



REVIEW

Pyroptosis and inflammasomes in cancer and inflammation

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Abstract

Nonprogrammed cell death (NPCD) and programmed cell death (PCD) are two types of cell death. Cell death is significantly linked to tumor development, medication resistance, cancer recurrence, and metastatic dissemination. Therefore, a comprehensive understanding of cell death is essential for the treatment of cancer. Pyroptosis is a kind of PCD distinct from autophagy and apoptosis in terms of the structure and function of cells. The defining features of pyroptosis include the release of an inflammatory cascade reaction and the expulsion of lysosomes, inflammatory mediators, and other cellular substances from within the cell. Additionally, it displays variations in osmotic pressure both within and outside the cell. Pyroptosis, as evidenced by a growing body of research, is critical for controlling the development of inflammatory diseases and cancer. In this paper, we reviewed the current level of knowledge on the mechanism of pyroptosis and inflammasomes and their connection to cancer and inflammatory diseases. This article presents a theoretical framework for investigating the potential of therapeutic targets in cancer and inflammatory diseases, overcoming medication resistance, establishing nanomedicines associated with pyroptosis, and developing risk prediction models in refractory cancer. Given the link between pyroptosis and the emergence of cancer and inflammatory diseases, pyroptosis-targeted treatments may be a cutting-edge treatment strategy.

KEYWORDS

cancer, inflammasome, inflammation, pyroptosis, targeted treatment

Jie-Lin Wang and Sheng-Ni Hua contributed equally to this work.

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1 | INTRODUCTION

It is vital to understand how to effectively eradicate cancer cells while protecting healthy cells in cancer treatment. Apoptosis promotion is one of the most effective methods to treat cancer. Unfortunately, the use of apoptosis in tumor therapy is restricted. According to existing studies, certain cancers exhibit resistance to chemotherapeutic treatments because of abnormal apoptosis.¹ Hence, a strategy for fighting cancer that involves turning on other programmed cell deaths (like pyroptosis) instead of apoptosis appears promising.

Pyroptosis is a kind of PCD distinct from autophagy and apoptosis in terms of the structure and function of cells. Its defining characteristics include the release of an inflammatory cascade reaction and the expulsion of inflammatory mediators, and other cellular substances from within the cell. It also presents variations in the osmotic pressure within and outside the cell.² Inflammasomes are a complex of proteins charged with initiating the inflammatory response and activating pyroptosis. The activation of inflammasomes is a crucial step in initiating the pyroptotic pathway.^{3,4} In addition to causing PCD, pyroptosis and inflammasomes also regulate immune responses by promoting the maturation and secretion of proinflammatory cytokines.^{5,6} Furthermore, they contribute to the recruitment and activation of immune cells.⁷ In the end, they affect the tumor microenvironment (TME), triggering an inflammatory response that can be procancer or antitumor. Globally, cancer is a serious public health problem. For example, the United States is anticipated to experience 1,918,030 new cases of cancer along with 609,360 cancer-related deaths in 2022.⁸ The pressing need for effective prevention, early identification, and treatment strategies is highlighted by these statistics. Pyroptosis can effectively eliminate cancer cells by triggering inflammation and immune responses. This emerging understanding of pyroptosis offers exciting opportunities for the development of innovative therapies and tailored treatments for various types of cancer. Understanding the mechanisms of pyroptosis and inflammasomes in cancer and inflammation is crucial for developing targeted therapies.

On the other hand, pyroptosis can trigger the release of proinflammatory cytokines, leading to an amplification of the inflammatory response.^{9,10} Additionally, understanding the regulation of pyroptosis could also help in identifying potential therapeutic targets for diseases characterized by chronic inflammation. Furthermore, inflammasomes, which are multiprotein complexes, play a crucial role in triggering and regulating pyroptosis. Inflammasomes can sense danger signals and activate caspases, which then cleave and activate cytokines like interleukin-1 β (IL-1 β) and IL-18.^{3,4} Therefore, targeting inflammasomes

could be another promising avenue for developing anti-inflammatory therapies.

Roles of pyroptosis and inflammasomes in inflammatory diseases and cancer and their promise as a cutting-edge treatment approach are covered in this review. In addition, we emphasized the necessity of comprehending the mechanisms driving pyroptosis in various types of cancer as well as some associated inhibitors, chemo drugs, and nano drugs to modulate tumor progression and immune response in the manner of pyroptosis. Moreover, we discussed the challenges and limits of targeting pyroptosis in cancer treatment. It is beneficial for the development of targeted therapies that selectively induce cancer cell death while sparing normal cells by understanding the molecular pathways behind pyroptosis.

2 | PYROPTOSIS AND ITS MECHANISMS

2.1 | Definition and background of pyroptosis

Pyroptosis, which combines the Greek words “pyro” (which means fire) and “ptosis” (which means failure), is a comparatively modern term for inflammatory PCD.¹¹ During the 1990s, it was widely understood that *Shigella flexneri* infections might induce macrophage mortality in mice or humans.² *Shigella flexneri* might activate caspase 1 in host cells based on research conducted by Zychlinsky et al. in 1997.¹² Two years later, the scientists found that the caspase 1 knockdown prevented the cell death induced by *Shigella flexneri*.¹³ In 2001, Cookson demonstrated that the cell death brought on by a bacterial infection was separate from apoptosis and named it “pyroptosis.”¹¹ Martinon et al. discovered the caspase activating complex known as the inflammasome in 2002. They noticed that the inflammasome comprised the nucleotide-binding oligomerization domain (NOD)-like receptor (NLR) family, pyrin domain containing 1 (NLRP1), caspase 1, and apoptosis-associated speck-like protein (ASC), which was engaged in caspase activation.¹⁴ Since then, classical inflammasomes composed of several receptors have been identified. Shi’s team reported that gasdermin-D (GSDMD) was in a state of self-inhibition in a typical microenvironment in 2015. The action of caspase 1 degraded GSDMD into two peptides, the N- and C-terminal fragments. The N-terminal segment created an incredibly small hole in the cell membrane. The GSDMD protein was subsequently discovered to be the pyroptotic execution protein.⁶ The GSDMA, GSDMB, GSDMC, DFNA5/GSDME, and DFNB59 are all GSDM family members. Members of the GSDM family can trigger pyroptosis by generating plasma membrane pores on

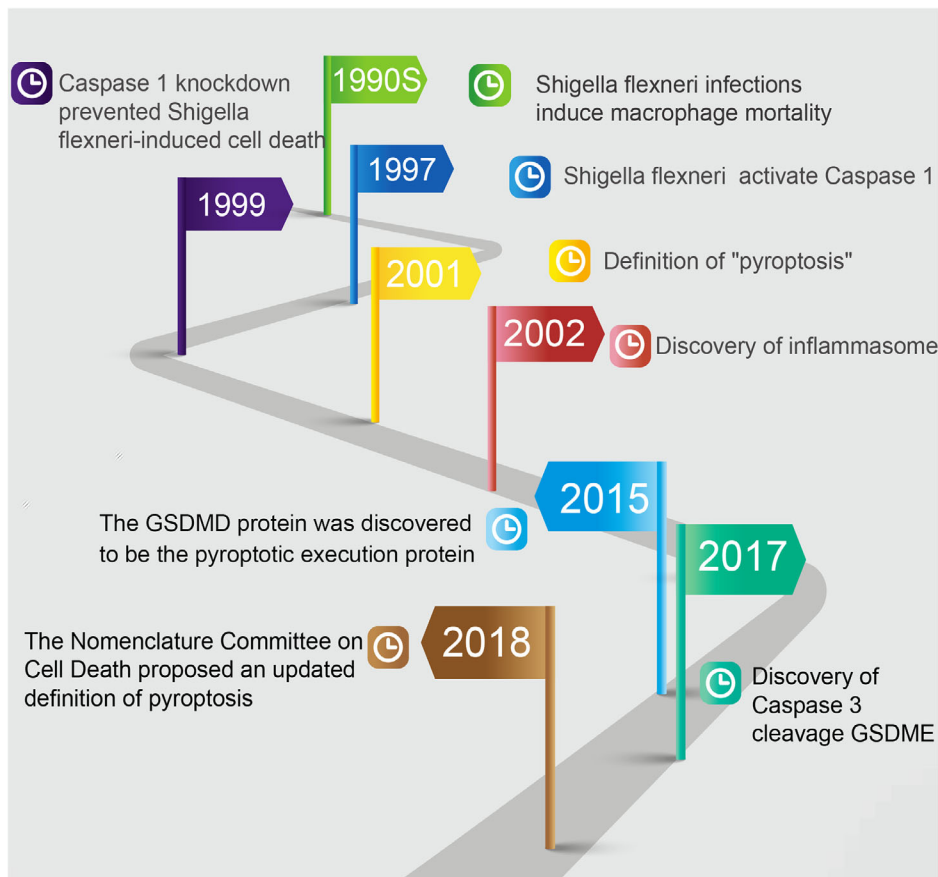


FIGURE 1 Major developments in the history of pyroptosis. The development of pyroptosis from the initial discovery, discovery of key molecules, and definition.

cell membranes.¹⁵ Particularly, the discovery that caspase 3 cleaved GSDME protein and induced pyroptosis in 2017 is an important turning point in the study of pyroptosis.¹⁶ The Nomenclature Committee on Cell Death proposed an updated definition of pyroptosis in 2018.¹⁷ Since that time, pyroptosis has been well defined. The significant advancements in the history of pyroptosis are summarized in Figure 1.

2.2 | Activation of pyroptosis pathways

Pyroptosis has already been proven to play a crucial function in the immune response against various pathogens, including bacteria and viruses. Therefore, many substances, including inflammatory mediators, drugs, and so on, can activate pyroptosis. Detection of pathogen-associated molecular patterns (PAMPs) and danger-associated molecular patterns (DAMPs) by pattern recognition receptors (PRRs), initiates the typical process of pyroptosis.^{3,4} In addition, immediately inflammatory substances like lipopolysaccharide (LPS) can trigger pyroptosis in a noncanonical inflammasome

pathway. Extracellular LPS stimulates the expression of Type I interferon, which in turn activates the interferon Type I receptor and results in the synthesis of caspase 11.^{18,19} Chemo-drugs may activate caspase 3, triggering pyroptosis via the cleavage of GSDME.¹⁶ Tumor necrosis factor- α (TNF- α) activates caspase 8 in tumor cells to activate pyroptosis.²⁰ Granzyme, which functions as an inducer of pyroptosis, enters the target cells by way of perforin and is generated by cytotoxic T lymphocytes (CTLs) and natural killer (NK) cells.²¹

2.3 | Key molecules and pathways involved in pyroptosis

Pyroptosis, an inflammatory mode of PCD, requires the protein families GSDM and caspase. The cleavage of GSDMs and the production of cytokines such as IL-1 β , IL-18, and high mobility group box 1 (HMGB1), are the outcomes of pyroptosis.^{5,6} In the end, this caused the cells to swell, break apart, and respond in an inflammatory cascade.

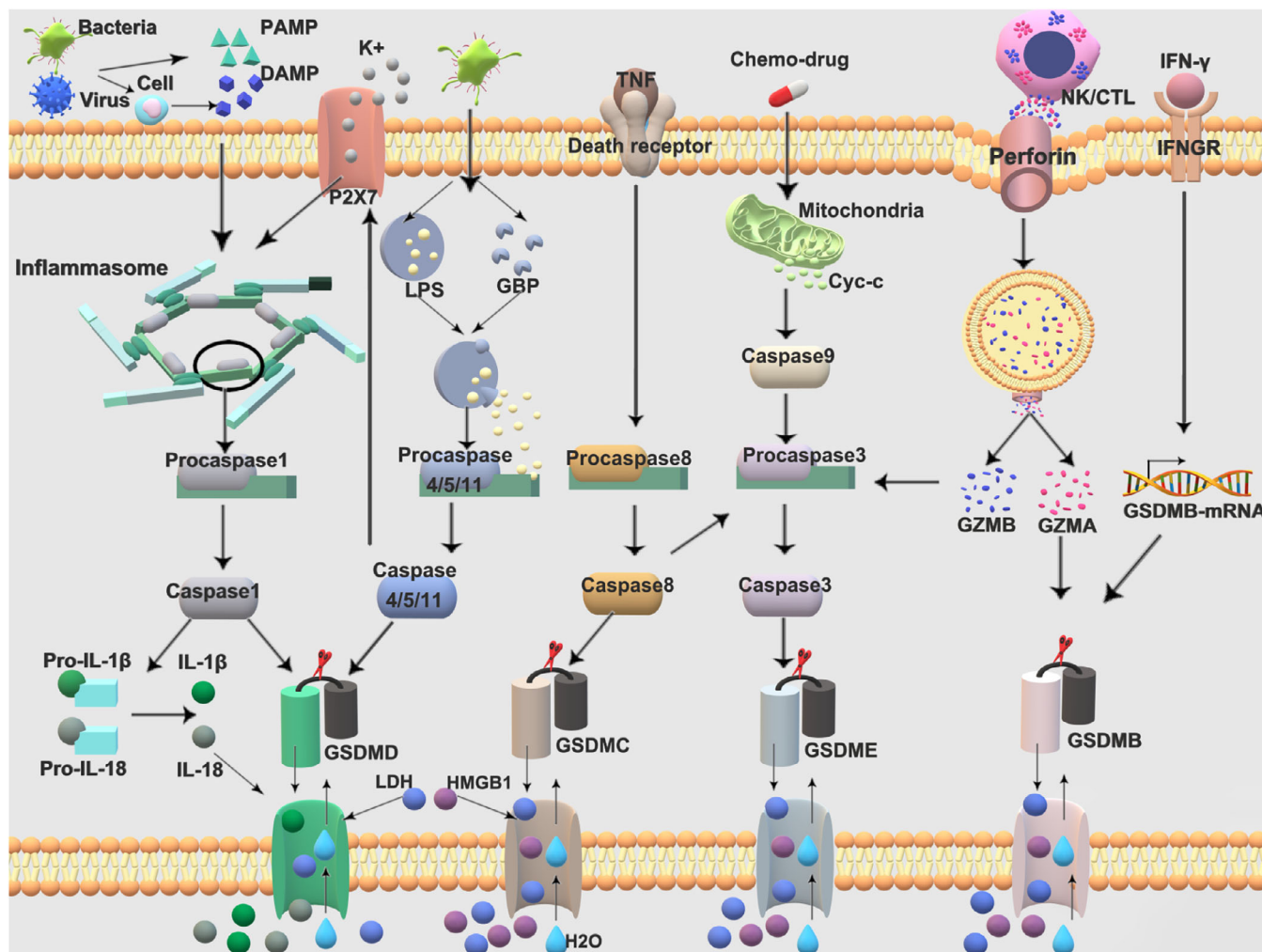


FIGURE 2 Schematic illustration of the different pyroptosis pathways. At present, there are mainly four distinct signaling pathways that have been identified to induce pyroptosis, including the classical caspase 1-dependent pathway, which depend on the inflammasomes, nonclassical caspase 4/5/11-dependent pathway, caspase 3/caspase 8-mediated pathway, and granzymes-mediated pathway. DAMP, danger-associated molecular patterns; PAMP, pathogen-associated molecular patterns; LPS, lipopolysaccharide; IL-1 β , interleukin-1 β ; IL-18, interleukin-18; LDH, lactate dehydrogenase; HMGB1, high mobility group box 1; GZMA, granzyme A; GZMB, granzyme B; GBP, guanylate-binding proteins; TNF, tumor necrosis factor; IFN- γ , interferon- γ ; IFNGR, IFN-gamma receptor; Cyc-c, cytochrome c; NK, natural killer cells; CTL, cytotoxic T lymphocytes.

In addition to the early finding of the traditional caspase 1-dependent pathway and the nonclassical caspase 4/5/11-dependent pathway, recent studies illustrate more detail on newly discovered pathways that lead to pyroptosis, such as the caspase 3/caspase 8-mediated pathway and granzymes-mediated pathway (GZMA/GZMB). Figure 2 depicts the key molecules and pathways involved in pyroptosis. A thorough description of each pathway process for pyroptosis follows.

2.3.1 | Canonical pathway of pyroptosis

The canonical pathway is another name for the caspase 1-dependent pathway. Pro-caspase 1, the unreactive zymo-

gen form of caspase 1, exists in the cytoplasm under normal circumstances. It is only activated when the canonical inflammasomes are functioning. Inflammasomes are multimolecular complexes composed of pro-caspase 1, ASC, and PRRs.²² The majority of PRRs are NLRs, which include absent in melanoma 2 (AIM2), leucine-rich repeat and pyrin domain-containing protein 1 (NLRP1) and its murine homolog, NLRP1B, leucine-rich repeat and pyrin domain-containing protein 3 (NLRP3) and NLR family CARD domain-containing protein 4 (NLRC4), and pyrin.^{23,24}

When PRRs detect DAMPs and PAMPs, the typical process of pyroptosis begins.^{3,4} When tissue homeostasis is disrupted and monomeric PRR proteins oligomerize, PRRs undergo a conformational change to function as the oligomerization core.²⁵ When activated, several PRRs

containing caspase activation and recruitment domains (CARD), such as NLRC4,²⁶ and NLRP1B,²⁷ may directly assemble pro-caspase 1 via CARD–CARD interactions, removing the requirement for an adaptor molecule. Certain PRRs that do not include CARD must initially recruit ASC to recruit pro-caspase 1. Due to its possession of both pyrin and CARD domains, ASC can act as a molecular bridge between proteins containing the pyrin domain (PYD), such as NLRP3, AIM2, and pyrin, and the CARD domain of pro-caspase 1.²⁸ Notably, NLRP1 can draw pro-caspase 1 with or without the presence of ASC.^{27,29} The structure and function of inflammasomes are discussed in further depth in Section 3. The proximity of the integral inflammasome increased caspase 1 activation via autoproteolysis during inflammasome assembly. According to recent research, the inflammasome–caspase 1 complex possesses an inherent self-limiting mechanism that guarantees prompt caspase 1 inactivation.³⁰ Caspases 1 transforms pro-IL-18 and pro-IL-1 into their mature forms.³¹ Moreover, caspase 1 cleaves GSDMD to produce an N-terminal domain (GSDMD-NT), which results in the formation of pores in the cell membrane.⁶ Influx of salt and water and subsequent cell swelling, is ultimately brought on by the pore. Meanwhile, it facilitates the release of mature IL-1 β , IL-18, and HMGB1, all of which are inflammatory mediators. Recent studies have demonstrated that GSDMB is also involved in the pyroptotic canonical pathway in addition to GSDM. Caspase 1 cleaves GSDMB at position 236, leading to the generation of N-terminal fragments, oligomerization, and pore formation in the cell membrane, eventually resulting in pyroptosis.³²

2.3.2 | Noncanonical inflammasome pathway

In 2011, it was proven that infections with Gram-negative bacteria cause pyroptosis through a novel noncanonical caspase 11 pathway.¹⁹ Compared with the conventional pathway, the crucial stage in the noncanonical inflammasome pathway is the activation of caspase 4/5/11, which is triggered immediately by inflammatory substances like LPS and does not require an inflammasome.¹⁸ Interferon (IFN) and LPS boost the expression of interferon-inducible guanylate-binding proteins (GBP) by activating the interferon receptor and Toll-like receptor 4 (TLR4)/MD-2.³³ LPS may reach the cytoplasm due to the ruptured vacuoles induced by GBP.³⁴ Human homologue caspase 4, human homologue caspase 5, and mouse caspase 11 display excellent specificity and affinity for binding to intracellular LPS. LPS and its lipid component A bind to caspase through the CARD module of the caspase.³⁵ Caspase 4/5/11 activation provokes GSDMD and pyroptosis.³⁶

In contrast to the canonical pathway, the noncanonical route cannot develop pro-IL-18 and pro-IL-1 β directly.¹⁹ However, it may ultimately lead to the creation and emission of IL-18 and IL-1 β by inadvertently activating caspase 1 and NLRP3. LPS triggers Pannexin-I channel cleavage and caspase 11-associated adenosine triphosphate (ATP) release, which sequentially activates ATP-gated P2 \times 7 and enhances K⁺ efflux as well as caspase 1/NLRP3 activation in macrophages.³⁷ Caspase 11 decreases cellular potassium levels to activate NLRP3.³⁸ Caspase 4 via potassium efflux will adequately activate the NLRP3 and speed up IL-1 β generation.³⁹ GSDMB induces the noncanonical inflammasome pathway by directly interacting with the CARD domain of caspase 4 and gradually increasing caspase 4 activity. In the meantime, GSDMB overexpression promotes GSDMD cleavage, which is associated with an upsurge in lactate dehydrogenase (LDH) release.⁴⁰

2.3.3 | Caspase 3/caspase 8-mediated pathway

Apart from the caspase proteins mentioned above, pyroptosis can be triggered by other apoptotic caspases. Active caspase 3 cleaves the DFNA5/GSDME to generate a necrotic GSDME-NT that punctures the plasma membrane and provokes pyroptosis after apoptosis is induced successfully, as described by Rogers et al. in 2017.⁴¹ According to the research conducted by Wang et al.¹⁶ in the same year, chemo-drugs, including doxorubicin (DOX), cisplatin, and actinomycin-D, may activate caspase 3, activating pyroptosis via the cleavage of GSDME. Although the caspase 3/GSDME route does not need the inflammasome, the synthesis of GSDME-NT enables the NLRP3 inflammasome, which further activates the conventional pathway and boosts the growth of IL-1 β and IL-18.⁴² Meanwhile, HMGB1 and LDH are released from pyroptotic cells by the GSDME.^{43,44} GSDMB probably participates in cellular sulfatide transport because caspase 3/–6/–7 cleave GSDMB-NT at 88DNVD91, which binds sulfatide-containing liposomes.⁴⁵

These findings contradict the traditional view that pyroptosis cannot be provoked only by inflammatory caspases. The activation of caspases, particularly caspase 3, was thought to be one of the essential characteristics of the apoptosis process in prior decades. We are currently aware that caspase 3 activation can occur without apoptosis. Caspase 3-mediated pyroptosis and apoptosis share the same upstream signaling mechanism. This indicates that chemotherapy set off the transfer of BAX/BAK to the outer mitochondrial membrane, resulting in holes development and release of mitochondrial outer membrane permeabilization and cytochrome C.⁴⁶ This activates caspase 9 and caspase 3 in turn.⁴⁷ Simply put, GSDME expression

levels are the primary determinants influencing the transition from pyroptosis to apoptosis. High levels of GSDME production cause GSDME to be cleaved into two terminals by active caspase 3, which appears in pyroptosis. Conversely, apoptosis will occur if GSDME expression is minimal.^{48,49} Likewise, ATP induces pyroptosis by activating the caspase 3/GSDME pathway in macrophages when the classic NLRP3 pathway is blocked.⁵⁰

TNF- α activates caspase 8 in tumor cells. Caspase 8 can stimulate caspase 3. The metabolite-ketoglutarate boosts the growth of the death receptor DR6, which is located in the plasma membrane and activates caspase 8. Pyroptosis rather than apoptosis occurs when caspase 8 cleaves GSDMC at D365 and releases its N-terminal domain.²⁰ Active caspase 8 cleaves both GSDMD and GSDME in *Yersinia*-infected murine macrophages, ending in pyroptosis.⁵¹ In addition, caspase 8 cleaves GSDMC to create GSDMC-NT, which triggers tumor necrosis by forcing cancer cells to undergo pyroptosis instead of apoptosis.⁵²

2.3.4 | GZMA/GZMB

Granzymes play an important role in cytotoxic lymphocyte-mediated immunity.⁵³ Granzyme enters the target cells by way of perforin and is generated by CTLs and NK cells.²¹ They are considered to defeat cells via inducing apoptosis under prior studies.⁵⁴ Granzymes have recently been revealed to also function as inducers of pyroptosis. According to research by Zhou et al.,⁵⁵ GZMA from CTLs and NK cells destroys GSDMB to form membrane holes that trigger pyroptosis. IFN- γ stimulates this process by raising GSDMB expression. This research identifies that GSDM-mediated pyroptosis kills the cytotoxic lymphocyte, which may improve antitumor immunity. For GZMA-mediated pyroptosis, the expression of GSDMB is necessary. GSDMB is expressed in both healthy tissues and malignant tissues.⁵⁶ GZMB, which is generated by NK cells, evokes pyroptosis in tumor targets by cleaving GSDME at the same site as caspase 3. In addition, GZMB activates and cleaves caspase 3.⁵⁷ The granzyme-mediated pyroptosis pathway sheds fresh light on antitumor treatment.

2.4 | Morphological changes in pyroptosis

The pathway described above ultimately leads to the cleavage of the GSDMs protein into its functional form, the N-terminus domains. This enables it to fulfill its biological role. During pyroptosis, the N-terminal domain

translocates to the plasma membrane, where it can bind membrane lipids like phosphoinositide and cardiolipin, oligomerize in the membrane to make pores, and show cytotoxicity that breaks down the membrane.^{15,58} Recent studies have shown that the pores formed in liposomes, with internal diameters of 10–20 nm, are large enough to allow the passing of IL-1 β , IL-18, and other cellular proteins.^{15,59} Lamkanfi and coworkers⁶⁰ observe pyroptotic cell and create a model of pyroptotic cell disintegration. They demonstrate that early Ca²⁺ influx and mitochondrial degradation are conserved processes of GSDMD-mediated pyroptotic cell death. These processes occur before the breakdown of the plasma membrane after activation of caspase 11. Ionic flow, cell swelling, mitochondrial depolarization, and lysosome leakage all take place during pyroptosis long before cell lysis with nuclear condensation.⁶⁰ Eventually, the cell ruptures and water leaks inside, leading to cell swelling and rupture, the liberation of inflammatory chemicals inside the cell, and the induction of pyroptosis.

3 | INFLAMMASOMES AND THEIR FUNCTIONS

Using the term “inflammasome,” Tschopp and coworkers¹⁴ defined a molecular complex present in activated immune cells’ cytoplasm and contributing to the activation of the caspases 1. Inflammasomes are primarily utilized in inflammation and immunity. The inflammasome and the microenvironment of tumor cells are associated with the development of cancer. Thus, the regulation of inflammasome generation and activation is crucial for the pathogenesis, progression, and therapeutic response of cancer. In this section, we are going to give you a detailed review of how the inflammasome works and how it gets activated.

3.1 | Structure of inflammasomes

The inflammasome is a complex assembly that comprises PRRs, pro-caspase 1, and ASC. NLRP3, NLRP1, NLRC4, AIM2, and PYRIN make up the majority of PRRs. Figure 3 depicts the basic structure of the inflammasome straightforwardly. NLRP3 is a member of the canonical inflammasomes that generate NLRs. An N-terminal PYD, a C-terminal leucine-rich repeat (LRR), and a central nucleotide-binding and oligomerization domain (NACTH) comprise NLRP3, but no C-terminal CRAD.⁶¹ NLRP1 is unique among the members of this family. Besides the NACTH domain, N-terminal PYD, and the C-terminal LRR, NLRP1 encodes two more domains at its C

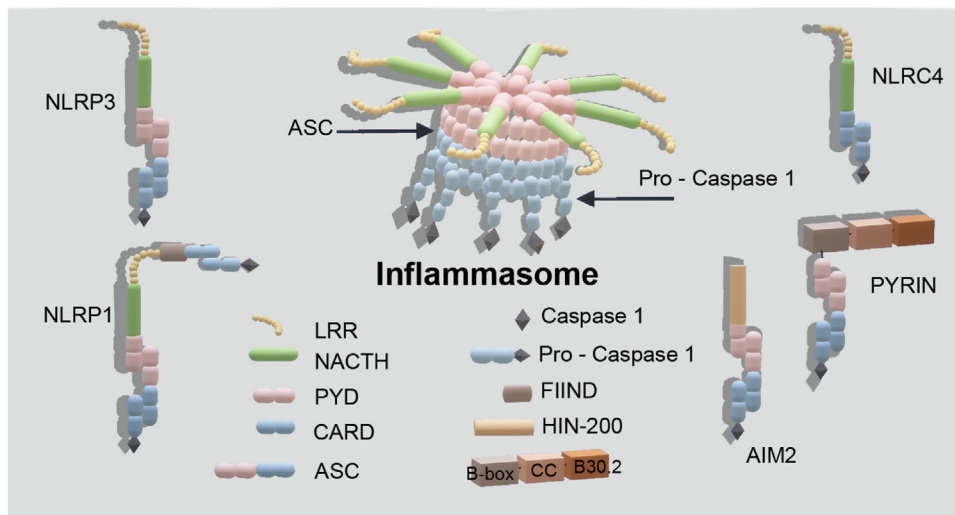


FIGURE 3 Structure of inflammasome. The structure of the five inflammasome (NLRP3, NLRP1, NLR4, AIM2, and PYRIN). PYD, the pyrin domain; CARD, caspase activation and recruitment domains; LRR, leucine-rich repeat; NACTH, central nucleotide-binding and oligomerization domain; NLRP3, leucine-rich repeat and pyrin domain-containing protein 3; NLRP1, leucine-rich repeat and pyrin domain-containing protein 1; NLR4, NLR family CARD domain-containing protein 4; AIM2, absent in melanoma 2.

terminus, a FIIND (function to find domain) and a CARD. The autolytic proteolytic cleavage of the C-terminal FIIND structural domain is necessary for NLRP1 activity.⁶² A C-terminal LRR domain, an N-terminal CARD domain, and a NACTH domain encompass the NLRC4 protein. In addition to containing the PYD and CARD structural domains, the C-terminal HIN-200 domain of AIM2 serves as distinguishing features.⁶³ PYRIN contains not only the PYD and card domains, but also a linker region connecting the B-box, coiled-coil (CC) and B30.2 domains. The oligomerization of pyrin is mediated by the CC and B-box domains.⁶⁴

3.2 | Activation of inflammasomes and downstream signaling

There are a variety of substances that activate NLRP3, involving ATP, reactive oxygen species (ROS), potassium efflux, and internal sources of damage signal.^{65,66} NACTH domain ATPase activity is necessary for the formation of NLRP3 oligomers following activation.⁶⁷ The extensively used NLRP3 inhibitor MCC950 has recently been proven to target this ATPase activity. When the NLRP3 PYD attaches to the ASC PYD, the inflammasome is initiated.²⁸ Inflammasome activation is mediated by the NLRP3 inflammasome sensor component in response to anomalies in membrane integrity, leading to pyroptosis along with the secretion of IL-1 β and IL-18.⁶⁸ Inflammasomes, especially NLRP3, are downregulated in dormant cells but upregulated by the NF- κ B pathway.⁶⁹ Anthrax lethal toxin, muramyl dipeptide, and components of *Toxoplasma gondii* can activate NLRP1.⁷⁰ NLRP1 activates

pro-caspase 1 in two ways. One of these pathways is that anthrax lethal factor cleaves NLRP1, which drives N-terminal degradation and release of CARD at the C-terminus as well as allowing NLRP1 to directly bind caspase 1 to create an inflammasome.⁷¹ Another pathway involves NACTH domain hydrolyses ATP, which changes the protein conformation of NLRP1, completes NLRP1 activation, and integrates it into the ASC-dependent inflammasome. This pathway is activated when LRR binds double-stranded DNA (dsRNA) from the virus.⁷² The Type III secretion system proteins and flagellin are recognized by NLRC4.²⁶ AIM2 recognizes innate immune receptors on cell membranes as dsDNA generated in response to cellular disruption and pathogen assault. AIM2 triggers the inflammasome to mature and culminate in pyroptosis by detecting dsDNA. The C-terminal HIN-200 domain and the N-terminal PYD of AIM2 are served as distinguishing features. While the HIN200 domain binds dsDNA from cellular damage and microbial infections, the PYD links with the ASC to cause pyroptosis.⁶³ Pyrin serves to detect pathogen modification and Rho GTPase silencing.⁷³ Pyrin has previously been demonstrated to contribute to the maturation of caspase 1 and the release of IL-1 β , which in turn causes pyroptosis.⁷⁴ The PYRIN protein binds to the ASC via its N-terminal PYD to fulfill its function.⁶⁴

4 | PYROPTOSIS AND INFLAMMASOMES IN CANCER

Pyroptosis and inflammasomes is closely linked to tumor immunity and the TME. Pyroptosis and inflammasomes

is thus a promising entry point for research on targeted therapies. As research advances, inflammatory cell activities are becoming more well known and getting more attention in the TME. Pyroptosis has been identified as a double-edged sword in studies on cancer etiology. Pyroptosis occasionally aids the malignant progression of cancer. Long-term pyroptosis of cancer cells may occur from an adverse TME that accelerates the development of the disease. Chronic pyroptosis-derived proinflammatory cytokines construct and maintain an inflammatory environment that encourages tumor growth.⁷⁵ For instance, the early microenvironment of ovarian cancer may induce the production of DAMPs, which may subsequently activate AIM2 and NLRP3 inflammasomes. When triggered by microbial substances or endogenous cytokines, activation of NF- κ B causes overexpression of NLRP3, AIM2, pro-IL-1 β , and pro-IL-18. Inflammasome activation, pyroptosis, and maturation of IL-1 β and IL-18 all contribute to chronic inflammation in advanced stages.⁷⁶ Pyroptosis, on the other hand, may postpone the development and progression of tumors. Acute and widespread pyroptotic activation results in a major invasion of immune cells that strengthens antitumor immunity to prevent tumor growth and trigger substantial cancer cell death.⁷⁷

In this section, we will explore the impact of inflammasomes and mediators produced by pyroptosis on the TME and describe the application of pyroptosis in common tumors such as lung, breast, colorectal, gastric, and gynecological cancers. Other uncommon tumors will not be covered in this review due to space limitations.

4.1 | Impact of inflammasomes on the TME

The NLRP3 inflammasome facilitates the invasion of myeloid cells into TMEs like myeloid-derived suppressor cell (MDSC) and tumor-associated macrophage (TAM), which benefits tumor progression.⁷ Inflammasome suppression elevated CD8+ T and CD4+ cell infiltration, decreasing TAM infiltration and amplifying the therapeutic effect of PD-L1 inhibition in tumors with high levels of inflammasome signaling activity.⁷⁸ An approach that targets NLRP3, specifically its ATPase activity, in the TME may offer new cancer treatment options. However, in subsequent chapters describing the application of pyroptosis in cancer, it was found that many drugs inhibit cancer by activating NLRP3 to initiate pyroptosis. The use of NLRP3 in cancer is currently controversial. Dipeptidyl peptidase inhibition activates the NLRP1 inflammasome, which triggers the secretion of proinflammatory cytokines and activates the response of the Th1 cell. The CXCL10/CXCR3 axis is further activated, which induces the infiltration of T

and NK cells, strengthens the efficacy of anti-PD1 antibodies, and inhibits tumor progression.⁷⁹ In a subcutaneous mouse model of melanoma, NLRC4 is essential for the generation of cytokines in TAM as well as the development of IFN- γ -producing CD8+ and CD4+ T cells, both of which impede tumor progression.⁸⁰ Innate immune detection of cytosolic DNA in DC via the STING pathway is one major mechanism activating spontaneous T cell responses against malignancies. The AIM2 inflammasome can inhibit chronic STING signaling by inducing pyroptotic cell death.⁸¹ AIM2 accelerated tumor development by reducing CD4+ effector T cells while increasing the number of Treg cells. Moreover, IL-1 and IL-18 production needed AIM2, which enhanced Treg accumulation and tumor progression in vivo.⁸² A linker region domain of PYRIN has been demonstrated to interact with the proline serine threonine phosphatase-interacting protein (PSTPIP1/CD2BP1), which is crucial for the structure of the cytoskeleton.⁸³

4.2 | Influence of pyroptosis on the TME

When pyroptosis is activated, inflammatory mediators, such as IL-1 β , IL-18, and HMGB1, are produced, all of which can have a positive impact on the progression of the cancer.^{84–86} Yet, several investigations have indicated that IL-1 β , IL-18, and HMGB1 have a suppressive impact on cancer.^{85,87,88} These conflicting findings indicate that the impact of pyroptosis on the TME is complicated and context dependent. To better understand the role of pyroptosis in the TME and its potential as a therapeutic target for cancer treatment, more research is needed. The next section explores how pyroptosis affects the TME.

4.2.1 | IL-1 β

Inflammatory signals activate IL-1 β in a variety of immune cells. In the TME, IL-1 β has dual functions that are connected to the growth of tumors. IL-1 β signaling activates innate immune cells as well as antigen-presenting cells by polarizing CD4+ T cells toward Th1 and Th17 cells and activating them.^{89,90} IL-1 β has been attributed to have a significant benefit in terms of treating acute inflammations and evoking specific anticancer defenses. For instance, NLRP1 (–/–) mice exhibit increased inflammation and cancer burden when IL-1 β levels are low.⁹¹ TAMs and MDSCs were enhanced in the immunosuppressive environment induced by IL-1 β , which promotes tumor growth.⁸⁵ Dendritic cells (DCs) can be differentiated from monocytes, and IL-1 β stimulates their expansion. Besides, IL-1 β provokes hyperactive DCs to foster tumor lysates as

immunogens and attach them to lymphocytes to trigger cytotoxic CD8+T cell responses peculiar to the antigen.^{92,93}

4.2.2 | IL-18

Both procancer and anticancer properties are discovered in systemic, multifunctional cytokine IL-18. It is initially recognized as a potent IFN-production promoter.⁸⁴ It enhances the Th1 immune response and activates T and NK cells to generate IFN- γ , which potentially assists with tumor immunity. Th1 differentiation is facilitated by this cytokine in conjunction with IL-12.⁹⁴ IL-18 can support angiogenesis, metastasis, and growth. Moreover, it is capable of evading the immune system.⁸⁴ When an immune-suppressing microenvironment is established, IL-18 boosts tumor growth even further. According to Lim et al.,⁹⁵ IL-18 dramatically enhances monocytic MDSC (M-MDSC) through CD11b (-) bone marrow progenitor cell differentiation, suppressing in vitro T cell expansion and IFN production. IL-18, which is mediated by the NLRP3 inflammasome, elevates NK cell maturation, surface expression of the death ligand FasL, and the ability to eradicate FasL-sensitive malignancies.⁹⁶

4.2.3 | HMGB1

Pyroptosis generates HMGB1, a variable nuclear protein that plays a part in DNA recombination repair, transcription, and chromatin remodeling.⁹⁷ Extracellular HMGB1 activates the NLRP3 inflammasome after it interacts with several sensors and begins NF- κ B signaling.^{98,99} Besides, HMGB1 signaling via TLR2 and TLR4 receptors released cytokines, including IL-6, TNF, and IL-8, that are necessary for CD8 + T cell activation.¹⁰⁰ HMGB1 seems to have both tumor-promoting and tumor-suppressive properties in malignancies. Neo-angiogenesis and cancer immunity are both increased. HMGB1, a substance generated by dying tumor cells, interacts with TLR4, a receptor crucial for both innate and adaptive immune responses, to initiate the processing of tumor antigens by mature DCs and the anticancer immune response.¹⁰¹ At the same time, the immunosuppressive TME aids in the survival of tumor cells with HMGB1 by enhancing the viability and recruitment of MDSCs.^{86,102}

4.2.4 | GSDMs proteins

In response to diverse stimuli, GSDMs proteins rupture cell membranes, triggering the release of proinflammatory cytokines. This eventually leads to pyroptotic cell death.

Immune signaling and cytokines influence GSDMs. For example, IFN α , IFN β , IFN γ , and TNF α elevate GSDMB expression and stimulate pyroptosis.⁵⁵ IRF2, a transcription factor from the interferon regulatory factor (IRF) family, binds the GSDMD promoter and induces the expression of GSDMD and pyroptosis.¹⁰³

GSDME suppresses tumors by inducing pyroptosis, which produces IL-18, IL-1 β , and HMGB1 to convert “cold” tumors into “hot” tumors, promoting antitumor immunity. In mice with GSDME-expressing tumors, knocking out GSDME increases tumor development, whereas ectopic expression inhibits tumor development. This tumor suppression is mediated by killer cytotoxic lymphocytes, which are deficient in perforin-deficient or lymphocyte-depleted mice. The expression of GSDME leads to NK cells and CD8⁺ T cells infiltrate the tumor more frequently and functioning better, as well as TAMs phagocytose more effectively.⁵⁷ Chimeric antigen receptor (CAR) T cells deliver granzyme, which cleaves GSDME and activates caspase 3 in target cells. Similarly, pyroptosis elements trigger macrophages to activate caspase 1 for GSDMD cleavage, which causes the release of cytokines and the accompanying cytokine release syndrome (CRS). The amount of perforin/enzyme B used by CAR T cells, but not by preexisting CD8(+) T cells, is particularly critical for CAR T cells to induce pyroptosis in the target cell.¹⁰⁴ Using tumor cells expressing high levels of GSDME from lung, liver, breast, and glioma cancers, Cao et al.¹⁰⁵ showed that irradiation caused pyroptosis through caspase 9/caspase 3/GSDME signaling. The combination of chemotherapeutic drugs and irradiation increased the incidence of pyroptosis substantially. GSDME-overexpressing tumors had heightened antitumor immunity, as evidenced by noticeably higher quantities of CTLs and the secretion of related cytokines.¹⁰⁵ We summarized the role of inflammasomes and pyroptosis-related proteins in regulating immune cells as described previously in Table 1.

4.3 | Pyroptosis in lung cancer

Globally, lung cancer accounts for 18.4% of all cancer deaths, causing enormous societal burdens and economic losses.⁸ In lung cancer, the avoidance of apoptosis or the induction of other PCDs has been a focus of research and is essential for the discovery of innovative treatment strategies. P53-induced pyroptosis is a viable therapeutic strategy for the treatment of non-small cell lung cancer (NSCLC).¹⁰⁶ GSDMD protein levels are dramatically increased in NSCLC, which is correlated with aggressive traits like larger tumor sizes and advanced TNM stages.¹⁰⁷ In CTLs, the expression of GSDMD has a favorable

TABLE 1 The role of inflammasomes and pyroptosis-related proteins in immunity.

Inflammasomes or pyroptosis-related proteins	Role in immunity	References
NLRP3	Invasion of TAMs, MDSCs↑ Suppressant elevated CD8+ and CD4+ T cells infiltration	7,78
NLRP1	Response of Th1 cells ↑ Infiltration of T and NK cells ↑	79
NLRC4	Essential for CD8+ T cells, CD4+ T cells and TAMs	80
AIM2	Treg↑ CD4+ effector T cells↓	82
IL-1 β	Th1 cells, Th17 cells↑, TAMs↑, MDSC↑ DC↑	89,90 85 92,93
IL-18	Immune response↑: Th1 cells response↑, IFN- γ ↑ Immune response↓: M-MDSCs↑, IFN- γ ↓	94 95
HMGB1	Trigger dendritic cell tumor antigen processing *MDSCs↑	101 102
GSDME	NK cells, CD8+ T cells and TAMs ↑ *cytotoxic T lymphocytes	57 105

association with CD8⁺T cell markers. GSDMD colocalizes with GzmB near immune synapses to ensure the best CTL response to lung cancer cells.¹⁰⁸ In lung adenocarcinoma (LUAD), a high expression of GSDMC is an indication of a poor prognosis.¹⁰⁹ In NSCLC immunotherapy, the chimeric costimulatory converting receptor-modified NK92 cell (CCCR-NK92) is capable of converting the negative PD1 signal into an activating signal, leading to GSDME-induced pyroptosis.¹¹⁰

Pyroptosis has been discovered to contribute to the resistance of lung cancer chemotherapy. It may be possible to overcome treatment resistance and improve patient outcomes by understanding the relationship between pyroptosis and lung cancer chemotherapy. Peng et al.¹¹¹ prove that the knockout of GSDME induces a transition from apoptosis to pyroptosis. GSDME expression is reduced, whereas overexpression increases chemosensitivity in lung cancer tissue. Furthermore, higher GSDME expression facilitates chemokine release, which has an impact on T-cell activation and infiltration.¹¹¹ Both paclitaxel and cisplatin induce pyroptosis in lung cancer cells, with cisplatin causing more pyroptosis. In addition, cisplatin may provide significant benefits in the treatment of lung cancers with high GSDME expression.⁴⁹ These findings emphasize the potential immunotherapeutic implications of targeting GSDME in the treatment of lung cancer to minimize chemotherapy resistance.

Besides, pyroptosis in lung cancer can be induced or suppressed by many drugs, noncoding RNAs, and inhibitors. Cucurbitacin B (CuB), a compound extracted from muskmelon pedicel, inhibits tumor growth in NSCLC cells by directly binding to TLR4, activating the NLRP3

inflammasome and inducing pyroptosis.¹¹² Polyphyllin VI (PPVI), an active saponin, suppresses NSCLC proliferation by triggering caspase 1-dependent pyroptosis via the ROS/NF- κ B/NLRP3/GSDMD signaling axis.¹¹³ Simvastatin, an antihyperlipidemic drug, triggers pyroptosis to inhibit proliferation and migration in NSCLC.¹¹⁴ In lung cancer cells, dasatinib initiates pyroptosis and p53-independent elevations in GSDMD and GSDME protein levels.¹¹⁵ As reported by Lu et al.,¹¹⁶ GSDME overexpression made targeted small molecule inhibitors more sensitive. The widespread cooccurrence of apoptosis and pyroptosis in lung cancer cells is highlighted by factors such as Kirsten rat sarcoma virus, epidermal growth factor receptor, or anaplastic lymphoma kinase, stimulating apoptosis and pyroptosis in NSCLC cells.¹¹⁶ In human NSCLC, LncRNA-XIST is found to be upregulated, particularly in cisplatin-treated tumors. XIST promotes cell viability and raises DDP chemoresistance by preventing SMAD2 from moving to the nucleus, inhibiting p53 and NLRP3 transcription.¹¹⁷ While knocking down XIST promotes pyroptotic cell death in NSCLC through miR-335/SOD2/ROS signaling.¹¹⁸ Downregulation of NLRP3 may prohibit the pyroptotic cell death caused by the knockdown of miR-556-5p.¹¹⁹

As the investigation progressed, Xie et al., the researchers applied pyroptosis to nanomedicine in the treatment of lung cancer, created inhaled poly (lactic-co-glycolic acid) porous microspheres loaded with decitabine (DAC) and DOX (denoted as CO-MPs) to induce lung cancer pyroptotic cell death with fewer systemic side effects. In mechanism, CO-MPs promoted pyroptosis by reversing GSDME silencing and upregulating caspase 3

expression. Consequently, CO-MPs suppress lung tumor growth and promote immunological memory.¹²⁰

The application of pyroptosis in the therapy of lung cancer is so promising that clinical trials have already been carried out. Several late-stage anticancer clinical trials are investigating. RRx-001 (generic name: bromonitroimidazole) has been confirmed safe and well tolerated in humans, along with potential effectiveness in various diseases resulting from immune and inflammasome activation.¹²¹ The Phase 2 trial of RRx-001 showed that it not only made platinum-resistant SCLC sensitive to chemotherapy, but also reduced the side effects of platinum.¹²² In an ongoing Phase 3 trial, RRx-001 is being tested in combination with carboplatin/cisplatin and etoposide for the treatment of SCLC.¹²³

Pyroptosis-related genes have potential therapeutic applications, but they are also beneficial in the prediction of lung cancer prognosis. GSDME, caspase 3, and caspase 8 are more abundantly expressed in tumor tissue. Elevated GSDME expression is associated with a higher postoperative survival rate and a lower lymph node metastasis rate, which suggests that it may serve as a predictor of prognosis in lung cancer patients.¹²⁴ LUAD prognosis is also associated with new pyroptosis-related prognostic markers, including NOD1, NLRP1, NLRP2, NLRP7, and caspase 6. The notion that pyroptosis can mediate the TME to exert an antitumor effect is supported by these genes, which are intimately linked to immune infiltration.¹²⁵ We have summarized the mechanisms and effects of pyroptosis-related targets/agents in lung cancer in Table 2.

4.4 | Pyroptosis in breast cancer

Breast cancer causes significant harm to women's health, ranking second among cancer-related deaths in women.⁸ A new treatment strategy for patients with breast cancer is offered by research on pyroptosis in the breast. As in other cancers, GSDME is substantially downregulated in breast cancer and inhibits cell proliferation and invasion. Furthermore, GSDME methylation is only identified in cell lines that express the estrogen receptor.¹²⁶ Breast cancer cell proliferation and colony formation are negatively impacted by CDK7 inhibition in a p53-GSDME-dependent manner.¹²⁷

Several investigations have found that different chemotherapy drugs can stimulate distinct pyroptosis pathways. Cisplatin enhances complete response rates in patients with triple-negative breast cancer patients by activating the lncRNA MEG3/NLRP3/caspase 1/GSDMD pyroptosis pathway.¹²⁸ Decitabine triggers GSDME expression by DNA demethylation, boosting pyroptosis and the chemosensitivity of MCF-7/Taxol cells to Taxol.¹²⁹ TNF α -

induced apoptosis is converted to pyroptosis by antibiotic chemotherapy drugs (daunorubicin, DOX, epirubicin, and actinomycin D) that activate PD-L1. The interaction between p-Stat3 and PD-L1 during hypoxia facilitates its nuclear translocation, increasing GSDMC expression and triggering the GSDMC/caspase 8 pyroptosis pathway.⁵² DOX treatments elevate ROS accumulation, which activates the phosphorylation of JNK and causes pyroptosis via the caspase 3/GSDME pathway.¹³⁰

Along with chemotherapy drugs, other drugs used in the treatment of breast cancer are related to pyroptosis. Metformin treatment greatly decreased breast cancer cell, colon cancer cell, and liver cancer cell viability and induced pyroptosis by improving the AMPK/SIRT1 pathway, upregulating NF- κ B p65 expression, and cleaving GSDME with caspase 3,¹³¹ Docosahexaenoic acid (DHA) may trigger pyroptosis by boosting NF- κ B nuclear translocation, caspase 1, and GSDMD activation,¹³² as well as activating the AIM2/caspase 3/DFNA5 pathway,¹³³ Nobiletin (NOB), a retinoid acid receptor-related orphan receptors (RORs) agonist,¹³⁴ induces the pyroptosis of breast cancer cells via the miR-200b/JAZF1/NF- κ B axis to stop tumorigenesis.¹³⁵ Polydatin, a monocrystalline compound isolated from *Polygonum cuspidatum* Sieb,¹³⁶ blocks the JAK2/STAT3 pathway and raises the expression of NLRP3, caspase 1, IL-1 β , and IL-18 to contribute to the activation of pyroptosis in triple-negative breast cancer.¹³⁷ Tetraarsenic hexoxide (As₄O₆) could increase mitochondrial ROS generation by preventing STAT3 phosphorylation, causing caspase 3/GSDME-dependent pyroptotic cell death and ultimately inhibiting tumor proliferation and metastasis in triple-negative breast cancer cells.¹³⁸ In breast cancer, retinoic acid-inducible gene I (RIG-I) agonist therapy revealed a significant immunogenic and therapeutic effect. RIG-1 stimulated pyroptosis, increased lymphocytes, and decreased tumor growth via triggering STAT1 and NF- κ B.¹³⁹ PolyI: C, a frequently employed synthetic dsRNA analogue that activates RIG-I, facilitated triple-negative breast cancer cell death by inhibiting the antiapoptotic function of TGF- β .¹⁴⁰ Many nanomaterials in combination with PolyI: C can lead to tumor cell death. However, the mechanism of pyroptosis has not been investigated.^{141,142}

Nanomedicine was employed to treat breast cancer with pyroptosis. Zhao et al. created a biomimetic nanoparticle (BNP) that contained indocyanine green (ICG) and DAC. ICG-activated caspase 3 and DAC increased GSDME expression by inhibiting DNA methylation Through low-dose photo-activation. In the end, this photo-activated pyroptosis of nanodrug generates an impressive systemic antitumor immunity for tumor inhibition.¹⁴³ Su et al.¹⁴⁴ utilized oncolytic viruses in conjunction with inhibitor nano prodrugs MPNPs to promote GSDME-mediated pyroptosis, reversing an immunosuppressive

TABLE 2 Mechanisms and effects of pyroptosis-related target/agents in cancer.

Cancer	Target/agents	Type	Signal and molecules	pyroptosis	References
Lung cancer	CuB	Extracts	TLR4, NLRP3	↑	112
	PPVI	An active saponin	ROS/NF- κ B/ NLRP3/GSDMD/caspase 1	↑	113
	Simvastatin	Marketed medicine	\	↑	114
	LncRNA-XIST	Noncoding RNAs	p53 and NLRP3↓ miR-335/SOD2/ROS	↓	117 118
	miR-556-5p	Noncoding RNAs	Nlrp3↑	↑	119
	Dasatinib	Targeted drug	GSDMD GSDME↑	↑	115
	CO-MP	Nano drug	GSDME↑ caspase 3↑	↑	120
	RRX-001	Medicine in trial	inflammasome activation		121
	Breast cancer	Cisplatin	chemotherapeutic agent	lncRNA MEG3/NLRP3/caspase 1/GSDMD	
Decitabine		Chemotherapeutic agent	GSDME↑	↑	129
Doxorubicin		Chemotherapeutic agent	ROS↑ Caspase 3/GSDME	↑	130
metformin		Marketed medicine	AMPK/SIRT1 caspase 3/GSDME	↑	131
DHA		Marketed medicine	AIM2/caspase 3/DFNA5 caspase 1/GSDMD	↑	132
Nobiletin		RORs agonist	miR-200b/JAZF1/NF- κ B	↑	135
Polydatin		Extracts	JAK2/STAT3↓ NLRP3, caspase 1, IL-1 β , IL-18	↑	137
As4O6		Oxide	ROS↑, P-STAT3↓ caspase 3/GSDME	↑	138
RIG-1 agonist		Agonist of RIG-1	STAT1, NF- κ B	↑	139
BNP (ICG/DAC)		Nanomedicine	Caspase 3/GSDME	↑	143
MPNPs (oncolytic viruses)		Nanomedicine	GSDME	↑	144
Gastric cancer	Famotidine	Marketed medicine	NLPR3, IL-18, GSDME	↑	159
	Icariin	Medicine in trial	hsa_circ_0003159/miR-223-3p/ NLRP3 axis	↑	160
	Simvastatin	Marketed medicine	Caspase 3/GSDME	↑	161
	Diosbulbin-B	Extracts	Inhibit PD-L1 and activate NLRP3	↑	163
	BIX-01294	Inhibitor of histone methyltransferase	GSDME	↑	164
	LncRNA ADAMTS9-AS2	Noncoding RNAs	miR-223-3P↓/NLRP3↑	↑	165
	LP-R/C@AC	Nanomedicine	VEGFR2/STAT3	↑	166
	ZIF-8@TPZ/Ce6	Nanomedicine	ROS↑	↑	167
Colorectal cancer	lobaplatin	Chemotherapeutic agent	Caspase 3, GSDME	↑	177
	DAC	Chemotherapeutic agent	Inflammasome↑	↑	178
	Secoisolariciresinol diglucoside	Extracts	Caspase 1, GSDMD,	↑	179
	Arsenic trioxide & ascorbic acid	Marketed medicine	ROS↑, caspase 1	↑	180
	GW4064	Agonist of an FXR	BAX/caspase 3/GSDME	↑	181
	T22-PE24-H6	Nanomedicine	GSDMD	↑	182
	DAC-nano drugs/LipoDDP	Nanomedicine	caspase 3/GSDME	↑	184

(Continues)

TABLE 2 (Continued)

Cancer	Target/agents	Type	Signal and molecules	pyroptosis	References
Endometrial Cancer	HKDC1	Proteins	ROS↑ HOXC-AS2/miR-876-5p/HKDC1	↑	189
	hydrogen	GAS	ROS↑ pyroptosis-related protein↑	↑	191
Cervical cancer	SIRT1	Proteins	AIM2↓	↓	196
	Lobaplatin	chemotherapeutic agent	Caspase 3/GSDME	↑	198
	Δ-Ru1 & Taxol	Nanomedicine	Caspase 1/GSDMD	↑	199
	Tanshinone II A	Targeted drug	miR-214/GSDMD	↑	201
	miR-214	Noncoding RNAs	NLRP3↑	↑	202
Ovarian cancer	LncRNA GAS5	Noncoding RNAs	ASC, caspase 1	↑	218
	lncRNA HOTTIP	Noncoding RNAs	NLRP1	↓	217
	LncRNA DICER1-AS1	Noncoding RNAs	Pyroptosis-related	Not investigated	219
	FOSL2	Gene	ASC, caspase 1, IL-1β, IL-18	↓	220
	BI 2536	Medicine in trial	Caspase 3/GSDME	↑	43
	Bexarotene	Marketed medicine	Caspase 4/GSDME	↑	222
	Nobiletin	RORs agonist	GSDMD/GSDME, IL-1β, ASC	↑	223
	Osthole	Inhibitor of histamine H1 receptor	GSDME	↑	225
	α-NETA	Inhibitor of choline acetyltransferase	GSDMD/caspase 4.	↑	227
	Citric acid	Marketed medicine	TXNIP, caspase 4, NLRP3, GSDMD	↑	228

TME and augmenting the effectiveness of anti-PD-1 treatment. Following a study, anti-GSDMB antibody loaded into hyaluronic acid biocompatible nanocapsules has a significant and targeted impact on HER2-positive cancers that overexpress GSDMB. These effects include decreased migration, increased sensitivity to trastuzumab, reduced tumor growth, and lowered lung metastasis by elevating GSDMB binding to sulfatides.¹⁴⁵

Pyroptosis-related genes can be exploited as prognostic predictors and therapeutic targets for breast cancer. In the study of prognostic-related gene expression, breast cancers showed considerably lower levels of the pyroptosis pathway effector proteins caspase 1, IL-1β, and GSDMD compared with nearby normal tissue.¹⁴⁶ A study has found that GSDMB is a significant predictor of poor prognosis and therapeutic response in HER2-positive breast cancer. GSDMB expression was linked to a poor prognosis and treatment response in HER2-positive breast cancer. Additionally, GSDMB expression promoted cell viability and resistance to trastuzumab therapy.¹⁴⁷ GSDME methylation is a promising biomarker for the diagnosis and prognosis of breast cancer.¹⁴⁸ The prognosis of breast cancer can be independently attributed to three-gene regression models involving IL18, GSDMC, and TIRAP. In contrast, a high-risk score is associated with poorer progression, overall survival and relapse rates, while a low-risk score

is associated with immune cell infiltrations and immune checkpoints. Table 2 provides a summary of the mechanisms and effects of pyroptosis-related targets and agents in breast cancer.

Immune checkpoint inhibitors may be better for use in combination with chemotherapy drugs than they are for use alone.^{149,150} We hypothesized that it is the immune checkpoint inhibitors that enhance the induction of pyroptosis by chemotherapeutic agents, as pyroptosis is immunologically related. Therefore, the molecular and immunological mechanisms of chemotherapy-induced pyroptosis need to be investigated in depth.

4.5 | Pyroptosis in gastric cancer

Gastric cancer is the fifth most common cancer in the globe, with more than 1.08 million new cases diagnosed annually. It is also the fourth greatest cause of cancer-related fatalities worldwide, accounting for 770 thousand deaths each year.¹⁵¹ The search for innovative and effective treatments for gastric cancer is particularly critical. GSDMA, GSDMC, and GSDMD are down-regulated in gastric cancer,^{152,153} although GSDMB levels are high.¹⁵⁴ Reduced GSDMD expression speeds up tumor proliferation and S/G2 transition of cells by stimulating the

STAT3 and PI3K/PKB pathways.¹⁵³ GSDME is essential to the treatment of gastric cancer, as it is in other cancers. Wang et al.¹⁵⁵ indicated that GSDME converted caspase 3-dependent apoptosis into pyroptosis caused by chemotherapeutic agents 5-FU. Intracellular mucin 20 variant 2 (MUC20v2) expression maintains mitochondrial calcium homeostasis and mitochondrial membrane potential (MMP), promoting cell viability and chemotherapeutic resistance by suppressing pyroptosis and apoptosis in gastric cancer cells.¹⁵⁶ Pyroptosis and inflammation are inextricably linked. Infection with *Helicobacter pylori* infection is a major factor in gastric cancer. CagA, a *Helicobacter pylori* virulence factor, may trigger the migration and invasion of gastric cancer cells by activating the NLRP3 inflammasome.¹⁵⁷ Li et al.¹⁵⁸ have reported that the antibacterial activity of *Callicarpa nudiflora* can protect the gastric epithelium from *Helicobacter pylori* by inhibiting the ROS/NLRP3/caspase 1/IL-1 β signaling axis. Existing studies have shown that pyroptosis may both promote and inhibit gastric cancer, therefore more research into the connection between gastric cancer and pyroptosis is required.

Pyroptosis has been implicated in gastric cancer. Thus, numerous drugs and noncoding RNAs have been studied for their function in gastric cancer pyroptosis. Famotidine, for instance, stimulated cell pyroptosis in gastric cancer cells by activating NLRP3 inflammasomes, which resulted in increased IL-18 release and GSDME expression.¹⁵⁹ Icaritin, the primary active ingredient of *Epimedium*, controlled the hsa_circ_0003159/miR-223-3p/NLRP3 axis to suppress gastric cancer and trigger pyroptosis.¹⁶⁰ As it did in lung cancer, simvastatin caused pyroptotic cell death in gastric cancer by upregulating the expression of caspase 3 and GSDME.¹⁶¹ Low-dose Diosbulbin-B, a diterpene lactone isolated from *Dioscorea bulbifera* L,¹⁶² boosted the sensitivity of gastric cancer cells to cisplatin via inhibiting PD-L1 and activating NLRP3-mediated pyroptosis.¹⁶³ When combined with cisplatin, BIX-01294 (BIX), a specific inhibitor of euchromatic histone-lysine N-methyltransferase 2 (EHMT2) histone methyltransferase, lowers cell viability in gastric cancer cells through GSDME-mediated pyroptotic cell death.¹⁶⁴ LncRNA ADAMTS9-AS2 suppresses gastric cancer cells and raises cisplatin sensitivity by inhibiting miR-223-3p, which in turn stimulates NLRP3 expression and eventually enhances pyroptotic cell death.¹⁶⁵

Nanocomplexes have been widely explored in the pyroptosis of gastric cancer. Long et al.¹⁶⁶ created a pH-responsive liposome (Liposome-PEO, LP), which contained apatinib and cinobufagin, and was covered with a hybrid membrane (R/C). This nanocomplex LP-R/C@AC successfully cured gastric cancer, improved drug effects, reduced side effects, and had superior solubility and tar-

geting ability. It mechanically inhibited tumor growth through the VEGFR2/STAT3 pathway and stimulation of pyroptosis.¹⁶⁶ During the past few years, sonodynamic therapy has become a popular treatment in cancer research due to its noninvasive nature. Yu et al.¹⁶⁷ have established a nanodrug that integrates zeolitic imidazole frameworks-8 (ZIF-8), encapsulated Chlorin e6 (Ce6), and tirapazamine (TPZ) to provide synergistic sonodynamic chemotherapy. It was also changed by the cytomembrane of gastric cancer cells for targeting capabilities. With ultrasound irradiation, this complex (ZIF-8@TPZ/Ce6 (ZTC)) might generate ROS, induce pyroptosis, and perform antitumor functions.¹⁶⁷

Wang et al.¹⁶⁸ created a predictive signature related to pyroptosis. They discovered four novel pyroptosis-related lncRNAs, namely HAND2-AS1, LINC01354, RP11-276H19.1, and PGM5-AS1, with high expression correlated with a poor prognosis.¹⁶⁸ In a different investigation, Liang et al. looked into PRGs in gastric cancer and developed a ten-gene prognostic model (BIRC2, CD274, IRGM, ANXA2, GBP5, TXNIP, POPI, GBPI, DHX9, and TLR2). The study suggests that pyroptosis-related risk signals can predict gastric cancer prognosis and identify immune cell infiltration in high-risk patient tissues.¹⁶⁹ The mechanisms and effects of pyroptosis-related targets and substances in gastric cancer are summarized in Table 2.

4.6 | Pyroptosis in colorectal cancer

Colorectal cancer is the third most prevalent cancer and the fourth main cause of cancer death.¹⁷⁰ Inflammation is intimately connected to cancer, particularly colon cancer, and patients suffering from ulcerative colitis have a considerably elevated risk of colorectal cancer.¹⁷¹ According to Allen et al.,¹⁷² components of the inflammasome are protective against both recurrent and acute colitis as well as colitis-associated cancer (CAC). According to bone marrow reconstitution experiments that have been performed, the NLRP3 gene, which is expressed in hematopoietic cells rather than intestinal epithelial or stromal cells, may be important for tumorigenesis prevention.¹⁷² Microbiome-derived stimuli can enhance the cleavage of GSDMs into an active state, inducing pyroptosis and facilitating the release of inflammatory mediators. Eventually, the tumor burden is reduced, or a tumor-promoting microenvironment is established. Moreover, GSDMB can generate pores in bacterial membranes, triggering intracellular pathogens to die.¹⁷³ In different research, GSDME cleavage promoted pyroptosis and inhibited HCT116 cell viability by apoptin, a protein encoded by the chicken anemia virus VP3 gene.¹⁷⁴ In colorectal cancer, GSDMD levels are decreased, and these levels are negatively correlated with tumor

metastasis, tumor aggressiveness, and 5-year survival rates.^{175,176} Yet other articles suggest that pyroptosis contributes to colon cancer. GSDME-mediated pyroptosis accelerates the progression of CAC by releasing HMGB1, which stimulates tumor cell proliferation and PCNA expression via the ERK1/2 pathway.⁴⁴

Surprisingly, many chemotherapeutic medications and other agents suppress cancer through pyroptotic mechanisms. In a dose-dependent manner, lobaplatin-induced caspase 3-GSDME-dependent pyroptosis lowers the viability of colorectal cancer cells.¹⁷⁷ DAC treatment can inhibit colon cancer growth by stimulating inflammasome expression and causing pyroptosis.¹⁷⁸ The enhancement of the GSDMD-dependent pyroptosis brought on by LPS increases the chemosensitivity of oxaliplatin in colon cancer cells.¹⁷⁶ Secoisolariciresinol diglucoside, the main lignan in wholegrain flaxseed, reduced cell viability and triggered pyroptosis by improving cleavage of the N-terminal fragment of GSDMD and promoting caspase 1 cleavage, which is connected with the ROS/PI3K/AKT/BAX mitochondrial apoptotic pathway.¹⁷⁹ The combination of arsenic trioxide and ascorbic acid substantially inhibits colorectal cancer cell viability by producing ROS, upregulating caspase 1 expression, and promoting the development of inflammasomes to induce pyroptosis.¹⁸⁰ GW4064, a Farnesoid X receptor (FXR) agonist, increased the chemosensitivity of cells to oxaliplatin by activating BAX/caspase 3/GSDME-mediated pyroptosis.¹⁸¹

A nanoparticle-based approach known as T22-PE24-H6 and T22-DITOX-H6 was created by the researchers. It targets colorectal cancer cells, inhibits tumor growth, and blocks lymphatic and hematogenous metastasis by triggering pyroptotic activation.^{182,183} Zhang and coworkers¹⁸⁴ combine DAC with chemotherapeutic nano drugs to predemethylate and upregulate the GSDME in colon adenocarcinoma cells. After that, by delivering cisplatin-loaded nanoliposomes (LipoDDP) to tumor cells, drugs are delivered to activate the caspase 3 pathway and induce pyroptosis to achieve excellent tumor suppression. Table 2 provides a summary of the mechanisms and effects of pyroptosis-related targets and agents in colorectal cancer.

In conclusion, these investigations shed light on the presumed mechanisms and function of pyroptosis in colorectal cancer. Consequently, these findings may offer an ideal method for improving the treatment and prognosis of this malignancy.

4.7 | Pyroptosis in gynecological oncology

The three most common types of gynecologic malignancies are cervical cancer, ovarian cancer, and endome-

trial cancer, which pose a health threat to women around the world. The primary treatment for gynecological cancers is surgery, often accompanied by radiotherapy, chemotherapy, and immunotherapy. Some of these targeted medicines, like poly adenosine diphosphate ribose polymerase (PARP) inhibitors, have achieved considerable clinical effectiveness in ovarian cancer. Despite this, the generally disappointing prognosis for patients with gynecological tumors and there are still enormous obstacles that require more advancements in therapeutic approaches.¹⁸⁵ Therefore, pyroptosis is an excellent starting point.

4.7.1 | Endometrial cancer

Endometrial cancer is one of the most prevalent gynecological cancers in women. Its incidence progressively climbed over 30 years, increasing by 132% overall.¹⁸⁶ The three primary risk factors for endometrial cancer are hypertension, obesity, and diabetes. In this way, endometrial cancer may be classified as a metabolic disorder.¹⁸⁷ Inflammation may be activated and promote tumor growth as well as invasion in endometrial cancer patients due to oxidative stress and elevated systemic inflammation produced by the metabolic syndrome.¹⁸⁸ Endometrial cancer and inflammation are strongly associated, and pyroptosis and inflammation are inextricably linked. This makes it very interesting to explore the connection between pyroptosis and endometrial cancer.

In diabetic endometrial cancer patients, hexokinase domain-containing 1 (HKDC1) is upregulated. HKDC1 causes pyroptosis and metabolic advantage in lactate-rich environments by boosting ROS and glycolysis activation, resulting in the creation of acidic TME and favorable inflammatory that leads to endometrial cancer cell proliferation and migration. In terms of mechanisms, pyroptosis is controlled by the HOXC-AS2/miR-876-5p/HKDC1 signaling axis.¹⁸⁹ The study discovered that estrogen activates the NLPR3 inflammasome, triggering increased expression of NLPR3, ER β , pro-IL-1 β , IL-1 β , and endometrial cancer cell proliferation. Endometrial cancer progression and poor survival were associated with the upregulation of NLPR3, ASC, caspase 1, and IL-1 β .¹⁹⁰ Another study reveals the opposite that hydrogen pretreatment suppresses endometrial cancer growth by raising ROS and pyroptosis-related protein expression.¹⁹¹ Liang et al.¹⁹² evaluated nine pyroptosis-related lncRNAs in the TCGA database and established a risk model that could be applied to forecast prognosis and assess response to immunotherapy. Zhang et al.¹⁹³ identified four prognosis-associated PRG (ELANE, GPX4, GSDMD, and TIRAP). This panel is also capable of forecasting the

immune microenvironment and prognosis of endometrial cancer.

4.7.2 | Cervical cancer

There is no doubt that cervical cancer threatens women's health, as it is the fourth most common cause of death and incidence among women.¹⁹⁴ Human papillomavirus (HPV) infection, particularly the type 16 and 18, exacerbates cervical cancer risk. Despite increasing HPV vaccination coverage, the treatment of cervical cancer resulting from HPV infection remains a clinical challenge.¹⁹⁵ In HPV-infected cervical cancer cells, sirtuin 1 (SIRT1) is overexpressed and represses NF- κ B-driven transcription of the AIM2 gene along with pyroptotic death signaling.¹⁹⁶ According to studies, HPV E7 reduces the self-evasion from immune surveillance, induced cell pyroptosis, inflammatory activation, and generation of IL-18 and IL-1 β by interacting with the E3 ligase TRIM21 to ubiquitinate and degrade the IFI16 inflammasome.¹⁹⁶ According to the study, cells expressing the E6 oncogene could avoid immune surveillance by downregulating the expression of IL-18 and preventing downstream cell damage because the HPV16 E6 lowered IL-18 expression via an independent pathway of p53 degradation.¹⁹⁷ Cell viability was substantially decreased and caspase 3/GSDME-dependent pyroptosis was elevated in cervical cancer cells after lobaplatin treatment.¹⁹⁸ The metal complex chemotherapeutic agent ruthenium (II) polypyridyl complex, Δ -[Ru(bpy)₂(HPIP)] (ClO₄)₂(Δ -Ru1), is effective and safe enough to replace platinum drugs in the future. Taxol and Δ -Ru1 inhibit tumor development and adverse effects via caspase 1/GSDMD-dependent pyroptosis.¹⁹⁹ Tanshinone II A, which may target the protein kinase domains of VEGF/VEGFR2,²⁰⁰ was reported to limit cell proliferation and increased pyroptosis in HeLa cells by upregulating the expression of miR-145 and GSDMD.²⁰¹ Meanwhile, overexpression of miR-214 might facilitate pyroptosis and inhibit proliferation by targeting NLRP3 in cervical cancer.²⁰² CHMP4C, GZMB, and TNF were identified in cervical cancer as differentially expressed pyroptosis-related genes by Hu et al.,²⁰³ which can be a predictor for the outcome of cervical cancer.

4.7.3 | Ovarian cancer

Ovarian cancer, one of the most common gynecological malignancies, has a high mortality rate and unfavorable prognoses.²⁰⁴ In their TMEs, ovarian cancer patients have greater GSDMD and lower GSDME protein levels.²⁰⁵ Serous ovarian cancer has higher expression of GSDMD

and GSDMC, compared with lower levels of GSDME and PJVK. In the genes that code for GSDMC, GSDMD, GSDME, and PJVK, ovarian cancer has the highest rate of copy number variation events of any cancer type.²⁰⁶ A disequilibrium of phosphatidylinositol and cholesterol in the cell membrane hinders GSDM integration and pores formation.²⁰⁷ Given the prevalence of this imbalance in malignancies, the hypothesis is that higher levels of phosphatidylinositol and cholesterol in the cell membrane keep cancer cells alive.²⁰⁸ This imbalance is usual in cancers, particularly ovarian cancer. Pyroptosis-restricting metabolic changes are necessary for cancer cell survival.²⁰⁹ Li et al.²¹⁰ found that IL-1 α and IL-1 β were overexpressed in a 1992 investigation on epithelial tumor cell lines and tumor cells derived from the ascitic fluid of ovarian cancer patients. In ovarian cancer cells with the 185delAG founder mutation in the breast cancer susceptibility gene 1, there was an increase in active IL-1 and elevation in caspase 1 cleavage mediated by inflammasome.²¹¹ Olaparib, a PARP inhibitor, exhibits considerable cytotoxic effects and safety when combined with an IL-1 β inhibitor.²¹²

NK cell-mediated immunity removes ovarian cancer via cytokine-induced memory-like NK cells, which generate IFN- γ and TNF- α after seven days of IL-18 exposure.²¹³ When coupled with pegylated liposomal DOX, the immunostimulatory cytokine recombinant IL-18 (SB-485232) displays anticancer activity in preclinical models. Moreover, it has been proven to be safe and therapeutically effective in Phase I clinical trials in recurrent ovarian cancer.²¹⁴ NLRP3 is involved in ovarian cancer chemoresistance with downregulation increasing drug sensitivity in gemcitabine-resistant cell lines and overexpression inducing IL-1 β , EMT, and Wnt/ β -catenin signaling.²¹⁵ Carboplatin therapy increases the activation of the NLRP3 inflammasome in macrophages, indicating NLRP3 implications for ovarian cancer and potential chemoresistance.²¹⁶

NLRP1 inflammasome-induced pyroptosis was exacerbated by the inhibition of lncRNA HOTTIP, which suppressed ovarian cancer.²¹⁷ lncRNA GAS5 prevents the progression of ovarian cancer by activating ASC, caspase 1, and IL-1 in a time-dependent manner to create inflammasomes and induce pyroptosis.²¹⁸ Additionally, one of the eight pyroptosis-related lncRNAs, lncRNA (DICER1-AS1), drastically suppressed the proliferation of ovarian cancer cells.²¹⁹ Inhibition of fos-like antigen 2 (FOSL2) limits ovarian cancer development through upregulation of proteins associated with inflammasome formation, including ASC, pro-caspase 1, caspase 1, pro-IL-1, pro-IL-18, and IL-18.²²⁰ The latest small molecule inhibitor, BI 2536, inhibits the proliferation of ovarian cancer cells, triggers cell cycle halt at the G2/M phase, and accumulates CD8+ T lymphocyte cells at tumor sites via initiating pyroptosis in

ovarian cancer through the caspase 3/GSDME pathway.⁴³ Bexarotene, a retinoid X receptor-selective agonist,²²¹ provokes pyroptotic cell death in an ovarian cancer cell line by a caspase 4-GSDME-dependent signaling cascade.²²² NOB, a polymethoxyflavonoid, stimulates traditional autophagy, ROS production, and a decline in MMP, all of which contribute to initiating GSDMD/GSDME-mediated pyroptosis and upregulating the expression of IL-1 β and ASC in ovarian cancer.²²³ Osthole, a potential inhibitor of histamine H1 receptor activity,²²⁴ also accelerates autophagy, apoptosis, and GSDME-dependent pyroptosis while raising ROS generation and diminishing MMP.²²⁵ A new drug known as 2-(anaphthoyl)ethyltrimethylammonium iodide (α -NETA), a choline acetyltransferase inhibitor,²²⁶ hinders the development of epithelial ovarian cancer by activating pyroptosis via the GSDMD/caspase 4 pathway.²²⁷ The caspase 4/TXNIP-NLRP3-GSDMD pathway increases pyroptosis in response to treatment with citric acid for ovarian cancer.²²⁸

In addition to therapeutic applications, pyroptosis in ovarian cancer has prognostic applications. Antiangiogenic therapy effectiveness in ovarian cancer is predicted by AIM2. Higher levels of AIM2 in bevacizumab-resistant patients are related to poorer progression-free survival.²²⁹ Greater NLRP3 expression was related to worse overall survival in ovarian cancer.²³⁰ Cao et al.²¹⁹ investigated the mutation frequency of NLRP3 was explored to have the maximum mutation frequency among the 33 PRGs. In ovarian cancer and healthy tissues, Qi and coworkers²³¹ identified 31 distinct PRGs, with 13 downregulated and 18 upregulated. They established prognostic models and risk patterns. Another research employed 51 PRGs to construct the Pysig score, which clarified the immunological and prognostic relevance of ovarian cancer pyroptosis.²³² The mechanisms and effects of pyroptosis-related targets and agents in gynecological oncology are summarized in Table 2.

We summarized the relevant applications of pyroptosis in cancer in Figure 4. Personalized treatment approaches will be achieved by exploring the possibility of targeting specific pyroptosis pathways in different types of cancer. In addition, understanding the interactions between pyroptosis and other immune cell death pathways may provide valuable insights into novel therapeutic strategies for cancer patients.

5 | PYROPTOSIS AND INFLAMMASOMES IN INFLAMMATION

Pyroptosis, mediated by inflammasomes, is a highly inflammatory form of cell death that plays a crucial role in the body's immune response. Pyroptosis and inflam-

masomes are responsible for processing inflammatory cytokines and initiating an inflammatory cascade. Understanding the association between pyroptosis, inflammasomes, and inflammatory diseases is essential for curing inflammatory diseases.

5.1 | Involvement of pyroptosis and inflammasomes in inflammatory diseases

Pyroptosis and inflammasomes have been implicated in various inflammatory diseases. For example, in rheumatoid arthritis, the assembly of NLRP3 plays a crucial role in activating immune cells and releasing IL-1 β and IL-18, leading to joint inflammation and damage.²³³ Targeting these inflammasomes could potentially alleviate symptoms and slow down disease progression. Similarly, in Crohn's disease, GSDME-mediated pyroptosis to release proinflammatory cytokines in epithelial cells can contribute to tissue damage and chronic inflammation.²³⁴ It has been discovered that IL-18 levels are higher in Crohn's disease patients and that it contributes to the promotion of TH1 cell responses.²³⁵ Furthermore, recent studies have shown that dysregulation of pyroptosis and inflammasome activation can also play a role in the pathogenesis of cardiovascular diseases, such as atherosclerosis and myocardial infarction.^{236,237} There is evidence that plaques and ruptured lesions linked to acute coronary events in atherosclerosis exhibit large elevations in caspase 1 expression.²³⁸ Additionally, the activation of inflammasomes has been implicated in the development and progression of neurodegenerative disorders, such as Alzheimer's disease and Parkinson's disease.²³⁹ Therefore, targeting pyroptosis and inflammasomes may offer promising therapeutic opportunities for a wide range of inflammatory diseases beyond the traditionally studied conditions.

5.2 | Molecular mechanisms linking pyroptosis and inflammation

IL-1 β and IL-18 are two proinflammatory cytokines that are directly produced during pyroptosis. Both cytokines have key roles in the pathophysiology of a spectrum of inflammatory disorders. Vasodilation, fever, hematopoiesis, leukocyte infiltration, antibody generation, and the expression of cytokines and chemokines are all events triggered by IL-1 β binding to IL-1 receptors on the surface of immune cells.⁹ A key factor in immunological responses, IL-18 is involved in angiogenesis and the induction of IFN γ , the activation of T cells, macrophages, and NK cells.^{240,241} In general, pyroptosis is beneficial to the host because it fights infections and cellular stress. Despite these two proinflammatory cytokines are known

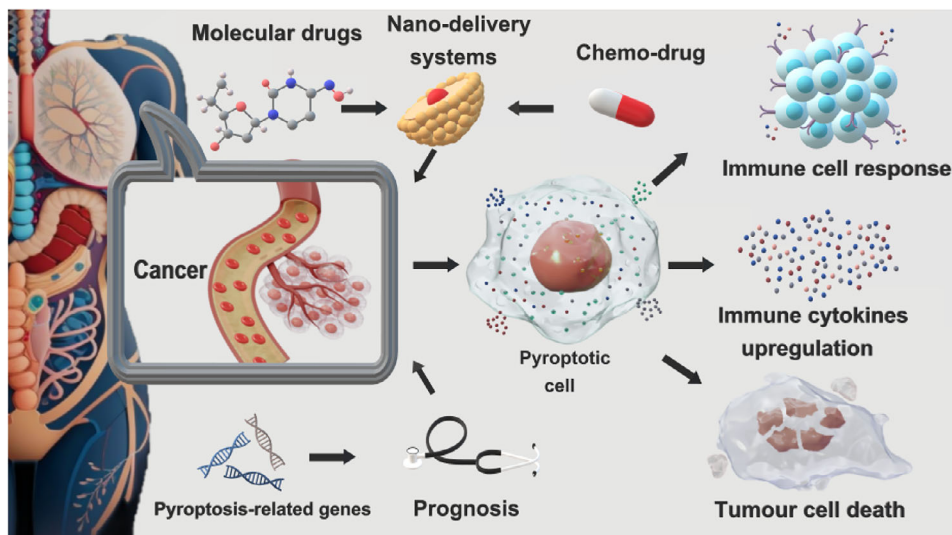


FIGURE 4 Prospects for pyroptosis-related targeted therapy in cancer. Molecular drugs and chemo-drugs loaded into the nanodelivery system to target cancer cells and activate pyroptosis, resulting in immune cell response, elevated immune cytokines and tumor cell death.

to be produced directly by inflammasome activation, other cytokines, such as TNF- β , IL-6, and IL-16,^{242,243} are indirectly produced, which can cause an inflammatory storm and tissue damage. Additionally, it was shown that the IFN γ and TNF α boosted the proinflammatory response and triggered pyroptosis.²⁴⁴ By activating the inflammasome, proinflammatory cytokines can be made, which can cause an inflammatory storm and damage to tissues. This can make pyroptosis less effective at fighting infections and cellular stress; it could even cause damage. More research is needed to understand the role of the inflammasome and pyroptosis in inflammatory diseases. By developing inhibitors or agonists that target the pyroptosis pathway and lead to a therapeutic effect, researchers hope to find new treatments for inflammatory diseases.

5.3 | Therapeutic implications of targeting pyroptosis and inflammasomes in inflammation

Targeting pyroptosis and inflammasomes in inflammation diseases could be used as a way to treat inflammation by going after the NLRP3 and GSDMD proteins. Some of these inhibitors are already adopted in clinical trials. MCC950, a nanomolar potent and specific inhibitor of NLRP3 signaling, was active in several models of inflammatory disease.²⁴⁵ MCC950 inhibits the ATPase activity of NLRP3 and also attaches to the NACTH domain, trapping NLRP3 in an inactive state.^{68,246} Punicalagin, which affects plasma membrane fluidity, may have implications for its potential role in modulating N-GSDMD insertion or oligomerization.²⁴⁷

6 | CONCLUSION AND PERSPECTIVES

Pyroptosis is a specific form of PCD. Activation of inflammasomes is a crucial factor in inducing pyroptosis. In this review, we describe the mechanisms of pyroptosis and activation of inflammasomes and their applications in cancer and inflammatory diseases. Pyroptosis leads to the secretion of proinflammatory cytokines, which not only contribute to inflammation but also play a crucial role in the immune response against cancer cells. Therefore, targeting the pyroptosis pathway using nanomedicines and inhibitors holds great potential for therapeutic interventions in both cancer and inflammatory diseases, and we therefore summarize this review. Pyroptosis-related genes may aid in predicting the prognosis and treatment efficacy of tumors. These genes have been linked to tumor progression and therapeutic response. Besides, their levels of expression can serve as potential biomarkers in personalized cancer treatment strategies. However, additional in-depth research and clinical applications are required since the understanding of pyroptosis-related genes in tumor biology is continually evolving. Further studies are needed to determine the exact mechanisms through which pyroptosis-related genes impact tumor growth and treatment response. Beyond that, clinical trials are needed to validate the efficacy of these genes as predictive biomarkers in cancer patients, which would facilitate the development of personalized therapeutics. The use of PRG as a new and accurate diagnostic and prognostic for tumors is anticipated in the future.

Pyroptosis has an essential effect on the growth and chemotherapeutic treatment resistance of tumors because GSDME has a great impact on the response to

chemotherapy or immunotherapy. Low levels of GSDME, generated by hypermethylation of the GSDME mRNA in tumor cells, impair the ability of most tumor cells to undergo pyroptosis and stimulate tumor growth. This interaction may enhance the resistance of tumor cells to chemotherapeutic drugs and hinder the effectiveness of immunotherapy. Additionally, the response to these treatments may be improved by targeting GSDME methylation and restoring the ability of tumor cells to undergo pyroptosis and restrain tumor development. For instance, DAC can demethylate GSDME, restoring normal expression of the GSDME protein and boosting the effectiveness of antitumor treatment. In addition, certain inhibitors and drugs, like those that activate the caspase 1/GSDMD or caspase 3/GSDME pathway, can cause the onset of pyroptosis. These agents can effectively eliminate cancer cells and prevent tumor growth by provoking pyroptosis in tumor cells. As a result, it has great potential for improving the outcomes of antitumor therapy by utilizing pyroptosis-inducing agents, especially those that target GSDME methylation.

Pyroptosis can be anticancer or procancer, but in most cases, it is a cancer suppressor in most types of cancer, although its function in cancer is not fully understood. Therefore, the following therapeutic recommendations will promote the process of pyroptosis in cancer. There is also an unavoidable problem. The fatal CRS might occur after pyroptosis therapy as an inflammatory way for cells to die, injuring surrounding or other normal tissues and creating a range of additional problems. Researchers are experimenting with several strategies to mitigate the risks associated with CRS during pyroptosis therapy. One approach is to create targeted delivery systems that can specifically induce pyroptosis in cancer cells while sparing healthy tissues. Moreover, efforts are conducted to identify biomarkers or molecular signatures that may forecast the probability of CRS development, enabling the plan of customized treatment programs and more thorough monitoring of patients.

Although inducing substances may evoke pyroptosis, they have considerable systemic adverse effects because they are insoluble, nonspecific, and disintegrate fast *in vivo*. Nanodelivery systems can boost the efficacy of pyroptosis-inducing agents by improving their stability and specificity. These systems can also distribute the agents in a regulated manner, allowing for continuous and targeted delivery to cancer cells. Meanwhile, nanodelivery systems can overcome the limitations of insolubility and fast degradation, making them a valuable tool in cancer treatment. Many investigations on nanomedicine for tumors in the field of pyroptosis have been conducted. These studies have yielded encouraging findings in terms of increased cancer cell death and decreased toxicity to

healthy cells. Nevertheless, most of them have never been used in clinical practice. The challenges of scaling up production and ensuring consistent quality control are linked to the limited usage of nanomedicines in clinical practice. On the other hand, the expensive cost of developing and manufacturing nanomedicine products may impede their broad use in healthcare settings. Therefore, further research and clinical trials are required to demonstrate the efficacy and safety of nanomedicines, paving the way for their widespread adoption and incorporation into healthcare systems.

Certain pyroptosis inflammatory factors can lead to immune cell responses that modify the TME and have a procancer or anticancer effect. There are few investigations on this subject because the use of pyroptosis-associated inflammatory factors for cancer therapy is still in its early phases. The inflammasome appears to be a promising treatment target as well as a valuable biomarker for cancer. It could potentially lead to the development of targeted therapies that exploit its procancer or anticancer effects if the function of the inflammasome in cancer is understood. Further research into the use of pyroptosis-associated inflammatory factors as prospective therapeutic alternatives may provide insights into improving the effectiveness of cancer treatment. These studies will concentrate on the involvement of the inflammasome in cancer as well as the application of particular inflammasome-related treatments in clinical and preclinical trials.

Understanding the mechanisms of pyroptosis and inflammasomes in disease contexts is crucial for developing targeted therapeutic strategies. By targeting these pathways, we may be able to modulate immune responses and inflammation, leading to improved outcomes in cancer or inflammatory diseases. Further research in this area is required to fully comprehend the complex interplay between pyroptosis, inflammasomes, and disease progression, which could pave the way for innovative treatments and personalized medicine approaches.

AUTHOR CONTRIBUTIONS

J. W. and S. H. are responsible for the collection of data, collation, and writing of the original manuscript. H. B. and Y. J. are responsible for reviewing the literature. S. C. and Y. Z. are responsible for the concept development, revision, and review of the manuscript. All authors contributed to the article and approved the submitted version.

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CONFLICT OF INTEREST STATEMENT

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. The authors declare that they have no conflicts of interest pertaining to this study.

DATA AVAILABILITY STATEMENT

Not applicable.

ETHICS STATEMENT

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