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REVIEW

Pyroptosis in cancer: a dual regulator of tumor cell fate and immune activation

Yuewen Zhang[1,2], Mengshi Luo[1,2], Zhiqi Liao[1,2], Qiuyang Xu[1,2], Ding Ma[1,2], Qinglei Gao[1,2], Tao Zhu[1,2], Yong Fang[1,2]

[1]Department of Obstetrics and Gynecology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430030, China; [2]National Clinical Research Center for Obstetrics and Gynecology, Cancer Biology Research Center (Key Laboratory of the Ministry of Education), Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430030, China

ABSTRACT Pyroptosis is a form of programmed cell death (PCD) that triggers inflammation. Pyroptosis is activated by specific inflammasomes and caspases, leading to the cleavage of gasdermin protein families, especially gasdermin D (GSDMD) and gasdermin E (GSDME). While pyroptosis has been extensively linked to innate immunity and diseases, such as atherosclerosis, the role in cancer remains an area of active investigation. Studies have suggested that pyroptosis influences tumor behavior, including proliferation and invasion, across different tissue types and genetic backgrounds. This process occurs through both canonical and non-canonical pathways involving GSDMD and GSDME. Tumors tend to thrive in the chronic inflammatory environment created by pyroptosis but tumors are more likely to be eradicated if pyroptosis occurs suddenly and extensively. Indeed, targeting pyroptosis pathways holds promise as an anticancer strategy. To date, several drugs are found to have the ability of inducing pyroptosis to enhance tumor clearance. Moreover, pyroptosis-related genes (PRGs) have emerged as valuable biomarkers for prognosis and monitoring the tumor microenvironment (TME). This review explores the mechanisms underlying endogenous and exogenous pyroptosis in cancer, examines the dual role within tumors, discusses the potential for targeting pyroptosis in cancer treatment and prognosis, and highlights the interactions between pyroptosis and other forms of PCD in cancer.

KEYWORDS Pyroptosis; gasdermin; tumor immunity; anticancer therapy; prognosis

Introduction

In addition to surgery, chemotherapy, and radiation therapy, the treatment of malignant tumors now includes emerging strategies, like targeted therapy and immunotherapy. The primary goal of these therapies is to selectively induce cancer cell death while minimizing damage to surrounding healthy tissue. To achieve this goal, one key mechanism is the induction of tumor cell apoptosis[1]. Over the years, drugs and biotechnologies aimed at triggering apoptosis have been developed and successfully applied in cancer treatment. However, tumor cells that escape normal apoptotic regulation often develop resistance to chemotherapy and radiation, posing a stumbling block in anticancer therapy[2]. Moreover, researchers have identified anti-apoptotic proteins, such as Bcl-X_L, in malignant tumors that have a significant role in the resistance to cancer therapy[3]. Consequently, inducing apoptosis in tumor cells remains a formidable challenge. In addition to apoptosis resistance, the immunosuppressive tumor microenvironment (TME) is another culprit of poor response to cancer therapy[4]. For instance, signaling molecules, like Notch3, which is overexpressed in colorectal cancer (CRC), have been confirmed to enhance the immunosuppressive TME by efficiently promoting the infiltration of macrophage[5]. Quiescent cancer cells that resist immunotherapy also cooperate with the immunosuppressive TME to evade T cell attacks, exacerbating tumor progression[6].

Given these challenges, another form of programmed cell death (PCD) emerges as a promising solution to both problems (pyroptosis)[7,8]. PCD currently includes apoptosis, necroptosis, pyroptosis, ferroptosis, autophagy, and PANoptosis[7]. Comparatively speaking, the occurrence, regulatory mechanism, and morphologic characteristics of pyroptosis are distinct from other PCDs. Pyroptosis typically occurs

Correspondence to: Tao Zhu and Yong Fang
E-mail: tjogzt@gmail.com and tongjify@tjh.tjmu.edu.cn
ORCID ID: https://orcid.org/0009-0001-0779-2245 and https://orcid.org/0000-0003-3412-8208
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in immune cells, like monocytes, macrophages, and dendritic cells (DCs), in normal tissues. Pyroptotic cells maintain intact nuclei when activated by pathogen-associated molecular patterns (PAMPs) from bacteria, viruses, fungi or protozoa, and cell-derived damage-associated molecular patterns (DAMPs), unlike apoptosis and necrosis, but undergo swelling until the cell membrane ruptures, releasing intracellular molecules that activate strong inflammatory responses to eliminate pathogenic infections and internal danger signals[8]. It is also worth noting that pyroptosis has a dual influence on cancer cells. Intense pyroptosis triggers a robust inflammatory response, promoting significant tumor regression and improving the tumor immune microenvironment (TIME), thereby stimulating anti-tumor immunity[9]. In contrast, prolonged pyroptosis leads to the accumulation of cytokines, such as IL-1β and IL-18, create a chronic inflammatory environment that may increase the possibility of tumor occurrence and metastasis when continuously released[10].

Based on a comprehensive consideration of the pyroptosis characteristics between immune and tumor cells, inducing pyroptosis in cancer cells may contribute to tumor-specific elimination, which offers a promising approach to cancer therapy. In this review we explore the mechanisms underlying pyroptosis in cancer cells and examine existing drugs and potential targets that may be leveraged for therapeutic purposes. Therapies targeting pyroptosis pathways represent an ideal strategy for improving cancer treatment outcomes (**Figure 1**).

Pyroptosis

Cookson and Brennan introduced the concept of pyroptosis in 2001, distinguishing pyroptosis from apoptosis based on the pro-inflammatory features[11]. As research advanced, it became clear that inflammatory caspases have a critical role in initiating pyroptosis[12]. Most recently, the executor of pyroptosis, gasdermin D (GSDMD), was identified. GSDMD is cleaved by upstream inflammatory caspases, leading to the characteristic cell membrane pore formation and pyroptotic cell death[13]. GSDMD belongs to the gasdermin (GSDM) family, which also exhibits similar membrane-pore forming activity[14]. Other GSDM family members have since been shown to have comparable roles in pyroptosis[15]. Therefore, pyroptosis is now recognized as a form of PCD triggered by caspases and mediated by the GSDM family. Herein we mainly focus on the specific role of the GSDM family in pyroptosis, examining the pathways involved in normal and cancer cells.

GSDM family

The GSDM family includes the following 6 members: GSDMA; GSDMB; GSDMC; GSDMD; GSDME (also known as DFNA5); and GSDMF (also known as PVJK or DFNB59). Among the GSDM family members, GSDMF is structurally divergent from the other family members, lacks the canonical pore-forming domain, and has not been implicated in pyroptosis. Therefore, GSDMF will not be discussed in detail in this review. Except for GSDMF, most GSDM proteins share the following three structural domains: a cytotoxic N-terminal (GSDM-NT) pore-forming domain; a flexible linker domain; and a C-terminal (GSDM-CT) auto-inhibitory domain[16]. The GSDM-NT domain is crucial for the induction of pyroptosis. Studies have shown that GSDM family members, such as GSDMD and GSDME, are cleaved by inflammatory caspases (caspase-1, -4, -5, and -11), apoptosis-associated caspases (caspase-3 and -8), and granzymes, especially granzyme A (GZMA) and granzyme B (GZMB). The cleavage releases the GSDM-NT domain, which forms pores in the cell membrane, triggering pyroptosis[17-20]. Interestingly, after cleavage GSDM-NT may also serve as a feedback inhibitor to prevent the continuous activation of caspases[21], highlighting the central role of the GSMD family in the pyroptosis pathways. The expression of *GSDM* genes varies significantly across different tumor types. Furthermore, even the same *GSDM* gene has been shown to have opposite effects in different tumors and has a great influence on drug resistance[22-25] (**Figure 2**).

GSDMA

GSDMA is primarily expressed in the upper digestive tract, skin epithelium, and lungs[26,27]. Recent breakthrough findings have revealed that GSDMA functions not merely as an effector but also as a direct sensor of bacterial infection. The cysteine protease, SpeB, is a *Streptococcus pyogenes* virulence factor. *S. pyogenes*, also known as Group A *Streptococcus* (GAS), triggers caspase-independent pyroptosis in keratinocytes by directly cleaving GSDMA after Gln246 to release the active GSDMA-NT fragment[28]. This process positions GSDMA as a unique frontline defender that directly recognizes pathogen-derived virulence factors and an effector of pyroptosis, contributing to the broader understanding of pyroptosis mechanisms. The physiologic significance of this SpeB-GSDMA axis has been firmly established *in vivo*. Mice lacking all three murine *Gsdma* homologues (or specifically *Gsdma1*) are more susceptible to invasive infection by pandemic hypervirulent M1T1 clones of GAS, exhibiting uncontrolled bacterial dissemination and increased mortality[29]. In addition to roles in host defense, GSDMA has also been implicated in cancer biology, although in a context-dependent manner. *GSDMA* expression is often silenced in cancer cell lines. However, paradoxical upregulation has been reported in CRC[30]. Collectively, these findings point to multiple therapeutic opportunities centered on the SpeB-GSDMA axis. Small-molecule stabilization of SpeB protease activity or inhibition of SpeB downregulation potentially restores GSDMA-mediated pyroptosis in infectious diseases, offering host-directed therapy against invasive GAS. The exquisite specificity of SpeB for GSDMA raises the possibility

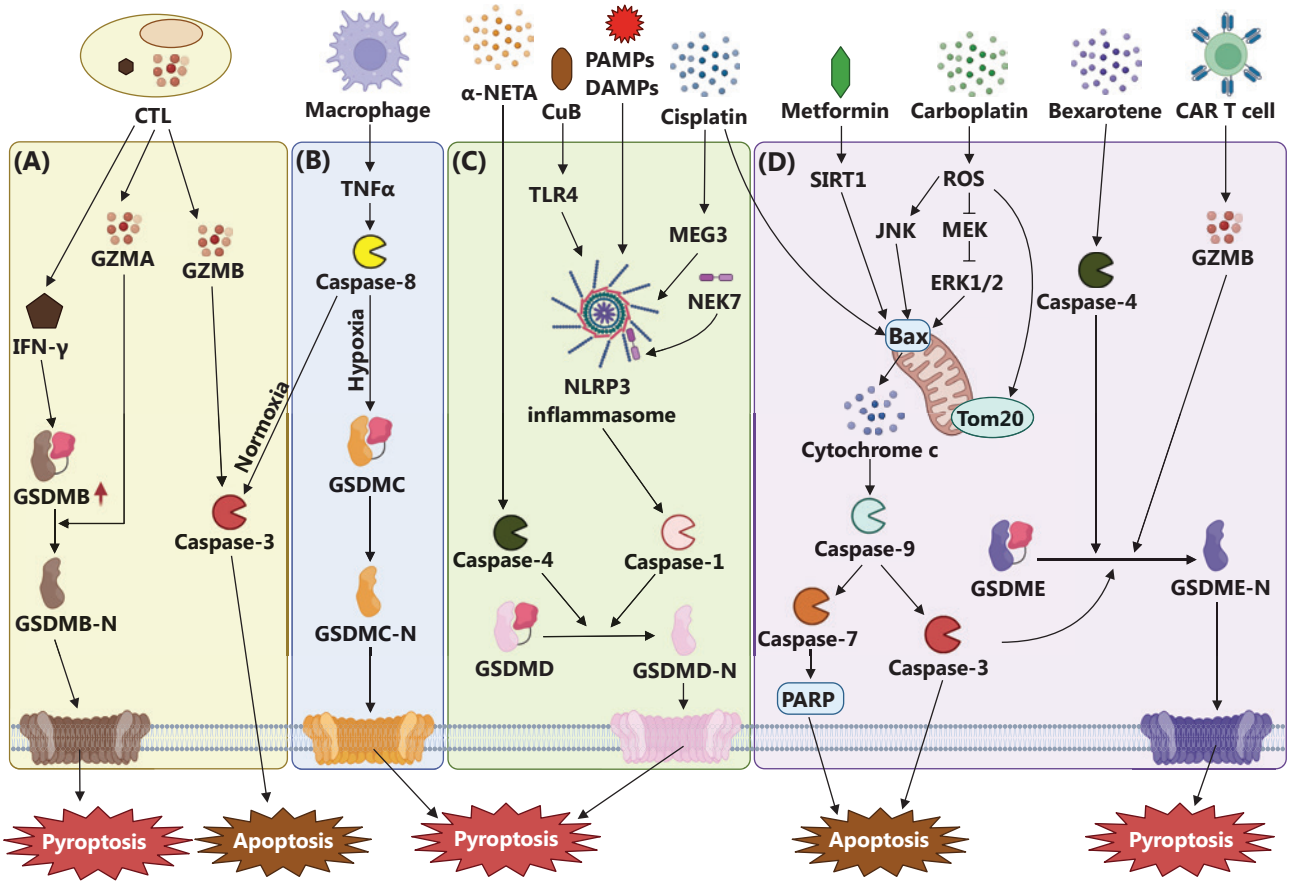

Figure 1 Pyroptosis has a regulatory role in tumor cell fate. Pyroptosis can overcome apoptosis resistance and an immunosuppressive TME, representing a promising means of PCD in cancer therapy. Diverse signals trigger the activation of specific caspases, which in turn cleave GSDM family members, leading to apoptosis or pyroptosis. (A) GSDMB-mediated pyroptosis driven by CTLs. Upon stimulation, CTLs secrete IFN-γ, GZMA, and GZMB. IFN-γ upregulates GSDMB expression, thereby increasing substrate availability for pyroptosis. GZMA directly cleaves GSDMB to release GSDMB-N, which forms membrane pores and triggers pyroptosis. In contrast, GZMB activates caspase-3, the classic executor of apoptosis. Thus, CTLs orchestrate pyroptotic and apoptotic cell death pathways, enhancing the cytotoxic potential against cancer cells. (B) Macrophage-derived TNF-α signaling switches between apoptosis and pyroptosis. Activated macrophages secrete TNF-α, which engages distinct cell death pathways depending on oxygen availability. Under normoxia, TNF-α activates caspase-8, followed by activation of caspase-3, which proceeds without GSDM-mediated pore formation, resulting in apoptosis. In contrast, activated caspase-8 cleaves GSDMC under hypoxia to generate GSDMC-N and induce pyroptosis, highlighting oxygen availability as a key determinant of tumor cell fate. (C) Chemotherapeutic agents engage pyroptosis and apoptosis. The chemotherapeutic agent, α-NETA, directly activates caspase-4 to cleave GSDMD, engaging a non-canonical inflammasome pathway that converges on GSDMD-mediated pyroptosis. Other stimuli, such as the natural compound (CuB), the danger signals (PAMPs and DAMPs), and the chemotherapeutic agent (cisplatin), activate distinct upstream regulators (e.g., TLR4 and MEG3), leading to assembly of the NLRP3 inflammasome. The kinase (NEK7) facilitates NLRP3 inflammasome activation. Once activated, NLRP3 recruits and activates caspase-1, which cleaves GSDMD and trigger pyroptosis within TME. In parallel, cisplatin primarily induces apoptosis through the mitochondrial pathway by multiple stress signals at the mitochondria. Cisplatin promotes activation of pro-apoptotic Bcl-2 family members, such as Bax, resulting in the release of cytochrome c from the mitochondrial intermembrane space into the cytosol. Cytochrome c then recruits and activates caspase-9, which in turn activates the executioner caspase-3, ultimately culminating in apoptosis. (D) Anti-cancer therapies regulate tumor cell death through interconnected apoptotic and pyroptotic pathways. Metformin and carboplatin facilitate mitochondrial permeabilization through Bax, leading to cytochrome c release into the cytosol. Cytochrome c subsequently activates caspase-9, followed by caspase-3 and caspase-7. Notably, caspase-3 cleaves GSDME to generate GSDME-N, converting apoptotic signaling into pyroptosis, whereas caspase-7-mediated PARP cleavage completes apoptosis. In addition, bexarotene induces caspase-4 activation, while CAR T cells deliver GZMB into target cells. Both caspase-4 and GZMB cleave GSDME, generating GSDME-N and promoting pyroptosis. α-NETA, α-napthoyl-ethyltrimethylammonium iodide; Bax, Bcl-2-associated x protein; CAR T cell, chimeric antigen receptor T

cell; CTL, cytotoxic T lymphocyte; CuB, cucurbitacin B; DAMPs, damage-associated molecular patterns; ERK1/2, extracellular signal-regulated kinase 1/2; GSDM, gasdermin; GSDMB, gasdermin B; GSDMB-N, gasdermin B N-terminal domain; GSDMC, gasdermin C; GSDMC-N, gasdermin C N-terminal domain; GSDMD, gasdermin D; GSDMD-N, gasdermin D N-terminal domain; GSDME, gasdermin E; GSDME-N, gasdermin E N-terminal domain; GZMA, granzyme A; GZMB, granzyme B; IFN-γ, interferon-gamma; JNK, c-Jun N-terminal kinase; MEG3, maternally expressed gene 3; MEK, MAPK/ERK kinase; NEK7, NIMA-related kinase 7; NLRP3, NOD-like receptor family pyrin domain-containing 3; PAMPs, pathogen-associated molecular patterns; PARP, poly(ADP-ribose) polymerase; PCD, programmed cell death; ROS, reactive oxygen species; SIRT1, sirtuin 1; TLR4, Toll-like receptor 4; TME, tumor microenvironment; TNF-α, tumor necrosis factor-alpha; Tom20, translocase of outer mitochondrial membrane 20. The figure was created using BioRender.com.

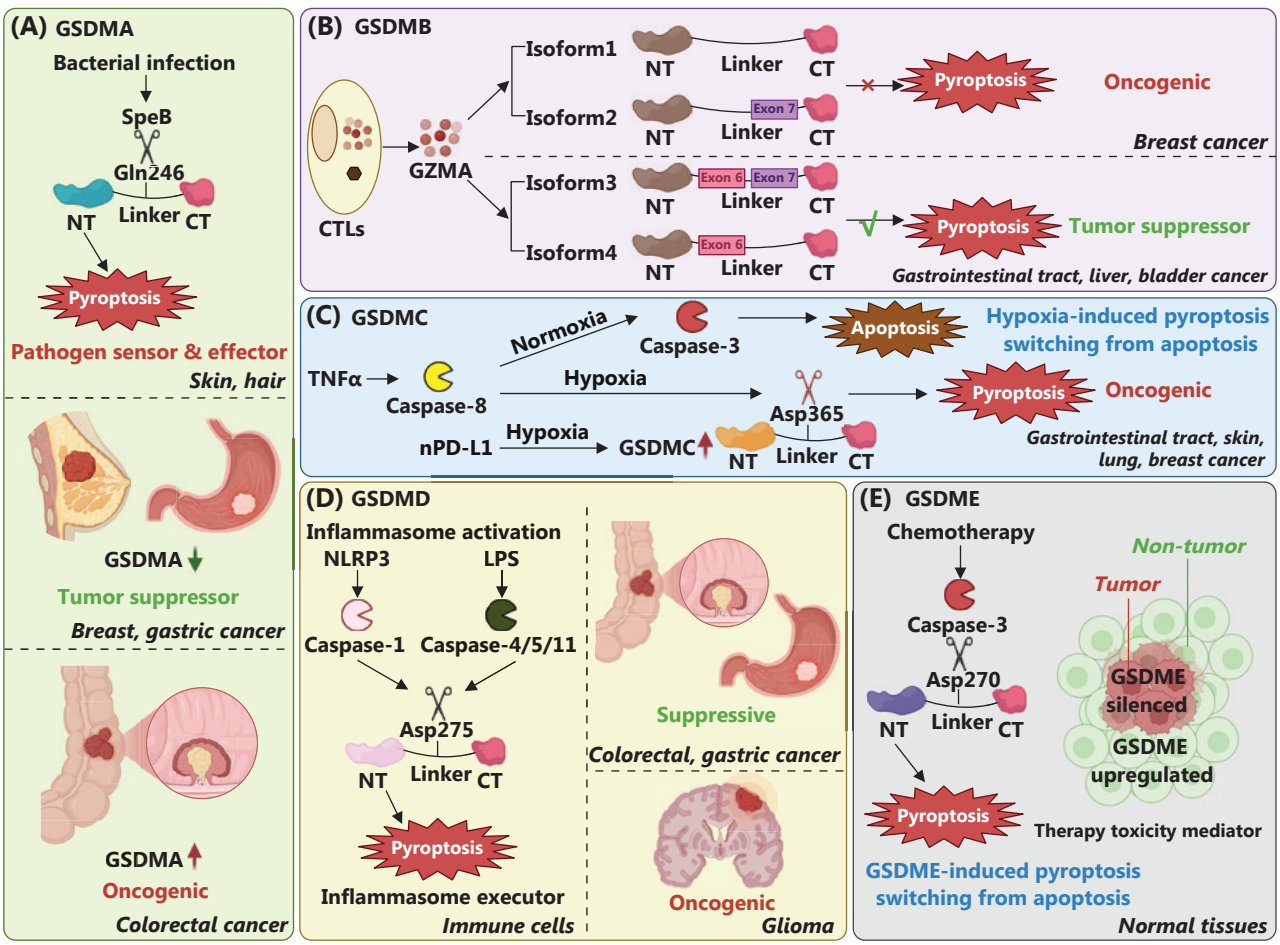

Figure 2 Distinctive features of GSDM family members (GSDMA-E). The upstream activators, cleavage mechanisms, functional outcomes, and context-dependent roles of GSDM family members vary. (A) GSDMA functions as a bacterial pathogen sensor and context-dependent tumor regulator. During *Streptococcus pyogenes* infection, the virulence factor, SpeB, cleaves GSDMA at Gln246 within the interdomain linker, releasing the NT fragment from CT-mediated auto-inhibition. Liberated GSDMA-N induces pyroptosis in epithelial barrier tissues, such as skin and hair, positioning GSDMA as a pathogen sensor and effector. GSDMA expression exhibits context-dependent regulation in cancer. GSDMA is frequently silenced in breast and gastric cancers, consistent with tumor-suppressive functions, but upregulated in colorectal cancer where GSDMA may display oncogenic properties. (B) GSDMB exhibits isoform-specific regulation underlying dual roles in tumors. Alternative splicing of exon 6 within the linker region generates multiple GSDMB isoforms, such as isoforms 1–4, with distinct functional capacities. Upon delivery by CTLs, GZMA cleaves GSDMB to induce pyroptosis. Isoforms 1 and 2 lack exon 6, exhibit reduced pyroptosis-inducing capacity, and are associated with pro-tumorigenic effects in cancers, such as breast cancer. Conversely, isoforms 3 and 4, which retain exon 6, undergo efficient cleavage, and confer anti-tumor effects in the gastrointestinal tract, and liver and bladder cancers. (C) GSDMC serves as a hypoxia-driven molecular switch from apoptosis-to-pyroptosis. TNF-α activates caspase-8, which directs two distinct cell death pathways depending on

oxygen conditions. Caspase-8 cleaves caspase-3, which leads to apoptosis under normoxia. GSDMC expression is upregulated *via* nPD-L1 under hypoxic conditions and caspase-8 subsequently cleaves GSDMC at Asp365 within the linker region, releasing GSDMC-N to induce pyroptosis. This hypoxia-induced switch from apoptosis-to-pyroptosis contributes to oncogenic processes in the gastrointestinal tract, and skin, lung, and breast cancers. (D) GSDMD is the inflammasome executor with context-dependent tumor effects. NLRP3 recruits and activates caspase-1 upon inflammasome activation, while cytosolic LPS activates caspase-4, -5, and -11. These inflammatory caspases cleave GSDMD at Asp275 within the linker region, releasing the pore-forming NT fragment. GSDMD-N inserts into the plasma membrane to execute pyroptosis, functioning as the principal inflammasome effector in immune cells. GSDMD exhibits dual roles in cancer. GSDMD exerts tumor-suppressive effects in colorectal and gastric cancers but displays oncogenic properties in glioma. (E) GSDME functions as a chemotherapy-induced switch from apoptosis-to-pyroptosis. Chemotherapy activates caspase-3, which cleaves GSDME at Asp270 within the linker region. The resulting GSDME-N fragment induces membrane pore formation and pyroptosis. GSDME is frequently silenced in cancer cells, limiting pyroptosis and favoring apoptosis, whereas GSDME remains highly expressed in normal tissues. Thus, GSDME functions as a mediator of therapy-related toxicity, a tumor suppressor, and a switch from apoptosis-to-pyroptosis, depending on expression and tissue context. CT, C-terminal domain; CTL, cytotoxic T lymphocyte; GSDMA, gasdermin A; GSDMA-N, gasdermin A N-terminal domain; GSDMB, gasdermin B; GSDMC, gasdermin C; GSDMC-N, gasdermin C N-terminal domain; GSDMD, gasdermin D; GSDMD-N, gasdermin D N-terminal domain; GSDME, gasdermin E; GSDME-N, gasdermin E N-terminal domain; GZMA, granzyme A; LPS, lipopolysaccharide; NLRP3, NOD-like receptor family pyrin domain containing 3; nPD-L1, nuclear PD-L1 (programmed death-ligand 1); NT, N-terminal domain; SpeB, streptococcal pyrogenic exotoxin B; TNF-α, tumor necrosis factor-alpha. The figure was created using BioRender.com.

of engineering SpeB as a targeted pyroptosis-inducing biologic for GSDMA-expressing tumors, a conceptually attractive strategy that requires addressing immunogenicity of SpeB and ensuring tumor-specific delivery.

Emerging evidence further reveals that viruses have evolved strategies to evade GSDMA-mediated pyroptosis. Seneca Valley virus (SVV), an oncolytic picornavirus, encodes a 3C protease that cleaves both porcine and human GSDMA, generating a truncated fragment that fails to localize to the plasma membrane and thus fails to induce pyroptosis[31]. This viral immune evasion mechanism not only advances our understanding of host-virus interactions but also has therapeutic implications. SVV is being developed as an oncolytic agent[32]. The ability of SVV to suppress GSDMA-mediated inflammation may influence the anti-tumor efficacy and safety profile. Therefore, further research is needed to focus on characterizing human polymorphisms that affect GSDMA function in infection and autoimmunity, and investigating whether GSDMA status predicts response to oncolytic viruses or chemotherapy to fully understand the expression and functional implications of GSDMA in cancer cells.

GSDMB

GSDMB is expressed in several organs, including the liver, and the gastrointestinal tract[33]. However, the functional characterization of GSDMB has been complicated by the existence of multiple alternative splicing variants that exhibit distinct and even opposing activities. Specifically, GSDMB has at least six isoforms (isoforms 1–6)[34]. Based on the exon composition and functional properties, these isoforms are categorized, as follows: isoforms 1–4 represent the major isoforms with well-characterized functions; isoforms 1 and 2 lack exon 6 and fail to induce pyroptosis; in contrast, isoforms 3 and 4 retain exon 6 and upon GZMA cleavage, trigger pyroptosis efficiently; isoform 5 lacks the N-terminal pore-forming domain and therefore fails to form membrane pores or induce pyroptosis; and the functional relevance of isoform 6 at the protein level remains to be established[35,36]. One study demonstrated that introducing GZMA-cleavable GSDMB into mouse cancer cells induced pyroptosis, which contributed to tumor elimination[19]. This finding suggested that GSDMB may hold potential as a therapeutic target in cancer treatment. However, recent studies indicated that endogenous expression of GSDMB in cancers may be linked to increased tumor aggressiveness and poor prognosis. For example, Cui et al.[37] reported that overexpression of GSDMB in clear cell renal cell carcinoma (ccRCC) is strongly associated with immune infiltration and worse patient outcomes. In addition, GSDMB enhances resistance to therapy in HER2(+) breast cancer (BRCA) by promoting Rab7-mediated autophagosome maturation[38]. The isoform-dependent duality of GSDMB raises critical questions for translational research. Whether GSDMB-mediated pyroptosis occurs in clinical tumor samples likely depends on the relative expression of cleavable *vs.* non-cleavable isoforms, which remains largely uncharacterized. Therapeutic strategies targeting GSDMB must consider this isoform complexity. Approaches that aim to activate GSDMB-mediated pyroptosis need to selectively engage cleavable isoforms, whereas efforts to block the pro-tumorigenic functions might target non-cleavable variants.

GSDMC

GSDMC is preferentially present in the epithelium of the gastrointestinal tract and skin[39]. In normal cells, such as human skin keratinocytes, the GSDMC expression is upregulated by ultraviolet radiation through a calcium-dependent signaling pathway[40]. Overexpression of GSDMC has been associated with poor prognosis in cancers, such as lung cancer and

BRCA[41,42], suggesting that *GSDMC* might be an oncogene driving tumor progression and metastasis. However, the precise role of GSDMC in cancer cells has not been fully elucidated. Recent studies have revealed that GSDMC functions as a direct substrate of caspase-8, which cleaves GSDMC at $_{362}$LELD$_{365}$ to induce pyroptosis and promote cancer cell death[43,44]. This activation mechanism is particularly significant under hypoxic conditions. Within the central hypoxic regions of tumors, a small population of cancer cells responds to hypoxic stress by inducing the translocation of nuclear PD-L1 (nPD-L1), which upregulates GSDMC expression and thereby diverts the induction of apoptosis by TNF-α toward GSDMC-mediated pyroptosis[43]. In contrast, TNF-α signaling engages the caspase-8/caspase-3 pathway under normoxia, leading to apoptosis[45]. Given the high expression of GSDMC in several cancers and the association with poor survival outcomes, GSDMC represents a promising therapeutic target that warrants further investigation.

GSDMD

GSDMD was the first member of the GSDM family identified as a key substrate for inflammatory caspases and is recognized as the executor of inflammasome-induced pyroptosis[13]. GSDMD is expressed in a variety of cells, including gastrointestinal epithelial, placental, and immune cells (especially macrophages and DCs), as well as cancers, like melanoma and esophageal, gastric, pancreatic, and prostate cancer[46]. NLRP3 recruits and activates caspase-1 upon inflammasome activation, while cytosolic lipopolysaccharide (LPS) activates caspase-4/5/11 *via* the non-canonical inflammasome pathway. These inflammatory caspases cleave GSDMD after Asp275 within the linker region, releasing the pore-forming N-terminal (NT) fragment. GSDMD-N then inserts into the plasma membrane to execute pyroptosis, functioning as the principal inflammasome effector in immune cells[13,47]. In contradiction with the common belief that GSDMD-induced pyroptosis in macrophages has a protective role against infections, recent findings have suggested that GSDMD may facilitate the escape of *Candida albicans* within macrophages, thus impairing anti-infection activity[48]. Similarly, existing experiments have also shown that high expression of GSDMD may have opposite roles in cancer cells, as exemplified by the tumor suppressive effect in gastric cancer (GC) and CRC, and the tumor-promoting effect in glioma[23-25]. In this case, studies have undertaken an in-depth investigation of the GSDMD effects, highlighting that the GSDMD effects may vary depending on subcellular location. High expression of nuclear GSDMD, for example, has been shown to increase the sensitivity of cancer cells to chemotherapy[49], reminding us that the specific role of GSDMD in cancer should be evaluated in conjunction with the subcellular localization.

GSDME

GSDME expression is limited in most cancers, including GC, CRC, and invasive BRCA. Both epigenetic silencing and high methylation in different cancer types suggest that *GSDME* may function as a tumor suppressor gene[20,50]. Consequently, activation of GSDME expression in tumor cells is a potential anti-cancer strategy. Mechanistically, GSDME mediates pyroptosis through caspase-3-dependent cleavage. Chemotherapeutic agents, such as lobaplatin, activate caspase-3, which cleaves GSDME at Asp270 within the linker region, releasing the pore-forming N-terminal fragment to execute pyroptosis[51]. Recently, epithelial-mesenchymal transition (EMT) has been shown to have the ability to stimulate *GSDME* transcription, leading to pyroptosis[52]. GSDME is relatively highly expressed in adjacent non-tumor normal tissues in contrast to the silenced expression in tumor cells, where GSDME is closely associated with radiation-related toxicity after radiotherapy due to the pro-inflammatory cytokines released by GSDME-mediated pyroptosis[53]. There is currently a study suggesting that GSDME expression in immune cells may have a significant effect on reducing the side effects of radiotherapy[54]. However, further research is needed to draw a firm conclusion. Nevertheless, it is apparent that targeting GSDME is beneficial in treating cancers and reducing side effects.

Signaling mechanisms underlying GSDM-mediated pyroptosis

To date research has established several key pyroptosis pathways, including the canonical inflammasome pathway, non-canonical inflammasome pathway, and granzyme-triggered pyroptosis. In response to different stimuli, different cells induce pyroptosis through different pathways in different microenvironments. In this section the mechanisms underlying the pathways are introduced (**Figure 3**).

Canonical inflammasome pathway

The inflammasome is a crucial component of the innate immune system that recognizes PAMPs and DAMPs to activate the inflammatory response. Inflammasome formation requires pattern recognition receptors (PRRs) to serve as sensors[55]. To date, several receptor proteins have been confirmed to assemble inflammasomes, including Z-DNA binding protein 1 (ZBP1), the nucleotide-binding oligomerization domain (NOD), leucine-rich repeat (LRR)-containing protein (NLR) family members (NLRP1, NLRP3, and NLRC4), as well as the proteins absent in melanoma 2 (AIM2) and pyrin[56-58].

ZBP1 acts as an innate sensor of viruses and fungi, and engages receptor-interacting serine/threonine-protein kinase 3 (RIPK3) to recruit fas-associated with death domain protein (FADD) and caspase-8, to activate the ZBP1-NLRP3 inflammasome[59,60]. NLR undergoes conformational changes upon detecting different stimuli, deactivating the inhibitory state through the LRR domains. This process allows the amino terminal pyrin domain (PYD) to interact with the N-terminal PYD of apoptosis-associated speck-like protein containing a

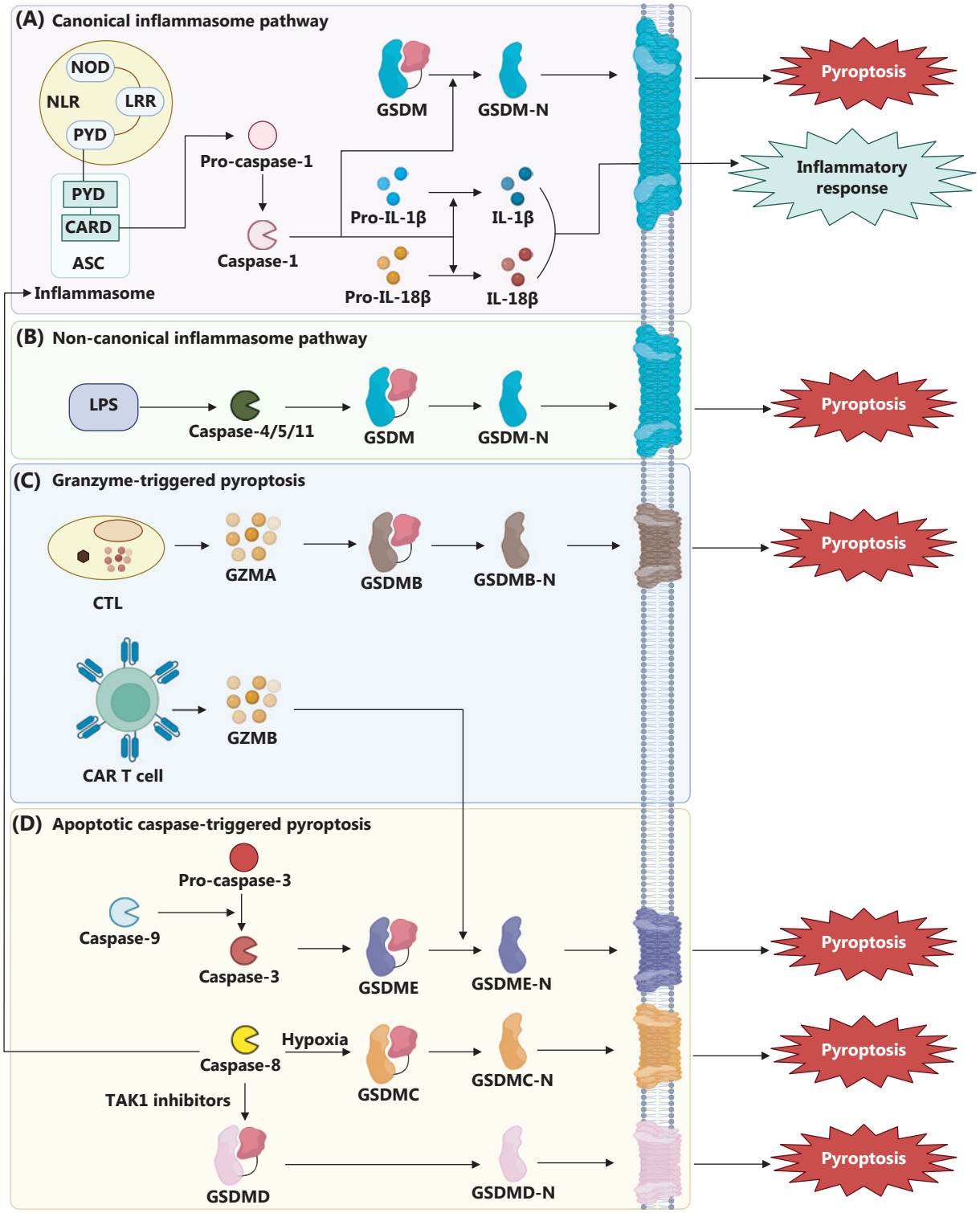

Figure 3 Activation mechanisms of major pyroptosis pathways. (A) Canonical inflammasome pathway. Activation of pattern recognition receptors, such as NLR family members (containing NOD, LRR, and PYD domains), promotes assembly of the inflammasome. The NLR protein oligomerizes *via* its NOD domain upon ligand recognition by the LRR domain and recruits the adaptor protein, ASC, through homotypic PYD-PYD interactions. ASC, which contains both PYD and CARD domains, then recruits pro-caspase-1 *via* the CARD domain, leading to caspase-1 activation. Caspase-1 cleaves GSDM to generate GSDM-N and simultaneously processes pro-IL-1β and pro-IL-18 into mature

cytokines. GSDM-N inserts into the plasma membrane, inducing pyroptosis and facilitating inflammatory cytokine release. (B) Non-canonical inflammasome pathway. Cytosolic LPS directly activates caspase-4 and -5 (human) or caspase-11 (mouse), leading to GSDM cleavage and formation of GSDM-N, driving pyroptotic cell death. (C) Granzyme-mediated pyroptosis. CTLs and CAR T cells induce pyroptosis by delivering granzymes into target cells. GZMA directly cleaves GSDMB, generating GSDMB-N to trigger pyroptosis, linking immune cytotoxicity to inflammatory tumor cell death. GZMB promotes the GSDME-mediated pyroptosis. (D) Apoptotic caspase-triggered pyroptosis. Apoptotic signaling is redirected to pyroptosis through gasdermin activation. Caspase-9 and -3 signaling cleaves GSDME, while caspase-8 preferentially cleaves GSDMC under hypoxia. TAK1 inhibition promotes the caspase-8/GSDMD pathway. In all cases, release of GSDM-N resulted in membrane pore formation and pyroptosis. ASC, apoptosis-associated speck-like protein containing a CARD; CAR T, chimeric antigen receptor T cell; CARD, caspase recruitment domain; CTL, cytotoxic T Lymphocyte; GSDM, gasdermin; GSDMB, gasdermin B; GSDMC, gasdermin C; GSDMD, gasdermin D; GSDME, gasdermin E; GZMA, granzyme A; GZMB, granzyme B; IL-18, interleukin-18; IL-1β, interleukin-1β; LPS, lipopolysaccharide; LRR, leucine-rich repeat; NLR, NOD-like receptor; NOD, nucleotide-binding oligomerization domain; PYD, pyrin domain; TAK1, transforming growth factor-β–activated kinase 1. The figure was created using BioRender.com.

caspase activation and recruitment domain [CARD] (ASC) in the cytoplasm, which then recruits pro-caspase-1[61,62]. NLRC4 directly associates with pro-caspase-1 *via* a CARD-CARD interaction compared to NLRP1 and NLRP3, which further leads to caspase-1 activation[63]. AIM2 also has the same PYD to interact with ASC and recruit pro-caspase-1[64]. Once activated, caspase-1 then matures the pro-inflammatory cytokine pro-IL-1β and pro-IL-18 into bioactive forms to induce a proinflammatory response. Activated caspase-1 cleaves GSDMD to release its N-terminus, which targets the cell membrane to assemble pore structures and induce pyroptosis. This pyroptotic pathway is conserved and has been observed in normal and cancer cells.

Non-canonical inflammasome pathway

When the body is exposed to bacterial infections, particularly gram-negative bacteria, immune cells tend to initiate pyroptosis through activation of caspase-4, -5, and -11, triggering the non-canonical inflammasome pathway to combat the infection. Human caspase-4 and -5 and mouse caspase-11 are inflammatory caspases similar to caspase-1 and have a key role in this process. LPS, derived from gram-negative bacteria, or host-derived oxidized phospholipids, recognizes and activates caspase-4, -5, and -11, which then cleaves GSDM family members to induce pyroptosis[13,18]. In addition to LPS, other lipids also act as activators of these inflammatory caspases, such as heme[65]. Current studies have shown that caspase-4 is more efficient at cleaving GSDMD compared to the canonical inflammatory pathway and responds to LPS more broadly than caspase-1 and -5, making caspase-4 a primary enzyme in pyroptosis induction and tissue damage[65,66]. This finding suggested that targeting human caspase-4 may be a more effective approach for cancer treatment.

Granzyme-triggered pyroptosis

Granzymes are cytoplasmic particles released by cytotoxic T lymphocytes (CTLs) and natural killer (NK) cells, which have been traditionally thought to induce target cell death mainly through apoptosis[67]. The following five granzymes have been identified to exist in humans: GZMA; GZMB; GZMH; GZMK; and GZMM. However, recent studies have revealed that granzymes also have a role in inducing pyroptosis. For example, GZMB has been shown to activate caspase-3, which cleaves GSDME indirectly and directly, triggering pyroptosis in tumor cells[20,68]. In addition, GZMA from CTLs cleaves GSDMB at Lys244, generating the GSDMB-N fragment that induces pyroptosis[19]. While these findings suggest a pyroptotic role for some granzymes, there is currently no research confirming whether other granzymes also induce pyroptosis in the same manner.

Interaction between pyroptosis and other PCD forms

Recent studies have pointed out the crosstalk between different forms of PCD, such as apoptosis and pyroptosis[69-71]. Hence, this finding has led to the introduction of PANoptosis, a newly discovered cell death pathway first proposed in 2019[72]. PANoptosis is executed through the PANoptosome, a multi-protein complex that assembles key molecules from pyroptosis, apoptosis, and necroptosis into a single signaling platform[73,74]. This integration provides functional redundancy. Specifically, if one pathway is blocked, alternative effectors within the PANoptosome remain active, ensuring a robust host defense. Herein we mainly discuss the relationship between pyroptosis and other PCDs.

Existing research confirmed that apoptosis-related caspases have a significant role in inducing pyroptosis. Caspase-8, which was formerly considered an initiator of apoptosis, also functions as a protein scaffold that directly cleaves GSDMD or activates the caspase-1/GSDMD pathway, thereby inducing pyroptosis[75,76]. This positions caspase-8 as a switch between pyroptosis and apoptosis. Consequently, activation of caspase-8 enzyme activity or overexpression of caspase-8 coding genes may contribute to the induction of apoptosis and pyroptosis in cancer cells. Studies also highlighted the essential roles of caspase-3 and -9 in apoptin-induced

pyroptosis[69]. Evidence has shown that GSDME is cleaved by activated caspase-3, then forms an N-terminal domain that punches holes in the cell membrane, triggering pyroptosis[51,77]. Inhibition of pyroptosis also promotes apoptosis to a certain extent. Depletion of *GSDMD* in non-small cell lung cancer (NSCLC) induces apoptosis through activation of caspase-3 and cleavage of poly ADP-ribose polymerase (PARP), which retards tumor growth[78]. Striking a balance between pyroptosis and apoptosis may contribute to the maximized efficacy of anti-cancer therapy.

Emerging evidence reveals that necroptosis and pyroptosis share overlapping regulatory mechanisms and synergistically amplifies inflammatory responses. Necroptosis is executed by the receptor-interacting serine/threonine-protein kinase 3 (RIPK3) and the substrate mixed lineage kinase domain-like protein (MLKL), which form the necrosome complex to induce plasma membrane rupture[79]. In addition to independent functions, RIPK3 directly collaborates with GSDMD to drive tissue injury. Double deletion of *Ripk3* and *Gsdmd* in mice provides enhanced protection against septic shock and multi-organ injury compared to single gene deletions[80]. This synergy extends to the tumor setting, where simultaneous activation of necroptosis and pyroptosis enhances $CD8^+$ T cell recruitment and suppresses tumor growth in melanoma and lung cancers[81]. Central to the interplay is caspase-8, which serves as a molecular switch that suppresses necroptosis *via* RIPK3 cleavage, while activating pyroptosis *via* GSDMD cleavage[75]. This interplay determines whether cancer cells undergo immunogenic cell death or immune evasion, highlighting the therapeutic potential of simultaneously targeting both pathways to enhance anti-tumor immunity.

Autophagy is a conserved catabolic process that primarily functions as a survival mechanism, maintaining cellular homeostasis through degradation and recycling of cytoplasmic components. However, under certain conditions, such as excessive stress or when an irreversible extent is reached, autophagy also culminates in a type of PCD, often referred to as autophagic cell death[82]. Recent studies have revealed crosstalk between autophagy and pyroptosis. The traditional view is that autophagy inhibits pyroptosis, which has also been confirmed by recent studies. For example, the drug, 3,4-dimethoxychalcone, was shown to suppress pyroptosis after spinal cord injury by upregulating nuclear translocation of transcription factor EB (TFEB), which enhances autophagy[83]. Overexpression of TFEB has an indispensable role in regulating autophagy through the lysosomal pathway[84]. Another study further revealed that autophagy inhibits pyroptosis induced by zinc oxide nanoparticles (ZnO NPs) *via* the TFEB-TRAF-6 pathway[85]. However, the most evidence reflected another possibility between autophagy and pyroptosis. Ju et al.[86] discovered that downregulation of MAPK14, a sensor of reactive oxygen species (ROS) that modulates autophagy, efficiently inhibits the caspase-3/GSDME-mediated pyroptosis induced by Shikonin in cancer cell lines. In addition, there is study that showed inhibition of autophagy decreased GSDME cleavage, induced pyroptosis *via* activation of caspase-8, -9, and -3 to cleave GSDME, and regulated apoptosis upstream[87]. Therefore, autophagy seems to promote and collaborate with pyroptosis to cause cell death in some models.

Pyroptosis in tumors

Pyroptosis has a dual effect in tumors. The exact role of pyroptosis in tumorigenesis and anti-tumor immunity mainly depends on factors, such as tumor type, host inflammatory status, and the TME at various stages of tumor development[88]. Long-term chronic inflammation stimulates the development of tumors and pyroptosis-induced inflammation helps to generate and maintain the TIME. In contrast, acute activation of pyroptosis leads to the "suicide" of tumor cells and the infiltration of various immune cells, thus limiting tumor progression[89,90]. Taken together, the induction of pyroptosis within tumors may be considered a potential strategy in the treatment of various cancer types. Herein we list some endogenous stimulations that trigger pyroptosis within tumors and explore the underlying regulatory mechanisms (**Figure 4**).

Inflammation

Persistent low-grade inflammatory irritation is an important cause of tumorigenesis and progression[91], which accelerates the development of tumor stem cells. Upregulation of the NLRP3 inflammasome has been observed universally in cancers, such as head and neck squamous cell carcinoma (HNSCC)[92] and the expression is positively correlated with the presence of tumor stem cells. Upon activation by DAMPs, the NLRP3 inflammasome triggers caspase-1-dependent pyroptosis, leading to the release of IL-1β and IL-18. These cytokines contribute to the maintenance of a chronic inflammatory microenvironment, promoting tumor growth. IL-1β, a major product of NLRP3 activation, has been shown to directly promote cancer stem cell expansion through the Smad/ID1 signaling pathway, which upregulates stemness-associated transcription factors, such as SOX2 and OCT4[93]. Accordingly, targeting NLRP3 or downstream effectors reduces cancer stem cell populations and sensitizes tumors to therapy[94], underscoring NLRP3 as a functional driver of cancer stem cell maintenance and tumor progression.

In addition a role in sustaining cancer stem cells, chronic inflammation driven by pyroptosis promotes tumor progression through multiple interconnected mechanisms. Sustained IL-1β and IL-18 release fosters an immunosuppressive TME by recruiting myeloid-derived suppressor cells (MDSCs) and regulatory T cells (Tregs), while suppressing CTL function[95]. Thus, in the absence of exogenous stimuli, pyroptosis in cancer cells tends to support tumor development through a self-perpetuating cycle of inflammation that sustains stemness,

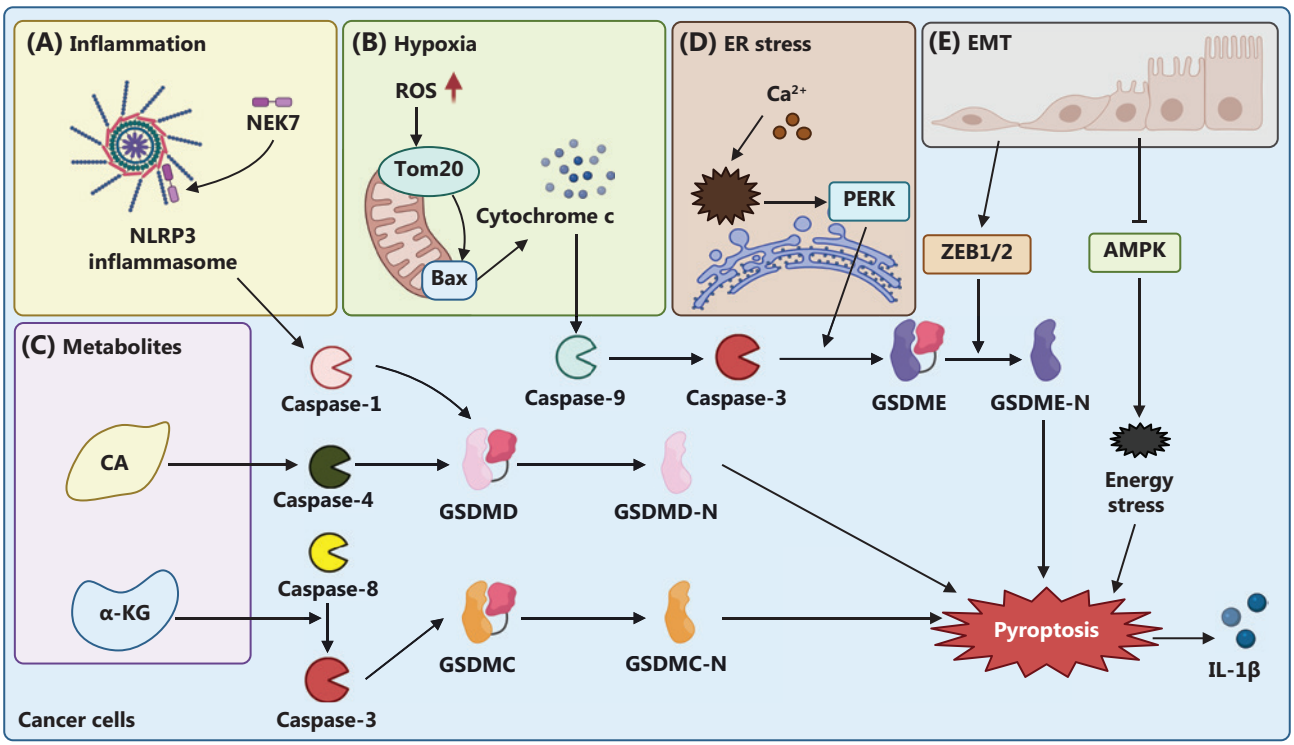

Figure 4 Stress-driven regulation of pyroptosis in cancer cells. Diverse TME and intracellular stress signals converge on distinct caspase-GSDM axes to induce pyroptosis in cancer cells. (A) Inflammation. Inflammatory signaling activates the NLRP3 inflammasome with NEK7 serving as a regulatory component that facilitates inflammasome assembly. Activated NLRP3 promotes caspase-1 activation and caspase-1 subsequently cleaves GSDMD to generate the GSDMD-N fragment, which executes pyroptosis and promotes the release of pro-inflammatory cytokines, such as IL-1β. (B) Hypoxia. Accumulated ROS induce mitochondrial dysfunction under hypoxic conditions. ROS activates Bax, which translocates to mitochondria *via* the outer membrane receptor, Tom20, leading to cytochrome c release. Cytochrome c activates caspase-9, which in turn activates caspase-3. Caspase-3 then cleaves GSDME, generating GSDME-N and inducing pyroptosis. (C) Metabolites. Metabolic alterations activate caspase signaling that converges on gasdermin. CA activates caspase-4, which cleaves GSDMD to trigger pyroptosis, while α-KG promotes the caspase-8-mediated activation of caspase-3 to cleave GSDMC. In both cases, gasdermin activation results in membrane pore formation and pyroptotic cell death. (D) ER stress. ER stress, marked by Ca^{2+} imbalance, activates PERK, which promotes caspase-3-dependent cleavage of GSDME, thereby triggering pyroptosis. (E) EMT. EMT influences GSDME-mediated pyroptosis by activating transcription factors (ZEB1/2). In addition, inhibition of AMPK during EMT exacerbates energy stress, thereby inducing pyroptosis. α-KG, α-ketoglutarate; AMPK, AMP-activated protein kinase; Bax, Bcl-2-associated x protein; CA, crotonic acid; EMT, epithelial-mesenchymal transition; ER, endoplasmic reticulum; GSDM, gasdermin; GSDMC, gasdermin C; GSDMD, gasdermin D; GSDMD-N, gasdermin D N-terminal domain; GSDME, gasdermin E; GSDME-N, gasdermin E N-terminal domain; IL-1β, interleukin-1 beta; NEK7, NIMA-related kinase 7; NLRP3, NOD-like receptor family pyrin domain containing 3; PERK, protein kinase RNA-like endoplasmic reticulum kinase; ROS, reactive oxygen species; TME, tumor microenvironment; Tom20, translocase of outer mitochondrial membrane 20; ZEB1/2, zinc finger E-box-binding homeobox 1/2. The figure was created using BioRender.com.

suppresses immunity, and facilitates metastasis, positioning pyroptosis as a potential therapeutic ally and a pathologic driver.

Hypoxia

The high metabolic rate and oxygen consumption of cancer cells create a chronic hypoxic environment that promotes tumorigenesis and migration. Hypoxia also influences TIME remodeling and promotes pyroptosis, leading to poor prognosis and reduced chemosensitivity. The accumulation of ROS caused by hypoxia within tumors also contribute to pyroptosis through a variety of potential pathways[96]. For example, increased ROS levels in tumor cells cause oxidation and oligomerization of the mitochondrial outer membrane protein, Tom20. Bax is then recruited to mitochondria by oxidized Tom20, leading to cytochrome *c* release, which further activates caspase-9. Caspase-9 then activates downstream caspase-7 and -3. In the presence of GSDME, instead of cleaving PARP to induce apoptosis, activated caspase-3

preferentially cleaves GSDME to form GSDME-NT, which is eventually inserted into the cell membrane to induce pyroptosis[69]. Research has also shown that enhanced expression of GSDMC efficiently transforms caspase-8-induced apoptosis to pyroptosis under hypoxia[43,97]. Moreover, in the absence of oxygen, PD-L1 interacts with p-Stat3 to facilitate the nuclear translocation of PD-L1, thus inducing transcription of the *GSDMC* gene. The increased expression of *GSDMC* further promotes pyroptosis in cancer cells[43]. In addition, recent studies have suggested that hypoxia leads to the nuclear translocation of GSDMD in CRC, which further interacts with PARP-1 to inhibit DNA damage repair, thus leading to pyroptosis-independent cell death[49].

Hypoxia also elevates the expression of hypoxia inducible factor-1α (HIF-1α) in cancers. A recent study demonstrated that HIF-1α efficiently promotes the expression of pyroptosis-related proteins in cancers and induces pyroptosis in neurogenic bladder (NB)[98]. Despite this finding, the relationship between HIF-1α and pyroptosis in cancers has not been established. Chen et al.[99] investigated the role of HIF-1α in bladder cancer (BLCA) and found that HIF-1α promotes activation of the NLRP3 inflammasome but was not sufficient to induce pyroptosis to achieve tumor reduction in BLCA. Instead, NLRP3 activation promotes tumor development and metastasis as discussed above. To date there is not enough evidence to draw an exact conclusion about the effects of hypoxia on tumor cell pyroptosis.

Metabolite

Metabolic dysregulation is another critical factor in the development of tumors. Researchers have shown that tumor metabolites regulate tumor growth by inducing pyroptosis through canonical and non-canonical inflammasome pathways. Wang et al.[100] reported that the metabolite, citric acid (CA), promotes the expression of caspase-4 to cleave GSDMD in ovarian cancer, thus inducing pyroptosis. Similarly, α-ketoglutarate (α-KG), an essential and common metabolite involved in multiple metabolic pathways, has been shown to induce pyroptosis within tumors through caspase-8-mediated cleavage of GSDMC. This process also enhances the sensitivity of cancer cells to pyroptosis in the acidic TME[44]. These findings suggest that targeting metabolites in cancers to induce pyroptosis may be a feasible anti-cancer route.

EMT

The EMT has a key role in tumorigenesis, invasion, progression, and metastasis[101]. EMT downregulates the expression of AMP-activated protein kinase (AMPK), a critical regulator of energy homeostasis, under energy stress, which leads to pyroptosis in cancer cells through activation of GSDMD cleavage in epithelial cancer cells[102]. In addition, EMT may have a positive effect on reversing silenced expression of *GSDME* in tumor cells by activating transcription factors, such as ZEB1 and ZEB2[52].

Endoplasmic reticulum (ER) stress

The ER has a considerable role in cell survival. ER homeostasis is often disrupted in malignant tumor cells due to the chaotic TME, thus leading to ER stress. PRKR-like ER kinase (PERK) is involved in alleviation of ER stress. Han et al.[103] showed that Ca^{2+}-induced ER stress contributes to the occurrence of caspase-12/caspase-3/GSDME-dependent pyroptosis in lung cancer cells, confirming that pyroptosis is regulated by the ER. Another study also showed that PERK-mediated ER stress is essential for the induction of caspase-3/GSDME-dependent pyroptosis in triple-negative breast cancer (TNBC)[104], suggesting that enhancing ER stress may be an efficient way to activate pyroptosis. However, research about ER stress related pathways and the role in pyroptosis has yet to be supplemented.

Targeting pyroptosis as cancer therapy

Pyroptosis in cancer cells not only inhibits tumor growth but also activates anti-tumor immunity, a function not typically associated with apoptosis. This finding makes targeting pyroptosis pathways an effective way to treat cancer. Currently, a number of possible pyroptosis signaling pathways within tumors have been identified, which are primarily GSDMD- or GSDME-mediated. In this section we summarize some anti-tumor pathways activated by exogenous stimulus and agents, and some potential molecular targets that have been shown to induce pyroptosis (**Figure 5**).

Inducing GSDMD-mediated pyroptosis

An increasing number of studies have focused on GSDMD-dependent pyroptosis in cancers that have the NLRP3/caspase-1/GSDMD signaling axis, which is one of the most well-known pathways. Researchers have shown that some drugs, such as cisplatin, ophiopogonin B, and cucurbitacin B, induce pyroptosis through the canonical inflammasome pathway to promote elimination of tumors[105-107]. In addition, ROS accumulation caused by drug stimulation has been shown to activate the GSDMD-mediated pyroptosis pathway in tumors[108,109]. The non-canonical inflammasome pathway has also been shown to induce pyroptosis within tumors, especially ovarian cancer, as exemplified by the caspase-4/GSDMD pathway[100,110].

In addition to common drugs, novel techniques have been developed to induce pyroptosis in cancer cells. Sala et al.[111] developed T22-PE24-H6, a therapeutic protein-only

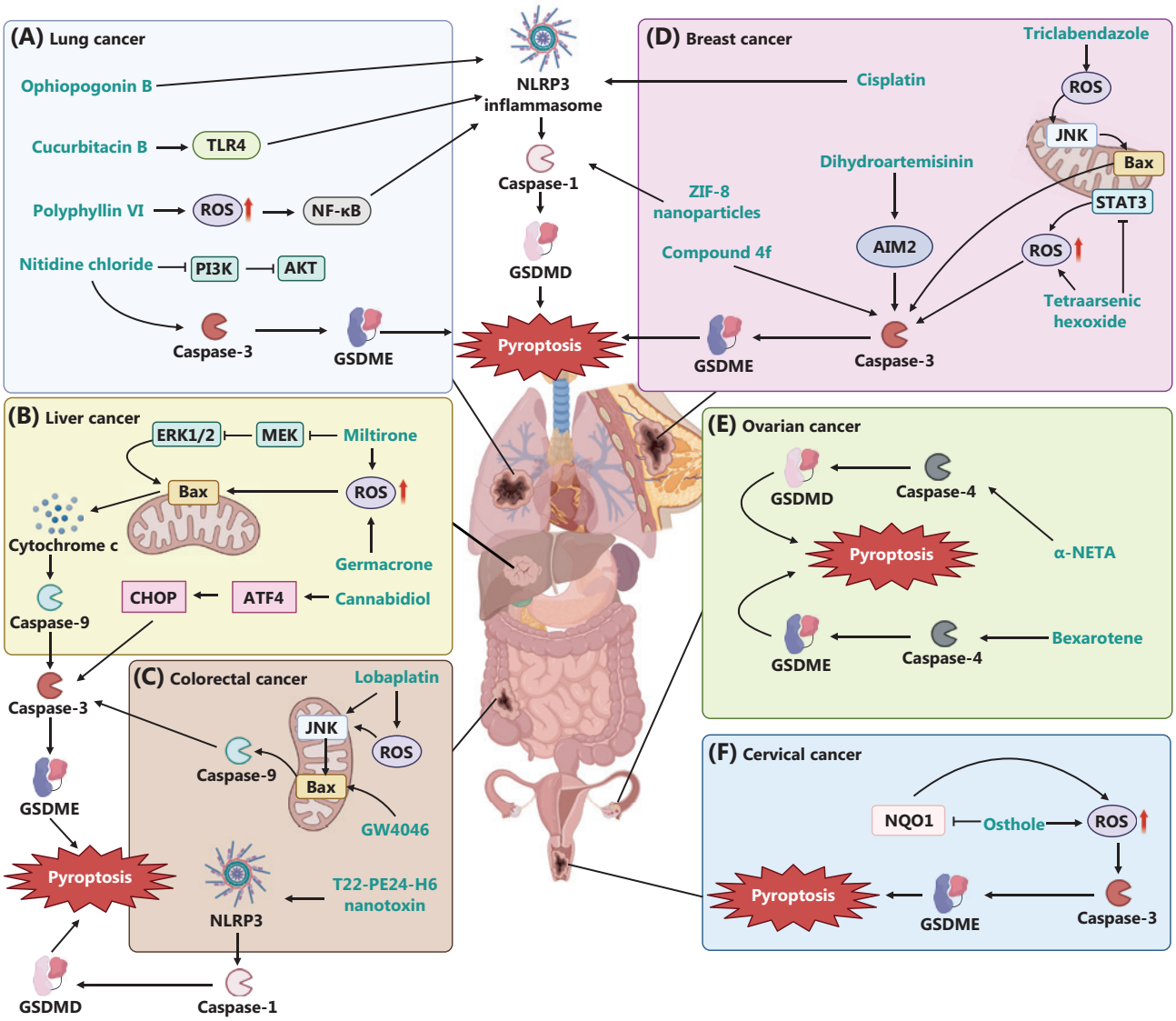

Figure 5 Therapeutic induction of pyroptosis across cancer types. Multiple agents induce pyroptosis through distinct yet convergent signaling pathways that vary by cancer type. (A) Lung cancer. Ophiopogonin B, cucurbitacin B, and polyphyllin VI activate the NLRP3 inflammasome, leading to caspase-1/GSDMD-mediated pyroptosis. Nitidine chloride inhibits the PI3K/AKT axis and activates the caspase-3/GSDME pathway to trigger pyroptosis. (B) Liver cancer. Pyroptosis is triggered by mitochondrial and ER stress signaling. Miltirone inhibits the MEK-ERK1/2 pathway, elevating ROS levels and promoting Bax-mediated mitochondrial dysfunction with cytochrome c release. In addition, germacrone promotes ROS accumulation and enhances mitochondrial stress. Cannabidiol activates the ATF4-CHOP stress response. These signals activate caspase-3, leading to GSDME-mediated pyroptosis. (C) Colorectal cancer. Therapeutic agents activate apoptotic and inflammasome pathways. Lobaplatin and GW4046 induce mitochondrial stress through JNK/ROS/Bax signaling, activating caspase-3 to cleave GSDME. In parallel, T22-PE24-H6 nanotoxin activates the NLRP3/caspase-1 axis, promoting GSDMD-dependent pyroptosis. (D) Breast cancer. Pyroptosis is induced through combined inflammasome and mitochondrial signaling. Cisplatin and ZIF-8 nanoparticles activate the caspase-1/GSDMD axis to induce pyroptosis. Dihydroartemisinin activates AIM2, while triclabendazole and tetraarsenic hexoxide elevate ROS. Compound 4f promotes the activation of caspase-3. These pathways converge on caspase-3 activation, leading to GSDME-mediated pyroptosis. (E) Ovarian cancer. Small molecules promote pyroptosis through inflammatory caspase activation. α-NETA activates caspase-4, leading to GSDMD cleavage, while bexarotene induces caspase-4-mediated GSDME cleavage, resulting in pyroptotic cell death. (F) Cervical cancer. Osthole induces ROS accumulation through NQO1-dependent signaling, activating caspase-3 and subsequent GSDME cleavage, leading to pyroptosis. α-NETA, α-napthoyl-ethyltrimethylammonium iodide; AIM2, absent in melanoma 2; AKT, protein kinase B; ATF4, activating transcription factor 4; Bax, Bcl-2-associated x protein; CHOP, C/EBP homologous protein; ERK1/2, extracellular signal-regulated kinase 1/2; GSDMD, gasdermin D;

GSDME, gasdermin E; JNK, c-Jun N-terminal kinase; MEK, MAPK/ERK kinase; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NLRP3, NOD-like receptor family pyrin domain-containing 3; NQO1, NAD(P)H quinone dehydrogenase 1; PI3K, phosphoinositide 3-kinase; ROS, reactive oxygen species; STAT3, signal transducer and activator of transcription 3; TLR4, Toll-like receptor 4. The figure was created using BioRender.com.

nanoparticle, and proved a role in inducing pyroptosis in CXCR4-overexpressed CRC cancer cells by upregulating NLRP3 to activate caspase-1 to cleave GSDMD. Zeolitic imidazolate framework-8 (ZIF-8), a widely used anti-cancer agent, has also demonstrated nanoparticle-induced pyroptosis in BRCA cell lines through the caspase-1/GSDMD pathway[112]. Furthermore, ZIF-8-based nanoplatforms incorporating additional therapeutic agents, such as quercetin and photosensitizers, have demonstrated enhanced pyroptosis induction through synergistic ROS generation and mitochondrial damage[113,114]. Despite promising preclinical data, the clinical feasibility of ZIF-8-based therapies remains uncertain due to several critical hurdles. These hurdles include unresolved long-term biosafety concerns, such as metabolic fate and clearance, the questionable translatability of the enhanced permeability and retention (EPR) effect from murine models-to-humans, and significant manufacturing challenges, such as reproducible good manufacturing practice (GMP) synthesis, sterilization, and storage stability[115]. Recent studies successfully induced pyroptosis by targeted delivering GSDMD-N fragments into tumor cells through engineered extracellular vesicles to eliminate tumors[116], offering a new strategy for anti-tumor treatment.

Targets involved in GSDMD-mediated pathway

Cluster of differentiation 38 (CD38) functions as an ecto-enzyme involved in the regulation of cellular calcium levels. Overexpression of CD38 has been shown to induce caspase-1/GSDMD mediated pyroptosis in HNSCC cell lines[117]. Of note, the most recent research has shown that the absence of CD38 expression in immune cells exacerbates pyroptosis, thus leading to severe tissue injury in normal tissues[118]. Yan et al.[119] reported that NIMA-related kinase 7 (NEK7) in hepatocellular carcinoma (HCC) cells is co-expressed with the classic pyroptosis marker, GSDMD, and downregulation of NEK7 induces pyroptosis of cancer cells. Knockdown of lncRNA MEG3 was investigated and shown to efficiently promote NLRP3, GSDMD-NT, and IL-1β expression[105], suggesting that MEG3 inhibition significantly promotes pyroptosis *via* a caspase-1/GSDMD-dependent pathway.

Inducing GSDME-mediated pyroptosis

Caspase-3/GSDME dependent pyroptosis has been shown to occur in various tumors, such as liver cancer, ovarian cancer, cervical cancer, and HNSCC[120-124]. Currently, considerable studies have confirmed the role of the mitochondrial apoptotic signaling pathways in activating pyroptosis through the caspase-3/GSDME axis to treat cancer. Significant evidence has demonstrated that drugs targeting apoptosis, such as lobaplatin[51], metformin[125], triclabendazole[126], and GW4064[127], induce pyroptosis to cause cell death in cancers as well. One of the most studied pathways is the Bax/caspase-3/GSDME pathway[128,129] and the ROS/JNK signaling pathway is a key upstream regulator in many cancer cell types[126,130,131]. In addition, a recent study showed that bexarotene induces pyroptosis in ovarian cancer by activating caspase-4 and cleaving GSDME, which has not been previously reported[132]. Wedelolactone (WDL) induces pyroptosis in retinoblastoma through caspase-1/GSDMD- and caspase-3/GSDME-mediated pathways[133].

Inhibition of molecules upstream of apoptotic pathways is an effective strategy to promote pyroptosis due to the cross-talk between GSDME-induced pyroptosis and apoptosis. Currently, studies have shown that inhibiting the PI3K/Akt and MEK/ERK1/2 pathways promote caspase-3/GSDME-dependent pyroptosis[134-136].

It is worth noting that GSDME is highly expressed in some tumors, which contradicts the tumor suppressive role of GSDME. The most recent study showed that nuclear GSDME regulates pancreatic adenocarcinoma (PDAC) growth[137], suggesting that whether GSDME has a role in promoting tumor growth or inhibiting tumor proliferation might depend on the subcellular location. Although arsenic trioxide, dioscin, oncolytic parapoxvirus, and compound 4f all have been shown to have the ability of inducing caspase-3/GSDME-dependent pyroptosis[138-141], whether other signaling molecules are involved upstream of the pathway has not been determined.

The most recent studies confirmed the GSDME-dependent pyroptosis has an important role in increasing the radiosensitivity of tumor cells[53,142]. In addition, Guo et al.[127] found that GW4064 efficiently increases the chemosensitivity of CRC to oxaliplatin by inducing pyroptosis through the caspase-3/GSDME-mediated pathway, revealing the synergistic effect of pyroptosis. BIX-01294 has also been researched and shown to have the capacity to enhance the chemosensitivity of GC cells to cisplatin through the same pathway[143]. Therefore, targeting GSDME-induced pyroptosis has a promising future in tumor therapy.

Targets involved in the GSDME-mediated pathway

Several targets have been identified that positively influence pyroptosis induction. P53 is a well-known tumor suppressor gene. Wang et al.[144] revealed a positive correlation between *P53* expression and GSDME in BRCA cells, suggesting that *P53*

may be also involved in GSDME-mediated pyroptosis. Ovarian tumor family deubiquitinase 4 (OTUD4) has been shown to have the ability to deubiquitinate and stabilize GSDME to promote pyroptosis in nasopharyngeal carcinoma[142]. Overexpression of mitochondrial uncoupling protein 1 (UCP1), one of the mitochondrial anion carrier proteins, increases caspase-3 activation, as well as GSDME cleavage in TNBC cell lines to induce pyroptosis[145]. Calpain-1 (CAPN1) and calpain-2 (CAPN2) are overexpressed in esophageal cancer cell lines. A recent study showed that cisplatin activates CAPN1 and CAPN2 to induce caspase-3/GSDME-dependent pyroptosis, suggesting that CAPN1/2 may be the promising target for pyroptosis[146]. Zhou et al.[147] noted that oxidation of Tom20 is caused by iron-boosted ROS and that Tom20 facilitates Bax to induce caspase-3/GSDME-dependent pyroptosis, suggesting that Tom20 is also a potential target for pyroptosis. D2 dopamine receptor (DRD2) is a member of dopamine receptors family that transforms macrophages (Mϕ) to the M1 phenotype[148]. The most recent study showed that Mϕ reprogrammed by DRD2 expressed in BRCA upregulates GSDME and GSDME-NT expression, as well as IL-1β, indicating that the *DRD2* gene expression contributes to Mϕ-triggered pyroptosis in BRCA cells[149]. Additional research is needed to determine the molecular mechanism underlying DRD2-induced pyroptosis.

However, some targets appear to have a role in inhibiting pyroptosis. Cyclin-dependent kinase (CDK7) is highly expressed in BRCA and is associated with a poor prognosis. Inhibiting CDK7 efficiently upregulates GSDME expression[144], indicating that CDK7 may be related to pyroptosis. Signal transducer and activator of transcription 3 (STAT3) has a negative role in the induction of pyroptosis in cancers. Su et al.[150] reported that STAT3 is activated by β5-integrin, one of the transmembrane receptors that has an important role in cancer cell survival and chemosensitivity to upregulate sphingolipid metabolic enzyme ceramidase (ASAH2), driving the sphingolipid metabolic axis to inactivate canonical pyroptosis within tumors, thus conferring cancer chemoresistance. The inhibited phosphorylation of mitochondrial STAT3 caused by tetra-arsenic hexoxide was also shown to promote pyroptosis in TNBC cells[151]. However, STAT3β, a splice variant of STAT3, was shown to enhance the chemosensitivity of esophageal cancer cells to cisplatin *via* a GSDME-mediated pyroptotic pathway[152]. Taken together, STAT3 appears to have a negative effect on the induction of pyroptosis. Downregulation of pyruvate kinase M2 (PKM2), a kinase that has a key role in glucose metabolism of cancer cells, activated GSDME-dependent pyroptosis in esophageal carcinoma[153,154], indicating that suppressing PKM2 expression efficiently induces pyroptosis. Because high expression of PKM2 has been identified in most types of tumors, it may be an adaptable target for anti-cancer treatment. Wang et al.[155] found that silenced expression of NAD(P)H: quinone oxidoreductase 1 (NQO1) caused the accumulation of ROS in Hela cells, further leading to GSDME-mediated pyroptosis promotion.

Others

ZDHHC1 is expressed in normal tissues and is usually downregulated in cancer cell types and is therefore considered a tumor suppressor. Le et al.[156] suggested that ZDHHC1 overexpressed tumor cells promote pyroptosis by inducing oxidative and ER stress, thus upregulating the expression of NLRP3, IL-1β, and IL-18 but the specific substrate of ZDHHC1-induced pyroptosis has not been confirmed. Finding ways to restore and even enhance the expression of ZDHHC1 in tumor cell lines is another promising strategy for targeted cancer therapy.

With the deepening understanding of pyroptosis, an increasing number of studies have focused on the expression of pyroptosis-related genes (PRGs) in cancer cells with evidence showing that PRGs are indispensable for the regulation of tumor progression. In addition to the GSDM family genes mentioned above, more PRGs are left to be discovered to gain insight into the role of pyroptosis in cancers and seek reliable therapeutic targets. The molecular mechanism underlying PRGs that have been confirmed to be related to the development and treatment of cancers has not been established, therefore further exploration is needed.

Although multiple therapeutic strategies, including chemotherapy, photodynamic therapy, nanotoxins, and targeted delivery systems, have been shown to induce pyroptosis in cancer cells, no small-molecule compounds have been developed that specifically and selectively target pyroptosis pathways. The agents currently reported to trigger pyroptosis are primarily repurposed from other indications and exert effects through pleiotropic mechanisms (**Table 1**). *Pyrotech Therapeutics* was co-founded in China by Shao Feng and Deng Tianjing in 2020. According to the company's official website, the company's publicly disclosed platforms include DNA-encoded libraries (DEL), fragment-based drug design (FBDD), and AI-driven drug discovery (AIDD). The pipeline includes preclinical programs targeting GSDM family proteins for oncology and inflammatory indications. These efforts underscore the growing translational interest in harnessing pyroptosis for therapeutic benefit.

Clinical utility of pyroptosis in cancers

Pyroptosis has emerged as a critical determinant of therapeutic efficacy, influencing tumor cell fate and anti-tumor immunity. Elucidating how distinct pyroptotic signatures shape the TIME is therefore essential for the development of predictive biomarkers and optimization of pyroptosis-targeted therapeutic strategies. Toward this end, many studies have established risk models by signing PRGs and pyroptosis-related lncRNA (PRLs) to predict prognosis and the TME of different tumor types[157,158].

Table 1 Pyroptosis-inducing agents with the primary targets

Category	Agent	Cancer types	Primary target	Pyroptosis executor
Chemotherapeutic agents	Cisplatin	Multiple cancers	DNA crosslinking	GSDMD GSDME
	Lobaplatin	Colorectal, cervical cancer	DNA crosslinking	GSDME
Targeted drugs	BI 2536	Ovarian cancer	PLK1 inhibitor	GSDME
	GW4064	Colorectal cancer	FXR agonist	GSDME
Natural products	Shikonin	Gastric cancer	Multitarget naphthoquinone	GSDME
	Osthole	Ovarian, cervical cancer	Coumarin derivative	GSDME
	Myricetin	Lung cancer	Flavonoid	GSDME
Nanomaterials	ZIF-8	Breast cancer	Metal-organic framework	GSDMD
Biologics	T22-PE24-H6	Colorectal cancer	CXCR4-targeted toxin	GSDMD GSDME

GSDMD, gasdermin D; GSDME, gasdermin E.

Among the GSDM family genes, *GSDMD* has been identified as a therapeutic target to predict the TME and a biomarker to predict the therapeutic effect of immune checkpoint inhibitors[159]. BAK1 and CYCS expression has been shown to contribute to the poor prognosis in lung adenocarcinoma, yet NLRP1 and NOD1 may inhibit tumor growth[160]. The PEPScore, which is based on six pyroptosis-related genes [PRGs] (*CSF2*, *FGA*, *AKAP12*, *CYP2C18*, *IRS4*, and *TSLP*), is a prospective model to predict prognosis and immune microenvironment of lung squamous cell carcinoma[161]. Eight PRLs are contained to predict the prognosis in GC, which include JPX, TUG1, and MGC12916[162]. Four PRGs (*CXCL8*, *IL13RA2*, *MELK*, and *POP1*) in CRC precisely form a model that predicts survival rate and prognosis[163]. One study suggested that a seven-PRG signature (*NFKB1*, *EEF2K*, *CTSV*, *MDM2*, *GZMB*, *PANX1*, and *PTEN*) were able to predict prognosis in patients with endometrial carcinoma[164]. A six-PRG signature (*ZDHHC1*, *ATG7*, *CHMP1A*, *HDAC6*, *IRF1*, and *IRF3*) has been verified to have good accuracy in predicting prognosis. *ZDHHC1* was shown to activate caspase-1 and -3 to induce pyroptosis[165]. The effective PRG signature in BLCA consists of *AIM2*, *CASP1*, *CASP6*, *CASP9*, *GSDMB*, *GSDMD* and *PRKACA*[166]. Upregulated PRGs (GSDMA and CHMP4C) are favorable prognostic factors in BLCA patients[158]. The chemotherapy resistance of tumor cells is correlated to the *SLC31A2* and *COL4A5* genes in melanoma[167].

lncRNAs are defined as RNA transcripts with >200 nucleotides that do not encode proteins. All the anomalies about lncRNAs that include abnormal sequence and spatial structure, abnormal expression level, and abnormal interaction with binding proteins, lead to the occurrence of diseases, such as cancers. For example, LINC01133 was defined as a PRL in pancreatic cancer[168]. Because LINC01133 was also shown to promote tumor progression through the Wnt/β-catenin pathway[169], whether an interaction exists between the Wnt signaling pathway and pyroptosis awaits further research. In addition, four lncRNAs (RBMS3-AS3, SLC12A5-AS1, RAP2C-AS1, and HMGA2-AS1) are related to pyroptosis in BLCA and contribute to tumor proliferation[170].

It is worth noting that there exist many challenges to translating these prognostic models into clinical applications. In addition, due to the limited clinical data and tumor samples, the establishment of risk models is also limited. Further research on the PRGs will be conducive to the discovery of anti-cancer therapeutic targets and effective biomarkers for prognosis. In addition, differences in the roles of PRGs across different cancers also warrant further investigation. Despite these challenges, a growing body of research on the relationship between pyroptosis regulators and cancer immunity provides a promising foundation for future studies. Manipulating pyroptosis characteristics may represent an emerging and effective anti-tumor strategy. More in-depth studies are necessary to clarify these interactions and the potential clinical applications.

Conclusions

The induction of non-apoptotic cell death has emerged as a promising anti-cancer therapeutic strategy. As an inflammatory form of cell death executed by the GSDM family proteins following caspase activation, pyroptosis occupies a unique position in this landscape due to the dual role in tumor biology. Cancer cells undergo pyroptosis under

hypoxia, leading to the release of inflammatory cytokines, such as IL-1β and IL-18. In the absence of therapeutic intervention, this endogenous, low-level pyroptosis contributes to tumor progression by remodeling the TME to favor proliferation and immune evasion. However, this very mechanism is therapeutically exploited, specifically expanding pyroptosis within cancer cells shifts the balance from chronic inflammation-to-acute cell death, positioning pyroptosis as a hot spot in anti-cancer treatment research. In addition to these two core functions, studies have also identified the synergistic effect between induced pyroptosis and anti-cancer treatment, which is embodied in the enhanced sensitivity of cancer cells to chemotherapy and radiotherapy. Moreover, current research has uncovered several potential pyroptotic targets involved in pyroptosis, particularly those pyroptotic targets related to GSDMD or GSDME cleavage. In this review we have summarized these promising therapeutic targets and highlight the drugs that have been shown to induce pyroptosis in cancers, aiming to offer new insights into the anti-cancer treatment targeting pyroptosis. However, it is important to note that most findings derive from a narrow range of cell lines under artificial overexpression conditions and validation is called for in primary tumors, patient-derived organoids, and *in vivo* models across diverse cancer types. Without such validation, it remains unclear whether the proposed mechanisms represent universal principles or cell line-specific artifacts. In addition, the functional interplay between multiple pyroptotic pathways within the same TME is poorly characterized. While GSDM family members have been studied in isolation, the relative contributions and context-dependent dominance in actual tumors remain undefined. Emphasis is placed on the need to employ pathway-specific reporters or genetic disruption models to dissect which pyroptotic axis predominates in specific tumors under defined microenvironmental conditions (hypoxia, nutrient deprivation, and immune infiltration). Furthermore, the functional significance of GSDM subcellular localization remains a largely unexplored dimension. Varying subcellular localizations of pyroptotic factors dictate distinct functional outcomes, as exemplified by nuclear GSDMD, which promotes chemosensitivity independent of pyroptosis. It remains unknown whether this phenomenon is generalizable across GSDM family members, whether it occurs in other cancer types, and if so, what functional consequences it may entail. These questions underscore the need to investigate the determinants, dynamics, and functional implications of GSDM subcellular localization.

The successful translation of pyroptosis-targeting therapies from bench-to-bedside will necessitate innovative clinical trial designs. Given the marked heterogeneity of GSDM expression across tumors, trials should incorporate pre-treatment tumor biopsies to assess baseline expression of relevant GSDMs and the upstream activators, thereby enabling enrichment of patient populations most likely to derive clinical benefit. The immunogenic nature of pyroptosis provides a strong rationale for combining pyroptosis-inducing agents with immune checkpoint inhibitors. Early-phase trials should prioritize such combinations with careful dose optimization to maximize immunogenic cell death while mitigating the risk of cytokine release syndrome or other hyperinflammatory toxicities. Serial tumor biopsies or liquid biopsies should be integrated into trial protocols to confirm on-target engagement (e.g., by detecting cleaved GSDM fragments or pyroptosis-specific extracellular vesicles). Such pharmacodynamic monitoring would not only provide an essential proof-of-mechanism but also guide dose selection for later-stage trials. Given the potential for pyroptosis to cause tissue damage in normal organs (e.g., GSDME-mediated toxicity in radiotherapy), trials need to include rigorous safety monitoring for off-tumor pyroptosis, particularly in tissues with high baseline GSDME expression.

The clinical development of pyroptosis-targeted therapies will depend on robust biomarkers for patient selection, response monitoring, and toxicity prediction. Such biomarkers span from direct pharmacodynamic markers to predictive and safety biomarkers. At the most proximal level, the development and validation of immunohistochemistry (IHC) assays capable of detecting cleaved GSDM fragments in formalin-fixed paraffin-embedded tumor tissues is essential. Unlike total GSDM expression, which is often measured in current studies, cleaved fragments directly indicate pathway activation and target engagement. Complementing such tissue-based approaches, liquid biopsy strategies offer the potential for longitudinal monitoring without repeated biopsies, including detection of cell-free GSDM N-terminal fragments in plasma or characterization of pyroptosis-specific extracellular vesicle signatures. Beyond these dynamic markers of pathway activity, germline genetic variants in *GSDM* genes or regulators (e.g., caspases and inflammasome components) may identify patients predisposed to enhanced pyroptotic responses, or conversely, to intrinsic resistance. Equally important for clinical safety are early off-pyroptosis indicators that would enable proactive management of potential adverse events, such as specific cytokine signatures or epithelial cell-derived DAMPs in the circulation.

In conclusion, pyroptosis has a dual function in cancer. Specifically, pyroptosis is a potential ally in tumor progression when dysregulated but a powerful weapon when therapeutically harnessed. The field now stands at a critical juncture, transitioning from discovery science-to-translational development. By pursuing the priority research areas, embracing innovative trial designs, and investing in biomarker development, the coming decade holds promise for translating our mechanistic understanding of pyroptosis into tangible benefits for cancer patients.

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Conflict of interest statement

No potential conflicts of interest are disclosed.

Author contributions

Conceptualization: Ding Ma, Qinglei Gao, Tao Zhu, Yong Fang.
Data curation: Yuewen Zhang, Mengshi Luo.
Investigation: Yuewen Zhang, Zhiqi Liao, Qiuyang Xu.
Writing: Yuewen Zhang.

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