Role of gasdermin family proteins in cancers (Review)

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Abstract. The gasdermin (GSDM) family comprises six proteins, including GSDMA-GSDME and Pejvakin. Most of these proteins have a crucial role in inducing pyroptosis; in particular, GSDMD and GSDME are the most extensively studied proteins as the executioners of the pyroptosis process. Pyroptosis is a highly pro-inflammatory form of programmed cell death and is closely associated with the incidence, development and prognosis of multiple cancer types. The present review focused on the current knowledge of the molecular mechanism of GSDM-mediated pyroptosis, its intricate role in cancer and the potential therapeutic value of its anti-tumor effects.

Contents

1. Introduction
2. GSDMA
3. GSDMB
4. GSDMC
5. GSDMD
6. GSDME
7. PJVK
8. Discussion and perspectives

1. Introduction

Cancer endangers the health of the population worldwide and its incidence is increasing annually with the accumulation of risk factors, such as the aging of the population, accelerated industrialization and poor lifestyle habits (1). Although the survival rate of cancer patients has improved due to treatments such as surgery, targeted therapy, radiotherapy and immunotherapy, cancer remains a major challenge due to its highly aggressive and drug-resistant nature.

The long-recognized modes of cell death comprise apoptosis and necrosis. Apoptosis is characterized by cell shrinkage and the formation of apoptotic bodies. The surrounding phagocytic cells engulf these bodies without causing an inflammatory response. Necrosis was previously thought to be an unregulated and passive death process; however, with further research, it has now been indicated that certain forms of necrosis may be controlled and are called programmed necrosis (2), of which pyroptosis is one of the main forms. Pyroptosis may intensify the inflammatory response by activating the inflammasome and inflammatory cytokines in the extracellular space in addition to rupturing cells and releasing inflammatory cytokines that promote inflammation.

The gasdermin (GSDM) family of proteins are key effector molecules that mediate the onset of pyroptosis and include GSDMA-GSDME and Pejvakin (PJVK), also known as deafness, autosomal recessive 59 (DFNB59). The GSDM family of proteins have similar structures and are characterized by a conserved domain called the GSDM-N domain (GSDM-N), which is responsible for executing the process of pyroptosis. The GSDM-N domain consists of a six-stranded β-sheet flanked by α-helices and is crucial for the pore-forming activity of the protein. In addition to the GSDM-N domain, the GSDM family proteins possess a C-terminal domain known as GSDM-C, which aids in membrane binding (3). Most of the GSDM family proteins exert their effects via inducing pyroptosis, and all of them influence the incidence, development and prognosis of multiple cancer types. The purpose of the present study was to summarize the molecular mechanisms of GSDM-mediated pyroptosis and the latest progress in its application in cancer research, and to provide new strategies for cancer prevention and treatment.

2. GSDMA

The gene encoding GSDMA is located on human chromosome region 17q21 and mouse chromosome region 11. There is only one copy of the gene in humans, whereas mice have three copies of the gene (GSDMA1-3) (4). GSDMA expression patterns differ between humans and mice. Human GSDMA is mainly expressed in epithelial cells of the skin, tongue, mammary glands, bladder, umbilical cord and gastrointestinal tract, such as the esophagus and stomach (5).

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Furthermore, GSDMA was detected in T lymphocytes (6). Mouse GSDMA1-3 is expressed in distinct tissues. GSDMA1 is mainly expressed in the suprabasal epidermis, cornea, hair follicles and forestomach (5); GSDMA2 is expressed in the stomach; and GSDMA3 is mainly detected in the sebaceous glands of the skin (7). Overexpression of the N-terminal domain of GSDMA or GSDMA3 induces pore formation in the plasma membranes and leads to significant pyroptosis (3,8). However, the inflammatory caspase responsible for the cleavage of GSDMA remains to be determined.

Limited evidence has demonstrated an association between GSDMA and cancer. Saeki *et al* (9) detected the expression level in a pan-cancer analysis and observed that GSDMA was amplified in 4/4 (100%) breast cancer cell lines and 2/8 (25%) gastric HER2-positive cell lines. However, northern blot analysis showed no GSDMA expression in any of the 24 cancer cell lines examined in this study. GSDMA is expressed in the upper gastrointestinal tract but is frequently silenced in gastric cancers. Reverse transcription-quantitative PCR analysis was performed to determine the expression level of GSDMA in esophageal and gastric cancer cell lines and the results indicated that GSDMA was expressed in only 3/10 (33%) gastric cancer cell lines and 1/11 (9%) esophageal cancer cell lines. GSDMA expression was observed in only 2 of the 60 primary cancer tissues, including esophageal and gastric cancer (10). Saeki *et al* (11) found that hypermethylation of the promoters of GSDMA and its expression was able to be restored by demethylation of the promoter. GSDMA overexpression induces apoptosis in gastric epithelial cells. Peng *et al* (12) found that the expression level of GSDMA was upregulated in lung adenocarcinoma, whereas the methylation level of GSDMA was reduced in cancer tissues compared to that in normal tissues, which may account for the abnormal expression in lung adenocarcinoma. Furthermore, the expression of GSDMA is positively correlated with the infiltration of immune cells in the TME, including B cells, $CD8^+$ T cells, $CD4^+$ T cells, macrophages, neutrophils and dendritic cells, suggesting an underlying association between GSDMA and the effect of immunotherapy (12). A similar trend was observed in ccRCC, in which the expression level of GSDMA was significantly higher and positively associated with the tumor grade, whereas the methylation level of GSDMA decreased. The expression level of GSDMA was positively correlated with the infiltration of macrophages, neutrophils and dendritic cells; however, the GSDMA expression level was not associated with relapse-free survival or overall survival (13). In luminal B breast cancer, Yang *et al* (14) found that the GSDMA expression level was higher than that in normal tissues. Bioinformatics analysis showed that GSDMA was overexpressed in ovarian cancer, and had a cancer-promoting role and a negative impact on survival time (15); however, the mechanism by which GSDMA acts in ovarian cancer remains elusive (Table I). The protease cleavage of GSDMA and its potential regulatory mechanisms require further exploration to elucidate the association between GSDMA and cancer.

3. GSDMB

GSDMB is located on 17q12 and the protein comprises 411 amino acids. Unlike other GSDM family members that are highly homologous between humans and mice, GSDMB is absent in mice (16). GSDMB has six splicing variants in humans, each encoding a protein with a molecular weight of 35-50 kDa. The expression levels and cellular localization of the different isoforms vary. The domains of these isoforms are more unstable than those of other GSDMs due to the unique sequence of the connector between the C- and N-terminal domains, except for isoform 5, which consists only of the C-terminal domain (17,18). GSDMB may be cleaved by caspase-1, -3, -6 and -7, which promotes the cleavage of GSDMB and the release of the N-terminal effector domain, which oligomerizes in the cell membrane and forms pores, resulting in pyroptosis (3). GSDMB is not a substrate of caspase-4, -5 and -11 due to the absence of the specific sequence (such as that in GSDMD) of the connector between the C- and N-terminal domains (17). Although GSDMB cannot be cleaved by caspase-4, it may induce the oligomerization of caspase-4 proteins, thus increasing its activity and promoting the cleavage of GSDMD, finally inducing non-canonical pyroptosis (19). In addition to specific caspases, granzyme A from cytotoxic lymphocytes may directly cleave and activate GSDMB to induce cell pyroptosis and promote cytotoxic T lymphocyte-mediated tumor clearance in mice (20) (Fig. 1).

GSDMB is highly expressed in certain cancer types, such as breast, cervical, uterine, and gastric cancers (21). Hergueta-Redondo *et al* (22) found that GSDMB was significantly upregulated in breast cancer compared to normal controls and elucidated that isoform 2 of GSDMB induced invasion, progression and metastasis of breast cancer cells and that GSDMB may be a potential prognostic marker in breast cancer. Further studies revealed that overexpression of GSDMB indicated invasive behavior and poor prognosis, particularly in Erb-B2 receptor tyrosine kinase 2 (HER2)-positive breast cancer, by increasing therapy resistance (23-25), which also suggests that GSDMB may be a potential therapeutic target. Molina-Crespo *et al* (25) developed a GSDMB antibody-based nanomedicine targeting intracellular oncoproteins that inhibited the proliferation of breast cancer cells *in vitro*, reduced tumor growth and metastasis *in vivo* and enhanced therapy sensitivity. The mechanism of action of GSDMB in breast cancer remains unclear and its potential therapeutic role requires further study.

Similar to breast cancer, Komiyama *et al* (26) detected the expression level of GSDMB in normal gastric tissues and gastric cancer and observed that GSDMB expression was low in normal tissues, whereas it was highly amplified and overexpressed in gastric cancers, indicating its role in cancer development. GSDMB is overexpressed in hepatic and colon cancer tissues (10). Komiyama *et al* (26) revealed that an Alu element, as well as a putative IKAROS family zinc finger-binding motif, had a crucial role in increasing the expression level of GSDMB (26). Saeki *et al* (27) found that GSDMB expression was driven by a cellular promoter and a long terminal repeat (LTR)-derived promoter. These studies suggest that GSDMB, Alu elements and LTR-derived promoters may be useful markers for evaluating the incidence and development of gastric cancer.

Lutkowska *et al* (21) determined that a single-nucleotide polymorphism (SNP), rs8067378, located 9.5 kb downstream of GSDMB, was associated with the development

Table I. Expression and functional roles of GSDMA in cancers.

Cancer type	Expression and function	(Refs.)
Breast, gastric and ovarian cancer	Amplified in 4/4 (100%) breast cell lines and 2/8 (25%) gastric HER2 cell lines, northern blot technology showed no expression of GSDMA in any of twenty-four cancer cell lines	(9)
Breast cancer	Upregulated in luminal-B breast cancer	(14)
Esophageal and gastric cancer	Expressed only in 3/10 (33%) gastric cancer cell lines and 1/11 (9%) esophageal cancer cell lines	(10)
Lung cancer	Upregulated in lung cancer, associated with immune infiltration	(12)
ccRCC	Upregulated in ccRCC, associated with tumor grade and immune infiltration, no association between expression level and relapse-free survival or overall survival	(13)
Ovarian cancer	Upregulated in ovarian cancer, overexpression promoted tumor progression and negatively associated with survival time	(15)

Chromosomal location: Human GSDMA, [17q21.1]; mouse GSDMA1/2/3, [11D]. Overexpression of N-terminal domain of GSDMA or GSDMA3 induced pyroptosis, mechanisms remain unclear. GSDM, gasdermin; ccRCC, clear cell renal cell carcinoma.

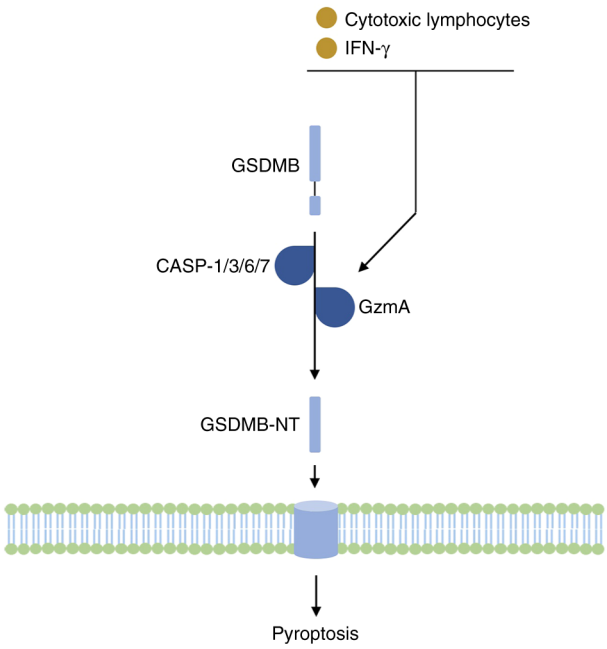

Figure 1. Summary of GSDMB activation and pore-forming functions. GSDMB may be cleaved by caspase-1, -3, -6 and -7. Such caspases promote the cleavage of GSDMB and the release of N-terminal effector domain, which oligomerizes in the cell membrane and forms pores, resulting in pyroptosis. Granzyme A from cytotoxic lymphocytes mediated by IFN-γ may cleave and activate GSDMB directly to induce cell pyroptosis. GSDMB, gasdermin B; CASP, caspase; GZM, granzyme; IFN, interferon; NT, N-terminal domain.

and progression of cervical squamous cell carcinoma by potentially increased GSDMB expression in a Polish cohort. Therefore, GSDMB may be a risk factor for cervical squamous cell carcinoma. By contrast, Li *et al* (28) found no significant association between the rs8067378 SNP of GSDMB and the progression of cervical cancer; however, the polymorphism may still reduce the risk of squamous intraepithelial lesions (SIL) in the Han population in Northeast China during the progression of SIL. Therefore, the association between GSDMB expression and cervical cancer requires further investigation.

In addition to the above cancers, it was recently found that GSDMB overexpression promotes bladder cancer progression by interacting with STAT3, increasing its phosphorylation and modulating glucose metabolism, thus promoting tumor proliferation of bladder cancer (29). Bioinformatics analysis revealed that the upregulated expression of GSDMB is associated with immune infiltrates and poor survival in ccRCC (13,30). The expression level of GSDMB is upregulated in lung adenocarcinoma; accordingly, the methylation level is lower in tumor tissues than in normal tissues. Furthermore, the expression levels of GSDMB positively correlated with the infiltration of B cells, $CD4^+$ T cells and dendritic cells, indicating that GSDMB may modulate the TME, as a higher expression level of GSDMB suggests a poorer prognosis (12) (Table II). Further studies are required to determine the triggers underlying the mechanism by which GSDMB participates in pyroptosis and the role of GSDMB in cancer.

4. GSDMC

GSDMC was originally identified as a tumor-processing marker in human melanoma, which is located on 8q24 in humans, and there are four orthologous genes in mice (GSDMC1-4) (5). GSDMC is expressed in the trachea, spleen and gastrointestinal tract, such as the esophagus, stomach, large and small intestines, cecum and colon (16,31,32). There are differences in the expression patterns between humans and mice, but the N-terminal domain has intrinsic cytotoxicity and may induce pyroptosis in both human and mouse cells.

Hou *et al* (33) found that under hypoxic conditions, the expression levels of GSDMC were upregulated via the interaction between phosphorylated STAT3 and programmed death ligand 1, which was then specifically cleaved by caspase-8 upon TNF-α treatment to generate the N-terminal domain, which induced the formation of cell membrane pores and activated pyroptosis (Fig. 2). Furthermore, upregulated

Table II. Expression and functional roles of GSDMB in cancers.

Cancer type	Expression and function	(Refs.)
Breast cancer	Upregulated in breast cancer, overexpression induced invasion, progression and metastasis, indicated poor prognosis, enhanced therapy sensitivity	(21-25)
Gastric cancer	Upregulated in gastric cancer	(26)
Hepatic and colon cancer	Upregulated in hepatic and colon cancer	(10)
Cervical squamous cell carcinoma	Upregulated by SNP (rs8067378), associated with tumor development and progression in a Polish population	(21)
Cervical cancer	No significant association between rs8067378 SNP and tumor progression, rs8067378 could reduce the risk of squamous intraepithelial lesion in the Han population in Northeast China	(28)
Bladder canner	Upregulated in bladder cancer, overexpression promoted tumor progression by modulating glucose metabolism	(29)
ccRCC	Upregulated in ccRCC, associated with immune infiltration, overexpression indicated poor prognosis	(13,30)
Lung cancer	Upregulated in lung cancer, associated with immune infiltration, overexpression indicated poor prognosis	(12)

Chromosomal location: Human GSDMB, [17q21.1]; not present in mouse. GSDMB is cleaved by caspase-1, -3, -6, -7 or granzyme A, activating pyroptosis. GSDM, gasdermin; ccRCC, clear cell renal cell carcinoma; SNP, single nucleotide polymorphism.

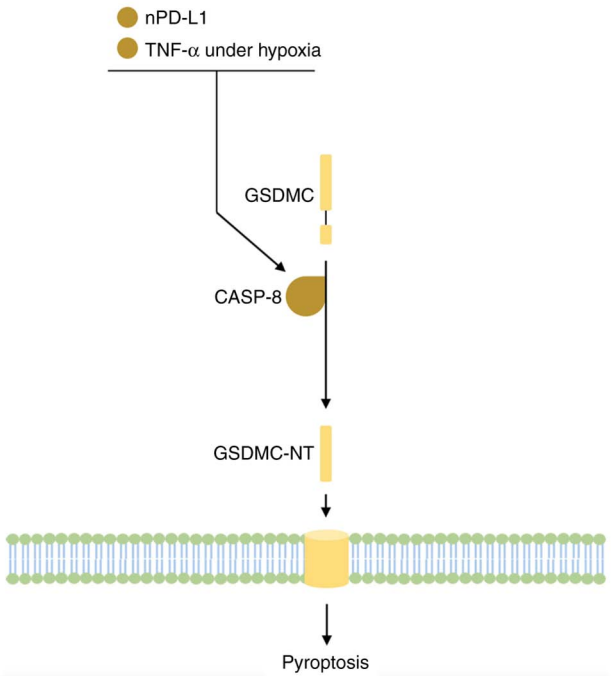

Figure 2. Summary of GSDMC activation and pore-forming functions. Under hypoxic conditions, the expression levels of GSDMC were upregulated via nuclear PD-L1, and GSDMC is then cleaved by caspase-8 upon TNF-α treatment to generate the N-terminal domain and in turn induce the formation of cell membrane pores, thus activating pyroptosis. GSDMC, gasdermin C; PD-L1, programmed death ligand 1; CASP, caspase; TNF-α, tumor necrosis factor α; NT, N-terminal domain.

GSDMC expression was associated with poor overall survival in patients with breast cancer (33). GSDMC had an anti-tumor role in this study. Xu *et al* (34) also found that GSDMC may be a risk factor for breast cancer prognosis. Sun *et al* (35) showed that the LINC00511/hsa-miR-573 axis could regulate the high expression level of GSDMC and that upregulated GSDMC was associated with a poor prognosis in patients with breast cancer. Zhang *et al* (36) showed that the oxidation of plasma membrane-localized death receptor 6 was induced by the enhancement of ROS and recruited both pro-caspase-8 and GSDMC to the cytosol, which activated GSDMC cleavage by caspase-8, thus inducing pyroptosis. Considering the induction of pyroptosis in tumor cells and the immunogenic nature of pyroptosis, which could enhance anti-tumor immunity, GSDMC may be a promising therapeutic target in cancer. In lung adenocarcinoma, the expression of GSDMC is higher in tumor tissues than in normal tissues, and overexpression of GSDMC may be an independent indicator of poor overall survival in patients with lung adenocarcinoma and a potential predictor of prognosis (12,37). A similar trend was observed in ccRCC; GSDMC expression levels were upregulated in tumor tissues and positively correlated with $CD4^+$ T cell and macrophage infiltration (13). Higher expression of GSDMC was correlated with poor survival (13). In colorectal cancer (38) and metastatic melanoma (32), the expression levels of GSDMC was also significantly increased. GSDMC acts as a promoter of cell proliferation in colorectal cancer because upregulated GSDMC may induce the growth of colorectal cancer cell lines, whereas knockdown of GSDMC resulted in a significant reduction in tumor cell proliferation. The expression levels of GSDMC2 and GSDMC4 in mice are also increased in colon cancer; however, the underlying mechanisms remain elusive (38). However, in esophageal and gastric cancer, Saeki *et al* (10) found that GSDMC expression tended to be suppressed in ESCC and diffuse-type gastric cancer, indicating GSDMC may be a tumor suppressor in these cancer types. Pereira *et al* (39) showed that a higher expression level of GSDMC is related to advanced gastric cancer and

Table III. Expression and functional roles of GSDMC in cancers.

Cancer type	Expression and function	(Refs.)
Breast cancer	Upregulated in breast cancer, overexpression indicated poor prognosis	(33-35)
Lung cancer	Upregulated in lung cancer, associated with immune infiltration, overexpression indicated poor prognosis	(12,37)
ccRCC	Upregulated in ccRCC, associated with immune infiltration, overexpression indicated poor prognosis	(13)
Colorectal cancer	Upregulated in colorectal cancer, overexpression induced tumor cell proliferation	(38)
Melanoma	Upregulated in metastatic melanoma	(32)
Ovarian cancer	Upregulated in serous ovarian cancer	(41)
Esophageal and gastric cancer	Downregulated in esophageal squamous cell carcinoma and diffuse-type gastric cancer, higher expression was related to advanced gastric cancer and also associated with moderately or well-differentiated cancer types	(10,39)
Pancreatic adenocarcinoma	Overexpression promoted cell proliferation and invasion, knockdown decreased tumor growth	(40)

Chromosomal location: Human GSDMC, [8q24.21]; mouse GSDMC1-4, [15D1]. GSDMC is cleaved by caspase-8 to activate pyroptosis. GSDM, gasdermin; ccRCC, clear cell renal cell carcinoma.

moderately or well-differentiated cancer types. Yan *et al* (40) suggested that upregulated GSDMC may induce the proliferation and migration of pancreatic adenocarcinoma cell lines, whereas GSDMC depletion inhibited tumor cell growth and migration, indicating that GSDMC may be a potential therapeutic target for the treatment of pancreatic adenocarcinoma. Berkel and Cacan (41) reported that GSDMC expression increased in serous ovarian cancer and that copy number gains were highly frequent in genes encoding GSDMC, indicating that copy number variations in GSDMC may be related to the development of serous ovarian cancer; however, the mechanisms require further research (Table III).

GSDMC has been found to be associated with the development, stage, differentiation, therapeutic effect and prognosis of multiple cancer types, which may or may not be accompanied by pyroptosis; however, the underlying complex mechanisms require further exploration.

5. GSDMD

GSDMD was primarily identified in two separate studies in 2015; Kayagaki *et al* (42) found that GSDMD has a key role in lipopolysaccharide (LPS)-induced activation of non-canonical inflammasomes by screening chemically induced mutant mice, whereas Shi *et al* (43) performed a genome-wide screen for caspase-11 and caspase-1-induced pyroptosis pathways in cell lines, which revealed that GSDMD is the substrate of all inflammatory caspases and is the true executor of pyroptosis. These two studies unveiled, for the first time, the mystery of the molecular mechanisms of pyroptosis. The gene encoding GSDMD is located on chromosome 8q24.3 and the protein comprises a 31 kDa N-terminal and a 22 kDa C-terminal. Upon activation, the peptide linker between the N- and C-terminal regions is cleaved, and subsequently, the N-terminal forms a cell membrane pore, inducing the release of cytokines such as interleukin (IL)-1β and IL-18, in turn leading to pyroptosis (44). Multiple caspases, such as caspase-1, -4, -5, -8 and -11, are able to cleave and activate GSDMD. Caspase-1 activates GSDMD through inflammasome complexes, such as absent in melanoma 2, NOD-like receptor C4 (NLR)C4, or NLR family pyrin domain containing 3 (NLRP3) (45). Activation of GSDMD by caspase-4 is regulated by interferon (IFN) regulatory factor 2 (46,47). Caspase-8-dependent GSDMD cleavage relies on the dimerization and autoprocessing of caspase-8 (48). The LPS-triggered caspase-11-GSDMD signaling pathway is upregulated by IFN-γ and IFN-β (49,50). By contrast, GSDMD was reported to be cleaved by caspase-3, which led to decreased pyroptosis by the inhibition of oligomerization and pore formation of the GSDMD N-terminal domain (31) (Fig. 3).

Almost all human organs and tissues, including different subsets of leukocytes, express GSDMD at the mRNA and protein levels (6,51). GSDMD participates in various biological processes and has a role in numerous cancer types.

Zhang *et al* (52) reported that dasatinib increased the cleavage of GSDMD and promoted pyroptosis in A549 cells, thus inhibiting the development of non-small cell lung cancer (NSCLC). Further, GSDMD was required for the infiltration of $CD8^+$ T cells into the tumor microenvironment (TME) of NSCLC to ensure an immune response, whereas GSDMD deficiency increased the cytolytic capacity of $CD8^+$ T cells (53). GSDMD knockout markedly decreased lung cancer metastasis in a metastatic lung carcinoma cell model (54). Chen *et al* (19) reported that in NSCLC cell lines, GSDMD knockdown promoted caspase-3-induced apoptosis independent of other apoptotic stimuli, and GSDMD suppression inhibited tumor growth in a mouse model. Furthermore, upregulated expression of GSDMD is associated with higher lung cancer incidence and a poorer prognosis (12,55). Similarly, GSDMD overexpression has been reported to be associated with the development of bladder cancer (56). Wang *et al* (57) showed that the microRNA (miR)-497/proline, glutamic acid and

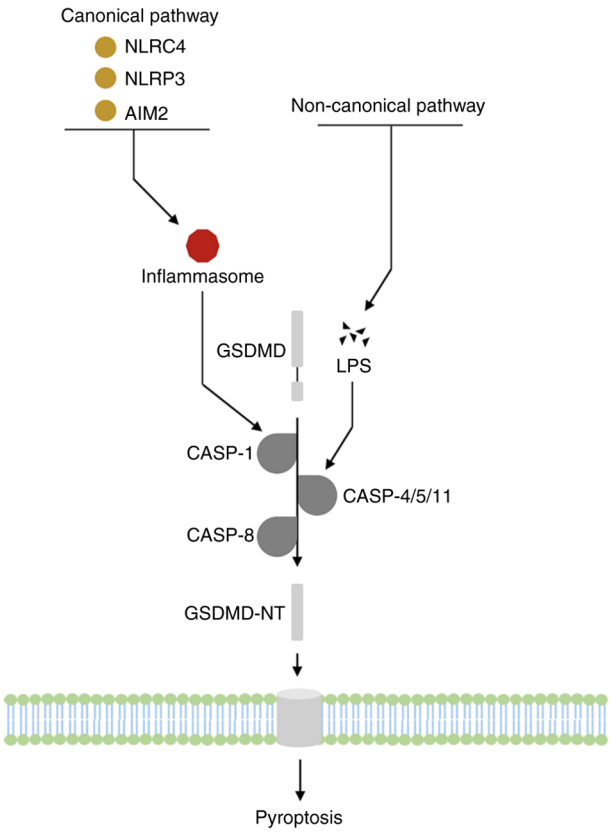

Figure 3. Summary of GSDMD activation and pore-forming functions. Multiple caspases, such as caspase-1, -4, -5, -8 and -11, may cleave and activate GSDMD. Caspase-1 activates GSDMD through inflammasome complexes such as AIM2, NLRC4 or NLRP3 via a canonical pathway. The activation of GSDMD by caspase-4, -5 and -11 is induced by LPS via a non-canonical pathway. Caspase-8-dependent GSDMD cleavage relies on caspase-8 dimerization and autoprocessing. GSDMD, gasdermin D; AIM2, absent in melanoma 2; NLRC4, NOD-like receptor C4; NLRP3, NLR family pyrin domain containing 3; LPS, lipopolysaccharide; CASP, caspase; NT, N-terminal domain.

leucine-rich protein-1 axis-mediated GSDMD-induced pyroptosis could be targeted by metformin in esophageal squamous cell carcinoma (ESCC), indicating that GSDMD-induced pyroptosis may be an alternative therapeutic target in cancer. It has been reported that GSDMD is upregulated in breast cancer tissues compared to normal tissues and overexpression of GSDMD was revealed to be an independent prognostic factor for breast cancer (14). Docosahexaenoic acid inhibits the growth of breast cancer cells by activating caspase-1-mediated GSDMD cleavage and promoting pyroptosis (58). Cisplatin induces pyroptosis by activating the maternally expressed gene 3/NLRP3/caspase-1/GSDMD pathway in triple-negative breast cancer to exert an anti-tumor effect (59). Yang *et al* (60) found that GSDMD is upregulated in endometrial cancer and that hydrogen may inhibit tumor growth via the reactive oxygen species (ROS)/NLRP3/caspase-1/GSDMD-mediated pyroptosis pathway. GSDMD was reported to be upregulated in adenoid cystic carcinoma and its overexpression promoted the invasion of these cells (61). In clear cell renal cell carcinoma (ccRCC), the GSDMD expression level was higher than that in normal tissues and was positively associated with $CD8^+$ T cells, $CD4^+$ T cells, B cells and dendritic cells, while it was negatively associated with macrophages (13). The expression of GSDMD and its N-terminus was upregulated in hepatocellular carcinoma (HCC) tissues or metastatic HCC tissues compared with that in normal tissues and upregulated GSDMD expression indicated poor prognosis. GSDMD inhibitors combined with anti-programmed cell death protein 1 immune therapy may be an effective treatment option for patients with HCC exhibiting GSDMD upregulation (62,63).

By contrast, GSDMD was observed to be downregulated or silenced in several cancer types, such as colorectal, gastric and ovarian cancers, in which pyroptosis-induced tumor proliferation or metastasis is suppressed (44,64,65). Saeki *et al* (10) reported that GSDMD inhibited the proliferation of the gastric cancer cell line MKN28 in a colony-formation assay and acted as a tumor suppressor. In addition, inhibition of GSDMD expression affected the cell cycle and accelerated the S/G2-phase transition by activating the signal transducer and activator of transcription 3 (STAT3) and PI3K/AKT signaling pathways, indicating that the inhibition of GSDMD may be a therapeutic target for gastric cancer (66). Tanaka *et al* (67) revealed that GSDMD deficiency increases the development of colon cancer, partly due to decreased apoptosis caused by the downregulation of IFN-γ-STAT1 signaling. Wang *et al* (68) found that not only the expression level but also the subcellular localization patterns were associated with colon cancer progression and immune reactions; however, the underlying mechanisms remain elusive (Table IV).

Therefore, despite the dual function (pro- and anti-tumor) of GSDMD, it is closely involved in cancer incidence, development and prognosis and may serve as a new and promising target for cancer therapies.

6. GSDME

GSDME was primarily identified as a deafness-related autosomal dominant gene, DFNA5, and an its encoding gene is located on human chromosome 7q15, with the protein comprising 496 amino acids (69). Unlike GSDMD, GSDME-induced pyroptosis mainly relies on the activation of caspase-3. Traditionally, caspase-3 is an apoptosis-related caspase that may be activated under the treatment of TNF-α or chemotherapy drugs, inducing cell apoptosis. However, when GSDME is present, activated caspase-3 cleaves GSDME at Asp270 and induces pyroptosis instead of apoptosis (70). In addition to caspase-3, Zhang *et al* (71) found that granzyme B may also cleave and activate GSDME directly at the same site as that cleaved by caspase-3, and that the activation by granzyme B could not be suppressed by a caspase-3 inhibitor (Fig. 4).

The expression of GSDME in cancer cells determines the type of cell death (72,73). In cancer cells with low or silenced expression levels of GSDME, such as HeLa and Jurkat cells, anti-tumor drugs would activate caspase-3, which cleaves the downstream poly(ADP-ribose) polymerase protein rather than GSDME, thus inducing apoptosis. Cancer cells expressing higher levels of GSDME, such as MeWo, SH-SY5Y and A549, were treated with anti-tumor drugs, and activated caspase-3 cleaved and activated GSDME, leading to pyroptosis. The transcriptional activation of GSDME is also regulated by epithelial-mesenchymal transition (74). The caspase-3 activator raptinal was able to rapidly promote GSDME-induced

Table IV. Expression and functional roles of GSDMD in cancers.

Cancer type	Expression and function	(Refs.)
Lung cancer	Upregulated in lung cancer, induced the infiltration of immune cells, knockout decreased tumor growth and metastasis	(12,52-55)
Bladder cancer	Upregulated in bladder cancer	(56)
ESCC	Upregulated in ESCC, but cytoplasm-to-membrane translocation and cleavage were inhibited	(57)
Breast cancer	Upregulated in breast cancer, overexpression indicated poor prognosis	(14)
Endometrial cancer	Upregulated in endometrial cancer	(60)
Adenoid cystic carcinoma	Upregulated in adenoid cystic carcinoma, overexpression promoted tumor invasion	(61)
ccRCC	Upregulated in ccRCC, associated with the infiltration of immune cells	(13)
HCC	Upregulated in HCC and metastatic HCC, overexpression indicated poor prognosis, enhanced immune therapy	(62,63)
Gastric cancer	Downregulated in gastric cancer	(44,64,66)
Ovarian cancer	Downregulated in ovarian cancer	(65)
Colorectal cancer	Downregulated in colorectal cancer, associated with tumor development and immune reaction	(67,68)

Chromosomal location: Human GSDMD, [8q24.3]; mouse GSDMD, [15D3-E1]. GSDMD is cleaved by caspase-1, -4, -5, -8 and -11 to activate pyroptosis, and cleaved by caspase-3 to decrease pyroptosis. GSDM, gasdermin; ESCC, esophageal squamous cell carcinoma; ccRCC, clear cell renal cell carcinoma; HCC, hepatocellular carcinoma.

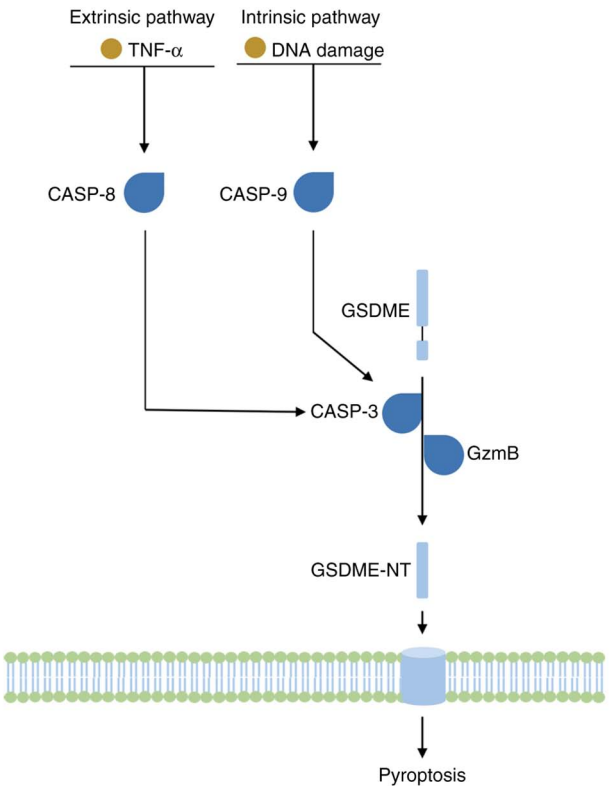

Figure 4. Summary of GSDME activation and pore-forming functions. Caspase-3 may be activated by either the extrinsic pathway (e.g., TNF-α) or intrinsic pathway (e.g., DNA damage) and subsequently cleave and activate GSDME, thus inducing pyroptosis. GSDME, gasdermin E; TNF-α, tumor necrosis factor α; CASP, caspase; GZM, granzyme; NT, N-terminal domain.

pyroptosis in melanoma (75). Induction of pyroptosis in GSDME-expressing cancer cells not only affects cell proliferation and migration but also affects the TME, recruitment and infiltration of immune cells, and the development of multiple cancer types (71,76).

Yao *et al* (13) found that the expression level of GSDME was higher in ccRCC compared to normal tissues. Furthermore, a higher expression level of GSDME correlated with poor relapse-free and overall survival, indicating that GSDME could be a potential therapeutic target and prognostic biomarker for patients with ccRCC. Similarly, GSDME is upregulated in lung adenocarcinoma and is significantly correlated with poor prognosis (12). In ESCC and head and neck squamous cell carcinoma (HNSCC), the expression level of GSDME was higher than that in normal tissues, and analysis revealed that upregulated expression levels of GSDME indicated a favorable therapeutic response and prognosis in ESCC and poorer prognosis in HNSCC (77,78). In addition, higher expression levels of GSDME have prognostic significance for gastric cancer (79). Melanoma cell lines with GSMDE deficiency tended to generate larger tumors than wild-type melanoma cells, indicating the tumor-suppressive function of GSDME (80). Liu *et al* (81) showed that apoptosis could inhibit tumor growth in colorectal cancer by inducing the GSDME-dependent pathway, and doxorubicin- or tetraarsenic hexoxide-treated breast cancer by activating caspase-3 mediated GSDME to induce pyroptosis through the ROS-related signaling pathway (82,83).

The expression level of GSDME is downregulated in breast cancer (14,84), gastric cancer (85) and colorectal cancer (86), and lower GSDME expression is related to high methylation levels (71). When *in vitro* GSDME expression was induced by DNA methyltransferase inhibitors, colony formation of gastric and colorectal cancers and invasiveness of breast cancer were reduced (87). Guo *et al* (88) revealed that GSDME inhibits

Table V. Expression and functional roles of GSDME in cancers.

Cancer type	Expression and function	(Refs.)
ccRCC	Upregulated in ccRCC, associated with poor prognosis	(13)
Lung cancer	Upregulated in lung cancer, associated with poor prognosis	(12)
ESCC	Upregulated in ESCC, higher expression indicated better therapy response and prognosis	(77)
HNSCC	Upregulated in HNSCC, associated with immune infiltration, higher expression indicated poor prognosis	(78)
Gastric cancer	Upregulated in gastric cancer, associated with poor prognosis	(79)
Gastric cancer	Downregulated in gastric cancer, higher expression reduced colony formation	(85,87)
Breast cancer	Downregulated in breast cancer, higher expression reduced invasiveness	(14,84,87)
Colorectal cancer	Downregulated in colorectal cancer, higher expression inhibited tumor growth and enhanced radiosensitivity	(86-89)
Nasopharyngeal carcinoma	Relatively high expression in cell lines, enhanced radiosensitivity	(90)
Retinoblastoma	Downregulated in tumor and cell lines, lower expression was associated with tumor-node-metastasis, higher expression increased chemotherapeutic drug sensitivity	(91)

Chromosomal location: Human GSDME, [7p15.3]; mouse GSDME, [6B2.3]. GSDME is cleaved by caspase-3 and granzyme B to activate pyroptosis. GSDM, gasdermin; ESCC, esophageal squamous cell carcinoma; ccRCC, clear cell renal cell carcinoma; HNSCC, head and neck squamous cell carcinoma.

the proliferation and tumor formation of colon cancer cells by suppressing the mammalian target of rapamycin 1/2 signaling pathway. Furthermore, activated GSDME-induced pyroptosis enhances the radiosensitivity of colorectal cancer (89), and Di *et al* (90) revealed that the effect of GSDME on radiosensitivity is associated with GSDME deubiquitylation mediated by OTU deubiquitinase 4 in nasopharyngeal carcinoma. High GSDME expression may also increase chemotherapeutic drug sensitivity by inducing pyroptosis in retinoblastoma cells (91). Importantly, the tumor-suppressive effect of GSDME was abrogated in mice lacking all lymphocytes, suggesting that the GSDME-mediated tumor-suppressive function requires pyroptosis-dependent induction of anti-tumor immunity (71) (Table V).

GSDME has an important role in regulating the biological functions of tumors. In terms of tumor detection, GSDME methylation may be an early detection biomarker. In terms of treatment, immunotherapy and chemotherapy could kill tumor cells through GSDME-induced pyroptosis. Combination with DNA methylation inhibitors may improve its anti-tumor efficacy (92). However, GSDME-induced pyroptosis may result in side effects such as nephrotoxicity (93) and lung injury (94). The related mechanisms are not fully understood, and further research and support from clinical data are required.

7. PJVK

The gene encoding PJVK, also known as PVJK, is located on human chromosome 2q31.2. Unlike other GSDMs, PJVK has a truncated non-homologous C-terminal domain and lacks a cleavable linker domain (31). PJVK was reported to be the causative gene for autosomal recessive nonsyndromic sensorineural hearing loss (95) and it was classified as a GSDM member owing to its divergent expression patterns, mutant-associated phenotypes and amino acid sequences compared with those of other GSDMs (96). Human PJVK is mainly expressed in the auditory system, including neurons, hair cells, supporting cells and spiral ganglion cells in the inner ear (96). However, whether PJVK participates in membrane pore formation or the induction of pyroptosis remains to be clarified. Only a small number of studies have focused on the expression levels of PJVK in various cancer types.

Peng *et al* (12) found that the expression levels of PJVK were higher in lung adenocarcinoma tissues than in normal tissues and that PJVK was positively correlated with $CD4^+$ T cells in the TME. A different trend was observed in ccRCC. Yao *et al* (13) found that the expression level of PJVK decreased in tumor tissues, whereas the DNA methylation level increased. Furthermore, the mRNA expression level of PJVK is negatively associated with tumor stage and positively associated with relapse-free survival. Ye *et al* (15) also reported that the expression level of DNFB59 was decreased in ovarian tumor tissues, and its low expression was associated with poor survival rates, indicating that DNFB59 may function as a tumor suppressor (Table VI). However, to date, the role of DNFB59 in cancer has not been extensively studied. Further analysis is required to determine whether PJVK may be activated via inflammatory caspases to mediate pyroptosis.

8. Discussion and perspectives

Studies have revealed that GSDMs are mainly cleaved and activated by specific caspases, and have a crucial role in pyroptosis. New mechanisms have also been proposed for mediating pyroptosis. Demarco *et al* (48) reported that caspase-8-induced GSDMD cleavage relies on caspase-8 dimerization and autoprocessing, and that activated GSDMD imparts vulnerability to TNF-induced mortality

Table VI. Expression and functional roles of PJVK in cancers.

Cancer type	Expression and function	(Refs.)
Lung cancer	Upregulated in lung cancer, associated with immune infiltration	(12)
ccRCC	Downregulated in ccRCC, negatively associated with tumor stage, positively associated with relapse-free survival	(13)
Ovarian cancer	Downregulated in ovarian cancer, lower expression indicated poor survival rates	(15)

Chromosomal location: Human PJVK, [2q31.2]; mouse PJVK, [2C3]. Pyroptosis activation remains elusive. PJVK, Pejvakin; ccRCC, clear cell renal cell carcinoma.

independent of caspase-1. Orning *et al* (97) found that in macrophages, caspase-8 was also able to act as a regulator of GSDMD-driven cell death, and caspase-8-mediated GSDMD led to the NLRP3 inflammasome-dependent release of IL-1β. Evavold *et al* (98) described macrophage hyperactivation, which is a state in which the cell secretes IL-1 while retaining viability, and GSDMD was indicated to have a key role and exert a non-pyroptotic pore-forming function in the process, suggesting a more complex nature of GSDMD. Certain GSDM family members have been reported to exert synergistic effects. Rogers *et al* (80) showed that GSDMD-mediated pyroptosis facilitates the release of GSDME, which then amplifies pyroptosis, leading to enhanced inflammation and immune responses. Although the effects and mechanisms of pyroptosis in cancer development remain to be fully elucidated, numerous studies have indicated that the GSDM family of proteins have a role in the incidence, development and prognosis of various cancer types. Most GSDM proteins exhibit anti-tumor functions and are effective targets for cancer therapy. Furthermore, the enhanced activity of GSDM proteins increases the sensitivity to chemotherapy and radiotherapy. Several studies have analyzed the relationship between the expression levels of each GSDM family member. Mu *et al* (99) systematically analyzed the molecular characteristics and oncogenic role of the GSDM family and found a correlation between the expression of the GSDM genes and patient survival, indicating the prognostic value of the expression of the GSDM genes. Zheng *et al* (100) systematically evaluated the gene expression, genetic variations and prognostic values of GSDM family members and found that expression levels were associated with prognosis, clinical characteristics, TME features, and stemness scores in several cancer types. Huo *et al* (101) confirmed that the risk or protective effects of GSDM family members on prognosis depend on the cancer type; the mutation frequency appeared to be high and the mutation group had a worse prognosis. GSDMs may be upregulated, downregulated or even silenced in cancers, and their expression levels are mainly associated with the DNA methylation level of their promoters. Higher methylation levels inhibited GSDM expression, whereas demethylation was able to activate the expression of GSDMs, indicating that GSDM methylation may be an early diagnostic biomarker, a prognostic marker and a therapeutic target for combined treatment.

Although pyroptosis may be harnessed to kill cancer cells, it must be noted that during the process of pyroptosis, large amounts of inflammatory substances, such as IL-1β and IL-18, are released, resulting in a cascade of inflammatory reactions that may be harmful to normal cells. Liu *et al* (102) also reported a complication after chimeric antigen receptor (CAR) T-cell therapy called cytokine release syndrome (CRS). CAR-T cells promote the release of granzyme B, activate caspase-3-dependent cleavage of GSDME and induce the release of pyroptosis-related inflammatory factor by macrophages, further activating caspase-1-mediated GSDMD cleavage in macrophages and causing the release of more cytokines and subsequent CRS. However, CRS did not occur after the knockout of GSDME, reduction in macrophages or inhibition of caspase-1 (102). Pyroptosis causes local inflammation and acts as a highly immunogenic form of cell death with the release of multiple chemokines, leading to the recruitment and infiltration of immune cells, providing a great opportunity to relieve the immunosuppression of the tumor immune microenvironment and induce systemic immune responses in the treatment of solid tumors. GSDMD-, GSDME-, GSDMC- and GSDMB-mediated pyroptosis has been reported to enhance the immune response in various cancer types (70). However, chronic tumor pyroptosis may also suppress anti-tumor immunity and accelerate tumor growth. Hou *et al* (33) found that solid tumors had hypoxic areas in which the expression of GSDMC was enhanced and cleaved by TNFα-activated caspase-8, which led to pyroptosis and subsequent chronic tumor necrosis while suppressing anti-tumor immune responses. Therefore, GSDM-induced pyroptosis has a dual role in tumorigenesis, regression and the tumor immune microenvironment (103,104).

A pan-cancer analysis of the genetic variation in GSDM genes revealed that in pan-cancer tissues, the overall mutation frequency in GSDM genes was relatively low, and missense mutations were the most frequent form of mutation. Studies have partly elucidated the relationship between GSDM mutations and specific diseases, including various cancers. Ruan *et al* (105) analyzed the structure of the GSDMA3 membrane pores using cryo-electron microscopy and partly revealed the mechanisms by which the cleavage of GSDMA3 formed membrane pores and the mechanisms of autoinhibition. Due to a loss of autoinhibition, disease-related mutations in GSDMA3 and its N terminus alone can initiate pyroptosis and are closely associated with spontaneous alopecia and hyperkeratosis (3). SNPs in GSDMA and GSDMB have been reported to be related to childhood asthma and, to a lesser extent, adult asthma (96). The GSDMB SNPs are also associated with cancer development and progression (21,28).

Somatic mutations in GSDMC have been reported in breast cancer (34). Mutations in GSDME and PJVK induce deafness through different mechanisms. Mutations in GSDME result in its overexpression, leading to pyroptosis in HeLa cells (72), whereas PJVK mutations exert non-pyroptosis functions (95). Xia *et al* (106) reported the cryo-electron microscopy structures of the pores of GSDMD, elucidating the process of GSDMD-dependent membrane pore formation and the GSDMD-mediated release of IL-1β. Liu *et al* (107) revealed the mechanisms of autoinhibition, lipid binding and oligomerization of the GSDMD-N-terminus by virtue of its crystal structures. These molecular structure studies provide an explanation for the mode of action of several mutant GSDM family members, including mutants linked to cancer (105).

Considering that pyroptosis signaling pathways are deeply involved in the incidence and development of different cancer types, certain agents have been developed or discovered to exert protective effects against cancers by targeting pyroptosis pathways, either by inducing or inhibiting pyroptosis. Small-molecule inhibitors of di-peptidyl-peptidase 8/9, two serine proteases in host cells, have been reported to activate NLRP1 and caspase recruitment domain-containing protein 8, and induce pyroptosis via the caspase-1/GSDMD pathway, thus inhibiting the progression of acute myeloid leukemia (108,109). It was also revealed that FL118, anthocyanin and docosahexaenoic acid have anti-tumor activity against colorectal cancer (110), oral squamous cell carcinoma (111) and breast cancer (58) partly by promoting NLRP3/caspase1/GSDMD-mediated pyroptosis. Traditional chemotherapy drugs, such as cisplatin, paclitaxel, doxorubicin and lobaplatin, have also been found to induce pyroptosis via the caspase-3/GSDME pathway to inhibit the development of lung cancer (112), ESCC (77), melanoma (113) and colon cancer (114). Previously, the mechanisms of the above chemotherapy drugs in exerting anti-cancer effects were thought to be mainly dependent on apoptosis, and updated evidence has shown that it is important to identify whether the therapeutic effects are due to the differential activation of apoptosis or pyroptosis. Due to the double-edged sword effect of pyroptosis in cancer development, pyroptosis inhibitors also show therapeutic potential, most of which were developed to target the molecules upstream of GSDMs. Rathkey *et al* (115) reported that necrosulfonamide (NSA) was able to directly bind to GSDMD and inhibit the cleavage of GSDMD, blocking pyroptosis cell death and IL-1β release. Zhou *et al* (116) also found that NSA represses NLRP3 inflammasome-mediated pyroptosis, indicating that NSA may be an effective agent for targeting pyroptosis. Disulfiram inhibits pyroptosis by blocking GSDMD-induced membrane pore formation, indicating its potential as a therapeutic method for cancer and other inflammatory illnesses exacerbated by pyroptosis (117). NLRP3 and caspase inhibitors have been explored for the treatment of neurodegenerative diseases by targeting overactivated pyroptosis and have shown certain effects (44,118,119). Recently, LDC7559, a newly developed selective GSDMD inhibitor, was reported to promote brain functional recovery by inhibiting over-activated pyroptosis by directly blocking the GSDMD-N-terminus (120,121). However, whether these inhibitors may also be used for cancer treatment remains to be investigated. To the best of our knowledge, there are currently no other specific inhibitors of the GSDM family members, and this would be a further direction for exploring more potent anti-tumor treatments.

Regarding the effects of GSDMs and their regulatory mechanisms, we are beginning to understand the molecular, biological and pathological functions of GSDMs in pyroptosis. Further research to elucidate the mechanisms of GSDM-mediated pyroptosis will deepen our understanding of the roles of GSDM family proteins in cancers and provide new ideas for developing more potent anti-tumor methods.

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Authors' contributions

XY carried out the primary literature search and drafted and revised the manuscript. ZT contributed to drafting and revising the manuscript. XY and ZT performed literature analyses. All the authors have read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

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Not applicable.

Competing interests

The authors declare that they have no competing interests.

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