



REVIEW ARTICLE

The implication of pyroptosis in cancer immunology: Current advances and prospects

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Abstract Pyroptosis is a regulated cell death pathway involved in numerous human diseases, especially malignant tumors. Recent studies have identified multiple pyroptosis-associated signaling molecules, like caspases, gasdermin family and inflammasomes. In addition, increasing *in vitro* and *in vivo* studies have shown the significant linkage between pyroptosis and immune regulation of cancers. Pyroptosis-associated biomarkers regulate the infiltration of tumor immune cells, such as CD4⁺ and CD8⁺ T cells, thus strengthening the sensitivity to therapeutic strategies. In this review, we explained the relationship between pyroptosis and cancer immunology and focused on the significance of pyroptosis in immune regulation. We also proposed the future application of pyroptosis-associated biomarkers in basic research and clinical practices to address malignant behaviors. Exploration of the underlying

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mechanisms and biological functions of pyroptosis is critical for immune response and cancer immunotherapy.

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Introduction

Immunity-related studies have revealed the regulation of multiple human diseases by the immune response, such as infections and cancers.^{1,2} Immune systems can be activated by metabolite-related signals, contributing to the functional changes of immune cells in response to oxidative stress.³ In recent years, many reports have demonstrated the significance of immune response in tumor progression and therapeutic response.⁴ Immune systems can inhibit cancer cell proliferation and tumor progression. Consequently, a better understanding of the relationship between immune response and cancer progression will improve treatment efficiency.^{5,6}

Under stress, cancer cells disrupt the host homeostasis, which in turn activates the host immune response.⁷ Increasing cell death pathways have been proved to participate in immune regulation, such as apoptosis, necroptosis and pyroptosis.^{8–10} Among them, pyroptosis is an inflammation-related cell death pathway,^{11,12} which is vital in immune response activation.^{13,14} After the activation of caspases and proinflammatory interleukins (ILs), pyroptosis is induced to trigger the immune response to infections and tumor cell invasions.¹⁵ A recent study has shown that the targeted inhibitor-induced pyroptosis increases intra-tumoral T-cell infiltration and triggers anti-cancer immune responses.¹⁶

The relationship between pyroptosis, innately programmed self-destruction of cells, and cancer immunology is extremely complex.¹⁷ The expression levels of gasdermin B (GSDMB) can be elevated by interferon- γ (IFN- γ), which promotes pyroptosis and anti-cancer immunity.¹⁸ Additionally, GSDMB leads to the infiltration of immune cells, e.g., CD4⁺ and CD8⁺ T lymphocytes, enhancing the sensitivity to immune checkpoint agents, e.g., the programmed cell death-1 (PD-1) monoclonal antibodies (mAbs).¹⁹ Moreover, pyroptosis mediated by cleaved GSDME modulates inflammasome activation under pathological conditions and inhibits tumorigenesis.²⁰ Thus, it can promote a systemic immune response in human cancer treatment, implying the promising wide application of pyroptosis-mediated immune amplification in anti-cancer therapies.

This paper mainly summarized previous reports regarding the roles of pyroptosis in regulating immune responses to various cancers. Moreover, the underlying effects of pyroptosis modulators in improving cancer immunotherapeutic efficacy were discussed.

Pyroptosis and cancer immune response

Nowadays, immune regulation has become a research hotspot owing to its change of tumor microenvironment and effect on cancer initiation and progression.^{21,22} Increasing

evidence has shown the significant effect of pyroptosis induction on immune response.^{19,23} Exploring the underlying molecules and appropriate management of pyroptosis might provide a promising strategy for immune regulation and anti-cancer immunotherapy.

Inflammasomes

Inflammasomes play a crucial role in tumor cell proliferation and immune response to cancer. As a kind of large cytoplasmic multi-protein signaling complex, inflammasomes can trigger inflammation and pyroptosis in the face of various pathogens or signaling molecules.²⁴ Increasing family members of inflammasomes have been found (Fig. 1) and can be divided into the absent in melanoma 2 (AIM2), NAIP-NLRC4, NLRP1, NLRP3, NLRP6, NLRP9b, pyrin inflammasomes, and caspase-11 noncanonical inflammasomes, according to different receptor proteins.²⁵

NLRP3 inflammasome

Unlike other inflammasome receptor proteins, most inflammasomes are activated indirectly or directly by combining with only one or a few specific agonists. NLRP3 inflammasome can respond to substantial agonists unrelated in source, nature, and structure.²⁶ To stay in the human stomach for a long timescale, *Helicobacter pylori* upregulates the secretion and maturity of IL-1 β . Notably, the inflammasome disorder caused by *H. pylori* is easily affected by external stimuli and then induces the formation of NLRP3 inflammasome. In addition, the secretion of numerous mature IL-1 β could lead to representative features of pyroptosis in human gastric cancer cells.²⁷ CagA protein from *H. pylori* can also promote the assembly of the NLRP3 inflammasome, facilitating the migration and invasion of gastric cancer cells.²⁸ Famotidine, the antagonist of histamine H2-receptor, can also trigger pyroptotic cell death in gastric cancer cells by increasing NLRP3/caspase-1 inflammasomes and the secretion of mature IL-18.²⁹ By inducing NLRP3-dependent pyroptosis by NLRP3-dependent cell lysis, dead cells release oxidized mitochondrial DNA (ox-mtDNA), and then ox-mtDNA induces inflammatory oligomerization through DNA sensors. This mechanism is found in patients with myelodysplastic syndromes (MDS). This suggests that the quantifiable ox-mtDNA released in plasma can be used as a biomarker for MDS and indicate the degree of pyroptosis.³⁰ High-frequency irreversible electroporation (H-FIRE) is a novel tumor ablation technique that acts on tumor cells and changes the tumor microenvironment from anti-inflammation to proinflammation. In this process, four media (i.e., ATP, HMGB1, ROS, and

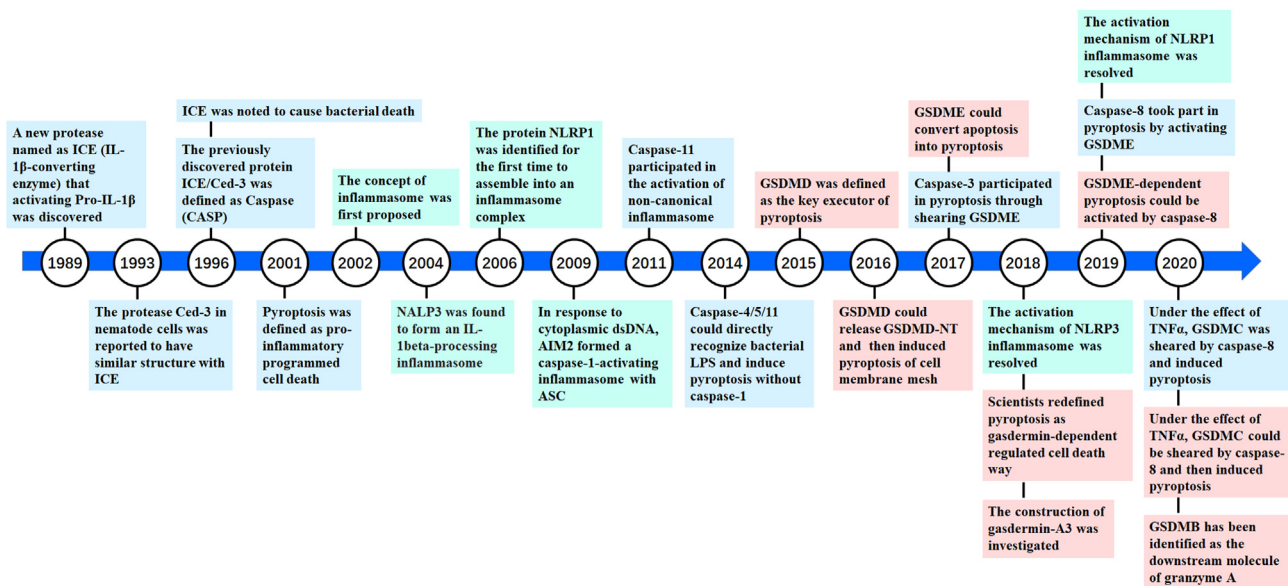


Figure 1 The timeline of key discoveries of inflammasomes, caspases and gasdermin family in pyroptosis. The light green landmarks indicated the roles of inflammasomes in pyroptosis. The light blue landmarks indicated the roles of caspases in pyroptosis. The light red landmarks indicated the roles of gasdermin family members in pyroptosis.

calreticulin) are utilized as damage-associated molecular patterns (DAMPs) to induce NLRP3-mediated pyroptosis within a few hours.³¹ NLRP3-induced caspase-1-dependent pyroptosis can lead to hematopoietic stem cell death in MDS patients. In the bone marrow mononuclear cells, the NLRP3 expression in MDS patients is 48 times higher than that of the average person, while the expression level of caspase-3 is identical to that of the normal.^{32,33}

AIM2 inflammasome

AIM2 inflammasome was initially discovered and manifested a decreased level in melanoma.³⁴ Furthermore, it is inactivated or mutated in various tumors, including endometrial cancer, gastric cancer, and colon cancer.^{35,36} AIM2 was regarded as a tumor suppressor gene in the early years. Later AIM2 was demonstrated to be overexpressed in nasopharyngeal carcinoma and non-small cell lung cancer (NSCLC).³⁷ This indicates that AIM2 may play various roles in different tumors. AIM2 contains an N-terminal PYD domain and a positively charged HIN-200 domain.³⁸ HIN-200 domain can form an electrostatic attraction with the negatively charged cytoplasmic dsDNA sugar-phosphate backbone, and the Pyrin domain binds to ASC (apoptosis-related dot-shaped protein containing caspase activation and recruitment domains) to activate NF- κ B and caspase-1.^{39–42} Compared with normal mice, mice lacking AIM2 were proved to have higher expression of colon cancer. This kind of tumor is caused not by the activation of inflammasome and IL-1 β but by the non-bone marrow-derived AIM2.⁴³ In addition, Corrales et al found that the activation of AIM2 inflammasomes in mouse macrophages and dendritic cells inhibited the functional output of the STING pathway, a key signaling pathway involved in the spontaneous anti-tumor innate

immune response.⁴⁴ Sirtuin 1 (a homolog of mammalian yeast Sir2) can provide an enabling environment for HPV-infected cervical cancer cells through neutralizing AIM2 inflammasome-mediated immunity. Knockdown of Sirtuin 1 enhances the inflammasome-mediated pyroptosis and cellular antiviral immunity by weakening the NF- κ B-driven transcriptional repression of the AIM2 gene.⁴⁵

Other inflammasomes

Vrentas et al found that in different species, *Bacillus anthracis* lethal toxin (LT) could activate NLRP1 inflammasomes by N-terminal proteolysis, resulting in macrophage pyroptosis and innate immune responses.⁴⁶ Inhibitors of dipeptidyl peptidases 8 and 9 (DPP8/9) could activate CARD8 or NLRP1 inflammasomes, leading to rapid pyroptotic cell death in resting lymphocytes of rodents and humans. Interestingly, activated CD4⁺ and CD8⁺ T cells are resistant to DPP8/9 inhibitors.⁴⁷ These inconsistent results may be attributed to different molecular characteristics in resting and activated T cells. Potential inflammasome-based immunotherapy strategies are expected to be provided if we can clarify the underlying mechanisms for sensibilizing DPP8/9 inhibitors. Activation of NLRP1 inflammasomes was associated with diseases of the skin and other epithelial tissues.⁴⁸ Thus, interference with the NLRP1-dependent pyroptosis could be a potential therapeutic strategy for controlling NLRP1 dysfunction-induced diseases.

After lung infection with *Staphylococcus aureus*, the NLRP6 knockout (KO) mice presented a higher survival rate than wild-type (WT) mice. Deactivation of NLRP6 could increase NADPH oxidase-dependent ROS production and inhibit NLRP6-mediated pyroptosis, thereby enhancing the anti-infection function of neutrophils. These results

suggested that NLRP6 inhibitors might become promising drugs to treat Gram-positive pathogen infection.⁴⁹ Activation of NLRP6 inflammasome also regulates periodontitis. *Porphyromonas gingivalis* infection could activate caspase-1 and gasdermin-D by promoting the production of the NLRP6 inflammasome, thus inducing pyroptotic cell death in gingival tissue of periodontitis.⁵⁰ Infection of *Salmonella enterica* serovar Typhimurium, a type of Gram-negative pathogen, could enhance the caspase-1 activation and proinflammatory cytokine secretion by triggering NAIP/NLRC4 inflammasome assembly, thus inducing pyroptosis of infected human macrophages. Moreover, further exploration of detailed regulation mechanisms could provide a theoretical strategy for controlling *Salmonella* in host immune response.⁵¹ Conditional inhibition of Nlrp9b inflammasome components improved the ability of hosts to resist rotavirus infection, indicating that Nlrp9b inflammasomes might play a critical role in limiting rotavirus infection.⁵²

Caspase family

The caspase family played a pivotal part in natural immune defense.⁵³ Cysteiny aspartate proteinases (caspases) are a group of cysteine proteases that significantly influence the cell death pathway of cancer. Further investigation of the underlying mechanisms of caspase activation will promote the clinical treatment of inflammatory diseases and malignant tumors.⁵⁴

Caspase-1

Caspase-1 was first reported in 1989 and can convert the IL-1 beta precursor into mature ones.⁵⁵ Cells after D089 (a benzofuran that can induce cell death in multiple myelomas) treatment showed a high expression level of sheared executioner caspase 8 and activated effector caspase 1. This suggested that D089 might have the potential to treat multiple myeloma.⁵⁶ A549 NSCLC cells secrete IL-1 β after sea hare hydrolysate (SHH) treatment, showing caspase-1-dependent pyroptosis. It should be noted that the activation of caspase-1 will be inhibited by the combination of colivelin (a STAT3 activator) and SHH, which suggests that inhibition of STAT3 and the utilization of SHH may have the potential for lung cancer treatment through pyroptosis.⁵⁷ Intriguingly, relying on the recruitment of E3 ligase TRIM21 for the ubiquitination and degradation of IFI16 inflammasomes, HPV E7 could inhibit AIM2 inflammasome-dependent pyroptosis, thus evading the attack of innate immunity.⁵⁸ Takasu et al has found that mice infected with squamous cell carcinoma (SSC) at high multiples of infection (MOI) produced DAMPs after inducing cell death by RH2 infection. This process could be inhibited by z-VAD-fmk (a pan-caspase inhibitor) and z-YVAD-fmk (a caspase-1 inhibitor), implying the involvement of pyroptosis.⁵⁹ Of note, a recent study has shown that active caspase-1 could be added as an adjuvant to anti-melanoma DNA vaccines to activate lymphocyte responses and improve the anti-cancer effect of vaccines. This study provides new ideas for the pyroptosis application in clinic.⁶⁰

Caspase-4/5

Without inflammatory complexes, human caspase-4/5 or mouse caspase-11 can detect lipopolysaccharide (LPS) released by gram-negative bacteria and induce pyroptosis. Then, with the outflow of cell K ions, the NLRP3 inflammasome is activated and finally induces pyroptosis, leading to the shearing of pro-IL-1 β and pro-IL-18.^{53,61} Yokoyama et al has reported that secretoglobin family 3A member 2 (SCGB3A2) could induce pyroptosis in non-classical inflammatory pathways via delivering cytoplasmic LPS to the cytoplasm. SCGB3A2 exerts antitumor effects on lung cancer cells. These findings might have a certain potential value for cancer treatment.⁶² Jiao et al has discovered that in the pyroptosis of breast cancer MCF7 cells, the expression level of caspase-4 was upregulated. As a pyroptosis-associated gene, caspase-4 was involved in the noncanonical pathway of cell pyroptosis.⁶³

Gasdermin family

In 2015, another inflammatory caspase effector protein, i.e., GSDMD, was found after the discovery of IL-18/IL-1 β , and pyroptosis was defined as gasdermin-mediated programmed death.^{64–66} GSDMD is a member of a protein superfamily, which is encoded by six genes in the human genome: gasdermin A/B/C/D (GSDMA/B/C/D),^{67–71} gasdermin E (GSDME, also known as DFNA5) and DFNB59 (Pejvakin, PJVK).⁷² In addition to DFNB59, the mastermind usually comprises a cytotoxic domain (named the N-terminal domain) and a repressor protein domain (named the C-terminal domain), which are connected by a flexible linker, which releases the cytotoxic domain after being cut by caspase. The activated gasdermin N-terminal can directly contact cell membrane lipids to form an oligomeric pore. The oligomeric pore results in imbalanced ions inside and outside the cell, causing cell death.^{72–77}

GSDMD

A GSDMD-recognition model can be constructed by combining caspase-4/11 with GSDMD, a pyroptosis protein. The combined structure of caspase-4/11 and GSDMD-C can insert the tetrapeptide into the catalytic part. These findings implied that GSDMD-C might be a crucial factor in cell pyroptosis.⁷⁸ Moreover, LPS could contribute to pyroptosis mediated by the GSDMD signaling pathway.⁷⁹ Additionally, GSDMD was the vital molecule of adipocyte pyroptosis suppressed by melatonin. The synergy between GSDMD and interferon regulatory factor 7 (IRF7) can also induce adipocyte pyroptosis.⁸⁰ Two reports from Okondo et al identified that Val-boroPro (Talabostat, PT-100), the inhibitor of serine protease DPP8/DPP9, could activate the inflammasome sensor protein Nlrp1b, thereby activating pro-caspase-1 to induce GSDMD cleavage. After then, Val-boroPro treatment induced pyroptosis of monocytes and macrophages to activate anti-tumor immunity.^{81,82} Intriguingly, without GSDMD, caspase-1 activated caspase-3/7 to induce cell apoptosis. Moreover, caspase-3/7 cleaved GSDMD by acting on the site different from that of

inflammatory caspase and disabled GSDMD, blocking pyroptosis.⁸³ These studies have indicated that the GSDMD-mediated signaling network participated in the anti-tumor immune response.

GSDME

GSDME was first cloned as a deafness gene and was originally named *DFNA5*.⁸⁴ As a member of the gasdermin family of membrane punching proteins, GSDME exerts its function not merely in the hearing system and thus was named gasdermin-E.⁸⁵ Recent studies have revealed the positive connection of fusions of long noncoding RNA (lncRNA) with DNA damage and cancer stemness. The chimeric protein EPS15L1-lncOR7C2-1 produced by mRNA-lncRNA fusion can promote tumors by regulating GSDME-dependent pyroptosis probably, suggesting that lncRNA fusions might play a key role in regulating tumor immunity by pyroptosis.⁸⁶ Decitabine inhibits DNA methylation to increase the expression level of GSDME. Indocyanine green (ICG) increased the cytoplasmic Ca^{2+} concentration through low-dose infrared light to promote cytochrome C release and caspase-3 activation. After then, the caspase-3-mediated GSDME-dependent pyroptosis could be obviously induced. Furthermore, photo-activated pyroptosis mediated by ICG-loaded biomimetic nanoparticle could inhibit primary and metastatic solid tumors and provide a new tactic for the immunotherapy of solid tumors.⁸⁷ In colon cancer cells, lobaplatin upregulated the levels of reactive oxygen species (ROS) and phosphorylation of JNK. In addition, the transfer of Bax to mitochondria was further enhanced via provoking JNK, which initiated caspase-3, triggered the lysis of GSDME and ultimately induced colon tumor pyroptosis.⁸⁸ In addition, Ding et al found that dioscin could also induce the production of GSDME-N and activate pyroptosis to inhibit the proliferation of osteosarcoma cells.⁸⁹ Recent evidence suggested that BRAF inhibitors and MEK inhibitors (BRAFi + MEKi) could promote the release of GSDME lysate and HMGB1 in melanoma, inducing pyroptosis and inhibiting tumor development. Significantly, BRAFi + MEKi-resistant diseases reduced T cell infiltration in tumors. Moreover, pyroptosis-mediated chemotherapy exerted a significant effect and provided new ideas for future treatments of melanoma.¹⁶ A recent study has shown that GSDME expression levels have a significant advantage in predicting immune cell infiltration of hepatocellular carcinoma (HCC) and lung adenocarcinoma (LUAD).⁹⁰ Epigenetic silencing mediated by DNA methylation resulted in the non-expression of GSDME in some cancer cells. Moreover, many normal tissues exhibited high expression of GSDME. When caspase-3 was activated by chemotherapeutic drugs, many normal tissue cells activated the shearing of GSDME and were killed by pyroptosis.^{91–93} Due to the low sensitivity of cancerous tissue and the toxicity of surrounding normal tissue, radiation therapy was difficult to apply to colorectal cancer (CRC). After receiving radiotherapy, mice with low GSDME expression presented greater anti-tumor immunity and less damage to surrounding tissues such as intestines and livers than normal mice.⁹⁴ In addition, by increasing the dose, ionizing radiation (IR) could upregulate GSDME-dependent pyroptosis to kill human CRC cells HCT116, which was

closely related to the lncRNA NEAT1 modulation of miR-448 expression, rather than the activation of GSDME.⁹⁵

Other gasdermin family members

In the hypoxic environment, STAT3 phosphorylation promotes PD-L1 nuclear translocation and GSDMC transcription. After TNF α treatment, caspase-8 specifically cleaves GSDMC and generates N-GSDMC to form pores on the cell membrane and facilitate pyroptosis.⁹⁶ It has been reported that more than half of patients with serum ovarian cancer showed elevated expression levels of GSDMC and GSDMD, indicating that pyroptosis might be related to the occurrence and development of ovarian cancer. However, the specific mechanism still remains unclear.⁹⁷

Pyroptosis and tumor immunotherapy

RIG-I agonists have been identified to activate caspase-1 in breast cancer cells, inducing gasdermin D-dependent pyroptosis and tumor cell death. RIG-I activation in tumor cells could induce the accumulation of tumor lymphocytes and reduce tumor migration and growth, providing a basis for the application of RIG-1 agonists in the clinical treatment of breast cancer.⁹⁸ Luteolin is a natural flavonoid compound and could inhibit cell proliferation of NSCLC and epithelial–mesenchymal transition (EMT) by inhibiting AIM2 expression.⁹⁹ High expression of hepatitis B virus X protein (HBx) could downregulate AIM2 expression and promote the metastasis of liver cancer cells. CircNEIL3, a type of circular RNAs (circRNAs), showed a downward trend after A549 cells received increasing-dose radiotherapy, while pyroptosis and anti-tumor effects presented an upward trend. This suggested that inhibitors of circNEIL3 might be a potential adjuvant to enhance the efficacy of radiation therapy for lung cancer.¹⁰⁰

Moreover, HBx can induce AIM2 ubiquitination degradation, indicating a potential therapeutic effect of AIM2 on tumor metastasis.¹⁰¹ Furthermore, the underlying mechanisms of inflammasomes in anti-cancer immunity regulated by CD8⁺ T cells have been investigated; the results showed that inflammasomes with overexpressed dendritic cells could trigger anti-cancer activities mediated by CD8⁺ T cells, conducive to immunotherapy.¹⁰² Pyroptosis could stimulate immune responses, and pyroptosis-associated treatment has been advanced clinically. Pyroptosis and pyroptosis-activated molecules could trigger the tumor immune microenvironment.

Additionally, those molecules could activate immune systems and promote immunotherapy. Pyroptosis presented a strong relationship with PD-1 and programmed death-ligand 1 (PD-L1).¹⁰³ It could suppress cancer cell growth and induce cell proliferation. Moreover, it could activate inflammation and trigger immune responses. According to the immune systems, pyroptosis-related activators could exert anti-cancer effects on tumor cells.¹⁰⁴ The release of molecules activated by pyroptosis could enhance the effects of immune checkpoint blockade (ICB) therapy. On this basis, the ROS/glutathione was established, which contributed to the nano-prodrug response and finally found

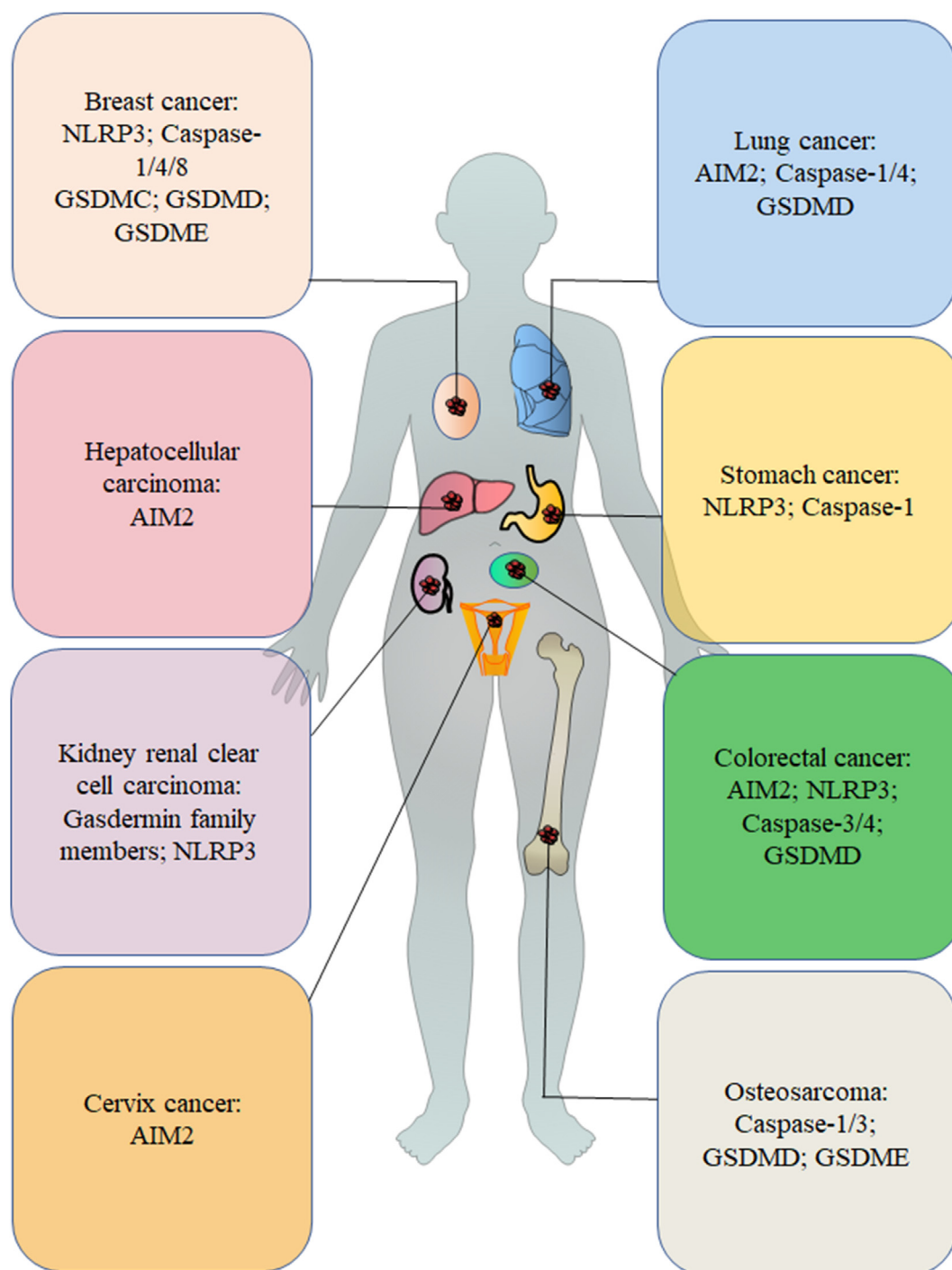


Figure 2 Schematic of pyroptosis-associated biomarkers in many different forms of cancers. The profiles of pyroptosis-related molecules have been proved to be well-established mediators of immune response, affecting the tumor progression and therapeutic response. These organic hallmarks presented the tissues associated with cancers, including breast cancer, lung cancer, colon cancer and so on.

an appropriate drug release in cancer cells. Damage-associated molecular patterns (DAMPs) triggered by pyroptosis could activate cancer immunity and decrease recurrence. The present study pointed out that using nano-prodrug, the chemo-photodynamic treatment could be more favorable in pyroptosis induction and ICB effect improvement.¹⁰⁵

Discussion

Pyroptosis is a programmed cell death pathway that relies on hydrolysis of the gasdermin protein family. The pyroptosis mechanism has been described clearly in recent years. The activation of caspase1/4/5 contributed to the release

of proinflammatory molecules and mediated the GSDMD pathway.¹⁰⁶ Pyroptosis participated in various kinds of human diseases, including cancers (Fig. 2). It played a significant role in osteoarthritis. Inflammasomes, including NLRP3, could be a diagnostic biomarker and potentially be used in osteoarthritis treatment in clinical.¹⁰⁷ Moreover, the inhibition of pyroptosis-associated molecules, like caspases and IL-1, could influence liver disease development. However, suppressing inhibition might lead to opportunistic infection.¹⁰⁸ To ameliorate the condition of diabetic kidney disease, some strategies have been employed to interfere with the pyroptosis pathway of *in vivo* and *in vitro* models. The regulation of cell pyroptosis could provide novel approaches to alleviate diabetic kidney disease.¹⁰⁹ Moreover, pyroptosis was crucial in malignant tumors as it participated in the tumor progression induced by the adverse tumor microenvironment.¹¹⁰ Yao et al demonstrated that gasdermin family members of abnormal expression and methylation are potential therapeutic targets and immunoregulatory biomarkers for patients with kidney renal clear cell carcinoma.¹¹¹ Dual prognostic signatures based on pyroptosis- and immune-associated genes could be used to predict the immunotherapy efficacy in kidney renal clear cell carcinoma patients.¹¹² In addition, downregulation of bromodomain containing protein 4 (BRD4) could decrease cell proliferation and EMT in renal cell carcinoma cells via activating the death of NLRP3 inflammasome-mediated pyroptotic cell.¹¹³ Furthermore, miltirone could trigger pyroptosis by inducing ROS accumulation and suppressing cancer cell proliferation in the syngeneic murine HCC Hepa1-6 model. The result implied that miltirone could be applied in HCC therapy by mediating pyroptosis through the GSDME signaling pathway.¹¹⁴ DPP8/9 inhibitors were identified to exert antitumor activities on acute myeloid leukemia (AML) via inducing pyroptosis in AML cells. They could also suppress AML development in animal models.¹¹⁵ Pyroptosis is mediated by some inflammasomes and trigger cell death in different kinds of cancers, including gastric cancer, HCC and CRC.¹¹⁶

M1 and M2 macrophages were linked to pyroptosis activation in response to various stimuli.¹¹⁷ In sepsis-related acute lung injury (ALI), exosomes induced by polymorphonuclear neutrophils (PMNs) could initiate the transformation of macrophages to the M1 phenotype, through which pyroptosis was induced and the severity of lung inflammation increased.¹¹⁸ Monaco et al has found that intra-tumoral infection of *Salmonella* in melanoma mice contributed to a shift in the M1 phenotype of macrophages and caused caspase-1/11-dependent pyroptosis.¹¹⁹ However, detailed mechanisms of the correlation between M1 or M2 macrophage and pyroptosis require further elucidation. The exploration of pathways and factors could provide strategies for the future development of immunotherapy.

During cancer therapy in clinic, many cancers cells become insensitive or resistant to anti-cancer drugs, making it necessary to explore other novel anti-cancer alternatives. In recent years, several chemotherapeutic drugs have been discovered to reduce the growth and metastasis of cancer cells by inducing pyroptosis, such as baplatin,⁸⁸ luteolin,⁹⁹ doxorubicin,¹²⁰ cisplatin,¹²¹ taxol,¹²² and anthocyanin.¹²³ These drugs induce pyroptosis through different signaling pathways (classical or non-classical) for cancer treatment.

Additionally, it is significant to clarify the mechanism of drug action in pyroptosis. Furthermore, selectively finding target biomarkers of these pathways could contain the complications within an acceptable range. Ac-FLTD-CMK, a GSDMD-derived inhibitor, was found to reduce the nephrotoxicity induced by cisplatin or doxorubicin by inhibiting caspase-3-related pyroptosis.¹²⁴ The concomitant application of vitamin D with cisplatin has been proven to alleviate pyroptosis of normal tissue cells by inhibiting GSDME.¹²⁵ Radix Ophiopogon Japonicus, a traditional Chinese medicine commonly used for lung disease treatment, presented an evident advantage in lowering cisplatin-resistant A549 (A549/DDP) with its active ingredient Ophiopogonin B (OP-B).¹²⁶

Notably, GSDME is unexpressed in most cancer-derived cell lines of *in vitro* culture. In addition, in few cancer cell lines with a high expression of GSDNE, treatment with traditionally chemotherapeutic agents caused DNA damage, which induced caspase-3 activation and shearing of endogenous GSDME, intense pyroptosis and killing of cancer cells.¹²⁷ Epigenetic silencing mediated by DNA methylation resulted in GSDME non-expression in some cancer cells. Moreover, many normal tissues exhibited high expression of GSDME. When caspase-3 was activated by chemotherapeutic drugs, many normal tissue cells activated the shearing of GSDME and were killed by pyroptosis,^{91–93} suggesting the highly toxic side effects of some conventional chemotherapeutic drugs. How to increase GSDME expression in cancer cells and decrease GSDME expression in normal tissue cells with clinical application is expected to be addressed in the future.

Various kinds of signaling pathways and biomarkers, e.g., inflammatory molecules, caspase family and gasdermin family members, are involved in cancer pyroptosis (Table 1). Although the impact of inflammatory cell death on the immune system has been continuously explored, it is still insignificant for further study in this field. As the final executor of pyroptosis, the gasdermin protein plays a crucial role in pyroptosis occurrence through its expression. Among them, gasdermin-D and gasdermin-E are members studied in detail, and gasdermin-A, B, and C also have N-terminal domains. Recent studies have shown that Granzyme-A could enter target cells via perforin and induce pyroptosis by hydrolyzing GSDMB.¹⁸ The role of other gasdermin proteins in pyroptosis still needs further exploration. In addition, the cleaver of the gasdermin protein was not limited to the caspase family. For example, Zhang et al verified the cleavage of gasdermin-E by another serine protease, i.e., Granzyme B, and induced gasdermin-E-dependent pyroptosis.⁸⁵ They concluded that pyroptosis could only be activated by the caspase family, indicating that more research is needed on the upstream molecules of gasdermin. In addition to GSDMD and GSDME studied in detail, how are the other family members activated? Which physiopathology are they in to play a role? Is there any specificity for different tissues or organs? Which molecules in these signaling pathways of gasdermin proteins could be targeted? Could their expression levels be artificially up- or down-regulated? Although pyroptosis activation usually appears as an anti-tumor response, it is hard to conclude whether the additional cell pyroptosis exerts a positive or negative effect on cancer patients.

Table 1 The signaling pathways and biological functions of pyroptosis in cancers.

Cancers	Signaling pathways	Modulated factors	Pyroptosis	Biological functions	References
Squamous cell carcinoma	Caspase-1 mediated pathway	RH2	Induce	Inducing cell death, enhancing antitumor immunity	59
Solid tumor	GSDME-dependent pathway	ICG	Induce	Inducing antitumor immunity	87
Osteosarcoma	GSDME-dependent pathway	Dioscin	Induce	Inhibiting cancer cell growth	89
Lung cancer	Caspase-1 mediated pathway	SHH	Inhibit	Exerting anticancer effects	57
	AIM2 inflammasome-dependent pathway	Luteolin	Inhibit	Contributing to non-small cell lung cancer treatment	99
Multiple myeloma	Caspase-1 mediated pathway	D089	Induce	Inducing cell death	56
Melanoma	GSDME-dependent pathways	BRAF, MEK, HMGB1	Inhibit	Inhibiting cell pyroptosis	16
Hepatocellular carcinoma	AIM2 inflammasome-dependent pathway	HBx	Inhibit	Contributing to hepatocellular carcinoma metastasis	101
Gastric cancer	NLRP3 inflammasome-dependent pathway	Helicobacter	Inhibit	Inducing gastric tumorigenesis	27
Cervical cancer	GSDMD-dependent pathway	HPV E7	Inhibit	Inhibiting cell pyroptosis	58
	AIM2 inflammasome-dependent pathway	Sirtuin 1	Inhibit	Enabling HPV-infected cervical cancer cells to continue growing	45
Breast cancer	GSDMC/caspase-8 mediated pathway	PD-L1, STAT3	Induce	Switching TNF α -induced apoptosis to pyroptosis in cancer cells	96
	GSDME-dependent pathway	lncRNA, the fusion of KDM4B and EPS15L1		The EPS15L1 fusion protein may regulate GSDME-dependent pathways	86
	GSDMD-dependent pathway	RIG-I	Induce	Increasing tumor lymphocytes and decreasing tumor growth and metastasis	98
	NLRP3 inflammasome-dependent pathway	DCs	Induce	Attacking tumors that are sensitive or resistant to PD-1 inhibition	132
	NLRP3 inflammasome-dependent pathway	H-FIRE	Induce	Attenuating tumor progression via immune systems	31
Colorectal cancer	AIM2 inflammasome-dependent pathway	IFN- β , TANK-binding kinase 1, IFN regulatory factor 3	Induce	Reducing activation of the STING pathway, Slowing down tumorigenesis	44
	Caspase-4/11 mediated pathway	SCGB3A2	Induce	Eliminating cancer cells	62

Recently, several studies have revealed that pyroptosis was significantly correlated to the immune regulation of tumors. The study of immune systems is a vital approach to exploring human biology. Immune cells could sensitively discover minute changes in human bodies.¹²⁸ GSDME could suppress the cell proliferation of breast cancer through immune cells such as CD8⁺ T cells and NK cells. GSDMB

could enhance cell growth inhibition through synergized effects of the anti-PD-1 blockade and pyroptosis.¹²⁹ Pyroptosis plays a crucial role in innate immunity by combining beneficial and worse effects. GSDMD served as the executioner of pyroptosis. Both GSDME and GSDMA were significantly associated with autoimmune diseases and some cancers.¹³⁰ The complex of inflammasomes could

activate the production and pyroptosis of IL-1 β and IL-18. Of all the inflammasomes, NLRP3 participated in cancer progression.¹³¹ Hyperactivating stimuli might exert anti-cancer activities mediated by cytotoxic T lymphocyte (CTL), and the hyperactivation of dendritic cells could yield protective effects. These results pointed out a new target for DC-related immunotherapy.¹³² Both animal experiments and *in vitro* trials concerning HCC have revealed that macrophages and NK cells were beneficial for inhibiting cancer cell growth. Macrophages treated with sorafenib could trigger pyroptosis progression and decrease tumor responses to immunotherapies.¹³³

Conclusion

In conclusion, exploration of underlying pyroptosis mechanisms of human diseases, especially cancer, will provide a new perspective for future clinical treatment. Various pyroptosis-related pathways participated in tumor immune responses, including inflammasomes, caspases, and the gasdermin family. Pyroptosis is a cell death pathway and plays a significant role in the immune regulation of cancer. Some trials *in vivo* and *in vitro* showed the great effects of pyroptosis on anti-cancer immunity, implying that research on pyroptosis can promote immunotherapy application. Research on the correlation between pyroptosis and malignant tumors can be found. Such being the case, more studies are still required to figure out the mechanisms of the relationship between pyroptosis and clinical therapy. Furthermore, the investigations of immunotherapy employment are also necessary for further cancer treatment.

Author contributions

Liu W, Peng J, Xu Z and Yan Y contributed to the conception and design of the study. Liu W, Xiao M, Cai Y, Peng B, Zhang W and Yan Y contributed to the writing, review, and revision of the manuscript. Li J, Kang F, Hong Q and Liang Q performed the administrative, technical and material support. All authors approved the final version of the manuscript.

Conflict of interests

The authors declare that there are no conflicts of interest.

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Abbreviations

ALI	acute lung injury
AML	acute myeloid leukemia
BRAFi + MEKi	BRAF inhibitors and MEK inhibitors
circRNAs	circular RNAs
CRC	colorectal cancer
CTL	cytotoxic T lymphocyte
DAMPs	damage-associated molecular patterns
DPP8/9	dipeptidyl peptidases 8 and 9
EMT	epithelial–mesenchymal transition
HBx	hepatitis B virus X protein
H-FIRE	high-frequency irreversible electroporation
ICB	immune checkpoint blockade
IFN- γ	interferon- γ
ILs	interleukins
IR	ionizing radiation
KO	knockout
LIHC	liver hepatocellular carcinoma
lncRNA	long noncoding RNA
LPS	lipopolysaccharide
LT	lethal toxin
LUAD	lung adenocarcinoma
mAbs	monoclonal antibodies
MDS	myelodysplastic syndromes
MOI	multiples of infection
NSCLC	non-small cell lung cancer
OP-B	Ophiopogonin B
OS	osteosarcoma
ox-mtDNA	oxidized mitochondrial DNA
PD-1	programmed cell death-1
PD-L1	programmed death-ligand 1
pHCE	primary human corneal epithelial
PJVK	Pejvakin
PMNs	polymorphonuclear neutrophils
ROS	reactive oxygen species
SCGB	secretoglobulin
SHH	sea hare hydrolysates
SSC	squamous cell carcinoma
WT	wild-type

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