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Targeting pyroptosis for cancer immunotherapy: mechanistic insights and clinical perspectives

Chen Huang[1†], Jiayi Li[2†], Ruiyan Wu[3], Yangqian Li[2] and Chenliang Zhang[4*]

Abstract

Pyroptosis is a distinct form of programmed cell death characterized by the rupture of the cell membrane and robust inflammatory responses. Increasing evidence suggests that pyroptosis significantly affects the tumor microenvironment and antitumor immunity by releasing damage-associated molecular patterns (DAMPs) and pro-inflammatory mediators, thereby establishing it as a pivotal target in cancer immunotherapy. This review thoroughly explores the molecular mechanisms underlying pyroptosis, with a particular focus on inflammasome activation and the gasdermin family of proteins (GSDMs). It examines the role of pyroptotic cell death in reshaping the tumor immune microenvironment (TIME) involving both tumor and immune cells, and discusses recent advancements in targeting pyroptotic pathways through therapeutic strategies such as small molecule modulators, engineered nanocarriers, and combinatory treatments with immune checkpoint inhibitors. We also review recent advances and future directions in targeting pyroptosis to enhance tumor immunotherapy with immune checkpoint inhibitors, adoptive cell therapy, and tumor vaccines. This study suggested that targeting pyroptosis offers a promising avenue to amplify antitumor immune responses and surmount resistance to existing immunotherapies, potentially leading to more efficacious cancer treatments.

Keywords Pyroptosis, Cancer immunotherapy, Gasdermin, Tumor microenvironment, Inflammatory cell death, Immune response

Introduction

Pyroptosis, a form of regulated cell death (RCD), is a critical immune response mechanism in organisms that inhibits infections and endogenous damage signals. This process is characterized by homeostasis, tissue integrity, and overall health [1]. Although the activation of pyroptosis may lead to the release of inflammatory mediators, potentially promoting tumor initiation and progression [2], increasing studies have demonstrated that pyroptotic cell death not only directly kills tumor cells but also initiates robust anti-tumor immune responses by releasing tumor antigens and inflammatory mediators, thereby highlighting its potential to enhance the efficacy of cancer immunotherapy [3].

†Chen Huang and Jiayi Li contributed equally to this work.

*Correspondence:
Chenliang Zhang
zhangchenliang@wchscu.edu.cn
[1]Department of Biotherapy, Cancer Center, State Key Laboratory of Biotherapy, West China Hospital, Sichuan University, Chengdu, Sichuan Province, China
[2]Institute of Respiratory Health, Frontiers Science Center for Disease-related Molecular Network, West China Hospital, Sichuan University, Chengdu, Sichuan Province, China
[3]West China Hospital, Sichuan University, Chengdu, Sichuan Province, China
[4]Division of Abdominal Tumor Multimodality Treatment, Department of Medical Oncology, Cancer Center and Laboratory of Molecular Targeted Therapy in Oncology, West China Hospital, Sichuan University, Chengdu, Sichuan Province, China

In a healthy organism, the immune system, particularly T cells, can detect and eliminate abnormal proteins or antigens within the body. However, cancer cells evade or suppress immune responses through various mechanisms, including low immunogenicity, antigen variation, and establishment of an immunosuppressive microenvironment, allowing tumors to grow unchecked [4]. When tumor cells undergo pyroptosis, they release damage-associated molecular patterns (DAMPs) and pro-inflammatory cytokines that transform the local microenvironment, promoting dendritic cell maturation and enhancing T cell infiltration. This process converts immunologically "cold" tumors into "hot" ones that are more responsive to treatment [5]. Thus, understanding the characteristics and molecular mechanisms of pyroptosis, as well as its role in antitumor immunity, is crucial for enhancing therapeutic strategies and efficacy.

In this review, we thoroughly explored the molecular pathways governing pyroptosis, including both canonical and non-canonical inflammasome activation, and highlights the vital role of the gasdermin (GSDM) family proteins. We assess how pyroptotic cell death impacts both tumor and immune cells within the tumor microenvironment and examine emerging therapeutic strategies targeting pyroptosis. These strategies range from small molecule modulators to engineered nanocarriers, with a specific focus on their potential to improve the efficacy of cancer immunotherapy. This paper aims to provide insightful perspectives for the future development of pyroptosis-based antitumor immunotherapies by delivering a detailed understanding of the features and molecular mechanisms of pyroptosis and its dual role in tumor progression and immune response.

Pyroptosis

In 2001, D'Souza et al. coined the term "pyroptosis," derived from the Greek "pyro," meaning fire, to describe a form of regulated cell death (RCD) characterized by intense inflammatory responses [6]. The term "ptosis" is derived from the Greek word for "falling", and is used to describe the cellular swelling and membrane rupture evident during pyroptosis [6]. Pyroptosis, different from apoptosis, is mediated by the GSDM family of proteins and is induced by cysteine aspartate specific proteases (caspases) in immune cells during microbial infections [7]. The regulation of pyroptosis is primarily attributed to inflammatory vesicle-associated caspases, including caspase-1, caspase-4, caspase-5, and caspase-11. Some proteases typically associated with apoptosis also contribute to this process [5, 8]. Additionally, particular enzymes, such as caspase-3 [9] and caspase-8 [10], are implicated in the pyroptosis process. The cleavage of GSDM proteins, particularly GSDMD and GSDME, is essential for initiating pyroptosis and facilitates their localization in the cell membrane. Pyroptosis can be triggered via several pathways, including the classical and non-classical inflammatory pathways, as well as through selectable signaling pathways (Fig. 1).

Canonical inflammasome pathway

The canonical inflammasome pathway is orchestrated by pattern-recognition receptors (PRRs), specifically the NOD-like receptor (NLR) family. This family includes NLR family pyrin domain containing 1 (NLRP1), NLR family pyrin domain containing 3 (NLRP3), NLR Family caspase recruitment domain (CARD) domain-containing 4 (NLRC4), Absent in Melanoma 2 (AIM2), and pyrin proteins, which recognize pathogen-associated molecular patterns (PAMPs) or DAMPs [11, 12]. PRRs stimulate the recruitment of caspase-1 and the assembly of inflammasomes by binding to caspase-1 and the adaptor protein Apoptosis-associated speck-like protein containing a CARD (ASC) [13–15]. Caspase-1, a crucial enzyme in the conventional inflammasome pathway, leads to cellular pyroptosis. Upon activation by inflammasomes, caspase-1 cleaves both pro-IL-18 and pro-IL-1β to generate their active forms, while also cleaving GSDMD into GSDMD-C and GSDMD-N [14]. Caspase-1, a crucial enzyme in the conventional inflammasome pathway, leads to cellular pyroptosis. Upon activation by inflammasomes, caspase-1 cleaves both pro-IL-18 and pro-IL-1β to generate their active forms, while also cleaving GSDMD into GSDMD-C and GSDMD-N [14, 16]. However, the degree of cell death varies significantly among different inflammasomes.

NLRP1 forms inflammasomes that trigger cellular pyroptosis and inflammatory reactions [17]. While human genomes contain a single *NLRP1* gene, mice possess three homologs (*Nlrp1a*, *Nlrp1b*, and *Nlrp1*) [18]. Upon pathogen recognition, NLRP1, NLRP1a or NLRP1b subsequently assemble into the NLRP1 inflammasome by interacting with adaptor proteins and pro-caspase-1 through the CARD [13, 19, 20]. Notably, mice do not require adaptor proteins for NLRP1 inflammasome assembly [13, 19, 20]. Additionally, inhibition of dipeptidyl peptidase 8 and 9 (DPP8 and DPP9) and cytoplasmic serine dipeptidyl peptidases promotes the activation and assembly of NLRP1b inflammasomes, thereby triggering caspase-1-dependent pyroptosis [20].

The NLRP3 inflammasome, comprising NLRP3, adaptor proteins, and pro-caspase-1, can be activated through two distinct pathways requiring sequential signals [21]. The initiation signal (signal 1) increases NLRP3 and pro-IL-1β expression, while the activation signal (signal 2) facilitates inflammasome assembly [22]. Activation of signal 2 is contingent upon the completion of signal 1 [22]. During signal 1, Toll-like receptor 4 (TLR4), Myeloid Differentiation Primary Response 88 (MyD88),

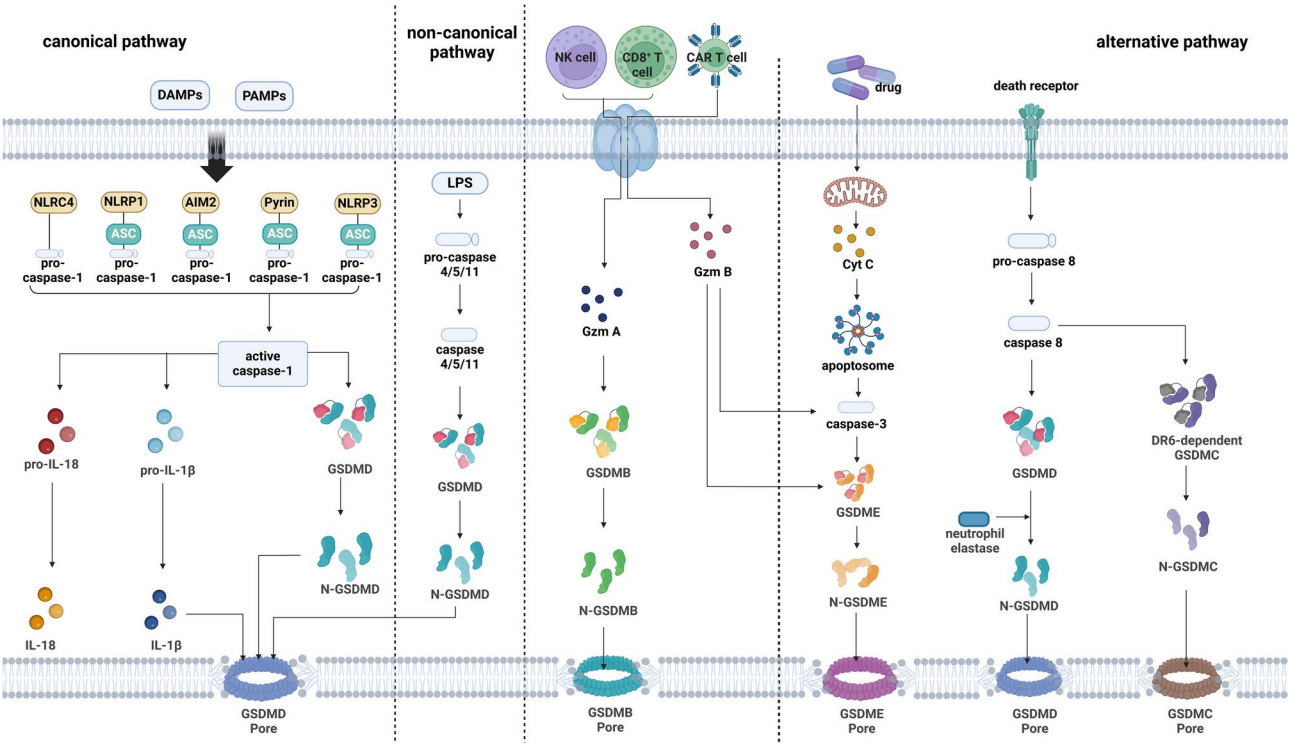

Fig. 1 Molecular mechanism of pyroptosis. Three major pyroptosis activation pathways: canonical, non-canonical, and alternative pathways. In the canonical pathway, pattern recognition receptors (NLRC4, NLRP3, AIM2, Pyrin) recognize PAMPs/DAMPs, leading to inflammasome formation and caspase-1 activation, which cleaves pro-IL-1β/IL-18 and GSDMD. The non-canonical pathway is initiated by intracellular LPS recognition through caspase-4/5/11, directly cleaving GSDMD. Granzymes (GzmA/B) from cytotoxic cells can activate GSDMB-mediated pyroptosis, while death receptor signaling and caspase-8 activation leads to GSDMC-dependent pyroptosis in the alternative pathway. All pathways culminate in the formation of gasdermin pores in the plasma membrane, resulting in cell lysis and release of inflammatory mediators

or Time-Restricted Feeding (TRF) receptors respond to microbial agents or pro-inflammatory factors, enhancing *NLRP3* and *pro-IL-1β* transcription via IL-1 Receptor-Associated Kinase (IRAK) or Nuclear Factor-kappa B (NF-κB) pathways [23, 24]. Various activators, including mitochondrial reactive oxygen species (ROS), cholesterol crystals, and calcium mobilization, can trigger signal 2 [23–26].

The NLRC4 inflammasome is activated by Salmonella, flagellin from Legionella pneumophila, and the rod portion of the Type III Secretion System (TTSS). These components are not directly recognized by NLRC4 but rather by NAIP and the NLR family of apoptosis inhibitory proteins [27–29].

AIM2 is recognized as a DNA sensor that detects cytosolic DNA, particularly double-stranded DNA (dsDNA) [30, 31]. It is important to note that only dsDNA with a minimum length of 80 base pairs can bind to the HIN-200 domain [32, 33]. Negatively charged bacterial dsDNA displaces the pyrin domain (PYD) of AIM2 and binds to the positively charged HIN-200 domain through electrostatic interactions, activating the PYD domain. Subsequently, AIM2 assembles with ASC and caspase-1 to form the AIM2 inflammasome [31, 33–35].

Pyrin indirectly detects inactivated proteins under bacterial influence [36, 37]. In humans, RhoA-activated Protein Kinase N1 (PKN1) and Protein Kinase N2 (PKN2), members of the Protein Kinase C (PKC) superfamily, bind to pyrin and phosphorylate S208 and S242 [37]. This phosphorylation promotes assembly with 14-3-3ε or 14-3-3τ, suppressing pyrin activation [37]. In mice, the phosphorylation of Ser-205 and Ser241 and subsequent binding to 14-3-3 proteins inhibit pyrin activation [38]. This phosphorylation promotes assembly with 14-3-3ε or 14-3-3τ, suppressing pyrin activation [7, 39].

Non-canonical inflammasome pathway

The non-canonical NLRP3 inflammasome activation pathway is mediated by caspase-4/5 in humans and caspase-11 in mice [40–45]. In the cytoplasm, pathogen-associated lipopolysaccharide (LPS) from Gram-negative bacteria binds directly to caspase-4/5/11 through CARD domains, rather than through the inflammasome [45]. In this pathway, cytoplasmic LPS from Gram-negative bacteria binds directly to caspase-4/5/11 through CARD domains, bypassing the inflammasome complex. Caspase-4 activation requires guanylate-binding proteins, which recruit and activate caspase-4 on bacterial

membranes, while caspase-11 activation is facilitated by High Mobility Group Box 1 (HMGB1) [46, 47]. Once activated, caspase-4/5/11 cleaves GSDMD at Asp 276, generating GSDMD-C and the pore-forming GSDMD-N fragments. GSDMD-N facilitates the extracellular release of IL-1 and IL-18, compromises membrane integrity, and triggers pyroptosis [48]. Additionally, caspase-4/5/11 cleaves the Pannexin-1 (Panx-1) channel protein, leading to ATP synthesis and P2X purinergic receptor 7 (P2RX7) activation, which subsequently activates the NLRP3 inflammasome and induces pyroptosis [7, 39].

Alternative signaling pathways

Pyroptosis can also be activated through alternative pathways. Caspase-3 initiates pyroptosis via GSDME-generated pores in the cell membrane. During *Yersinia* infection, the Receptor-interacting serine/threonine-protein kinase 1 (RIPK1)-caspase-8 complex induces pyroptosis by cleaving GSDMD through a mechanism dependent on the Folliculin-Folliculin-interacting protein 2-Rag-Ragulator complex [49]. Active caspase-8 also cleaves oxidized death receptor DR6-dependent GSDMC to generate GSDMC-N fragments, triggering pyroptosis [50]. Beyond caspase-mediated pathways, pyroptosis is regulated by additional factors. In neutrophils, GSDMD cleavage and subsequent pyroptosis require neutrophil elastase [51]. During apoptosis, cytotoxic T lymphocytes and natural killer (NK) cells generate Granzyme A (GzmA), which translocate into cells [52]. When GSDMB is present in the cytoplasm, GzmA cleaves it to produce the GSDMB N-terminus, leading to apoptosis [52]. Additionally, Granzyme B (GzmB) plays a pivotal role in initiating GSDME-mediated pyroptosis and may serve as a predictive biomarker for identifying patients most likely to benefit from neoadjuvant immunotherapy [53].

Gasdermin family and pyroptosis

GSDMs are intracellular proteins that regulate cellular pyroptosis. The human genome encodes six GSDM proteins (GSDMA, GSDMB, GSDMC, GSDMD, GSDME, and DFNB59), while mice express ten GSDM proteins (GSDMA1-3, GSDMC1-4, GSDMD, GSDME, and DFNB59) [54, 55]. All GSDM family members except DFNB59 share a common structure: a C-terminal inhibitory domain connected to an N-terminal domain by an intermediate transition region. The N-terminal domain binds to cell membrane lipids to form pores, disrupting membrane integrity and inducing pyroptosis through cellular content release [55, 56]. GSDMD is the primary substrate for inflammatory caspases and uniquely serves as the sole caspase-1 substrate capable of inducing pyroptosis [57–60]. The linker region between GSDMD-C and GSDMD-N contains a caspase-1 cleavage site (D276 in mice and D275 in humans) that can be activated by downstream inflammasome complexes [61]. Cleavage reduces GSDMD-C's inhibition of GSDMD-N, allowing GSDMD-N to bind to membrane phospholipids (phosphatidylinositol, phosphatidic acid, and phosphatidylserine). This binding leads to GSDMD-N oligomerization and the formation of pyroptotic pores [61]. GSDME facilitates the conversion of caspase-3-mediated apoptosis to pyroptosis, thereby enhancing anti-tumor activity of NK cells and $CD8^+$ cytotoxic T lymphocytes, ultimately suppressing tumor [62].

Distinctive roles of pyroptosis in immunogenic cell death

RCD occurs when cells receive specific signals that activate molecular pathways, leading to ordered cellular disintegration and homeostasis maintenance [63]. The well-studied RCDs include apoptosis, ferroptosis, pyroptosis, and necroptosis, each with distinct characteristics and affects cellular immune response in different ways (Table 1).

Apoptosis is an active, caspase-regulated form of programmed cell death. Although traditionally considered immunologically silent, increasing evidence indicates that apoptotic cell antigens can serve as targets for autoantibodies in autoimmune diseases [64], highlighting a potential link between apoptosis and immune system activation. The immunogenicity of apoptosis largely depends on the degree of endoplasmic reticulum stress (ERS) [65, 66]. Apoptosis proceeds through three interconnected pathways: the death receptor pathway, mitochondrial pathway, and endoplasmic reticulum pathway [67]. When apoptosis adopts an immunogenic phenotype, it involves the surface exposure of calreticulin (CRT), secretion of ATP, and release of HMGB1 [68]. These DAMPs further bind to PRRs on DCs, promoting their maturation and activating immune responses [66]. Inducing immunogenic apoptosis in neoplastic cells can disrupt the immunosuppressive tumor microenvironment and trigger T cell-mediated adaptive immune responses, potentially leading to tumor regression [69]. While both apoptosis and pyroptosis can enhance antitumor immunity through DAMP release and immune cell activation, they differ significantly in their execution mechanisms and inflammatory consequences. Most cancer cells develop resistance to apoptosis [70], whereas pyroptosis generates a more direct and potent proinflammatory response through the release of cytokines such as IL-1β and IL-18. Morphologically, both processes involve DNA damage and chromatin condensation [71, 72], but pyroptotic cells uniquely exhibit cellular swelling prior to membrane rupture and develop characteristic vesicular protrusions on the cell membrane [16]. Moreover, while apoptosis is a non-inflammatory process maintaining tissue homeostasis by removing damaged

Table 1 Comparison of different forms of cell death

	Apoptosis	Ferroptosis	Pyroptosis	Necroptosis	Autophagy
Type	PCD	PCD	PCD	PCD	PCD
Causes	Death receptor pathway initiated by death ligand binding, ER pathway triggered by ER stress, mitochondrial pathway induced by DNA damage	Iron overload, lipid peroxidation, GPX4 inhibition, depletion of glutathione	Inflammasome stimulation, pathogen recognition, intracellular LPS sensing, activation of caspase-3/GSDME	death receptor activation when apoptosis is inhibited, pathogen recognition, caspase-8 inhibition, interferon signaling	Nutrient deprivation, metabolic stress, Gene regulation to use lysosomes to degrade damaged organelles and macromolecular substances
Morphology	Cell shrinkage, chromatin condensation, nuclear fragmentation, membrane blebbing, formation of apoptotic bodies	Mitochondrial shrinkage, increased membrane density, loss of mitochondrial cristae, normal nuclear size	Cell swelling and expansion, pore formation, vesicular protrusions (pyroptosomes), nuclear condensation. DNA fragmentation	Cytoplasmic organelles swelling, cytoplasmic and nuclear disintegration	Autophagosomes with bilayer membranes, inflated organelles, pyknotic nuclei
Cell Membrane	Integrity	Rupture	Rupture	Rupture	Integrity
Characteristics	Highly regulated, energy dependent, PS externalization, DNA fragmentation at internucleosomal sites, non-inflammatory under physiological conditions	Iron accumulation, lipid peroxidation, oxidative stress-dependent, redox imbalance	IL-1β and IL-18 release, inflammasome activation, rapid cell lysis, release of pro-inflammatory cytokines	RIPK1 / RIPK3 /MLKL complex formation, backup mechanism to apoptosis under caspase-8 inhibition	Highly regulated, autophagosome engulfs damaged organelles or proteins, increased lysosomal activity, LC3 lipidation, context-dependent immunomodulation
Molecular mechanism	Activation of initiator and executioner caspases, mitochondrial cytochrome c release, Bcl-2 family protein regulation	Inhibition of GPX4, depletion of glutathione, Fenton reaction producing ROS, accumulation of lipid peroxides, iron-catalyzed oxidative damage	Caspase-dependent, GSDMs cleavage, N-terminal fragment oligomerization	RIPK1 activation, RIPK3 and MLKL phosphorylation, MLKL-mediated membrane permeabilization	mTOR inhibition, ULK1 complex activation, Beclin-1/PI3K complex formation, autophagosome-lysosome fusion
Effects on immunity	Typical immunologically silent, CRT exposure, ATP and HMGB1 release during immunogenic apoptosis, tolerogenic when cleared efficiently	Modulation of TIME, reduces MDSCs, polarizes TAMs, not universally immunogenic	Highly inflammatory and immunogenic, releases IL-1β and IL-18, activation of innate and adaptive immunity	Release of DAMPs, long genomic DNA and IL-6, low levels of ecto-CRT, effective for $CD8^+$ T cell cross-priming	Extracellular release of DAMPs, PS exposure, context-dependent immunomodulatory effects, regulates inflammation

PCD, programmed cell death; ROS, reactive oxygen species; DAMPs, damage-associated molecular patterns; LC3, microtubule-associated protein 1 light chain 3; RIPK1/RIPK3, receptor interacting protein kinases 1/3; MLKL, mixed lineage kinase domain-like; mTOR, mammalian target of rapamycin; GSDMs, gasdermins; GPX4: Glutathione peroxidase 4; PS: phosphatidylserine; CRT: calreticulin; LPS: lipopolysaccharide; ULK1: Unc-51 like autophagy activating kinase; PI3K: phosphoinositide 3-kinase; TIME: tumor immune microenvironment

or unnecessary cells [73], pyroptosis serves as a defense mechanism against infection, where released inflammatory cytokines and cellular debris recruit immune cells to infection sites, promoting inflammatory responses [74].

Necroptosis represents a caspase-independent form of programmed necrosis mediated primarily by RIPK1, RIPK3, and mixed lineage kinase domain-like protein (MLKL) [75, 76]. This process is initiated by death receptors or pattern recognition receptors and is characterized by cytoplasmic swelling, organelle enlargement, plasma membrane disruption, and eventual cellular rupture [77]. These events culminate in the release of intracellular contents that trigger inflammatory responses. Necroptotic cells release HMGB1, ATP, long genomic DNA, IL-6, and low levels of surface CRT [78], collectively facilitating adaptive immune responses, particularly antigen presentation and $CD8^+$ T cell cross-priming [79]. Though necroptosis and pyroptosis both represent lytic forms of immunogenic cell death involving membrane disruption and DAMP release, they employ distinct molecular mechanisms. Membrane disruption in necroptosis is orchestrated by kinase signaling—particularly the RIPK3-MLKL axis—and typically occurs when caspase-8 is inhibited [80], whereas pyroptosis is caspase-dependent and uses gasdermin family proteins to form pores and cause cell lysis. A distinguishing morphological feature of pyroptosis is the formation of vesicular protrusions on the cell surface, known as pyroptosomes, which are not observed in necroptosis [16].

Autophagy functions as a lysosome-dependent mechanism through which cells selectively degrade damaged organelles and macromolecules to maintain cellular homeostasis [81]. This process is characterized by the formation of double-membraned autophagosomes that encapsulate cytoplasmic components before fusing with lysosomes to form autolysosomes, where the enclosed material undergoes enzymatic degradation. Morphologically, autophagy is distinguished by the presence of swollen organelles and autophagosomes with bilayer membranes [82]. In the context of immunogenic cell death, autophagy can facilitate the extracellular release of DAMPs, including ATP, HMGB1, and lysophosphatidylcholine (LPC) [69, 83], as well as the surface exposure of phosphatidylserine (PS) [84]. Unlike pyroptosis, which elicits rapid inflammatory responses through caspase-dependent membrane permeabilization, autophagy operates primarily through caspase-independent mechanisms and exhibits context-dependent immunomodulatory effects that vary according to the cellular environment and external stimuli [68, 85, 86].

Ferroptosis is an iron-dependent programmed cell death characterized by lipid peroxide accumulation, primarily regulated by GPX4 and lipid metabolism pathways [87]. During ferroptosis, CRT translocate to the cell surface, enhancing tumor antigen presentation and pro-inflammatory cytokine release, which activates the local immune microenvironment and facilitates immunogenic cell death (ICD) [88]. Unlike pyroptosis, which triggers robust inflammation through IL-1β and IL-18 secretion, ferroptosis modulates the tumor immune landscape by reducing myeloid-derived suppressor cells (MDSCs), reprogramming tumor-associated macrophages from M2 to M1 phenotype, and enhancing immune cell infiltration [89]. A bidirectional relationship exists where $CD8^+$ T cells secrete IFN-γ, promoting fatty acid incorporation into phospholipids, leading to lipid peroxidation and ferroptosis in tumor cells [90]. Therapeutic strategies increasing intracellular iron can amplify the Fenton reaction and ROS-mediated lipid peroxidation [91]. However, ferroptosis is not universally immunogenic and may sometimes suppress apoptotic immunogenicity [92]. Morphologically, ferroptosis features mitochondrial shrinkage, increased membrane density, and cristae loss, occurring independently of pore-forming proteins [93].

Recent research has revealed extensive crosstalk between cell death pathways, challenging the traditional view of their parallel operation [94]. This interconnection, termed "PANoptosis," highlights the coordination between pyroptosis, apoptosis, and necroptosis [95]. Studies in rat sepsis-associated encephalopathy models demonstrate that inhibiting one pathway can activate others [96]. The "PANoptosome" molecular complex facilitates interaction between key pathway molecules, regulating specific cell death modes [97, 98]. Z-DNA binding protein 1 (ZBP1), a crucial PANoptosome component, mediates PANoptotic cell death that inhibits tumor development in mice [99]. RIP1 regulation of PANoptosis is essential for cell death and inflammatory responses [100, 101]. L61H10 and N-substituted EF24 13d both effectively induces lung cancer cell transition from apoptosis to pyroptosis, creating an immune-inflammatory tumor microenvironment and achieving anti-tumor effects through NF-κB signaling pathway inhibition [102, 103]. These studies suggest that in future studies of pyroptosis, understanding the effects of pyroptosis on tumor growth and therapy from the perspective of PANoptosis may be more comprehensive and accurate.

Pyroptosis and tumor immunity

Tumor immunotherapy leverages the body's immune system to fight cancer. Its basic principle involves activating specific immune responses to recognize and eliminate tumor cells. Several immune checkpoint inhibitors (ICIs), such as Ipilimumab, Nivolumab, and Atezolizumab, have been approved and markedly improved survival rates and the quality of life for many cancer patients. In 2013, Chen and Mellman proposed the concept of the "Cancer-Immunity Cycle" [104]. In this cycle, emerging

tumors produce novel antigens that dendritic cells capture and present to T cells, thereby activating effector T cells and eliciting targeted anti-tumor responses [104]. These activated T cells then migrate to the tumor site, where they specifically recognize and eliminate tumor cells [104]. As tumor cells perish, they release new cancer antigens, thus triggering subsequent rounds of immune responses. This cycle progressively widens and intensifies the immune response [104]. Given paraptosis cells can release a variety of immune factors, pyroptotic tumor cells can affect TIME, thereby affecting tumor immunotherapy. In the following part, we will discuss the mechanism of paraptosis-remodeled TIME and its effect on tumor immunotherapy.

Pyroptosis and tumor immune microenvironment

The TIME comprises various cell types, including tumor cells, endothelial cells, and immune cells that interact through pyroptosis-mediated mechanisms. Pyroptosis of tumor cells can significantly reshape the immune landscape by releasing DAMPs and inflammatory factors that recruit and activate immune cells [105]. In terms of immune cells, pyroptosis plays distinct roles: When dendritic cells (DCs) undergo pyroptosis, they release tumor antigens and inflammatory mediators that enhance T cell priming [106]. However, excessive DC pyroptosis may impair antigen presentation [106]. T cell pyroptosis can limit anti-tumor responses, while NK cell pyroptosis reduces direct tumor cell killing [106]. In contrast, infiltrating immune cells like macrophages and neutrophils may facilitate tumor growth and escape [106]. The impact of pyroptosis on myeloid cells is complex: M1 macrophage pyroptosis releases pro-inflammatory factors that can promote anti-tumor immunity [107, 108]. In contrast, pyroptosis of M2-like macrophages may actually benefit the anti-tumor response by reducing their immunosuppressive effects [107, 108]. However, the inflammatory mediators released during macrophage pyroptosis, including metalloproteases and growth factors like TGF-β and VEGF, can promote tumor progression [109–111].

Pyroptosis of endothelial cells can disrupt the tumor vasculature and affect immune cell infiltration. While this may limit nutrient supply to tumors, it can also create hypoxic regions that promote immunosuppression [112]. Additionally, pyroptotic cell death of MDSCs and regulatory T cells may help overcome immune suppression in the TIME [113]. The tumor microenvironment (TME) resembles a Darwinian natural selection arena with dynamic competition [112]. The inflammatory state triggered by pyroptosis is a key driver of TIME dynamics [113]. While acute inflammation from pyroptosis can enhance anti-tumor immunity, chronic inflammation may promote tumor growth by recruiting suppressive immune cells and releasing growth factors [114, 115]. Understanding how to modulate pyroptosis in different cell types within the TIME is crucial for improving cancer immunotherapy outcomes.

Pyroptosis-mediated anti-tumor immunity

As delineated previously, pyroptosis can significantly alter the TIME. Considering the substantial effects of tumor cell pyroptosis on the immune landscape within the TIME, it is plausible to suggest that triggering pyroptosis in tumor cells might amplify the effectiveness of cancer immunotherapy. Numerous studies corroborate that pyroptosis in tumor cells bolsters anti-tumor immunity via multiple molecular routes (Fig. 2). Subsequent sections will explore the regulation of pyroptosis-mediated tumor immunity and elucidate its molecular underpinnings in depth.

Pyroptosis promotes antigen-presenting cell maturation

Pyroptosis triggers the release of DAMPs, including HMGB1, ATP, DNA, and various pro-inflammatory cytokines such as IL-1β and IL-18 [116]. These DAMPs not only promote dendritic cell maturation but also enhance immune cell recruitment and activation, significantly strengthening anti-tumor immune responses [117]. Additionally, during pyroptosis, GSDM family proteins form pores in the cell membrane, resulting in cell lysis and the release of tumor antigens and pro-inflammatory factors [116]. These molecules are seized by antigen-presenting cells, which then enter a "hyperactive" state, characterized by enhanced membrane protrusion, migration capabilities, and continuous pro-inflammatory cytokine release [118]. This sequence of events effectively activates T cells, significantly amplifying the intensity and scope of anti-tumor immune responses beyond conventional antigen presentation methods. Inflammasomes play a pivotal role in this context, especially in activating caspase-1 and caspase-11, crucial for GSDMD cleavage and pore formation [7]. DAMPs can also directly activate pro-survival pathways in tumor cells through TLRs, potentially leading to tumor growth and immune evasion [117].

Pyroptosis promotes pro-inflammatory TME formation

Pyroptosis can transform the suppressive TME, converting "cold" tumors into "hot" tumors, thereby increasing immune cell infiltration. Initially, DAMPs released during pyroptosis stimulate dendritic cell maturation [74]. Mature DCs then upregulate co-stimulatory molecules CD80 and CD86, augment the production of pro-inflammatory cytokines such as IL-12 and TNF-α, and enhance their antigen uptake, processing, and presentation capabilities [119]. These changes enable DCs to more effectively activate and expand tumor-specific T cells. Concurrently, pyroptosis reshapes the phenotype and function of tumor-associated macrophages. In

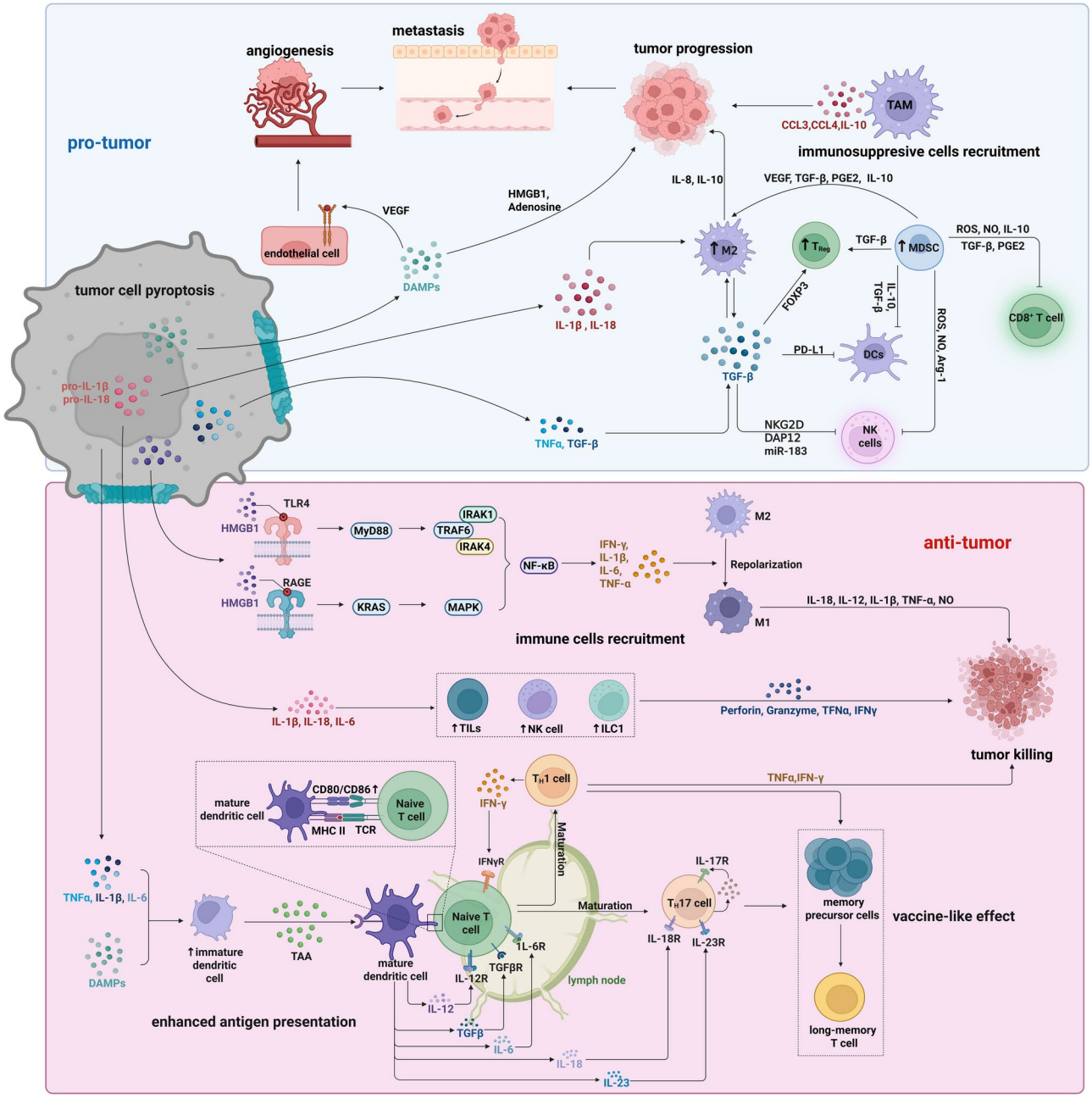

Fig. 2 The dual role of pyroptosis in the tumor microenvironment: anti-tumor immunity vs. pro-tumor progression

Pro-tumor: Pyroptotic tumor cells release pro-inflammatory cytokines (IL-1β, IL-18) and damage-associated molecular patterns (DAMPs), initiating the recruitment and activation of various immunosuppressive cells within the tumor microenvironment (TME). These cells include myeloid-derived suppressor cells (MDSCs), regulatory T cells (Treg), tumor-associated macrophages (TAMs), and M2 macrophages. The process is supported by cytokines such as TGF-β, IL-1βand IL-18. Additional factors like HMGB1 and adenosine from pyroptotic cells, along with IL-8 and IL-10 from M2 macrophages, and CCL3, CCL4, and IL-10 from TAMs, collectively exacerbate tumor progression. Moreover, VEGF released from pyroptotic cells binds to receptors on endothelial cells, promoting angiogenesis. Growing tumor and angiogenesis can further result in tumor metastasis. **Anti-tumor**: Pyroptotic tumor cells release damage-associated molecular patterns (DAMPs), cytokines (e.g., TNFα, IL-6), and high-mobility group box 1 (HMGB1). HMGB1 binds to Toll-like receptor 4 (TLR4) on immune cells, initiating signaling cascades via MyD88/IRAK1/TRAF6, activating NF-κB and MAPK pathways. These cascades induce production of pro-inflammatory cytokines (IL-1β, IL-6, TNFα, IFN-γ), driving the repolarization of anti-inflammatory M2 macrophages into pro-inflammatory M1 macrophages, which mediate tumor cell killing. The cytokines IL-1β, IL-18, and IL-6 recruit immune effector cells, including tumor-infiltrating lymphocytes (TILs), natural killer (NK) cells, and type 1 innate lymphoid cells (ILC1), promoting the secretion of cytotoxic mediators such as perforin, granzyme, TNFα, and IFNγ to facilitate tumor elimination. Additionally, DAMPs and cytokines enhance antigen presentation by dendritic cells, resulting in more effective T-cell priming and activation against tumor-associated antigens. This immune response promotes the generation of memory precursor cells and long-lived memory T cells, establishing a durable vaccine-like protective effect against future tumor development

the inflammatory microenvironment induced by pyroptosis, HMGB1 transforms macrophages from an immunosuppressive M2-like phenotype to a pro-inflammatory M1-like phenotype, characterized by the upregulation of MHC-II and co-stimulatory molecules and increased secretion of IL-1β, TNF-α, and IL-12 [120]. Additionally, M1-like macrophages exhibit enhanced phagocytic activity, helping to clear tumor cells and pyroptotic cell debris, further promoting antigen presentation and processing [121]. NK cells, significantly impacted by pyroptosis, experience increased activation from cytokines like IL-18, produced during pyroptosis [122]. Activated NK cells then produce more perforin and granzymes, boosting their ability to recognize and eliminate tumor cells [52, 62, 123]. Interleukin-12 and interferon-γ are critical cytokines initiating downstream signaling cascades for Th1 cell development [124]. After activation through pattern recognition receptors, antigen-presenting cells (APCs) secrete copious amounts of IL-12, which induces NK cells to produce IFN-γ, promoting Th1-type immune responses [125–127]. Pyroptosis also regulates $CD8^+$ T cells, enhancing their proliferation, expansion, and effector functions in response to activated DCs, while $CD4^+$ T cells are more likely to differentiate into Th1 and Th17 subtypes in a pro-inflammatory environment, producing more IFN-γ and IL-17 to support $CD8^+$ T cells and B cells [128, 129]. Ultimately, the TME undergoing pyroptosis shows an increase in $CD4^+$ T, $CD8^+$ T, NK cells, and M1 cells, whereas pro-tumor cells such as monocytes, neutrophils, MDSCs, and M2 marker-positive cells decrease [130].

Pyroptosis promotes the exposure of tumor antigens as vaccines

Beyond its effects on cells and the TME, the inherent nature of pyroptosis allows it to function as a form of in situ tumor vaccine, stimulating adaptive immunity and potentially long-lasting immunological memory [131, 132]. The core mechanism involves the lytic nature of pyroptotic cell death, which leads to the simultaneous release of tumor-associated antigens (TAAs) and potent immunoadjuvant signals, primarily DAMPs and pro-inflammatory cytokines. DAMPs activate and mature APCs, primarily DCs, through engagement with receptors like TLR4 and P2×7 [112]. This enables DCs to effectively capture, process, and present tumor antigens to T cells, initiating robust anti-tumor immune responses [112]. Simultaneously, pyroptosis triggers the release of pro-inflammatory cytokines, enhancing T cell and NK cell functions and promoting tumor cell killing [133]. Beyond tumor cells themselves undergoing pyroptosis, immune cells within the TME, such as macrophages and MDSCs, can also be induced to undergo pyroptosis [134]. This can either enhance anti-tumor immunity through the release of additional cytokines and DAMPs, or in some cases, promote tumor growth by creating a chronic inflammatory environment [112]. This efficient antigen presentation, coupled with inflammatory milieu, leads to robust priming and activation of tumor-specific T cells, initiating a targeted adaptive immune response [133]. This process essentially mimics vaccination, using the dying tumor cell itself as the source of both antigen and adjuvant, potentially establishing durable anti-tumor immunity.

The dual nature of pyroptosis in tumor immunity

The TME is shaped by dynamic interactions between pro-inflammatory and suppressive factors, which are critical in determining the direction and intensity of immune responses. Cytokines like IL-18 and IL-1β play dual roles in this balance, both promoting anti-tumor immunity and, under certain conditions, facilitating tumor growth. For instance, IL-18 can promote tumor growth, angiogenesis, invasion, and metastasis, yet it also enhances interferon-γ production, activates cytotoxic T lymphocytes (CTLs), neutrophils, and NK cells [135], and promotes Th1 and Th17 cell differentiation, thereby strengthening anti-tumor immune responses [136]. IL-18 regulates both innate and adaptive immune responses through the recruitment or differentiation of NK cells, T cells, monocytes, and other immune cells, thus inhibiting various types of tumor growth and metastasis. Additionally, IL-18 supports effective anti-tumor immunity by maintaining Th1 cell activity. IL-1β interacts with IL-1R to activate MyD88-STAT-dependent signaling pathways, which drive $CD4^+$ and $CD8^+$ T cell polarization into helper and effector subtypes [128, 129]. This polarization enhances both primary and secondary antigen-specific responses of T cells [137, 138] and upregulates expression of effector-like genes (GzmB, GzmA, Perforin 1, Interleukin 2 receptor alpha chain, and Inhibitor of DNA binding 2, increasing local accumulation and anti-tumor functions of $CD8^+$ T cells [139]. Additionally, IL-18 can promote anti-tumor immunity via enhancing NK cells maturation [122] and sustaining Th1 cells activity [140], which is essential for maintaining an effective antitumor response.

Pro-inflammatory cytokines, including IL-1β, HMGB1, and IL-18, released after tumor cell pyroptosis can suppress anti-tumor immunity within the TME by aiding tumor cells in evading immune surveillance and by producing cytokines and soluble factors that support tumor angiogenesis [141–143]. Moreover, the chronic inflammatory environment formed by pro-inflammatory factors recruits immunosuppressive cells such as MDSCs and Tregs, thereby suppressing immune responses of CTLs, NK cells, and $CD8^+$ T cells [144]. Additionally, not only tumor cells but also immune cells themselves

can undergo pyroptosis, further reducing anti-tumor immune responses. For instance, chemotherapy-induced MDSC pyroptosis releases IL-1β, which in turn stimulates IL-17 production by $CD4^+$ T cells, ultimately suppressing anti-cancer immune responses [145, 146]. Therefore, the effect of pyroptosis on tumor immunity is not always as expected, that is, to promote the tumor cell death (Fig. 2). This may be influenced by the induction conditions, degree, and the accuracy of tumor cell pyroptosis, which should be focused in future research.

Therapeutic strategies for targeting pyroptosis

As discussed previously, activation of pyroptosis signaling pathways can enhance anti-tumor immunity, while suppression of these pathways may promote tumor growth and metastasis. Therefore, targeting pyroptosis is a potential strategy to enhance tumor immunotherapy. In the following section, we summarize and discuss recent studies on the strategies of targeting pyroptosis to enhance tumor immunotherapy.

Inflammasome-targeted therapeutic strategies

The NLRP3 inflammasome serves as a central hub of innate immunity mediating pro-inflammatory cytokine secretion, playing a crucial role in regulating inflammatory responses through interactions with other cellular compartments [122]. NLRP3 inflammasomes respond to cellular perturbations and various microorganisms [147–152]. This cytoplasmic protein comprises three domains: a C-terminal leucine-rich repeat sequence, a central nucleotide-binding and oligomerization domain (NACHT) with ATPase activity, and an N-terminal PYD [153]. The basal expression level of NLRP3 is typically insufficient for inflammasome activation, necessitating a two-step priming and activation process [154]. The priming step is induced by TLRs and cytokine receptors, such as tumor necrosis factor receptors or IL-1 receptors, which recognize PAMPs or DAMPs and upregulate NLRP3 and IL1B transcription. Subsequently, PAMPs and DAMPs promote NLRP3 inflammasome assembly, leading to caspase-1-mediated pro-inflammatory cytokine maturation, release, and cellular pyroptosis [155]. Inflammasomes induce pyroptosis in various cancers. In Barrett's cell lines, LPS activates the NLRP3 inflammasome and pyroptosis pathway, enhancing pro-inflammatory factor secretion [156]. LPS initiates the inflammasome signaling pathway by stimulating TLR-4, promoting the release of pro-inflammatory mediators [112]. Simultaneously, LPS can activate the NLRP3 inflammasome by increasing mitochondrial ROS production, leading to caspase-1 activation and subsequent release of pro-inflammatory molecules such as IL-18, IL-1, and lactate dehydrogenase (LDH) [2]. Thus, LPS-induced pyroptosis regulates cell death and exacerbates the pathological state of Barrett's esophagus [157, 158]. Triple-negative breast cancer (TNBC), comprising 10–20% of all breast cancers, lacks expression of estrogen receptor, progesterone receptor, and HER2, making it unsuitable for receptor-targeted therapies [159]. Pizato et al. discovered that Docosahexaenoic acid (DHA) induced NLRP3 inflammasome activation, significantly reducing TNBC cell viability within 24 h, with notably selective toxicity toward cancer cells compared to non-cancer cells [160]. This research demonstrates DHA's potential in pyroptosis-targeted therapeutic strategies for TNBC. Tang et al. proved that NLRP3 and caspase-1 inflammasome pathway participating in colorectal cancer (CRC) development and progression [161]. Fl118 induces CRC cell pyroptosis by activating the NLRP3-ASC-caspase-1-IL-18 and IL-1 signaling pathway [161]. According to Liu et al., upregulation of lncRNA-XIST may promote non-small cell lung cancer progression by inhibiting pyroptotic cell death mediated through the miR-335/SOD2/ROS/NLRP3 signaling pathway [162]. Compared to direct NLRP3 activation, inducing cell pyroptosis through ROS generation to activate NLRP3 may provide a more precise and effective strategy for tumor immunotherapy. While tumor cells maintain higher basal ROS levels than normal cells, supporting proliferation and migration, elevated ROS levels can lead to oxidative stress and tumor cell death [163]. Modulating ROS generation levels can specifically induce ROS in tumor cells, targeting them for pyroptosis while minimizing damage to surrounding healthy tissues.

Caspase-targeted therapeutic strategies

Since caspases are critical regulators for pyroptosis, remodeling their expression level or enzymatic can also be used to explore the induction of pyroptosis in tumor cells. In different cancer, caspase-1 has different effects on tumorigenesis. For example, the expression levels of caspase-1 were significantly lower in liver cancer tissues compared to surrounding normal tissues [155, 157], suggesting caspase-1 may suppress liver cancer. Zou et al. identified guanylate-binding protein 5 (GBP5) as a key regulator of the TIME that inhibits ovarian cancer progression [164]. GBP5 activates canonical pyroptosis by engaging the JAK2/STAT1 signaling pathway, which upregulates caspase-1 expression and promotes GSDMD cleavage [164]. However, Research by Hu et al. showed that caspase-1 gene deficiency promoted tumor development in azoxymethane and dextran sulfate sodium-induced colitis-associated CRC mouse models [165]. These studies suggest that targeting caspase-1 to induce pyroptosis may show different efficiency in different tumors. Beyond caspase-1, pyroptosis can be mediated by LPS-activated caspase-4/5/11 [45]. These caspases can be directly stimulated by intracellular Gram-negative

bacterial LPS, leading to self-activation and hydrolysis, subsequently acting on GSDMD to form cell membrane pores. Activated caspase-4/5/11 can physically interact with caspase-1 in the presence of NLRP3 and ASC [5, 42, 166, 167], promoting its activation. Moreover, Rogers et al. discovered that activated caspase-3, after successfully inducing apoptosis, could cleave deafness autosomal dominant 5 (DFNA5)/GSDME, generating N-terminal fragments (GSDME-NT) and inducing pyroptosis [9]. Indeed, Vernon et al. reported that raptinal, a caspase-3 activator, induces pyroptosis in melanoma cells and suppressed tumor growth in vivo [168]. Given numerous chemotherapy drugs can activate caspase-3 that mainly used to identify apoptosis in previous studies, chemotherapy drugs may also be potential pyroptosis inducers. Wang et al. confirmed caspase-3's role in GSDME cleavage and activation, further establishing pyroptosis as a mechanism for chemotherapy drug side effects [169]. Both paclitaxel and cisplatin induce apoptosis and pyroptosis in A549 cells, with cisplatin showing more pronounced pyroptotic effects [170]. Cisplatin treatment results in significantly higher caspase-3 activation levels and GSDME-NT generation compared to paclitaxel [170]. While paclitaxel-treated cells exhibit cell shrinkage and membrane blebbing with maintained membrane integrity, cisplatin-treated cells show membrane integrity loss and large vesicle formation [170]. It was demonstrated that the caspase-1 cleavage site on GSDMD could be substituted with the caspase-3 cleavage site in HeLa cells [171]. The combined use of TNF-α and cycloheximide activated caspase-3, which further cleaved GSDMD to produce GSDMD-cNT and induced an apoptosis-to-focal transition [171]. Besides, Yi et al. reported that tetracaine hydrochloride, a local anesthetic, could induce pyroptosis in uveal melanoma by activating caspase-3/GSDME pathway in uveal melanoma that exhibits higher GSDME expression [172]. Moreover, Chalcone compounds containing α, β-unsaturated ketone functional groups demonstrate significant anti-lung cancer effects by upregulating intracellular ROS generation, triggering caspase-3-mediated pyroptosis [173]. Ganoderma lucidum extract (GLE), a traditional Chinese herbal with excellent antitumor activity, elevated significantly ROS levels in breast cancer cells, activated caspase-3/GSDME pyroptosis [174]. GLE prevented capillary tube formation in human umbilical vein endothelial cells (HUVECs) and inhibited tumor adhesion, migration and invasion [174]. Furthermore, physical therapies like photodynamic therapy (PDT) can harness caspase pathways. Zhou et al. demonstrated that mitochondria-targeted PDT using the photosensitizer IR700DX-6T generates ROS, activating a p38/MAPK/caspase-3 signaling cascade [175]. This targeted caspase-3 activation leads to GSDME cleavage and pyroptosis in CRC models [175].

Moreover, as an upstream activator of caspase-3, caspase-9 can also be targeted to induce pyroptosis in tumor cells. For example, studies have shown that in CRC cells, chemodynamic therapy (CDT) induces GSDME-mediated pyroptosis by causing DNA damage and activating ROS signaling pathways, which in turn activate caspase-9 and caspase-3 [168]. Additionally, while cold atmospheric plasma (CAP) treatment, which increases intracellular ROS levels and activates caspase-9/3, has been found to be insufficient to trigger pyroptosis in ovarian cancer cells, it significantly enhances the sensitivity of tumor cells to pyroptosis when combined with decitabine. This combination works by increasing GSDME protein expression through demethylation. These findings suggest that the activation of caspase-9 and caspase-3 creates favorable conditions for the induction of pyroptosis; however, this alone is not enough. Combining these treatments with other drugs or strategies that activate additional pyroptosis regulators may represent a promising approach to effectively induce pyroptosis in tumor cells. Future research should place greater emphasis on the combined application of established caspase-3/9 activation strategies with other potential pyroptosis-inducing approaches in cancer therapy. In summary, caspases are promising targets for inducing pyroptosis. In addition to their role in pyroptosis, caspases also regulate other forms of PCD, such as apoptosis and necroptosis, which can similarly modulate the TME and influence the effectiveness of cancer immunotherapy. Therefore, targeting caspases may enhance therapeutic outcomes in cancer treatment.

GSDMs-targeted therapeutic strategies

As mentioned above, the expression level of GSDMs is an important determinant for tumor cell responding to pyroptosis inducers, GSDMs can be used as molecular markers to evaluate pyroptosis. Notably, GSDMs such as GSDMD and GSDME, while present in diverse human tissues, may lead to adverse effects in non-targeted therapies [176]. Wu et al. reported upregulated GSDME expression in esophageal squamous cell carcinoma cell lines, which induced cell apoptosis and pyroptosis-related signaling pathways [158]. Yet, it remains uncertain whether elevated GSDME levels directly drive esophageal squamous cell carcinoma progression. In pancreatic ductal adenocarcinoma (PDAC), GSDME expression was reported significantly increased in tumor tissue compared to adjacent normal tissues [177]. High levels of GSDME correlate with poorer patient outcomes, suggesting a potential tumor-promoting role in PDAC [177]. These studies implicate that pyroptosis may be easy induced in esophageal squamous cell carcinoma and PDAC. However, GSDMs have been reported to be carcinogenic in certain tumors. For instance, GSDMC was

upregulated in transforming growth factor beta receptor 2 (TGFBR2) mutant high-frequency microsatellite instability (MSI-H) CRC mouse model, and further promoted tumor cell progression [178]. GSDMD promotes tumor proliferation through regulation of EGFR/Akt signaling and inhibits apoptosis, as evidenced by higher GSDMD expression correlating with more aggressive tumor features and worse patient prognosis in lung adenocarcinoma (LUAD) patients [179]. Although the high expression of GSDMs promotes tumorigenesis to some extent, it also creates favorable conditions for inducing pyroptosis in tumor cells. Numerous studies have shown that elevated levels of GSDMs are crucial for triggering pyroptosis. For instance, Hydrogen attenuated tumor volume and weight in an endometrial tumor xenograft mouse model though increasing GSDMD expression and triggering the pyroptotic pathway [180]. Tanshinone II A significantly elevated GSDMD expression and thus promotes pyroptosis, exerting anticancer activity on HeLa cells by regulating miR-145/GSDMD signaling pathway [161]. α-NETA increased expression of pyroptosis-related proteins, while caspase-4 and GSDMD knockdown significantly reduced α-NETA's anti-invasion effects, indicating activation of the pyroptosis signaling pathway [181]. Decitabine, a DNA methyltransferase inhibitor, reverses the epigenetic silencing of GSDME, thereby inducing pyroptosis and enhancing chemosensitivity. This effect has been demonstrated in MCF-7/Taxol cells treated with paclitaxel [182], and in oral squamous cell carcinoma treated with cisplatin [183]. Further highlighting the clinical relevance of GSDME silencing, Li et al. identified KIAA1199 as a critical factor in CRC immunotherapy resistance. They showed that KIAA1199 stabilizes DNA methyltransferase 1 (DNMT1), leading to methylation-mediated suppression of GSDME expression and reduced pyroptosis [184]. Another approach involves synergistically upregulating GSDME expression. Euphohelioscopin A, a PKC activator, stimulates NK cells to produce IFN-γ [185]. Gong et al. found that this NK-derived IFN-γ, in concert with Eupho-A itself, significantly increases GSDME expression in target tumor cells [185]. This increased GSDME level makes the tumor cells highly susceptible to pyroptosis induced by subsequently released NK cell GzmB, representing a novel strategy to prime tumor cells for NK-mediated pyroptotic killing [185].

In addition to modulating GSDM expression levels, activating GSDM cleavage represents a promising approach to induce pyroptosis in cancer cells. This process typically involves caspase-dependent cleavage of GSDMs into their N-terminal pore-forming fragments (e.g., GSDMD-N, GSDME-N), which disrupts cellular membranes and triggers inflammatory cytokine release. LPS induces pyroptosis through activation of caspase-1, leading to GSDMD cleavage and GSDMD-N translocation to the plasma membrane [186]. Notably, LPS enhances oxaliplatin chemosensitivity in CRC by promoting GSDMD-dependent pyroptosis, as demonstrated in HT29 cells and mouse models [186]. This mechanism increases membrane permeability, facilitating chemotherapy drug entry and apoptosis induction. Arsenic trioxide activates pyroptosis via dual cleavage of GSDMD and GSDME in various cancer models, including leukemia and solid tumors [187]. Arsenic trioxide-induced pyroptosis is associated with IL-1β/IL-18 secretion and reduced tumor survival, offering a potential adjuvant therapy for drug-resistant cancers. Osthole, a coumarin derivative, suppresses ovarian cancer (OC) progression by inducing GSDME cleavage. This leads to pyroptotic cell death and inhibition of tumor growth, highlighting its therapeutic potential as a natural anticancer agent [188]. DHA, an omega-3 fatty acid, increases GSDMD-N membrane translocation, promoting cell death and reducing tumor invasiveness in TNBC models [160].

Recent studies have uncovered novel mechanisms to activate GSDM-mediated pyroptosis without relying on traditional cleavage pathways or upstream signaling. GSDMD activation requires S-palmitoylation at cysteine residue 191 (Cys191), a post-translational modification that stabilizes its membrane localization and overcomes self-inhibition [189–192]. This process is enhanced by ROS, which promote palmitoylation and disrupt the intramolecular interaction of GSDMD, enabling full-length GSDMD (FL-GSDMD) to form pores in the plasma membrane. Importantly, this pathway bypasses the need for caspase-dependent cleavage, offering a new angle for targeted interventions. Zhou et al. identified a non-cleavage mechanism for GSDME-mediated pyroptosis in cervical cancer and other cancer cell lines [193]. High-dose UVC induces DNA damage, activating poly (ADP-ribose) polymerase 1 (PARP1), which generates massive PAR polymers. These PAR chains are released into the cytoplasm and bind to PARP5, triggering its activation. PARP5 then mediates PARylation of GSDME, causing conformational changes that disrupt the N- and C-terminal inhibitory domains of GSDME [193]. Simultaneously, UVC induces mitochondrial fission, leading to excessive ROS production. The PARylated GSDME senses these ROS, undergoes oxidative oligomerization, and translocate to the membrane, ultimately forming pores and inducing pyroptotic cell death [193]. These discoveries highlight the potential of directly targeting GSDMs to induce selective tumor cell pyroptosis. By bypassing canonical caspase pathways and focusing on post-translational modifications (e.g., palmitoylation, PARylation) or ROS-mediated activation, therapies may achieve greater precision in cancer treatment while

minimizing off-target effects associated with traditional immunotherapies.

Nanomedicines

While numerous small molecules, natural products, and chemotherapeutics have shown potential to induce pyroptosis [170, 194–199], their clinical application often faces significant hurdles. These include poor solubility, rapid systemic clearance, non-specific biodistribution leading to off-target toxicity, and inefficient intracellular delivery.

Emerging nanotechnologies can effectively overcome these limitations and show promise in improving disease diagnosis and treatment specificity [200]. Nanotechnology continues to transform our world by utilizing established principles, methods, and approaches in nanomedicine, offering unprecedented prospects for modifying or potentially revolutionizing our lifestyle [201, 202]. Photothermal therapy (PTT), PDT, sonodynamic therapy (SDT), and CDT are emerging physical and chemical therapeutic approaches that induce cellular pyroptosis through different mechanisms, demonstrating significant anti-tumor effects. These approaches not only improve the targeting and effectiveness of tumor therapy but also reduce damage to normal tissues, representing innovative directions in modern cancer treatment.

Nanomaterials that induce cellular pyroptosis can be classified into five major categories: non-metallic nanoparticles, metallic nanoparticles, quantum dots, biological nanoparticles, and carrier-mediated drugs [203]. Inorganic nanoparticles are typical non-metallic pyroptosis inducers, with carbon nanotubes [204] and graphene [205] effectively absorbing light or sound energy to generate heat or ROS, commonly used in photothermal and sonodynamic therapies. Under LPS stimulation, carbon black nanoparticles can promote caspase-1 expression, induce IL-1β secretion, and kill human lung macrophages [206]. Zheng et al. presented a drug-free inorganic $C_4H_4Na_2O_4$ NPs to enhance immunotherapy [207]. The nanoparticles uniquely upregulated the expression of MHC-I on tumor cells, avoiding tumor evasion and enabling better antigen presentation [207]. Under white light irradiation, photocatalytic CDs are capable of generating substantial amounts of hydroxyl radicals and can effectively decrease cytoplasmic pH values, resulting in ROS upregulation and subsequent pyroptosis [208]. Additionally, nano-silica [209–211] and two-dimensional graphene oxide [212] have also proven to be effective non-metallic nanoparticles. While utilizing the endogenous immune system to prevent tumor recurrence and spread is promising, clinical outcomes often fall short of expectations. Li et al. proposed targeting tumor metabolism as a strategy to improve immunotherapy efficacy, synthesizing sodium citrate nanoparticles (PSCT NPs) based on the TCA cycle [213]. PSCT NPs release Na^+ and $C_6H_5O_7^-$ ions intracellularly, causing a dramatic increase in intracellular osmotic pressure and activating ROS generation. This triggers two pyroptotic pathways - caspase-1/GSDMD and caspase-8/GSDMC - ultimately inducing pyroptosis. Zhang et al. developed a covalent organic framework (COF) which integrated with aggregation-induced emission luminogens (AIEgens), capable of triggering both pyroptosis and ferroptosis simultaneously [214]. COF-919 improves synergistically the response rate of αPD-1, and effectively inhibits tumor metastasis and recurrence [214]. Both bimetallic and monometallic nanoparticles have demonstrated anticancer activity through pyroptosis induction and are widely used in PTT and PDT. Gold and silver alloys (AgAu NPs) show particularly high potential [215], with MDA-MB-231 cells co-incubated with AgNPs or AgAu alloy NPs showing significantly increased NLRP3 gene expression and elevated IL-1β mRNA and secretion levels. Quantum dots are semiconductor nanocrystals with unique photophysical properties, primarily used in PDT as photosensitizer carriers. They can generate ROS when excited at specific wavelengths, enhancing photodynamic effects. Lu et al. modified CdSe/ZnS QDs and found that these quantum dots could induce hepatocyte pyroptosis by activating the NLRP3 inflammasome [216]. GOx-Mn/HA nanoparticles represent multi-enzyme nanomaterials [217], combining the dual enzymatic activities of glucose oxidase (GOx) and manganese-based nanoenzymes (Mn-NP). These particles can regulate glucose metabolism in the tumor microenvironment and induce cellular pyroptosis. Additionally, their surface modification with hyaluronic acid enhances their application in targeted tumor therapy. Gao et al. introduced an innovative human cell membrane vesicle-based nanoplatform (HCNP) that incorporates the photosensitizer TAPP, designed to selectively trigger pyroptosis in lung cancer cells via the caspase-3/GSDME pathway [218].

SDT generally requires a chemical sonosensitizer and focused ultrasound. Xu et al. developed an acid-responsive HSA-based nanocarrier loaded with tetrazine-functionalized ruthenium (II) sonosensitizers (HSA@Tz-Ru1) that, upon bio-orthogonal activation, enabled membrane-targeted sonodynamic therapy generating dual type I/II reactive oxygen species, inducing oncolytic pyroptosis and enhancing antitumor immunity [219]. Sun et al. developed fluorinated titanium oxide ($TiO_{2-x}F_x$) nanoparticles as sonosensitizers that can effectively trigger tumor cell pyroptosis under ultrasound stimulation, leading to enhanced antitumor immunity [220]. The fluorine doping creates oxygen vacancies and reduces the band gap in TiO_2, enabling more efficient ROS generation under ultrasound [220]. Xu et al.'s strategy offers better targeting specificity but with increased complexity,

while Sun et al.'s approach provides simpler implementation with potentially broader applicability. Both strategies demonstrate the potential of SDT-induced pyroptosis for cancer immunotherapy, but through different technical approaches.

To expand the application scope of pyroptosis-related drugs, various nanomaterials are being employed as carriers to improve solubility and delivery efficiency. This approach enhances pyroptotic effects for tumor cell killing or suppresses pyroptosis to alleviate inflammatory diseases. Nanocarriers can encapsulate hydrophobic or labile pyroptosis-inducing agents, improving their stability and bioavailability. By tuning nanoparticle size and surface properties, circulation time can be extended, facilitating passive accumulation in tumor tissue via the enhanced permeability and retention (EPR) effect, although the heterogeneity of EPR remains a challenge. These strategies range in sophistication from enhancing the delivery of known pyroptosis agents to engineering complex nanoplatforms that actively orchestrate the pyroptotic pathway within tumor cells.

As its simplest, nanomedicine can improve the delivery and local efficacy of existing pyroptosis-inducing drugs. Using 5-fluorouracil (5-FU) as an example, this antimetabolite drug treats various tumors by stimulating p53 and caspase-1 expression at both genetic and protein levels, promoting ROS generation, and inducing pyroptosis through increased IL-1β and IL-18 release [221–223]. In gastric cancer cells, 5-FU activates caspase-3, which cleaves the N-terminus of GSDME, triggering pyroptosis [224]. Balahura et al. developed cellulose nanofiber-based hydrogels incorporating pectin to embed 5-FU [225]. This nanostructured scaffold served as a local depot, facilitating sustained release of 5-FU and promoting its known pyroptotic activity within breast cancer cells, thereby enhancing the drug's localized anti-tumor effect while providing a potential matrix for tissue engineering. Moving towards more controlled induction, nanocarriers can deliver agents that trigger pyroptosis only upon external activation, allowing for spatial and temporal precision. Wang et al. engineered a pH-responsive, cell membrane-anchoring nanoparticle (YBS-BMS NPs-RKC) carrying a dual-type NIR photosensitizer and an ICI [226]. Triggered by the acidic tumor microenvironment, the nanoparticle anchored to the prostate cancer cell membrane. Subsequent NIR irradiation activated YBS, generating localized Type I/II ROS which initiated caspase-1/GSDMD-mediated pyroptosis. The co-delivered BMS-202 simultaneously blocked PD-1/PD-L1 interactions, resulting in highly effective photo-immunotherapy. A further level of sophistication where the nanomaterial structure itself, formed or transformed in situ, acts as the pyroptosis trigger. Zhang et al. developed NP-NH-D_5 platform which utilizes an initial nanoparticle, formed by co-assembling F-C6-NH2 and a stimuli-responsive peptide, primarily as a 'pro-assembly' nanocarrier [227]. Extracellular MMP-2 triggers surface charge reversal to enhance tumor cell uptake, while intracellular redox conditions induce disulfide bond cleavage within lysosomes, enabling precise release of the core non-peptidic amphiphile, F-C_6-NH_2. The liberated F-C_6-NH_2 monomers undergo in situ self-assembly specifically within the lysosomal compartment, forming highly structured, rigid nanofibers. These fibers potently induce lysosomal membrane permeabilization (LMP) through mechanisms including physical disruption and the 'proton sponge effect [227]. This LMP leads to the release of Cathepsin B into the cytosol, subsequently activating the NLRP3 inflammasome/caspase-1 pathway and culminating in efficient GSDMD-mediated pyroptosis. The system operates without light or oxygen and remains stable in lysosomes, offering a promising strategy for treating deep and metastatic tumor [227]. The most advanced strategies utilize nanomedicine to actively engineer the pyroptotic pathway within the tumor cell through precise co-delivery of cooperating agents. Wang et al. created a cooperative Nano-CRISPR scaffold (Nano-CD) that simultaneously delivered cisplatin and a CRISPR activation (CRISPRa) plasmid designed to induce endogenous GSDME expression [228]. This approach cleverly forces the tumor cell to 'self-supply' the pyroptotic substrate via gene activation, while the co-delivered cisplatin activates the executioner caspase-3 [228]. Neither component alone was sufficient, but together within the nanoplatform, they cooperatively and effectively induced pyroptosis, bypassing limitations associated with low basal GSDME levels. Similarly, Zhong et al. developed a GSH-responsive nanoplatform, PL@SD, capable of inducing a switch from non-immunogenic apoptosis to immunogenic pyroptosis through the combined delivery of decitabine and chemotherapy metabolite SN38 [229]. Decitabine reversed epigenetic silencing to increase GSDME expression, while SN38 provided the caspase-3 activation trigger. Concurrently, the release of tumor-derived DNA activates the cGAS-STING pathway in DCs, thereby initiating innate immune responses [229]. Differently, Li et al. developed mRNA lipid nanoparticles (LNPs) to deliver mRNA encoding only GSDMBNT to directly trigger pyroptosis in tumor cells [230]. By delivering this engineered mRNA construct via LNPs directly into tumor cells, the cellular translation machinery produces the constitutively active GSDMBNT fragment, bypassing the requirement for upstream protease cleavage of a full-length gasdermin protein. This allows for direct and efficient initiation of pyroptosis through membrane pore formation, independent of endogenous gasdermin levels or specific caspase activation states [230]. Importantly, they found that even modest levels of

pyroptosis (~20%) through this single-agent mRNA/LNP approach was sufficient to generate potent immunogenic responses, transforming immunologically 'cold' tumors and sensitizing them effectively to checkpoint immunotherapy [230].

Researchers take advantage of not only pyroptosis, but also other cell death. Liu created the Cu-THBQ/AX nanosized metal-organic framework (MOF), which effectively triggers pyroptosis, cuproptosis, and secondary necrosis in cancer cells [231]. This process leads to the activation of a robust antitumor immune response. Zhu et al. present a multifunctional copper-phenolic nanopills to deplete polyamines in tumor cells, leading to mitochondrial dysfunction and enhanced pyroptosis and cuproptosis [232]. The $Bi_2Sn_2O_7$ nanozymes are engineered to mimic multiple enzymes, enhancing ROS production and promoting mitochondrial dysfunction, which is critical for initiating PANoptosis [233]. The incorporation of ultrasound significantly amplifies the therapeutic efficacy of $Bi_2Sn_2O_7$ by enhancing ROS generation and facilitating deeper tissue penetration, which traditional light-based therapies cannot achieve [233].

Biodegradable nanoparticles now draw rising attention in therapeutic anti-tumor treatment. Biodegradable K_3ZrF_7:Yb/Er upconversion nanoparticles (ZrNPs) induce pyroptosis in cancer cells by releasing K^+ and $[ZrF7]^{3-}$ ions, triggering oxidative stress, ROS production, and immune activation. This leads to enhanced dendritic cell maturation, increased T cell populations, and significant tumor growth inhibition, positioning ZrNPs as promising candidates for cancer immunotherapy [234]. Liu et al. developed tunable inorganic nanoparticles Na_3ZrF_7:x%Yb^{3+}, with smaller particles showing superior therapeutic efficacy [235]. This nanoparticle provokes higher levels of ROS generation, increased pyroptosis and mitochondrial damage, leading to enhanced immune responses [235]. Biodegradable inorganic nanoparticles (BINPs) demonstrate distinctive advantages in cancer therapy through their dual-functional properties. Acting as "Trojan horse" carriers, these nanostructures effectively circumvent cellular membrane barriers and facilitate targeted ion delivery to cancer cells through endocytosis-mediated uptake. Their therapeutic selectivity stems from cancer cells' inherent vulnerability to osmotic perturbations, enabling preferential targeting of malignant tissues. Furthermore, the biodegradable characteristics of these nanoparticles address key limitations of conventional chemotherapy by minimizing long-term tissue accumulation and reducing systemic toxicity. This combination of targeted delivery, selective activity, and enhanced safety profile positions BINPs as promising candidates for next-generation cancer therapeutics.

Nanobiotechnology enables precise intracellular delivery and retention of pro- or anti-pyroptotic drugs through appropriate ligand modification of carriers. Customized nanobiology and nanomaterials are specifically designed to form complexes that can activate pyroptosis through dual pathways or simultaneously activate pyroptosis and modify the tumor microenvironment. This approach enhances anti-tumor immune effects compared to traditional therapies that can only conduct anti-tumor immunotherapy through a single pathway, offering new therapeutic strategies for immunologically "cold" tumors. Table 2 summarized the important research on the strategy of targeting pyroptosis to enhance tumor immunotherapy.

Targeting pyroptosis to enhance tumor immunotherapy

Given the crucial role of pyroptosis in modulating anti-tumor immunity, targeting pyroptosis represents a promising strategy to enhance immunotherapy outcomes. Recent studies have explored various approaches to harness pyroptosis-mediated immune responses in combination with established immunotherapies. Here, we discuss emerging strategies that combine pyroptosis induction with ICIs, cellular immunotherapy, and tumor vaccines to achieve superior therapeutic efficacy.

Immune checkpoint inhibitor

ICIs, a prominent form of immunotherapy, have received significant attention as compelling treatment options [236]. Among immune checkpoint regulators, CTLA-4, PD-1, and PD-L1 are prominent, drawing substantial interest in the field of oncology as promising and powerful targets for cancer therapeutics [237]. However, immune checkpoint blockade (ICB) therapy shows promise, it often proves insufficient to overcome immune escape mechanisms [237]. PD-L1 interaction with PD-1 on T cells suppresses target recognition and T cell function, and tumor cells frequently evade immune surveillance by expressing immune checkpoint molecules such as PD-L1 [238]. Recent single-cell transcriptome analysis in melanoma has revealed that pyroptosis-related genes (PRGs) are predominantly expressed in immune cells, particularly $CD8^+$ T cells and NK cells, with their reduced presence correlating with decreased immunotherapy efficacy [239]. Xu et al. analyzed expression profiles of 52 PRGs in bladder cancer patients and identified four distinct PRG-based subtypes [240]. CXCL9/CXCL10 are upregulated in immune-hot tumors whereas SPINK1/DHES9 are upregulated in immune-cold ones. This finding suggests connections between PRGs, TIME and immunotherapy efficacy [240]. Studies have shown that inducing tumor cell pyroptosis can increase tumor sensitivity to ICB (such as anti-PD-L1 treatment), thereby improving immunotherapy efficacy [130, 241]. Notably, while PD-L1 expression in tumor cells does

Table 2 pyroptosis-targeted anti-tumor strategies

Drug/ Strategy	Target	Cancer	Mechanism	Impact on Tumor Immunotherapy	Ref.
DHA	NLRP3, caspase-1, GSDMD	BC	Activates caspase-1, induces GSDMD cleavage, promotes IL-1β secretion, facilitates HMGB1 cytoplasmic translocation.	Enhances anti-tumor immune cell activity, promotes anti-tumor factors, reduces immunosuppressive cells, strengthens anti-tumor immune response.	[160]
siRNA- lncRNA-XIST	NLRP3, caspase-1, SOD2	NSCLC	Induces pyroptosis through ROS level upregulation and NLRP3 inflammasome activation	Influences tumor microenvironment through ROS and inflammatory response regulation	[162]
cisplatin	NLRP3, caspase-1, GSDMD	TNBC	Activates NLRP3/caspase-1/GSDMD pathway through long non-coding RNA MEG3 upregulation	Enhances immune response in TME, improves chemotherapy sensitivity	[195]
Anthocyanin	NLRP3, caspase-1, GSDMD, IL-1β	OSCC	Activates NLRP3/caspase-1 pathway, induces GSDMD cleavage,	Enhances anti-tumor immune response, improves chemotherapy sensitivity	[275]
FL118	NLRP3, caspase-1, IL-1β	CC	Activates NLRP3 inflammasome, promotes caspase-1 activation, increases GSDMD expression	Inhibits colorectal cancer cell proliferation, migration, and metastasis, enhances tumor cell sensitivity, promotes local inflammatory response	[276]
siRNA- ATP5F1D	NLRP3, caspase-1	EC	Reduces mitochondrial ROS levels, suppresses NLRP3 inflammasome activation	Affects TME inflammatory response	[277]
XCT790	NLRP3, caspase-1, GSDMD	En-C	Promotes pyroptosis through ERRα downregulation	Enhances cisplatin sensitivity, improves immune response	[278]
Dasatinib	NLRP3, caspase-1, GSDMD	PC, LC	Restores GSDMD activity by countering β5-integrin-mediated suppression through Src-STAT3 pathway	Improves chemotherapy response, enhances immune response	[279]
Doxorubicin	DFNA5, caspase-3	Melanoma	Activates caspase-3 to cleave DFNA5, induces GSDM-mediated pyroptosis	Enhances anti-tumor immune response, increases chemotherapy sensitivity	[280]
4-HBA	caspase-1	LC	Induces transcription of caspase-1 encoding genes	Promotes immune cell recruitment, enhances tumor immune response	[281]
α-NETA	caspase-4, GSDMD	OC	Induces pyroptosis through activation of GSDMD/caspase-4 pathway	Functions both as a direct cytotoxic agent, enhances anti-tumor immunity	[181]
Iron	Tom20, ROS, GSDME	Melanoma	Enhances ROS signaling, leads to Tom20 oxidation and aggregation, promotes Bax transport to mitochondria, releases cytochrome c, activates caspase-3, induces GSDME cleavage	Enhances anti-tumor immune response, promotes tumor cell death	[282]
neobractatin	Tom20, ROS, GSDME	Es-C	Induces GSDME cleavage through ROS/TOM20/BAX signaling pathway	Enhances immune response through pyroptosis induction, inhibits tumor growth	[283]
L61H10	NF-κB, caspase-3, GSDME	LC	Induces pyroptosis through NF-κB pathway inhibition, triggers G2/M phase arrest, promotes transition from apoptosis to pyroptosis	Enhances anti-tumor immune response through transition from apoptosis to pyroptosis	[102]
N-substituted EF24 analog 13d	NF-κB, caspase-3, GSDME	LC	Induces transition from apoptosis to pyroptosis through NF-κB activity inhibition	Enhances anti-tumor immune response through transition from apoptosis to pyroptosis	[103]
BI2536	caspase-3, GSDME	ESCC	Induces caspase-3 activation and GSDME cleavage	Enhances immunotherapy sensitivity	[158]
Tanshinone II A	miR-145, caspase-3, caspase-9, GSDMD	CC	Induces pyroptosis through GSDMD upregulation and caspase-3/9 activation	Enhances anti-tumor immune response	[161]
cisplatin	caspase-3, GSDME	LC	Induces caspase-3 activation, cleaves GSDME, leading to pyroptosis and secondary necrosis	Enhances immunotherapy efficacy through pyroptosis induction and immune response activation	[170]
Paclitaxel	caspase-3, GSDME	LC	Activates caspase-3, leads to GSDME cleavage, induces both pyroptosis and apoptosis	Enhances anti-tumor immune response	[170]

Table 2 (continued)

Drug/ Strategy	Target	Cancer	Mechanism	Impact on Tumor Immunotherapy	Ref.
Chalcone Derivative 8	caspase-3	LC	Induces ROS level upregulation	Enhances anti-tumor immune response	[173]
GLE	ROS, caspase-3	BC	Elevates ROS level, activates caspase-3 / GSDME	Prevents capillary tube formation, inhibits tumor adhesion, migration	[174]
5-FU	caspase-3, GSDME	GC	Induces pyroptosis through caspase-3-mediated GSDME cleavage	Improves immunotherapy efficacy through altered cell death mechanisms, affects chemotherapy tolerance	[224]
Pladienolide B	Caspase-3, GSDME	OC	Inhibits SF3B1, reduces BCL2L2, induces caspase-3/GSDME-mediated pyroptosis, releases mtDNA	Activates macrophages via cGAS-STING, increases CTL infiltration, synergizes with immunotherapy, upregulates PD-L1	[244]
Cisplatin	Capase-3/GSDME	SCLC			
IR700DX-6T	Mitochondria (TSPO) caspase-3	CRC	Generates ROS, activates p38/MAPK/caspase-3 signaling cascade	Promotes DCs maturation and $CD8^+$T cell infiltration, sensitizes to immunotherapy	[284]
CAP	ROS, caspase-9, caspase-3, GSDME	LC, GC	Activates caspase-9 and caspase-3 through ROS generation, leads to GSDME cleavage and pyroptosis	Enhances anti-tumor immune response	[285]
PL analogue L50377	ROS, caspase-3, GSDME	NSCLC	Inhibits NF-κB through ROS generation, leading to pyroptosis	Enhances anti-tumor immune response	[286]
Decitabine + CAP	ROS, caspase-3, GSDME	OC	Upregulates GSDME through DFNA5 gene demethylation, activates caspase-3, inducing pyroptosis	Enhances anti-tumor immune response	[287]
CDT	ROS, caspase-9, caspase-3, GSDME	CRC	Induces GSDME cleavage through ROS/caspase-9/caspase-3 pathway	Enhances anti-tumor immune response	[288]
galanin	caspase-3, GSDME	GBM	Induces both apoptosis and pyroptosis through GSDME and caspase-3 pathway activation	Enhances anti-tumor immune response through dual cell death pathway activation	[289]
Tetraarsenic Hexoxide	caspase-3, GSDME	TNBC	Induces pyroptosis through mitochondrial ROS generation and STAT3 phosphorylation inhibition	Enhances anti-tumor immune response	[290]
Decitabine + Paclitaxel	GSDME	BC (MCF-7/ Taxol resistant)	Reverse GSDME enhancer methylation, increases GSDME expression, enables Paclitaxel-induced caspase-3 activation	Restores chemosensitivity to Paclitaxel	[182]
Decitabine	GSDME	OSCC	Reverse GSDME enhancer methylation, increases GSDME expression, enables cisplatin-induced caspase-3 activation	Restores chemosensitivity to cisplatin	[183]
Euphohelioscopin A	GSDME	NSCLC	Activates PKC in NK cells, produces IFN-γ, upregulates GSDME expression	Enhances NK cell-mediated tumor lysis, promotes NK-dependent tumor regression in vivo	[185]
LPS	GSDMD	CRC	Induces pyroptosis through GSDMD expression and GSDMD-N membrane translocation	Enhances tumor cell sensitivity to immune cells, improves chemotherapy efficacy	[186]
Osthole	GSDME	OC	Triggers GSDME-dependent pyroptosis through GSDME expression induction	Enhances anti-tumor immune response	[188]
Disulfiram	GSDMD	CRC	Prevents GSDMD pore formation through covalent modification at Cys191	Enhances immune cell recognition and killing of tumor cells	[199]
Apcin	GSDME	PCa	Inhibits CDC20-mediated GSDME ubiquitination, increases GSDME levels, shifts to pyroptosis	Promotes $CD8^+$T cell infiltration, synergizes with anti-PD-L1 therapy, enhances anti-tumor immunity	[243]
Decitabine	GSDME	CRC	Inhibits DNMT1, reverses KIAA1199-mediated GSDME methylation, increases GSDME expression	Reverses immunotherapy resistance associated with high KIAA1199, enhances $CD8^+$T cells infiltration, synergizes with ICIs	[184]
Curcumin	ROS, GSDME	HCC	Induces pyroptosis through ROS upregulation and GSDME activation	Promotes anti-cancer effects through apoptosis and pyroptosis regulation	[291]

Table 2 (continued)

Drug/ Strategy	Target	Cancer	Mechanism	Impact on Tumor Immunotherapy	Ref.
cadmium	GSDME	TNBC	Induces pyroptosis through ROS generation and NLRP3 inflammasome activation	Enhances anti-tumor immune response, affects immune cell activity	[292]
ORFV	GSDME	PC, melanoma	Induces pyroptosis through caspase-3 activation and GSDME cleavage	Promotes $CD8^+$T cell infiltration, enhances anti-tumor immune response	[273]
GOx-Mn/HA NPs	GSDMD	BC	Induces tumor cell pyroptosis through tumor glucose metabolism regulation, combined with anti-PD-L1	Increases PD-L1 expression, activates T cells, enhances anti-PD-L1 immunotherapy efficacy	[217]
$GSDMB^{NT}$ mRNA@LNPs	GSDMB	BC	Delivers $GSDMB^{NT}$ mRNA into tumor cells	Enhances response to anti-PD-1 therapy, increases proinflammatory cytokines, promotes DCs maturation, enhances T cell infiltration	[230]
NP-NH-D5	NLRP3	BC, PC	Accumulates lysosomes, assembles in situ nanofiber, triggers LMP, releases CatB, activates NLRP3	Enhances DCs maturation and T cells infiltration, reduces Tregs, inhibits metastasis	[227]
FeMn@R@H	NLRP3	BC	Activates NLRP3 inflammasome through Fe^{2+} and Mn^{2+} release in acidic microenvironment	Induces immunogenic cell death, promotes anti-tumor immune response, enhances DC maturation	[293]
Pd2Sn@GOx-SP	NLRP3	CRC	Induces pyroptosis and disulfidptosis through catalytic ROS generation	Promotes anti-tumor immune response through immunogenic cellular content release, enhances T cell infiltration	[294]
TBD-3 C	ROS, caspase-1, GSDMD	PC	Induces pyroptosis through photodynamic therapy-activated GSDMD cleavage	Promotes M1 macrophage polarization, dendritic cell maturation, and $CD8^+$T cell activation	[267]
YBS-BMS NPs-RKC	ROS, caspase-1, GSDMD	PC	Induces immunogenic pyroptosis through NIR-activated ROS generation	Promotes $CD8^+$ T cell infiltration and enhances anti-tumor immune response	[226]
$C_4H_4Na_2O_4$ NPs	ROS, caspase-1, GSDMD	BC	Ionic overload triggers oxidative stress and activates caspase-1	Upregulates MHC-I expression, avoids tumor evasion, enhances antigen presentation	[207]
PSCT NPs	Caspase-1, GSDMD, α-KG, GSDMC	BC	Activates caspase-1/GSDMD and caspase-8/GSDMC-mediated pyroptosis through sodium ion and citrate release	Induces immunogenic cell death, enhances anti-tumor immune response	[213]
HSA@Tz-Ru1	ROS, caspase-1, GSDMD	BC	Activates pyroptosis via ROS generation, activates caspase-1	Two types of ROS lead to significant membrane disruption, enhances anti-tumor immune response	[219]
P.CNF/5-FU	Caspase-1	BC	Activates inflammasome complex and caspase-1, generates ROS, modulates p53 pathway	Enhances anti-tumor immune response, supports hASCs, promotes tissue regeneration	[225]
Cu-Pic/HA NPs	caspase-1, GSDMD	BC	Depletes polyamines, accumulates ROS	Enhances pyroptosis and cuproptosis	[232]
K_3ZrF_7:Yb/Er	ROS, caspase-1, GSDMD	BC	Releases $K^+$and $[ZrF7]^{3-}$ ions, accumulates ROS, activates caspase-1	Enhances DCs maturation, increases T cells, inhibits tumor growth and metastasis	[234]
Na_3ZrF_7:x%Yb^{3+}	Caspase-1, GSDMD	BC	Ion overload from nanoparticles induces ROS generation, mitochondrial damage	Enhances antitumor immunity, promotes T cell infiltration, and reduces tumor growth	[235]
NaHCO3 NPs	ROS, caspase-1, GSDMD	BC	Induces pyroptosis through lactate metabolism regulation and increases intracellular osmotic pressure	Reverses tumor microenvironment acidity, enhances anti-tumor immune response	[295]
Au–Cu2-xSe@ZIF-8	Caspase-1, GSDMD	Melanoma	Regulates zinc ion levels, induces DNA damage	Enhances anti-tumor immune response	[296]
NIR-II Z1 NPs	ROS, caspase-1, GSDMD	BC	Produces type-I ROS upon irradiation, causes mitochondrial dysfunction	Combined pyroptosis and apoptosis augments immunotherapy, overcomes apoptosis resistance	[284]
MS-275 +V-9302	Caspase-1, GSDMD	UVM	Inhibits mTOR pathway, reduces glutamine uptake, accumulates ROS	Recruits immune cells, enhances immune memory	[297]
As_2O_3-NPs	Caspase-3, GSDME	HCC	Induces G2/M phase arrest and apoptosis, activates caspase-3	Enhances anti-tumor immune response	[187]

Table 2 (continued)

Drug/ Strategy	Target	Cancer	Mechanism	Impact on Tumor Immunotherapy	Ref.
Photocatalytic carbon dots	ROS, caspase-3, GSDME	Melanoma, BC	Generates hydroxyl radicals, decreases pH values under radiation, accumulates ROS	Activates antigen-presenting cells, inhibits cancer stem cells, forms long-memory T cells for further tumor prevention	[208]
COF-919	ROS, caspase-3	BC	Generates ROS, leads to lipid peroxidation, activates GPX4-mediated ferroptosis and caspase-3-mediated pyroptosis	Triggers ferroptosis and pyroptosis simultaneously, improves the response rate of immunotherapy	[214]
HCNP	ROS, caspase-3, GSDME	LC	Accumulates ROS under laser irradiation, activates caspase-3, cleavage of GSDME	Enhances effectiveness of immunotherapy, stimulates antitumor immunity	[218]
$TiO_{2-x}F_x$	ROS, caspase-3, GSDME	CC	Increases oxygen vacancies, improves sono-catalytic efficiency, accumulates ROS	Increases DC maturation, enhances T cell infiltration, reduces M2-polarized macrophages, inhibits tumor recurrence, enhances penetration depth	[220]
Nano-CD	GSDME, caspase-3	Melanoma	Co-delivers CRISPRa plasmid (sgRNA for GSDME) and cisplatin. CRISPRa upregulates GSDME; Cisplatin activates Caspase-3	Enhances DCs maturation and T cells responses, inhibits recurrence and metastasis, synergizes with immunotherapy	[228]
PL@SD	GSDME, caspase-3	BC	DEC upregulates GSDME, SN38 activates caspase-3 and causes DNA damage, activates cGAS-STING	Induces apoptosis-to-pyroptosis switch, enhances DCs maturation, improves innate and adaptive immunity	[229]
Cu-THBQ/AX	ROS, caspase-3, GSDME	BC	Generates ROS, triggers caspase-3, induces the oligomerization of dihydrolipoamide S-acetyltransferase	Pyroptosis, cuproptosis and necrosis results in inflammatory TME, enhances antigen presentation	[231]
$Bi_2Sn_2O_7$	Caspase-3, NLRP3, GSDMD, caspase-1, p-MLKL, RIPK3	HCC	Generates ROS, induces PANoptosis	Triggers PANoptosis, overcomes therapeutic resistance	[233]
CaZCH NPs	ROS, caspase-3, GSDME	CRC	Induces pyroptosis through Ca^{2+}, H_2O_2, and CUR release in acidic environment, leads to mitochondrial Ca^{2+} overload and oxidative stress	Enhances anti-tumor immune response and tumor-associated macrophage reprogram	[298]
M-Cu-T	ROS, caspase-3, GSDME	LC	Induces pyroptosis through photo-activated ROS generation, depletes GSH, activates caspase-3/GSDME pathway	Induces immunogenic cell death, releases DAMPs, enhances anti-tumor immune response	[299]
PHDT-Pt-In	Caspase-3, GSDME	PC	Enhances platinum drug-induced pyroptosis through COX-2 expression inhibition	Increases secretion of immune-promoting factors, promotes CD8 + T cell infiltration	[300]
MCPP	ROS, caspase-3, GSDME	CRC	Releases PTX and ROS, activates caspase-3/ GSDME pathway	Promotes DCs maturation and T cells proliferation, forms memory T cells, enhances ICB therapy	[301]
MPNPs	ROS, caspase-3, GSDME	TNBC	Inhibits STAT3, reduces tumor stemness, generates ROS	Stimulates T cells infiltration, reduces immunosuppressive cells	[302]
MF@SOR	Caspase-1/3, GSDMD, GSDME	HCC	Fe^{3+} activates caspase-1, SOR activates caspase-3	Promotes DCs matration, activates cGAS-STING pathway, reduces tumor recurrence and metastasis	[303]
MMSN-cRGD@Ce6	ROS, Caspase-1/3, GSDMD, GSDME	BC	Generates ROS, mitigates hypoxia, activates caspase-1/3	Promotes immune responses, reduces tumor growth, enhances antitumor efficacy	[304]
GM@LR	Caspase-3, GSDME	TNBC	MnCO generates Mn^{2+} and CO, activates caspase-3 to cleave GSDME	Enhances antitumor immune response, promotes DCs maturation, activates CD8 + T cells.	[305]
nano-Erda@PLT	Caspase-3, GSDME	BLC	Erda activated by ADP, triggers caspase-3, cleaves GSDME	Enhances targeted drug delivery, stimulates immune response	[306]
OPDEA-PDCA	Caspase-3, GSDMD	OS	Inhibits PDHK1, accumulates ROS, releases cytochrome C	Enhances antitumor immune response, reshapes TME	[307]
TPL@TFBF	Caspase-3, GSDME	Melanoma	Inhibits Nrf2, reduces glutathione synthesis, elevates ROS	Enhances DCs maturation, combines with ICB to enhances antitumor efficacy, inhibits metastasis	[308]

Table 2 (continued)

Drug/ Strategy	Target	Cancer	Mechanism	Impact on Tumor Immunotherapy	Ref.
CG/RH-NPs	Caspase-3, GSDME	BC	Ca^{2+} overload activates ROS generation, CQ blocks autophagy	Enhances $CD8^+$ T cell infiltration, promotes tumor immune response, suppresses metastasis	[309]
Apt-OMVs	LPS, caspase-4, GSDMD	BC	Delivers LPS into the tumor cells, triggers caspase-4/5 and caspase-11	Triggers LPS noncanonical pathway, enhances antitumor immunity, reshape TME	[310]

GSDMD, gasdermin D; ROS, reactive oxygen species, HMGB1, high mobility group box 1; SOD2, superoxide dismutase 2; NLRP3, NOD-, LRR- and pyrin domain-containing protein 3; ERRα, Estrogen-Related Receptor alpha; STAT3, Signal transducer and activator of transcription 3; DFNA5, deafness autosomal dominant 5; Tom20, translocase of the outer mitochondrial membrane complex subunit 20; DC, dendritic cell; hASCs, human adipose-derived stem cells; NIR, near-infrared; GSH, glutathione; PTX, paclitaxel; cGAS-STING, cyclic GMP-AMP synthase-stimulator of interferon genes pathway; CQ, chloroquine; LPS, lipopolysaccharides; ICB, immune checkpoint blockade; Nrf2, Nuclear factor erythroid 2-related factor 2; PDHK1, pyruvate dehydrogenase kinase1; BC, breast cancer; OSCC, oral squamous cell carcinoma; CC, cervical cancer; CRC, colorectal cancer; En-C, Endometrial cancer; PC, pancreatic cancer; PCa, prostate cancer; LC, lung cancer; OC, ovarian cancer; Es-C, esophageal cancer; HCC, hepatocellular carcinoma; TNBC, triple-negative breast cancer; UVM, uveal melanoma; BLC, bladder cancer; OS, osteosarcoma; ESCC, esophageal squamous-cell carcinoma; GC, gastric cancer; GBM: glioblastoma; LMP, lysosomal membrane permeabilization

not significantly affect tumor growth in immunocompetent mice, combining GSDMB activation with anti-PD-L1 antibodies substantially hampers tumor progression [130, 242]. CDC20, an E3 ubiquitin ligase significantly overexpressed in prostate cancer, promotes the proteasomal degradation of GSDME through ubiquitination [243]. Inhibition of CDC20 increases GSDME levels, shifting cell death from apoptosis to pyroptosis and thereby enhancing the therapeutic efficacy of anti-PD-1 immunotherapy [243]. Decitabine enhances the efficacy of ICIs by inhibiting DNMT1, thereby reversing the epigenetic silencing of GSDME and restoring pyroptosis [184]. This reactivation promotes $CD8^+$ T cell infiltration and offers a potential strategy to overcome immunotherapy resistance in tumors with high KIAA1199 expression [184]. By targeting KIAA1199/DNMT1/GSDME axis with the combination of decitabine and ICIs can overcome immunotherapy resistance in CRC [184]. Pladienolide B inhibits splicing factor 3b subunit 1 (SF3B1), induces pyroptosis in ovarian cancer cells via caspase-3/GSDME and upregulates PD-L1 expression on tumor cells, and therefore enhancing antitumor effects [244]. PD-L1 functions not only as an immune checkpoint but also possesses nuclear transcriptional activity. Under hypoxic conditions, PD-L1 binds to p-Y705-STAT3, promoting GSDMC transcription and subsequently inducing pyroptosis through caspase-8 cleavage [245]. An integrated strategy that combines pro-inflammatory cytokines released by pyroptotic cells with immune checkpoint blockade can effectively boost immune activation, enhance immune cell infiltration, and synergistically facilitate tumor clearance. In immune cells, particularly T cells, pyroptosis-mediated inflammation affects multiple checkpoint molecules. GSDMD-mediated pyroptosis in T cells can influence PD-1 expression, potentially through inflammatory signaling pathways involving caspase-1 [246]. Combination of ICIs with chemotherapy shows potential in improving patients' outcomes. For example, cisplatin, a chemotherapy agent known to induce GSDME-mediated pyroptosis in susceptible cells, has been shown to enhance the efficacy of PD-L1 inhibitors specifically in small-cell lung cancer (SCLC) [247]. Xu et al. elucidated that this synergy relies on GSDME expression, where cisplatin-induced pyroptosis activates the IL12RB1-IL12 pathway, subsequently improving $CD4^+$ effector memory T cell responses and reshaping the tumor microenvironment [247]. While the specific mechanisms of CTLA-4 activity remain unknown, it is postulated that its presence on the surface of T cells dampens T cell activation [248]. This occurs through the active conveyance of inhibitory signals to T cells, achieved by outcompeting CD28 in binding CD80 and CD86 [248].

Beyond PD-1/PD-L1 and CTLA-4, emerging checkpoints like T-cell Immunoglobulin and Mucin-domain containing-3 (TIM-3) and Lymphocyte Activation Gene 3 (LAG3) are being explored in clinical trials [249]. TIM-3, expressed on exhausted T cells and myeloid cells, synergizes with PD-1 blockade in preclinical models, though its expression varies across cancers [249, 250]. Zhuang et al. analyzed the correlation between pyroptosis-related risk scores and immune checkpoint expression [251]. The study hypothesizes that pyroptosis remodels the immune microenvironment, potentially activating cancer stem cells (CSCs) and promoting metastasis, which could explain the poor prognosis associated with high TIM-3 expression [251]. Similarly, LAG3 is linked to T cell dysfunction in immunosuppressive TMEs, though direct evidence of pyroptosis-driven regulation is lacking [250, 252]. V-domain Ig suppressor of T cell activation (VISTA) expression is highest in the most hypoxic and inflammatory regions of tumors, suggesting inflammation helps create specialized niches where VISTA's immunosuppressive activity is maximized [253]. While pyroptosis-induced cytokines (e.g., IL-1β, IL-18) may indirectly upregulate these checkpoints, precise pathways remain uncharacterized [254, 255]. The interplay between pyroptosis-induced inflammatory microenvironment and immune checkpoint regulation provides a plausible mechanism by which pyroptosis could influence these immune checkpoints expression. Further research is needed to elucidate the precise molecular pathways involved.

By targeting both inflammatory pathways and immune checkpoints, this dual approach can potentially transform immunologically "cold" tumors into "hot" ones, significantly enhancing cancer immunotherapy outcomes. Uncontrolled inflammation can adversely impact the body, but inducing pyroptosis strategically and within certain limits to modulate the tumor microenvironment can transform inflammation into a potent tool for boosting anti-tumor immune responses and enhancing the efficacy of ICB therapy.

Adoptive cell therapy

Cellular immunotherapy is continually evolving, offering new treatment options for cancer patients. Among these, adoptive cell therapies—such as CART and CARNK cell therapies—have garnered significant attention. CART cell therapy involves the genetic modification of T cells to express chimeric antigen receptors (CARs) that specifically target tumor antigens [256]. These modified T cells target inhibitory signaling molecules present in tumor cells [257]. Major limitations include life-threatening toxicities, limited efficacy against solid tumors, resistance to B cell malignancies, antigen escape, limited persistence, poor trafficking, tumor infiltration, and as well as the presence of an immunosuppressive microenvironment [258]. When CART cells engage tumor cells, they release granzyme B, which rapidly activates caspase-3 in the target cells [74]. This activation results in the cleavage of GSDME, triggering pyroptosis—a form of inflammatory, lytic cell death [74]. Similarly, CAR-NK cells induce pyroptosis via GzmA and GzmB. GzmA cleaves GSDMB and GzmB activates GSDME, collectively leading to effective tumor cell lysis and subsequent immune activation [259]. A chimeric costimulatory converting receptor (CCCR) -modified NK92 cells exhibited enhanced antitumor immunity by inducing extensive GSDME-mediated pyroptosis in H1299 cells [260]. Notably, the cytokine profile of CARNK cells is inherently different from that of CART cells, which may translate into a lower risk of CRS and an "offtheshelf" adaptability advantage [261]. To sustain an effective anti-tumor response, T cells must not only be present in adequate numbers but also maintain their functionality and longevity to continuously attack cancer cells over time [262]. Moreover, engineered TCR therapy aims to expand the range of targetable tumor-associated antigens. Drakes et al. have demonstrated that an inflammatory microenvironment—induced by cytokines such as IL-18—can enhance the persistence and functionality of adoptively transferred T cells, ultimately improving overall survival in preclinical models [263]. However, evidence linking engineered TCR therapy to enhanced efficacy through pyroptosis remains limited.

Pyroptosis is a double-edged sword in cellular immunotherapy. While it enhances tumor cell killing and immune activation, it also drives CRS. Strategies to harness pyroptosis—such as engineering GSDMs, combining therapies, or modulating cytokine profiles—hold promise for improving cellular immunotherapy efficacy while mitigating toxicity. Future studies should focus on tumor-specific pyroptosis induction and personalized biomarker-driven approaches.

Tumor vaccine

The principle of a tumor vaccine involves providing effective antigens and powerful immune stimulators to stimulate the patient's immune system to recognize, target, and destroy cancer cells. While traditional vaccines use exogenous antigens or whole cells, a compelling strategy involves inducing immunogenic cell death pathways, particularly pyroptosis, within the tumor itself to generate an in situ vaccine effect. By causing lytic release of TAAs alongside potent DAMPs and cytokines, pyroptosis effectively provides both the 'signal 1' (antigen) and 'signal 2' (co-stimulation/adjuvant) required for robust immune priming [133].

Various approaches are being explored to leverage for in situ vaccination. Studies have demonstrated that 293 cells, after undergoing UV-B induced pyroptosis

and being co-cultured with dendritic cells and T cells for seven days, activate cytotoxic T lymphocytes, highlighting how tumor cell death can reveal antigens to the immune system and prompt anti-tumor responses [264]. Similarly, MHC class I (H-2b)-restricted OVA257–26-specific B2Z mouse hybridoma cells and MHC class II (I-Ab)-restricted OVA323-339-specific B09710 mouse hybridoma cells can be activated by bone marrow-derived DCs loaded with dead ovalbumin (OVA)-expressing EG7 mouse thymoma cells [265]. Likewise, in immunocompetent mice, pyroptotic tumor cells can recruit T cells and clear tumor transplants, while this effect is absent in immunodeficient mice or under T cell exhaustion conditions [130]. Tumor cell pyroptosis can not only activate CTLs [266, 267], but also increase the number of $CD4^+$T and $CD8^+$T cells [130]. Pyroptosis enhances the frequency of $CD4^+$ T, $CD8^+$ T cells, and effector memory T cells, promoting lasting protective immunity. In addition, GSDME-mediated CRC cell pyroptosis increases the proportion of $CD3^+$ T cells, CTLs, and effector memory T cells, indicating the generation of robust memory responses [268]. Building on this, engineered tumor cell vaccines have been developed. Tumor cells genetically modified to overexpress full-length GSDME or chemically cleavable GSDMA3 act as potent vaccines upon induction of pyroptosis [62, 130]. He et al. genetically engineered tumor cells to overexpress GSDMD-NT and resulted in robust systemic and local anti-tumor immunity, effectively preventing the growth of subsequent wild-type tumors [269]. Pyroptosis of these engineered cells leads to enhanced phagocytosis by macrophages, improved T cell responses, clearance of primary tumors, and crucially, resistance to subsequent rechallenge with wild-type tumor cells, demonstrating the generation of immunological memory [62, 130]. Similar vaccine-like effect results have been identified in multiple studies, proving that pyroptosis-mediated immune responses can inhibit the growth of primary and metastatic tumors [217, 241, 270–272].

Beyond genetically engineered cells, therapies designed to induce pyroptosis in unmodified tumor cells in situ can also serve as vaccines. Cheng et al. utilized pyroptotic cancer cells induced by photocatalytic carbon dots as effective whole cancer cell vaccines [208]. Xu et al. employed biorthogonal-activated sonodynamic therapy to induce pyroptosis locally, effectively converting tumor cells into an in situ vaccine that enhanced systemic antitumor immunity [219]. Additionally, oncolytic parapoxvirus ovis (ORFV) demonstrates potential as a tumor vaccine by activating caspase-3-mediated GSDME cleavage, resulting in significant tumor suppression and enhanced checkpoint blockade therapy efficacy in resistant tumors [273]. Additionally, nanoparticle-induced pyroptosis can further enhance anti-tumor immunity by promoting DC maturation, increasing effector memory T cell frequency, and significantly suppressing tumor rechallenge and lung metastasis [217, 226, 234]. Bioinformatic approaches are also identifying potential antigens for more targeted vaccine development based on pyroptosis pathways. Lin et al. identified four pyroptosis-related genes (ANO6, PAK2, CHMP2B, and RAB5A) as potential mRNA vaccine antigens in pancreatic adenocarcinoma (PAAD) through bioinformatics analysis [274]. While requiring experimental validation, such computational methods provide a framework for antigen selection and patient stratification in developing pyroptosis-based mRNA vaccines, aiming to convert immunologically 'cold' tumors into 'hot' ones [274].

Collectively, these strategies highlight that inducing pyroptosis, whether through engineered cells, targeted therapies, or oncolytic agents, serves as a powerful method to generate an in situ tumor vaccine, activating potent and potentially durable systemic anti-tumor immunity.

Conclusions and future perspectives

Pyroptosis, a form of programmed cell death distinct from apoptosis, has recently gained significant attention for its potential role in anti-tumor immunity. Unlike the "quiet" cell death of apoptosis, pyroptosis involves cell membrane rupture and intense inflammatory responses, primarily driven by GSDM family proteins activated by caspases-1/3/4/11. Pyroptosis significantly alters the TIME, transforming "cold" non-immunogenic tumors into "hot" immunogenic ones, thereby activating various immune cells and modifying tumor immune escape mechanisms. The release of DAMPs and tumor-associated antigens during pyroptosis enhances the ability of DCs, cytotoxic T lymphocytes, and NK cells to recognize and eliminate pyroptotic cells, crucial for bolstering anti-tumor immunity.

Pyroptosis-targeted therapy shares similarities with chemotherapy but with reduced side effects, positioning it as a promising approach for anti-tumor immunotherapy. While pyroptosis can boost anti-tumor immunity, its dual nature may also introduce drawbacks. The main benefit of using pyroptosis in anti-tumor treatments is its potential to increase tumor immunogenicity by elevating local pro-inflammatory cytokines and tumor antigens, making tumors more detectable and susceptible to immune attacks. However, high levels of pro-inflammatory factors can lead to excessive inflammation, potentially triggering systemic inflammatory responses detrimental to patients. Uncontrolled activation of pyroptosis might also increase susceptibility to infections and could inadvertently promote tumor growth and metastasis by creating favorable conditions for cancer cell proliferation and immune evasion. Sustained

inflammation might paradoxically foster tumor growth, angiogenesis, and metastasis, or recruit immunosuppressive cells like MDSCs and Tregs, ultimately counteracting the therapeutic intent. Therefore, achieving a 'therapeutic window' of controlled, beneficial inflammation is paramount. Second, many pyroptosis executioner proteins, particularly GSDME which is activated by the common apoptotic effector caspase-3, are expressed in various normal tissues, although often at lower levels or subject to silencing in tumors. Therapeutic strategies that broadly activate caspases could induce pyroptosis in healthy GSDME-expressing cells, leading to significantly off-target toxicity. This is a major concern, as uncontrolled systemic pyroptosis could lead to excessive cytokine release, potentially mimicking aspects of cytokine release syndrome (CRS) or increasing susceptibility to infections. Strategies employing highly targeted delivery or spatially controlled activation aim to mitigate this, but achieving sufficient tumor specificity remains a key challenge. Third, the outcome of inducing pyroptosis is highly context-dependent. The intrinsic state of the tumor cell – including the expression levels of GSDMs, caspases and their upstream regulators – dictates its susceptibility to pyroptosis and the subsequent immune consequences. For example, therapies relying on GSDME cleavage will be ineffective in GSDME-low or silenced tumors unless combined with agents like Decitabine [182, 183]. Furthermore, the baseline immune status of the tumor microenvironment will influence whether the induced inflammation is beneficial or detrimental. This necessitates the development of predictive biomarker to stratify patients and tailor pyroptosis-based therapies appropriately. Regarding crosstalk among PCD, cellular decision-making is complex in terms of death pathways. Modulating one pathway might lead to compensatory activation or inhibition of others, potentially altering therapeutic outcomes in unexpected ways. Strategies like the PL@SD nanoplatform [229] deliberately leverage this switch, but unintended consequences of pathway modulation need careful investigation. Advanced drug delivery systems, particularly nanomedicine, offer potential solutions to specificity and control issues but introduce their own limitations. While nanoplatforms an achieve targeted delivery, stimuli-responsiveness, and co-delivery of synergistic agents, significant translational hurdles remain. These include challenges in scalable manufacturing, overcoming in vivo biological barriers, ensuring biocompatibility and managing potential long-term toxicity of carrier materials. For pyroptosis, imprecise nanocarrier delivery could still exacerbate off-target inflammatory toxicity.

Future research should explore how factors like GSDM expression, immune status, and the tumor microenvironment affect pyroptosis outcomes. This includes examining interactions between pyroptosis and other cell death pathways such as apoptosis, necrosis, and ferroptosis, and how these interactions influence anti-tumor immune responses. Understanding the molecular mechanisms that control switches between cell death pathways will be vital for designing therapies that can modulate these pathways as needed. Additionally, advancements in cryo-electron microscopy and tools like AlphaFold 3 are enriching our understanding of molecular structures critical to targeting pyroptotic pathways, enhancing rational drug design. Optimizing drug delivery is essential, focusing on highly targeted and controllable nanomedicine platforms with improved safety profiles. Identifying reliable biomarkers for patient selection and response monitoring is crucial for clinical success. Exploring synergies between pyroptosis and innovative technologies like CAR-T cells and oncolytic viruses may open new avenues for anti-tumor immunotherapy. Leveraging computational tools like digital twin technology may accelerate clinical translation.

In conclusion, as regulatory mechanisms of pyroptosis become clearer and methods to precisely induce pyroptosis in tumor cells improve, we anticipate the development of more effective, personalized, and less toxic strategies for targeting pyroptosis in cancer treatment, potentially offering significant benefits to patients.

Abbreviations

DAMPs	Damage-associated molecular patterns
GSDM	Gasdermin
RCD	Regulated cell death
Caspase	Cysteine aspartate specific proteases
PRRs	Pattern-recognition receptors
NLR	NOD-like receptor
NLRP1/3	NLR family pyrin domain containing 1/3
CARD	Caspase recruitment domain
NLRC4	NLR family CARD domain-containing 4
AIM2	Absent in melanoma 2
PAMPs	Pathogen-associated molecular patterns
ASC	Apoptosis-associated speck-like protein containing a CARD
DPP8/9	Dipeptidyl peptidase 8/9
TLR4	Toll-like receptor 4
MyD88	Myeloid differentiation primary response 88
TRF	Time-restricted feeding
IRAK	IL-1 receptor-associated kinase
NF-kB	Nuclear factor – kappa B
ROS	Reactive oxygen species
TTSS	Type III secretion system
dsDNA	Double-stranded DNA
PYD	Pyrin domain
PKN1/2	Protein kinase N1/2
PKC	Protein kinase C
LPS	Lipopolysaccharide
HMGB1	High mobility group box 1
Panx-1	Pannexin-1
P2RX7	P2X purinergic receptor 7
RIPK1	Receptor-interacting serine/threonine-protein kinase 1
NK	Natural killer
GzmA	Granzyme A
GzmB	Granzyme B
ERS	Endoplasmic reticulum stress
MLKL	Mixed lineage kinase domain-like protein
CRT	Calreticulin

LPC	Lysophosphatidylcholine
PS	Phosphatidylserine
ICD	Immunogenic cell death
ZBP1	Z-DNA binding protein 1
ICIs	Immune checkpoint inhibitors
DCs	Dendritic cells
MDSC	Myeloid-derived suppressor cells
TIME	Tumor immune microenvironment
TME	Tumor microenvironment
APCs	Antigen-presenting cells
TAAs	Tumor-associated antigens
CTLs	Cytotoxic T lymphocytes
NACHT	Nucleotide-binding and oligomerization domain
LDH	Lactate dehydrogenase
TNBC	Triple-negative breast cancer
DHA	Docosahexaenoic acid
GBP5	Guanylate-binding protein 5
GLE	Ganoderma lucidum extract
HUVECs	Human umbilical vein endothelial cells
PDT	Photodynamic therapy
CDT	Chemodynamic therapy
CAP	Cold atmospheric plasma
PDAC	Pancreatic ductal adenocarcinoma
TGFBR2	Transforming growth factor beta receptor 2
MSI-H	High-frequency microsatellite instability
LUAD	Lung adenocarcinoma
DNMT1	DNA methyltransferase 1
CRC	Colorectal cancer
OC	Ovarian cancer
Cyc191	Cysteine residue 191
FL-GSDMD	Full-length GSDMD
PARP1	Poly (ADP-ribose) polymerase 1
PTT	Photothermal therapy
SDT	Sonodynamic therapy
AIEgens	Aggregation-induced emission luminogens
COF	Covalent organic framework
HCNP	Human cell membrane vesicle-based nanoplatform
EPR	Enhanced permeability and retention
5-FU	5-fluorouracil
LMP	Lysosomal membrane permeabilization
LNPs	Lipid nanoparticles
MOF	Metal-organic framework
BINPs	Biodegradable inorganic nanoparticles
ICB	Immune checkpoint blockade
PRGs	Pyroptosis-related genes
SF3B1	Splicing factor 3b subunit 1
SCLC	Small-cell lung cancer
TIM3	T-cell Immunoglobulin and Mucin-domain containing-3
LAG3	Lymphocyte Activation Gene 3
CSCs	Cancer stem cells
VISTA	V-domain Ig suppressor of T cell activation
CARs	Chimeric antigen receptors
CCCR	Costimulatory converting receptor
ORFV	Oncolytic parapoxvirus ovis
PAAD	Pancreatic adenocarcinoma
CRS	Cytokine release syndrome

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Data availability
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Declarations

Ethics approval and consent to participate
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