^{2+} release from the ER and loading into mitochondria [37].

As a consequence, organelle swelling and fragmentation were detected that were paralleled by the release of cytochrome c. However, Bcl-2 overexpression was reported to decrease the size of the ER Ca^{2+} released and to prevent the process of MOMP [38].

Death receptor pathway of apoptosis

The initiation of exogenous apoptosis depends on the binding of external tumor necrosis factor (TNF), TNF-related apoptosis-inducing ligand (TRAIL) and Fas Ligand (FASL) proteins to corresponding cell membrane receptors [39]. Like mitochondrial pathway, the death receptor pathway of apoptosis converges at the level of effector caspase activation to implement cell death.

TNF pathway The anticancer activity now known as TNF was first described more than a century ago. TNF released by immune cells mediates the inflammatory response to resist invasion of foreign matters and can be implicated in the pathogenesis of a wide spectrum of human diseases at the same time. TNF initiates a complex cascade of signaling events that can lead to induction of proinflammatory cytokines, cell proliferation, differentiation, or cell death.

The first step in TNF signaling involves the binding of the TNF to the extracellular domain of TNFR1 and releasing of silencer of death domains (SODD), the competitive ligand of TNF. Thus, upon ligand binding, death receptors are aggregated and trimerized in the cell membrane (a phenomenon called capping) and subsequently recruit adaptor proteins such as TNF receptor–associated death domain (TRADD), Fas -associated death domain proteins (FADD), receptor interacting protein (RIP) and TNFR–associated factor 2 (TRAF2) [40–42]. TRAF2 or FADD bound to TNFR1 will guide the cell to the different fate by recruiting key enzymes of different kind. Specifically, TRAF2 recruits cellular inhibitor of apoptosis protein-1 (cIAP-1) and cIAP-2 forming Complex I (TNFR1 signaling complex;TNFR1-SC), to restrain cell death and bring cells to JNK and NF-κB signal way [43]. In contrast, Caspase8 is recruited by FADD to the TNF-R1 forming complex II, where it becomes activated and initiates a protease cascade that leads to apoptosis. Ubiquitination serves as an important level of regulation that dictates the pro-survival output of Complex I and serves as a major checkpoint for death via Complex II formation. First, XIAP is crucial for the control of cell death with its function of polyubiquitylating caspases to cause the catalytic inactivation of these proteins [44]. Although c-IAP proteins are not physiological inhibitors of Caspases, it can promote the ubiquitylation of Caspase 3 and Caspase 7 as well, thus enhancing cell survival [44]. All of these proteins push cells toward NF-κB signaling pathways that help them survive. It is interesting that c-IAP1 can mediate the ubiquitylation of other IAP proteins, namely XIAP and c-IAP2, which probably fine-tunes their levels to ensure an optimal balance. Moreover, linear ubiquitin chain assembly complex (LUBAC), composed of HOIL1, SHARPIN, and HOIP, induces the ubiquitination of cIAP1/2, which enhances Complex I binding with NEMO(NF-κB essential modulator, IKKγ), the kinases TGF-β activated kinase-1 (TAK1) and TGF-beta activated kinase2/3 (TAB2/3), subsequently activates the IκB kinase (IKK) complex [45]. Destabilization of Complex I by inhibition of cIAP1/2 or removal of the ubiquitin chain of Receptor-interacting protein kinase 1 (RIPK1) by the action of deubiquitinating enzymes allows the release of TRADD and RIPK1. Thus, modification of RIPK1 provide a unique 'ubiquitin code' that determines whether a cell activates nuclear NF-κB-mediated inflammatory response or induces cell death by apoptosis [46] (Fig. 1).Otherwise, TAK1 acts like a switch of cytotoxicity which inhibition elicits the formation of RIPK1-FADD-Casp8 complex and initiates cell death while infected by Yersinia [47]. In this case, Caspase-8 is activated to process Caspase-1 along with inhibition of NF-κB and mitogen-activated protein kinase (MAPK) signaling, which showing us an innate immune signaling pathway of antimicrobial defense [48].

In the pro-apoptotic conformation of the complex, TRADD and RIPK1 recruit FADD and Caspase-8, leading to Caspase activation and apoptosis. In the absence of FADD, RIPK1 is capable of activating RIPK3, thereby initiating the necroptotic pathway. Conversely, FLICE-like inhibitory protein (FLIP) exerts its inhibitory effects on both apoptosis and RIPK-dependent necroptosis complexes via its Caspase-like domain, effectively preventing the activation of these cell death pathways [49]. The interaction between necroptosis and apoptosis, as well as other forms of regulatory necrosis like pyroptosis or ferroptosis are currently areas with active investigation, and drug effects on these interactions will be relevant to cancer therapy ultimately.

Fas pathway Fas/FasL system is considered as the major regulator of apoptosis at the cell membrane in mammalian cells through a receptor/ligand interaction. FasL triggers the Fas pathway by binding to the Fas receptor (also known as CD95). In this case, FADD initiated by Fas signals recruits its downstream interaction factor proCaspase-8 through homotypic interaction in the death effector domain (DED), after that, proCaspase-8 performs the automatic cleavage to generate active Caspase-8, thus initiating the execution phase of cell death. Consequently,

activation of Fas results in receptor aggregation and formation of the so-called "death-inducing signaling complex" (DISC) containing trimerized Fas, FADD and pro-Caspase8. Caspase8 then cuts proCaspase3 to produce active Caspase3 which is responsible for ultimately performing various proteolytic degradation in cell [39].

Other death receptor pathway of apoptosis A third extrinsic apoptotic pathway has been shown to be therapeutically exploitable, the TNF-related apoptosis-inducing ligand (TRAIL) pathway [50]. TRAIL, alternatively known as Apo2L, was first identified by its sequence homology to FasL. It is a type II transmembrane protein containing an extracellular region which, upon proteolytic cleavage by protease, releases a soluble portion that acts as a ligand. Trimeric TRAIL binds to receptors on the membrane, namely death receptors (DR), which then trigger intracellular signaling cascade similar to the Fas pathway. The TRAIL-DR4/DR5 pathway is proposed to function in a wide range of physiological processes such as T cell activation and tumorigenesis. DR3 is a third member of TNFR family activated by its ligand Apo3L which can stimulate the formation of FADD-containing and caspase-8-containing DISC and induces apoptosis [51]. Another member of TNFR family termed DR6 has also been identified to interact with TRADD and induce apoptosis or activation of both NF-kappaB and JNK [52]. In summary, the signaling pathways by which these receptors induce apoptosis are similar and rely on oligomerization of the receptor by death ligand binding, recruitment of an adapter protein through homophilic interaction of cytoplasmic domains, and subsequent activation of an inducer caspase which initiates execution of the cell death program.

Cells undergoing apoptosis reveal a characteristic sequence of cytological alterations including membrane blebbing and nuclear and cytoplasmic condensation.

Apoptosis in tumor progression and tumor immunity

Apoptosis maintains the dynamic balance of the number of cells in the body by eliminating the excess cells. Particularly, apoptosis is widely known as programmed cell death eliciting no inflammatory responses on account of efficient and timely clearance of apoptotic cells. However, one of the hallmarks of cancer is evasion of apoptosis, meaning insufficient apoptosis overwhelmed by the limitless replicative potential of cells leading to the proliferation of tumors. Apart from that, apoptotic signaling through death receptors can be attenuated by cell-surface decoy receptors that bind to death ligands and compete for them, thereby reducing the activation of proapoptotic death receptors. Decoy receptors with Fas ligands are known to be over-expressed in some colorectal and lung tumor cells [53], and two species of TRAIL receptor decoys (DcR1 or TRID and DcRII or TRUND) are overexpressed in normal cells, thereby abrogating TRAIL activation in normal tissues [54]. As a result, apoptosis of cancer cells is usually attenuated in TME with reduced apoptotic signaling [55]. Notably, apoptosis induced by cytotoxic immune cells is one of the major pathways of cancer cell clearance in TME. CD8 + cytotoxic T lymphocytes (CTLs) take essential roles for killing cancer cells by FasL on cell membrane. Interestingly, under specific conditions, such as Caspase deficiency, apoptosis can trigger adaptive antitumor or antiviral immune responses by activating the cGAS/STING pathway and NF-kB signaling [56–58].

Autophagy

In humans, cells and intracellular components are constantly remodeled and recycled. The metabolic processes including the protein degradation as well as the organelle degradation and recycling are important for eliminating intracellular hazardous wastes, impeding the accumulation of proteins and maintaining cellular homeostasis [59]. Also, this process helps cells replace old components with fresh, better-quality ones. During critical situations, especially in the presence of the hypoxia, metabolic stress, nutritional deprivation and oxidative stress, the phagocytosis of intracellular substances becomes more frequent [60]. Therefore, cells rely on a pattern of self-phagocytosis to achieve intracellular energy balance termed as autophagy. Autophagy is characterized by the rearrangement of subcellular membranes to sequester a portion of cytoplasm and organelles into a structure called the autophagosome, which is then transported to the lysosome for proteolysis of the sequestered materials. Considering the broad term "autophagy" which has been used with rather variable and sometimes misleading connotations, we need to discriminate autophagy that operates on freely accessible cytosolic proteins from vesicular trafficking that originates at the plasma membrane, which also culminates in lysosomal degradation [61]. We also need to discriminate them from other catabolic pathways involved in cytoplasmic material, such as proteasomal degradation.

Up to date, various types of organelle-specific autophagy have been observed in different organelles, including the mitochondrial autophagy, peroxisome autophagy, endoplasmic reticulum phagocytosis, nucleoprotein autophagy, hemolytic autophagy and nuclear autophagy [62]. The absence of these specific autophagy processes would lead to the damage of the cell structure, dysfunction and even death. For example, the endoplasmic reticulum, Golgi and lysosomes of

lung fibroblasts were extensively disordered in patients within the COPD (Chronic Obstructive Pulmonary Disease), accompanied by the ER stress and the activation of apoptotic pathways [63]. However, the molecular connections between autophagy and cell death are complicated and, in different contexts, autophagy may promote or inhibit cell death. It has been known that autophagy-related genes modulate cell death in a pattern that scarcely interfere with apoptosis-related Caspase enzymes [64]. Simultaneously, autophagy presents extensive interactions with programmed cell death including apoptosis, necroptosis and ferroptosis, concretely performed in the mutual regulation of autophagy-related genes with other cell death pathways especially between autophagy and apoptosis [65]. On the one hand, autophagy can withstand cell death in physiological or pathological states by mobilization of intracellular nutrients to meet energy requirements or by removal of damaged organelles to maintain homeostasis. On the other hand, autophagy-mediated self-digestion can directly lead to cell death officially named as autophagy-dependent cell death. In many cases, the evidence of a causal role for autophagy was not established while other observations were based mainly on morphological characteristics. Autophagy-dependent cell death is considerably different from apoptosis in morphological characteristics, which is accompanied by the formation of autophagosomes that can degrade cell debris without phagocytes [64]. Even so, it remains controversial to clear the specific roles of autophagy in mediating cell death. We will focus on illustrating the mechanisms of autophagic cell death and discussing the interplay between autophagy and other forms of cell death in the following section.

Mechanism of autophagy

There are three main forms of autophagy, known as macroautophagy (herein referred to as autophagy), microautophagy and chaperone-mediated autophagy (CMA). Microautophagy is a form of autophagy during which cell components destined for degradation are directly taken up by the vacuole via membrane invagination [66]. CMA has a distinctive pattern of transferring substrates to lysosomes, since substrates reach the lysosomal lumen through a protein-translocation complex at the lysosomal membrane without vesicles or membrane invaginations [67]. Macroautophagy is the variant of autophagy best characterized for its dedicated vesicles which sequester large portions of the cytoplasm including organelles, now known as autophagosomes [61].

Initiation

Genetic studies have found that the gene ATG1 (ULK1, the ATG1 homolog in mammals) is a key factor in regulating the initiation of autophagy. Nevertheless, ULK1 is regulated by upstream signals AMP kinase (AMPK) and mammalian target of rapamycin (mTOR) according to different nutritional status of cells. Within sufficient intracellular energy, mTOR disrupts the ULK1-AMPK interaction and inhibits autophagy by phosphorylating ULK1 Ser 757 [68]. Otherwise, when cells are in an energy-deficient state, such as low glucose levels, the phosphorylation of ULK1 by mTOR is inhibited by AMPK, which directly activates ULK1 by phosphorylation of Ser 317 and Ser 777 to promote the initiation of autophagy [68]. AMPK and mTOR can be considered as receptors that sense the energy level of cells and face intracellular stress. Thus, the dual regulation of ULK1 activity is conducive to preventing metabolic disorders caused by long-term loss of intracellular energy and maintaining the stability of the intracellular states. Besides, dimethylation of ULK1 through decreasing KDM5C(a kind of demethylase) activity under hypoxia states promotes autophosphorylation at T180, a prerequisite for ULK1 activation [69]. Next, ULK1 phosphorylates ATG13 and FIP200 to form the ULK1-ATG13-FIP200 complex, which promotes the formation of autophagosomes [70]. ATG13 is supposed to be an adaptor mediating the interaction between ULK1 and FIP200 [71]. ATG13 and FIP200 have synergic effects during autophagy induction [71]. Both FIP200 and ATG13 are critical for locating ULK1 to the pre-autophagosome and enhancing the stability as well as activity of ULK1 protein [72]. Meanwhile, there are other proteins involved in the stabilization of ULK1-ATG13-FIP200 complex, such as ATG101 [73], ATG8 [74], ATG 9A [75]. Apart from that, Syntaxin 17 can be phosphorylated by TBK1 whereby phospho-Stx17 controls the formation of the ATG13-FIP200-regulated pre-autophagosome [76]. What's more, the capability of NDP52 to induce mitophagy is dependent on its interaction with the FIP200/ULK1 complex, which is also facilitated by TBK1 [77]. In brief, the main content of initiation of autophagy is the correct localization of ULK1 to the pre-autophagosome and the stability of ULK1 protein, which is important to take the next step, that is the elongation of autophagosomes.

Elongation (VPS34/VPS15/Beclin1/ATG14L)

Following the initiation step of autophagy, the activated ULK1 phosphorylates Beclin-1 on Ser 14, enhancing the activity of the ATG14L-containing Vps34 complexes [78]. It is remarkable that Vps34 presenting in two multiprotein complexes in which Complex I is composed

of Vps34-Vps15-Beclin1-ATG14L generating the autophagosome while Complex II is crucial for endosomal trafficking [79]. Notably, AMPK activates Vps34 Complex I by phosphorylating S91/S94 in Beclin1 to induce autophagy [80]. Vps34 is a phosphatidylinositol trikinase (PI3K) within mammals phosphorylating phosphatidylinositol (PI) to phosphatidylinositol 3-phosphate (PI3P) which is enriched in the intracellular lumen of the pre-autophagy structure (PAS/omegasome). Subsequently, PI3P assisted with Vps34 and Beclin-1 widely recruits PI3P-binding proteins such as ATG18(WIPI 1/2 in mammals) and double FYVE domain-containing protein 1(DCFP1) which is dynamically associated with the endoplasmic reticulum that directly influences the formation, localization and extension of early autophagosome membrane [81, 82]. Lactylation of Vps34 mediated by ULK1-activated glycolytic enzyme lactate dehydrogenase A (LDHA) under nutritional deficiency states enhances the association of Vps34 with Beclin1, ATG14L, and UVRAG, and then increases Vps34 lipid kinase activity [83]. Also, Vps15 kinase domain engages the Vps34 activation loop to regulate its activity [84].Besides the activation of Vps34, Beclin1-ATG14L protein–protein interaction is also important for Complex I formation [85]. ATG14L is an autophagy-essential gene presenting which dictates the differential regulation (either inhibition or activation) of different Vps34 complexes in response to glucose starvation. Remarkably, Beclin1-Vps34 complex bound with ATG14L/UVRAG functions in two different steps of autophagy by altering the subunit composition [86]. To be specific, ATG14L bind with Beclin1 to determine the localization of the autophagosome while UVRAG(Vps38) bind with Beclin1 to plays a role in autophagosome maturation [86]. Additional regulatory proteins also interact with Vps34 and Beclin1 to either promote autophagy. Dapper1 (Dpr1) acts as a critical regulator of autophagy by enhancing the formation of the autophagy-initiation Beclin1-Vps34-ATG14L complex and thus increasing Vps34 activity [87]. RACK1, a member of WD40-repeat proteins, facilitates the assembly of the ATG14L-Beclin 1-Vps34-Vps15 complex upon its phosphorylation by AMPK at Thr50 [88]. In a word, Vps34-Vps15-Beclin1-ATG14L complex facilitates the elongation of autophagosomes to advance the progress of autophagy.

Maturation of autophagosome membrane

ATG5, which forms a constitutive complex with ATG12, is a key protein involved in membrane extension in autophagy vacuoles. In brief, ATG12 is activated by an E1-like ubiquitin-activating enzyme ATG7 and is then transferred to the E2-like ubiquitin-transferase ATG10 [89]. Finally, ATG12-ATG5 complex further interacts with ATG16L to form the ATG12-ATG5-ATG16L complex, which is located on the outer membrane of the autophagosome. The ATG12-ATG5-ATG16L1 complex, which ultimately participates the autophagosome membrane maturation, is recruited to membrane contributing to the lipidation of LC3(Microtubule-associated protein 1A/1B-light chain 3, ATG8 family) by recruiting ATG3–LC3 to the membrane and to facilitating the transfer reaction to phosphatidylethanolamine (PE) with the assistance of the PI3P-binding protein WIPI [81]. The LC3 proteins undergo two proteolytic processing steps after being newly synthesized as a precursor. The ATG4 family is thought to regulate autophagosome formation exclusively by processing LC3 to the free cytoplasmic LC3-I form [90]. It has been recently discovered that human ATG4 proteins can facilitate autophagosome formation by regulating ATG9A trafficking and promoting interactions between the phagophore and ER, independent of their protease activity and their role in LC3 processing [91, 92]. Next, ATG12-ATG5-ATG16L1 enrolls E1-like protein ATG7 and E2-like protein ATG3 (already bound to LC3-I) into the autophagosome. Then, ATG12 activates ATG3 whereby the activated ATG3 facilitates LC3-I to combine with PE and convert to LC3-II [93]. Notably, the presence of ATG12-ATG5-ATG16L1 accelerates LC3/GABARAP lipidation and hampers LC3/GABARAP capacity to induce inter-vesicular lipid fusion at the same time [94]. It is remarkable that the stability of ATG12-ATG5-ATG16L1 is supported by many proteins. For example, RAB37 and RAB26 involve in a direct and activation-dependent manner in autophagy through promoting the formation of the ATG12-ATG5-ATG16L1 complex in a GTP-dependent manner [95, 96]. It is surprising to find that the ATG19-ATG11-ATG9 complex also participates in the LC3 lipidation [97].

The LC3 family is critical for the autophagosome lipid membrane expansion, autophagosome-lysosome fusion, and degradation of the inner autophagosomal membrane [98]. LC3-I is cytosolic, whereas LC3-II is membrane bound. Deacetylation of LC3 at K49 and K51 allows LC3 to interact with the nuclear protein DOR and to shift distribution of LC3from the nucleus toward the cytoplasm, where it is able to bind with ATG7 and other autophagy factors and undergo phosphatidylethanolamine conjugation to autophagosome [99]. LC3-II correlated with the extent of autophagosome formation is degraded along with the combination of autophagosome and lysosome, which reflects the immunofluorescence monitoring function of LC3-II to indicate the autophagy stage [100].

Fusion with lysosomes

After closure of the phagophore, the double-membrane autophagosome matures and fuses with lysosomes to

degrade its contents. Interaction between the scattered autophagosomes in the cytoplasm and the perinuclear-enriched lysosomes depends on their bidirectional movement on microtubules, especially dynein-mediated autophagosome perinuclear movement. The fusion of autophagosome with the lysosome requires the coordination of SNAREs, small GTPases, tethering complex HOPS, and other proteins [101]. A major event during autophagosome-lysosome fusion is the SNARE complex-mediated fusion process, which includes STX17(Q-SNARE), SNAP29 and VAMP8(R- SNARE). Upon autophagy induction, STX17 is recruited from the ER and mitochondria to completed autophagosomes, and then interacts with SNAP29 and the endosomal/lysosomal VAMP8 to form a trans-SNARE complex, which mediates autophagosome-lysosome fusion [102]. It is reported that acetylation of STX17 regulates its SNARE activity and autophagic degradation while deacetylation of STX17 also enhances the interaction between STX17 and the tethering complex HOPS, thereby further promoting autophagosome-lysosome fusion [103]. SNAP29 localizes to multiple trafficking organelles, exerting an effect on protein trafficking. Deficiency of SNAP29 causes distinctive epithelial architecture defects and accumulation of large amounts of autophagosomes [104]. Sec1 family domain containing 1 (SCFD1) located in the autolysosome, is required for SNARE complex formation and autophagosome-lysosome fusion [105, 106]. SCFD1 can be recruited to autolysosomes by dephosphorylated VAMP8 while this process can be inhibited by mTOR [105]. Conversely, SCFD1 acetylation inhibits autophagy, specifically by blocking STX17-SNAP29-VAMP8 SNARE complex formation [106]. The core tethering factor for autophagosome-lysosome fusion is the HOPS complex consisting of Vps11, Vps16, Vps18, Vps33A, Vps39, and Vps41. The HOPS complex interacts with STX17 on autophagosome and facilitates assembly of the trans-SNARE complex to mediate autophagosome-lysosome fusion [107]. It is worth mentioning that although LC3 plays an important role in autophagosome maturation, deconjugation of LC3-PE by ATG4 facilitates the maturation of these structures into fusion-capable autophagosomes at the later stage of autophagy [108].

Furthermore, the key regulator of lysosomal function TFEB regulates genes involved in several steps of the lysosome–autophagic pathway, including formation of the isolation membrane, conjugation of ubiquitin-like molecules of the Atg8 family(LC3) and elongation of the autophagosomal membrane, cargo recruitment, autophagosome–lysosome fusion, lysosome-mediated degradation and lysosomal biogenesis [109, 110]. TFEB promotes the process of cellular endocytosis leading to activation of mTORC1 and autophagy, thus playing important roles in cellular clearance [111]. In addition, lysosomal Ca2+is key for various lysosomal functions as releasing Ca2+is required for the fusion of lysosomes with autophagosomes [110]. Lysosomal Ca2+channels respond to a variety of stimuli, such as pH, nutrients and cellular stress, suggesting that lysosome activity can be differentially modulated depending on cell conditions, thus allowing more selective signal responses that are tailored to the needs of the cell.

Selective degradation

Before proteins are transferred into autophagosomes, they need to be ubiquitinated, and recognized by proteins containing ubiquitin-binding domains. P62 is such the adaptor that identifies ubiquitinated protein aggregates, dysfunctional peroxisomes and impaired mitochondrial outer membranes (MOM) within UBA domains. The abnormal substances are transferred into the lysosome-bound autophagosome by P62 and subsequently eliminated through the interaction between the LIR domain with LC3 (ATG8) [112] (Fig. 2).

Induction of autophagy

Autophagy can be constitutive or adaptive. The main functions of constitutive autophagy are removal of damaged or senescent organelles and maintenance of basal energy balance. By contrast, adaptive autophagy is characterized by the mobilization of intracellular nutrients to meet energy requirements in the event of nutrient deficiency. We will illustrate factors involved in autophagy induction in this part.

Metabolic pressure

As mentioned above, the phosphorylation of ULK1 by AMPK is conclusive in the initiation of autophagy. Reduced intracellular energy changes the ratio of ATP to ADP/AMP, thereby activating AMPK in an allosteric mechanism. AMPK maintains the stability of intracellular ATP levels by switching intracellular energy and controlling cell growth factors, such as glucose and lipid metabolism [113]. However, mTOR which consumes ATP to promote the synthesis of substances under adequate nutritional conditions functions opposite to AMPK. Also, mTOR can be phosphorylated by AMPK when energy is lacking, thus losing its inhibitory effect on ULK1 [68]. In addition, the decrease of amino acid concentration inhibits mTORC1 activity, sequentially initiates autophagy [114]. mTORC1 regulates autophagy not only by phosphorylating ULK1, but also by affecting autophagy proteins such as coupled ATG13- ATG1 and the Atg14-Vps34 complex [114]. Initiating autophagy can replenish the nutrients essential for cells in response to cell starvation.

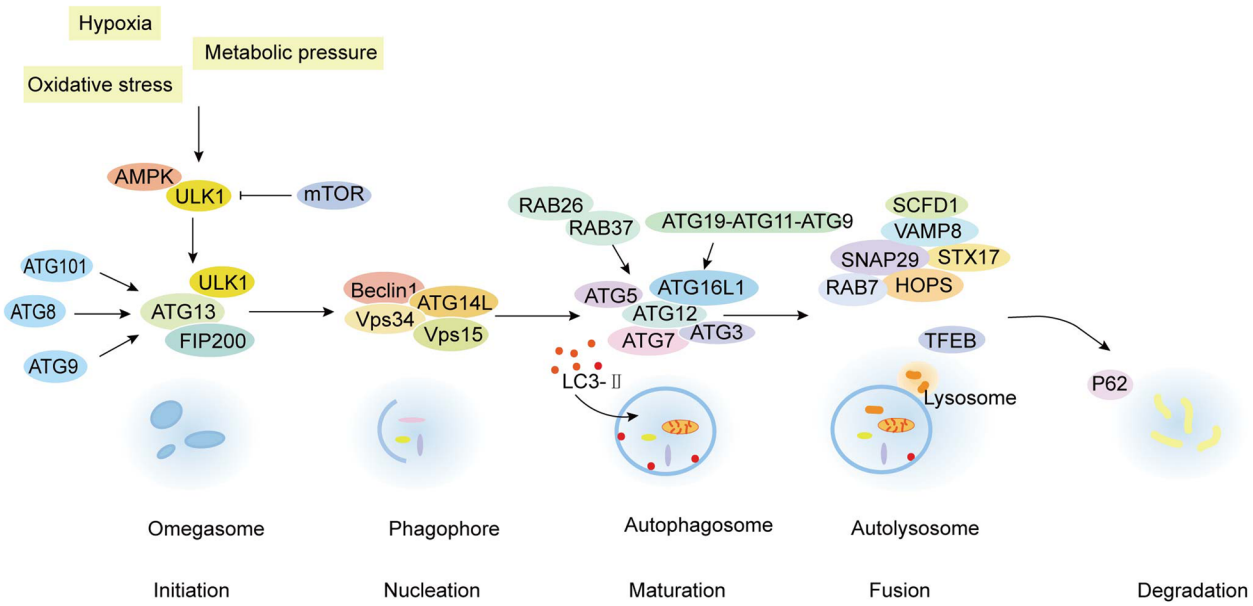

Fig. 2 Cellular and molecular mechanisms of autophagy. (1) Initiation. Activated ULK1 phosphorylates ATG13 and FIP200 to form the ULK1-ATG13-FIP200 complex, which promotes the formation of autophagosomes. (2) Nucleation. Complex I, composed of Vps34-Vps15-Beclin1-ATG14L, facilitates the elongation of autophagosomes. (3) Maturation. The ATG12-ATG5-ATG16L1 complex contributes to the lipidation of LC3. (4) Fusion. The fusion of autophagosome with the lysosome requires the coordination of SNAREs, small GTPases, tethering complex HOPS, and other proteins. (5) Degradation. P62 mediates the degradation of proteins

Hypoxia

Further studies found that hypoxia could induce autophagy. Hypoxia results in the decrease of the intracellular oxygen content and limitation of the oxidative phosphorylation. Therefore, hypoxia causes a short-term reduction in producing ATP which can activate AMPK and AMPK targets ULK1, Beclin1 and mTORC1 to induce autophagy. Besides, hypoxia can up-regulate HIF-1α, which is transported to nucleus and induces the expression of downstream genes including BCL2, BNIP3 and BNIP3L that dissociates Beclin1 from BCL2, thereby activating the autophagy [115]. It has been put forward that hypoxia-induced autophagy is related to tumors because cancer cells can utilize autophagy to maintain cell integrity in a hypoxic TME. For example, hypoxia promotes the phosphorylation of autophagy protein ATG5 by PAK1, which is correlated with tumor growth [116].

Oxidative stress

The correlation between oxidative stress and autophagy is vital in maintaining homeostasis in response to various physiological and pathological conditions. Reactive oxygen species (ROS) produced during oxidative stress mediates ATM (Ataxic telangiectasia mutation)-CHK2 (cell cycle checkpoint kinase 2), a DNA damage response pathway (DDR) that phosphorylates Beclin1 and evokes phagocytosis of damaged mitochondria and peroxisome, thus protecting cells from being damaged by excessive ROS [116]. ATM can also phosphorylate phosphatase and tensin homolog (PTEN) to translocate and induce the autophagy [117]. In addition, direct oxidation of thiol groups of key proteins such as ATG4, ATM and TFEB by peroxides can regulate autophagosome membrane expansion, cargo recognition and autophagy gene transcription, respectively [118]. Oxidative stress can also mediate NF-κB phosphorylation, up-regulate the P62 / SQSTM1 level, and promote autophagy to help retinal pigment epithelial cells survive [119].

Autophagy in tumor progression and tumor immunity

Autophagy can play neutral, tumor-suppressive, or tumor-promoting roles in different contexts and stages of cancer development. The exploration in the relationship between autophagy and carcinogenic process is step by step. At first, it was found that Beclin1 which can inhibit tumorigenesis is absent in most breast tumor or ovarian cancer tissues [120]. Next, a large number of studies have found that artificial suppression of the ATG family proteins can lead to the occurrence of tumors, and low expression of the ATG family proteins is often found in tumors as well [121, 122]. Of note, normal levels of autophagy related genes expression in most tumor tissues suggests that autophagy is also necessary for tumor

growth [123]. It was found that p62 was essential for the oncogene RAS to trigger IkappaB kinase and activate NF-κB to promote tumor cells survival in autophagy-deficient tumor cells [124, 125]. What's more, inactivation of ATG5 was detrimental to the progression of the oncogene kRAS-driven lung cancers and compelled tumor cells susceptible to DNA damage and oxidative stress instead [126]. To sum up, autophagy affects tumor progression bilaterally and intricately. On one hand, autophagy can maintain genome stability, prevent cell stress damage and then bring its superiority to tumor suppressive mechanism via its protein and organelle quality control function. On the other hand, autophagy can enhance the survival and resistance of the cancer cells against stress and promote cell survival once the tumors progress to late stage. It is speculated that the role of autophagy in tumor progression may be intrinsically related with the status of *p53*. Generally, the deletion in autophagy genes expression induces tumorigenesis at early stage, but it is not conducive further invasion and migration of tumor cells. Conversely, in mice absence of *p53*, the deletion of autophagy gene is beneficial to tumor growth and invasion [127]. However, this standpoint is still premature and controversial. There are other studies find that autophagy is important for the tumor development of pancreatic cancer regardless of *p53* status [128].

The relationship between autophagy and tumor immunity is complicated and intimate. The immune system monitors cell growth and prevents the abnormal growth and proliferation of tumor cells while tumor cells reduce the immunogenicity as a countermeasure to avoid surveillance of the immune system. The impact of autophagy on immune activity is evident, as it serves as a dual-purpose mechanism for both offensive and defensive strategies of tumor cells and immune cells. First, Autophagy in tumor cells transforms the activity of antigen presentation. For instance, selective autophagy assists pancreatic ductal adenocarcinoma to undergo immune evasion by impairing the expression of MHC-I on cell surface and the presentation of MHC-I antigen, whereas the inhibition of autophagy can recover anti-tumor immunity depending on transmitted signals from MHC-I to CD8 + T cells [129]. For another, mitophagy can increase MHC-I antigen presentation and induce CD8 + T mediated anti-tumor immunity in intestinal epithelial STAT3-deficient tumor models [130].It can be speculated that the role of the tumor autophagy in antigen presentation depends on the specific tumor microenvironment. Secondly, autophagy can impact the expression of chemokines in cancer cells, which contributes to recruitment of immune cells in TME [131]. Deficiency of the autophagy-related protein FIP200 or ATG7 can promote the expression of CXCL9 and CXCL10 and recruit CD8 + T cells to inhibit the tumorigenesis and progression of breast cancer [132]. Apart from that, performance of immune cells can be affected by intracellular autophagy in TME. The inhibition of autophagy in NK cells and CD8 + T cells of hypoxic status restores the intracellular granzyme B contents which acts as a weapon to kill tumor cells [133]. Autophagy defects itself, however, also can cause cell activity decreased and cell death. Autophagy defects in naive T cells activate generation of reactive oxygen species in mitochondria and drive the suicide of T cells in ovarian cancer and lower the immune response [134]. The PIK3C3/VPS34 subunit of the class III phosphatidylinositol 3-kinase (Class III PI3K) complex plays a crucial role in the initial stages of autophagy. It has been revealed that the loss of PIK3C3 hampers helper T cell differentiation and restricts adaptive immunity [135].

Necroptosis

Necrosis is the term currently used for nonapoptotic, accidental cell death. The occurrence of necrosis is indicated by irreversible alterations in the nucleus, such as karyolysis, pyknosis, and karyorhexis, as well as changes in the cytoplasm including condensation and intense eosinophilia, loss of structural integrity, and fragmentation [136]. In the traditional views, necrosis was commonly considered non-programmed and continues to be recognized as a form of passive cell death. Fortunately, a new world of cell death has been opened by the understanding that necrosis can occur in a highly regulated and genetically controlled manner. The discovery that various cell types succumb to TNF-induced death did not occur until 1988. The subsequent discovery revealed that Fas/TNFR family stimulation can induce the conventional apoptotic pathway, as well as activate the prevalent non-apoptotic death pathway independently of intracellular apoptotic signaling molecules like Caspases, thereby designating this specific form of cell death as necroptosis [137]. Necroptosis is primarily mediated by RIPK1, RIPK3 and mixed lineage kinase domain-like pseudokinase (MLKL), which can be inhibited by necrostatin-1 (NEC1), a RIPK1 inhibitor [138]. The down-regulation of numerous key molecules in the necroptosis signaling pathway has been observed across various cancer cell types, indicating a potential evasion mechanism employed by cancer cells to ensure their survival.

Mechanisms of necroptosis

We have mentioned before that TNFα stimulation triggers the formation of two consecutive protein complexes, namely complex I and complex IIa, which subsequently activate NF-κB and induce apoptosis, respectively. There is evidence that a second complex named complex IIb

forms in necroptosis. The activation of necroptosis relies on protein kinases, which closely coincide with cytokines that induce extrinsic apoptosis, such as Fas, TNFR, or TRAIL receptors. However, it lacks the proteolytic activity of the apoptotic effector factor Caspase-8, but mainly depends on MLKL, RIPK1 and RIPK3 instead [139]. At present, the main mechanism of programmed necroptosis can be divided into three steps: activation of necroptosis, MLKL phosphorylation and cell rupture.

Activation of necroptosis: death receptor and RIPKs

The death receptor (DR) is a member of the tumor necrosis factor receptor (TNFR) superfamily, possessing both extracellular and intracellular death domains (DD) that are rich in cysteine residues. Death receptors are activated in cells subjected to ischemia–reperfusion, physical or chemical trauma, viral or bacterial infection, or neurodegenerative processes. Common death receptors currently include CD95 (FAS)、TNFR、 TRAILR and DR6 [140–146]. The death signal is transmitted into the cell by the death-inducing signaling complex (DISC) and induces the activation of RIPK1 and RIPK3 [145]. Researches shows that the dissociation of complex I is a prerequisite for TNFα-stimulated activation of RIPK3 signaling, which is mediated by DUBs such as OTULIN (OTU deubiquitinase with linear linkage specificity), CYLD (cylindromatosis) or A20 [147]. Multiple factors such as ROS also stimulate the initiation of RIPK1 through initiating the autophosphorylation of RIPK1 [148]. The autophosphorylation of RIPK1 not only regulates the sequential oligomerization of RIPK1, but also plays a crucial role in facilitating the proper organization of RIPK3 homo-oligomerization initiated by RIPK1 [149]. The interaction between RIPK1 and RIPK3 via the RIP homotypic interaction motif (RHIM) is crucial for the formation of complex IIb, which plays a pivotal role in necroptosis. To be specific, amyloid signalling platform in RIPK1-RIPK3 interaction could be essential to sustain or amplify crucial signals in necroptosis [46, 149].

In addition, the initiation of necroptosis can also be achieved through Z-DNA Binding Protein 1 (ZBP1). ZBP1 plays an indispensable role in the inflammatory response and host defense. Preliminary studies reported that both B-DNA and Z-DNA derived from multiple sources (synthetic DNA or DNA of bacterial, viral, or mammalian origin) induce strong expression of ZBP1 and IRF to mediate IFN expression and antiviral response [150]. Also, ZBP1 acted as an innate sensor of influenza virus (IAV) recognizing Z-RNA in the viral ribonucleoprotein (vRNP) complex to induce necroptosis to resist virus infection [150].

It is reported that ZBP1 initiates RIPK3-driven necroptosis by sensing Z-nucleic acid and activating RIPK3 [151]. Moreover, ZBP1 is required for both type I (β) and type II (γ) IFN-induced necroptosis, for its RHIM domain in the C-terminal region interacts with RIPK3 to initiate RIPK3-dependent necroptosis [152]. Caspase8 plays an inhibitory role in ZBP1-induced necroptosis [152]. Interestingly, RHIM in RIPK1 prevents the RHIM-containing adaptor protein ZBP1 from activating RIPK3 since RIPK1 deficiency or mutation of RHIM triggers ZBP1-dependent necroptosis [153]. Therefore, we hypothesized that RIPK1-mediated RIPK3 activation and ZBP1-mediated RIPK3 activation were in competition with each other. What's more, mutants of ADAR1 (an RNA editing enzyme) can alter its domain through ZBP1-dependent signaling to activate RIPK1 and RIPK3, which provides a readily translatable avenue for rekindling the immune responsiveness of ICB-resistant human cancers [154, 155].

MLKL phosphorylation and cell rupture

The formation of RIPK1-RIPK3 complex further phosphorylates the necrotic specific executive protein mixed-lineage kinase domain-like (MLKL) [156]. The phosphorylation sites of RIPK3 exist on the MLKL activation loop residues, mouse serine 345 or human threonine 357/serine 358, in the pseudokinase domain [157]. After MLKL is phosphorylated by RIPK3, TAM (Tyro3, Axl, and Mer) kinase phosphorylates MLKL at the pseudokinase domain to initiate oligomerization of MLKL [158, 159]. Then MLKL is conjugated to heat shock protein 90 (Hsp90) and Hsp70 to achieve membrane translocation [160, 161]. HSP90 plays a complex role in necroptosis through binding and regulating the activity of RIPK1, RIPK3, or MLKL in a context-dependent manner [162]. MLKL consists of a four-helical bundle (4HB) domain at the amino terminal, which performs a membrane permeability function upon phosphorylation [163]. MLKL embedded in cell membranes forms a cationic channel inducing the influx of Mg^{2+} and Ca^{2+}, leading to the destruction of cell membranes and organelles, ultimately the uncontrollable release of intracellular material [164]. In contrast, some proteins function as negative modulators of MLKL. Flotillin-mediated endocytosis and ALIX-syntenin-1-mediated exocytosis can prevent contact between phosphorylated MLKL (p-MLKL) and the plasma membrane to inhibit necroptosis [165]. Also, Beclin1 and BCL-2 can inhibit necroptosis through binding to the coiled-coil domain and BCL-2 homology (BH)-3 domain of MLKL, respectively [166, 167]. Modulation of MLKL activity plays a critical role in determining cell fate. The absence of MLKL rescues abnormal embryonic necroptosis induced by the loss of Caspase 8 or FADD [168]. Studies in MLKl-deficient mice showed that it significantly reduced CCl4 and bile duct ligation

(BDL) induced liver injury and fibrosis, suggesting that liver fibrosis can be blocked by reducing MLKL-induced hepatocyte necroptosis and hepatic stellate cell (HSC) activation [169] (Fig. 3).

Necroptosis in tumor progression and tumor immunity

Tumor cell necroptosis is particularly prominent in the central region of the tumor mass and is believed to be a consequence of cellular stress, such as deprivation of nutrients and reduced oxygen levels. However, the impact of necroptosis on tumorigenesis appears to be context-dependent, with both antitumorigenic and pro-tumorigenic effects observed across different tumor types under varying conditions. First, it has been noted that a significant proportion of cancer cell lines demonstrate either a lack or decrease in the expression of RIPK3 [170, 171]. The knockout of RIPK3 in mice has been reported to be associated with an increased susceptibility to colitis-related colorectal cancer and enhanced production of pro-inflammatory or pro-tumor factors [172]. Similarly, low RIPK3 expression has been shown to have a poor prognosis in breast cancer patients [171]. Increased RIPK3 expression is associated with increased glial tumor cell mortality [173]. What else, RIPK3 may restrict myeloid leukemogenesis by promoting RIPK3-MLKL-mediated necroptosis and differentiation of leukemia-initiating cells [174]. These studies suggest that RIPK3 may play an anti-inflammatory and anti-tumor role in cancer. Nevertheless, through gene ontology (GO) and pathway enrichment analysis of lncRNAs associated with programmed necrosis, it has been found that six lncRNAs linked to necroptosis are involved in the survival of glioma tumor cells [175]. For another, the upregulation of RIPK3 is required for the robust proliferation of cancer cells in an aggressive form of recurrent breast cancer [176]. One potential explanation for the seemingly contradictory effects of RIPK3-mediated necroptosis on tumorigenesis is that, in addition to its role in mediating necroptosis, RIPK3 also plays a crucial role in modulating inflammatory responses across various pathological conditions which contributes to the maintenance of tumor environment. The expression of RIPK3 varies across different tissues, while the regulation of MLKL in cancer cells is also influenced by interferon signaling [177]. MLKL knockout had little effect on tumor growth, but significantly reduced metastasis to the lung, suggesting that necroptosis of tumors mainly promoted the metastasis of mammary tumors in mice [178].Therefore, the susceptibility of tumor cells to necroptosis and its impact on tumor progression in different tumor types and settings may be influenced by variations in the tumor microenvironment.

Cells undergoing necroptosis play a crucial role in activating the immune system, particularly in antigen presentation and the cross-priming of CD8 + T cells. It was found that ectopic introduction of necroptotic cells to

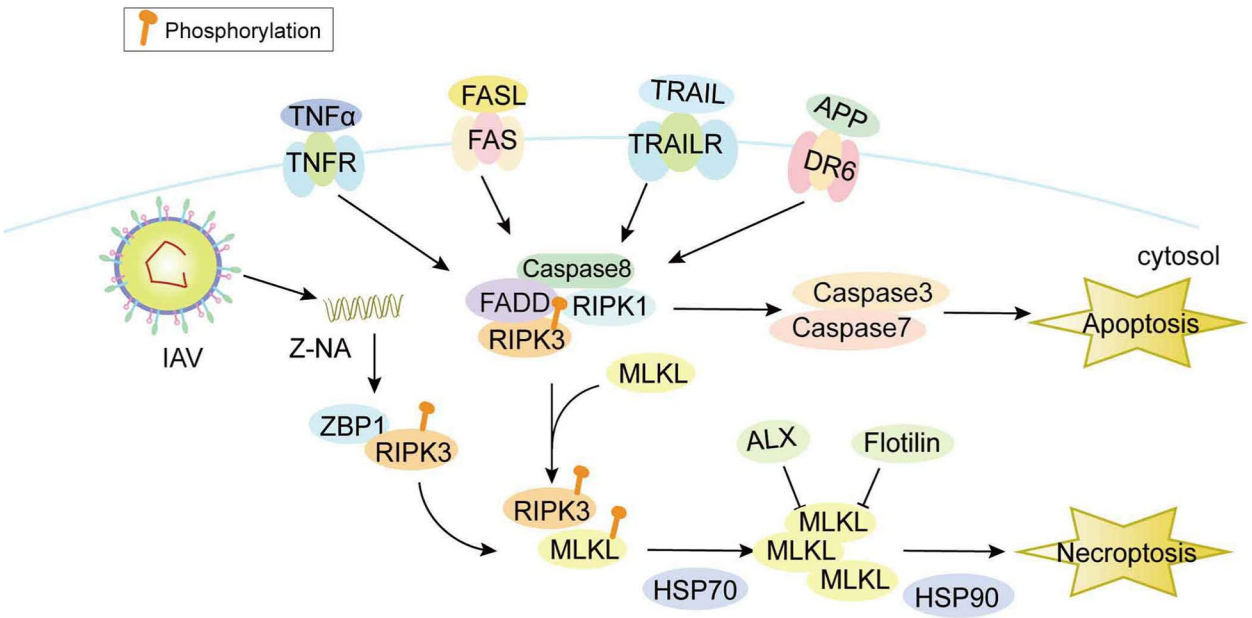

Fig. 3 Cellular and molecular mechanisms of necroptosis. The death signal is transmitted into the cell by the death-inducing signaling complex (DISC) and induces the activation of RIPK1 and RIPK3. ZBP1 initiates RIPK3-driven necroptosis by sensing Z-nucleic acid which is activated by viral infections. The formation of RIPK1-RIPK3 complex further phosphorylates the necrotic specific executive protein MLKL. Then MLKL is conjugated to heat shock protein 90 (Hsp90) and Hsp70 to achieve membrane translocation and induce necroptosis

the tumor microenvironment promotes BATF3^{+}cDC1-dependent and CD8^{+}leukocyte-dependent antitumor immunity accompanied by increased tumor antigen loading [179]. Delivery of RIPK3 gene encoding to tumor cells can synergize with immune checkpoint blockade to promote durable tumor clearance. These findings support a role for RIPK1/RIPK3 activation as a beneficial proximal target in the initiation of tumor immunity [179].Apart from that, dying cells generated by RIPK3 initiate adaptive immunity by providing both antigens and inflammatory stimuli for dendritic cells, which in turn activate CD8 + T cells through antigen cross-priming [180]. Furthermore, necroptotic tumor cells were shown to induce antitumor immunogenicity by releasing damage-associated molecular patterns and promoting maturation of dendritic cells [181].

Pyroptosis

Pyroptosis is a programmed cell death that is triggered by the activation of inflammasomes and relies on the involvement of caspase families. The cell undergoes expansion until its membrane ruptures, leading to the release of cellular contents and subsequent activation of a potent inflammatory response [182]. The earliest investigations into pyroptosis were conducted by Friedlander in 1986, wherein the treatment of primary mouse macrophages with anthrax lethal toxin (LT) resulted in cellular demise and prompt release of intracellular contents [183]. The electron microscope observations conducted by Zychlinsky et al. in 1992 revealed that this mode of cell death is characterized by chromatin condensation, vesiculation of the cell membrane, vacuolation of the cytoplasm, expansion of the endoplasmic reticulum, preservation of cellular organelle structure, fragmentation of genomic DNA, and other features; however, it was still attributed to apoptosis [184]. The concept of "pyroptosis" was formally proposed in 2001, marking the first distinction between pyroptosis and apoptosis [185]. The activation of various Caspases, including Caspase-1, through inflammasomes is believed to be the primary mechanism underlying pyroptosis. Apart from that, multiple members of the Gasdermin family, such as GSDMD, undergo shearing and polymerization processes that ultimately lead to cell perforation and subsequent cell death. Compared to apoptosis, pyroptosis occurred faster and was accompanied by the release of a large number of pro-inflammatory cytokines.

The term pyroptosis, also referred to as secondary necrosis, is believed to arise from incomplete apoptosis. After the initiation of apoptosis, apoptotic cells undergo disintegration into bodies or vesicles containing intracellular components, which are subsequently phagocytosed by macrophages for subsequent elimination. However, in the absence of phagocyte clearance, "secondary necrosis" will follow despite the expression of phagocytic signals on apoptotic cells. Subsequently, this process leads to a series of events such as cell swelling and loss of cell membrane integrity, and ultimately lead to plasma membrane rupture and release of inflammatory stimuli [186, 187].

Mechanisms of pyroptosis

The morphological characteristics, occurrence and regulation mechanism of pyroptosis are different from other cell death modes such as apoptosis and necroptosis. The main signaling molecules involved include: partial proteins of the Caspase family, Gasdermin protein family, and inflammatory bodies. The inflammasome triggers the activation of Caspase family proteins, which cleave Gasdermin proteins. The activated Gasdermin proteins then translocate to the membrane, where they form pores that cause cell swelling and cytoplasmic efflux. Ultimately, this leads to cell membrane rupture and pyroptosis [188]. Inflammatory Caspases (Caspase-1, -4, -5 and -11) are critical for innate defence. The activation of Caspase-1 is induced by ligands from various canonical inflammasomes, while Caspase-4, -5, and -11 directly recognize bacterial lipopolysaccharide, both of which initiate the process of pyroptosis. There are three classifications of Pyroptosis, namely canonical pathway, also known as Caspase1-dependent pathway; noncanonical pathway and alternative pathway. These three molecular mechanisms exhibit interdependent interactions with each other.

Canonical pathway (Caspase1-dependent pathway)

NOD-like receptor (NLR) family pyrin domain-containing 3 (NLRP3) is an important PRR in the cytoplasm acting as a sensor in response to pathogen-associated molecular patterns (PAMPs) and danger-associated molecular patterns (DAMPs), thus defensing against pathogen invasion on the first line [189]. Oligomerized NLRP3 recruits ASC via homotypic PYD–PYD domain interactions and forms ternary inflammasome complexes, known as NLRP3 complex, through Caspase activation and recruitment domain (CARD) interactions between ASC and Caspase-1 [190]. Once the NLRP3 inflammasome is activated, it induces pro-Caspase-1 self-cleavage and activation, which results in the maturation of the proinflammatory cytokines interleukin 1β (IL-1β) and interleukin 18 (IL-18) [191]. Afterwards, activated Caspase-1 cleaves gasdermin D (GSDMD) by cutting its N-terminal domain, which is transferred to the cell membrane and forms pores, mediating the release of cellular contents, including the inflammatory cytokines IL-1β and IL-18, and inducing pyroptosis [192]. Excessive pores formation enables release of pro-inflammatory cytokines

IL-1β, IL-18 to extracellular environments, leading to immune cells infiltration and establishment of an inflammatory microenvironment. Pyroptosis also contributes to release of DAMPs such as the protein high-mobility group box 1 (HMGB1) and lactate dehydrogenase (LDH), resulting in amplifying inflammation and recruiting immune cells in the tissue [193, 194].

Currently, it is generally accepted that canonical NLRP3 inflammasome activation requires two steps: the priming step and the activation step. In priming step, cells must be exposed to specific stimuli, such as ligands for toll-like receptors (TLRs), NLRs (e.g. NOD1 and NOD2), or cytokine receptors, which activate the transcription factor NF-κB [195]. NF-κB is required for initiation of NLRP3 and production of pro-IL-1β [196]. In addition, lipopolysaccharides (LPS), IL-1 receptor associated kinase 1 (IRAK-1) and BRCC3 (which is a JAMM domain-containing Zn2 + metalloprotease) function as priming signals of NLRP3 inflammations [195]. In activation step, NLRP3 can be stimulated by a wide range of stimuli following this priming step, including ATP, K + ionophores, heme, particulate matter [197], pathogen-associated RNA [198], and bacterial and fungal toxins and components [199]. A recent study shows that mitochondrial DNA (mtDNA) induced by transcriptional factor IRF1 is important for NLRP3 activation [200].

Noncanonical pathway (Caspase4, 5, 11- dependent pathway)

Caspase-4/5 (in humans) and caspase-11 (in mice) can be activated directly in contact with bacterial LPS through the CARD domain of the caspases [201]. Then the cleavage of GSDMD by caspases at Asp276 (Asp275 in human GSDMD) generates peptide segments, leading to the induction of cell membrane perforation and subsequent release of cellular contents, similar to the canonical pathway. Interestingly, activated Caspase-4/5/11 can interact with Caspase-1 in the presence of NLRP3 and ASC to promote its activation, mediate the maturation and release of downstream IL-1β and IL-18, and indirectly activate Caspase-1, leading to pyroptosis [202]. The priming step that activating Caspase-11 in murine cells is induced by the ligands of TLRs and cytokine receptors which activate transcription factor NF-κB and the type I interferons, the upstream of JAK/ STAT pathway or the complement C3–C3aR axis [203]. By the way, Caspase-11 can mediate pyroptosis via the pannexin-1 channel and the purinergic P2X7 pore [204].

Alternative pathway

GSDME, originally defined as a putative tumor suppressor protein, undergoes specific cleavage by Caspase-3 in the linker region, resulting in the generation of a GSDME-N fragment that possesses membrane-perforating properties for inducing pyroptosis [205]. Caspase-3 is a member of apoptosis executor located at the end of the Caspase cascades, activated by endogenous or exogenous apoptotic pathways. It is interesting that pyroptosis can be mediated thorugh BAK/BAX-Caspase-3-GSDME pathway, which provide a cross-talk between apoptosis and pyroptosis [6]. Caspase-3 inducing either apoptosis or pyroptosis may depends on the intracellular GSDME content. Researches shows that caspase-3 cleavage of GSDME switches apoptosis to pyroptosis in high-GSDME-expressing cancer cells following chemotherapy drugs treatment [206]. Caspase8 also plays a role in pyroptosis in recent studies. The metabolic product α-ketoglutarate (α-KG) has been demonstrated to induce pyroptosis through its reduction to L-2HG, leading to an increase in ROS levels that subsequently oxidizes and internalizes the plasma membrane-localized death receptor DR6 [207]. Ultimately, this process triggers Caspase-8 mediated cleavage of GSDMC. Notably, the PD-L1 protein, a prominent player in the field of antitumor research, modulates TNFα-induced apoptosis to Caspase-8-GSDMC mediated pyroptosis in cancer cells through direct interaction with phosphorylated Stat3 and augmentation of GSDMC gene transcription [208]. In addition, RIPK1–Caspase-8–GSDMD mediated pyroptosis rather than inflammasome mediated pyroptosis can be triggered to counteract virulence factor under Yersinia infection [209]. NLRP3 inflammasome can also be activated through the TLR4–TRIF–RIPK1–FADD–Caspase8 signaling pathway and initiates canonical pathway of pyroptosis [210] (Fig. 4).

Pyroptosis in tumor progression and tumor immunity

Pyroptosis plays a pivotal role in tumor development and antitumor immunity, serving as a double-edged sword that can exhibit both pro-tumorigenic and anti-tumorigenic effects. On one hand, long-term chronic pyroptosis of cancer cells triggered by the adverse TME is more likely to promote cancer progression. For example, high levels of GSDMB in breast cancer are associated with tumor progression, and over-expression of GSDMB indicates a poor response to HER-2 targeted therapy, suggesting that GSDMB may be a novel prognostic marker for tumors [211, 212]. In addition, high levels of GSDMC are associated with poor survival in breast cancer patients while GSDMC downregulation leads to significantly reduced proliferation and proliferation of colorectal cancer cells, which indicates that GSDMC may be a promising therapeutic target for colorectal cancer [213]. This may be because chronic pyroptosis triggers proinflammatory cytokines and the formation and maintenance of an inflammatory microenvironment that promotes tumor

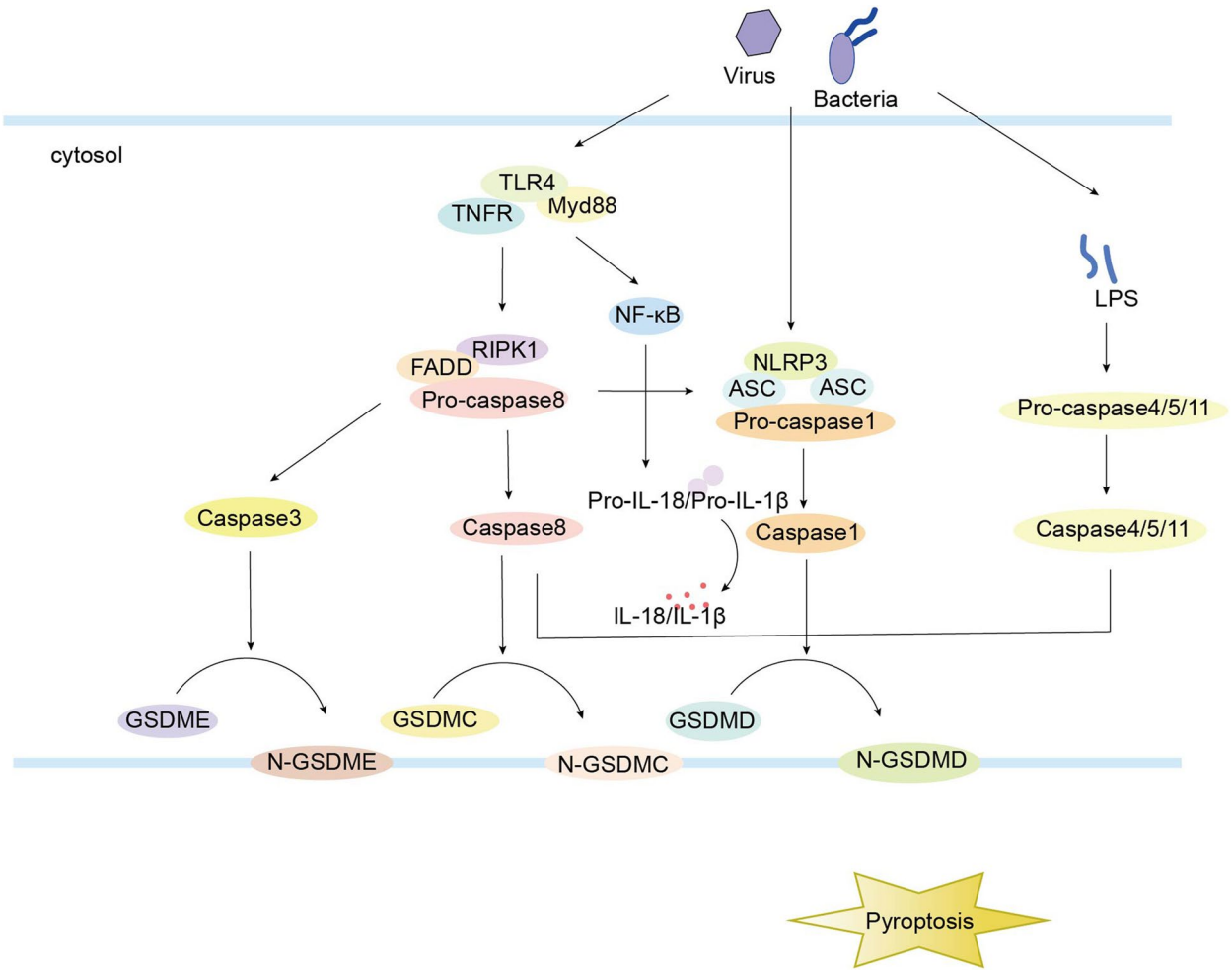

Fig. 4 Cellular and molecular mechanisms of pyroptosis. There are three classifications of pyroptosis, namely canonical pathway, also known as Caspase1-dependent pathway; noncanonical pathway and alternative pathway. (1) Canonical pathway: These inflammasomes recruit and bind to ASC, leading to ASC focus, which recruit procaspase-1 and activate caspase-1. Caspase-1 involves in the cleavage and maturation of proIL-18 /1β and cleavage of gasdermin D (GSDMD). The N-terminal fragment of GSDMD (GSDMD-NT) releases and forms the pores in the plasma membrane, resulting in the secretion of IL-18 /1β and water influx, generating cell swelling and pyroptosis. (2) Noncanonical inflammasome pathway: LPS derived from bacteria recognizes and activates caspase-4/5/11, inducing pyroptosis by cleavage of GSDMD. (3) Alternative pathway: Muture caspase-3 induces the cleavage of GSDME while Caspase-8 mediates cleavage of GSDMC

growth. Additionally, the reported findings suggest that GSDME-mediated pyroptosis plays a crucial role in the progression of colitis-associated colorectal cancer by releasing high-mobility group box protein 1, which subsequently triggers tumor cell proliferation and upregulates the expression of proliferating nuclear antigen through activation of the ERK1/2 pathway [214].

Conversely, acute and extensive activation of pyroptosis leads to significant infiltration of immune cells, which not only causes extensive tumor cell death but also enhances antitumor immunity, thereby inhibiting tumor growth. The extensive antitumor immunity of pyroptosis involves the release of damage-associated molecular patterns and inflammatory cytokines which enhances the recruitment of adaptive immune cells along with increased antigen presentation. IL-18 plays critical role in natural killer (NK) cell recruitment and activation, as well as Th-1 polarization [215]. What's more, pyroptosis-induced inflammation can synergize with checkpoint blockade to trigger robust antitumour immunity [216]. Studies have shown that GSDMA and GSDMC are tumor suppressor genes in gastric cancer [217, 218]. Also, the presence of GSDMD in tumor cells is closely correlated with the viability of CTL cells, indicating that GSDMD plays a crucial role in maintaining CTL-mediated antitumor immunity [219].

Ferroptosis

Ferroptosis is a regulation of cell death formally proposed by Scott J Dixon in 2012. The accumulation of iron determines the occurrence of cell death, which is mediated by lipid peroxidation and accompanied by the generation of reactive oxygen species (ROS). They found that this non-apoptotic pathway holds promise as a new target for eliminating tumor cells as well as oncogenetic mutations [4]. Back in 2003, when Dolma et al. was trying to target an oncogenetic protein as an anticancer therapy, they found that a compound with a genotype-selective activity called erastin could induce tumor cells to enter non-apoptotic cell death [220]. Later, WS Yang et al. suggested that RAS-selective lethal-3 (RSL3) and RAS-selective lethal-5 (RSL5) are potent compounds that can induce iron-dependent oxidative cell death in a RAS-selective manner [221]. As researchers gain a better understanding of the mechanism of ferroptosis, more and more molecules have been invented as inducers of ferroptosis [222]. Ferroptosis has unique morphological and bioenergetic features, including mitochondrial shrinkage, increased mitochondrial membrane density, destruction of membrane integrity and depletion of intracellular NADH, whereas, without Caspase activation. Lipid peroxides accumulation and iron dependence are two major characteristics of ferroptosis. Furthermore, ferroptosis is not sensitive to inhibition of RIP1/RIP3 or Cyclophilin D (CyPD), which are key regulators of necroptosis. Apart from that, inhibition of autophagy by 3-MA(3-methyladenine, an autophagy inhibitor) does not modulate this cell death process [4].

Cancer cells have their own way of escaping cellular stress and ferroptosis to survive in the tumor microenvironment, which has brought about dramatic changes in anticancer therapy [223, 224]. Therefore, it is important to increase the sensitivity of tumor cells to ferroptosis. Recently, epigenetic alterations have been recognized as important contributors to cancer development. Epigenetic modifications significantly affect gene expression and subsequently regulate different biological processes, which is an important link between externally induced signals and different biological functions. There is increasing evidence that epigenetic modifications play an important role in ferroptosis [225].

Mechanisms of ferroptosis

Iron accumulation

Ferroptosis is morphologically and biochemically distinct from apoptosis, pyroptosis, and necroptosis. Before this concept was proposed, iron chelators had been shown to hold promise for cancer therapy [226]. The researchers then found that this cell death was induced by RSL3 or erastin, which is involved in the Fenton reaction and ROS, rather than by a caspase-dependent pathway [221]. Iron acts as a reducing agent in the Fenton reaction, generating reactive oxygen species, leading to DNA damage and lipid peroxidation in cell membranes [227]. Iron chelators such as DFOM are able to counteract RSL3 or erastin and inhibit cell death. In BJ-TERT/LT/ST/RASV12 cells (synthetic mutant cells), the expression level of transferrin receptor 1 (TfR1) is elevated to uptake higher levels of iron and in response to oncogenic RAS signaling. Meanwhile, oncogenic RAS signaling has bidirectional mechanisms to enhance cellular destabilized iron stores: one by up-regulating TfR1 to increase iron uptake and the other by down -regulating ferritin heavy chain 1 (FTH1) and ferritin light chain (FTL) to reduce iron storage capacity [221]. Transferrin binds to the transferrin receptor and forms a Tf-TfR complex that transports Fe3 + into cells, which are later reduced to the ferrous form by the six transmembrane epithelial antigen of prostate 3 (STEAP3) [228]. Cancer cells have higher transferrin receptor 1 and more ferritin expression than other normal tissues [229]. Ferritin is a protein used to store iron. Iron accumulation may occur in senescent cells due to phagocytosis by ferritin. On the contrary, sequestration of iron within ferritin confers cellular resistance to ferroptosis [230]. In addition, ferritin can inhibit ferroptosis by forming ferritin-containing exosomes [231]. Hypoxic primary human macrophages reduce intracellular free iron and increase ferritin expression, including mitochondrial ferritin (FTMT), for iron storage. Nuclear receptor coactivator 4 (NCOA4), a master regulator of ferritin phagocytosis, was shown to directly regulate FTMT expression and inhibit ferroptosis [232]. Currently, some iron-containing proteins have been shown to promote ferroptosis. Nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (NOX) is a heme-containing protein that catalyzes the production of ROS in a regulatory manner [233], suggesting that cells with elevated intracellular iron death is more sensitive. Given that cancer cells disrupt normal iron metabolism to increase intracellular iron, ferroptosis may be a promising new therapeutic target. In addition to this, epidemiological studies support the association between elevated iron levels in the body and cancer through biomarkers: circulating iron binding [protein transferrin (TF) and ferritin (FT)] and transferrin saturation positive correlation view [234]. Studies have found that dietary iron is absorbed by enterocytes in the gut as inorganic iron or heme, and dietary ferric iron is reduced to ferrous iron via duodenal cytochrome B (DcytB) and via divalent metal transporter 1 (DMT1) into enterocytes [235]. Heme is degraded by heme oxygenase 1 (HO-1) present in the endoplasmic reticulum, releasing iron. Ferroportin

(FPN) is transported out of enterocytes, oxidized by heparin (HEPH) and loaded onto TF for systemic circulation. It can be recovered from senescent erythrocytes by endocytosis of macrophages and then re-entered into the circulation by FPN, or transported to the liver for storage [236]. Iron is imported into cells of peripheral tissues through the binding of TF to its receptor, transferrin receptor 1 (TFR1). The complex is endocytosed and ferric iron is released from TF, reduced by STEAP proteins, and exported into the cytoplasm via DMT1. Iron enters the metabolically active labile iron pool (LIP) [237], and the non-canonical pathway can induce ferroptosis by increasing intracellular LIP [238].

Intercellular interactions

Recently, cell-to-cell interactions have been shown to play a role in ferroptosis. E-cadherin-mediated intercellular interactions have been reported to inhibit ferroptosis through intracellular Merlin-Hippo signaling. Antagonism of this signaling axis releases the activity of the proto-oncogenic transcriptional coactivator YAP, which promotes ferroptosis by upregulating multiple ferroptosis regulators, including acyl-CoA synthase long-chain family member 4 (ACSL4) and the transferrin receptor. Malignant mutations in Merlin-YAP signaling may serve as biomarkers for predicting cancer cell response to future ferroptosis-inducing therapy [239].

Lipid peroxidation Lipid peroxidation is a process in which lipids, especially fatty acids, are attacked by free radicals such as ROS. Fatty acids are essential for normal cellular function and structure as cellular building blocks. There are three types of fatty acids, saturated fatty acids (SFAs), monounsaturated fatty acids (MUFAs) and polyunsaturated fatty acids (PUFAs). Peroxidation of lipid synthesis PUFAs at bisallyl sites is an important step in promoting ferroptosis. Increased PUFA synthesis promotes subsequent lipid peroxidation under conditions of oxidative stress, which contains phosphatidylethanolamine (PE), fatty acyl-arachidonoyl (AA) and epinephrine (AdA) [240]. Ferroptosis can be inhibited by blocking the production of these lipids [241]. Many enzymes are involved in the lipid peroxidation process. Oxidoreductases, including NADPH-cytochrome P450 reductase (POR) and NADH-cytochrome b5 reductase (CYB5R1), transfer electrons to oxygen and generate hydrogen peroxide, which generates reactive hydroxyl radicals through the Fenton reaction and leads to oxidation of membrane phospholipids [242]. Peroxidases can indirectly promote ferroptosis by synthesizing polyunsaturated ether phospholipids (PUFA-ePL), which subsequently trigger lipid oxidation [243]. ACSL4 is a member of the long-chain family of acyl-CoA synthetase proteins responsible for the esterification of PUFAs to acyl-CoA [244]. LPCAT3 then catalyzes the biosynthesis of AA/AdA-CoA and membrane PE to form AA/AdA-PE [245]. The formation of lipid hydroperoxides (LOOH) is the main process of lipid peroxidation. During this process, lipids are attacked by pre-oxidants to form lipid free radicals, which rapidly react with oxygen to form lipid peroxidation groups, which obtain hydrogen gas to produce lipid hydrogen peroxide (LOOH) [246]. Knockdown of upstream regulators of PUFA metabolism (ACSL4, LPCAT3) and inhibition of lipoxygenase prevents cell death due to inhibition of GPX4 [247]. The ALOX family is an important regulator of lipid peroxidation in ferroptosis, and the mammalian ALOX family consists of six members (ALOXE3, ALOX5, ALOX12, ALOX12B, ALOX15 and ALOX15B) that organize the production of AA/AdA-PE-OOHs or cell-dependent action, leading to ferroptosis. For example, spermidine /spermine N1-acetyltransferase 1 (SAT1), a target gene of *Tp53*, mediates the expression of ALOX15 (but not ALOX5 and ALOX12) and is involved in *TP53*-mediated ferroptosis in H1299 cells [248]. In contrast, ferroptosis caused by *TP53*-mediated downregulation of SLC7A11 in H1299 cells requires ALOX12, but not other ALOX members [249]. Therefore, different *TP53* pathways utilize different ALOX to induce ferroptosis.

ALOXs are not the only regulators of lipid peroxidation in ferroptosis. In fact, POR binds to two cofactors, flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD), and supplies P450 enzymes directly from nicotinamide adenine dinucleotide phosphate (NADPH) electrons, thereby promoting PUFA peroxidation in cancer cells in an ALOX-independent manner [250]. In addition, GPX4 reduces lipid peroxidation by oxidizing GSH to GSSG, which acts as an antioxidant and helps cells escape from ferroptosis. RSL3-triggered ferroptosis works by covalently binding to and inhibiting GPX4 activity [250].

GPX4-dependent pathway ① System xc-

Iron inducers such as erastin inhibit the uptake of cystine by the cystine/glutamate anti-transporter (system xc-), reduce intracellular GSH levels, thereby block the cellular antioxidant defenses, and ultimately lead to ferroptosis. System xc- consists of two core components: the light chain subunit SLC7A11 and the heavy chain subunit SLC3A2, which is an amino acid anti-transporter that mediates the transport of extracellular cystine and intracellular glutamate at the plasma membrane. The exchange on glutathione is essential for the synthesis of the antioxidant glutathione (GSH) [4]. SLC7A11 expression levels generally correlate positively with antiporter

activity. Transcription factor 3 (ATF3) is normally expressed under cellular stress and, by binding to the SLC7A11 promoter, represses system Xc- and promotes ferroptosis [251]. Beclin1 (BECN1) can be phosphorylated by adenosine 5'-phosphate- dependent protein kinase (AMPK) and bind directly to SLC7A11 to inhibit system Xc—activity [252]. Deubiquitinase 1 (OTUB1) of the ovarian tumor domain proteolytic enzyme subfamily stabilizes SLC7A11 activity, and its overexpression in cancer cells favors tumor progression [253]. Transcription factors such as BAP1, P53, Nrf2, and STAT3 are also involved in SLC7A11 repression to control tumor development, so their inactivation may lead to ferroptosis resistance in cancer cells [254–257].

② Glutathione synthesis

Reduced glutathione (GSH) is a tripeptide composed of glutathione, cysteine and glycine combined with a sulfhydryl group, which has antioxidant and comprehensive detoxification effects. Oxidation from GSH to oxidized glutathione (GSSG) protects membrane lipids from peroxidation [258]. GSH is stably present in cells due to its unique structure, as glutamate participates in peptide bonds with a γ-carboxyl group rather than an α-carboxyl group, a structural feature that makes it essential in cellular antioxidants. The synthesis of GSH is mainly catalyzed by γ-glutamylcysteine synthase (GSH1) and glutathione synthase (GSH2). GSH1 catalyzes the formation of γ-glutamylcysteine from L-cysteine and L-glutamate [258–260]. GSH2 catalyzes the formation of glutathine from γ-glutamylcysteine and glycine. The first step in GSH1 control is the rate-limiting step in which overexpression of GSH2 fails to increase GSH2 levels, whereas overexpression of GSH1 increases GSH levels [261]. Therefore, modulating GSH1 expression in cells affects GSH expression levels [262]. GSH1 is affected by many factors at the gene transcription level, such as oxidative stress, insulin and glucocorticoids [263–266]. GSH1 and GSH levels represent negative feedback regulation. TGF-β1 can downregulate GSH1 levels and induce GSH depletion [267]. In addition to the cystine uptake pathway described above, cystine can also be produced by utilizing methionine (also known as the trans-sulfurization pathway). The methylation reaction that converts SAM to SAH limits the production of homocysteine, thereby limiting the rate of cysteine production through the transsulfurization pathway. Transsulfide-mediated cysteine synthesis is critical for promoting tumor growth in vivo [268].

③ GPX4

GPX4 is an important regulator of ferroptosis. GPX4 is the most abundant selenoprotein in mammals. Each GPX4 molecule has four selenium atoms bound to it, forming the active center of the enzyme molecule. Changes in selenium content directly affect the activity of this enzyme, so GPX4 is also known as a selenium-dependent enzyme [269]. Studies have demonstrated that drug-resistant cancer cells exhibit a dependence on GPX4, highlighting its potential as a therapeutic target for mitigating acquired drug resistance in cancer patients [270]. FINO2 indirectly inhibits the enzymatic function of GPX4, accompanied by iron oxidation, causing extensive lipid peroxidation [271]. GPX4 inhibitors may be more effective against cancer cells after TGF-β1 pretreatment [272].

FSP1 pathway Ferroptosis inhibitory protein 1 (FSP1) (formerly known as apoptosis-inducing factor mitochondria 2 (AIFM2)) is an effective resistance factor for ferroptosis. FSP1 acts as an antioxidant independent of GPX4 by working in concert with Coenzyme Q10 (CoQ10). Specifically, FSP1 reduces oxidized CoQ10 to reduced CoQ10 in the cell membrane, thereby clearing peroxides from the membrane lipids, inhibiting lipid peroxidation and ferroptosis [273].Despite its role within the mitochondria, FSP1 translocate from mitochondria to the cell membrane after N-myristoylatyion, where it uses NADPH to catalyze the regeneration of non-mitochondrial reduced CoQ10 to capture lipid peroxidation [273]. In some cases, FSP1 inhibits ferroptosis by activating transport-essential endosomal sorting complex III (ESCRT-III) -dependent membrane repair rather than its oxidoreductase function. This ferroptosis-inhibiting pathway brings new hope for chemotherapeutic drugs that target ferroptosis and block tumor growth. The activity of FSP1 in preventing ferroptosis can be specifically inhibited by a small molecule compound called iFSP1 [274]. The mevalonate pathway is a key metabolic pathway responsible for the synthesis of CoQ10, which can be targeted by statins that inhibit CoQ10 production and GPX4 function, making them potential ferroptosis enhancers [275].

DHODH pathway DHODH is an enzyme located in the inner mitochondrial membrane and is mainly involved in pyrimidine anabolism [276]. A recent study using global metabolomic analysis combined with metabolic tracing analysis demonstrated a unique function of DHODH in mitigating mitochondrial lipid peroxidation and ferroptosis independent of its conventional role in the production of pyrimidine nucleotides [277]. DHODH acts in parallel with GPX4 in regulating mitochondrial ferroptosis, but this is another antioxidant system that is neither

GPX4- nor FSP1-dependent and has a prominent role in inhibiting ferroptosis. This novel effect of DHODH may be due to the reduction of ubiquinone to ubiquinol [278]. This study shows that DHODH inhibitors can suppress tumors in cancers with low GPX4 expression alone, or in combination with ferroptosis inducers in cancers with high GPX4 expression [277]. DHODH has been intensively explored as a promising target for cancer therapy, and DHODH inhibitors are a promising drug target for cancer therapy (Fig. 5).

Ferroptosis in tumor progression and tumor immunity

Ferroptosis has a longstanding entanglement with cancer. Ferroptosis was first recognized for its RAS-selective lethality induced by erastin in melanoma cells which is morphologically, biochemically and genetically distinct from other forms of cell death. Unlike drug resistence occurred in apoptosis-induced cancer therapy and accidental injuries to normal cells in pyroptosis/necroptosis-targetted drugs, ferroptosis seems to be gaining favor with tumor cells. In simple terms, cancer cells extremely susceptible to ferroptosis. This can be manifested in the strong dependence of ferroptosis-regulated proteins in tumor cells. For example, ccRCC (clear cell renal cell carcinoma) cells are highly sensitive to the depletion GSH, especially under β-oxidation inhibition, while the growth of normal renal epithelial cells is not affected [279]. It is also found that therapy-resistant high-mesenchymal cell state in multiple human cancers exist in a GPX4-dependent way which provide a druggable pathway for inducing vulnerability to ferroptosis in therapy-resistant cancer cells [247]. This ferroptosis-sensitive characteristic can be rationalized by oncogenic pathways which contribute to ferroptosis. *p53* is known to be a classic tumor suppressor mutated in most cancer cells and failed to induce cell cycle arrest, senescence and apoptosis. Surprisingly, *p53* (3KR) retains the ability

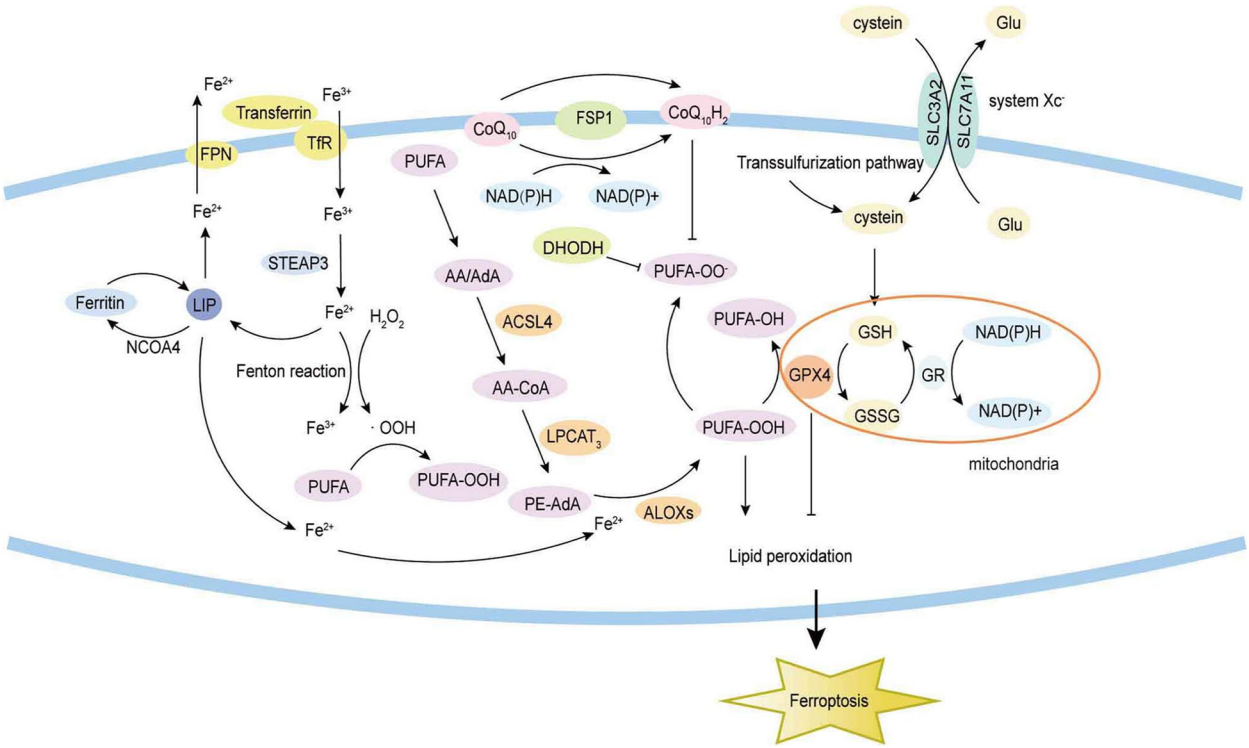

Fig. 5 Cellular and molecular mechanisms of ferroptosis. (1) Iron accumulation. Transferrin binds to the transferrin receptor and forms a complex to transport Fe^{3+} into cells, which are later reduced to the by STEAP3. Fe^{2+} acts as a reducing agent in the Fenton reaction, generating reactive oxygen species, leading to DNA damage and lipid peroxidation in cell membranes. (2) Lipid peroxidation. ACSL4 functions on the esterification of PUFAs to acyl-CoA. LPCAT3 then catalyzes the biosynthesis of AA/AdA-CoA and membrane PE to form AA/AdA-PE. Lipids are attacked by pre-oxidants to form lipid free radicals, which rapidly react with oxygen to form lipid peroxidation groups under the catalization of ALOX family. (3) GPX4-dependent pathway. Oxidation from the antioxidant glutathione (GSH) to oxidized glutathione (GSSG) induced by GPX4 protects membrane lipids from peroxidation. The exchange on glutathione mediated by system Xc^- is essential for the synthesis of GSH. (4) FSP1 pathway. FSP1 translocates from mitochondria to the cell membrane, where it uses NADPH to catalyze the regeneration of non-mitochondrial reduced CoQ10 to capture lipid peroxidation in a GPX4-independent manner. (5) DHODH pathway. DHODH acts as an independent antioxidation system to inhibit ferroptosis

to regulate SLC7A11 expression and induce ferroptosis upon reactive oxygen species (ROS)-induced stress. Notably, cancer cells are suggested to require higher levels of iron and lipid metabolism than normal cells. For one thing, cancer cells exhibit an iron-seeking phenotype achieved by increasing iron uptake and storage as well as decreasing iron export and this process correlates with poor prognosis [272]. It has been put forward that regulations of iron uptake and iron storage were reached mainly by overexpression of TF and inhibition of ferritin, and expression of the proto-oncogene MYC in B cells induces IRP2 which post-transcriptionally repress ferritin expression and increase TFR1 expression [280]. Even TFR1 has been established as a tumor marker. Beyond that, it is revealed that HRAS oncogene controls the downregulation of ferritin increasing the labile iron pool and stimulating proliferation [7]. For another, cancer cells can internalize PUFAs to favor the different steps of the metastatic cascade, ranging from the generation of metastasis-initiating cells to metastatic outgrowth [281]. ACSL4 which fuels proliferation and migration of colon cancer cells is one of the key catalysts of lipid peroxidation in ferroptosis [282, 283]. Thus, elevated levels of iron in cancer cells engaged in free radical formation and propagation of lipid peroxidation promote cell proliferation and increase the vulnerability to ferroptosis at the same time. In this way, sensitization of cancer cells to ferroptosis by increasing the amount of PUFAs and iron absorbtion can be exploited to overcome certain therapy resistances, which also explains the high dependence of cancer cells upon GPX4 activity and GSH biosynthesis.

However, cancer cells can also endure in ferroptosis-sensitive states. This may be related to immune evasion in the tumor microenvironment shaped by ferroptosis-targeted genes, especially GPX4 [284]. GPX4 can assist T regulatory (Treg) cells escaping from ferroptosis and suppress anti-tumor immunity [285]. On the contrary, redox homeostasis maintained by GPX4 facilitates stimulator-of-interferon genes (STING) activation initiate innate immune responses against tumors [286]. Additionally, $CD8^+$ T cells can promote ACSL4-dependent tumor ferroptosis induced by IFNγ and exert anti-tumor immunity in the tumor microenvironment [287].

Disulfidptosis

It has been mentioned above that SLC7A11-mediated cystine uptake is critical to defense ferroptosis for the importing cystine acts as rate-limiting precursor for glutathione biosynthesis which can withstand lipid peroxidation. However, excessive cystine uptake and subsequent cystine reduction to cysteine promote disulfide stress and NADPH depletion under glucose deprivation [288]. This comes at a significant cost for cancer cells with high levels of SLC7A11 to elude from ferroptosis [288]. In response to oxidative stress, cysteine residues form mixed disulfide bridges with glutathione in redox-sensitive proteins through glutathionylation which later causes the disulfide-bond formation and migration retardation in actin cytoskeleton proteins [289, 290]. Ulteriorly, it is proposed that an uncharacterized form of cell death distinct from apoptosis and ferroptosis can be triggered in SLC7A11 high cells with disulfide-bond formation under glucose starvation. This form of cell death is termed as disulfidptosis [290]. Hopefully, glucose starvation-induced disulfidptosis might be an effective therapeutic strategy for treating SLC7A11high tumors, which are common in human cancers [291].

Cuproptosis

Similar to iron, copper is an intracellular trace metal that plays an indispensable role in maintaining the function of proteins [292]. Importantly, the intracellular Cu is regulated by a complex network of Cu-dependent proteins, including cuproenzymes, Cu chaperones, and membrane transporters to keep Cu concentration at a relatively low range [293]. A new kind of cell death induced by copper adds credence to the notion that copper homeostasis is required for executing a wide range of physiological processes [294]. Last year, Tsvetkov et al. discovered a copper-dependent regulated cell death termed as cuproptosis [294]. In this study, cuproptosis tightly relies on the function of tricarboxylic acid (TCA) cycle and it can be regulated by FDX1 induced DLAT lipoylation [294]. The copper carrier elesclomol is chosen as cell death inducer. Of note, this kind of cell death is impertinent with apoptosis pathway because the inhibition of BAX and BAK1 can't influence the killing effect by elesclomol [294]. Just like the role of ferritin and transferrin in ferroptosis, the protein ATP7A/B and SLC31A1 are responsible for importing or exporting cuppor to cells and controlling the cuppor flux.

Mitochondrial permeability transition (MPT)-driven necrosis

MPT-driven necrosis is a form of RCD triggered by specific perturbations of the intracellular microenvironment, such as severe oxidative stress and cytoplasmic overload, and usually manifests in a necrotic form [295, 296]. The occurrence of MPT is attributed to significant intracellular disturbances in REDOX and Calcium ion homeostasis, such as those induced by potent oxidizing agents (e.g., hydrogen peroxide) or ionophores, or naturally occurring due to ischemic injury [296, 297]. To date, cyclophilin D (CYPD) is the only protein whose requirements for MPT induction in vivo have been formally validated by genetic tools [298–300]. Thus, pharmacological inhibitors of

CYPD such as cyclosporin A (CsA) [301–303], Samfilin A (SfA) and JW47 limit MPT-driven necrosis and provide protection in a variety of rodent disease models in which oxidative stress and cytoplasmic overload constitute major etiologic determinants [304–306].

Parthanatos

Parthanatos is a poly(ADP-ribose) polymerase 1 (PARP1) -dependent cell death pathway, which is caused by DNA damage [307]. The mechanisms of parthanatos mainly include DNA damage, PARP1 hyper-activation, PAR accumulation, NAD^+ and ATP depletion, and apoptosis-inducing factor (AIF) nucleus translocation [307]. Parthanatos is a multi-step pathway that plays a key role in tumor formation. There are many molecules in the parthanatos cascade that can be used to investigate therapeutic interventions in cancer, including PARP1, PARG, ARH3, AIF and MIF. These key molecules are involved in the proliferation, progression, invasion and metastasis of tumor cells. Therefore, these molecular signals in the parthanatos cascade represent promising therapeutic targets for cancer therapy [308]. In pathophysiological situations, overactivation of PARP1, usually induced by DNA damage, leads to accumulation of PAR polymers and nuclear translocation of apoptosis-inducing factor (AIF), all of which ultimately trigger parthanatos [309].

NETosis

NETosis is a form of RCD driven by the release of neutrophil extracellular traps (NETs), an extracellular reticular DNA protein structure released by cells in response to infection or injury [310]. NETs can also be produced by other leukocyte groups (such as mast cells, eosinophils and basophils), epithelial and cancer cells in response to various stresses [310]. Elevated NETosis not only prevents the spread of infection by trapping pathogenic microorganisms such as bacteria and viruses, but also promotes DAMP (damage-associated molecular patterns) development, which may contribute to autoimmune diseases (such as systemic lupus erythematosus, rheumatoid arthritis, asthma, vasculitis, and psoriasis), ischemia–reperfusion injury and tumor development [311–313]. A recent study showed that NETs production associated with inflammation can wake nearby dormant cancer cells to divide again [314]. This effect may depend on the degradation of laminin, a major binding component of basement membranes; however, this requires further mechanistic exploration [315].

NETosis is a dynamic process that depends on multiple signals and steps, including NADPH oxidase-mediated ROS production, autophagy, granzymes (such as elastase, neutrophil expression, matrix metalloproteinase [MMP] and myeloperoxidase [MPO]) and peptides of the ductin family from the cytoplasm to the nucleus (such as ductin antibacterial peptide [CAMP, also known as LL37]) followed by histone citrullination, which facilitates chromatin de-concentration, disruption of the nuclear membrane and release of chromatin fibers [3, 316, 317]. Peptidyl arginine deiminase 4 (PAD4), the enzyme critical for NETosis, is responsible for catalyzing the conversion of arginine residues to citrulline residues in histones. The recently identified PAD4-independent NETosis pathway may occur in the downstream of death signals that are commonly involved in other types of RCD, such as pyroptosis, necroptosis, and autophagy-dependent cell death [318].

Lysosome-dependent cell death

Lysosome-dependent cell death (LDCD) is a form of cell death caused by lysosomal membrane damage and lysosomal dysfunction, which is first proposed as "suicide bag hypothesis" by Christian de Duve [319]. Lysosomes are membrane-enclosed organelles that mediate the intracellular degradation of macromolecules. They contain a variety of cathepsins and are responsible for the decomposition of various biological macromolecules. When the lysosomal membrane is damaged or ruptured, the enzymes within the lysosome are released into the cytoplasm and trigger the self-destruction process of the cell, termed as the process of lysosomal membrane permeabilization (LMP) [320]. LMP can be initiated in a variety of different ways, including sphingosine, fungal and snake toxins, pore-forming proteins from the BCL-2 family of apoptosis regulators and ROS [321]. Increasing cholesterol levels protects lysosomes against LMP, while hydrolysis of sphingomyelin sensitizes cells to LMP [322]. It has been indicated that tumor cell lysosomes are more fragile than normal lysosomes, they are more susceptible to LMP, leading to tumor demise by apoptotic and nonapoptotic death mechanisms. Thus, drugs target acid sphingomyelinase(ASM) from lysosomal membranes have been invented to increase tumor LMP and cell death [320, 323].

Cellular senescence

Cell senescence is an irreversible state of cell cycle arrest, usually triggered by stress, DNA damage, shortened telomeres or other metabolic signals. Aging cells no longer divide, but they still have active metabolism and can influence their surroundings by secreting specific cytokines, chemokines, and matrix metalloproteinases (senescence-associated secretory phenotype, SASP). Cell senescence is different from other forms of cell death in that it does not cause cells to die immediately, but rather leads to their persistent presence within the body and profound effects on the tissue microenvironment.

Cellular senescence includes a range of triggers. Exposure to radiation, chemical agents, and oxidative stress can induce breaks in DNA double strands, subsequently activating the *p53-p21* and p16-*Rb* signaling pathways, thereby initiating cellular senescence [324]. The growth arrest of senescent cells occurs through a cell cycle blockade in the G1 phase to prevent DNA replication initiation in damaged cells. Then senescent cells may stop in G2 to block mitosis in the presence of DNA damage [325]. DNA damage signaling is also involved in the initiation of stress-induced premature senescence in response to acute cellular stresses, such as oxidative damage generated by ROS and oncogene activation. The overactivation of the RAS signaling pathway can induce cellular senescence, acting as one of the mechanisms that inhibit oncogenesis [326]. Activated oncogenes disrupt cell cycle entry by increasing the activity of CDK (cyclin-dependent kinase) as a positive regulator of S phase. As cellular division occurs, telomeres progressively shorten. Upon reaching a critical length, telomeres are particularly susceptible to oxidation-induced damage and the cell transitions into a senescent state [325].

Cell senescence plays a dual role in tumorigenesis and progression, functioning both as an anti-tumor mechanism and as a pro-tumor factor. On one hand, cellular aging represents a significant obstacle to the prevention of malignant transformation. By inhibiting the cell cycle via the *p53-p21* or *p16-Rb* pathways, cells harboring unstable genomes can be effectively prevented from undergoing uncontrolled proliferation. What's more, aging cells are typically identified and trigger efficient and protective CD8-dependent antitumor immune responses to prevent their accumulation, thereby mitigating the risk of cancer [327]. While cellular senescence may inhibit tumor progression in the initial stages, the prolonged existence of senescent cells and their secretion of the SASP can contribute to the degradation of the tumor microenvironment in certain instances. The SASP factors encompass pro-inflammatory cytokines, including IL-6 and IL-8, as well as matrix remodeling enzymes such as MMPs. These components can alter the local microenvironment and foster chronic inflammation, consequently heightening the risk of tumorigenesis [328]. SASP-secreted IL-6 and IL-8 have the capacity to activate the STAT3 signaling pathway in cancer cells, thereby facilitating their proliferation and metastasis [328]. Apart from that, these factors significantly reshape the tumor microenvironment (TME), enabling tumors to evade immune destruction [328]. Given the dual role of cellular aging in tumorigenesis, researchers are investigating strategies to harness or modulate cellular aging for cancer treatment. The proliferation of tumor cells can be suppressed by certain drugs through the induction of cellular senescence. For example, DNA damage agents or epigenetic regulatory drugs can suppress tumor growth by activating the cell senescence pathway as well as inhibiting the proinflammatory SASP [329]. Futhermore, the development of targeted therapeutics capable of selectively eliminating senescent cells, termed 'senolytics', has emerged as a promising strategy in cancer treatment [330]. Senomorphics are drugs that modify the phenotype of senescent cells, restoring them to a more youthful state without inducing apoptosis [331].

Immunogenic cell death

Although cells can undergo apoptosis, autophagy or necroptosis when experiencing intracellular stress or cell death-related signals, the signaling pathways of cells have extended their reach beyond the domain of single cells and have acquired the capacity to inform the host about a potential danger in evolution [332]. That is to say, stressed and dying mammalian cells release numerous bioactive molecules, that interact with the immune system to dictate the immunogenic correlates of cellular stress and death. Immunogenic cell death (ICD) is a special form of cell death that can drive antigen-specific immune responses culminating in immunological memory, differentiating with other RCDs (eg. necroptosis, necroptosis) that only engage innate immune mechanisms [333]. It has also been put forward that ICD can initiate adaptive immune responses only when accompanied by antigenicity, adjuvanticity and a permissive microenvironment [332].

One of the main features of ICD is that it releases or exposes a series of dangerous signals during cell death, which are called damage-associated molecular patterns (DAMPs). When cells are in ICD, calreticulin will be transferred to the cell surface as a "eat me" signal to attract immune cells to clear dead cells [334]. At the same time, they release large amounts of ATP, which can act as a chemical chemokine to attract dendritic cells and macrophages [335]. Of note, the release of HMGB1 can activate dendritic cells and other immune cells, enhancing antigen presentation function [335]. These ICD-specific DAMPs become effective targets for anti-cancer therapies especially under combined action of ROS and ER stress [335]. Indeed, various treatments including specific chemotherapeutics, radiation therapy (RT) and some targeted anticancer agents mediate tumor-targeting to raise treatment efficacy [336, 337].

Mitotic catastrophe

Mitotic catastrophe is a cellular response that triggers programmed cell death when a cell fails to properly complete mitosis. This phenomenon is usually triggered by DNA damage, faulty spindle assembly, or misallocation of

chromosomes, and the inability of cells to complete division properly leads to cell death. Although it is not typical of apoptosis, it can be used as part of the cell clearance mechanism to prevent cells with substantial genetic damage from continuing to proliferate. It is of great value that mitotic catastrophe acts as an onco-suppressive mechanism for the avoidance of genomic instability (Tables 1 and 2).

Cross-talk between different forms of programmed cell death

We have reorganized the research progress of signals and mechanisms that related to different types of cell death. Even though different types of cell death are equipped with their own pathways, we can still find the intersections between these pathways. External environmental disturbance or artificial interference can drive cells turning around to another direction.

Cross-talk between autophagy and apoptosis

Autophagy and apoptosis have extensive interactions due to their roles in controlling cellular homeostasis. The relationship between autophagy and apoptosis on the regulation of cell fate can be come down to three aspects, that is, autophagy protects cells from apoptosis; excessive autophagy induces autophagy-dependent cell death which is mutually exclusive with apoptosis; autophagy and apoptosis can concomitantly take place. From a certain perspective, the relationship between autophagy and apoptosis can be described as a dynamic interplay of antagonistic competition and mutual inhibition. However, simultaneously, autophagy and apoptosis serve analogous physiological purposes, namely the elimination of aged or impaired cells and organelles to sustain the vitality of tissues and organs. The initiation of both autophagy and apoptosis can be triggered by shared upstream signals, resulting in the occurrence of concurrent autophagy and apoptosis in specific scenarios. The exploration and

Table 1 Events that cause the various types of cell death

Cell death type	The initiating pressure/event	Reference
Apoptosis	Oxidative stress, DNA damage, cytokines, ER stress, cytotoxic agents, radiation damage	[27]
Autophagy	Nutrient deficiency, oxidative stress, hypoxia, mitochondrial damage	[113, 115, 116]
Necroptosis	TNF-α, viral infection, Toll-like receptor activation (TLR3, TLR4 etc.)	[139]
Pyroptosis	Pathogen infection (bacteria, viruses), inflammasome activation	[189]
Ferroptosis	Oxidative stress, iron accumulation, lipid peroxidation, depletion of GSH, inhibition of GPX4	[221]
Disulfidptosis	Excessive oxidative-reduction stress, disrupted disulfide bond formation, glucose metabolic dysregulation	[288]
Cuproptosis	Accumulation of copper ions, oxidative stress in mitochondrial proteins, dysregulation of glutamate metabolism	[294]
MPT-driven necrosis	Calcium overload, ROS, mitochondrial permeability transition pore (MPTP) opening	[295, 296]
Parthanatos	DNA damage, excessive activation of PARP-1, oxidative stress, glutamate toxicity	[307]
NETosis	Pathogen infection (bacteria, fungi, viruses), LPS	[310]
LDCD	Changes in the permeability of lysosomal membrane, release of lysosomal hydrolases, ROS	[320, 321]
ICD	Pathogen infection	[333]
Mitotic catastrophe	Abnormal cell cycle regulation, radiation, centrosome assembly defects, chromosomal instability	[338]

Table 2 Potential tumor therapy targets in the cell death pathway

Cell death type	Potential therapeutic targets	Reference
Apoptosis	Bcl-2 family, p53, Caspases, TNF	[338]
Autophagy	mTOR, Beclin-1, AMPK	[339]
Necroptosis	RIPK1, RIPK3, MLKL	[340]
Pyroptosis	NLRP3, Gasdermin D, Caspase1	[340]
Ferroptosis	GPX4, SLC7A11, ACSL4, FSP1	[340]
Disulfidptosis	SLC7A11	[291]
Cuproptosis	SLC31A1, FDX1, DLAT	[340, 341]
Parthanatos	PARP-1, AIF	[308]
NETosis	Pathogen infection (bacteria, fungi, viruses), LPS	[314]
ICD	Calreticulin, HMGB1	[342]
Mitotic catastrophe	microtubule, spindle assembly checkpoint kinase	[343]

discussion of the decision-making process in cells under external stimulation or intracellular stress holds significant value.

Autophagy as a protective mechanism preceding apoptosis

The dysregulation of cellular homeostasis often leads to the activation of two self-destructive processes, autophagy and apoptosis. Notably, when cells are exposed to stress signals that cause a decrease in intracellular metabolite concentrations, the autophagy resulting from apoptosis inhibition actually provides cellular protection against cell death by replenishing the vanishing energy reserves of the starving cells.

The accumulation of folding-incompetent or misfolded proteins above a critical threshold initiates a compensatory signal transduction pathway, known as the UPR (unfolded protein response), during ER (endoplasmic reticulum) stress. It has been illustrated anteriorly that UPR-dependent cell death can be triggered in response to imbalance of cellular homeostasis in an apoptotic way by initiating IRE1-XBP1 signaling, PERK-eIF2α-ATF4-CHOP signaling and ATF6 signaling. Simultaneously, the process of autophagy is regarded as a cellular self-defense mechanism which can be activated in response to various forms of cellular stress. Multiple studies have consistently demonstrated that activation of the UPR can induce cytoprotective autophagy, which promotes cell survival by recycling damaged organelles and proteins. The induction of ER stress can initiate alterations in apoptosis or autophagy, thereby modulating UPR to regulate cellular fate. First of all, the activation of PERK and IRE1 UPR pathways induced by radiation exposure-mediated ROS accumulation can induce pro-survival autophagy in a dose- and time-dependent way [344]. CO-induced PERK activation temporarily halts protein translation and induces protective autophagy, which increases antitumor T-cell function [345]. Secondly, activated ATF4 pathway upregulates DDIT4 to suppress mTOR, thereby inducing a pro-survival autophagy response during inhibition of glutaminolysis [346]. What's more, the GADD34 protein, which is activated by both CHOP and TFEB, dephosphorylates eIF2α and plays a crucial role in autophagy during periods of starvation [347, 348].

Meanwhile, the induction of autophagy frequently concomitant with the suppression of the apoptotic pathways. ATG7 suppresses apoptosis induced by *p53* activator to promote cell survival [349]. TRAF2-RIPK1-mediated JNK could provoke activation of cytoprotective autophagy as well as expression of anti-apoptosis factors [350]. Additionally, mitochondrial translation elongation factor Tu, a mitophagy-associated protein encoded by the TUFM gene, locates in part on the outer membrane of mitochondria where it acts as an inhibitor of Caspase-8-mediated apoptosis through its autophagic function [351]. It has been confirmed that the inactivation of ATG genes can cause cell death. Inhibition of autophagy by knockdown of ATG5 or ATG7 or inhibition of Vps34 killed $Bax^{-/-}$ $Bak^{-/-}$ cells, which indicates that autophagy functions as a survival mechanism [352]. These findings underscore the extent to which the process of autophagy serves as a highly efficient mechanism for cellular protection against apoptosis.

Apoptosis develops when autophagy is inhibited. Notably, the phenotype of the cells (before they undergo apoptosis) is profoundly influenced by the stage at which autophagy is inhibited. The inhibition of genes involved in the initial stages of autophagy, such as ATG5, ATG12, Vps34, often results in apoptotic cell death, whereas the inhibition of genes involved in late-stage of autophagy, particularly those responsible for lysosome-autophagosome fusion, can lead to autophagy dependent cell death [353]. The mechanisms through which the inhibition of autophagy may favor cell death are not entirely clear. It is possible that the inhibition of autophagy results in a bioenergetic shortage and subvert the capacity of cells to remove damaged organelles or to remove misfolded proteins that triggers apoptosis.

Autophagy-dependent cell death develops when apoptosis is inhibited

Although autophagy serves as a protective mechanism against cell death, excessive degradation of cytoplasm and organelles through autophagy can surpass a critical threshold, resulting in irreversible cellular atrophy, impairment of vital cellular functions, and disruption of cellular homeostasis. Ultimately, this culminates in the occurrence of autophagy-dependent cell death (ADCD) [354]. ADCD is a Caspase-independent form of programmed cell death (PCD), characterized by an over-activation of autophagy, leading to prominent self-digestion of cellular material in autolysosomes. The specific mechanism of autophagy-dependent cell death is not very clear, but studies suggest that it may be related to the inactivation of Na^+, K^+ -ATPase on cell membrane [355]. The occurrence of autophagy-induced cell death has been observed in studies where apoptosis is inhibited. The initial investigation revealed that $Bax^{-/-}$ $Bak^{-/-}$ mouse embryonic fibroblast (MEFs) were incapable of undergoing apoptosis, instead exhibiting extensive autophagy and delayed cell death [352]. TRADD is a direct regulator of apoptosis. However, inhibition of TRADD by ICCB-19 or Apt-1 blocks apoptosis and restores cellular homeostasis by activating autophagy in cells with accumulated mutant tau, α-synuclein, or huntingtin [356]. The deletion of Caspase8 in HSV-1-infected mouse embryo fibroblasts

has been demonstrated to be associated with an upregulation of autophagy, as indicated by increased levels of Beclin1 and decreased levels of p62/SQSTM1, along with enhanced conversion from LC3-I to LC3-II [357]. The excessive activation of Caspases in S1-induced apoptosis, on the contrary, may impede the autophagy-inducing function of Beclin1 [358]. It has been found that Caspases can cleave Beclin1, thereby destroying its pro-autophagic activity [359]. Caspase inhibition has also been reported leading to cell death by means of autophagy involves reactive oxygen species (ROS) accumulation, membrane lipid oxidation, and loss of plasma membrane integrity [360]. The aberrant accumulation of reactive oxygen species (ROS) in autophagic phenotype is attributed to the selective autophagic degradation of catalase, which serves as the principal scavenging enzyme for ROS [360]. It seems that induction of ADCD is an important pathway to compensate while apoptosis is inhibited.

It has been proposed that ferroptosis is a type of autophagy-dependent cell death since NCOA4-facilitated ferritinophagy, RAB7A-dependent lipophagy, BECN1-mediated system x_c^-inhibition, STAT3-induced lysosomal membrane permeabilization, and HSP90-associated chaperone-mediated autophagy can promote ferroptosis [361].

Interestingly, autophagy can induce apoptosis in a unique way. For example, HIV-infected cells can induce autophagy in CD4 + T lymphocytes through the contact between Env and CXCR4, which eventually leads to apoptosis and causes immune deficiency [362].

Common upstream triggers

It has been suggested that endoplasmic ER stress serves as a common upstream pathway, triggering both autophagy and apoptosis. Furthermore, other molecules such as the sphingolipid ceramide and free Ca 2 + ion exhibit activating effects on both apoptosis and autophagy [363]. In particular, BCL-2 families play a role in regulation of autophagy. It was found that the anti-apoptotic protein BCL-2 prevents autophagy by binding with autophagy regulatory protein Beclin1 [364]. However, DAPK (death associated protein kinase) and JNK (JUN N-terminal kinase) can stimulate autophagy by phosphorylating Beclin1, which enables its dissociation from BCL-2 and its association with VPS34,thus promoting autophagy [365]. Moreover, BIM (BH3-only protein) directly interacts with Beclin1 and transports it to dynein light chain 1 (DYNLL1), thereby inhibiting Beclin1 and autophagy activation [366]. In contrast, other BH3-only proteins such as BAD, competitively disrupt the interaction between beclin-1 and BCL-2 or BCL-X, thus liberating Beclin-1 from an inhibitory complex and allowing it to allosterically activate Vps34 [367] (Fig. 6).

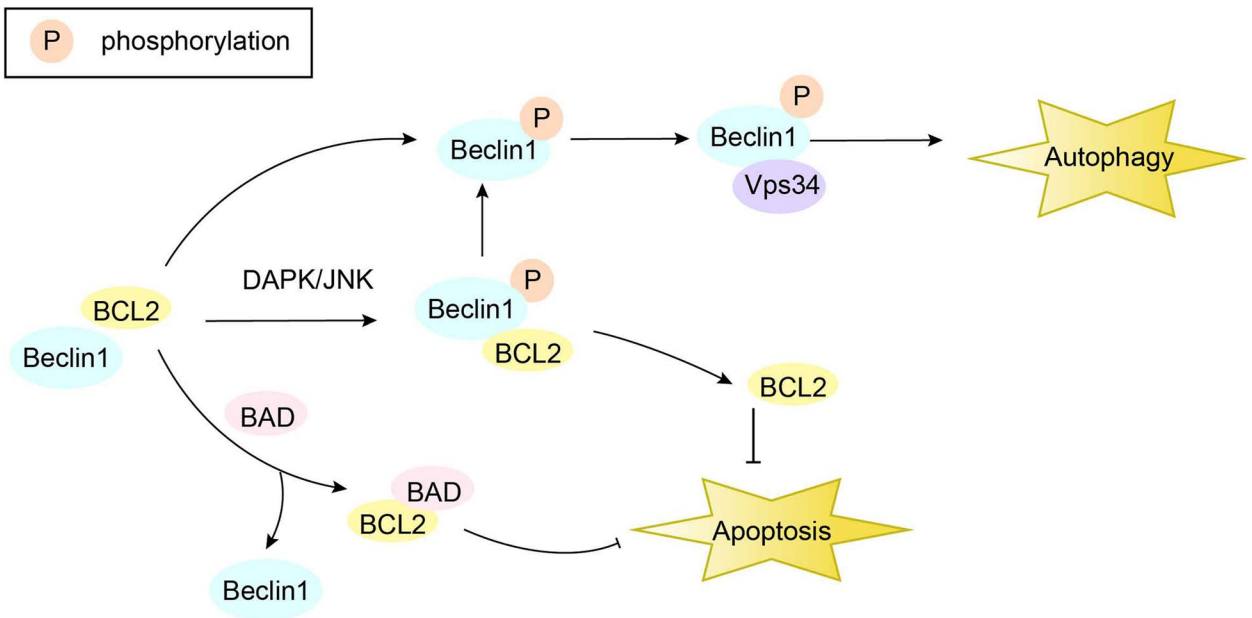

Fig. 6 Common upstream triggers of apoptosis and autophagy. BCL-2 prevents autophagy by binding with autophagy regulatory protein Beclin1. However, DAPK and JNK can stimulate autophagy by phosphorylating Beclin1, which enables its dissociation from BCL-2 and its association with VPS34, thus promoting autophagy. Other BH3-only proteins such as BAD, competitively disrupt the interaction between beclin-1 and BCL2 or BCL-X, thus liberating Beclin-1 from an inhibitory complex and allowing it to allosterically activate Vps34

Cross-talk between apoptosis, necroptosis and pyroptosis

In traditional concepts, apoptosis is commonly regarded as a "silent" form of cell death, while necroptosis and pyroptosis are considered to be more "audible" modes of demise. The process of apoptosis is characterized by self-degradation, devoid of triggering an inflammatory response or releasing inflammasomes, whereas both necroptosis and pyroptosis are associated with the induction of inflammation and contribute to the pathological conditions of tissues and organs. However, subsequent studies have revealed that apoptosis does not occur in isolation but rather interacts extensively with necroptosis and pyroptosis, thereby collectively referred to as panoptosis. We will elucidate the mechanisms underlying the interplay between these death pathways via the molecules at pivotal forks that dictate cellular fate.

TNF

The cytokine TNF, known for its role in initiating panoptosis, is tightly regulated by numerous signaling pathways that function akin to computer commands. On one hand, the activation of TNFR1 by TNF leads to the formation of the TNFR1 signaling complex (TNFR1-SC), also known as complex I, which initiates NF-κB signaling and gene transcription to facilitate cell survival [368]. On the other hand, TNFR1 signaling pathway can induce cell death through the recruitment of Fas-associated protein with a death domain (FADD) and Caspase-8 to RIPK1, forming a complex known as complex II [42]. The RIPK1 and TRADD proteins serve as the primary mediators linking TNF signaling to cellular survival or death, while other proteins can modulate these key mediators or exert independent effects to determine the ultimate fate of cells [369].

TRADD

TRADD is a 34-kDa adaptor protein with an N-terminal TRAF2-binding domain and a C-terminal death domain and is the first protein to be recruited to complex I. The TRADD-N protein in complex I interacts with TRAF2 and cIAP1/2 to facilitate the K63-linked ubiquitination of RIPK1 [370]. However, cIAP1/2-mediated ubiquitination is involved in the suppression of RIPK1 activation by ICCB-19 or Apt-1 [370]. Otherwise, loss of cIAPs and XIAP in the myeloid lineage caused overproduction of many proinflammatory cytokines, resulting in granulocytosis and severe sterile inflammation [371]. Activities of cIAP are important for recruitment of LUBAC [372, 373]. The linear ubiquitin chain assembly complex (LUBAC), composed of HOIP, HOIL-1 and SHARPIN, is required for TNF-induced activation of NF-κB and prevention of cell death achieved by stabilizing the interaction between TNFR1-SC and NEMO which enables recruitment of IKKα/β and NF-κB activation [45]. LUBAC activity also enables TBK1 and IKKε recruitment to and activation at the TNFR1-signalling complex (TNFR1-SC) [374]. Moreover, LUBAC inhibits the formation of complex II to inhibit cell death. Deletion of HOIP, HOIL-1 or SHARPIN results in severe inflammation causing postnatal lethality by TNFR1-induced, Caspase8-mediated apoptosis [375–377]. Interestingly, Co-deletion of Caspase-8 with RIPK3 or MLKL prevents cell death in Hoil-$1^{-/-}$ embryos, which may relate to inhibited execution of apoptosis or necroptosis, respectively [376]. Additionally, removal of linear polyubiquitin from proteins that have been modified by LUBAC by OTU deubiquitinase with linear linkage specificity (OTULIN) prevents the autoubiquitination activity of LUBAC and causes embryonic lethality [378]. Unexpectedly, LUBAC and OTULIN regulate autophagy initiation and maturation by mediating the linear ubiquitination and the stabilization of ATG13 [379]. Another important intermediate TAK1-TABs complex phosphorylates IKKβ at Ser177 and Ser181, which is required for the activation of NF-κB signaling [380]. TAK1-TABs complex is supposed to suppress RIPK1-driven apoptosis while pathogen blockade of TAK1 triggers Caspase-8-dependent cleavage of gasdermin D and pyroptosis [47, 381].

Persistent pathway activation and deubiquitination of RIPK1 can induce complex II formation. CYLD, A20 and OTULIN are deubiquitinases which induce deubiquitination of RIPK1 and inhibition of NF-κB signals by removing K63 and M1 polyubiquitin chains [382, 383]. Absence of the K376 ubiquitination site diminishes linear ubiquitination of RIPK1, and promotes complex II formation [384]. Also, when core components of TNF complex I, such as TAK1or cIAP1/2, are inhibited or depleted, TNFR1 in turn promotes the binding of FADD, RIPK1 and Caspase-8 to assemble into complex II and initiate apoptosis [385, 386].

Caspase8

Caspase8 is a molecular switch of apoptosis, necrosis and pyroptosis in complex II. In brief, Caspase8 is cleaved and induces apoptosis in the platform of complex II while RIPK1 recruits RIPK3 which activates mixed lineage kinase domain-like protein (MLKL) and necroptosis when Caspase8 is inhibited. For one thing, Caspase8 has long been shown to be an effector protein of apoptosis [387]. It has been previously described that upon binding of FAS/TNFR1 to the death receptor, FADD is recruited and initiates apoptotic signaling by interacting with Caspase8 DED (death effector domain) to form DISC (death receptor complex). For another thing, Caspase8 prevents

RIPK1 and MLKL-mediated necroptosis [388, 389]. The inhibition of Caspase8 instead causes the initiation of necroptosis. Caspase8 deficiency has been found to cause embryonic death in mice and link with inflammatory bowel disease in humans [390]. When Caspase8 and MLKL are both absent, it leads to inflammasome activation and tissue pathology [391]. Interestingly, Caspase8 also plays a direct role in controlling pyroptosis. Inhibition of TNF complex II and ripoptosome with AZD 5582 triggers Caspase-8-dependent GSDMD cleavage and pyroptosis [392]. Expression of CASP8(C362S) triggered the formation of ASC specks, activation of Caspase-1 and secretion of IL-1β, which are the precursors of pyroptosis [391]. In addition, LPS triggers RIPK3 to activate Caspase-8, promoting apoptosis and NLRP3-Caspase-1 activation, independent of RIPK3 kinase activity and MLKL [386]. Both embryonic lethality and premature death can be completely rescued in mice with neither MLKL expression nor ASC or Caspase1 expression, indicating that the activation of the inflammasome promotes Caspase8-mediated tissue pathology when necroptosis is blocked [391]. ZBP1 is characterized as a critical immune sensor which can stimulate pyroptosis, apoptosis, and necroptosis [393]. ZBP1 interacts with RIPK3 or triggers the NLRP3 inflammasome to mediate virus-induced programmed necroptosis by binding to viral genomic DNA or RNA [394, 395]. Nevertheless, Caspase-8 and FADD prevent spontaneous ZBP1 expression and necroptosis [396].

The pyroptosis or apoptosis pathway induced by Caspase8 has important biological significance, which can help cells resist pathogen infection. When infected by Yersinia bacteria, Caspase8 activation induces GSDMD /E cleavage and eventually leads to pyroptosis, while the loss of GSDMD leads to the apoptosis pathway [397]. Of greater significance, α-ketoglutarate (α-KG) induces pyroptosis through Caspase-8-mediated cleavage of pyroptosis effector protein GSDMC, and GSDMC is highly expressed in tumor cells, which provides a good solution to the problem of drug resistance in tumor chemotherapy [207]. In conclusion, which pathway the cell finally chooses is closely related to the stimulation of external environment and fluctuations of cell contents such as invasion of pathogens, ROS accumulation (Fig. 7).

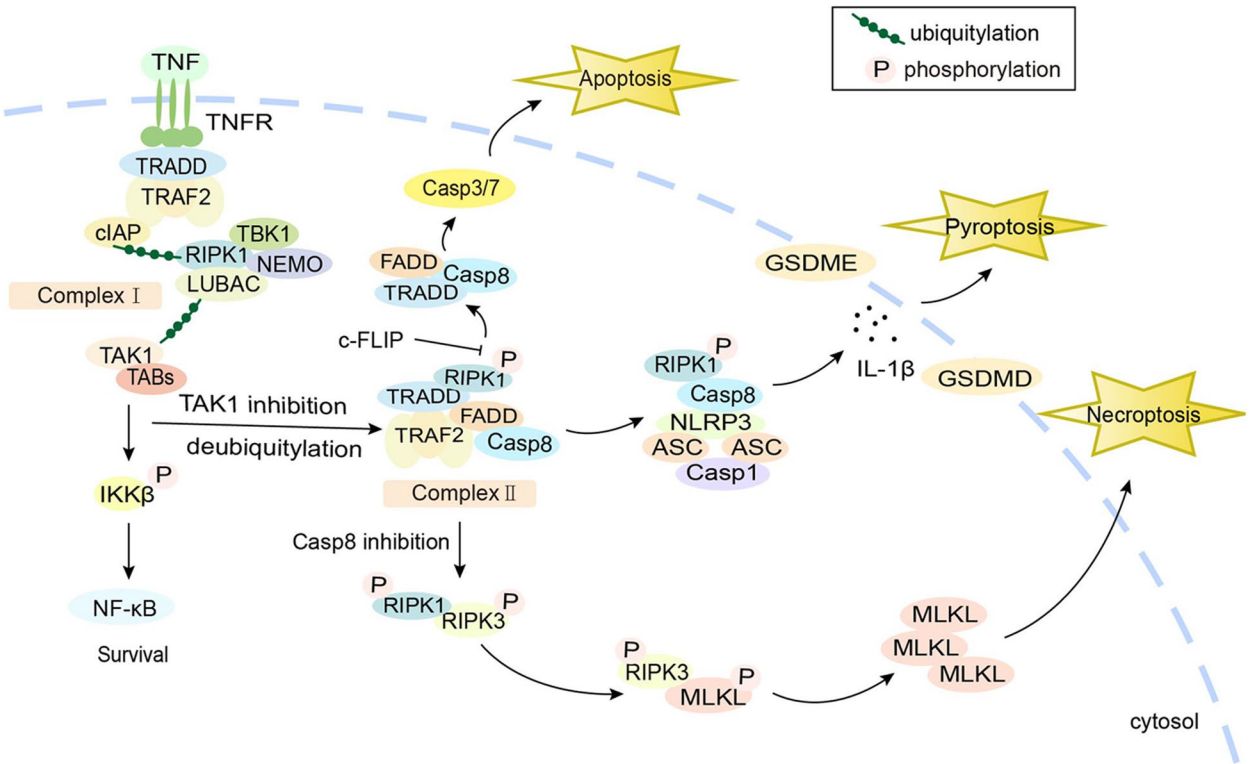

Fig. 7 Interactions between PANoptosis. TNFR which is activated by TNF can recruit TRAF2 and TRADD to form complex I and transmit extracellular signals. The TRADD protein has the ability to recruit a diverse array of downstream proteins and initiate distinct signaling pathways, leading to various functional outcomes including cell survival, apoptosis, and inflammatory signaling. LUBAC recruited by cIAP enables recruitment of IKKα/β and NF-κB activation. However, deubiquitination of RIPK1 by OTULIN can inhibit NF-κB pathway and induce complex II formation. Notably, ZBP1 is a critical immune sensor which can stimulate pyroptosis, apoptosis, and necroptosis

Cross-talk between autophagy and necroptosis

The decision of cells to undergo apoptosis, autophagy, or necrosis is regulated by a variety of factors, including energy levels, the extent of injury or stress, and deficiency of specific pathways. When autophagy fails to rescue cells, mild injury and low levels of death signals usually induce apoptosis, while severe injury and high levels of death signals often initiate necroptosis [398].

Autophagy and necroptosis are mutually exclusive. On one hand, autophagy serves as a remedial approach for preventing necroptosis. For example, mTOR inhibits RIPK3 expression in the intestinal epithelium through autophagy to prevent intestinal inflammation and tumor development [399]. On the other hand, TNF-mediated necroptosis inhibits autophagy by regulating the fusion protein SNARE to block the binding of late autophagosomes to lysosomes [400]. It was also confirmed that RIPK3 regulates the formation of P62-LC3 complex by binding to P62, thus acting as a selective negative regulator of autophagy [401].

Interestingly, RIPK3 was also found to be an AMPK kinase that promotes the early initiation of autophagy [400].For this seemingly contradictory phenomenon, we can suggest that the induction of RIPK3-dependent early autophagy signaling events may enlightens cell's self-protective function and slow down the execution of necroptosis. It is also possible that complexes formed in autophagy act as stepping stones to necroptosis. RIPK1-mediated recruitment of P62 is involved in the assembly of necrosome, and necrosome have also been found on mature autophagosomes [402].

Cross-talk between autophagy and pyroptosis

The NLRP3 inflammasome is cytosolic multi-protein complex that induces inflammation and pyroptosis in response to both pathogen (PAMPs) and endogenous activators (DAMPs). Inflammasome signals can regulate autophagic process to achieve balance between necessary inflammatory response and detrimental inflammation. Firstly, the autophagy can restrict diseases with hyper-inflammation and excessive activation of NLRP3 inflammasome. For instance, autophagy activation can reduce the accumulation of reactive oxygen species (ROS) in the cell by clearing NLRP3 and inhibiting pyroptosis [403]. Wherein, USP19 acts as an anti-inflammatory switch and promotes M2-like macrophage polarization by manipulating NLRP3 function via increasing autophagy flux [404]. Deficient autophagy promotes inflammation and atherosclerosis by hindering degradation of the NLRP3 protein [405].

It is worth noting that the suppression or enhancement of this inflammation is related to intracellular stress. Hypoxia is supposed to counteract inflammation through the downregulation of the binding of mTOR and NLRP3 and activation of autophagy, which are protective in mouse models of colitis [406]. In addition, it was found that FLT4-AMPK module inhibited Caspase1-dependent inflammasome activation and pyroptosis but enhanced LC3 activation for elimination of the bacteria [407]. Many drugs also function through activating autophagy and inhibiting NLRP3 to treat a variety of inflammatory diseases [408, 409]. Therefore, the quality control of multiple organelles through organelle-specific autophagy is of great importance in maintaining the survival and function of cells and could be a potential therapeutic target for human diseases.

Cross-talk between ferroptosis and autophagy

Ferroptosis is a mechanism of cell death caused by the Fenton reaction of iron ions, ultimately leading to lipid peroxidation. This process involves the uptake and release of iron ions and lipids by multiple cellular organelles, so the pathway of ferroptosis have extensive crosstalk with autophagy. In particular, the overactivation of selective autophagy, including ferritinophagy, lipophagy, clockophagy and chaperone-mediated autophagy, promotes ferroptosis by degrading ferritin, lipid droplets, circadian proteins, and GPX4, respectively. Ferritinophagy, a process involving selective autophagy of ferritin facilitated by nuclear receptor coactivator 4 (NCOA4), entails the recognition of ferritin by NCOA4 and subsequent delivery to the autophagosome [410]. Within the autophagosome, ferritin undergoes degradation, leading to the release of iron in the lysosome. Ferritinophagy promotes ferroptosis through releasing free iron from ferritin to cytoplasm, where cytoplasmic Fe^{2+} is transported into mitochondria, giving rise to the production of mitochondrial ROS and ferroptosis [411]. Thus, the depletion or inhibition of NCOA4 or ATG protein inhibits ferritin degradation and therefore reduce free iron levels and thus limit subsequent oxidative injury during ferroptosis [412, 413]. It has also been reported that NCOA4 is suppressed under hypoxia, so ferritin escapes being degraded and stores iron ions to prevent ferroptosis [414]. Another form of autophagy takes places in ferroptosis is lipophagy, which is defined as the autophagic degradation of intracellular lipid droplets. Lipophagy regulated by RAB7 mediates the digestion of lipid droplets and releases free fatty acids served as a fuel for mitochondrial oxidation and ferroptosis [415]. Clockophagy, namely the selective autophagic degradation of the circadian clock regulator ARNTL/BMAL1, promotes lipid peroxidation and subsequent ferroptosis through blocking HIF1A-dependent fatty

acid uptake and lipid storage [416]. Ferroptosis can also be promoted by facilitating chaperone-mediated autophagy (CMA), which is a cellular lysosome-mediated degradative mechanism. CMA regulated by HSP90 mediates the degradation of GPX4 and executes ferroptosis [417]. Interestingly, autophagy can be induced when ferroptosis has been triggered, which in return enhance the ferroptotic effects. This may be related to the initiation of autophagy caused by lipid peroxidation products and ROS [418, 419].

Cross-talk between ferroptosis and apoptosis

Studies have shown that lipid peroxidation can also trigger apoptosis. Lipid peroxidation products interact with membrane receptors and transcription factors to induce apoptotic signaling and stimulate the activation of intracellular and exogenous apoptotic signaling pathways [391]. Lipid peroxides can regulate apoptotic signaling through NF-κB pathway and anti-apoptotic protein BCL-2 [420–422]. In addition, lipid peroxidation products form complexes with ERK, JNK and P38, activate MAPKs (mitogen-activated protein kinases) and Caspase signals to initiate apoptosis [423].

Epigenetic regulations in cell death

The phenomenon of cells within individuals sharing the same genome adopting phenotypic states of increasing specificity is widely acknowledged. This trait of cells can be attributed to cell differentiation, the process of stable changes in morphology, structure and physiological function of the offspring cells. How can differentiated cells maintain their selective expression patterns for a long time without changing into other kinds of cells? Though normal differentiation outcomes are genetically encoded, cells are programmed to incorporate different epigenetic modifications that turn different gene groups on or off during development and these epigenetic modifications can be passed from parent cells to offspring. This is the molecular mechanism of gene selective expression and the substantive cause of cell differentiation. The remarkable aspect of epigenetics lies in its inheritability and quantifiability. In essence, cells exert control over gene switches by regulating higher-order chromosome structures, and epigenetic regulation involves the interpretation of genetic information at the chromatin level.

The term "epigenetics" was originally advanced by Conrad Waddington to describe mitotically and meiotically descendible changes in a cellular phenotype that were independent of alterations in the DNA sequence [424]. Epigenetic regulations make it possible for researchers to rebuilt specific differentiation events and constrain distinct phenotypic and gene expression states.

DNA modifications

The process of DNA methylation involves the enzymatic catalysis of cytosine within CpG dinucleotides by DNA methyltransferases (DNMTs), utilizing S-adenosylmethionine (SAM) as a methyl donor to establish covalent bonds and acquire a methyl group. DNA methylation is the earliest and most common epigenetic phenomenon, which plays an important role in maintaining genome stability and regulating important physiological functions such as cell cycle, apoptosis and embryonic development in eukaryotes [425]. Altered DNA methylation patterns can contribute to the molecular pathology of all kinds of disease. Low level of DNA methylation can not only lead to the decrease of genomic stability and the increase of mutation rate, but also lead to the occurrence of malignant tumors by abnormally activating the expression of various proto-oncogenes [426]. High levels of DNA methylation can indirectly induce the occurrence of malignant tumors by reducing the transcriptional activity of tumor suppressor genes and then affecting their expression, such as reduced expression and silencing of expression. Some features of DNA methylation such as early and frequent occurrence of changes in cancer and cell-type specificity make them promising biomarkers [427].

Regulation of DNA methylation

DNA methylation is an epigenetic mechanism involving the addition of a methyl group of the cytosine on the C5 position to form 5-methylcytosine. Multiple forms of DNA methylation have been identified in mammals, including 5-methylcytosine(5mC), 5-hydroxymethylcytosine (5hmC) and 5-formylcytosine (5fC) [424]. The major epigenetic modification 5mC and its hydroxylated derivative 5hmC are widespread in vertebrate genomes and they are predominantly found within CpG dinucleotides [424, 428]. Methylation can be inherited through somatic cell divisions by a mechanism involving an enzyme that recognizes hemimethylated CpG palindromes [429]. Some mediators are pivotal for DNA methylation and demethylation, including DNA methyltransferases (DNMTs), methyl-CpG binding proteins (MeCPs), ten-eleven translocation cytosine dioxygenases (TETs) and base excision repair (BER) DNA glycosylases.

The canonical DNMTs including DNMT1, DNMT3A and DNMT3B have an impact on establishing and maintaining DNA methylation patterns thus keeping the differentiated states as cells divide [430]. In mammals, male and female gametes originate from embryonic cells marked with their own landscape of DNA methylation.

However, zygote which is producted by fusion of male and female gametes is the only totipotent cell of the organism. It means that epigenetic marks of zygote must be updated to guarantee its totipotency and this process is termed as epigenetic reprogramming [431]. Of which, DNA methylation is established de novo by DNMT3A and DNMT3B [432]. DNMT3L also facilitates DNA methylation by serving as a cofactor of DNMT3A/3B to enhance their methyltransferase activities [433]. Beyond that, the E3 ubiquitin ligase UHRF1 (also known as NP95) with higher affinity for hemi-methylated DNA assists DNMT1 finding the cytosine to be methylated to maintain DNA methylation in dividing cells [434]. In addition, LSH facilitate in DNA methylation by DNMT1 through enhancing UHRF1 chromatin association [435]. However, CpG islands (CGIs), some regions rich in CpG dinucleotides, remaining refractory to DNA methylation mostly at the sites of promoter have a great role in gene transcription [436]. In contrast to the CGIs at promoters, orphan CGIs located at intragenic regions are more frequently methylated and this is likely a consequence of DNMT3B-mediated genic DNA methylation [437]. Research has demonstrated that CpG methylation near a gene's promoter is often incompatible with efficient transcription. This effect is mediated by MeCPs, which recognize and bind to methylated genes, thereby interfering with transcription [438, 439]. Though the maintenance mechanism of DNA methylation is stable, this process can still be reversed. DNA demethylation can be mediated by TET and TDG through iterative oxidation of 5mC to 5-hydroxymethylcytosine(5hmC), 5-formylcytosine (5fC) and 5-carboxylcytosine (5caC) or base excision repair(BER) of 5fC and 5caC, respectively [440]. What's more, many non-enzymatic proteins, such as TFs, could regulate the establishment and maintenance of the local DNA methylation levels in a sequence-specific fashion [441]. During development, the pattern of DNA methylation in the genome changes as a result of a dynamic process involving both de novo DNA methylation and demethylation. As a consequence, differentiated cells develop a stable and unique DNA methylation pattern that regulates tissue-specific gene transcription.

DNA methylation and gene transcription

DNA methylation patterns vary between cell types and this lead to direct differential expression of genes [442]. In prime conceptions, DNA methylation directly silences genes. However, the relationship between DNA methylation and gene silencing is still skeptical. Indeed, the location of a modification is tightly regulated and is crucial for its effect on transcription. Large-scale analyses of gene expression profiles and DNA methylomes have revealed that a substantial proportion of DNA methylation sites are positively correlated with gene expression [443]. CpG island shore, sequences up to 2 kb distant, was strongly related to tissue-specific differential methylation and gene expression [443]. It has been shown that DNA methylation of downstream of the transcription start site was correlated with increased transcription of a target gene. What's more, DNA methylation of a promoter or an enhancer can inhibit the transcription of target gene [444, 445]. For example, Set2-mediated methylation of histone H3K36 normally occurs within the ORF of actively transcribed genes. However, if Set2 is mistargeted to the promoter region through artificial recruitment, it represses transcription [446]. In general, gene bodies of highly expressed genes are heavily methylated [447, 448], whereas active gene regulatory elements have a low degree of methylation [449]. In cancer, a limited number of genomic loci gain DNA methylation, particularly at CpG islands in promoters of tumor suppressor genes (TSGs), leading to gene silencing [450]. Hypomethylation of repetitive elements is also observed in cancer cells [451].

It is also surprising that transcription factors (TFs) can act as DNA methylation readers to influence gene transcription and the interaction between TFs and DNA methylation is reciprocal [441]. On one hand, DNA methylation can impact gene transcription by affecting the binding of TFs which is particularly important for reprogramming of cells [452, 453]. On the other hand, TFs can directly shape the local DNA methylation patterns [454, 455]. Expression of cell-type-specific transcription factors causes reduced methylation of their binding sites during development [456]. It is interesting that a methylation-insensitive transcription factor functions as a pioneer factor and creates a site of reduced methylation that allows a methylation-sensitive factor to bind.

DNA methylation and cell death

DNA methylation regulators have become the mainstay for treatment of certain malignancies due to their abilities to reactivate genes, including tumor suppressors. DNA methylation inhibitors 5-azacytidine and 5-aza-2'-deoxycytidine (Decitabine) can be used as a therapeutic agent for cancers in which epigenetic silencing of critical regulatory genes has occurred [457]. Certainly, DNA methylation plays a crucial role in upstream regulation of the cellular death mechanism. Aberrant DNA methylation activity is observed in tumor cells, leading to dysregulation of cell death control and key protein inactivation. Exploiting DNA methylation sites as targets for tumor therapy holds great potential.

DNA methylation and apoptosis

The methylation status of specific genes has been identified as a regulatory mechanism for apoptosis. For example, the continuous exposure of mice to gibberellin A3 from weaning to sexual maturity resulted in the induction of apoptosis in ovarian granulosa cells, which was achieved through hypomethylation of the Caspase-3 gene promoter [458]. The heterochromatin protein 1 (HP1) family specifically recognizes and binds the tail of histone H3 tagged with H3K9me3 and plays a central role in the establishment of structural heterochromatin [459, 460]. The upregulation of HP1α protein and H3K9me3 has been observed in GOS3 and 1321N1 glioma cell lines, specifically at the FAS and PUMA promoter sites, the proteins involved in the facilitation of apoptosis. This suggests that the increased levels of Hp1α and H3K9me3 inhibit apoptotic activators, thereby preventing apoptosis [459, 460]. The immuno-modulatory properties of periodontal membrane stem cells (PDLSC) can be regulated by the Ten11 translocation (Tet) family, a group of DNA demethylases. It has been found that downregulation of TET1/2 would lead to hypermethylation of the DKK-1 promoter, activating the WNT signaling pathway, which in turn promotes expression of FasL [461]. Therefore, the utilization of PDLSC enhances the efficiency of T cell apoptosis induction and ameliorates the disease phenotype in mice with colitis [461]. Additionally, the upregulation of DNA methyltransferase leads to an increase in DNA methylation, which exerts a potent pro-apoptotic effect on motor neurons in postnatal and adult mice as well as photoreceptors in a mouse model of retinitis pigmentosa [462]. In other studies, modulation of the degree of DNA methylation inhibited apoptosis. Epidermal growth factor (EGF) protects against high-glucose (HG)-induced podocyte injury by promoting cell proliferation and inhibiting apoptosis. This role may be related to the regulation of autophagy and PI3K/AKT/mTOR signaling pathway through DNA methylation [463]. In addition, DNA methylation-mediated Caspase-8 downregulation is associated with anti-apoptotic activity and human malignant glioma grading [464]. Thus, combination therapy with demethylating agents may overcome treatment resistance in the same malignancy. Downregulation of lncRNA H19 reduces methylation and enhances expression of insulin-like growth factor 2 (IGF2), thereby inhibiting apoptosis and oxidative stress (OS) in hippocampal neurons of streptozotocin (STZ)-induced diabetic (DM) mice [465]. Based on the evidence from this study, downregulation of lncRNAH19 is a potential target for the treatment of apoptosis in diabetic hippocampal neurons.

Similarly, certain compounds are able to induce apoptosis through DNA methylation, thus conferring their anticancer value. Clofarabine (CIF) has a range of anticancer activities, including the ability to modulate DNA methylation marks. CIF, in combination with the phytochemicals RSV or ATRA, effectively inhibits tumor cell growth and induces Caspase-3-dependent apoptosis by up-regulating key modifiers of DNA methylation machinery, including DNA Methyltransferase 1 (DNMT1) and Cyclin dependent kinase inhibitor 1A (CDKN1A), in CML cells [466]. This observation predicts the potential of CIF in epigenetic treatment of anti-leukemia. DNA hypomethylating drugs 5-aza-DC or SGI-110 cooperating with IR improves the anticancer effect by inhibiting cell proliferation and promoting apoptosis or autophagy [467]. In addition, DNA demethylation-induced high expression of RASSF4 plays an important role in T-2 toxin-induced apoptosis in BRL cells by activating PI3K-Akt/Caspase/NF-κB signaling pathway [468]. It is also proposed that moderate DNA hypomethylation is sufficient to suppress intestinal tumorigenesis by promoting Caspase-3 expression and apoptosis [469]. Therefore, regulating DNA methylation may provide new avenues for the diagnosis and treatment of certain diseases.

DNA methylation and necroptosis

The low expression of RIPK3, the pivotal executive protein in necroptosis, has been unveiled to confer a survival advantage upon cancer cells and contribute to chemoresistance as well as poor prognosis in malignant tumors. The silencing of the RIPK3 gene in cancer cells may be attributed to epigenetic modifications resulting from DNA methylation [171, 470]. The precise molecular mechanism underlying DNA methylation-mediated downregulation of RIPK3 expression is currently under investigation. The study found that the mutated IDH1-produced 2-HG binds to DNMT1, leading to hypermethylation of the RIPK3 promoter and consequently enhancing tumor cell resistance against necroptosis [471]. Conversely, the up-regulation of lncRNA PVT1 was found to be associated with increased expression of necroptosis-related proteins,including ZBP1, RIPK3, and MLKL [472]. The lncRNA PVT1 can interact with DNMT1 through EZH2, a methyltransferase responsible for dimethylation and trimethylation, thereby enhancing the methylation of the ZBP1 promoter and subsequently promoting necroptosis [472]. Apart from that, demethylation of highly expressed TET1 gene promotes the upregulation of ZBP1 and induces necroptosis.

There are still some potential mechanisms of DNA methylation inducing or inhibiting cell necroptosis to be explored. Epstein-Barr virus (EBV) infection is a recognized epigenetic driver of carcinogenesis. The metabolites associated with EBV can be modified through DNA methylation to inhibit the necroptosis signaling pathway,

suggesting a potential link between carcinogenesis and the suppression of necroptosis, thereby elucidating the mechanism underlying EBV-related carcinogenesis [473]. Accumulation of myeloid-derived suppressor cells (MDSCs) is a hallmark of cancer in tumor environment. However, TNFα-RIPK1-mediated necroptosis regulates accumulation of MDSCs [474]. To be specific, DNA methyltransferase inhibitor decitabine (DAC) decreases MDSC accumulation and promotes necroptosis by disrupting DNA methylation of TNFα. Otherwise, IL6 treatment of MDSC-like cells activated STAT3, increased expression of DNMT1 and DNMT3b, and enhanced survival [474]. These findings demonstrated that modulating DNA methylase activity to induce cell death could be a potentially effective strategy for inhibiting the survival and aggregation of MDSCs in the tumor microenvironment.

DNA methylation and pyroptosis

Differential expression of pyroptosis related genes was evident in various cancers and associated with prognosis which was driven by genomic variations and epigenetic abnormalities, such as single nucleotide variations (SNVs), copy number variation (CNV) and DNA methylation level [475]. Zinc Finger DHHC-Type Containing 1 (ZDHHC1, also known as ZNF377), frequently silenced due to epigenetic modification among various cancers, which exerts significant anti-tumor effects through metabolic regulation [476]. Restoration of ZDHHC1 expression can curb cancer cell progression via stimulating pyroptosis through increment of oxidative stress and endoplasmic reticulum (ER) stress [476]. The epigenetic mechanism underlying tumor suppression through pyroptosis is also evident in the executing proteins of pyroptosis. The silencing of GSDME expression caused by hypermethylation of GSDME promoter is associated with gastric cancer. DNA methyltransferase inhibitor 5-Aza-2'-deoxycytidine (5-Aza-CdR) upregulates GSDME expression effectively and exerts tumor inhibition effects [477]. Likewise, GSDMD, a key protein in the pyroptosis process, is low expressed in the majority of tumor cells. DNA methyltransferase inhibitor decitabine (DAC) up-regulates the expression of GSDMD and achieves effective cancer cell pyroptosis, thus inducing a significant systemic antitumor immunity for impressive tumor suppression [478]. What's more, biomimetic nanoparticle (BNP) loaded with indocyanine green and DAC were designed for photo-activated cancer cell pyroptosis and solid tumor immunotherapy [479].

DNA methylation and ferroptosis

DNA methylation can directly regulate key proteins of ferroptosis. It was found that TET2 regulate lipid peroxidation through GPX4, thus alleviating airway epithelial cell ferroptosis in COPD [480]. Ferroptosis is associated with an epigenomic stress response, which might advance the therapeutic applicability of ferroptosis-related compounds. For example, MM1 multiple myeloma cells are sensitive to ferroptosis induction and epigenetic reprogramming by RSL3 [481]. Significant DNA methylation changes in ferroptosis myeloma cells demonstrated an enrichment of CpG probes located in genes associated with cell cycle progression and senescence [481]. Alternatively, identification and validation of ferroptosis-related DNA methylation signature can be used for predicting the prognosis and guiding the treatment in cutaneous melanoma [482].

Some genes are aberrantly expressed in tumor cells and have an epigenetic inhibitory effect on ferroptosis. Lymphoid-specific helicase (LSH), which is a DNA methylation modifier, interacts with WDR76 to inhibit ferroptosis by activating lipid metabolism-associated genes involved in the Warburg effect [483]. Runt-related transcription factor 3 (RUNX3), a member of the runt-domain family, induces ferroptosis by activating ING1 transcription, thereby repressing SLC7A11 in a *p53*-dependent manner [484]. Downregulation of RUNX3 caused by DNMT1-mediated methylation in GBC cells is associated with poor prognosis of GBC patients [484].

Histone modifications

The DNA inside a human cell containing the genetic information is two meters long while the nucleus is only seven microns in diameter. Thus, a highly compressed structure known as chromatin is required to pack such a huge amount of genetic information into the nucleus. DNA is wrapped around histone proteins forming a "nucleosome core particle" which contains 147 base pairs of DNA and a histone octamer that consists of two copies each of histones H2A, H2B, H3 and H4 [485]. The residues of histone proteins can be post-transcriptionally modified and influence chromatin compaction as well as DNA-based processes, such as transcription, DNA repair and replication [486]. There are different modification sites on the histones including tail regions and globular domains which may contribute to diverse consequence for gene transcription. The histone code hypothesis assumes that histone modifications act as local information carriers, which are interpreted by chromatin-binding proteins termed 'readers' capable of recognizing varied modified nucleosomes. The main types of histones modification include acetylation, methylation, phosphorylation, ubiquitination, SUMO and ADP-ribosylation. The most common modification forms are histone methylation and acetylation, which can affect human diseases

especially cancer and immune disease. The mechanisms of histone modifications are operated by chromatin-modifying enzymes in a highly regulated manner [485].

Regulation of histone modifications (writers and erasers)

Histone methylation

Methyl modifications of histone are tightly regulated by the lysine methyltransferases (KMTs) and lysine demethylases (KDMs). KMTs catalyze the various lysine methylation events decorating the core histone proteins. In the human proteome, there are two domains with lysine methyltransferase activity: the SET domain and the seven-beta-strand (7βS) domain. Chemically, lysine methylation entails the addition of one, two or three methyl groups to the ε-nitrogen of a lysine side chain, forming mono-, di- and trimethylated derivatives, which greatly increases the information encoded within the molecule [487]. In humans, the canonical lysine methylation sites are found on histone H3 at lysine 4 (H3K4), lysine 9 (H3K9), lysine 27 (H3K27), lysine 36 (H3K36) and lysine 79 (H3K79), and on histone H4 at lysine 20 (H4K20). Also, KMTs have a high degree of specificity for particular lysine residues and the degree of methylation. For example, the enzymes that methylate H3K36 do not methylate a different lysine if K36 is mutated. What's more, SETD2 prefers unmethylated H3K36 as the initial recognized substrate of the nucleosome to H3K36me2. These multiple methylation events mediated by different enzymes causes the enzymatic redundancy which can be used for targeting specific activities at differential genomic localization to selectively generate different methylation states.

There are eight KDM subfamilies (KDM1-8), which vary in terms of their structure and lysine targets. KDM1 contains a flavin adenine dinucleotide-dependent amine oxidase domain, which erases mono- and dimethylation marks [488]. KDM2-8 subfamilies contain a catalytic Jumonji C (JmjC) domain and remove mono-, di- and trimethylation marks on lysines [489]. Activity of transmethylases can also be regulated by RNA methylation. For example, m^6A reader YTHDC1 physically interacts with and recruits H3K9me2 demethylase KDM3B to m^6A-associated chromatin regions, promoting H3K9me2 demethylation and gene expression [490].

The disfunction of KMTs and KDMs is related with tumorigenesis. Studies have identified recurrent SETD2 mutations across a broad spectrum of human malignancies and biallelic loss of SETD2 in patients is unfortunately associated with significantly lower survival rates [487]. Thus, SETD2 has been identified as a top candidate in multiple cancer models in vivo screens [487].

Histone acetylation

Histone lysine acetylation is highly reversible. Histone acetylation level is controlled by two classes of enzyme: the lysine acetyltransferases (KATs), which catalyze the transfer of an acetyl moiety to a Lys residue; and histone deacetylases (HDACs), which catalyze acetyl group removal [491]. Acetylation of the ε-amino group leads to neutralization of the inherent positive charge of the Lys residue, which can affect protein functions through multiple mechanisms including regulation of protein stability, enzymatic activity, subcellular localization, crosstalk with other post-translational modifications as well as regulation of protein–protein and protein-DNA interactions, thus influencing transcription by altering chromatin structure [492]. For example, H4K16 acetylation disrupts inter-nucleosome interactions and abolishes the folding of nucleosomes into higher-order arrays [492].

Currently, most KATs belong to one of three families based on amino acid sequence homology: the MYST family, the p300/CBP family and the Gcn5-related acetyltransferase family (GCN5/PCAF, also known as KAT2A /KAT2B) [493]. The MYST family members share a highly conserved MYST domain consisting of Acetyl-CoA-binding motif and a PHD (plant homeodomain)-type zinc finger domain which are required for histone H3 binding and the nuclear localization to chromatin [493]. KAT6A and KAT6B form stoichiometric complexes with bromodomain- and PHD finger-containing protein 1 (BRPF1) through their MYST domain for acetylation of H3K23, which are associated with transcriptionally active genes [494]. KAT6 proteins play an important role in craniofacial development, maintenance of stem cells, regulation of the hematopoietic and immune system, while mutant KAT6 is related with developmental disorders and cancers [493]. p300 and CBP are in a family of their own because of little sequence homology between them and other acetyltransferases in the human genome [495]. p300/CBP family consists of two acetyltransferase domains,including three cysteine/histidine-rich domains and a bromodomain, which roles in catalyzing the reaction of transferring the acetyl group from acetyl-CoA to a protein lysine side chain [495]. Acetylation activity of p300/CBP family can be stimulated by RNAs due to an RNA binding region in the acetyltransferase (HAT) domain of CBP [496]. p300/CBP also acts as downstream effectors of several signals including calcium signaling, stress response pathways, Notch signaling, and NF-κB signaling to regulate cellular functions [495]. It has been confirmed that the acetylation activity of p300/CBP has roles in diverse functions including cell migration and invasion, maintenance of the differentiated state, tau-mediated neurodegeneration,

and learning and memory [495]. All the known metazoan GCN5 homologues can be divided in two parts: The N-terminal half which contains the so-called PCAF homology domain, and the C-terminal half which contains two other conserved domains: the AT domain and the bromodomain [497]. GCN5 and PCAF have a preference for acetylation of H3K14, H4K8 and H4K16 [497]. It is interesting to find that GCN5/PCAF-mediated H3K9 acetylation and CBP/p300-mediated H3K18/27 acetylation correlate with nuclear receptor target gene activation [498]. The catalytic activity of KATs is affected by many factors. KAT8 switches catalytic activity and function depending on its associated proteins which means it catalyzes H4K5ac and H4K8ac as part of the NSL complex, whereas it catalyzes the bulk of H4K16ac as part of the MSL complex [499].

Histone deacetylase Enzymes are erasers of histone acetylation. In humans, there are 18 HDAC enzymes grouped into four classes: the Class I Rpd3-like proteins (HDAC1, HDAC2, HDAC3, and HDAC8); the Class II Hda1-like proteins (HDAC4, HDAC5, HDAC6, HDAC7, HDAC9, and HDAC10); the Class III Sir2-like proteins (SIRT1, SIRT2, SIRT3, SIRT4, SIRT5, SIRT6, and SIRT7); and the Class IV protein (HDAC11) [500]. HDACs can be further subdivided into two categories, zinc-dependent HDACs, also known as classical (classes I, II and IV) as well as NAD + -dependent, also known as sirtuins (class III) [501]. HDACs can not only alter transcription, but also change the dynamics of histone modification "cross talk", such as methylation, ubiquitination, and sumoylation [500].

Histone acetylation can be regulated by many signals. Recent studies have indicated that AMPK/Snf1 activation can control histone acetylation through phosphorylation of different HATs and HDACs affecting not only gene transcription but also many other epigenetic functions [502]. In addition, hypoxic stress influences the activity and gene expression of HATs, which induces gene activation under hypoxic conditions [503].

Histone modifications and gene transcription (readers)

Distinct qualities of well-regulated chromatin, such as euchromatic or heterochromatic domains, are largely dependent on the local concentration and combination of differentially modified nucleosomes [504]. This "nucleosome code" permits the assembly of different epigenetic states, which leads to distinct compiling of the genetic information, no matter gene activation or gene silence. The enzymes transducing these histone modifications are highly specific for particular amino acid positions, thereby extending the information content of the genome past the DNA code.

Histone methylation

Histone methylation functions on transcription by changing the chromatin compaction states. H4K20 can be methylated at different degree(H4K20me1/2/3) to directly facilitate chromatin openness and accessibility at different phases of cell cycle [505]. However, methylated lysines in histone proteins do not directly alter the chromatin structure. Histone methylation predominantly functions on transcription by providing dynamic binding platforms for a large number of effector proteins. Histone H3 trimethylation at lysine 36 prompts N^6-Methyladenosine (m^6A) mRNA modification which plays critical roles in various normal and pathological bioprocesses [506]. Mechanistically, H3K36me3 bind with MTC which facilitates the binding of the m^6A MTC to adjacent RNA polymerase II, thereby transcribing nascent RNAs and depositing m^6A actively [506]. Trimethylated H3K4 recruit the integrator complex subunit 11 (INTS11) which is essential for the eviction of paused RNA polymerase II and transcriptional elongation [507]. Diverse methylation content at the same methylation site impact on transcription differentially. For example, H3K36me1/2 and H3K36me3 have unique and shared functions, particularly regarding the suppression of antisense transcription [508].

The process of histone methylation is implicated in various cellular activities. Methylation of H3K79 can not only regulate elongation rates across various genes, but also determine post-transcriptional events such as alternative splicing, DNA repair and cell cycle checkpoint activation [509]. In addition, H3K9me ensures silencing in differentiated tissues by restricting the activity of a defined set of transcription factors at promoters and enhancers [510].

Histone acetylation

Histone tail acetylation is most strongly correlated with transcriptional activation. Although the correlation between histone tail acetylation and gene activation is firmly established, the mechanisms by which acetylation facilitates this fundamental biological process remain poorly understood. On one hand, histone acetylation creates a local chromatin environment permitting transcriptional activation [511]. On the other hand, the majority of histone acetylation is transcription-dependent, as promoter-bound HATs are unable to acetylate histones in the absence of active transcription [512]. The presence of RNA polymerase II (RNAPII) is crucial for facilitating the interaction between H4 histone acetyltransferases (HATs) and gene bodies [512]. In Metazoa, promoters of transcriptionally active genes are generally devoid of physically repressive nucleosomes, consistent with the

contemporaneous binding of the large RNA polymerase II transcription machinery. The removal of these nucleosomes is dependent on histone acetylation on specific sites. The histone acetyltransferase p300 is detected at active gene promoters in the range of histone hyperacetylation regions, which acetylates H3K14 to mediated dissociation of the histone octamer from the promoter DNA [513]. Interestingly, the inhibition of catalytic P300 can dynamically disrupt steady-state acetylation kinetics and suppress oncogenic gene transcription, making it a potential anti-cancer treatment regimen [514]. Also, H3K64ac regulates nucleosome stability and facilitates nucleosome eviction and hence gene expression in vivo [515]. In addition, ACSS2 (acyl-CoA synthetase short-chain family member 2) functions in recycling of nuclear acetate for histone acetylation to promote lysosomal and autophagy-related gene expression and counteract nutritional stress [516].

The process of histone acetylation is also involved in various other cellular processes. Histone acetylation controls the early differentiation of embryonic stem cells [517]. What's more, histone acetylation engages in the lymphangiogenesis mediated by fatty acid β-oxidation-related genes (CPT1A) [518]. Mitotic histone acetylation patterns may constitute the bookmarks that restore lineage-specific transcription patterns after mitosis [519].

Histone phosphorylation

Histone phosphorylation tends to be very site-specific and there are far fewer sites compared with acetylated sites. The single-site modifications, similar to H4K16ac, can potentially induce significant structural alterations within chromatin. For instance, phosphorylation of H3S10 during mitosis occurs genome-wide and is associated with chromatin compaction [520].

Histone modification and cell death

The development of tumors is intricately related to histone modifications. Clusters of histone modifications are linked to melanoma progression, EMT, and metastasis [521]. Various oncogenic and tumor suppressor proteins involve cell death through histone modifications, thereby regulating tumor growth and therapeutic response. Histone deacetylases (HDACs) catalyze protein deacetylation and are frequently dysregulated in tumors. This has spurred the development of HDAC inhibitors (HDACi). Such epigenetic drugs modulate protein acetylation, eliminate tumor cells, and are approved for the treatment of cancers.

Histone modification and apoptosis

Aberrant expression of HATs and HDACs in cells has been confirmed to elicit human tumorigenesis. The effective inhibition of tumor progression can be achieved through the regulation of histone acetylation on key genes in the apoptotic pathway. Histone deacetylase (HDAC) inhibitors have emerged as a new class of anti-tumor agents for various types of tumors. HDAC2 down-regulates *P53* expression and thus inhibiting apoptosis. The novel HDAC inhibitor MPT0B291 enhances *p53* acetylation and upregulates the expression of apoptosis-related genes PUMA, Bax, and Apaf1, leading to a significant reduction in cell viability and induction of apoptosis in human glioma cell lines [522]. The HDAC6-selective inhibitor A452 also enhances wild-type *p53* levels by promoting acetylation of *p53* at Lys381/382 [523].What's more, retinoic acid (RA) with ability to exert apoptosis-inducing effects on prostate cancer cell lines by inhibiting HDCAC2 expression is expected to be a novel agent for the treatment of prostate cancer [524]. Parthenolide (PT) has cytotoxic effects on tumor cells by inhibiting HDACs and blocking NF-κB pathway [525]. Clove buds (CLO) showed significant pro-apoptotic effects in breast cancer by increasing histone lysine trimethylation and acetylation level (H4K20me3, H4K16ac) in cancer cells [526]. Additionally, the novel dual BET/HDAC inhibitor TW09 can mediate apoptosis of rhabdomyosarcoma (RMS) cells [527]. Bromodomain and extra-terminal motif (BET) are epigenetic modulators and have been associated with proto-oncogene overexpression in cancer. The BET inhibitor JQ1 has a synergistic effect with HDAC inhibitors (HDACIs) to induce RMS cell apoptosis, which was achieved by synergistically upregulating BIM and BMF while downregulating BCL-XL [528].

Moreover, drugs have been revealed to treat tumors using death receptors as the target of histone modifications. For example, sequential treatment with azacitidine and valproic acid (VPA) in combination with carboplatin can lead to a reduction in DR4 methylation and overcome resistance to platinum-based therapy. Azacitidine inhibits the methylation of replicative DNA through stoichiometric binding of DNA methyltransferase 1, which induces the re-expression of epigenetically silenced genes such as DR4. Valproic acid (VPA) is a histone deacetylase inhibitor that induces a hyperacetylated state of histones, leading to a more open chromatin structure and making cells more susceptible to apoptosis induced by chemotherapy [529]. This suggests that the combination of DNA methylation inhibitors and histone deacetylase inhibitors has a synergistic effect in gene expression activation and can overcome platinum resistance. Lignocaine, a natural compound, was able to cause a significant decrease in the survival of human leukemia cells. It has been shown that lignans can induce the expression of Fas and FasL by increasing the acetylation of histone H3, which in turn triggers the extrinsic apoptotic pathway [530].

In embryonic development, extrinsic apoptosis plays a pivotal role, which is also regulated by the involvement of histone modifications. The initiation of the embryonic death process, rather than being dependent on death-specific signals, is due to the increased sensitivity of target cells to harmless signaling damage from neighboring cells destined to survive [531]. As key regulators of embryonic cell behavior, epigenetic modifications and chromatin remodeling regulate chromatin fragility by facilitating or hindering contact of transcription factors with their targets. The oogonia of mammalian embryos at the two-cell stage are protected from chromatin access by Caspase 3 activated DNA enzymes due to DNA methylation and histone deacetylation [532]. Furthermore, the process of interphalangeal remodeling involves massive interphalangeal cell death, which is closely associated with excessive activation of Caspases and lysosomes. Compared to adjacent finger bone forming tissues, interphalangeal progenitor cells endure greater genomic instability to X radiation, which is associated with strong DNA methylation and trimethylation regions of histone 3 on lysines 4, 9, and 27 (H3K4me; H3K9me; and H3K27me) [533]. This suggests that the regions of elevated DNA fragility depend on epigenetic alterations. General epigenetic modification rules for cell death in different systems cannot be expected to be considered, as different modifications may favor cell death in different cell populations [531].

Histone modifications and necroptosis

HDAC inhibitors can induce necroptosis to significantly affect tumor growth and progression. Suberoylanilide hydroxamic acid (SAHA) is a common inhibitor of HDAC and can inhibit cancer by significantly upregulating levels of phosphorylated RIP3 and MLKL [534]. The administration of the HDAC inhibitor Givinostat in refractory Hodgkin's lymphoma leads to sustained generation of reactive oxygen species (ROS) and induction of necroptosis [535]. Apart from that, ubiquitination is one of the main ways of histone modification. The ubiquitin specific peptidase 22 (USP22) is a component of the SAGA complex, which plays a crucial role in catalyzing the ubiquitination of RIPK3 at lysine residues 42, 351, and 518 during the process of necroptosis. Mutations at K518 of RIPK3 can reduce the ubiquitination of RIPK3 and contribute to the progression of necroptosis [536].

Histone modifications and pyroptosis

The transcription of pyroptosis-related genes can be regulated by histone modification, thereby inducing the activation of pyroptosis signals. HDAC11 promotes both NLRP3/caspase-1/GSDMD and caspase-3/GSDME pathways causing pyroptosis in vascular endothelial cells [537]. HDAC2 in hepatocytes plays a pivotal role in an ULK1-NLRP3 pathway driven auto-amplification of pyroptosis [538]. In addition, protein arginine methyltransferase 5 (PRMT5) is a methyltransferase that catalyzes the formation of methylated residues on histones a. Accumulating evidence suggested that PRMT5 might play a carcinogenic role in various cancers [539]. PRMT5 can promote pyroptosis by activating the nuclear factor kappa B (NF-κB) /NLRP3 axis [539].

Histone modifications and autophagy

The role of histone modification in the regulation of autophagy-related genes, particularly ATG family proteins, has been partially investigated. The NAD-dependent deacetylase SIRT1 regulates autophagy gene expression through histone deacetylation, with lysine 16 on histone H4 (H4K16) as the primary deacetylation target [540]. H4K16 deacetylation inhibits the transcription of genes involved in the early and late steps of autophagy in multiple cell types, including ATG1, ATG8, ATG9 [541]. Moreover, SIRT1 indirectly regulates autophagy by deacetylation of FOXO3, leading to increased expression of autophagy-related genes, including Bnip3 [542]. In addition, accumulation of nucleocytosolic acetyl-CoA represses autophagy in yeast via hyperacetylation of histone 3 (on K9, K14, and K18) and repression of ATG7 transcription [543]. In contrast, in human cell lines acetyl-CoA influences autophagy through cytosolic effects that are independent of transcriptional changes of autophagy genes [544]. Besides, several histone methylation marks have been implicated in autophagy regulation. The H3K9 methyltransferase EHMT2/G9A is thought to be a repressor of autophagy under basal conditions [545].

The regulation of histone modification, like other mechanisms of cell death, plays a crucial role in inducing autophagy in tumor cells. However, the anti-tumor effect of modulating histone modification to induce autophagy is not consistently constant due to the dual effects of autophagy on tumor cell growth. The inhibition of HDAC has been demonstrated to activate mitophagy by mediating the acetylation of Parkin, an E3 ubiquitin ligase that targets damaged mitochondria for degradation, thereby leading to the suppression of cervical cancer cell proliferation [546]. HDAC3 is required to stabilize autophagy proteins and appears as a valid anti-cancer target for pharmacological intervention [547].Otherwise, the therapeutic potential and the underlying mechanism of traditional magazine has been explored. Metformin promotes histone deacetylation of optineurin and suppresses tumor growth through autophagy inhibition in ocular melanoma [548]. Histone modifications at critical loci of autophagy genes implicated in tumor development has also been investigated. For example, enhancer of zeste

homolog 2 (EZH2) has been reported to contribute to the initiation and progression of colon cancer through phosphorylation of H2B at tyrosine 37($H2B^{Y37ph}$), which elevates colon cancer cell autophagy possibly via activating transcriptional regulation of ATG genes [549].

Histone modifications and ferroptosis

Histone ubiquitination is an important form of ferroptosis involving epigenetic regulation. Histone 2A ubiquitination (H2Aub) epigenetically activates the expression of SLC7A11 to inhibit ferroptosis. The tumor suppressor BAP1 (BRCA1-associated protein 1), a member of the ubiquitin C-terminal hydrolase (UCH) subfamily of deubiquitinases, negatively regulates H2Aub, leading to SLC7A11 inhibition and accumulation of ferroptosis by lipid peroxidation [550]. Histone 2B ubiquitination (H2Bub) also epigenetically induces SLC7A11 expression during ferroptosis [551]. This process requires USP7 (ubiquitin-specific peptidase 7), a deubiquitinase responsible for the deubiquitination of histone 2B. *TP53* reduces H2Bub by interacting with USP7 and inducing nuclear translocation of USP7 through a transcription-independent mechanism, thereby reducing H2Bub levels [551]. *TP53* reduces H2Bub occupancy in the regulatory region of the SLC7A11 gene and suppresses SLC7A11 expression during erastin-induced ferroptosis [551]. These findings suggest that *TP53* has an atypical role in ferroptosis through H2Bub-mediated epigenetic control of gene expression.

Histone methylation also regulates ferroptosis. KDM3B (lysine demethylase 3B) is a histone H3 lysine 9 demethylase that prevents erastin-induced ferroptosis by activating the expression of SLC7A11 [552]. The acetylation of NFE2L2 by EP300 (E1A binding protein p300)-CREBBP/CBP (CREB binding protein) enhances its DNA binding and gene transactivation activity [553]. While CDKN2A/ARF (cyclin-dependent kinase inhibitor 2A) stabilizes and activates *TP53* by promoting the degradation of MDM2 (MDM2 proto-oncogene), ARF promotes ferroptosis in a *TP53*-independent manner. Alternatively, ARF impairs the interaction between CREBBP and NFE2L2, thereby impairing NFE2L2 acetylation and inhibiting NFE2L2-mediated SLC7A11 expression [554, 555]. The bromodomain-containing (BRD) family plays a role in epigenetic regulation by recognizing acetylated lysine residues on histones or other nuclear proteins. The BRD4 (bromodomain 4-containing) inhibitor JQ1 induces ferroptosis by downregulating the expression of GPX4, SLC7A11 and SLC3A2 in breast and lung cancer cells, suggesting that BRD4 is required for anti-ferroptosis gene expression [556].

Histone modifications can make tumor cells more sensitive to ferroptosis. The nuclear RB1CC1 recruits the elongator acetyltransferase complex subunit 3 (ELP3) through its fork head box (FOX)-binding motifs to enhance H4K12Ac histone modifications within enhancers associated with ferroptosis, thereby promoting early elevation of mitochondrial ROS and strengthening mitochondrial function following induction of ferroptosis [557]. Furthermore, inhibition of lysine-specific demethylase 1 (LSD1) transcriptionally upregulates the expression of transferrin receptor and ACSL4 by enhancing the binding of histone H3 lysine 4 dimethyl (H3K4me2) to their promoter sequences [558]. The combination of an LSD1 inhibitor and a ferroptosis inducer shows a synergistic anti-tumor effect in a xenograft model of non-small cell lung cancer [558]. Similarly, inhibition of protein arginine methyltransferase 1 (PRMT1) upregulates ACSL1 and increases lipid peroxidation through reducing the abundance of H4R3me2a in acute myeloid leukemia [559]. These findings offer potential guidance for the development of new strategies in the treatment of cancer.

Chromatin remodeling

The human genome is intricately packaged with histones and other proteins, creating a complex chromatin structure. Within chromatin, organization and compaction of the human genome are achieved by forming nucleosomes. Chromatin can be either packed in the form of accessible euchromatin, or densely as heterochromatin. The packaging of chromosomal DNA by nucleosomes condenses the genome and organizes gene expression through controlling the accessibility of transcription factors, and the molecular regulatory mechanism of chromatin accessibility is mainly observed through histone modification and ATP-dependent remodelers [9]. Due to compositional diversity, chromatin is highly dynamic and plastic, thereby providing it with high potential to modify genome topology and to orchestrate gene regulation in many aspects of cellular processes. A dynamic regulatory mechanism relying on chromatin remodelers keeps the process of transcription, chromosome segregation, DNA replication and DNA repair on track [560].

Regulation of chromatin remodeling

Chromatin remodeling plays important roles in normal physiology and diseases, particularly in cancer. Transcription factors rely on specific remodeling pathways for correct genomic binding. Chromatin remodeling links the genome with its functional phenotype through several primary mechanisms: (1) ATP-dependent chromatin-remodeling complexes ensure the proper distribution of nucleosomes; (2) remodeling complexes move or eject histones to allow transcription factors to bind

to DNA; and (3) remodeling complexes replace the histone with variants of the histone.

Chromatin remodelers are ATP-driven enzymes which utilize ATP hydrolysis to mobilize nucleosomes, thereby mediating the chromatin structure and the regulation of gene expression. All remodelers contain an ATPase/helicase of the SWI2/SNF2 (switch/sucrose non-fermenting) superfamily that generates the energy for selection and moving, ejecting or restructuring the composition of nucleosomes through the hydrolysis of ATP. Chromatin-remodeling complexes can be divided into four subfamilies, which is SWI/SNF family, ISWI family, CHD family and INO80 family [560]. The SWI/SNF family of chromatin-remodeling complexes share the BRG1 (also known as SMARCA4) subunit responsible for the main ATPase activity. SWI/SNF family members have distinct roles in DNA-damage repair (DDR) through modifying chromatin structure around DNA damage sites and recruiting proteins necessary for DDR [561]. Thus, several subunits of SWI/SNF family, such as ARID1A, BRG1 display bona fide tumor suppressor activity in various cancers [562, 563]. Furthermore, increasing evidence has shown that alterations in SWI/SNF complex subunits, especially in ARID1A/1B/2, SMARCA2/4, and BCL7A, are not only highly recurrent across a wide variety of lymphoid and myeloid malignancies, but also confer resistance to several antineoplastic agents routinely used for the treatment of hematological malignancies [564]. Recently, SWI/SNF emerged as a promising biomarker of immunotherapy in several cancers [565, 566].

ISWI possesses highly conserved SWI2/SNF2 family ATPase domain, belonging to the superfamily of DEAD/H-helicases, that provides the motor for chromatin remodeling and a characteristic HAND-SANT-SLIDE domains of C terminus with DNA binding activity [567]. Besides, accessory (non-ATPase) subunits of ISWI remodelers can recognize specific modified nucleosomes according to their modification state to confer their remodeling activity [568]. ISWI complexes use two catalytic subunits, SNF2H and SNF2L. SNF2H forms five remodeler complexes in mammal which slides nucleosomes along DNA in vitro and functions in ruling nucleosomal spacing in mammals, contributing to TF binding [569]. Recent studies have implicated that the basic motif in SNF2H plays a critical role in anchoring the remodeler to the nucleosomal surface, that is to say nucleosome acidic patch [570]. However, cancer-associated mutations can disrupt regularly spaced chromatin structure by inducing ISWI-mediated unidirectional nucleosome sliding [570]. Functional or componential alterations in ISWI subunits and ISWI-containing transcription complexes such as RSF complex, ACF complex, BAZ1B, NORC complex and CERF complex etc. are critical for tumor initiation and development [571].

The CHD complex contains a central ATPase domain, arranged in tandem with the chromodomains at the N-terminus that bind the methylated lysins in histone, a NegC domain, and a SANT–SLIDE domain at the C-terminus. CHD chromatin remodelers are known to interact with elongation and chromatin-modifying factors, such as Paf1, FACT, and SAGA [572]. The INO80 complex contains a central ATPase domain that includes a large insertion between the RecA-like lobes and an HSA domain at the C-terminus that binds actin-related components. INO80 was shown to play important roles in transcription regulation, mitosis and DNA double-strand break (DSB) repair [573].

Chromatin remodeling and gene transcription

Chromatin structure imposes significant obstacles on all aspects of transcription that are mediated by RNA polymerase II. There are two main groups of substances that regulate chromatin structure, that is histone modification enzyme and chromatin remodeling complex.

Histone modifications exert their effects via two main mechanisms. On one hand, histone modifications except for methylation result in a change in the net charge of nucleosomes, which could disrupt electrostatic interactions between histones and DNA. Histone methylation is unlikely to directly perturb chromatin structure since these modifications do not alter the charge of histones. On the other hand, specifically modified histones appeal to a large number of effector proteins that influence chromatin dynamics and function. Also, some modifications can directly influence higher-order chromatin structure. Histone acetylated lysines are often bound by bromodomains within chromatin-remodeling complexes. For example, SWI/SNF2 contains a bromodomain which targets acetylated histones and is in turn recruited by chromatin to exert its effects on acetylated promoter nucleosomes [574]. Apart from that, PHD fingers within chromatin-remodeling complex are capable of specifically recognizing as well as recruiting the BAF complex to acetylated histones [575]. It worth noting that histone modifications also functions disrupting the interaction between the histone and a chromatin factor. For instance, H3K4me3 (a mark of active transcription) can prevent the NuRD complex (a general transcriptional repressor) from binding to the H3 N-terminal tail [576].

Chromatin is divided into different categories based on the higher-order packaging of nucleosomes, histone post-translational modifications (PTMs) and histone variants. Modifications that are associated with highly active transcriptional regions, such as acetylation of histone 3 and histone 4 (H3 and H4) or H3K4me, are commonly

referred to as euchromatin modifications, while modifications that are localized to a condensed chromatin structure which is transcriptionally less active, such as H3K9me and H3K27me, are often termed heterochromatin modifications [446, 577]. In addition, there are regions of demarcation between heterochromatin and euchromatin named 'boundary elements' which are enriched for certain modifications such as H3K9me1 [578].

Induction of gene transcription is triggered by the binding of transcriptional activators to specific promoter elements. A nucleosome precisely placed on the TATA box and transcription start site (TSS) of the adenoviral major late promoter prevents the initiation of transcription owing to the strong histone–DNA interactions. Therefore, relief from repression involves unwrapping of the DNA by chromatin-remodeling complexes as well as allowing RNA polymerase engaged in transcription to invade the nucleosome. ATP-dependent chromatin remodelers alter the structure and positioning of nucleosomes, and allow regulatory proteins to access their target DNA sites in chromatin. The consequences of remodeling include transient displacement of the end DNA from histone octamers, forming the DNA loop, or moving nucleosomes to different translational positions, all of which change the accessibility of nucleosomal DNA to transcription factors (TFs).

Chromatin remodeling and cell death

Chromatin remodeling is a dynamic modification of chromatin structure that uses condensed genomic DNA to regulate transcription machinery. Dysregulation of chromatin remodeling complexes can be observed in cancer cells. The induction of cell death through targeting chromatin remodeling complexes may potentially confer anti-tumor effects.

Chromatin remodeling and apoptosis

The overexpression of chromatin remodeling complexes in tumor cells facilitates the initiation and progression of tumors, while inhibition of these genes can impede tumor progression by inducing apoptosis. INI1/hSNF5 is a component of the chromatin remodeling SWI/SNF complex which is inactivated in rhabdoid tumor (RT) resulting in overexpression of Aurora Kinase A, a high degree of mitotic gene. Knockdown of the Aurora A gene in RT cells impairs cell growth and induces Caspase 3/7-mediated apoptosis [579]. Snf2L is a chromatin remodeling gene expressed in a variety of tissues, cancers and derived cell lines and is involved in the formation of the chromatin remodeling complex. The inhibition of Snf2L expression has been demonstrated to selectively induce cell cycle arrest and apoptosis in cancer cells, as they exhibit greater sensitivity to Snf2L knockdown compared to normal cells [580]. ATRX, a chromatin remodeling protein of the Snf2 family, participates in diverse cellular functions including regulation of gene expression and chromosome alignment during mitosis and meiosis. ATRX deficiency in the mouse forebrain results in increased apoptosis in the hippocampal region and basal telencephalon in a P53-dependent pathway [581]. In addition, the chromatin-regulated and ATP-dependent nucleosome remodeling protein SMARCAD1 is involved in the induction of MMR-dependent apoptosis in human cells. Caspase-9 activation in SMARCAD1 knockout cells was significantly inhibited and their apoptosis is blocked [582].

Chromatin remodeling and necroptosis

The RIPK1 and RIPK3 protein serve as pivotal regulatory factors in the process of necroptosis, and they can interact with chromatin remodeling complexes to mediate induction of pro-inflammatory cytokines in necroptosis cells. Activated RIPK1 mediates phosphorylation of SMARCC2, a key component of the BAF complex, to promote chromatin remodeling and transcription of specific pro-inflammatory genes [583]. However, RIPK3 expression as well as RIPK3-driven inflammation can be attenuated by chromodomain helicase DNA-binding protein 4 (CHD4) [584].

Comprehensive multiomics studies on these regulatory factors can help to discover novel therapeutic strategies to overcome apoptotic resistance, and have potential protumor or anti-tumor effects in tumor occurrence, metastasis and immune monitoring [585].

Chromatin remodeling and ferroptosis

Ferroptosis is also regulated by chromatin remodeling complexes. HELLS/LSH, members of the SNF2 family of chromatin remodeling proteins, bind to WDR76 and inhibit ferroptosis by activating metabolic genes including SCD and FADS2 [483]. Upregulation of SCD and FADS2 prevents ferroptosis by reducing lipid ROS and iron levels. HELLS also induces epigenetic silencing of the cytosolic lncRNA LINC00472, which is downregulated in cancer and functions as a tumor suppressor. LINC00472 may promote ferroptosis by displacing TP53 from G3BP1, resulting in TP53 retention in the nucleus and ultimately affecting TP53-dependent metabolic gene expression [586]. In addition to inhibiting LINC00472, HELLS promotes nuclear lncRNA LINC00336 expression. LINC00336 competes with miR6852 to upregulate the expression of CBS, thereby mediating ferroptosis inhibition [587]. The expression of HELLS is positively regulated by the transcription factor MYC and negatively regulated by HIF1A. This enables HELLS to rapidly respond to changes in the hypoxic environment and

dynamically regulate many target genes [588]. Thus, the expression of HELLS is important for the integrated epigenetic and transcriptional regulation of ferroptosis.

NcRNA

Non-coding RNAs(ncRNAs) play an important role in epigenetic regulation. NcRNAs, including microRNAs (miRNAs), long noncoding RNAs (lncRNAs), and circular RNAs (circRNAs), are widely appreciated as pervasive regulators of multiple cancer hallmarks. Although they do not encode proteins, they affect gene expression, chromatin state, and genome function through a variety of mechanisms. The following is a detailed description of how ncRNA participate in the regulation of epigenetic modifications.

Roles of ncRNA in epigenetic regulations

Firstly, ncRNAs affect gene expression through direct or indirect mechanisms during DNA methylation to regulate gene silencing or activation. Certain lncRNAs recruit DNMTs to specific gene loci and promote local DNA methylation by binding to these enzymes. For example, lncRNA HOTAIRM1 mediates DNMTs away from the TSS of HOXA1 gene and reduces DNA methylation levels to regulate the expression of the oncogene HOXA1, which can promote cell proliferation, migration and invasion of malignant glioma [589]. Some lncRNAs can recruit histone modifying enzymes such as KMTs or KDMs to regulate histone modification. PH20 is a member of the human hyaluronidase family that degrades hyaluronan in the extracellular matrix and controls tumor progression. lncRNA PAS1 recruits histone methyltransferase SUV39H1to trigger the H3K9 methylation of PH20, resulting in its silencing and partially inhibiting breast cancer growth and metastasis [590]. Similarly, some lncRNAs can bind to chromatin remodeling complexes (such as SWI/SNF complex) and promote chromatin remodeling.

miRNA is a class of small non-coding RNA that usually suppresses the translation or promotes the degradation of mRNA by binding to it. LncRNA or circRNA can act as competitive endogenous RNA (ceRNA) and compete with miRNA for binding sites, thus reducing the inhibitory effect of miRNA on its target mRNA and indirectly regulating gene expression. LINC00336 which served as a ceRNA sponges miR-6825 and prevents it from binding to the target mRNA to inhibit ferroptosis [591].

NcRNA and cell death

NcRNA and apoptosis

It has been investigated that lncRNA HOTAIRM1 can inhibit GBM glioma cell apoptosis and promote tumor cell invasion by interacting with KMTs and DNMTs to mediate epigenetic regulation of HOXA1 gene [589]. NcRNAs can regulate the expression of key genes such as *p53* and Bcl-2 proteins in the apoptosis pathway by interacting with transcription factors, chromatin regulatory factors, or epigenetic modification enzymes. For example, miR-644-5p carried by exosomes can inhibit apoptosis by targeting *p53* [592]. In contrast, dysregulated ncRNAs contribute to tumorigenesis via their participation throughout the *p53* regulatory network [593]. In addition, HIF1α activated lncRNA H19-mediated miR-612/Bcl-2 pathway to promote cholangiocarcinoma, suggesting a promising therapeutic target for cholangiocarcinoma [594].

NcRNA and pyroptosis

NcRNAs in tumor cells can prevent tumor cell death by inhibiting key molecules of pyroptosis. LncRNA Malat1 acts as a suppressor of pyroptosis and promotes both tumor initiation and metastatic reactivation, making it a promising and clinically relevant target for drug development [595]. LINC00969 interacts with EZH2 and METTL3, transcriptionally regulates the level of H3K27me3 in the NLRP3 promoter region, thus epigenetically repressing NLRP3 expression to suppress the activation of the NLRP3/caspase-1/GSDMD-related classical pyroptosis signaling pathways, thereby endowing an anti-pyroptotic phenotype and promoting drug resistance in lung cancer [596]. The pyroptosis-related lncRNAs not only facilitate tumor progression but also serve as significant predictors of diverse overall survival (OS) rates, thereby demonstrating their clinical utility [597]. Of note, necroptosis-related lncRNAs are thought to be associated with poor prognosis and low survival rate in various cancer [598, 599].

NcRNA and ferroptosis

Recently, an increasing amount of evidence has demonstrated that ncRNAs play an important regulatory role in cancer progression via the ferroptosis pathway and might become new diagnostic markers or therapeutic targets of cancers. Several miRNAs play important roles in chemotherapeutic resistance via ferroptosis [600]. For example, exo-miR-522 secreted by cancer-associated fibroblasts interacted with ALOX15 to promote acquired chemotherapeutic resistance in gastrointestinal cancer by inhibiting ferroptosis in cancer cells [601]. Furthermore, lncRNAs also play relevant roles in lung cancer progression. It was reported that a novel lncRNA, LINC00336, which sponges miR-6825, served as a ceRNA and promoted lung cancer proliferation by inhibiting ferroptosis [591].In contrast, overexpression of lncRNA NEAT1 increased the anti-tumor activity of erastin and RSL3 by

modulating the miR-362-3p/MIOX axis as a ceRNA and enhancing ferroptosis [602].

Discussion

Cancer is the primary disease that poses a significant threat to human health and leads to mortality. The investigation of tumor cell death stands as a pivotal concern in cancer therapy. Over the past few decades, with profound exploration into the mechanisms of cell death, our understanding of various modes of cell death has expanded significantly. These encompass conventional apoptosis, pyroptosis, necroptosis, autophagy, ferroptosis, and cuproptosis. However, it should be noted that these forms of cellular death do not exist independently. On the contrary, they share common regulatory molecules across different pathways. Consequently, diverse cellular microenvironments such as inadequate energy supply, cellular stress, and enrichment of inflammatory cytokines can direct cell fate towards distinct paths.

In recent years, the field of epigenetics has witnessed significant advancements. Concurrently, the study of cell death mechanisms has also integrated into epigenetic regulation. Epigenetic regulation includes DNA methylation, histone modifications and chromatin remodeling. Epigenetic dysregulation is often found in tumor cells. Epigenetic-based anti-tumor drugs have been developed to a certain extent, exemplified by the widely used HDAC inhibitors and decitabine, which exhibits a discernible impact on various malignancies. However, the precise mechanism underlying cell death induced by these drugs remains elusive. Therefore, elucidating the specific molecular mechanisms associated with epigenetics that trigger cell death would be advantageous in identifying pivotal targets for anti-tumor therapy. The next years will certainly be exciting in the field as more light is shed on the complex regulatory mechanisms that govern cell death and inhibit tumor growth.

We acknowledge that our review does not exhaustively cover several intricate details, which represent important avenues for future research in understanding the role of cell death in tumor progression and its epigenetic regulation. For instance, we have not explored the mitochondrial contribution to cell death processes in depth, which is increasingly recognized as a crucial mediator in the epigenetic regulation of apoptosis and necrosis within cancer cells. Additionally, while we discussed the general role of HDACs, we did not delve into the differential effects of specific HDAC inhibitors or the unique responses these inhibitors elicit in various model systems. These differences can have significant implications for developing tailored therapeutic strategies and understanding drug resistance in specific tumor types.

Furthermore, the timing of observed histone modifications and the sequential loss of histone linker proteins are other factors that likely influence tumor cells' response to therapy, yet remain underexplored. Lastly, we recognize that our review does not delve into the controversial data surrounding the roles of various cell death pathways in embryonic development. While we focused primarily on cell death in the context of tumor progression and its epigenetic regulation, understanding how these pathways contribute to embryogenesis could offer valuable insights into their fundamental regulatory mechanisms and possible implications in cancer biology. Future studies that explore these detailed aspects could provide a more nuanced understanding of how specific epigenetic modifications govern cell death and survival in the tumor microenvironment. Such insights could pave the way for innovative therapeutic approaches that harness epigenetic regulation to enhance the efficacy of cancer treatments, potentially transforming the landscape of tumor therapy.

Abbreviations

RCD	Regulated cell death
MOMP	Mitochondrial outer membrane permeabilization
BCL-2	B-cell lymphoma 2
ER	Endoplasmic reticulum
UPR	Unfolded protein response
RIPK1	Receptor-interacting protein kinase 1
DED	Death effector domain
DR	Death receptors
DDR	DNA damage response
ROS	Reactive oxygen species
PE	Phosphatidylethanolamine
mTOR	Mammalian target of rapamycin
TNFR	Tumor necrosis factor receptor
DISC	Death-inducing signaling complex
ZBP1	Z-DNA Binding Protein 1
MLKL	Mixed-lineage kinase domain-like
NADPH	Nicotinamide adenine dinucleotide phosphate
FPN	Ferroportin
LIP	Labile iron pool
MUFAs	Monounsaturated fatty acids
LOOH	Lipid hydroperoxides
GSH	Antioxidant glutathione
GSSG	Oxidized glutathione
FSP1	Ferroptosis inhibitory protein 1
DNMTs	DNA methyltransferases
MeCPs	Methyl-CpG binding proteins
TETs	Ten-eleven translocation cytosine dioxygenases
EBV	Epstein-Barr virus
LSH	Lymphoid-specific helicase
KMTs	Lysine methyltransferases
KATs	Lysine acetyltransferases
HDACs	Histone deacetylases
EZH2	Enhancer of zeste homolog 2
KDM	Lysine demethylase
TSS	Transcription start site

Authors' contributions

All authors made substantial, direct and intellectual contribution to the review. Under the direction of the corresponding authors, Ruimin He orgnanized and wrote this review, Yifan Liu and weijie Fu provided editorial assistance, Xuan He edited image format. The authors read and approved the final manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
This study was conducted at the Xiangya Hospital, Central South University, Hunan, China. All of the protocols were reviewed and approved by the Joint Ethics Committee of the Central South University Health Authority and performed in accordance with national guidelines.

Consent for publication
This manuscript has been read and approved by all the authors to publish and is not submitted or under consideration for publication elsewhere.

Competing interests
The authors declare no competing interests.

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