



Role of GSDMB in Pyroptosis and Cancer

This article was published in the following Dove Press journal:
Cancer Management and Research

Lisha Li

Yanjing Li 

Yuxian Bai 

Department of Gastrointestinal
Oncology, Harbin Medical University
Cancer Hospital, Harbin, Heilongjiang
150081, People's Republic of China

Abstract: Gasdermin B (GSDMB) belongs to the gasdermin (GSDM) family which may adopt different mechanisms of intramolecular domain interactions to modulate their lipid-binding and pore-forming activities. The GSDM family has regulatory functions in cell proliferation and differentiation, especially in pyroptosis process. Pyroptosis is a pro-inflammatory form of regulated cell death and is designed to attract a nonspecific innate response to the site of infection. For cancer cells, the activation of pyroptosis may promote cell death and exert anticancer properties. Also, recent studies have observed the pyroptosis-like features in GSDMB and some researches have shown that GSDMB overexpression occurred in several kinds of cancers; these findings bring a contradiction with the participation of GSDMB in pyroptosis. Although people pay less attention to GSDMB, it still has some essential research value. It is a paradox that GSDMB might participate in programmed cell death, which might put forward a research direction of therapeutic targets for cancer. Here, we review the possible progress of how GSDMB participated in this inflammatory regulation mechanistically and the potential functions of GSDMB in cancer.

Keywords: GSDMB, pyroptosis, cancer, gasdermin family, pore-forming activities

Introduction

High incidence and high mortality making cancer one of the leading causes of death in the world and one of the most important public health issues. Incidence rates are highest among developed countries for a wide range of types of cancer, including prostate, lung, colorectal, and breast cancers. However, the highest rates of cervical, esophageal, liver, and stomach cancers also occur in some developed countries. Epidemiological data also revealed gender- and region-specific patterns in cancer prevalence worldwide.¹ Cancer mortality has been associated with a wide variety of risk factors, including physical inactivity level, infection, smoking status, and obesity. Despite improvements in therapies, cancers tend to progress extremely aggressively, yielding poor survival rates, and as such, cancer research remains extremely active.²⁻⁶

Pyroptosis is a novel type of programmed cell death that plays a critical role in both septic shock and immune defenses.⁷⁻¹⁰ It was first observed in macrophages infected with the Gram-negative bacteria *Shigella flexneri* in 1992, and the term was named by Lawrence H. Boise in 2001.¹¹⁻¹³ Pyroptosis is occurred through the action of various stimuli and inflammatory caspases and caspases trigger the cleavage of gasdermin family as well as the release of both its C-terminal inhibitory domain and N-terminal effector domain.¹⁴⁻¹⁷ The N-terminal domain oligomerizes in the cell membrane and forms pores, which leads to rapid plasma membrane rupture, thus releasing the intracellular contents and pro-inflammatory mediators such as

Correspondence: Yanjing Li; Yuxian Bai
Department of Gastrointestinal
Oncology, Harbin Medical University
Cancer Hospital, 150 Haping Street,
Nangang District, Harbin 150081,
People's Republic of China
Tel +86-451-86298303
Fax +86-451-86298961
Email liyanjing_hmu@126.com;
bai_yuxian@126.com

interleukin (IL)-18 and IL-1 β .¹⁸ The release of damage-associated molecular patterns from lysed pyroptotic cells can recruit immune cells and further promote inflammation. For cancer cells, the activation of pyroptosis may promote cell death and exert anticancer properties.^{7,19-22}

Pyroptosis is also called gasdermin-mediated programmed cell death. The gasdermin (GSDM) family has regulatory functions in normal cell proliferation and differentiation^{23,24} and include gasdermin A (GSDMA), gasdermin B (GSDMB), gasdermin C (GSDMC), gasdermin D (GSDMD), gasdermin E (GSDME), and DFNB59.²⁵⁻²⁷ GSDMA and GSDMB genes are located at 17q2, while GSDMC and GSDMD are located at 8q24.²⁸ With the exception of DFNB59, these gene family members share about 45% sequence homology, and all of the GSDM have two domains that are capable of binding to each other and are connected by a long flexible linker.^{29,30} Sequence homology suggests that the members of the GSDM family (except for DFNB59) share similar 3D structures.^{29,31,32} The gasdermin-N domain enables most GSDM members to function as a new type of pore-forming protein. In their pore-forming protein role, different GSDM family members may adopt different mechanisms of intramolecular domain interactions that modulate their lipid-binding and pore-forming activities, which may induce pyroptosis-like features in cells. GSDMB, as a member of GSDM family, also has been observed pyroptosis-like features, and some studies have shown that GSDMB overexpression occurs in several kinds of cancers, where it might be involved in cancer progression and metastasis.^{33,34} Here, we review the progress in uncovering how GSDMB participates in this inflammatory regulation mechanistically and the potential functions of GSDMB in cancer.

Characterization of GSDMB

GSDMB used to be known as GSDML (gasdermin-like protein) and is located at 17q21, which may also harbor genes that influence diseases associated with aberrant immune responses, and 17q21 also includes ORMDL3, which also regulates the expression of GSDMB. It is hypothesized that GSDMB might be generated due to a duplication of GSDMA gene which is also a member of GSDM family and is located at 17q21 too. The GSDMB protein is comprised of 411 amino acids.²⁸ As shown in [Figure 1](#), GSDMB is so different from other GSDM in its structure and domain architecture. However, there are two different promoters in the cis-regulatory elements of GSDMB, an Alu-derived promoter

which directs expression solely in normal stomach tissues and a long-terminal-repeat (LTR) derived promoter which directs GSDMB expression in various types of cancer and normal tissues. These two promoters drive all GSDMB transcriptions except for those starting from exon1a and exon1b.^{35,36} However, the molecular mechanisms by which the cellular promoter regulates GSDMB expression have not yet been elucidated.³⁷ Human GSDMB has six splicing variants, and each of them can encode a protein with a molecular weight ranging from 35 to 50 kDa. These isoforms have different expression profiles and subcellular localization patterns in different cell types and are also different in the sequence of their linkers between the N- and C-terminal domains which is weaker and instability than those of any other gasdermins, except for isoform 5, which comprises only the C-terminal domain of the protein.^{30,38} The C-terminal domain does not inhibit lipid binding because of the weaker N- and C-domain interactions in GSDMB.

Some studies discovered that the N-terminal domains of GSDMA3, GSDMA and GSDMD could bind phospholipids and cardiolipin and the C-terminal domains inhibit this ability to the full-length proteins.³⁹ Therefore, these GSDMs could function only upon cleavage between their N- and C-terminal domains because phospholipids were components of the cell membrane's inner leaflets. The lipid-binding activity of GSDMB is also located in its N-terminal domain, both the full-length GSDMB protein as well as the N-terminal domain of GSDMB uniquely bind phosphoinositides and sulfatides (sulfated galactocerebrosides and 3-O-sulfogalactosylceramides).⁴⁰ Strikingly, unlike other GSDMs, the presence of the GSDMB C-terminal domain in the full-length protein does not prevent phospholipid binding. The reason for this strange phenomenon is that the N-terminal domain bound liposomes containing sulfatide whereas the C-terminal domain does not. Sulfatides, which are esters of sulfuric acid with galactosylceramides, are synthesized from galactosylceramide in the Golgi apparatus and degraded in the lysosome. Sulfatides are multifunctional molecules, which have several important biological functions in the immune system, nervous system, microbial infections, cancer, and so on. Elevated levels of sulfatides are documented on the surface membrane of epithelial cells in many cancers, which suggests that GSDMB may have an important function in cellular transport of sulfatides. Abundant sulfatides on the surface of cancer cells are native ligands for P-selectin expressed by activated endothelial cells, which could

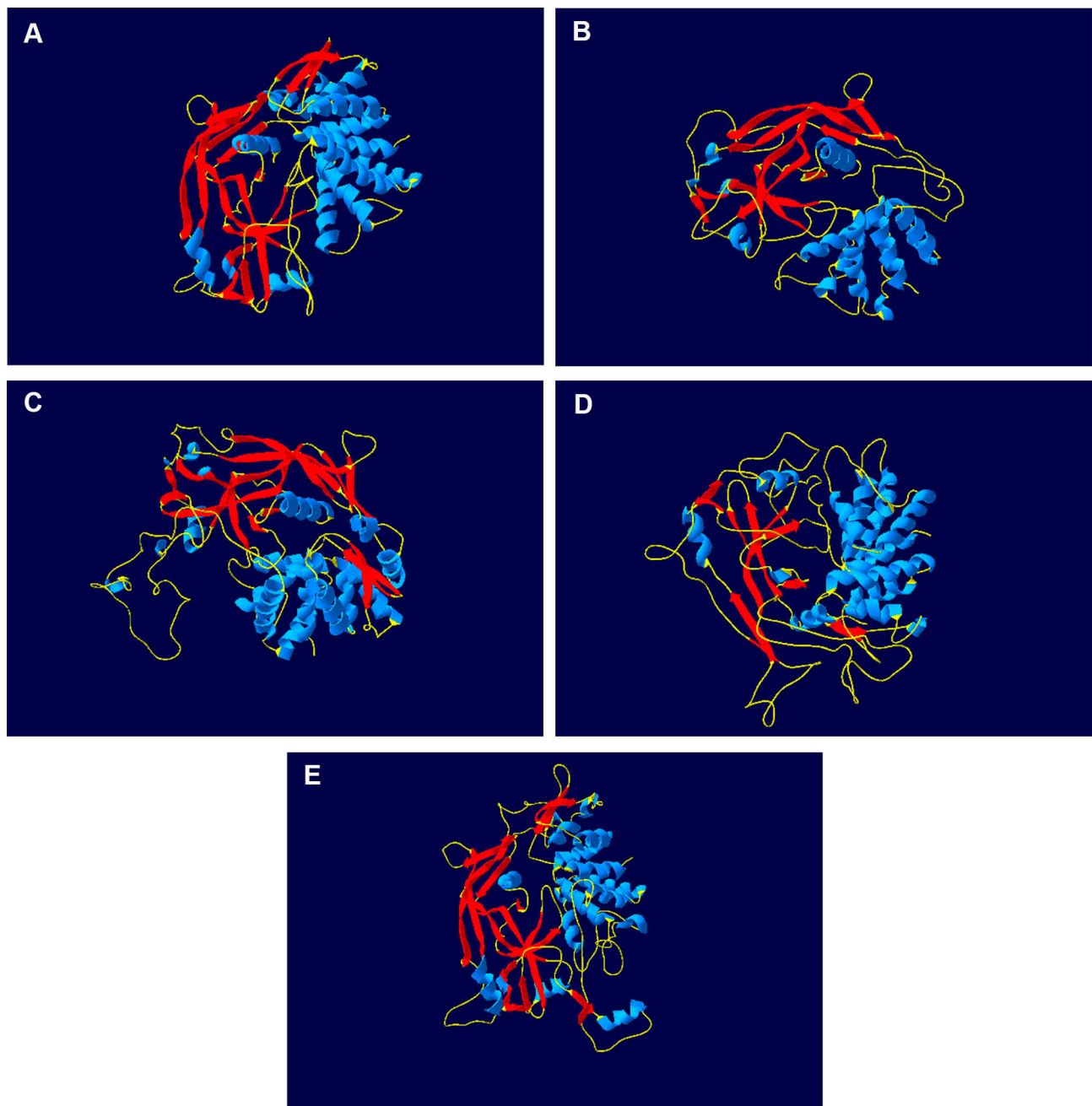


Figure 1 GSDMB is different from other gasdermins in its structure and domain architecture. The protein of GSDMA (A), GSDMB (B), GSDMC (C), GSDMD (D) and GSDME (E) is shown as cartoon. Blue cartoon represents the helices of protein. Red cartoon represents the sheets of protein. Yellow cartoon represents the coils of protein.

facilitate the formation of aggregates and promote cancer cell migration and metastasis. Overall, the N-terminal domain of GSDMB can bind with sulfatide uniquely, while sulfatide over-expression is frequently related to cancer progression, suggesting that GSDMB might play a significant role in cancer cell migration and metastasis.^{28,30,41-44}

Therefore, the difference in the inherent stability of these isoforms and susceptibility to cellular protein degradation

machinery may lead to different cellular concentrations, which may thus increase some disease risk.³⁰ A recent research has revealed an association between single nucleotide polymorphisms in GSDMB and type 1 diabetes and ankylosing spondylitis.³⁵ In particular, polymorphisms in GSDMB were also associated with an increased risk of developing complex-trait inflammatory diseases, such as asthma, inflammatory bowel disease, Crohn's disease, and ulcerative colitis.^{30,45} Humans may also be more susceptible

to inflammatory disease than mice because humans carry a gene encoding GSDMB but rodents do not. Recent research has observed that GSDMB has the ability to induce pyroptosis-like features, but it remains unclear whether GSDMB can induce pyroptosis or how GSDMB participates in this inflammatory regulation mechanistically.³⁵ In the process of exploring whether GSDM family members can induce programmed cell death, Shi et al found that GSDM family proteins were expressed normally in cells and that the N-terminal domains of GSDM family members, with exception of DFNB59, have the ability to induce cell death.²⁹ However, many scholars pay more attention to the role of GSDMB in pyroptosis.

GSDMB Participates in Pyroptosis Cleavage of GSDMB Protein by Caspase-1 Induces Pyroptosis

Ding et al found that the N-terminal domain of GSDMB indeed induces pyroptosis in HEK293T cells.³⁹ Accordingly, Panganiban et al found that expression of GSDMB proteins alone in the absence of caspase-1 did not induce pyroptosis.⁴⁶ Moreover, transfection of plasmids expressing GSDMB and caspase-1 into 293T cells induced GSDMB to be cleaved into two short forms. As shown in Figure 2, subsequent experiments have indicated that GSDMB is cleaved by caspase-1 at site 236. One of the cleaved forms is the N-terminus of the

GSDMB protein, which is about 20 kDa. The release of the N-terminal domain can induce cell pyroptosis. In contrast, the full-length N-terminal domain or the C-terminal fragment could not induce any increase in pyroptosis. Importantly, they investigated whether the splicing variant rs11078928, which corresponds to one of the single nucleotide polymorphisms in GSDMB, abolishes the biochemical ability of GSDMB to induce pyroptosis cell death, because genotypes of rs11078928 result in a change of proline to serine (P311S) at amino acid residue 311 of the GSDMB protein. This substitution destroys a splicing acceptor site and prevents the splicing of exon 643, leading to the deletion of 13 amino acids from the N-terminus of GSDMB.^{46,47}

GSDMB Promotes Non-Canonical Pyroptosis by Enhancing Caspase-4 Activity

Chen et al found that the N-terminus of GSDMB by itself was unlike other GSDM family proteins in its association with sulfatide, but without inducing pyroptosis.⁴⁸ The binding of full-length GSDMB with the CARD domain of caspase-4 may result in the oligomerization of caspase-4 proteins, which in turn causes conformational changes to caspase-4 proteins, thus increasing enzymatic activity and promoting GSDMB cleavage, thereby inducing non-canonical pyroptosis just as seen in Figure 3. In addition, Chen et al also posited that the positive

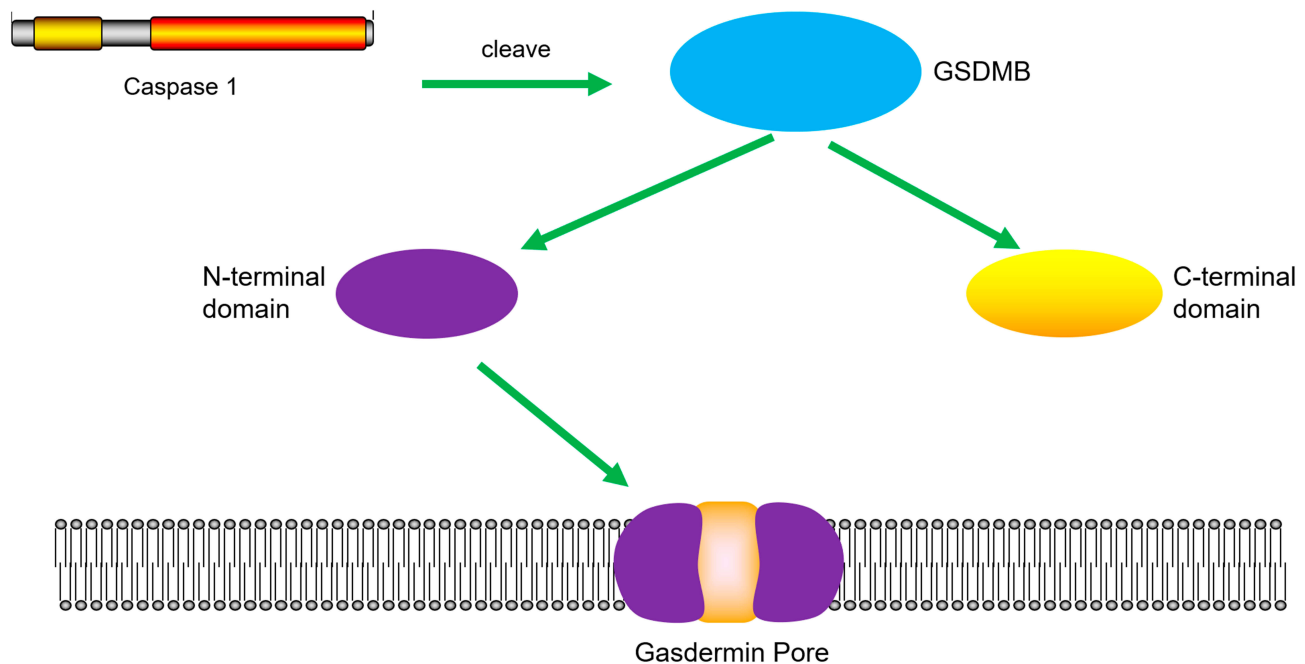


Figure 2 Cleavage of GSDMB protein by caspase-1 induces pyroptosis. Caspase-1 promotes the cleavage of GSDMB and the releasing of the N-terminal effector domain and the C-terminal inhibitory domain. The N-terminal domain oligomerizes in the cell membrane and forms pores, which leads to pyroptosis.

effect of GSDMB on caspase-4 in non-canonical pyroptosis can be terminated by a negative feedback mechanism, which may be an important protective function when excessive or prolonged pyroptosis in response to infectious pathogens is detrimental. Taken together, the authors concluded that the GSDMB N-terminus cannot form pores and that the enhanced cell death caused by GSDMB actually occurs through enhancing the enzymatic activity of caspase-4.⁴⁹

GSDMB Could Be Cleaved by Caspase-3/-6/-7

When Chao et al investigated whether GSDMB is a substrate of human apoptotic caspases, they found that GSDMB is not a substrate for the inflammatory caspases 1 and 4/5/11 because it lacks the specific interdomain linker region site, like the GSDMD cleavage sequence.³⁰ Accordingly, they characterized the phospholipid-binding activities of GSDMB and the cleavage profile of caspase and was also demonstrated that GSDMB proteins are substrates of the apoptotic executioner apoptotic caspases-3, -6, and -7 proteins, not inflammatory caspases, which implies potential cross-talk between the apoptosis pathway and the non-canonical pyroptosis pathway. The molecular weights of the proteolytic fragments indicate that the caspase recognition site is in the N-terminal domain of GSDMB and not in the interdomain linker region. Additionally, just as shown in Figure 4, the N-terminal sequence of the C-terminal fragment from a caspase-3 cleavage reaction revealed that the cleavage site is after 88DNVD91 and 304EDPD307, with a probability score of 0.803. Thus, human caspases did

not generate an entire GSDMB N-terminal domain, analogous to the pyroptosis N-terminal domain of GSDMD, which binds signaling lipids in contrast to other GSDM, whose C-terminal domains inhibit lipid binding, and only their cleaved forms can bind lipids, form pores, and kill cells. However, there has been no evidence that a stable N-terminal domain is generated from a proteolytic cleavage of GSDMB, and the pyroptosis activity of the N-terminal domain may be decoupled from its phospholipid-binding activity because the full-length GSDMB is noncytotoxic.^{30,35,39} In general, the cleavage by caspase-3/-6/-7 does not form a complete N domain. And whether the cleaved product can form pores and induce pyroptosis is currently exclusive. Thus, the functional significance of caspase-3/-6/-7 cleavage at an internal GSDMB's N-terminal domain and its impact on protein activity is worthy of in-depth study.

In conclusion, how GSDMB participates in pyroptosis is still debatable. Experiments have different ideas in the role of caspases in the cleavage of GSDMB in pyroptosis. As shown in Table 1, there are many differences in the experiments that were performed. Taken together, different cell lines and conditions lead to different cleavage sites for caspases. However, only GSDMB cleaved by special caspase at the particularly site can produce the N-terminus that have a pore-forming ability, which might be the possible reason resulted indifferent conclusions. Thus, further research should be undertaken to investigate whether GSDMB can induce cell pyroptosis by cleaving caspases and how GSDMB participates in pyroptosis mechanistically.

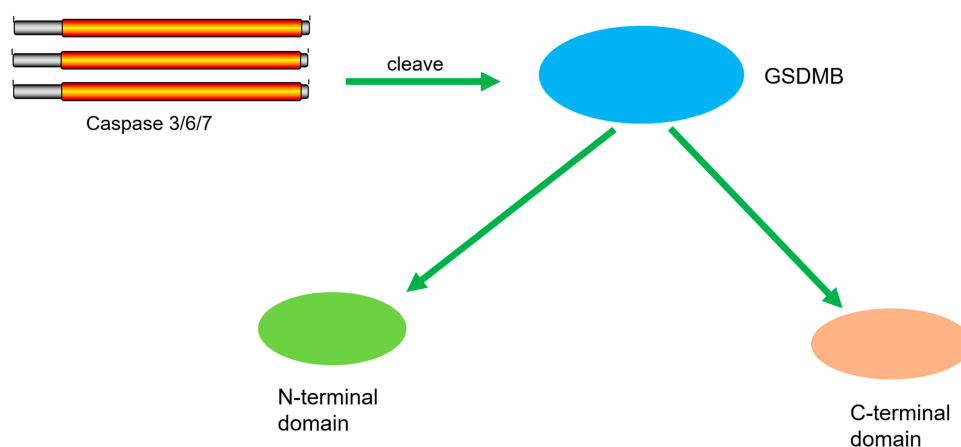


Figure 3 GSDMB promotes non-canonical pyroptosis by enhancing caspase-4 activity. The binding of GSDMB with the CARD domain of caspase-4 result in the oligomerization of the caspase-4 proteins, and caspase-4 promotes the cleavage of GSDMD and the releasing of the N-terminal effector domain and the C-terminal inhibitory domain. The N-terminal domain oligomerizes in the cell membrane and forms pores, which leads to pyroptosis.

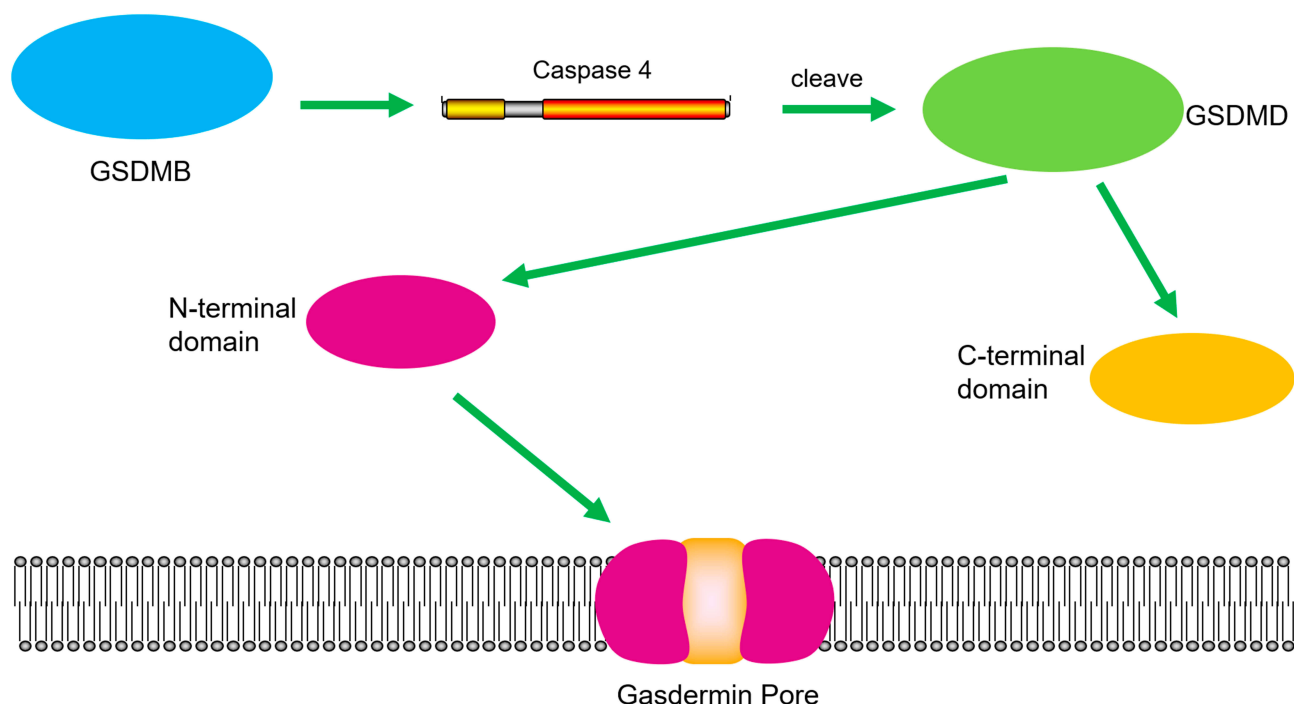


Figure 4 GSDMB could be cleaved by caspase-3/-6/-7. Caspase-3/-6/-7 promotes the cleavage of GSDMB and the releasing of the N-terminal effector domain and the C-terminal inhibitory domain.

GSDMB and Cancer

Recently, GSDMB expression has been detected in lymphocytes as well as esophagus, stomach, liver, colon, skin epithelium, gastrointestinal tract, and immune cells. Based on previous studies of human cancers, people have found that GSDMB is highly expressed not only in healthy tissues but also in cancer tissues, such as those of gastric, uterine, cervical, and breast cancers.³⁵ Researchers have demonstrated that GSDMB located in amplicons, genomic regions that are often amplified during cancer development.

Therefore, GSDMB may be involved in cancer progression and metastasis.³⁴ However, the specific functions of GSDMB in carcinogenesis, cancer metastasis, and progression are still not well understood.

GSDMB in Breast Cancer

The expression of fusion genes created by genomic rearrangements, such as GSDMB in the TATDN1–GSDMB fusion, was recently observed to be especially common in association with high-level DNA amplification, which may

Table 1 Differences in the Experiments About the Mechanism of GSDMB in Pyroptosis

Cell Signaling	Cell Lines	Activated Conditions	Methods	Cleavage Sites	References
Cleavage of GSDMB protein by caspase-1	Human ciliated airway epithelial cells	Pro-inflammatory stimuli such as viruses and allergens	Cytotoxicity assay, microscopic examination	D236A mutant	[39,46,47]
GSDMB promotes non-canonical pyroptosis by enhancing caspase-4 activity	Human embryonic kidney (HEK)	FuGENE HD	Measurement of caspase-4 activity, cytotoxicity assay, co-immunoprecipitation studies	–	[48,49]
Cleavage of GSDMB protein by caspase-3/-6/-7	The human GSDMB gene was amplified from a cDNA clone and was ligated for expression in <i>E. coli</i> .	–	In vitro caspase cleavage assay, Western analyses	88DNVD91 site	[30,35,39]

be associated with the selective advantage provided by DNA amplification and deletion. In human epidermal growth factor receptor 2-positive breast cancer, GSDMB overexpression has been shown to occur in approximately 60% of the cases, where it appears to promote cancer cell invasion, progression, and metastasis. Thus, GSDMB may be used as a novel marker in breast cancer screening. As demonstrated by Molina-Crespo et al intracellular delivery of an antibody targeting GSDMB can reduce human epidermal growth factor receptor 2 breast cancer metastasis, migration, and resistance to therapy efficiently and specifically. Thus, there is potential for aggressive human epidermal growth factor receptor 2 breast cancers to be effectively treated by inducing cytoplasmic overexpression of GSDMB. However, other researchers have found that GSDMB expression is also linked to poor prognosis, poor therapeutic responses in terms of relapse-free survival, and the development of distant metastasis in human epidermal growth factor receptor 2-positive breast cancer. As demonstrated across a range of human epidermal growth factor receptor 2-positive breast carcinoma cells, GSDMB expression promotes survival under treatment with trastuzumab. The same researchers also found that in vivo GSDMB expression is closely related to trastuzumab resistance in patient-derived xenografts.^{33,50-52} Overall, GSDMB is a critical determinant of poor prognosis and therapeutic response in human epidermal growth factor receptor 2-positive breast cancer, and the mechanisms underlying resistance remain somewhat unknown.

GSDMB in Gastric Cancer

Gastric cancer is a major malignant disease and the second most common cause of cancer death worldwide.⁵³ Recently, Komiyama et al examined GSDMB expression in healthy and cancerous stomach tissue samples.³⁴ They found that GSDMB had extremely low expression levels in most normal gastric tissues, and the expression level was low or effectively absent in the few healthy samples exhibiting GSDMB expression. Unlike the healthy tissues, GSDMB was amplified and overexpressed in gastric cancers, showing that GSDMB might play an important role in the regulation of cancer cell proliferation and have no cell-growth inhibition activity in gastric cancer cells. These findings indicated that GSDMB might be an oncogene.³⁴ Accordingly, Carl-McGrath et al found that GSDMB could also be overexpressed in hepatic carcinoma and colon cancer tissues.⁵⁴

Komiyama et al found an Alu element, approximately 300-bp-long and belonging to the SINE family of

retrotransposons, residing in the 5' region upstream of GSDMB. The Alu element was found to regulate GSDMB expression in cancer cells, and a putative IKZF binding motif in this element played an important role in upregulating GSDMB expression.³⁴ Another study, by Saeki et al found that GSDMB expression is also driven by two promoters, including a cellular promoter and LTR-derived promoter.⁵⁵ Additionally, the LTR promoter drives GSDMB expression in gastric cancer specimens. These two studies concluded that GSDMB expression levels and Alu versus LTR-derived promoter usage may be useful markers for the evaluation of gastric cancer development and progression. In addition, Saeki et al also identified a region downstream of the LTR promoter that showed transcriptional activity in gastric cancer cell lines.⁵⁵ They used this region to construct a herpes simplex virus thymidine kinase-expression viral vector, which could be used as a therapeutic vector for expression in cancer cells. Accordingly, the GSDMB-driven herpes simplex virus thymidine kinase expression vector can alter a targeted regulatory region through cancer cell-specific expression of cytotoxic genes, which could be used to treat gastric cancer with peritoneal dissemination, a condition that has a critical impact on patient survival.^{11,34,54-56}

GSDMB in Cervical Squamous Cell Carcinomas

Cervical cancer is both the third most common form of cancer and a major cause of mortality among women worldwide. Cervical cancer is caused by persistent infection with an oncogenic strain of high-risk human papillomavirus.^{57,58} Tumor stages, grade of differentiation, smoking status, use of oral contraceptives, and postmenopausal age may each increase cervical carcinogenesis risk. In squamous cell carcinomas, Lutkowska et al showed that polymorphisms within two non-major histocompatibility loci are associated with invasive Cervical cancer.⁵⁹ These polymorphisms include the single nucleotide polymorphism NC_000017.10:g.38051348A>G (rs8067378), which is located 9.5 kb downstream of GSDMB. This corresponds to the cellular promoter and the Long Terminal region, which can drive the expression of GSDMB. The same researchers also assessed the effect of rs8067378 genotype on GSDMB levels in both non-cancerous and squamous cell carcinomas tissues, finding a clear increase in the GSDMB levels observed in squamous cell carcinoma tissues. Accordingly, rs8067378 single nucleotide polymorphism variants appear to increase

GSDMB expression, as associated with the development and progression of cervical squamous cell carcinoma tissues. As such, GSDMB expression could be a risk factor of cervical squamous cell carcinoma tissues, in which it may promote cancer cell growth and accelerate metastasis beyond that of lower-grade cancerous cells. Thus, there is a potential link between GSDMB protein expression and the development and progression of uterine cervical cancer.^{59,60}

In conclusion, researchers found that GSDMB is highly expressed in human cancer tissues, including gastric, hepatic, colon, uterine, esophagus, stomach and cervical cancers, and other cancer-derived cell lines. But as shown in Table 2, there are some similarities and differences among these cancers. GSDMB expression is linked to poor prognosis, poor therapeutic responses in terms of relapse-free survival and the development of distant metastasis in cancer, and GSDMB also has been used as a novel marker. Additionally, GSDMB could be a potential therapeutic target involved in the treatment of cancer. At present the researches of GSDMB in cancer is still not clear, there is abundant room for future research to investigate therapeutic targets for cancer treatment.

GSDMB and Other Disease

Previous studies of GSDMB also revealed a correlation between GSDMB and an increased susceptibility to asthma, acute lymphoblastic leukemia, inflammatory bowel disease (IBD) and fat. Studies of asthma showed that susceptibility to asthma is influenced by genes and environment, and chromosome 17q12-21 remains the most highly replicated and significant locus. People also proved

that GSDMB is highly expressed in the bronchial epithelium of asthmatic human lungs and is reported as asthma susceptibility loci.^{61,62} Panganiban et al found a functional asthma variant in the GSDMB gene of the 17q21 locus.⁴⁶ Moffatt et al also demonstrated that variants at the ORM3/GSDMB locus are associated with childhood-onset disease.⁶³ Besides, studies of Kim et al indicated that genetic variations of GSDMB might be associated with the development of aspirin-exacerbated respiratory disease (AERD) and aspirin-induced bronchospasm.⁴⁰ In addition, Wiemels et al found two new genetic associations (at chromosomal locations 17q12 and 8q24.21) that impacted childhood acute lymphoblastic leukemia risk and could help us to clarify the etiology of this disease. They observed that the acute lymphoblastic leukemia association peak on chromosome 17q12 covers approximately 200 kb and includes IKZF3, single nucleotide polymorphism, and GSDMB is also present within 17q12. Thus, Wiemels et al found that GSDMB might impact gene expression locally and affect the risk of acute lymphoblastic leukemia.⁶⁴ Moreover, researchers found that multiple genes are implicated in altering IBD predisposition and there are potentially damaging mutations in the GSDMB gene in patients. Furthermore, people also proved that GSDMB affects the susceptibility to IBD via effects on apoptosis and cell proliferation.^{65,66} A study of the genetic determinants of body fat distribution showed that there are seven loci associated with ectopic-fat which included GSDMB, revealing the physiological roles for these genes in adipogenesis.⁶⁷

Table 2 GSDMB in Different Cancers

Cancer Type	Expression in Cancer	GSDMB in Cancer Cell Invasion, Progression, and Metastasis	The Role of GSDMB in Marker of Cancer	The Role of GSDMB in Prognosis	The Role of GSDMB in Therapy	References
Breast cancer	Upregulation	Correlation	A marker in cancer screening	A critical determinant	Antibody targeting GSDMB Cytoplasmic overexpression of GSDMB	[33,50–52]
Gastric cancer	Upregulation	Correlation	A marker for the evaluation of cancer development and progression	–	The GSDMB-driven expression vector	[34,54–56]
Cervical cancer	Upregulation	Correlation	An evaluation indicator in onset risk during the normal to cancer transition process	–	–	[59,60]

In short, people found that GSDMB plays an important role not only in cancers but also in other diseases. However, up to now there are a few studies discussing the specific mechanism of GSDMB in diseases and further research should be undertaken to investigate more GSDMB-associated diseases and whether GSDMB-mediated pyroptosis participates in them.

Summary and Prospects

This study set out to provide insights into the possible progress of how GSDMB participates in pyroptosis and the potential functions of GSDMB in cancer. GSDMB belongs to the GSDM family and may be able to uniquely bind liposomes containing sulfatide and to induce pyroptosis-like features. To date, researchers have posited three hypotheses about the pyroptosis pathway, including that GSDMB protein could be cleaved by caspase-1 to induce pyroptosis. In contrast, other researchers have found that GSDMB promotes non-canonical pyroptosis by enhancing caspase-4 activity. In addition, GSDMB protein could be cleaved by caspase-3/-6/-7 but whether it is possible to induce pyroptosis is not sure. Thus, further research should be undertaken to investigate whether GSDMB can induce cell pyroptosis and how GSDMB participates in the inflammatory regulation mechanistically. In addition, some studies have shown that GSDMB overexpression has been detected in several kinds of cancer cells. GSDMB has been considered an oncogene that appears to be involved in cancer progression and metastasis; there is a seeming contradiction here, as GSDMB participates in pyroptosis, but the role of GSDMB in programmed cell death suggests its dysfunction is itself oncogenic. In general, from our point of view, GSDMB is a downstream effector protein in the pathway of pyroptosis and the activation of pyroptosis depends on whether upstream pathway in this pathway is activated. We believe that once some stimulating factors activated caspases or other upstream regulation, GSDMB might be activated and induce pyroptosis. Therefore, GSDMB might be regarded as a potential target for cancer therapy and the trigger mechanism is the key to pyroptosis of GSDMB which may direct future research on therapeutic targets for cancer treatment. Overall, there is abundant room for further progress in determining the trigger mechanism of pyroptosis of GSDMB and how GSDMB participates in pyroptosis mechanistically and the role of GSDMB in cancer.

Acknowledgments

We are grateful to the teachers of the central cancer laboratory of Harbin Medical University for their kind help.

Funding

This work was supported by the National Natural Science Foundation of China (81602662); the Wu Jieping Medical Foundation (320.6750.16002); the Scientific Research Foundation of Harbin Medical University Cancer Hospital (BJQN2018-02).

Disclosure

The authors report no conflicts of interest in this work.

References

- Saika K, Sobue T. [Cancer statistics in the world]. *Gan To Kagaku Ryoho*. 2013;40(13):2475–2480.
- Feng R-M, Zong Y-N, Cao S-M, Xu R-H. Current cancer situation in China: good or bad news from the 2018 Global Cancer Statistics? *Cancer Commun*. 2019;39(1). doi:10.1186/s40880-019-0368-6
- Cai Z, Liu Q. Understanding the Global Cancer Statistics 2018: implications for cancer control. *Sci China Life Sci*. 2019. doi:10.1007/s11427-019-9816-1
- Ferlay J, Colombet M, Soerjomataram I, et al. Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. *Int J Cancer*. 2019;144(8):1941–1953. doi:10.1002/ijc.31937
- Wu C, Li M, Meng H, et al. Analysis of status and countermeasures of cancer incidence and mortality in China. *Sci China Life Sci*. 2019;62(5):640–647. doi:10.1007/s11427-018-9461-5
- Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. *CA Cancer J Clin*. 2019;69(1):7–34. doi:10.3322/caac.21551
- Jorgensen I, Rayamajhi M, Miao EA. Programmed cell death as a defence against infection. *Nat Rev Immunol*. 2017;17(3):151–164. doi:10.1038/nri.2016.147
- Xu YJ, Zheng L, Hu YW, Wang Q. Pyroptosis and its relationship to atherosclerosis. *Clin Chim Acta*. 2018;476:28–37. doi:10.1016/j.cca.2017.11.005
- Chaiteerakij R, Juran BD, Aboelsoud MM, et al. Association between variants in inflammation and cancer-associated genes and risk and survival of cholangiocarcinoma. *Cancer Med*. 2015;4(10):1599–1602. doi:10.1002/cam4.501
- Cookson BT, Brennan MA. Pro-inflammatory programmed cell death. *Trends Microbiol*. 2001;9(3):113–114. doi:10.1016/S0966-842X(00)01936-3
- Suzuki T, Franchi L, Toma C, et al. Differential regulation of caspase-1 activation, pyroptosis, and autophagy via Ipaf and ASC in Shigella-infected macrophages. *PLoS Pathog*. 2007;3(8):e111. doi:10.1371/journal.ppat.0030111
- Zychlinsky A, Prevost MC, Sansonetti PJ. Shigella flexneri induces apoptosis in infected macrophages. *Nature*. 1992;358(6382):167–169. doi:10.1038/358167a0
- Fink SL, Cookson BT. Pyroptosis and host cell death responses during Salmonella infection. *Cell Microbiol*. 2007;9(11):2562–2570. doi:10.1111/j.1462-5822.2007.01036.x
- Mariathasan S, Weiss DS, Dixit VM, Monack DM. Innate immunity against Francisella tularensis is dependent on the ASC/caspase-1 axis. *J Exp Med*. 2005;202(8):1043–1049. doi:10.1084/jem.20050977
- Shi J, Zhao Y, Wang Y, et al. Inflammatory caspases are innate immune receptors for intracellular LPS. *Nature*. 2014;514(7521):187–192. doi:10.1038/nature13683

16. Kang SJ, Wang S, Hara H, et al. Dual role of caspase-11 in mediating activation of caspase-1 and caspase-3 under pathological conditions. *J Cell Biol.* 2000;149(3):613–622. doi:10.1083/jcb.149.3.613
17. Kayagaki N, Warming S, Lamkanfi M, et al. Non-canonical inflammasome activation targets caspase-11. *Nature.* 2011;479(7371):117–121. doi:10.1038/nature10558
18. Pizzato N, Luzete BC, Kiffer L, et al. Omega-3 docosahexaenoic acid induces pyroptosis cell death in triple-negative breast cancer cells. *Sci Rep.* 2018;8(1):1952. doi:10.1038/s41598-018-20422-0
19. de Gassart A, Martinon F. Pyroptosis: caspase-11 unlocks the gates of death. *Immunity.* 2015;43(5):835–837. doi:10.1016/j.immuni.2015.10.024
20. Bollino D, Colunga A, Li B, Aurelian L. Δ PK oncolytic activity includes modulation of the tumour cell milieu. *J Gen Virol.* 2016;97(2):496–508. doi:10.1099/jgv.0.000353
21. de Vasconcelos NM, Van Opdenbosch N, Van Gorp H, Parthoens E, Lamkanfi M. Single-cell analysis of pyroptosis dynamics reveals conserved GSDMD-mediated subcellular events that precede plasma membrane rupture. *Cell Death Differ.* 2018;26(1):146–161. doi:10.1038/s41418-018-0106-7
22. Vande Walle L, Lamkanfi M. Pyroptosis. *Curr Biol.* 2016;26(13):R568–R572. doi:10.1016/j.cub.2016.02.019
23. Burgener SS, Leborgne NGF, Snipas SJ, Salvesen GS, Bird PI, Benarafa C. Cathepsin G inhibition by serpinb1 and serpinb6 prevents programmed necrosis in neutrophils and monocytes and reduces GSDMD-driven inflammation. *Cell Rep.* 2019;27(12):3646–3656 e3645. doi:10.1016/j.celrep.2019.05.065
24. Wang CJ, Tang L, Shen DW, et al. The expression and regulation of DFNA5 in human hepatocellular carcinoma DFNA5 in hepatocellular carcinoma. *Mol Biol Rep.* 2013;40(12):6525–6531. doi:10.1007/s11033-013-2581-8
25. Wang Y, Gao W, Shi X, et al. Chemotherapy drugs induce pyroptosis through caspase-3 cleavage of a gasdermin. *Nature.* 2017;547(7661):99–103. doi:10.1038/nature22393
26. Tamura M, Tanaka S, Fujii T, et al. Members of a novel gene family, GSDM, are expressed exclusively in the epithelium of the skin and gastrointestinal tract in a highly tissue-specific manner. *Genomics.* 2007;89(5):618–629. doi:10.1016/j.ygeno.2007.01.003
27. Wei Q, Zhu R, Zhu J, Zhao R, Li M. E2-induced activation of the NLRP3 inflammasome triggers pyroptosis and inhibits autophagy in HCC cells. *Oncol Res.* 2019;27(7):827–834. doi:10.3727/096504018X15462920753012
28. Das S, Miller M, Broide DH. Chromosome 17q21 genes ORMDL3 and GSDMB in asthma and immune diseases. *Adv Immunol.* 2017;135:1–52.
29. Shi J, Gao W, Shao F. Pyroptosis: gasdermin-mediated programmed necrotic cell death. *Trends Biochem Sci.* 2017;42(4):245–254. doi:10.1016/j.tibs.2016.10.004
30. Chao KL, Kulakova L, Herzberg O. Gene polymorphism linked to increased asthma and IBD risk alters gasdermin-B structure, a sulfatide and phosphoinositide binding protein. *Proc Natl Acad Sci U S A.* 2017;114(7):E1128–E1137. doi:10.1073/pnas.1616783114
31. Sarhan J, Liu BC, Muendlein HI, et al. Caspase-8 induces cleavage of gasdermin D to elicit pyroptosis during Yersinia infection. *Proc Natl Acad Sci U S A.* 2018;115(46):E10888–E10897. doi:10.1073/pnas.1809548115
32. Wang F, Liu W, Ning J, et al. Simvastatin suppresses proliferation and migration in non-small cell lung cancer via pyroptosis. *Int J Biol Sci.* 2018;14(4):406–417. doi:10.7150/ijbs.23542
33. Hergueta-Redondo M, Sarrío D, Molina-Crespo A, et al. Gasdermin B expression predicts poor clinical outcome in HER2-positive breast cancer. *Oncotarget.* 2016;7(35):56295–56308. doi:10.18632/oncotarget.10787
34. Komiyama H, Aoki A, Tanaka S, et al. Alu-derived cis-element regulates tumorigenesis-dependent gastric expression of Gasdermin B (GSDMB). *Genes Genet Syst.* 2010;85(1):75–83. doi:10.1266/ggs.85.75
35. Feng S, Fox D, Man SM. Mechanisms of gasdermin family members in inflammasome signaling and cell death. *J Mol Biol.* 2018;430(18Pt B):3068–3080. doi:10.1016/j.jmb.2018.07.002
36. Huh JW, Kim DS, Kang DW, et al. Transcriptional regulation of GSDML gene by antisense-oriented HERV-H LTR element. *Arch Virol.* 2008;153(6):1201–1205. doi:10.1007/s00705-008-0105-y
37. Sin HS, Huh JW, Kim DS, et al. Transcriptional control of the HERV-H LTR element of the GSDML gene in human tissues and cancer cells. *Arch Virol.* 2006;151(10):1985–1994. doi:10.1007/s00705-006-0764-5
38. Ruan J. Structural insight of gasdermin family driving pyroptotic cell death. *Adv Exp Med Biol.* 2019;1172:189–205.
39. Ding J, Wang K, Liu W, et al. Pore-forming activity and structural autoinhibition of the gasdermin family. *Nature.* 2016;535(7610):111–116. doi:10.1038/nature18590
40. Kim LH, Chang H, Namgoong S, et al. Genetic variants of the gasdermin B gene associated with the development of aspirin-exacerbated respiratory diseases. *Allergy Asthma Proc.* 2017;38(1):4–12. doi:10.2500/aap.2017.38.4014
41. Suchanski J, Grzegorzolka J, Owczarek T, et al. Sulfatide decreases the resistance to stress-induced apoptosis and increases P-selectin-mediated adhesion: a two-edged sword in breast cancer progression. *Breast Cancer Res.* 2018;20(1):133. doi:10.1186/s13058-018-1058-z
42. Merten M, Beythien C, Gutensohn K, Kuhn P, Meinertz T, Thiagarajan P. Sulfatides activate platelets through P-selectin and enhance platelet and platelet-leukocyte aggregation. *Arterioscler Thromb Vasc Biol.* 2005;25(1):258–263. doi:10.1161/01.ATV.000.0149675.83552.83
43. Garcia J, Callewaert N, Borsig L. P-selectin mediates metastatic progression through binding to sulfatides on tumor cells. *Glycobiology.* 2007;17(2):185–196. doi:10.1093/glycob/cw1059
44. Suchanski J, Ugorski M. [The biological role of sulfatides]. *Postep Hig Med Dosw.* 2016;70:489–504. Polish. doi:10.5604/17322693.1201720
45. Liu Z, Wang C, Rathkey JK, et al. Structures of the gasdermin D C-terminal domains reveal mechanisms of autoinhibition. *Structure.* 2018;26(5):778–784 e773. doi:10.1016/j.str.2018.03.002
46. Panganiban RA, Sun M, Dahlin A, et al. A functional splice variant associated with decreased asthma risk abolishes the ability of gasdermin B to induce epithelial cell pyroptosis. *J Allergy Clin Immunol.* 2018;142(5):1469–1478 e1462. doi:10.1016/j.jaci.2017.11.040
47. Shi P, Tang A, Xian L, et al. Loss of conserved GSDMA3 self-regulation causes autophagy and cell death. *Biochem J.* 2015;468(2):325–336. doi:10.1042/BJ20150204
48. Chen Q, Shi P, Wang Y, et al. GSDMB promotes non-canonical pyroptosis by enhancing caspase-4 activity. *J Mol Cell Biol.* 2019;11(6):496–508. doi:10.1093/jmcb/mjy056
49. Chen Q, Shi P, Wang Y, et al. GSDMB promotes non-canonical pyroptosis by enhancing caspase-4 activity. *J Mol Cell Biol.* 2018.
50. Molina-Crespo A, Cadete A, Sarrío D, Gamez-Chiachio M. Intracellular delivery of an antibody targeting Gasdermin-B reduces HER2 breast cancer aggressiveness. *Clin Cancer Res.* 2019; 25(15):4846–4858. doi:10.1158/1078-0432.CCR-18-2381
51. Hergueta-Redondo M, Sarrío D, Molina-Crespo A, et al. Gasdermin-B promotes invasion and metastasis in breast cancer cells. *PLoS One.* 2014;9(3):e90099. doi:10.1371/journal.pone.0090099
52. Edgren H, Murumagi A, Kangaspeka S, et al. Identification of fusion genes in breast cancer by paired-end RNA-sequencing. *Genome Biol.* 2011;12(1):R6. doi:10.1186/gb-2011-12-1-r6
53. Brenner H, Rothenbacher D, Arndt V. Epidemiology of stomach cancer. *Methods Mol Biol.* 2009;472:467–477.
54. Saeki N, Usui T, Aoyagi K, et al. Distinctive expression and function of four GSDM family genes (GSDMA-D) in normal and malignant upper gastrointestinal epithelium. *Genes Chromosomes Cancer.* 2009;48(3):261–271. doi:10.1002/gcc.20636

55. Saeki N, Komatsuzaki R, Chiwaki F, Yanagihara K, Sasaki H. A GSDMB enhancer-driven HSV thymidine kinase-expressing vector for controlling occult peritoneal dissemination of gastric cancer cells. *BMC Cancer*. 2015;15:439. doi:10.1186/s12885-015-1436-1
56. Carl-McGrath S, Schneider-Stock R, Ebert M, Rocken C. Differential expression and localisation of gasdermin-like (GSDML), a novel member of the cancer-associated GSDMDC protein family, in neoplastic and non-neoplastic gastric, hepatic, and colon tissues. *Pathology*. 2008;40(1):13–24. doi:10.1080/00313020701716250
57. Fuchs Y, Steller H. Programmed cell death in animal development and disease. *Cell*. 2011;147(4):742–758. doi:10.1016/j.cell.2011.10.033
58. Chao A, Huang HJ, Lai CH. Human papillomavirus research on the prevention, diagnosis, and prognosis of cervical cancer in Taiwan. *Chang Gung Med J*. 2012;35(4):297–308. doi:10.4103/2319-4170.106141
59. Lutkowska A, Roszak A, Lianeri M, Sowinska A, Sotiri E, Jagodzinski PP. Analysis of rs8067378 Polymorphism in the risk of uterine cervical cancer from a polish population and its impact on gasdermin B expression. *Mol Diagn Ther*. 2017;21(2):199–207. doi:10.1007/s40291-017-0256-1
60. Sun Q, Yang J, Xing G, Sun Q, Zhang L, He F. Expression of GSDML associates with tumor progression in uterine cervix cancer. *Transl Oncol*. 2008;1(2):73–83. doi:10.1593/tlo.08112
61. Bonnelykke K, Sleiman P, Nielsen K, et al. A genome-wide association study identifies CDHR3 as a susceptibility locus for early childhood asthma with severe exacerbations. *Nat Genet*. 2014;46(1):51–55. doi:10.1038/ng.2830
62. Stein MM, Thompson EE, Schoettler N, et al. A decade of research on the 17q12-21 asthma locus: piecing together the puzzle. *J Allergy Clin Immunol*. 2018;142(3):749–764 e743. doi:10.1016/j.jaci.2017.12.974
63. Moffatt MF, Gut IG, Demenais F, et al. A large-scale, consortium-based genomewide association study of asthma. *N Engl J Med*. 2010;363(13):1211–1221. doi:10.1056/NEJMoa0906312
64. Wiemels JL, Walsh KM, de Smith AJ, Metayer C, Gonseth S. GWAS in childhood acute lymphoblastic leukemia reveals novel genetic associations at chromosomes 17q12 and 8q24.21. *Nat Commun* 2018;9(1):286.
65. Soderman J, Berglind L, Almer S. Gene expression-genotype analysis implicates GSDMA, GSDMB, and LRRC3C as contributors to inflammatory bowel disease susceptibility. *Biomed Res Int*. 2015;2015:834805. doi:10.1155/2015/834805
66. Christodoulou K, Wiskin AE, Gibson J, et al. Next generation exome sequencing of paediatric inflammatory bowel disease patients identifies rare and novel variants in candidate genes. *Gut*. 2013;62(7):977–984. doi:10.1136/gutjnl-2011-301833
67. Chu AY, Deng X, Fisher VA, et al. Multiethnic genome-wide meta-analysis of ectopic fat depots identifies loci associated with adipocyte development and differentiation. *Nat Genet*. 2017;49(1):125–130. doi:10.1038/ng.3738

Cancer Management and Research

Dovepress

Publish your work in this journal

Cancer Management and Research is an international, peer-reviewed open access journal focusing on cancer research and the optimal use of preventative and integrated treatment interventions to achieve improved outcomes, enhanced survival and quality of life for the cancer patient.

The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.

Submit your manuscript here: <https://www.dovepress.com/cancer-management-and-research-journal>