Molecular Cancer

REVIEW

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Crosstalk of pyroptosis and cytokine in the tumor microenvironment: from mechanisms to clinical implication

Hua Wang[1,2†], Tao Wang[1,2†], Shuxiang Yan[3†], Jinxin Tang[1,2], Yibo Zhang[1,2], Liming Wang[4*], Haodong Xu[1,2,5*] and Chao Tu[1,2,6,7*]

Abstract

In the realm of cancer research, the tumor microenvironment (TME) plays a crucial role in tumor initiation and progression, shaped by complex interactions between cancer cells and surrounding non-cancerous cells. Cytokines, as essential immunomodulatory agents, are secreted by various cellular constituents within the TME, including immune cells, cancer-associated fibroblasts, and cancer cells themselves. These cytokines facilitate intricate communication networks that significantly influence tumor initiation, progression, metastasis, and immune suppression. Pyroptosis contributes to TME remodeling by promoting the release of pro-inflammatory cytokines and sustaining chronic inflammation, impacting processes such as immune escape and angiogenesis. However, challenges remain due to the complex interplay among cytokines, pyroptosis, and the TME, along with the dual effects of pyroptosis on cancer progression and therapy-related complications like cytokine release syndrome. Unraveling these complexities could facilitate strategies that balance inflammatory responses while minimizing tissue damage during therapy. This review delves into the complex crosstalk between cytokines, pyroptosis, and the TME, elucidating their contribution to tumor progression and metastasis. By synthesizing emerging therapeutic targets and innovative technologies concerning TME, this review aims to provide novel insights that could enhance treatment outcomes for cancer patients.

Keywords Pyroptosis, Cytokine, Tumor microenvironment, Mechanism, Clinical implication

[†]Hua Wang, Tao Wang and Shuxiang Yan contributed equally to this work.

*Correspondence:
Liming Wang
wangliming@hnu.edu.cn
Haodong Xu
xuhaodong@csu.edu.cn
Chao Tu
tuchao@csu.edu.cn
[1] Department of Orthopaedics, The Second Xiangya Hospital of Central South University, Changsha, Hunan 410011, China
[2] Hunan Key Laboratory of Tumor Models and Individualized Medicine, The Second Xiangya Hospital of Central South University, Changsha, Hunan 410011, China
[3] Department of Nephrology, The Second Xiangya Hospital of Central South University, Changsha, Hunan 410011, China
[4] School of Biomedical Sciences, Hunan University, Changsha, Hunan 410011, China
[5] Center for Precision Health, McWilliams School of Biomedical Informatics, The University of Texas Health Science Center at Houston, Houston, TX 77030, USA
[6] Shenzhen Research Institute of Central South University, Guangdong 518063, China
[7] Hunan Engineering Research Center of AI Medical Equipment, The Second Xiangya Hospital of Central, South University, Changsha, Hunan 410011, China

Background

Cancer represents a spectrum of diseases characterized by uncontrolled cell proliferation and is influenced by a multifaceted interplay of genetic, environmental, and microenvironmental factors [1, 2]. In tumor research, the primary focus has traditionally been on the intrinsic properties of cancer cells, such as their proliferation, apoptosis, and mechanisms of drug resistance [3, 4]. However, an increasing body of evidence underscores the necessity of viewing cancer as an intricate evolutionary and ecological process that encompasses extensive interactions between cancer cells and the tumor microenvironment (TME) [5, 6]. The TME constitutes a dynamic and supportive milieu comprising various cellular and non-cellular components, including stromal cells like cancer-associated fibroblasts (CAFs), immune cells (e.g., macrophages and neutrophils), endothelial cells, and the extracellular matrix (ECM) [7, 8]. This complex landscape facilitates sophisticated communications between cancer and non-cancerous cells through the release of soluble factors, such as cytokines and chemokines, as well as various signaling molecules and ECM components [9, 10].

Cytokines, produced by diverse cellular constituents within the TME, play a pivotal role in regulating tumor initiation, progression, and metastasis [10, 11]. For instance, CAFs release various cytokines (e.g. IL6), chemokines (e.g. CXCL12), and growth factors (e.g. LIF) that contribute to the sustenance of pro-tumor microenvironment [12–14]. Tumor-associated macrophages (TAMs) serve as a significant source of cytokines and chemokines and play a critical role in the initiation and perpetuation of chronic inflammation, which is closely associated with tumorigenesis and tumor progression [15]. TAMs secrete pro-inflammatory cytokines such as IL-1β, IL-6, and IL-23, thereby promoting tumor growth and progression in colorectal cancer and other malignancies [16–19]. Additionally, TAMs facilitate the angiogenic switch by releasing key pro-angiogenic factors, including vascular endothelial growth factors (VEGF) and IL-8, which enhance the recruitment and activation of endothelial cells and other cells that support the development of vascular networks [20–22]. Furthermore, TAMs contribute to adaptive resistance to targeted cancer therapies. For example, TAM-derived TNF-α, acting as a crucial melanoma growth factor, induces resistance to MAPK pathway inhibitors [23]. Thus, understanding the intricate crosstalk between cytokines and other signaling molecules is crucial for uncovering immune-related mechanisms of cancer development. This knowledge may lead to novel therapeutic strategies targeting the TME to disrupt tumor-promoting signaling pathways and bolster anti-tumor immunity.

In multicellular organisms, maintaining a delicate balance between cell proliferation and cell death is crucial. Regulation imbalance may result in cellular replicative immortality, hence subsequently leading to tumor formation, progression, and even therapeutic interventions [24]. In these intricate processes, programmed cell death (PCD) assumes a critical role in maintaining the internal balance [25]. Apoptosis, the most extensively studied modality of PCD, serves as a natural barrier against tumors; however, the emergence of chemotherapy resistance limits the efficacy of traditional therapies that rely solely on the induction of apoptosis [26]. Thus, in addressing apoptosis resistance, exploring novel therapeutic strategies that target non-apoptotic forms of PCD may offer effective alternatives for cancer treatment. Pyroptosis is a form of inflammatory PCD that is activated by inflammasomes. It is characterized by the cleavage of gasdermin family proteins, leading to the release of cytokines such as IL-1β and IL-18 [27, 28]. Recent years have witnessed promising descriptions of novel modes of cell death, such as cuproptosis [29], disulfidptosis [30], and ammonia-induced cell death [31]. Nevertheless, their roles within the TME and their potential clinical applications require further research and substantiation. Over the past few decades, various forms of PCD have been extensively investigated, including necroptosis, ferroptosis, and pyroptosis [32–34]. Compared with necroptosis and ferroptosis, pyroptosis is a more prevalent mechanism of immune defense that is intricately linked to immune cell infiltration into the TME across various cancers [25]. Additionally, the diversity of the gasdermin family and the complexity of inflammasomes contribute to a multifaceted regulatory network governing the pyroptosis pathway and its associated cytokines. Notably, in spite of the positive role of pyroptosis in TME, several studies have reported cytokine release syndrome, a severe side effect resulting from an exaggerated inflammatory response mediated by pyroptosis [35, 36]. Therefore, summarizing the precise mechanisms and elucidating the intricate interactions between pyroptosis and cytokines in the tumor microenvironment are significant for the development of more effective anticancer therapies.

The interplay between pyroptosis and cytokine signaling within the TME forms a complex network characterized by numerous pathways and feedback loops. However, the underlying molecular mechanism remains unclear. Pyroptosis is known to amplify inflammation and alter the TME, enhancing cytokine expression and consequently promoting cancer cell invasion and metastasis [37, 38]. Elevated levels of inflammatory cytokines have been associated with poor prognosis in cancer patients, underscoring their potential as valuable prognostic markers [10,

39]. However, the relationship between pyroptosis, cytokines, and tumor growth is multifaceted; while pyroptosis can promote tumor-promoting inflammation and enhance cancer cell invasiveness, it can also stimulate anti-tumor immune responses that inhibit tumor progression [40, 41]. Recent research has highlighted the potential of therapeutic strategies aimed at inducing pyroptosis within tumor cells. By triggering this form of cell death, it is possible to activate the immune system and bolster anti-tumor responses, thus providing a promising avenue for cancer therapy [42]. The intersection of pyroptosis and cytokine dynamics presents opportunities for innovative treatments that could modulate inflammation and immune response in the TME, potentially overcoming limitations associated with current therapies focused on apoptosis.

In this review, we provide a succinct overview of the fundamental principles and characteristics of cytokines and pyroptosis, as well as highlight their respective functions and recent advancements in the TME. Furthermore, we extensively discuss and elucidate the intricate crosstalk and connections between cytokines and pyroptosis within the TME, delving into the complex molecular mechanisms that regulate networks critical to tumor occurrence, metastasis, immune evasion, and angiogenesis. By synthesizing and summarizing emerging therapeutic targets and novel technologies (e.g. single-cell sequencing and spatial transcriptomics) in anti-tumor therapy, we hope to present novel insights that could drive future research and clinical applications aimed at improving cancer treatment outcomes in the context of tumor inflammation and immunobiology.

Definition and mechanism of pyroptosis

Pyroptosis is a notably inflammatory form of lytic PCD which has a key role in innate immunity and tumor development [34, 43, 44]. The term "pyroptosis" was initially proposed by Cookson and Brennan in 2001 to characterize this distinct process [45]. Originating from Greek roots, "pyroptosis" combines "*Pyro*," meaning fire, which signifies the inflammatory nature of this process, and "*Ptosis*," meaning to "fall off," commonly used as a suffix in cell death terminology to illustrate the falling off or dying of cells [46, 47]. Triggered by various inflammatory signals, pyroptosis exhibits both shared traits with other types of PCDs and unique characteristics like pro-inflammatory cytokines and the formation of gasdermin protein pores in the cell membrane that set it apart [48–50]. The role of diverse cytokines and related signal pathways in different PCDs were summarized (Table 1).

Various inflammasomes, triggered by stimuli originating from the extracellular or intracellular environment, serve as crucial platforms for the subsequent activation of various caspases, thereby initiating or executing cellular processes [63]. The pyroptosis pathways are distinguished by the involvement of different caspases, notably including caspase-1-dependent pathway, caspase-4/5/11-dependent pathway, and other pathways like caspase-3-dependent pathway, caspase-8-dependent pathway, caspase-free pathways, etc. (Fig. 1).

Caspase-1-dependent pathway

Caspase-1-dependent pathway is also named as canonical pyroptotic death, which is orchestrated by the assembly of inflammasomes and characterized by caspase 1 [64]. Upon recognition of PAMPs or DAMPs by classical inflammasome sensors (NLRs, AIM2, P2×7R, and

Table 1 Role of participated cytokines in diverse programmed cell death

Type	Related cytokine(s)	Direct effect	Role in TME	Peripheral reaction	Reference
Pyroptosis	IL-1β, IL-18	Inflammasome formation	Amplify inflammation, activate immune response	Inflammatory reaction	[51]
Apotosis	TNF-α, Fas	Caspase activation	Maintain cellular homeostasis, suppress inflammation	No inflammatory response	[52, 53]
Autophagy	HIF-1α	p27-E2F1 signaling pathway	Tumor angiogenesis, enhanced tumor growth	No inflammatory response	[54, 55]
Necroptosis	TNF-α, Fas, IFN-γ	RIPK3 activation, MLKL phosphorylation	Trigger inflammation	Inflammatory reaction	[56, 57]
Ferroptosis	TNF, IL-6, IL-1β	GPX4 regulation, TAM polarization	Induce inflammation-related immunosuppression	Inflammatory reaction	[58–60]
Cuproptosis	NA	NA	Promotion of tumor immune escape	Inflammatory reaction	[61]
Disulfidptosis	HMGB1	ICD hallmarks up-regulation	Antitumor immune response	Inflammatory reaction	[62]

Abbreviations: *NA* Not appliable, *IL* Interleukin, *TNF* Tumor necrosis factor, *HIF-1α* Hypoxia-inducible factor 1 α, *IFN* Interferon, *Fas* Fas receptor (CD95), *HMGB1* High mobility group box 1, *RIPK3* Receptor-interacting serine/threonine-protein kinase 3, *MLKL* Mixed lineage kinase domain-like pseudokinase, *GPX4* Glutathione peroxidase 4, *TAM* Tumor-associated macrophage, *ICD* Immunogenic cell death

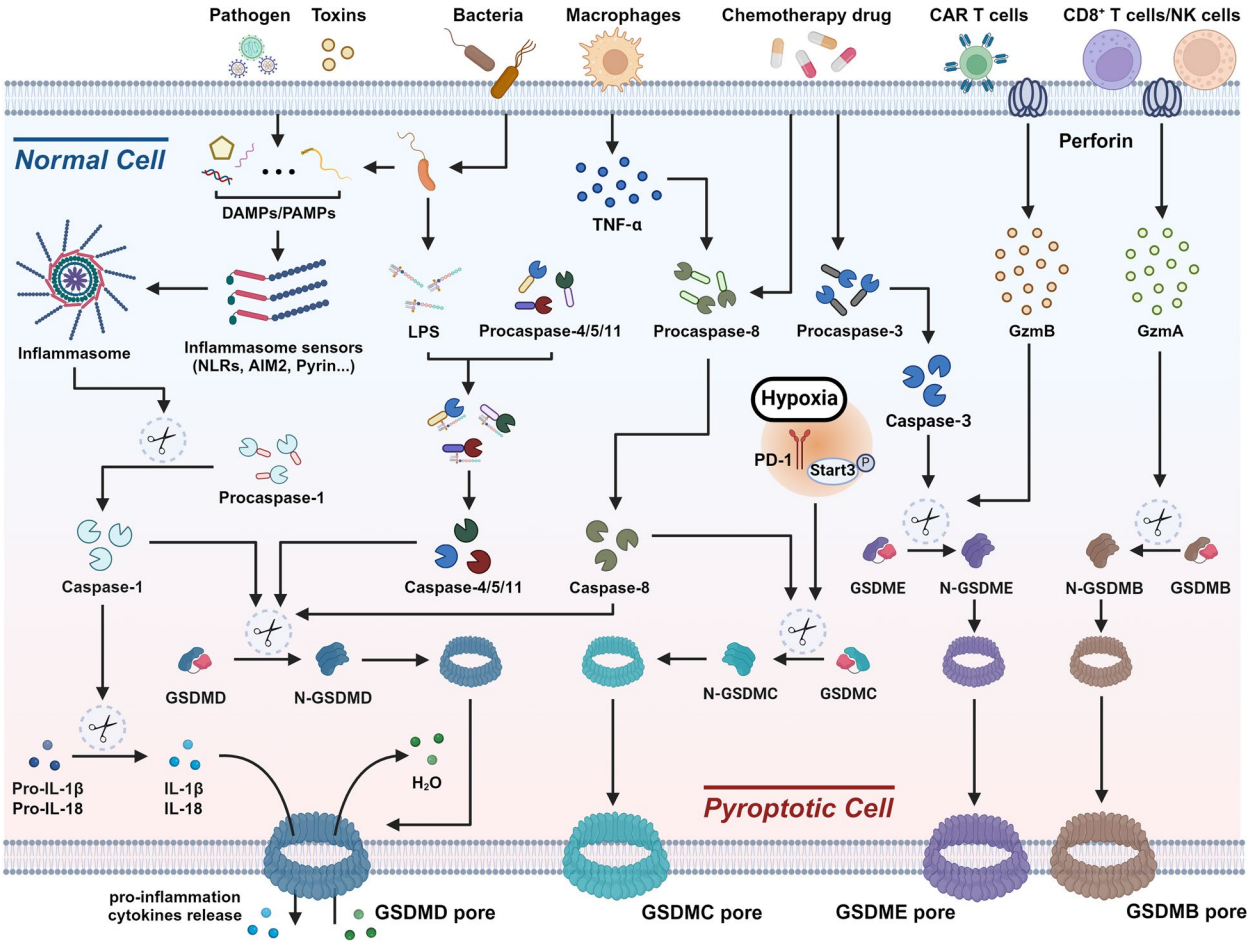

Fig. 1 Summary of the mechanism of pyroptosis. In caspase-1-dependent pathway, the inflammasome sensors triggered by DAMPs and/or PAMPs could activate caspase-1. Subsequently, a cascade of events like the cleavage of GSDMD, maturation of pro-IL-1β and pro-IL-18, release of pro-inflammation cytokines, formation of GSDMD pores and ultimately cell membrane rupture. In caspase-4/5/11-dependent pathway, inflammasome sensors can be directly activated by LPS, which is also a GSDMD-dependent pyroptotic pathway. In other pathways, caspase-3 triggers pyroptosis via GSDME while caspase-8 initiates pyroptosis via GSDMC. Additionally, pyroptosis can be activated without caspase family. CD8 + T cells and NK cells can secrete granzyme A and cause pyroptosis mediated by GSDMB, while release of granzyme B could induce pyroptosis via GSDME

pyrin), the inflammasomes undergo an automatic assembly process [65, 66]. This assembly event triggers the activation of pro-caspase-1, leading to its self-cleavage and the subsequent formation of the active p10/p20 heterotetramer [67, 68]. Upon activation, pro-caspase-1 initiates a cascade of events that include the cleavage of gasdermin D (GSDMD), resulting in the release of the functional gasdermin N-terminal fragment. Concurrently, pro-IL-1β and pro-IL-18, which are dormant precursors of the pro-inflammatory cytokine IL-1β and IL-18, are processed into their mature, secretory forms. The gasdermin N-terminal fragment translocates to the cell membrane where it interacts with acidic lipids, leading to the formation of gasdermin pores with a specific inner diameter of 10–14 nm [69]. These pores, characterized by a negative charge, play a crucial role in the selective release of IL-1β and IL-18 through electrostatic filtering mechanisms [70, 71]. The culmination of these processes ultimately results in cell membrane rupture and the induction of pyroptosis.

Caspase-4/5/11-dependent pathway

As opposed to the canonical pyroptosis featured by caspase 1, the pathway initiated by caspase-4/5 in human and caspase-11 in mice is known as a noncanonical pyroptotic pathway [72, 73]. In this alternative pathway, the inflammasome sensors can be directly activated by intracellular bacteria and lipopolysaccharide (LPS), subsequently activating caspase-4/5/11 [74, 75]. Specifically, caspase-4/5/11 have the ability to directly interact

with lipid A present in the outer membrane of Gram-negative bacteria, resulting in their oligomerization and subsequent activation [76–78]. Following activation, these caspases cleave GSDMD to release the gasdermin N-terminal p30 fragment, which has the capability to form pores leading to pyroptotic cell death [79, 80]. It is important to note that unlike the canonical pathway, caspase-4/5/11 pathways are involved in the maturation and secretion of pro-inflammatory cytokines such as IL-1β and IL-18 without directly cleaving them [81]. This distinction sets the noncanonical pathway apart from the canonical pathway in terms of its mechanism of action and downstream effects.

Other pathways

Apart from caspase-1-dependent and caspase-4/5/11-dependent pathways, pyroptosis can be triggered by caspase-3, caspase-8, and even caspase-independent pathways. Caspase-3 typically known as the executioner caspase in apoptosis [82], can cleave GSDME to release the gasdermin N-terminal that triggers pyroptosis when GSDME is highly expressed or caspase-3 is stimulated by chemotherapy drugs via the BAK/BAX-caspase-3-GSDME pathway [83]. Notably, tissue cells usually have higher expression of GSDME compared to most cancer cells, which might explain a range of chemotherapy-induced adverse effects such as inflammation and tissue damage [84, 85]. As a cell-permeable analog of α-KG, DM-αKG can activate caspase-8 in HeLa and other cancer cell lines [86]. Afterwards, the activated caspase-8 initiates the cleavage of gasdermin C (GSDMC), which subsequently ensembles and forms pores in the cell membrane [86]. This phenomenon is also observed under hypoxia conditions, PD-L1 in the nucleus together with p-Stat3 co-upregulate the expression of GSDMC, thus eventually causing pyroptosis [87]. Intriguingly, pyroptosis can be triggered without caspase family. In a study of cytokine release syndrome (CRS), CAR T cells release perforin to form pores and rapidly activate caspase 3 in target cells through the entry of granzyme B. This in turn cleaves GSDME, leading to extensive pyroptosis [35, 88]. In contrast, CD8 + T cells and NK cells can secrete granzyme A and cause pyroptosis mediated by gasdermin B (GSDMB) [89, 90].

Overview of pyroptosis and cytokine in TME

Pyroptosis is characterized by the release of pro-inflammatory cytokines such as IL-1β and IL-18 [91, 92], alongside the liberation of damage-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs) from expiring cells [93–95]. Within the TME, the pro-inflammatory cytokines emanating from pyroptotic cells play a pivotal role in fomenting inflammation and fostering the infiltration of immune cells, thereby potentially advancing tumor progression and metastasis [96–98]. Concurrently, the release of DAMPs from pyroptotic cells serves to activate immune cells and bolster the recruitment of immune cells to the TME, culminating in the initiation of anti-tumor immune responses and the suppression of tumor growth and metastasis [99, 100]. Consequently, the involvement of pyroptosis in TME restructuring and metastasis is intricate and multifaceted. The ensuing discourse will expound upon three focal points: an overview of the TME, the impact of pyroptosis on TME remodeling and metastasis, and the influence of cytokines on TME remodeling and metastasis.

Definition and composition of TME

The TME encompasses non-cancerous cells and their associated components within tumors, including the molecules they generate and release. Cancer cells directly engage with the TME and interact with non-cancerous elements, including infiltrating immune cells like TANs and TAMs, CAFs, and the extracellular matrix [101, 102]. These interactions are facilitated by signaling molecules such as cytokines and chemokines. The persistent interaction between tumor cells and the TME significantly influences the initiation, progression, metastasis, and response to treatment of tumors [103]. As a result, the TME has garnered significant research and clinical interest as a potential therapeutic target for tumors [104].

Among the diverse stromal cell populations within the TME, CAFs have been identified as the most abundant cell type [105]. The pro-tumor activities of CAFs have been extensively documented in various cancer types, including prostate cancer, breast cancer, pancreatic cancer, and colorectal cancer [13, 106–109]. TAMs, which are prevalent in the TME across different cancer types, have consistently been associated with unfavorable clinical outcomes in cancer patients [110, 111]. TANs represent a critical component of the TME and actively contribute to tumor progression and metastasis. In addition to secreting proinflammatory cytokines and chemokines, TANs also produce immunosuppressive factors such as arginase 1 and TGFβ, which effectively suppress adaptive immunity [112].

Researchers are dedicated to gaining a deeper understanding of the critical role played by the TME in tumor development and treatment resistance. By focusing on TME components, therapeutic benefits for cancer patients can be achieved. However, the successful implementation of this strategy necessitates a comprehensive understanding of the molecular and cellular distinctions between tumor-promoting host cells and normal host cells within the TME. By discerning these differences,

it becomes possible to identify specific targets within the TME that can be effectively manipulated to impede tumor progression and enhance treatment outcomes. This knowledge is crucial for the development of tailored therapeutic approaches that selectively target the TME, ultimately benefiting cancer patients.

The TME exerts a significant influence on immune cell responses, activation, differentiation, and cytokine secretion. It can either enhance the pro- or anti-tumor response, mediate inflammation, or contribute to oncogenesis depending on the interplay of cytokines. In the context of solid tumors, including breast cancer, the presence of diverse cell populations within the TME leads to intricate networks of interactions mediated by a variety of cytokines. Pyroptosis, a form of programmed cell death, can trigger the release of cytokines, facilitate the activation of macrophages and T lymphocytes, elicit a robust inflammatory response within the body, and induce immune phagocytosis [48, 113]. Furthermore, specific cytokines have been identified to regulate the expression and activation of crucial pyroptosis-related proteins, such as gasdermins [38]. This reciprocal relationship between pyroptosis and cytokine signaling transduction highlights the interconnectedness and complexity of these processes within the TME. Understanding this crosstalk is crucial for unraveling the mechanisms underlying cancer progression and developing targeted therapeutic approaches that exploit the interplay between pyroptosis and cytokine signaling.

Pyroptosis in TME remodeling and metastasis

Inducing factors of pyroptosis in TME

The TME is a complex circumstance composed of surrounding blood vessels, extracellular matrix (ECM), an array of signaling molecules and a variety of cells like immune cells, fibroblasts and so on [114–116]. Within this intricate landscape, inducing factors of pyroptosis in the TME mainly encompass inflammasome activation, pro-inflammatory cytokines, hypoxia, and therapy-related inducing factors (Fig. 2).

Inflammasome activation Inflammasomes, acting as receptors or sensors within the innate immune system, manage the activation of caspase-1 and stimulate inflammation in response to infectious microbes and molecules derived from host proteins [117]. Pattern Recognition Receptors (PRRs) are a type of immune receptor that identify PAMPs or DAMPs [118]. The stimulation of various PRRs can lead to the formation of inflammasomes within the TME. Activated PRRs promote the downstream signaling pathway, and cause type I interferons generation and pro-inflammatory cytokines release [119, 120].

So far, five PRRs (NLRP1, NLRP3, NLRC4, Pyrin, and AIM2) have been identified to form inflammasomes [65, 121]. In TME, NLRP1 has been implicated in promoting melanoma tumorigenesis by activating the inflammasome through caspase-1, while simultaneously inhibiting mitochondrial apoptosis associated with caspase-2 and caspase-9 [122]. Likewise, without NLRP3, the quantity of activated NK cells increased, leading to more IFN-γ secretion and enhanced tumor cell destruction, thereby reducing B16F10 lung metastasis [123, 124]. The activation of the NLRP3 inflammasome, induced by E2, can also initiate pyroptosis and impede autophagy in HCC cells [125]. The pro-tumor effect of microbes can be partially ascribed to the activation of inflammasomes and the subsequent stimulation of the IL-1β/NF-κB/IL-6/signal transducer and activator of transcription 3 (STAT3) pathways [126]. LPS can trigger non-standard inflammasome caspase-11-mediated pyroptosis in lung cancer cells [127]. Also, simvastatin provokes pyroptosis in A549 and H1299 cells by stimulating the NLRP3 pathway [128].

Pro-inflammatory cytokines The presence of pro-inflammatory cytokines within the TME can trigger pyroptosis in tumor cells. Tumor necrosis factor-α (TNF-α) is predominantly secreted by immune cells like macrophages, T cells, and natural killer cells upon encountering tumor cells or other activating signals [129, 130]. Studies have demonstrated that TNF-α can initiate the caspase-8-dependent pyroptotic pathway, leading to the cleavage of GSDMD and subsequent cellular swelling, lysis, and rupture [131–133]. Furthermore, IL-1β and IL-18, crucial components of pro-inflammatory cytokines, are downstream effectors of caspase-1 in the canonical pyroptotic pathway [134–136]. They significantly contribute to the peripheral inflammatory response associated with dying cells.

Hypoxia TME usually presents as hypoxic due to rapid tumor growth [137]. In hypoxic conditions, phosphorylated Stat3 physically associates with PD-L1, aiding its movement into the nucleus and boosting the transcription of GSDMC gene [87]. Upon treatment with TNFα, GSDMC is specifically cleaved by caspase-8, producing a GSDMC N-terminal domain [86, 87]. This domain forms pores on the cell membrane, leading to the induction of pyrop.

Therapy-related inducing factors Novel drug therapies can variously induce pyroptosis. ZIF-8 nanoparticles (NPs) can intrinsically induce pyroptosis by a caspase-1/GSDMD-dependent pathway [138]. Chemotherapeutic paclitaxel and cisplatin differentially induce pyroptosis in

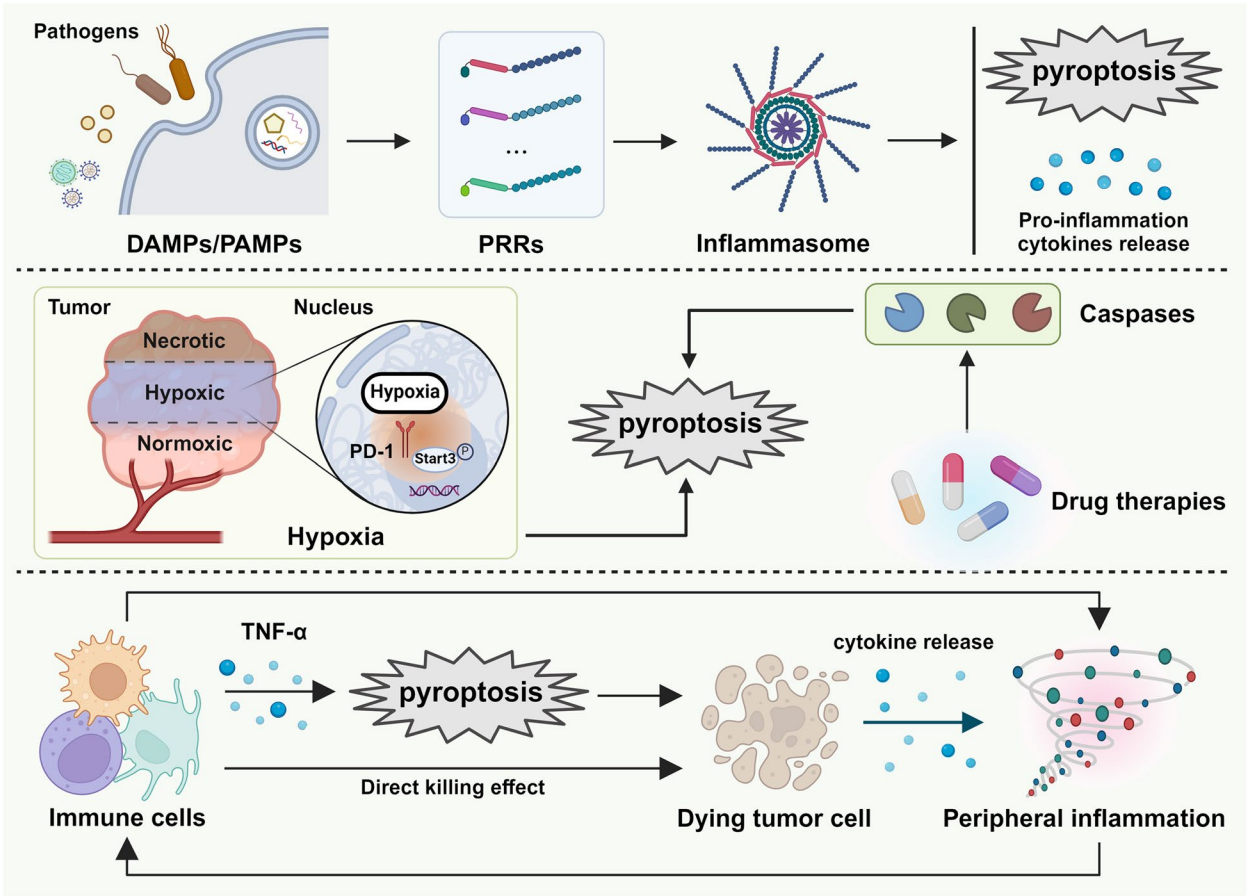

Fig. 2 The inducing factors of pyroptosis in tumor microenvironment. Inflammasome activation, pro-inflammatory cytokines, hypoxia, and drug therapies can initiate pyroptosis in the TME. PRRs identify PAMPs or DAMPs and further trigger the formation of inflammasomes within the TME. Eventually, pro-inflammatory cytokines release and pyroptosis occurs. Hypoxia in TME promotes the GSDMC-dependent pyroptosis with PD-L1 and phosphorylated Stat3. Diverse drug therapies can induce pyroptosis in multi-forms. Pro-inflammatory cytokines secreted by immune cells and released by pyroptotic tumor cells may cause peripheral inflammation, which may further recruit and activate more immune cells. Additionally, immune cells may directly kill tumor cells, thus enhancing the peripheral inflammation

A549 lung cancer cells via caspase-3/GSDME activation [139].

Role of pyroptosis in TME remodeling and metastasis

Pyroptosis serves as a pivotal mechanism in TME remodeling and metastasis through the facilitation of inflammation, activation of immune cells, and regulation of tumor cells [32, 41, 51]. The release of cytokines such as IL-1β and IL-18 via the pyroptosis pathway not only triggers inflammation and recruits immune cells but also potentially fosters tumor progression and metastasis [97, 140]. Furthermore, the discharge of DAMPs from pyroptotic cells can activate immune cells, thereby intensifying the inflammatory response and establishing a positive feedback loop [141]. This part will delve into the impact of pyroptosis in direct killing effect on tumor cells, regulation of immune cells, and the impact on tumor angiogenesis, metabolism, and metastasis (Fig. 3).

Direct killing effect on tumor cells There are two primary mechanisms through which pyroptosis mediates the killing of tumor cells: membrane lysis by gasdermins and disruption of cellular homeostasis [142, 143]. In the former, tumor cells are destroyed through cell lysis, which is mediated by the cleavage of GSDMD initiated by caspases, reducing the overall tumor burden [27]. In the latter, caspase activation can also cleave other cellular components, leading to the dysfunction of organelles, protein degradation, and metabolic shutdown, which may even ultimately contribute to cell death [144, 145].

Influence and regulation of immune cells Overall, the enrichment of pyroptosis showed a stronger positive

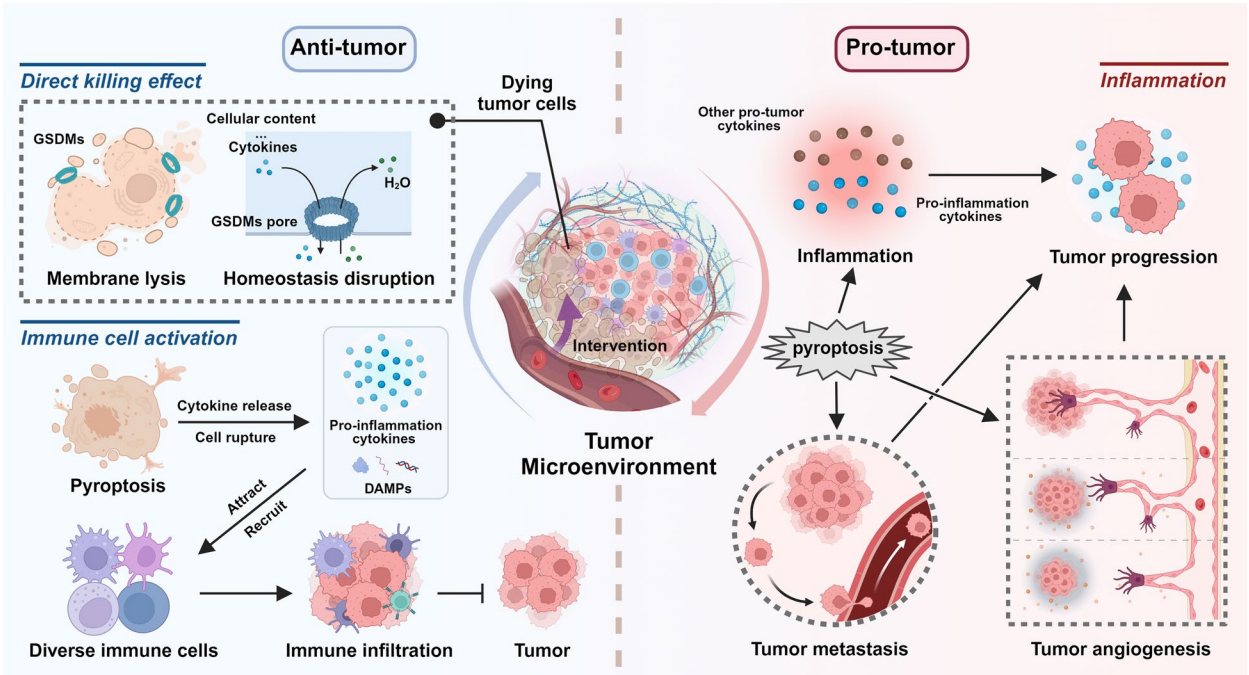

Fig. 3 Dual role of pyroptosis in tumor microenvironment remodeling and metastasis. Pyroptosis plays dual roles in TME. The anti-tumor effects could be concluded in two ways, the direct killing effect on tumor cells and immune cell activation. Membrane lysis by gasdermins and disruption of cellular homeostasis are two primary mechanisms through which pyroptosis mediates the killing of tumor cells. While dying cells may release pro-inflammation cytokines and DAMPs which may further attract and recruit immune cells. The pro-tumor effects of pyroptosis can be multifactorial. Peripheral inflammation caused by pyroptosis facilitates the tumor progression. Additionally, NLRP3 inflammasome-mediated pyroptosis can promote angiogenesis in tumors. The impact of pyroptosis on tumor metastasis is complex and context-dependent, and may enhance tumor infiltration and metastasis via IL-1 and IL-18 cytokine release

correlation with the immune score than with the stromal score [146]. Analyzing the immune composition of the TME revealed a significant positive correlation between pyroptosis levels and the infiltration of major T cell subtypes, consistent across various tumors [146, 147]. Meanwhile, pyroptosis leads to the release of DAMPs and pro-inflammatory cytokines like IL-1β and IL-18. These may further attract and activate immune cells, particularly dendritic cells, which can then prime T cells to attack cancer cells, activating adaptive immunity [148, 149].

Impact on tumor angiogenesis, metabolism, and metastasis Recent research shows that in some conditions, there is a positive correlation between angiogenic capacity and pyroptosis level which have something to do with NLRP3 inflammasome. The activation of NLRP3 inflammasome-mediated pyroptosis influences angiogenesis in endometriosis in a manner that is dependent on Notch1 [150]. NLRP3/IL-1β signaling pathway activation can also cause pathological micro-angiogenesis [151].

Theoretically, Caspase activation can disrupt essential metabolic pathways within tumor cells. However, Caspase-11 plays a significant role in maintaining dual-fuel bioenergetics glycolysis and oxidative phosphorylation (OXPHOS) to promote pyroptosis in macrophages [152]. A study also found pyroptosis leads to mitochondrial damage. GSDME promoted mitochondrial depolarization, trafficking defects, and neurite retraction. Frontotemporal dementia (FTD)/amyotrophic lateral sclerosis (ALS)-associated proteins TDP-43 and PR-50 induced GSDME-mediated damage to mitochondria and neurite loss [153].

The influence of pyroptosis on tumor metastasis is intricate and contingent on various factors. On one hand, as previously discussed, pyroptosis can exert a direct killing effect on tumor cells, thereby impeding metastasis. Moreover, the release of pro-inflammatory cytokines during pyroptosis can incite an immune response against the tumor, further hindering its spread. For instance, one study found CBD could induce an integrative stress response and mitochondrial stress in HCC tumor cells, leading to increased ATF4 activation and CHOP expression. This, in turn, promoted the expression of Bax protein from the BCL-2 family causing

caspase-3/9-GSDME-dependent pyroptosis [154]. Additionally, an immunotherapy system called Lmo@RBC-triggered GSDMC-dependent pyroptosis in tumors, can reverse the immunosuppressive TME and inhibit tumor metastasis [155]. On the other hand, The cytokine release triggered by pyroptosis, including IL-1 and IL-18, can enhance tumor infiltration, potentially increasing the likelihood of tumorigenesis and metastasis [156]. Overall, the impact of pyroptosis on tumor metastasis is complex and context-dependent. Further research is needed to fully understand the mechanisms underlying this process and to develop targeted therapies that can harness the potential anti-metastatic effects of pyroptosis.

Cytokines in TME remodeling and metastasis

Definition and types of cytokines in TME

Cytokines are small signaling proteins that play critical roles in the TME by mediating communication between cells. These signaling molecules can be broadly classified based on their functions and origins, influencing both the immune response and tumor behaviors. Cytokines serve as crucial mediators for cell communication within the TME [157]. Although cytokines like IL-2, IFNα and IFNγ play a role in anti-tumor responses within the TME [158], irregular cytokine production by malignant cells, immune cells, and stromal cells contributes to all stages of carcinogenesis and therapy responses [159]. Thus, there's therapeutic promise in utilizing cytokines' immune-stimulating effects and in mitigating their dysregulated actions [160]. Specific cytokines play a significant role in tumor development, advancement, and spread (Table 2).

Role of cytokines in TME remodeling

Cytokines play a vital role in shaping the TME by modulating immune responses and inflammation [162]. Pyroptosis, a form of inflammatory cell death, is closely linked with the action of these cytokines such as IL-1β and IL-18 [162]. These cytokines amplify local immune responses and actively recruit and activate immune cells, including macrophages and T cells, thereby further enhancing inflammation within the TME [163]. For instance, IL-1β can promote immune cell infiltration and angiogenesis, thereby contributing to tumor progression [164]. This reciprocal interaction between cytokines and pyroptosis not only remodels the TME but also influences tumor

Table 2 Different types of cytokines in tumor microenvironment

Category	Represent cytokines	Participated Pathways	Macroscopic effect	Microscopic effect	Reference
Pro-inflammatory Cytokines	IL-1β, IL-6, TNF-α	NF-κB pathway, MAPK pathway	Fever, systemic inflammation, pain, acute phase response	Immune cells recruitment, increased vascular permeability	[45]
Anti-inflammatory Cytokines	IL-10, TGF-β	JAK-STAT pathway, TGF-β/Smad pathway	Reduced inflammation and immune response, tumor growth promotion	Inhibition of immune cells, Promotion of Treg differentiation	[38, 39, 94]
Growth Factors	VEGF, EGF	PI3K/AKT pathway, MAPK/ERK pathway	Tumor angiogenesis and enhanced tumor growth	Endothelial cell proliferation and angiogenesis	[21, 103]
Chemokines	CXCL12, CCL2	GPCR signaling pathway	Immune cell recruitment, metastasis facilitation	Chemotaxis of leukocytes, increased cell migration gradients	[10, 161]
IFNs	IFN-α, IFN-β, IFN-γ	JAK-STAT pathway	Antitumor immune response, inhibited tumor cell proliferation	NK cells activation, upregulation of MHC molecules	[10, 50, 119]
CSFs	G-CSF, GM-CSF	JAK-STAT pathway, PI3K/AKT pathway	Enhanced immune recovery and white blood cell production	Stem cells proliferation and differentiation of granulocytes	[37]
TGF	TGF-β	TGF-β/Smad pathway, PI3K/AKT pathway	Tumor progression and immune suppression	Induction of EMT and inhibition of cytotoxic T cells	[146]
TNF Family	TNF-α, FasL	NF-κB pathway, MAPK pathway, Death	Increased inflammation and tumor cell death	Induction of apoptosis and inflammatory activation	[91, 93]

Abbreviations: *DNF-κB* Nuclear factor kappa B, *MAPK* Mitogen-Activated Protein Kinase, *JAK-STAT* Janus kinase/signal transducer and activator of transcription, *TGF-β/Smad* Transforming Growth Factor Beta/ SMA and MAD-related protein, *PI3K/AKT* Phosphoinositide 3-kinase/ Protein Kinase B, *MAPK/ERK* Mitogen-Activated Protein Kinase/ Extracellular Signal-Regulated Kinase, *GPCR G* Protein-Coupled Receptor, *IFNs* type I interferons, CSFs colony-stimulating factors, *TNF* tumor necrosis factor, *IL-1β* Interleukin-1 beta, *IL-6* Interleukin 6, *TNF-α* Tumor Necrosis Factor-alpha, *IL-10* Interleukin-10, *VEGF* Vascular Endothelial Growth Factor, *EGF* Epidermal Growth Factor, *CXCL12* C-X-C Motif Chemokine Ligand 12, *CCL2* C-C Motif Chemokine Ligand 2, *IFN-α* Interferon Alpha, *IFN-β* Interferon Beta, *IFN-γ* Interferon Gamma, *G-CSF* Granulocyte Colony-Stimulating Factor, *GM-CSF* Granulocyte-Macrophage Colony-Stimulating Factor, *FasL* Fas Ligand, *MHC* Major Histocompatibility Complex, *EMT* Epithelial-Mesenchymal Transition

growth and metastasis [165]. Consequently, a thorough understanding of the complex crosstalk between pyroptosis and cytokines is essential for elucidating how TME remodeling affects tumor dynamics and responses to immunotherapies [166]**.** In this context, we summarize the involvement of cytokines in the TME concisely to enhance understanding of their intricate interplay from two key perspectives: immune response and tumor progression (Fig. 4).

Immune cell-mediated pyroptosis activation and pro-inflammatory cytokines Cytokines play a pivotal role in remodeling TME, significantly influencing the behavior of tumor and immune cells [167]. In the context of pyroptosis, pro-inflammatory cytokines are not only key drivers of inflammation but also crucial mediators in pyroptotic signaling, which shapes immune cell behavior [168].

Pro-inflammatory cytokine IL-1β has been reported to accumulate in MDSCs via the IL-6-STAT3 axis in melanoma [169], suggesting its role in suppressing immune cell activity. Moreover, research indicates that M1 macrophages can induce PD-L1 expression in HCC through IL-1β [170], enabling tumor cells to evade immune responses. Additionally, IL-1β collaborates with VEGF to enhance endothelial cell permeability, promoting angiogenesis in retinal endothelial cells [171]. The induction of PD-L1 and colony-stimulating factor 1 (CSF1) through IL-1β-triggered pathways, including the αKG/HIF1α axis, promotes tumor-associated macrophage (TAM) and MDSC infiltration, underscoring the complex role of pyroptosis in immune regulation within the TME [172]. Targeting IL-1β-related pyroptotic pathways, therefore, presents a promising strategy to mitigate immune suppression and tumor progression. Tumor-infiltrating dendritic cells (DCs), crucial in orchestrating both innate and adaptive immunity, are heavily influenced by cytokines released during pyroptosis [173]. They achieve this through the high expression of class I and class II MHC complexes, adhesion molecules, and costimulatory molecules [174]. Interestingly, cytokines like IL-10 and TGF-β, also prevalent in the TME, can skew DCs toward a tolerogenic phenotype, dampening immune responses. The dual role of pyroptosis in either promoting immune activation or contributing to immunosuppressive environments hinges on the balance of these cytokines, reflecting its complex regulatory role in immune surveillance within the TME [168].

Pro-inflammatory cytokines also participate in natural killer (NK) cells mediated-pyroptosis activation. The

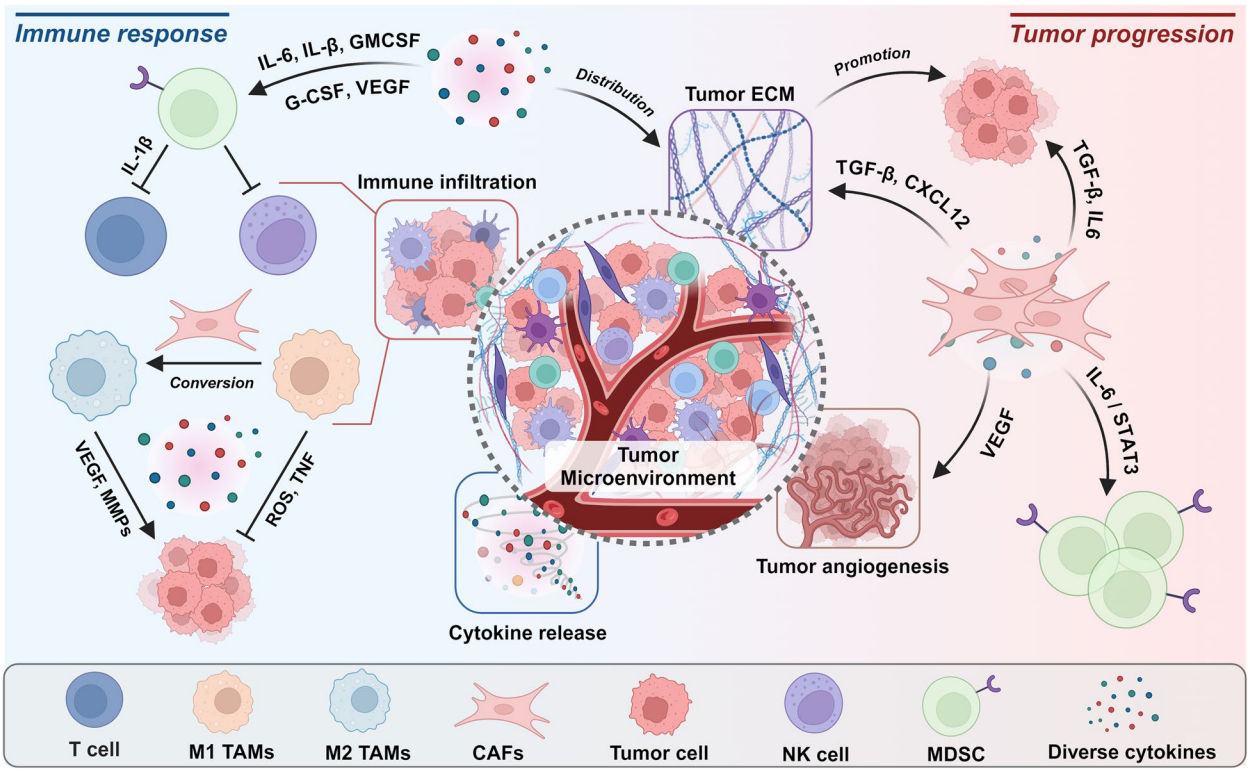

Fig. 4 Cytokines in tumor microenvironment participate in both immune response and tumor progression

effectiveness of NK cells relies on the expression and activation of receptors, either activating or inhibitory, on their cell surface [175]. In the context of NK cell activity, the induction of pyroptosis in tumor cells can potentially reverse immune evasion by releasing intracellular contents that activate NK cells [176]. Researchers found that Interferon-α (IFN-α), Interferon-β (IFN-β), IFN-γ, and to a lesser extent, TNF-α, enhanced GSDMB expression and promoted pyroptosis driven by GzmA [90]. This indicates that interferons can potentially boost NK cell-mediated pyroptosis. However, in solid tumors, soluble inhibitory factors and cellular components, such as CAFs, constitute the immunosuppressive TME, thereby contributing to the compromised functionality of infiltrating NK cells [177]. Research indicates that TGF-β significantly inhibits NK cell activation and cytotoxicity, potentially by reducing IFN-γ production and suppressing activating receptors like NKG2D [178, 179]. Additionally, TGF-β downregulates the transcription of DAP12 and decreases NKp30 and NKG2D expression, further attenuating NK cell activity [180, 181].

Cytokine-mediated enhancement of antitumor immunity Cytokines also play a key role in enhancing tumor immunity. Met supplementation might restore antitumor immunity by stimulating the secretion of IL-2, TNF-a, and IFN-r from TILs [182]. A study shows that NLRP3-dependent pyroptosis, induced by ChS-Ce6 nanovesicles in combination with laser treatment, significantly remodels the TME by enhancing the immunogenicity of the tumor [183]. This process involves the upregulation of NLRP3 and subsequent pyroptosis markers such as N-GSDMD, which leads to the release of immunogenic cell death (ICD) markers like CRT. The increased presence of CRT suggests a heightened antitumor immune response. Furthermore, the maturation of dendritic cells (DCs), essential for antigen presentation and the initiation of adaptive immune responses, is markedly enhanced in the ChS-Ce6 + laser group. This maturation promotes the activation and proliferation of cytotoxic T lymphocytes (CTLs) within the tumor, thereby strengthening the overall antitumor immune response. Consequently, ChS-Ce6 + laser-induced pyroptosis effectively boosts antitumor immunity by transforming the TME into a more immunogenic state and enhancing the immune system's ability to target and eliminate tumor cells [184]. Additionally, studies demonstrated that exogenous IL-24 significantly enhances IFN-γ production in CD4 + and CD8 + T cells [185]. IL-24 upregulation may result from HMGB1 downregulation induced by pyroptosis, as HMGB1 knockdown has been reported to elevate IL-24 levels [186].

ECM modulation of pyroptosis and cytokine signaling in TME The extracellular matrix (ECM) is a complex network of various macromolecules, such as collagens, fibrin, glycoproteins, and proteoglycans, which maintain the architecture, integrity, development, and homeostasis of normal tissue [187]. Alterations in the ECM within the tumor microenvironment (TME) are common in cancer tissues and are often associated with cancer progression [188]. In vitro studies demonstrated that MA blocked ECM degradation and reduced inflammation by suppressing the PI3K/AKT/NF-κB pathway and NLRP3 inflammasome-mediated pyroptosis. This led to higher anabolic protein expression, lower catabolic protein expression, and decreased secretion of inflammatory mediators like IL-18 and IL-1β [189]. Moreover, the ECM promotes the infiltration of other immunoinhibitory subpopulations. Increased collagen density or stiffness in the ECM triggers extensive FAK activation within cells, which subsequently leads to the direct exhaustion of CD8 + T cells and enhances the recruitment of Tregs, MDSCs, and TAMs, thereby contributing to the formation of an immunosuppressive TME [190].

Role of cytokines and related immune cells in TME metastasis

Cytokines play a critical role in tumor progression and metastasis within the TME by modulating immune responses, inflammation, and cellular communication [191]. Produced by immune cells and other cells, cytokines can either promote or inhibit tumor growth, depending on their types and context. Understanding their roles in TME metastasis is essential for developing targeted therapies that disrupt pro-tumorigenic interactions and enhance anti-tumor immunity (Table 3). Notably, pyroptosis is closely linked to cytokine release and the activity of immune cells, including myeloid-derived suppressor cells (MDSCs), cancer-associated fibroblasts (CAFs), Treg cells, tumor-associated macrophages (TAMs), and others. Certain cytokines can worsen the pro-inflammatory TME, thus influencing pyroptosis, while immune cells can modulate pyroptosis through cytokine signaling. Therefore, exploring the interplay between cytokines and pyroptosis in TME remodeling is crucial for identifying therapeutic targets that can disrupt tumor-promoting interactions and strengthen antitumor immunity.

Cytokine-pyroptosis interplay in MDSC-mediated immunosuppression Cytotoxic CD8 + T cells, CD4 + T cells, and NK cells collaborate to uphold immune surveillance. In contrast, various immune cells within tumors, such as MDSCs, Treg cells, and TAMs, aid in immune

Table 3 Regulation and role of diverse immune cells in tumor microenvironment

Type	Featured cytokines	Stimulus	Signal pathways	Role in metastasis	Target drugs/agents	Reference
MDSC	IL-6, IL-1b, GM-CSF, G-CSF, VEGF, and MCP-1	IL-6, IL-1b, GM-CSF, G-CSF, VEGF, and MCP-1	EZH2/NF-KB signaling, CCL26/CX3CR1, STAT3 pathway and NF-κB pathway	Promotion of immune suppression, Enhancement of angiogenesis and vascular permeability and Induction of tumor-induced immunosuppression	Sildenafil, Pexidartinib, AZD5069, Epacadostat	[192–195]
CAFs	TGF-β, HGF, PDGF, FGF-2, SDF-1, ROS	TGF-β, HGF, PDGF, FGF-2, SDF-1, ROS	IL-6/STA T3 pathway, TGF-β Signaling Pathway, Wnt/β-catenin Signaling Pathway, HGF/c-Met Signaling Pathway	Promotion of tumor growth and metastasis, Modulation of tumor microenvironment, Induction of immune evasion and Involvement in EMT process	FAP Inhibitors, Vismodegib, Galunisertib (LY2157299), Plerixafor (AMD3100)	[196–199]
Treg cells	IL-2, IL-10, TGF-β, IL-35, TNF-α and IFN-γ	interaction of TCR with IL-10 and TGF-b signaling	FoxP3 pathway, CTLA-4 pathway, IDO access, IL-2/STAT5 pathway:	Immunosuppressive, Promote immune evasion, Hyperactivity of Treg cells in tumor cell promotes tumor invasiveness and leads to a compromised T-cell immune response through Cytokines	Galunisertib (LY2157299), Ipilimumab, Epacadostat, Dacli-zumab, MEDI6383	[200–203]
TAM	IL-6, VEGF, Arg1, IL-10, TGF-β, IL-4, IL-13, CSF-1, CCL2, CXCL12, CTG, IDO, CCL17, CCL18, and CCL22	IL-4, IL-13, CSF-1, CCL2, CXCL12, and CTG	STAT3, NF-κB, TGF-β/Smad, PI3K/AKT, MAPK, HIF-1α and PD-1/PD-L1, CSF-1/CSF-1R	Promote tumor growth, promote tumor metastasis, suppress anti-tumor immune response and promote inflammation and immune regulation	Pexidartinib (PLX3397), IPI-549, Nivolumab	[204–208]
TANs	IL-8, VEGF, MMP-9, TGF-β, ROS, proteinases, IFN-γ	TGF-β	JAK/STAT, NF-κB, PI3K/AKT	Promote tumor growth, suppress immune response, direct tumor cell killing, and activate antitumor immunity	BMS-986,253, Galunisertib (LY2157299)	[209–212]

Abbreviations: *IL-6* Interleukin-6, *IL-1b* Interleukin-1 beta, *GM-CSF* Granulocyte-Macrophage Colony-Stimulating Factor, *G-CSF* Granulocyte Colony-Stimulating Factor, *VEGF* Vascular Endothelial Growth Factor, *MCP-1* Monocyte Chemoattractant Protein-1, *HGF* Hepatocyte growth factor, *PDGF* Platelet-derived growth factor, *FGF-2* Fibroblast growth factor 2, *SDF-1* Stromal-derived factor-1, *ROS* Reactive Oxygen Species, *MDSC* Myeloid-Derived Suppressor Cells, *CAFs* Cancer-Associated Fibroblasts, *TAM* Tumor-Associated Macrophages, *TANs* Tumor-Associated Neutrophils, *IL-2* Interleukin-2, *TGF-β* Transforming Growth Factor Beta, *IL-35* Interleukin-35, *TNF-α* Tumor Necrosis Factor Alpha, *Arg1* Arginase 1, *IL-10* Interleukin-10, *IL-4* Interleukin-4, *IL-13* Interleukin-13, *CSF-1* Colony Stimulating Factor 1, *CCL2* Chemokine (C-C motif) Ligand 2, *CXCL12* Chemokine (C-X-C motif) Ligand 12, *CTG* Common Terminology for Genetics, *IDO* Indoleamine 2,3-Dioxygenase, *CCL17* Chemokine (C-C motif) Ligand 17, *CCL18* Chemokine (C-C motif) Ligand 18, *CCL22* Chemokine (C-C motif) Ligand 22, *CCR6* Chemokine (C-C motif) Receptor 6, *CCL20* Chemokine (C-C motif) Ligand 20, *IL-8* Interleukin 8, *VEGF* Vascular Endothelial Growth Factor, *MMP-9* Matrix Metalloproteinase 9, *IFN-γ* Interferon gamma, *TCR* T-cell Receptor, *EZH2* Enhancer of Zeste Homolog 2, *NF-KB* Nuclear Factor-Kappa B, *CCL26* Chemokine Ligand 26, *CX3CR1* CXC Chemokine Receptor 1, *STAT3* Signal Transducer and Activator of Transcription 3, *IL-6* Interleukin 6, *HGF* Hepatocyte Growth Factor, *c-Met* Cellular-Mesenchymal-Epithelial Transition Factor, *FoxP3* Forkhead Box 3, *CTLA-4* Cytotoxic T-Lymphocyte-Associated Protein 4, *IL-2* Interleukin 2, *STAT5* Signal Transducer and Activator of Transcription 5, *Smad* SMA and MAD-related protein PI3K/AKT Phosphatidylinositol-3 Kinase/Protein Kinase B, *MAPK* Mitogen-Activated Protein Kinase, *HIF-1α* Hypoxia-Inducible Factor-1 alpha, *PD-1* Programmed Cell Death Protein-1, *PD-L1* Programmed Death-Ligand 1, *CSF-1* Colony-Stimulating Factor 1, *CSF-1R* Colony-Stimulating Factor 1 Receptor, *JAK/STAT* Janus Kinase/Signal Transducer and Activator of Transcription, *Treg* regulatory T

evasion and promote tumor progression. Normally, these cell types play essential roles in regulating the immune response, contributing to homeostasis and self-tolerance [213]. MDSCs are a diverse group of immature myeloid cells that inhibit the effector functions of CTLs and NK cells, exhibiting significant immunosuppressive activity in tumor-bearing hosts [214]. Numerous cytokines originating from tumors, including IL-6, IL-1β, GM-CSF, G-CSF, VEGF, and MCP-1, have been reported to induce MDSC accumulation in preclinical tumor cell models. These cytokines also closely connect with pyroptosis, for instance, IL-1β is a key inflammatory mediator released during this process [215]. One study found that in hepatocellular carcinoma (HCC), HCC-specific cell cycle-related kinase (CCRK) can upregulate IL-6 production through EZH2/NF-KB signaling, leading to extensive polymorphonuclear MDSC infiltration [216]. Similarly, hypoxia in tumors enhances pyroptosis-related inflammation through HIF-1α, further recruiting MDSCs via the CCL26/CX3CR1 pathway [217]. This interplay between cytokines and pyroptosis together regulates MDSCs, which helps shape the immune-suppressive environment.

CAF-mediated immune modulation and pyroptosis in TME Tissue-resident fibroblasts, also known as quiescent fibroblasts, represent a significant origin of CAFs [218]. In certain types of tumors, stellate cells may serve as an additional origin of CAFs [219, 220]. Numerous studies have suggested that mesenchymal stem cells (MSCs) serve as precursors for CAFs [167, 221]. Drawing from mounting evidence, CAFs within the TME exert significant influence over the anti-tumor functions of immune cells infiltrating the tumor, spanning both innate and adaptive immune responses in the TME [221]. Through the secretion of cytokines, chemokines, and other effector molecules, such as TGF-β, CXCL2, collagens, MMPs, and laminin, CAFs can stimulate immune cell involvement in cancer onset and progression, while also aiding in the degradation and remodeling of the ECM [222]. Certainly, certain notable impacts of various immune cells on CAFs have also been recognized. To this day, numerous investigations have demonstrated that the interplays among CAFs, immune cells, and other immune elements can regulate the TME, consequently impeding the anti-tumor immune response [223]. Tumor-associated fibroblasts (CAFs) can also promote pyroptosis [224]. One study found that human Fibroblast Activation Protein-Chimeric Antigen Receptor Natural killer-92 cells (hFAP-CAR-NK-92 cells) were successfully constructed by using CAFs and other cells. It was confirmed that hFAP-CAR-NK-92 cells can target hFAP-positive NSCLC and inhibit the progression of NSCLC by activating the Caspase-3/GSDME cell pyroptosis pathway [225].

Cytokine can influence Treg cells activity and tumor progression via pyroptosis The physiological role of Treg cells is to suppress excessive immune responses, maintaining homeostasis and autoimmune tolerance. However, the hyperactivity of Treg cells in tumor cell promotes tumor invasiveness and leads to a compromised T-cell immune response through Cytokines [226]. A greater number of CD4 + CD25 + Treg cells are enriched in the TME compared to healthy individuals. Treg cells are recruited through the CCR6 and CCL20 axis and activated by the interaction of TCR with IL-10 and TGF-b signaling [227]. Pyroptosis, as a form of inflammatory programmed cell death, can significantly influence this immune suppression by releasing cytokines such as ILs or activating pathways, which disrupt the Treg-mediated immunosuppressive environment. For example, Sorafenib, a multi-kinase inhibitor for HCC, has been shown to reduce hepatic Treg infiltration by suppressing TGF-b signaling. Moreover, IL-35, often associated with pyroptosis-driven immune evasion, correlates with the infiltration of CD39 + FoxP3 + Treg cells, underscoring its role in immune suppression and poor treatment outcomes [228].

Impact of cytokines and pyroptosis on TAMs in the TME Macrophages infiltrating tumors, referred to as TAMs, are categorized into two distinct subsets activated by diverse polarizing cytokines: M1 (stimulated by lipopolysaccharide (LPS) alone or with Th1 cytokines) and M2 (induced by Th2 cytokines) [229]. M1-type macrophages primarily exhibit an anti-tumor function within the TME by facilitating antibody-dependent cellular cytotoxicity and generating reactive oxygen species (ROS) along with tumor necrosis factor (TNF) [230]. M2-type macrophages promote tumor progression through their involvement in tumor angiogenesis, immune suppression, cancer cell invasion and metastasis, as well as extracellular matrix (ECM) remodeling [231].

As a major component of the TME, TAM often indicates a poorer prognosis in tumor cells [232]. TAMs originate from marrow-derived monocytes and acquire diverse immunosuppressive functions throughout differentiation. Numerous studies indicate that M1-polarized macrophages generate pro-inflammatory cytokines and inhibit malignancy progression, while M2-polarized cells produce tumor growth factors (IL-6), angiogenic molecules (VEGF), and immunosuppressive agents (Arg1, IL-10, TGF-b, and IDO) [233]. The interplay between Ca^{2+}-mediated pyroptosis and tumor-associated

macrophage (TAM) remodeling demonstrates a synergistic enhancement of antitumor efficacy in colorectal cancer models [166]. This induced immunogenic cell death (ICD) promotes M1-type TAM polarization, mitigating immunosuppression, fostering dendritic cell maturation, and activating $CD8^+$ T cell-dependent systemic antitumor immunity [166]. Such crosstalk highlights the potential of targeting pyroptosis and TAM dynamics to reshape the TME for improved cancer therapies.

Various cytokines originating from tumor cells, such as IL-4, IL-13, CSF-1, CCL2, CXCL12, and CTG, stimulate the differentiation of CCR2 + inflammatory monocytes into TAMs within the TME [234]. Furthermore, TGF-b derived from the TME enhances the expression of TIM-3 on TAMs, promoting both HCC progression and immune tolerance [235]. TAMs additionally generate cytokines and chemokines to promote immune suppression in tumor cell. For instance, CCL17, CCL18, and CCL22 derived from TAMs could facilitate the infiltration of Treg cells into the TME [235]. The interaction between MDSCs and TAMs decreases the synthesis of IL-6, IL-12, and MHC-II while enhancing IL-10 secretion. IL-10 from TAMs impairs the cytotoxicity of downstream CD8 + T cells and NK cells but elevates the frequency of CD4 + CD25 + FOXP3 + Treg cells [236]. Activated TAMs in the peritumoral stroma of tumor cells produce a range of pro-inflammatory cytokines, including IL-6, IL-23, IL-b, and TNF-a. These cytokines induce the proliferation of Th17 cells, which overexpress PD-1, CTLA-4, and GITR, thereby exerting an immunosuppressive effect [237]. In summary, TAMs represent a potential target for future cancer therapies.

Others Less frequent immunosuppressive cell types observed in human tumor cells including B cell subset expressing PD-1, Th17 cells, CD4 + T cells expressing CCR4 and CCR6, CD14 + DCs expressing CTLA-4 and PD-1, tumor-associated neutrophils, tumor-associated fibroblasts, and type-II T helper cells (Th2) [238–241]. The collaboration among these cells contributes to the establishment of an immunosuppressive environment, typically associated with a dismal prognosis in few cancers.

Other impact of cytokines in TME

In the above sections, we focused on the role of cytokines in TME remodeling and their interactions with related immune cells in TME metastasis in the context of pyroptosis. In this part, we concisely discussed other involvement of cytokines and its role in TME.

The dynamic interplay between cytokines participates in immune modulation by dictating the recruitment and polarization of various immune cell subsets [242, 243]. For example, the presence of GM-CSF and G-CSF can drive the accumulation of MDSCs, which suppress T cell activity and promote tumor growth [167]. Cytokines like IL-6, TNF-α, and IL-1β promote tumor growth by activating signaling pathways that prevent apoptosis and enhance cell cycle progression, while IL-10 fosters an immunosuppressive environment [244, 245]. Additionally, TGF-β and IL-8 facilitate tumor cell migration and invasion by inducing epithelial-mesenchymal transition and promoting matrix metalloproteinase expression, respectively [246–248]. Cytokines like VEGF, IL-8, and FGF (fibroblast growth factor) promote angiogenesis by stimulating endothelial cell proliferation and migration, which is essential for tumor growth and metastasis [249, 250]. Cytokines such as IL-6 and TNF-α influence metabolic reprogramming in tumor cells, enhancing aerobic glycolysis (the Warburg effect) in cancer cells [251, 252]. What's more, cytokines can modulate the metabolic activity of stromal cells within the TME, such as fibroblasts and immune cells, further supporting tumor growth and survival [253, 254].

In summary, cytokines in the TME significantly impact other aspects like tumor formation, proliferation, metabolism and so on. Understanding these processes is crucial for developing targeted therapies that can disrupt these cytokine-mediated interactions and inhibit tumor progression [250, 252–254].

Crosstalk between pyroptosis and cytokine in TME

The interplay between pyroptosis and cytokine

The interplay between pyroptosis and cytokines is integral to the dynamics of the TME, influencing both immune responses and tumor progression. This section will explore how pyroptosis regulates the generation and release of cytokines, the reciprocal role of cytokines in modulating pyroptotic pathways, and the intricate regulatory networks that govern these processes within the TME. By understanding these relationships, we can gain insight into the complex mechanisms that underlie tumor behavior and potential therapeutic avenues.

The regulation of pyroptosis in cytokine generation and release

Inflammasomes activation mechanisms Inflammasomes are large molecular complexes that assemble in response to DAMPs and PAMPs. Their activation leads to the maturation of interleukin-1 (IL-1) family members and GSDMD, resulting in the secretion of IL-1 and the induction of pyroptosis, respectively. Various types of

inflammasomes, each capable of detecting different types of threats, have been identified [191]. Inflammasome sensors briefly recruit caspase-1 family members, with or without the help of apoptosis-associated speck-like protein containing CARD (ASC), to initiate caspase-1 auto-cleavage. Activated caspase-1 then cleaves precursors of GSDMD and IL-1 family members, releasing these cytokines and inducing pyroptosis [191]. Canonical inflammasomes, composed of sensors, ASC, and caspase-1, play a crucial role in regulating pyroptosis and the subsequent generation and release of cytokines [121]. Upon activation, inflammasome sensors oligomerize and recruit ASC to form an"ASC speck," which then recruits caspase-1 [255]. Caspase-1 activation leads to the cleavage of pro-IL-1β and pro-IL-18 into their active forms, IL-1β and IL-18 [256]. Additionally, caspase-1 cleaves GSDMD, whose amino-terminal domain forms pores in the plasma membrane, resulting in pyroptosis [79, 257, 258]. These GSDMD pores facilitate the release of mature IL-1β and IL-18 into the extracellular environment, thereby contributing to the inflammatory response. This process highlights the intricate connection between inflammasome activation, pyroptosis, and cytokine release [70, 191]. Additionally, caspase-5 and caspase-11 are responsible for cleaving pro-IL-1α at D103 in senescent humans and mice [259]. Another noncanonical inflammasome component, caspase-8, is known to trigger various cell death pathways, including apoptosis, anoikis, necroptosis, autophagy, and pyroptosis [132]. Additionally, dendritic cell-associated C-type lectin-1 (dectin-1) triggers caspase-8 activation and subsequent IL-1β maturation in dendritic cells (DCs) stimulated by fungi and mycobacteria [260]. A similar effect has been observed in macrophages [261]. Coordination and crosstalk appear to exist between non-canonical caspase-8 inflammasomes and canonical inflammasomes via ASC and NLRP3[262, 263]. Canonical inflammasomes with ASC recruit caspase-8, which aids in IL-1β maturation independently of caspase-1 [263].

Pyroptosis in TME remodeling Pyroptosis, which involves the breakdown and recycling of cellular materials, has been reported to both inhibit and promote tumor progression. In the context of malignancy, autophagy activation can generate reactive oxygen species (ROS), leading to compensatory cell proliferation via protein kinase C (PKC) λ/ι in hepatocellular carcinoma (HCC) [264]. Some researchers have indicated that E2, which activates the NLRP3 inflammasome, can kill cancer cells. Autophagy inhibits caspase-1, which is strongly associated with inducing apoptosis and pyroptosis pathways via the E2/Erβ/AMPK/mTOR pathway in HepG2 cells, rather than inducing pyroptotic death in cancer cells [125]. Additionally, studies on alpinum isoflavone have shown that inhibiting autophagy can enhance the effectiveness of inducing inflammasome-mediated pyroptosis in HCC [265].

A study highlights a novel approach to modulate the TME by simultaneously activating pyroptosis and the cGAS-STING pathway through a light-controlled, tumor-specific nanotheranostic platform [266]. This strategy enhances the expression of STING and GSDME, promotes the release of DNA fragments to potentiate the cGAS-STING pathway, and activates caspase-3 to cleave GSDME, leading to pyroptosis [266]. The subsequent release of inflammatory cytokines matures antigen-presenting cells, triggering T cell-mediated antitumor immunity [266]. This approach shows significant promise in overcoming the limitations of current pyroptosis inducers and STING agonists, offering a potent method for reshaping the TME and enhancing systemic antitumor immunity [267].

Another study found that cisplatin-induced the activation of GSDME and the release of cytokines including IL-12, which enhance the expression of IFN-γ in T cells in the TME and subsequently improve anti-PD-L1 response [268]. Altogether, their work demonstrates that cisplatin could induce GSDME-dependent cell pyroptosis to improve the response of anti-PD-L1 therapy though switching the TME from "cold" to "hot" in small-cell lung cancer, indicating GSDME as a response biomarker and pyroptosis as a pathway for combination therapy of anti-PD-L1 and chemotherapy, as well as a potential target to sensitize the response to PD-L1 inhibitor therapy in future [268].

Role of cytokine in pyroptosis

As mentioned above, cytokines play a critical role in the initiation and amplification of pyroptosis. They prominently participate in the activation of inflammasomes, regulation of intracellular signaling pathways, and the release of inflammatory cytokines, etc. Understanding the role of cytokines in pyroptosis is crucial for comprehending the crosstalk between pyroptosis and cytokines and their roles in TME. Herein, we take IL family and TGF-β as examples to provide a detailed introduction to the role of cytokines in pyroptosis.

IL family As mentioned above, IL-1β and IL-18 participated in pyroptosis process and matured from pro-IL-1β and pro-IL-18, exerting a critical role in the pro-inflammation cytokines release [135]. One study demonstrated that N-GSDMD trafficking to neutrophil organelles facilitated IL-1β release independently of plasma membrane

pores and pyroptosis [269]. In inflammasome-activated macrophages, GSDMD cleavage leads to pyroptosis and IL-1β release, whereas in neutrophils, N-GSDMD is essential for IL-1β secretion via an autophagy-dependent mechanism without causing pyroptosis, demonstrating distinct GSDMD trafficking between these cell types [269]. Similar to IL-1β, IL-18 is also released during pyroptosis. Cells expressing IL-18 receptors, such as NK cells and Th1 cells, can be activated and produce interferon-γ (IFN-γ) [270]. Notably, IFN-γ can stimulate the production of granzyme B in CD8+ T lymphocytes, which can induce cancer cell apoptosis by triggering pyroptosis through GSDME [35] or modulate the expression of apoptosis-related genes [271]. Inhibition of pyroptosis via utilizing rapamycin could reduce the release of IL-1β and IL-18 in vitro in the septic response [272]. Interestingly, one research found that IL-1β can interact with IL-6 and IL-23 to activate naïve CD4+ T cells, leading to the formation of Th17 cells, which in turn recruit neutrophils and release pro-inflammatory factors [273–275]. Moreover, IL-1β can drive the differentiation of Th17 cells and diminish the effects of TGF-β, which promotes the differentiation of T cells into Tregs [276, 277]. In summary, IL-1β and IL-18 not only dive themselves into pyroptosis but can also affect antigen-presenting cells (APCs) and other immune cells to indirectly influence the process.

Several other IL family members are also discovered to participate in pyroptosis. For instance, IL-33 is produced through GSDMD-mediated pyroptosis and functions as a pro-inflammatory chemokine. It has been shown to mediate type 2 immunity by activating various immune cells, including macrophages, with the IL-33/ST2 signaling pathway playing a significant role. Consequently, some researchers are targeting this cytokine to inhibit inflammation [278]. IL-17A, primarily secreted by γδT cells in the colorectal TME, regulates the TME in various ways [279]. W. Q. Feng *et al.* [280] found that it induces mitochondrial dysfunction and pyroptosis through the ROS/NLRP3/caspase-4/GSDMD pathway, leading to intracellular ROS accumulation. Additionally, IL-17A promotes the secretion of inflammatory factors like IL-1β and IL-18, as well as immune antigens, and recruits CD8+ T cells to infiltrate tumors [280].

TGF-β Transforming growth factor-β (TGF-β) is a multifunctional cytokine expressed in almost all cell types [281]. Several studies discovered the involvement of TGF-β in pyroptosis. NLRP3-mediated pyroptosis in hepatic stellate cells (HSCs) can lead to the production of TGF-β through the IL-1β/IL-1R pathway, thereby regulating TGF-β expression [282]. Meanwhile, TGF-β can activate the NLRP3 inflammasome in HSCs through TGF-β receptor-mediated TAK1-NF-κB signaling or pathways generating ROS in the intracellular space, thus elevating NLRP3 inflammasome levels [282]. This creates a positive feedback loop. However, TGF-β recruitment of Tregs and inhibition of APCs make this type of pyroptosis detrimental to human body [282]. Similarly, another study found that lactate in the tumor microenvironment activates the NLRP3 inflammasome in macrophages, while TGF-β inhibits inflammasome activation and induces autophagy to clear reactive oxygen species (ROS), aiding tumor cells in evading immune surveillance. This indicates that tumor cells modulate TGF-β to counteract immune responses [283]. These findings suggest that targeting TGF-β may represent a viable strategy to inhibit the progression of tumor cells.

There are other cytokines involved in the process of pyroptosis. Inhibiting Nrf2 enhances the sensitivity of colorectal cancer (CRC) cells to oxaliplatin by promoting ferroptosis and pyroptosis, indicated by increased TNF-α release and the modulation of GPX4 expression, thereby offering a novel target to mitigate chemoresistance in CRC treatment [284]. Similarly, elevated levels of inflammatory cytokines like TNF-α and pyroptosis-related proteins were observed in bovine endometritis through neutrophil extracellular traps (NETs) released by neutrophils, resulting in inflammation and tissue damage [285]. Additionally, the combination of TNF-α and IFN-γ induced PANoptosis, a form of inflammatory cell death that exacerbated lung damage in COVID-19 by activating the JAK/STAT1/IRF1 signaling axis [93]. In summary, these studies indicate that inhibiting the cytokine-mediated inflammatory cell death signaling pathway identified could be advantageous for patients with cancer or other infectious and autoinflammatory diseases by reducing tissue damage and inflammation.

Regulation network of pyroptosis and cytokine in TME

Pyroptosis and cytokine interplay As pyroptotic cells release inflammatory factors, the resulting damaged plasma membranes stimulate chemokine production and attract a variety of immune cells [286, 287]. Studies have demonstrated that pyroptosis amplifies cellular immunity, as cytotoxic lymphocytes, including natural killer (NK) and CD8+T cells, release granzymes like GZMA and GZMB, which cleave GSDMB and GSDME, respectively [88, 90]. Furthermore, the key molecule in pyroptosis, NLRP3, is essential for the TH2 cell transcriptome program in CD4(+) T cells, and its deficiency modulates the TME and promotes tumor cells growth [288, 289]. Paradoxically, NLRP3 exerts an immunosuppressive

effect in some tumor cells such as melanoma tumor cells [288, 290] by recruiting MDSCs [291]. Additionally, in vivo experiments demonstrate that inhibiting GSDMC transcription, thereby suppressing pyroptosis, alleviates tumor necrosis symptoms and prolongs the survival of tumor-bearing mice [87]. These results indicate that pyroptosis functions as a double-edged sword in tumors, highlighting the importance of the specific executor involved and the cell type in which the process takes place.

Wenqiong Chen *et al.* [288]. conducted an association analysis between PScore and the enrichment score of hallmark gene sets from MSigDB across seven melanoma datasets. They observed significant positive correlations between PScore and immune-related hallmark pathways in all datasets. In contrast, multiple carcinogenic signaling pathways were found to correlate significantly negatively with PScore in multiple datasets [288]. This well explains the relationship between cytokines and the formation mechanism of pyroptosis, and the interaction forms a regulatory network.

Extracellular signaling in pyroptosis After cell rupture during pyroptosis, danger signals are released into the extracellular space. For instance, ATP can bind to and activate the P2X7 channel, a type of potassium ion channel [292]. In the physiological environment, the concentration of K+ inside the cell is higher than in the extracellular space. When the intracellular concentration decreases, this can activate the NLRP3 inflammasome through NEK7, an intracellular potassium sensor [293]. This process indicates that pyroptosis can propagate among cells. Regardless of the trigger, pyroptosis ultimately leads to the production of IL-1β and IL-18 via this pathway. Additionally, ATP can recruit macrophages and dendritic cells to the extracellular matrix (ECM), presenting an “eat-me” signal to pyroptotic cells [294]. The initiation of phagocytosis in pyroptotic cells by macrophages through these signaling pathways enhances CD8+ T-cell activation and promotes IFN-γ production [44].

Comprehensive effects of regulatory networks on TME As a form of inflammatory cell death (ICD), pyroptosis has the potential to transform the immune "cold" tumors into "hot" tumors by releasing proinflammatory factors and reshaping immune cells within the TME [88]. One of the distinctive features of pyroptosis is the release of inflammatory cytokines, including IL-1β, IL-18, and HMGB1 [295–297]. IL-1β and IL-18 are secreted through the GSDMD-forming pores, whereas HMGB1 is released after pyroptosis-induced cell lysis [297]. These inflammatory cytokines, particularly IL-1β and IL-18, play crucial roles in both innate and adaptive immunity [297]. Therefore, the regulation network of pyroptosis and cytokines in the TME shaping and modulation represents a crucial avenue of investigation. Pyroptosis, as a form of inflammatory cell death, not only transforms "cold" tumors into "hot" tumors by releasing proinflammatory factors but also plays a pivotal role in bridging the connection between innate and adaptive immunity. Understanding the intricate mechanisms underlying pyroptosis and its influence on TME reprogramming holds significant promise for devising innovative therapeutic strategies. By elucidating these pathways, novel targeting approaches may be developed to effectively modulate the TME and enhance antitumor immune responses, ultimately improving clinical outcomes for cancer patients.

Signaling pathway in the crosstalk of pyroptosis and cytokine

The interaction between pyroptosis and cytokine signaling pathways forms an intricate network involving numerous participants and potential feedback loops. Multiple pathways are involved in this regulation, including the cGAS-STING pathway (Fig. 5), NF-κB pathway, JAK/STAT pathway, MAPK pathway, and so on. By influencing these pathways, we may have the potential to adjust inflammation, bolster host defense against pathogens, and potentially manage diseases linked to dysregulated pyroptosis or cytokine signaling.

cGAS-STING pathway

Definition and role The cGAS-STING pathway is the primary sensor for cellular cytosolic double-stranded DNA (dsDNA), enabling the innate immune system to respond to infections, inflammation, and cancer [298–300]. Cyclic GMP-AMP synthase (cGAS) is a cytosolic DNA sensor/enzyme that catalyzes the formation of 2’-5’-cGAMP, an unusual cyclic di-nucleotide second messenger [301, 302]. This messenger binds to and activates the Stimulator of Interferon Genes (STING), leading to the recruitment of Tank Binding Kinase 1 (TBK1) [302], which results in the activation of the transcription factor Interferon Regulatory Factor 3 (IRF3), and the trans-activation of innate immune response genes [301], including type I Interferon cytokines (IFN-I). The activation of the pro-inflammatory cGAS-STING-IRF3 response is triggered by direct recognition of the DNA genomes of bacteria and viruses [302]. However, it can also occur during RNA virus infection, neoplastic transformation, tumor immunotherapy, and systemic autoinflammatory diseases [299]. After activation, it then

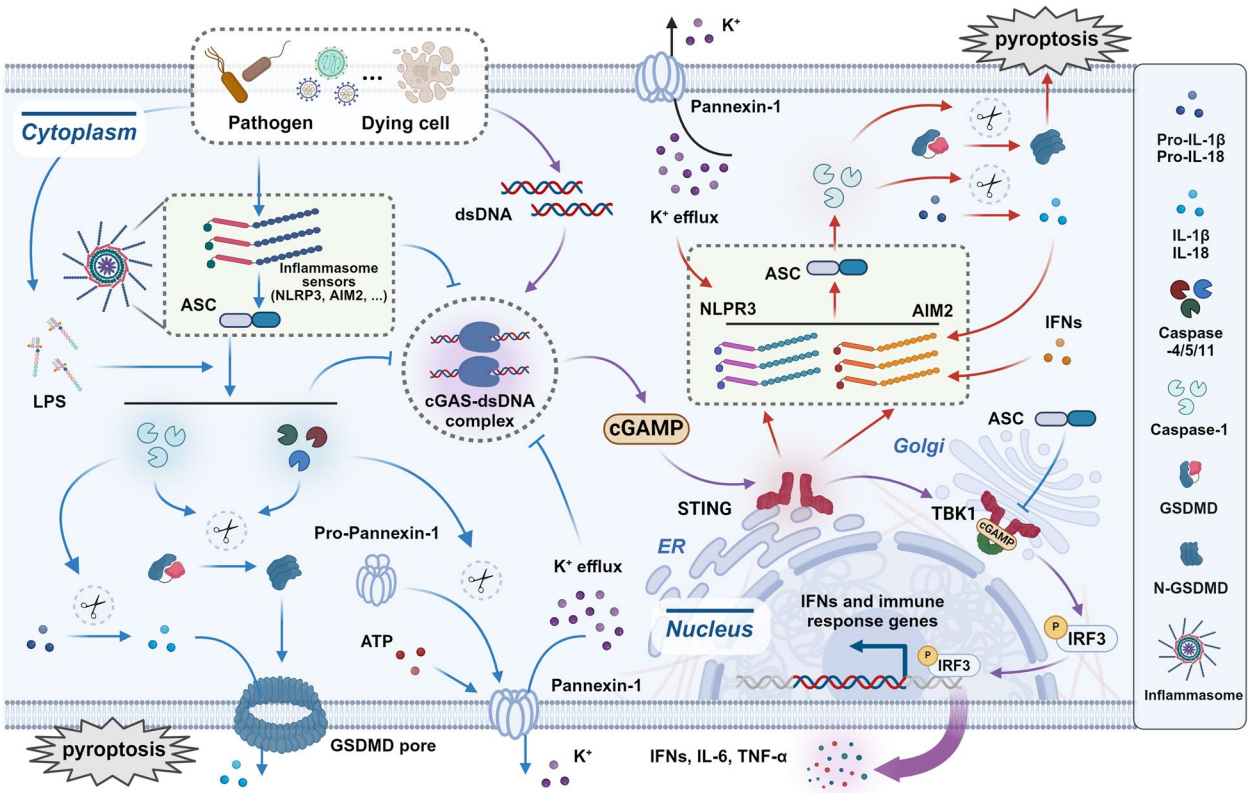

Fig. 5 The crosstalk between pyroptosis and cytokines in cGAS-STING pathway. The cGAS-STING pathway (*in purple arrow*) is the primary sensor for cellular cytosolic dsDNA, enabling the innate immune system to respond to diverse pathogens and dying cells. Cytosolic DNA sensor cGAS binds dsDNA to form cGAS-dsDNA complex, and subsequently activates cGAMP. This initiates a series of downstream effects including STING activation, recruitment of TBK1, and phosphorylation of IRF3. Ultimately, innate immune response and diverse cytokines release. Pyroptosis can regulate cGAS-STING pathway via different components and cytokines (*in blue arrow*). Additionally, the cGAS-STING pathway can also promote pyroptosis mainly through NLPR3 and AIM2 inflammasomes (*in red arrow*). The crosstalk between pyroptosis and cytokines in cGAS-STING pathway together forms a complex network

subsequently induces inflammasome activation and the onset of pyroptosis (Fig. 5).

The interplay of pyroptosis and cytokines in cGAS-STING pathway Caspase family could cleave cGAS to directly regulate cGAS-STING pathway. In activation of canonical pyroptosis, caspase-1 interacts with cGAS, cleaves cGAS, and inhibits STING-mediated interferon production [303]. Upon inflammasome activation, caspase-1 directly binds to cGAS via its p20 domain, cleaving human cGAS at the D140/157 site [303]. This reduces cGAMP production and cytokine expression. Additionally, in non-canonical pyroptotic pathways, caspase-4 and caspase-5 in humans, and caspase-11 in mice, cleave cGAS during lipopolysaccharide (LPS)-induced non-canonical inflammasome activation [303, 304]. In line with this, during Zika virus infection, caspase-1-induced cGAS cleavage inhibits TBK1 and IRF3 phosphorylation, reducing type I interferon production, and thus, bypassing the antiviral response [305].

The GSDMD-K+ efflux axis targets cGAS, decreasing cGAMP synthesis, which in turn inhibits STING signaling and reduces IFN-β production [304]. Researchers find that GSDMD-deficient mice showed an increased IFN-β response to Francisella novicida infection. GSDMD negatively regulates the IFN-β response independently of pyroptosis and IL-1β [306]. The AIM2 inflammasome-activated GSDMD depletes intracellular K+ through membrane pores, which is a process that is both essential and sufficient for inhibiting the cGAS-dependent IFN-β response. This, in turn, suppresses the cGAS-driven type I IFN response to DNA in macrophages [306].

The CARD domain of ASC participates in the regulation of cGAS-STING pathway. ASC protein, acting as a ligand, is composed of two domains: a PYD domain at the N-terminal and a CARD domain at the C-terminal. Through CARD-CARD interactions, ASC assembles the inflammasome by recruiting caspase-1, which also contains a CARD domain. During DNA virus infection, a

deficiency in ASC results in elevated IFN production [303]. The CARD domain of ASC in the AIM2 inflammasome binds to the N-terminal domain of STING, inhibiting its interaction with TBK1, thereby negatively regulating the cGAS-STING signaling pathway [307]. The NLRC3 protein, which includes the CARD domain, impedes the type I IFN response and IL-1β secretion by competing with ASC for caspase-1 binding, disrupting the formation of ASC specks, and interfering with the assembly and activation of the NLRP3 inflammasome [306].

Diverse inflammasomes are also involved in the regulation of cGAS-STING pathway. AIM2 inhibits the cGAS-STING-mediated production of type I IFN upon stimulation with various DNA forms [304]. Upon exposure to cytosolic DNA, dendritic cells (DCs) and macrophages lacking AIM2, ASC, or caspase-1 exhibited significantly increased cGAMP production, STING aggregation, and phosphorylation of TBK1 and IRF3 [308], demonstrating that AIM2 inhibition of the STING pathway affects upstream STING, thereby diminishing the activation cascade of the entire STING pathway. The NLRP3 inflammasome consists of the cytoplasmic sensor NLRP3, the adaptor ASC, and the effector caspase-1. In one study, mice subjected to whole abdomen radiation through timed exposure to X-rays at a cumulative dose exhibited heightened levels of p-TBK1 and p-IRF3 in colonic tissues, along with increased IFN-β levels following NLRP3 deficiency. The absence of NLRP3 resulted in elevated cGAS-STING-mediated IFN-β production following radiation. NLRP3 deficiency also amplified type I IFN production and bolstered the host's resistance [309].

Apart from those inflammasomes mentioned above, nod-like receptors (NLRs) families also participated in the regulation, including NLRX1, NLRP2, NLRC3, NLRC4, NLRC5, NLRP6, and NLRP12 [310–312]. The majority of NLRs have a positive impact on inflammatory responses, especially the inflammasome-forming NLRs. However, recent research has shown that NLRC3 has a negative effect on the type I interferon (IFN) response by sequestering and dampening STING activation [306, 313]. Additionally, NLRC3 interacts with pro-caspase 1 and ASC via its CARD domain, thereby obstructing the assembly of NLRP3 and NLRC4 inflammasomes and subsequently suppressing cell pyroptosis [306]. Similar to NLRC3, NLRX1 engages with STING via its nucleotide-binding domain (NBD), leading to the obstruction of STING-TBK1 interaction, consequently impeding the activation of TBK1 necessary for type I IFN production [314]. NLRP2 interacts directly with TBK1, disrupting the TBK1-IRF3 interaction and interfering with TBK1-induced IRF3 phosphorylation, thereby inhibiting IFN signaling [310]. NLRP4 negatively regulates type I IFN signal transduction by activating TBK1, which is then subjected to K48-linked ubiquitination and degradation by the E3 ubiquitin ligase DTX4 [315]. Furthermore, NLRP11 restricts type I IFN activation by hampering TBK1-induced IFN-β promoter activity, indicating its potential role in the cGAS-STING signaling pathway [316] (Fig. 5).

cGAS-STING pathway regulates NLRP3 inflammasome and pyroptosis The cGAS-STING-NLRP3 signaling axis is a specific mechanism that enables the activation of the NLRP3 inflammasome and the subsequent secretion of IL-1β. In human myeloid cells, the cGAS-STING pathway was essential for the activation of NLRP3 induced by cytoplasmic DNA during viral and bacterial infections [317]. Additionally, the STING-IRF3 axis could trigger LPS-induced cardiac dysfunction, inflammation and pyroptosis by activating the NLRP3 inflammasome in mice [318]. Furthermore, the cGAS-STING pathway was activated in myelodysplastic syndromes (MDS) to stimulate IFN-stimulated genes (ISG), leading to the activation of the NLRP3 inflammasome [319].

Available studies indicate that the interaction between STING and NLRP3 in response to cytoplasmic DNA stimulation promotes NLRP3 inflammasome activation through several mechanisms [304]. Firstly, STING recruits NLRP3 to facilitate its localization in the endoplasmic reticulum, thereby promoting the formation of the NLRP3 inflammasome [320]. Secondly, the TM5 (151-160aa) domain of STING interacts with the NACHT and LRR domains of NLRP3, attenuating its K48- and K63-linked polyubiquitination, effectively deubiquitinating NLRP3 to activate the inflammasome [320]. Thirdly, in an epistatic regulatory mechanism, the H3K4-specific histone methyltransferase WDR5 and the H3K79 methyltransferase DOT1L were found to significantly reduce STING overexpression-mediated NLRP3 upregulation, suggesting that STING promotes histone methylation in the NLRP3 promoter region via WDR5/DOT1L, thereby recruiting IRF3 to increase NLRP3 transcription [321].

Inflammasome pathway

Canonical pyroptotic death is facilitated by inflammasome assembly, which involves GSDMD cleavage and the release of IL-1β and IL-18 [40, 48]. Currently, the inflammasome sensors NLRP1, NLRP3, NLRC4, AIM2, and pyrin are known to form canonical inflammasomes and have been extensively studied [43].

The NLRP1 inflammasome was the first to be described. NLRP1 possesses a C-terminal extension housing a CARD domain, enabling direct interaction with procaspase-1 and circumventing the need for ASC. However, the inclusion of ASC in the complex enhanced the activity of the human NLRP1 inflammasome [322, 323]. Apart from caspase-1, NLRP1 also engages with caspase-5, potentially playing a role in IL-1β processing within human cells [324].

At present, the NLRP3 inflammasome stands as the most comprehensively characterized inflammasome, comprising the NLRP3 scaffold, the ASC (PYCARD) adaptor, and caspase-1 [324]. Exposure to complete pathogens, along with various structurally diverse PAMPs, DAMPs, and environmental irritants, triggers the activation of NLRP3. NLRP3 oligomerization results in the clustering of PYD domains, allowing for homotypic interaction with the adaptor ASC containing PYD and CARD. The CARD domain of ASC recruits the CARD of procaspase-1. Clustering of procaspase-1 enables autocleavage and the formation of the active caspase-1 p10/p20 tetramer, which subsequently processes cytokine proforms like IL-1β to produce active molecules. NLRC3 can also interact with pro-caspase 1 and ASC through its CARD domain, thus impeding the formation of NLRP3 and NLRC4 inflammasomes and consequently inhibiting cell pyroptosis [306].

AIM2 Inflammasome is the first identification of a non-NLR family member forming an inflammasome scaffold [322]. The AIM2 inflammasome comprises AIM2, ASC, and caspase-1. AIM2 features a PYD domain, which, similar to NLRP3, interacts with ASC through homotypic PYD-PYD interactions, enabling the ASC CARD domain to recruit procaspase-1 to the complex. Upon autoactivation, caspase-1, like in other inflammasomes, facilitates the maturation and secretion of proinflammatory cytokines such as IL-1β and IL-18. The ligand requirements for AIM2 are quite permissive, as cytosolic dsDNA from viruses, bacteria, or the host itself can activate the AIM2 inflammasome [325, 326].

Other pathways in the crosstalk of pyroptosis and cytokine in TME

Inflammation related pathways The transcription factor NF-κB (nuclear factor kappa B) plays a key role in regulating various functions of the innate and adaptive immune systems and acts as a central mediator of inflammatory responses including the activation of NLRP3 [327]. For example, research shows that Metformin promotes the AMPK/SIRT1/NF-κB signaling pathway, which drives the induction of pyroptosis in cancer cells [328]. The JAK/STAT pathway (Janus kinase/signal transducer and activator of transcription) forms a swift membrane-to-nucleus signaling system and triggers the production of numerous essential regulators of cancer and inflammation [329]. Studies revealed that type I interferon-mediated JAK-STAT signaling pathway facilitates the transition from apoptosis to pyroptosis, potentially through the upregulation of the anti-apoptotic Bcl-xL gene [330].

Granzyme-related signaling cascades Granzymes are serine proteases released from cytoplasmic granules in CD8+ T cells and NK cells, primarily consisting of granzyme A and B [331]. Granzyme-induced pyroptosis converts non-inflammatory cell death into an inflammatory form, enhancing the inflammatory properties within TME [297, 332]. Recent findings suggest that granzymes are involved in pyroptosis through two pathways. Firstly, after entering the target cell, granzyme A can cleave and activate GSDMB at the Lys229/Lys244 sites, leading to pyroptosis in target cells, resulting in cytoplasmic swelling, membrane rupture, and the release of inflammatory factors, eliciting a robust antitumor immune response [34, 80, 90]. The inactivation of granzyme A with 4-Octyl itaconate can inhibit GSDMB-induced pyroptosis and reduce inflammation [333]. Moreover, granzyme B can activate caspase-independent pyroptosis in target cells by directly cleaving GSDME at the same site as caspase 3, which in turn activates granzymes, establishing a positive feedback loop that amplifies the overall effect [334, 335]. Additionally, Euphohelioscopin A enhances the cleavage of GSDME, promoting granzyme B-induced pyroptosis and granzyme B silencing inhibits the activation of caspase-3 and Gasdermin E [336, 337].

Inspiration for treatments

Therapeutic targets (Fig. 6)

Pyroptosis-targeting agents

Therapeutic targeting of pyroptosis offers a promising strategy for enhancing anti-tumor immunity by inducing pro-inflammatory cell death in tumor cells, disrupting the tumor microenvironment (TME), and activating immune responses [34]. Several potential drug candidates and treatment strategies aim to modulate key components of the pyroptotic pathway, particularly focusing on inflammasomes, caspases, and gasdermin proteins (Table 4).

Disulfiram Gasdermins are the key executors of pyroptosis. Among them, Gasdermin D (GSDMD) plays a pivotal role in forming membrane pores, leading to cell swelling and eventual lysis [371]. For example, Disulfiram functions as an effective inhibitor of pyroptosis by covalently modifying Cysteine-191 (Cys191) on gasdermin

Table 4 Summary of therapeutic targets and application in treatment

Targets	Related pathways	Disease	Drugs/Agents	reference
GSDM proteins	NLRP3/caspase-1/GSDMD pyroptosis pathway	Breast cancer, lung cancer, acute myeloid leukemia, epithelial ovarian cancer	Disulfiram, Cisplatin, Anthocyanin, 4-hydroxybenzoic acid, Simvastatin, Val-boroPro, Docosahexaenoic acid, 2-(α-Naphthoyl) ethyltrimethylammonium	[338–341]
NLRP3	NLRP3 inflammasome pathway, Pyroptosis pathway, NF-κB signaling, MAPK pathway	Gastric cancer, hepatocellular carcinoma, breast cancer, colorectal cancer	Famotidine, Cisplatin, MCC950, CY-09	[151, 342–344]
Caspase enzymes	Caspase-1 pathway, intrinsic and extrinsic apoptosis pathways, necroptosis pathway	Leukemia, glioblastoma, pancreatic cancer, prostate cancer	VX-765, Z-VAD-FMK, Emricasan, Q-VD-OPh	[345–349]
ADC	Endocytosis and lysosomal degradation, pyroptosis induction, tubulysin-mediated microtubule disruption	Breast cancer, colon cancer, HER2-positive gastric cancer, Hodgkin's lymphoma	Trastuzumab emtansine (T-DM1), Brentuximab vedotin (SGN-35), Sacituzumab govitecan	[350–352] [353]
ICIs	PD-1/PD-L1, CTLA-4, Lymphocyte-activation gene 3 (LAG-3)	Skin cancer, lung cancer, head and neck cancer, lymphoma gastrointestinal cancer	Pembrolizumab (Keytruda), Nivolumab (Opdivo), atezolizumab (Tecentriq), Durvalumab (Imfinzi), Ipilimumab (Yervoy), Relatlimab	[354–357]
ILs	IL-6/JAK/STAT3 signaling pathway	Melanoma, gastrointestinal tumors, metastatic colorectal cancer, macular degeneration and rheumatoid arthritis	Tocilizumab, Aldesleukin, Anakinra, Canakinumab, Rilonacept, Gevokizumab	[358–362]
TGF-β	TGF-β signaling pathway, PI3K and AKT signaling pathways	Solid tumor, hematoma, fibrotic diseases, immune-related diseases	Galunisertib (LY21577299), Fresolimumab, Trabedersen (AP12009), LY3200882	[363–370]

Abbreviations: *ADC* Antibody-drug-conjugate, *ICIs* Immune checkpoint inhibitors, *GSDM* Gasdermin, *ILs* Interleukins, *TGF-β* Transforming growth factor β, *PD-1* Programmed cell death protein 1, *PD-L1* Programmed death-ligand 1, *PD-L2* Programmed death-ligand 2, *CTLA-4* Cytotoxic T-lymphocyte-associated protein 4, *LAG-3* Lymphocyte-activation gene 3, *IL-6* Interleukin 6, *VEGF* Vascular Endothelial Growth Factor, *CSF-1/CSF-1R* Colony Stimulating Factor 1/Colony Stimulating Factor 1 Receptor, *NLRP3* Nucleotide-binding Oligomerization Domain-like Receptor Protein 3, *IL-1β* Interleukin 1 beta, *GSDMD* Gasdermin D, *ROS* Reactive Oxygen Species, *CTLs* Cytotoxic T cells, *NK cells* Natural killer cells, *IL-6* Interleukin 6, *JAK* Janus Kinase, *STAT3* Signal Transducer and Activator of Transcription 3, *PI3K* Phosphoinositide 3-kinase, *AKT* Protein Kinase B, *PI3Kγ* Phosphoinositide 3-kinase gamma, *ATRA* All-trans Retinoic Acid

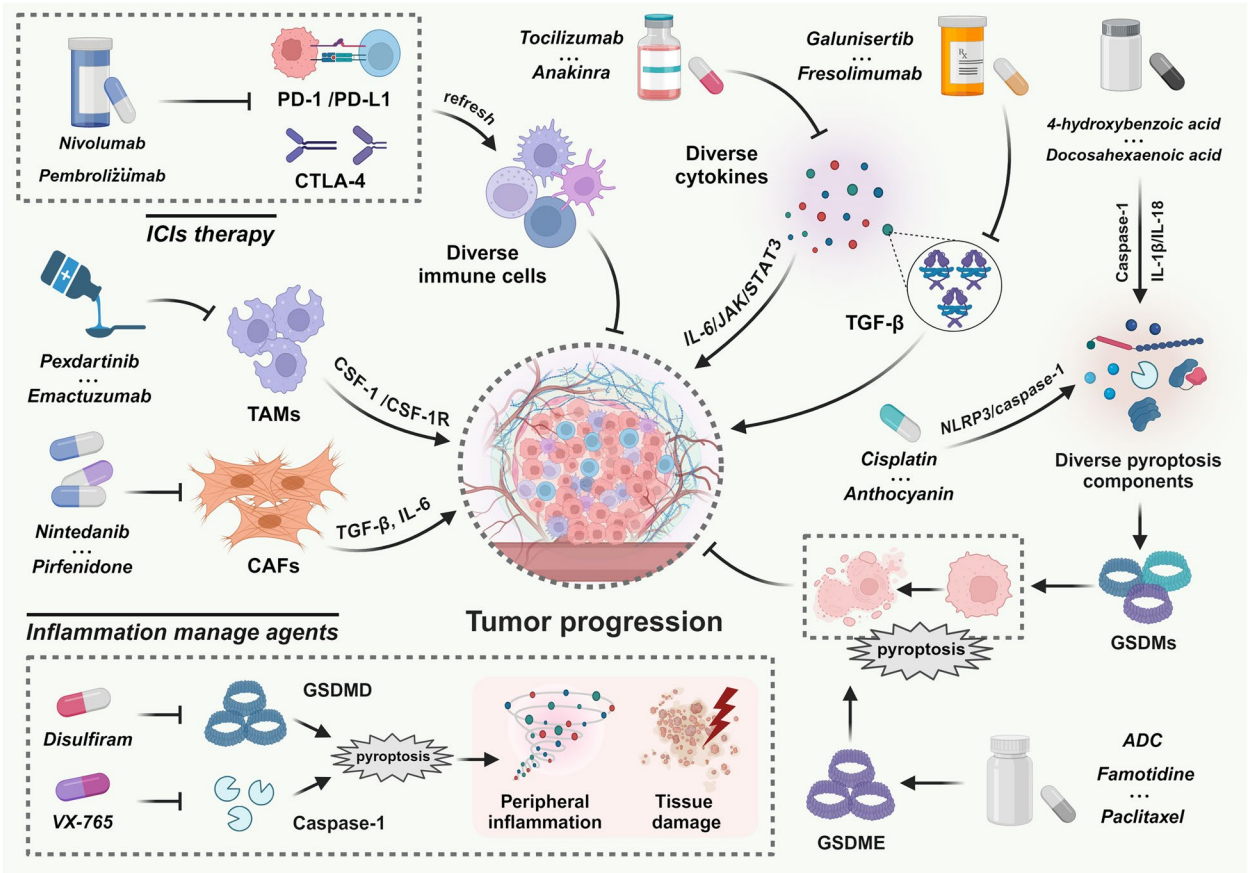

Fig. 6 Summary of the therapeutic targets in TME

D (GSDMD), preventing its pore formation. This inhibition occurs without affecting the upstream steps of inflammasome assembly or the cleavage of GSDMD and IL-1β, indicating that Disulfiram specifically targets the final stage of pyroptosis [372]. The ability to selectively inhibit GSDMD pore formation while allowing cytokine processing suggests that Disulfiram could be repurposed as a therapeutic agent to manage inflammatory diseases associated with excessive pyroptosis, making it a promising candidate in the context of inflammation-driven conditions [373, 374].

Famotidine A recent study demonstrated that famotidine (300 μm) induced cell pyroptosis, as confirmed by LDH assay. Additionally, famotidine activated NLPR3 inflammasomes, including ASC, Caspase-1, and NLRP, in gastric cancer cells, promoting the maturation and secretion of IL-18 but not IL-1β. Interestingly, famotidine increased GSDME, not GSDMD, in BGC823 and AGS cells. Mechanistically, famotidine significantly enhanced ERK1/2 phosphorylation, while the ERK1/2 inhibitor U0126 reversed famotidine's effect on IL-18 secretion [342, 343]. These results uncovered a new role of famotidine in gastric cancer cell pyroptosis, requiring careful consideration for treatment strategies.

Caspase Modulators and Chemotherapy-Induced Pyroptosis Caspase enzymes, particularly caspase-1, caspase-3, and caspase-11, are essential mediators of pyroptosis. Inhibitors or activators of these caspases offer a targeted approach to control pyroptosis [338]. For example, paclitaxel and cisplatin are chemotherapy drugs known to induce GSDME-mediated pyroptosis by activating caspase-3. This pathway has been particularly effective in cancers that express high levels of GSDME [375]. By shifting the mode of cell death from apoptosis to pyroptosis, these agents can trigger a stronger immune response, attracting immune cells like dendritic cells and T cells to the tumor site and amplifying anti-tumor immunity [139]. Additionally, caspase-1 inhibitors, such as VX-765, have been explored for modulating pyroptosis to reduce excessive inflammation, while maintaining enough immune activation to combat tumors [345, 346].

GSDM proteins In gastric cancer, decreased expression of GSDMD facilitates tumor growth [376]. GSDMD-mediated pyroptosis may occur during standard antitumor therapies. For instance, cisplatin has been shown to trigger the NLRP3/caspase-1/GSDMD pyroptosis pathway in breast cancer cells [344]. Indeed, numerous studies have identified numerous compounds that induce GSDMD-dependent pyroptosis in tumor cells through diverse mechanisms. Metformin, for instance, induces GSDMD-mediated pyroptosis in chemo-refractory esophageal squamous cell carcinoma [159]. Anthocyanin activates pyroptosis in oral squamous cell carcinoma cells by upregulating the expression of NLRP3, caspase-1, and IL-1β [377]. Similarly, 4-hydroxybenzoic acid selectively triggers pyroptosis in the lung cancer cell line A549 by enhancing the transcription of caspase-1, IL-1β, and IL-18, while leaving normal lung epithelial cells unaffected [378]. Simvastatin also induces pyroptosis in A549 and H1299 cells by activating the NLRP3 pathway [128]. Val-boroPro, a DPP8/9 inhibitor, induces caspase-1-dependent pyroptosis in human acute myeloid leukemia [379]. Docosahexaenoic acid triggers caspase-1 activation, GSDMD maturation, and IL-1β secretion in the breast cancer cell line MDA-MB-231 through lysosomal damage and ROS formation [380]. Lysosomal rupture appears to be a common downstream event of various interventions leading to pyroptosis in cancer cells [380–382]. In epithelial ovarian cancer cells, a non-canonical inflammasome signal, GSDMD/caspase-4, induced by 2-(α-Naphthoyl) ethyltrimethylammonium iodide, contributes to pyroptosis [383]. Additionally, LPS can evoke non-canonical inflammasome caspase-11-mediated pyroptosis in lung cancer cells [127]. Apart from numerous chemicals, various sophisticated nanoparticles have been designed to promote inflammasome-mediated pyroptosis [382].

GSDMNT, known for triggering pyroptosis and inducing antitumor immune responses, has emerged as a highly promising strategy for anticancer therapy. However, its broad cytotoxicity in mammalian cells poses challenges in the production and delivery of cancer cells. Lu et al. devised a method involving a recombinant adeno-associated virus expressing GSDMNT [384]. They utilized a mammal-specific promoter to drive GSDMNT expression and packaged the virus into insect cells to prevent its expression. Additionally, recombinant adeno-associated virus-Cre was used to restore GSDMNT expression. This approach not only induces pyroptosis but also enhances antitumor responses. Importantly, better therapeutic outcomes have been observed when combined with anti-PD-L1 therapy [384].

Antibody-drug-conjugate (ADC) associated with pyroptosis

As described above, in recent years, the cleavage of GSDME by various chemotherapy drugs has been shown to cause cell pyroptosis. Similarly, many studies have also proved that antibody-drug conjugate (ADC) therapy plays an increasingly important role in the armamentarium of anticancer therapies.

Pyroptosis differs from apoptosis by promoting the release of pro-inflammatory cytokines and causing the rupture of the cell membrane, which can enhance antitumor immune responses [41]. For instance, the study by Wittwer et al. demonstrated that a mesothelin-targeting ADC with a tubulysin payload induced pyroptosis in mouse models of breast and colon cancer. This pyroptotic effect was critical for the ADC's antitumor efficacy, as the cleavage of GSDME led to tumor cell death and stimulated the immune system by increasing the infiltration of cytotoxic T lymphocytes [350]. The combination of ADC therapy with dendritic cell-expanding agents, such as Fms-like tyrosine kinase-3 ligand (Flt3L), further boosted the immune response, especially in GSDME-silenced tumors, highlighting a potential therapeutic strategy for cancers with suppressed GSDME expression [350].

These studies underscore the potential of ADCs not only to directly kill cancer cells but also to reshape the tumor microenvironment by inducing pyroptosis and enhancing antitumor immunity. The use of ADCs that can trigger pyroptosis provides a promising approach to cancer treatment, particularly for tumors that are resistant to apoptosis.

ICIs

Blocking the interaction between immune checkpoints and their ligands with immune checkpoint inhibitors (ICIs) can relieve immune cells from checkpoint-induced inhibition, thereby reinvigorating them to exert antitumor effects. Currently, numerous ICIs have shown remarkable progress in clinical applications, representing a breakthrough in tumor therapy. Inhibitors targeting cytotoxic T lymphocyte-associated antigen-4 (CTLA-4), programmed death-1 (PD-1), and programmed death-ligand 1 (PD-L1) have been successfully approved for the treatment of various malignant tumors such as melanoma and non-small cell lung cancer. The success of CTLA-4 and PD-1/PD-L1 antibodies has sparked a surge of research into ICIs [385]. In 2017 and 2018, two PD-1 inhibitors, nivolumab and pembrolizumab, were approved as second-line treatments for HCC [386]. Significantly, the superior outcomes of atezolizumab plus bevacizumab compared to sorafenib for advanced HCC signaled a new direction in combination therapies [387]. Currently, numerous ongoing clinical trials involve ICIs,

either alone or combined with anti-VEGF agents or tyrosine kinase inhibitors (TKIs). A deeper understanding of the TME has sparked considerable interest in ICIs. Therefore, manipulating the TME directly or indirectly holds promise for new breakthroughs in clinical cancers treatment.

Recently, more immune checkpoints like lymphocyte activation gene-3 (LAG-3), T cell immunoglobulin and mucin domain-containing protein 3 (TIM-3), and cluster of differentiation 47 (CD47) have been identified. Consequently, extensive preclinical and clinical research on these proteins is underway [388].

Targeting cytokine and signaling pathways

ILRs and signaling pathways Prior research has shown that within the TME, IL-6 collaborates with the JAK/STAT3 signaling pathway to engage in activities that significantly inhibit the function of immune effector cells [389]. Tocilizumab, a humanized monoclonal antibody targeting IL-6R, has shown broad antitumor and anti-chemoresistance properties across various cancer types in preclinical investigations [390]. During a phase I clinical trial, administration of high-dose tocilizumab was found to promote CD8 + T cell activation and elevate levels of antitumor effectors like IFN-γ and TNF-α, consequently bolstering anticancer immune responses [391]. Additionally, preclinical data suggests that targeting IL-6/JAK/STAT3 signaling could enhance the effectiveness of immune checkpoint-inhibiting monoclonal antibodies in combating tumors [392].

Inflammatory cytokines released during pyroptosis play vital roles in regulating tumor progression and metastasis. Thus, targeting these cytokines presents potential opportunities for treating different cancers. Canakinumab, a human anti-IL-1β monoclonal antibody widely utilized in inflammatory diseases, has been applied in the treatment of various cancers such as lung cancer [393], breast cancer, colon cancer, and other tumor types [394]. Moreover, Yuan et al. [395]. demonstrated that inhibiting IL-1β with canakinumab notably decreased tumor growth in K-ras-mutant lung adenocarcinoma by restructuring the TME [395]. The anti-IL-1β monoclonal antibody (mAb) facilitated the infiltration and activation of CD8 + T cells while suppressing myeloid-derived suppressor cell function. Hence, blocking IL-1β presents a promising therapeutic avenue for K-ras–mutant lung adenocarcinoma. Similarly, inhibiting the IL-1β pathway using an IL-1 receptor antagonist (IL-1Ra) may play a pivotal role in curtailing tumor progression [396]. Anakinra, an IL-1Ra, has demonstrated its ability to inhibit breast cancer growth by reducing IL-1β and IL-22 secretion [397]. Furthermore, anakinra has proven effective in significantly attenuating cytokine release syndrome during CAR-T therapy, offering a promising strategy to mitigate the severe side effects associated with this treatment [398, 399].

TGF-β TGF-β assumes a significant role in activating CAFs and mediating their interaction with immune cells, as discussed earlier. This suggests that TGF-β inhibition therapy could potentially restore compromised immune responses within the TME [105]. Presently, numerous preclinical and clinical investigations into TGF-β-based immunotherapies are underway [178]. One such example is galunisertib (LY21577299), a small-molecule inhibitor targeting transforming growth factor beta receptor 1 (TGF-βR1), with infrequent reports of discernible cardiac toxicities during treatment [400]. Phase II clinical trials for pancreatic cancer and hepatocellular carcinoma have demonstrated significant therapeutic efficacy of galunisertib against tumors, whether administered in combination with gemcitabine or as monotherapy [401]. Other studies have shown that combining a therapy directed at TGF-β derived from CAFs with checkpoint inhibitors like anti-PD-L1 antibodies produces more significant immunological impacts on tumors compared to individual treatments [402]. Therefore, Ravi et al. [403] endeavored to create chimeric antibodies by fusing the TGF-βR2 extracellular domain with anti-CTLA4 or anti-PD-L1 antibodies, resulting in anti-CTLA4-TGF-βR2 and anti-PD-L1-TGF-βR2 constructs. In comparison to ipilimumab (an anti-CTLA-4 antibody), the anti-CTLA4-TGF-βR2 molecule demonstrates greater efficacy in reducing tumor-infiltrating Treg cells and inhibiting tumor progression [404].

With ongoing clinical trials for next-generation TGFβRI inhibitors and bifunctional antibodies that combine TGFβ and immune checkpoint inhibition, TGFβ has become an appealing therapeutic target in the era of immunotherapy [405]. Another option is targeting macrophages, as they are a major source of inflammatory factors [406]. Currently, some antibodies and inhibitors have demonstrated anti-tumor activities in preclinical studies, and a few have been explored in early-stage clinical trials. A key challenge in targeting inflammation is achieving selective inhibition of pro-tumor chronic inflammation without compromising anti-tumor immunity [110].

Novel application of pyroptosis in antitumor approaches (Fig. 6)

Recent advancements highlight the potential of pyroptosis in enhancing antitumor immunity. A notable development is the Phe-BF3 desilylation bio-orthogonal system,

which effectively transports desilylation catalyzed by Phe-BF3 with NP-GSDMA3-mediated delivery into specific mammary tumor cells in mice. This technique boosts T cell-dependent tumor regression by increasing CD4+, CD8+, NK cell, and M1 macrophage populations while reducing Treg cells, M2 macrophages, monocytes, neutrophils, and MDSCs. This system reveals the antitumor immune potential of pyroptosis, suggesting that a gasdermin agonist may enhance cancer immunotherapy efficacy [407].

Additionally, in patients with extrahepatic cholangiocarcinoma (CCA), tumor-cell-derived microvesicles containing methotrexate can induce pyroptosis in CCA cells via a GSDME-dependent pathway. The intracellular contents released from pyroptotic CCA cells activate macrophages to produce pro-inflammatory cytokines, attracting neutrophils to the tumor site and degrading the stromal barrier in the CCA TME, alleviating biliary obstruction in nearly 25% of patients [408].

Another application involves tumor-targeting nanoliposomes loaded with cisplatin. When combined with decitabine (DAC), these nanodrugs activate and upregulate the caspase-3/GSDME pathway, inducing pyroptosis in tumor cells and enhancing the immunological effect of chemotherapy in a mouse triple-negative breast cancer model. DAC also demethylates the GSDME gene in tumor cells [409].

Finally, a chimeric co-stimulatory converting receptor has been designed to disrupt the PD-1 pathway, enhancing the activity of chimeric antigen receptor (CAR)-NK cells against solid tumors. The antitumor activity of NK92 cells is significantly improved by the neo-complex PD1-NKG2D-41BB receptor, primarily through pyroptosis activation [410].

Emerging research and technologies (Fig. 7)

High-throughput cytokine assays

In recent years, the crosstalk between pyroptosis and cytokines within the TME has garnered significant attention due to its implications in cancer progression and therapy. High-throughput cytokine assays have emerged as invaluable tools in elucidating the intricate interplay between these processes. These assays allow for the simultaneous quantification of multiple cytokines in various biological samples, offering a comprehensive view of the cytokine landscape in the TME [411]. By employing advanced technologies such as multiplex immunoassays and microfluidic platforms, researchers can efficiently

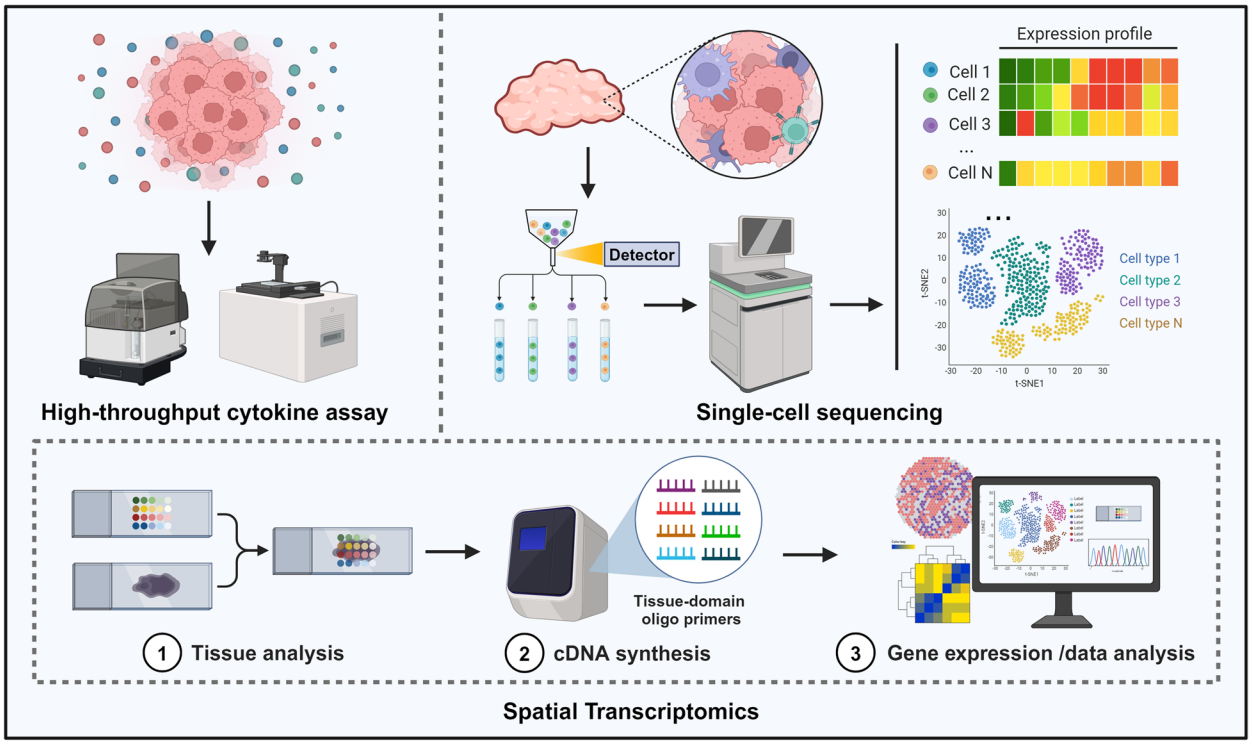

Fig. 7 Emerging research and technologies in TME. High-throughput cytokine assays provide a comprehensive view of cytokine profiles in the TME by quantifying multiple cytokines simultaneously. Single-cell sequencing allows for studying the co-evolution of tumor cells and TME components by profiling small quantities of cells. Spatial transcriptomics identifies cell types and their functional states within the TME by profiling thousands of genes across spatially defined tissue regions concurrently

profile cytokine expression patterns with high sensitivity and specificity. For instance, a study presents a system that enables the dynamic analysis of cellular interactions, proliferation, and therapeutic effectiveness through spatiotemporal monitoring and secretum profiling [411]. Lenalidomide, an immunomodulatory drug, demonstrated a direct anti-proliferative effect on activated B-cell-like Diffuse large B cell lymphoma (DLBCL) spheroids and decreased several cytokines and other markers (such as CCL2, CCL3, CCL4, CD137, and ANG-1 levels) [411]. Together, this innovative spheroid platform will facilitate high-throughput screening of anti-cancer therapeutics in a semi-automated fashion [411]. Furthermore, these assays enable the exploration of dynamic changes in cytokine levels during pyroptosis induction and its subsequent effects on tumor immune responses. Integrating high-throughput cytokine assays into studies investigating the crosstalk between pyroptosis and cytokines provides valuable insights into the underlying mechanisms driving tumor progression and facilitates the development of novel therapeutic strategies targeting these pathways.

Single-cell sequencing

Single-cell sequencing enables the simultaneous profiling of small quantities of tumor cells and TME cellular constituents, making it valuable for studying the co-evolution of tumor cells and the TME during tumor development. Analysis of pancreatic cancer precursors at single-cell resolution revealed an increase in proinflammatory immune components in the TME at an early stage, which were progressively depleted and replaced by stromal myofibroblast populations during neoplastic progression [412]. Profiling patients' melanoma at single-cell resolution uncovered two distinct tumor cell states, MITF-dominant and AXL-dominant, corresponding to specific tumor microenvironmental patterns, including specific interactions between cancer cells and their TME [413]. Single-cell sequencing can also track dynamic changes in the TME during therapeutic treatment. Using paired scRNA-seq and T-cell receptor sequencing of cells from patients with basal or squamous cell carcinoma before and after anti-PD-1 therapy, T-cells responding to checkpoint blockade were found to mainly derive from a distinct repertoire of T-cell clones not observed before treatment, rather than pre-existing tumor-infiltrating T lymphocytes [414]. Overall, single-cell sequencing of tumor and TME cells provides immense insights into tumor evolution, patient tumor classification, and guidance for cancer therapies.

Along with scRNA-seq, new methods and technologies for profiling genetic, epigenetic, proteomic, spatial, and lineage information in individual cells have been invented and are advancing rapidly. These single-cell multi-omics technologies can reveal cellular heterogeneity at multiple molecular levels. Integrative analysis of multi-omics data will provide profound novel insights into the fundamental mechanisms driving cellular diversity and help to identify targetable cellular subsets or signaling pathways essential for cancer cell adaptation to the TME [415].

Spatial transcriptomics

Spatial transcriptomics has emerged as a powerful tool for studying the spatial organization of gene expression within the TME [416]. This innovative technology allows researchers to visualize and analyze gene expression patterns in situ, providing insights into the complex interactions between tumor cells, stromal cells, and immune cells [416].

Spatial transcriptomics enables the simultaneous profiling of thousands of genes across spatially defined regions of tissue sections, allowing for the identification of cell types and their functional states within the TME [417]. By integrating spatial information with traditional transcriptomic data, researchers can gain a deeper understanding of the heterogeneity and dynamics of cellular interactions within the TME [418].

One key application of spatial transcriptomics in the study of pyroptosis and cytokine signaling in the TME is the identification of spatially distinct expression patterns of key genes involved in these processes. For example, spatial transcriptomic analysis can reveal the spatial distribution of pyroptosis-related genes within the tumor tissue, providing insights into the spatial heterogeneity of cell death mechanisms and their impact on tumor progression [288].

Furthermore, spatial transcriptomics can elucidate the spatial relationships between cytokine-producing cells, such as tumor-infiltrating immune cells, and their target cells within the TME [419]. This spatial information is crucial for understanding the localized effects of cytokines on neighboring cells and their contribution to immune regulation and tumor immunity.

Overall, spatial transcriptomics represents a promising approach for advancing our understanding of pyroptosis, cytokine signaling, and their roles in shaping the TME. By providing spatial context to gene expression data, this technology offers new opportunities for identifying novel therapeutic targets and developing personalized treatment strategies for cancer patients.

Perspective and conclusion

The complex interplay between pyroptosis and cytokine signaling in the tumor microenvironment represents a crucial frontier in cancer research. This review highlights the essential roles of pyroptosis in triggering

inflammatory responses and remodeling the TME, as well as the reciprocal effects of cytokines in either promoting tumor progression or facilitating immune-mediated tumor destruction.

Cytokines influence both immune responses and tumor progression within the TME, operating through pro-inflammatory and anti-inflammatory mechanisms [420–423]. They can induce pyroptosis in cells directly or indirectly, with significant contributions from both tumor and immune cells [39, 140, 424]. Our focus centers on the crosstalk between these cellular entities, pyroptosis, cytokines, and various signaling pathways. Pyroptosis serves a dual role in tumor development: it influences tumor advancement through gene expression linked to pyroptosis and enhances anti-tumor immune responses by promoting the infiltration of CD8 + T cells, NK cells, and M1 macrophages [407]. Additionally, the impact of effectors like RIPK1/3, inflammasomes, and the cytokines and DAMPs released through ICD on immune cells and immune responses remains debated. These findings point to a more intricate relationship between non-apoptotic PCD and immune responses across various tumor types and settings [32]. It is vital to investigate how diverse components of the TME—including immune, tumor, and stromal cells—interact to either inhibit or promote tumor progression via immune mechanisms and metabolic reprogramming. Therefore, novel therapies targeting pyroptosis and cytokine signaling could represent promising avenues for cancer treatment.

However, the application of pyroptosis as a therapeutic strategy in the development of anticancer agents presents considerable challenges. Designing effective drugs that specifically induce pyroptosis in human cells, while adhering to rigorous safety standards, is a significant obstacle in pharmaceutical research [141]. Combining targeted treatments that activate or suppress pyroptosis with immunotherapy offers substantial potential for advancing cancer therapy [425, 426]. This integrative approach could lead to significant breakthroughs, providing patients with more effective and personalized treatment options. While the combination of chemotherapy and ICIs has shown great promise, further investigation into the role of pyroptosis in chemotherapy-related toxicity is necessary [427]. Additionally, the initiation of pyroptosis by radiotherapy-induced DNA damage through various signaling mechanisms may enhance antitumor effects when combined with immunotherapy [428–430]. This strategy leverages the strengths of each modality to achieve optimal therapeutic outcomes. Ultimately, the integration of targeted therapies, radiotherapy, and chemotherapy with immunotherapy holds significant promise for improving cancer treatment. Nevertheless, optimizing the timing and sequence of these therapies is crucial to maximizing their efficacy and enhancing patient outcomes.

Despite the growing understanding of the molecular mechanisms underlying pyroptosis and the potential for new therapeutic targets, challenges remain. Firstly, the relationship between cytokines, pyroptosis, and the TME is complex and multifaceted. While significant progress has been made in defining pyroptosis pathways, further investigations are necessary to clarify the intricate signaling mechanisms, explore additional cytokines, and assess the roles of various GSDM family proteins, as well as their pathological significance. Secondly, pyroptosis does not uniformly exert a beneficial therapeutic effect in cancer treatment. For instance, elevated expression of GSDMC has been linked to poorer prognoses in invasive breast carcinoma, correlating with immune cell infiltration [431]. Similarly, upregulated GSDMB has been shown to enhance the proliferation and invasiveness of bladder cancer cells [432]. These contradictory effects may arise from the distinction between acute activation of pyroptosis, which tends to inhibit tumor formation, and sustained pyroptosis, which may promote tumor progression [34, 87]. Thirdly, attention should be paid to potential tissue damage and cytokine release syndrome (CRS). In certain tumor cell lines, GSDME expression levels are lower than in normal cell lines, risking unintentional damage to healthy tissues during chemotherapy [40, 63]. Research demonstrated that tumor cell pyroptosis initiated CRS during CAR T cell therapy by activating inflammatory pathways through granzyme B-mediated GSDME cleavage [35]. While a novel RGD-anchored curcumin-loaded liposome effectively targets macrophages to inhibit pyroptosis, potentially providing a strategy to mitigate CRS and improve outcomes in sepsis-related organ injuries [36].

In summary, targeting pyroptosis and other components within the TME holds significant promise for novel cancer treatments, and substantial efforts are being directed toward translating these findings into clinical applications. Importantly, pyroptosis has the potential to enhance the efficacy of immunotherapy by modulating tumor immunogenicity and increasing lymphocyte infiltration in the TME. However, it is crucial to acknowledge the possibility of negative outcomes despite promising experimental data suggesting the antitumor effects of pyroptosis. Future research will require more animal models to explore the broader consequences of pyroptosis, as well as more clinical trials investigating the modulation of pyroptosis in cancer patients.

Acknowledgements
We would like to express our gratitude to BioRender (https://app.biorender.com/) for assistance in creating the figures.

Authors' contributions
L.W., C.T. and H.X. participated in the conception and design of the study; H.W., T.W. and S.Y. wrote the manuscript; J.T., Y.Z. and L.W. reviewed and revised the manuscript; H.W., T.W. and S.Y. contributed equally to this work. C.T. and H.X. jointly supervised this work. All authors reviewed the manuscript.

Funding
This work was supported by the National Natural Science Foundation of China (82272664, 82172500, 32300528), the Science and Technology Innovation Program of Hunan Province (2023RC3085, 2023RC3080), Hunan Provincial Health High-Level Talent Scientific Research Project (R2023054), Hunan Provincial Natural Science Foundation of China (2022JJ30843), the Scientific Research Fund of Hunan Provincial Education Department (23B0023), the Excellent Youth Foundation of Hunan Scientific Committee (2024JJ2084), the Science and Technology Development Fund Guided by Central Government (2021Szvup169), Hunan Provincial Administration of Traditional Chinese Medicine Project (D2022117), the Scientific Research Program of Hunan Provincial Health Commission (B202304077077), the Fundamental Research Funds for the Central Universities of Central South University (2024ZZTS0961).

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

Declarations

Ethical approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Received: 13 July 2024 Accepted: 22 November 2024
Published online: 30 November 2024

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