What role does pyroptosis play in cancer?

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ABSTRACT

Background: Pyroptosis has been attracting much attention recently. We have briefly compared its differences and similarities with other programmed deaths and the process of its study. With further exploration of the caspase family, including caspase-1/3/4/5/8/11, new insights into the molecular pathways of action of pyroptosis have been gained. It is also closely related to the development of many cancers, which at the same time provides us with new ideas for the treatment of cancer.

Scope of Review: We describe what is known regarding the impact of pyroptosis on anticancer immunity and give insight into the potential of harnessing pyroptosis as a tool and applying it to novel or existing anticancer strategies.

Major Conclusions: Pyroptosis, a caspase-dependent cell death, causes pore formation, cell swelling, rupture of the plasma membrane, and release of all intracellular contents. The role of pyroptosis in cancer is an extremely complex issue. There is growing evidence that tumor pyroptosis has anti-tumor and pro-tumor roles. It should be discussed in different cancer periods according to the characteristics of cancer occurrence and development. In cancer treatment, pyroptosis provides us with some potential new targets. For the existing drugs, the study of pyroptosis also helps us make better use of existing drugs for anticancer treatment. Immunotherapy is a hot research direction in the field of cancer treatment.

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Keywords Pyroptosis; Cancer; Caspase; Gasdermin

1. INTRODUCTION

Cell death has numerous benefits on the health and function of the body, especially in cancer treatment [1]. There are mainly two types of cell death, necrosis and programmed cell death (PCD). Necrosis is a passive type of cell death that occurs as a result of pathological stimulation. The permeability of the plasma membrane of necrotic cells increases, which causes the cells to swell and rupture, thereby releasing the cellular content and leading to inflammation. Pyroptosis, apoptosis, autophagy, and necroptosis are manifestations of PCD. PCD is a process in which cells receive certain signals or are stimulated by certain factors to maintain the stability of the internal environment (Table 1) [2–4]. Apoptosis is a type of PCD in which genes control the mechanical self-destruction of cells, but the cell membrane remains intact, and the process does not induce an inflammatory reaction [3]. Recently, pyroptosis, a necrotic and lytic PCD, has attracted considerable attention for its capacity to elicit inflammatory response [6]. It was first studied in the context of immune defense against pathogens [7]. Pyroptosis is a critical immune response mechanism in organisms that inhibits infections and endogenous injury signals. It plays a significant role in the development of tumors, infectious diseases, metabolic diseases, neurological-related diseases, and atherosclerotic diseases [8] (Tables 2 and 3).

Although the precise mechanism by which pyroptosis participates in the tumor process is unknown, it is thought to have a dual role in tumor pathogenesis. The various signaling pathways and inflammatory mediators released during pyroptosis are directly associated with carcinogenesis and drug resistance to chemotherapeutic medicines. Pyroptosis acts as a type of cell death that prevent the occurrence and growth of tumors [9]. The role of pyroptosis in tumors is increasingly being studied. The purpose of this study is to discuss and assess the potential effects of pyroptosis on cancer as well as its role in anticancer treatment.

2. CHARACTERISTICS OF PYROPTOSIS

The term pyroptosis is derived from a Greek root "pyro", meaning fire or fever, and "ptosis", meaning decline. This term is used to describe a new type of proinflammatory PCD [7]. Pyroptosis, also known as gasdermin-mediated programmed necrosis, is a new type of PCD triggered by innate immunity-related disruptions of extracellular or intracellular homeostasis [5,10]. Pyroptotic cells are similar and yet distinct from apoptotic and necrotic cells in certain aspects. While pyroptosis and apoptotic cells share chromatin condensation and DNA fragmentation, they can be distinguished by their intact nucleus, cell swelling, pore formation, and osmotic lysis [11]. Pyroptosis, like necrosis, results in cell membrane pore formation, membrane rupture, and cellular swelling, all of which trigger the release of cellular contents and proinflammatory mediators, including IL-1β and IL-18 [12].

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Pyroptosis is a type of caspase-1 mediated PCD that is morphologically distinct from apoptosis, and it was first discovered by Arturo et al., in 1992 [13]. In 1997, Shigella dysenteriae was found to activate caspase-1 in host cells [14]. Another study in 1999 demonstrated that inhibiting caspase-1 prevented Salmonella-induced cell death [15]. It was until 2001 that Cookson et al. referred to such a proinflammatory PCD as “pyroptosis” [7]. Numerous studies have since been conducted on pyroptosis. In 2015, gasdermin D (GSDMD) was discovered to be a target for caspase-1 and caspase-4, 5, and 11 cleavages [16,17]. Additionally, emerging evidence demonstrated that other members of the gasdermin superfamily protein like gasdermin E (GSDME) are activated by caspase-3 to cause pyroptosis [18,19]. Recent studies have demonstrated that pathogen-induced or pharmacological inhibition of the kinase transforming growth factor-β (TGF-β)-activated kinase 1 (TAK1) or the inhibitor of apoptosis (IAP) can stimulate caspase-8 production and GSDMD cleavage to elicit pyroptosis [20–22].

### Table 1 — Comparison of several modes of cell death.

| Type Causes | Apoptosis | Autophagy | Pyroptosis | Necroptosis | Necrosis |
|-------------|-----------|-----------|------------|-------------|----------|
| Apoptosis   | PCD       | PCD       | PCD        | PCD         | Non-PCD  |
| Causes      | Gene regulation under physiological conditions | Nutritional deficiency or hormonal induction | Inflammasome stimulation | Pathological irritation or violent injury | Pathological process |
| Morphology  | Dying cell shrinkage; nucleus condense and fragmented apoptotic bodies | Accumulation of autophagic vacuoles | Cell swelling and deformation with violent inflammatory response | Swelling of cytoplasmic organelles | Cell swelling and lysis |
| Cell Integrity | Integrity | Rupture | Rupture | Rupture | Rupture |
| Membrane Degradation to 180—200 bp and its integer multiples | Random degradation and no chromatin condensation | Random degradation | Random degradation | Random degradation |
| DNA         | Degradation to 180—200 bp and its integer multiples | Random degradation and no chromatin condensation | Random degradation | Random degradation | Random degradation |

### Table 2 — (A) Expression of pyroptotic components in cancers. (B) The pathway of different cancers.

| Cancer type | Level of pyroptotic components | Associated consequences | References |
|-------------|--------------------------------|-------------------------|------------|
| (A) Esophagus cancer | NLRP3 ↑ | cell death and Barrett’s esophagus | [61] |
| Gastric cancer | GSDMD ↓ | cancer cell proliferation | [62] |
| | GSDMA ↓ | anti-oncogenic factor | [70,71] |
| | GSDMB ↑ | control tumor infringement | [49] |
| | GSDMC | cancer suppressor gene | [73] |
| | DPNA/GSDME signaling pathway | pyroptosis facilitates GC progression | [62] |
| Hepatocellular carcinoma | Caspase-1 protein ↓ | Tumor proliferation | [80,84] |
| | AIM2 ↑ | Promote pyroptosis and antitumor effects | [85,87] |
| Colorectal cancer | Caspase-1 ↑ | Promote epithelial cell proliferation and apoptosis | [54] |
| | Lack of AIM2 | Poor prognosis in CRC | [88] |
| | NLRP1 ↓ | Tumor progression | [86,89] |
| | GSDMC ↓ | Tumor cell proliferation | [70,73] |
| | GSDMD ↓ | Poor prognosis in CRC | [83] |
| | GSDME ↑ | Increase proliferation | [94] |
| Lung cancer | GSDMD ↓ | Tumor proliferation | [85,86] |
| | Knocking out GSDME | Flip from apoptosis to pyroptosis | [97] |
| Cervical cancer | Caspase-1 ↑ | Lower tumor weight and volume | [106] |
| | GSDMD ↑ | Lower tumor weight and volume | [92,105] |
| | NLRP1 ↑ | Lower tumor weight and volume | [105,106] |
| Ovarian cancer | GSDME ↓ | OC progression | [109] |
| | GSDMD ↓ | OC progression | [110] |
| | Caspase-4 ↓ | OC progression | [110] |
| Breast cancer | GSDMB ↑ | Metastasis | [117] |
| | GSDME ↓ | Metastasis | [79] |
| | GSDMD ↑ | Caustic death | [119] |
| Skin cancer | GSDMC | Invasion and metastasis | [73] |
| Cancer types | The canonical inflammasome pathway | The noncanonical inflammasome pathway | Other pathways |
| (B) Esophagus cancer | ✓ | ✓ |
| Gastric cancer | ✓ | |
| Hepatocellular carcinoma | ✓ | |
| Colorectal cancer | ✓ | |
| Lung cancer | ✓ | ✓ |
| Cervical cancer | ✓ | ✓ |
| Ovarian cancer | ✓ | ✓ |
| Breast cancer | ✓ | |

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3. MECHANISMS OF PYROPTOSIS

3.1. The canonical inflammasome pathway
Pathogen-associated molecular patterns (PAMPs) and danger-associated molecular patterns (DAMPs) activate cells’ respective canonical inflammasomes in response to infection or immunological challenges, thereby forming a cytoplasmic-multiprotein oligomeric complex that ultimately activates an innate immune response. The inflammasomes are composed of the nucleotide-binding oligomerization domain (NOD)-like receptor (NLR) family (NLRP3, NLRP1, NLRC4, AIM2, or pyrin proteins, which contain N-terminal caspase recruitment domain (CARD) or pyrin domain (PYD) [12,24,25]. The NLRP1 inflammasome recognizes only Bacillus lethal toxins and muramyl dipeptide [26]. The NLRP3 inflammasome can be activated by a variety of membrane-damaging agents, including bacteria, viruses, reactive oxygen species (ROS), DAMPs, and pore-forming toxins [27–29]. NLRC4 inflammasomes are activated only by PAMPs such as type III secretion apparatus and bacterial flagellin [30,31]. The AIM 2 inflammasome was reported to be specifically activated by endogenous or pathogen-derived double-stranded DNA (dsDNA) [32,33]. Pyrin inflammasomes indirectly detect inactivating modifications to the host Rho GTPases [33].

These studies indicate that for the innate immunity of cells, although cells have specific perception factors for different heterologous substances or antigens, the formation of immune bodies is essential for the initiation of pyroptosis. Therefore, further investigations are needed whether there is a conserved molecular structure and mechanism basis in the process of immune corpuscle formation to generate ideas for developing therapeutic targets for pyroptosis-related diseases. When activated, many of these sensors interact with the receptor complex apoptosis-associated speck-like protein containing CARD (ASC), which recruits and cleaves procaspase-1 and activates caspase-1. Caspase-1 converts pro-IL-1 and pro-IL-18 into IL-1 and IL-18, respectively, which are then released through the necrotic pores of the membrane created by GSDMD-N, in addition to releasing and activating the lethal N-terminal domain of GSDMD (GSDMD-N) [34]. NLRC4 can specifically recruit procaspase-1 without forming ASC [35,36]. Caspases are a family of proteases that are activated by inflammasomes and regulate the innate immune system.

3.2. The noncanonical inflammasome pathway
Human caspases 4 and 5 and mouse caspase 11 are involved in noncanonical pyroptotic cell death [37,38]. The gram-negative bacterium’s CARD domain binds directly to lipopolysaccharide (LPS), thus triggering the noncanonical inflammasome pathway. Caspase-4/5/11 can cleave GSDMD directly into an N-terminal fragment and a C-terminal fragment. By lysing on liposomes containing phosphoinositide or cardiolipin or liposomes comprising natural polar lipid mixtures, the N-terminal domain of GSDMD can generate large gastermin pores that release free IL-1 and IL-18 outside the cell [10,16,17,39,40]. These pathways activate the pyroptotic process, which results in the efflux of K++, activating the NLRP3 inflammasome and upregulating caspase-1 activity [17]. Caspases 4/5/11 can also cleave the panexin1 (Panx-1) channel protein, resulting in ATP synthesis and activation of P2X purinoceptor 7 (P2RX7), which activates the NLRP3 inflammasome, leading to pyroptosis [41,42].

3.3. Other caspase pathways
Recent studies have also established that Caspase-3 and/or Caspase-8 signaling pathways play a critical role in pyroptosis [8,43]. Caspase-1/2/4/5/11 has previously been demonstrated to activate pyroptosis through GSDMD cleavage, whereas caspase-3 is an important hallmark of apoptosis. More recently, caspase-3 has been shown to influence and activate GSDMD to induce pyroptosis [18]. Caspase-3, which is involved in pyroptosis and expresses high levels of GSDMD through Apaf-1 can be activated by chemotherapy drugs in cancer and normal cells [18,19,44]. As a proapoptotic protease, caspase-3 may rapidly identify and cleave GSDMD stimulating pore formation and cell death by pyroptosis [19,45]. Pyroptosis is rapidly induced in the presence of high GSDMD levels, whereas apoptosis occurs in the low GSDMD levels [18]. Caspase-8 induces the cleavage of gastermin C (GSDMC) and GSDME to elicit pyroptosis. TAK-1 is an essential factor in regulating NF-κB signaling mechanisms [46]. It has been demonstrated that inhibiting TAK-1 with Yersinia outer protein-J (Yop-J) or other relatively minor inhibitors facilitates caspase-8-mediated GSDMD cleavage to induce pore opening and cell membrane rupture and hence pyroptosis [21,22]. Apart from pyroptosis, GSDMD cleavage has also been observed in many physiological activities such as vesicle traffic, secretion of neurotransmitter, and anti-inflammation.

As mentioned above, casp3 and casp8 are important regulatory factors in apoptosis and cell necrosis. Under specific pathological conditions,
these regulatory factors can also contribute to pyroptosis. This suggests that there could be important crosstalk between different types of cell death, which needs to be further investigated.

3.4. GSDMD is a pyroptotic effector

Gasdermins are a family of pore-forming proteins that contribute to pyroptosis. Of note, GSDMA-E and Pejvakin (PJVK) are expressed in humans, whereas mice have three GSDMA homologs (GSDMA1-3), four GSDMC homologs (GSDMC1-4), one GSDMD or GSDME homolog, and PJVK. All GSDM proteins, except for PJVK, contain two predicted domains and a variable linker region [10]. GSDMA-E and GSDMA3 are cytotoxic and induce pyroptosis in cells when their N-terminal domains are cleaved, although their full-length fragments do not exhibit such effects [10, 47]. Thus far, one GSDMD protein has been identified as the primary pyroptosis mediator of inflammatory caspases [16, 17]. Subsequent research has revealed that the ability of GSDMD’s N-terminal fragment (GSDMD-NT) to form pores, which contributes to pyroptotic cell death [16]. The GSDMD-NT binds to phosphatidylinositol, phosphatic acid, and phosphatidylserine in cell membranes, causing them to oligomerize and resulting in the formation of pores [40, 48]. GSDMD can only cause cell lysis in mammalian cells due to the asymmetric distribution of phosphoinositides on the plasma membrane [10, 48].

Several other alternative pyroptosis pathways have been reported, including caspase-3 activation of GSDME [18], caspase-1 [49] or granzyme A (GzMA) and cleavage of GSDMD [50], caspase-8 cleavage of GSDMC and transcriptional upregulation by hypoxia-activated programmed death-ligand 1 (PD-L1) and pSTAT3 [51], and GSDMA pore formation through an unknown mechanism [52]. The abovementioned mechanisms of pyroptosis are summarized in Figure 2.

Abbreviations: PAMPs: Pathogen-associated molecular patterns, DAMPs: danger-associated molecular patterns, NLRP: nucleotide-binding oligomerization domain (NOD)-like receptor (NLR) family, ROS: reactive oxygen species, dsDNA: double-stranded DNA, ASC: apoptosis-associated speck-like protein containing CARD, LPS: lipopolysaccharide, P2RX7: P2X purinoceptor 7, GSDMC: cleaving gasdermin C, Yop-J: Yersinia outer protein-J, CARD: caspase recruitment, PYD: pyrin domain, AIM2: Absent In Melanoma 2, GZMA: granzyme A, TAK1: TGF-Beta Activated Kinase-1

4. PYROPTOSIS AND CANCER

The enigmatic involvement of pyroptosis in cancer appears to be contingent on the cell type, genetics, and the duration of pyroptosis induction. GSDMs, inflammasomes, and/or pro-inflammatory cytokines can contribute to tumor pathology by inducing immunosuppressive cells, which may promote epithelial-to-mesenchymal transition and/or upregulate matrix metalloproteinases for extracellular matrix remodeling following abnormal expression and prolonged activity [53]. Carcinogenesis is influenced by proto- and anticogene activity, immunological microenvironment, oxidative stress, and chronic inflammation. The risk of cancer is increased when tissues and/or cells are exposed to an inflammatory environment for an extended period. Activation of pyroptosis is accompanied by the release of inflammatory mediators IL-1 and IL-18, which may contribute to the development of cancer [54-56].

4.1. Relationship between pyroptosis and cancer

4.1.1. Esophagus and gastric cancer

Alcohol buildup has been reported to inhibit caspase-1 and increase the production of IL-18 and IL-1 in esophageal epithelial cells, both of which are associated with pyroptosis [57]. Alcohol can hasten the etiology and development of esophagitis by activating pyroptosis-signaling pathways [57]. Gastroesophageal reflux disease (GERD) destroys the esophageal mucosa membrane and exposes the esophageal epithelium for an extended period, allowing stimuli such as
alcohol accumulation to enter the body and induce chronic inflammatory responses. Additionally, GERD has been associated with Barrett’s esophagus and esophageal cancer [58,59]. In Barrett’s cell lines, lipopolysaccharide (LPS) activated the NLRP3 inflammasome and pyroptosis-signaling pathways, which enhanced pro-inflammatory factors [59]. LPS stimulates TLR-4, priming inflammasome-signaling pathways, and enhancing the release of pro-inflammatory mediators and the NLRP3 inflammasome. LPS can also activate the NLRP3 inflammasome leading to the activation of caspase-1 and release of pro-inflammatory molecules such as IL-18, IL-1, and LDH by increasing mitochondrial ROS production (an indicator of pyroptosis). As a result, LPS induces pyroptosis-regulated cell death thereby aggravating Barrett’s esophagus [60,61]. Wu and colleagues reported that GSDME expression was upregulated in esophageal squamous cell carcinoma (ESCC) cell lines [60]. Additionally, increased GSDME expression induced apoptosis and signaling pathways associated with pyroptosis [60]. However, it remains unclear whether high GSDME expression is a driver of ESCC. In addition, whether LPS regulates GSDME expression is unknown and deserves further investigation.

Pyroptosis is vital in the pathogenesis and progression of gastric cancer (GC). The expression of GSDMD protein, a pyroptosis marker, is decreased in GC cells, thus promoting cancer cell proliferation [62]. Suppression of activated GSDMD molecules through the PI3K/AKT, ERK1/2, and STAT3 signaling pathways has also been shown to inhibit cell cycle protein A2 and cell cycle protein-dependent kinase (CDK2) expression levels in GC cells [63–65]. Cdk2/cyclin A2 complexes regulate the phosphorylation of proteins involved in DNA synthesis and promote S phase advancement, whereas the downregulation of cyclinA2/CDK2 complexes causes S to G2/M transition arrest. These studies suggest that GSDMD may be a driving factor in GC development. However, it has also been reported that in addition to its role in pyroptosis, GSDMs also play this regulatory role in biological behaviors such as vesicle transport and immune resistance, which are not dependent on the function of pyroptosis effectors. Therefore, further rigorous experimental studies are needed to investigate whether GSDMD regulates GC by affecting pyroptosis [66,67]. The NLRP4 inflammasome initiates a variety of inflammatory responses [66]. GC cells express significantly higher levels of NLRP4 inflammasome than normal gastric epithelial cells [69]. GSDMA expression was downregulated in GC cells, and the GSDMA protein molecule functions as an anti-oncogenic factor [70,71]. Recent research indicates that abundant GSDMB expression has been detected in a few normal GC tissues [72]. Surprisingly, another study discovered that overexpression of GSDMB can inhibit tumor invasion [49]. According to Saeki et al., GSDMC acts as a tumor suppressor gene [69]. According to Miguchi et al. [73], GSDML is a potential subgroup of the GSDMC protein molecule, which is linked to cancer [74]. GSDML has previously been shown to promote the development of several cancers, including gastric, hepatic, colorectal, and nonlesion tissues [75]. The GSDML gene was found to be upregulated in human colon, stomach, and liver cell lines; neoplasms; and nonlesion tissues. Another study found that the GSDML protein was linked to the cell’s cytoplasm in both tumors and nonlesional tissues [75]. GSDML protein expression was shown to be greater in tumor tissues. GSDML exhibited a characteristic vesicular staining pattern in mucous cells on the colon surface, gastric chief cells in the apical area, and the basal part of neuroendocrine cells [75]. According to previous research, GSDMD expression levels are increased in both GC cell lines and experimental animal models [70,71]. The silencing of DFNA5/GSDME was initially observed in primary GC cell lines [76]. Additionally, DFNA5/GSDME transfection into GC cell lines decreased the number of colonies and

![Molecular mechanisms of pyroptosis.](https://www.molecularmetabolism.com)
inhibited cell growth as compared to cells transfected with an empty vector [77,78]. The p-53 gene regulates the expression of DFNAS/GSDME, indicating that DFNAS is a tumor suppressor gene [79]. Caspase-3-mediated pyroptosis enhances GC formation through the DFNAS/GSDME signaling pathways [62].

As mentioned above, GSDMs have diverse effects on the development of GC. It can be a tumor suppressor (such as GSDMA, GSDMB) or a tumor promoter (such as GSDML). This may be caused by different regulatory factors that act on GSDMs. Therefore, identification of the upstream regulatory factors of GSDMs in GC is the key to achieve comprehensive understanding of the influence of GSDMs on the occurrence and development of GC. In addition, it remains unclear whether the effect of these GSDMs on GC is related to cell pyroptosis. Therefore, the effect of GSDMs on GC is not sufficient to evaluate the effect of pyroptosis on GC.

4.1.2. Hepatocellular carcinoma

Hepatocellular carcinoma (HCC) is a cancer that affects hepatocytes. The role of pyroptosis in human HCC is not well understood. Chu and colleagues previously reported that caspase-1 protein and mRNA expression levels were decreased in both human tumor tissues and cell lines, indicating that HCC growth and progression may be promoted by heat-induced cell death [80]. Wei et al. conducted an ex vivo study and found that the downregulation of the NLRP3 inflammasome was associated with the genesis and development of HCC [81,82]. Additionally, Wei et al. observed that 17ß-estradiol possesses anticancer properties, which they attributed to its potential to induce pyroptosis via the NLRP3 inflammasome [81]. Wei and colleagues reported increasing caspase-1 dosages and IL-1 expression in HCC cells [83]. Chen and colleagues recently revealed that caspase-1, IL-1, and IL-18 expression was much lower in HCC tissues than in surrounding normal tissues [84]. Previous research has demonstrated that the AIM2 inflammasome can inhibit S6K1 activation and hence limit cancer cell progression by targeting mTOR and that its accumulation in HCC cells can result in pyroptosis, which has antitumor effects [85,86]. In a groundbreaking study, IF and western blotting analyses demonstrated an obvious decrease in downregulated AIM2 expression in HepG2215 cells [87]. On the basis of these findings, it could be stated that pyroptosis plays a role in the pathophysiology and development of HCC; however, its molecular mechanism needs to be further explored.

4.1.3. Colorectal cancer

According to Hu et al., caspase-1 gene deficiency promotes tumorigenesis in azoxymethane- and dextran sodium sulfate colitis-related colorectal cancer mice models [54]. The putative role in carcinogenesis has not been linked to the control of colonic inflammation, but in colon cells, it is involved in epithelial cell proliferation and death [54]. Animal models with caspase-1-gene deletion showed increased colonic epithelial cell proliferation and inhibited apoptosis in advanced tumors during the early stages of injury-stimulated tumor growth. Additionally, caspase-1 promotes the tumor suppressor activity of STAT1 in colitis-associated carcinogenesis [88]. AIM2 expression was previously determined in a subset of colorectal tumors with an exacerbated mutation in a study investigating the potential involvement of AIM2 in tumor cells and patient prognosis. Lower AIM2 expression was found to be closely associated with a poor prognosis in colorectal cancer [89]. Williams et al. found that NLRP1 expression was significantly reduced in IBD and colon cancer [90]. Inflammation, cancer, and morbidity may be promoted in NLRP1b-knockout mice [90]. As previously demonstrated, inflammasome formation to NLIRs, misdirected inflammation, and tumor progression were associated with decreased levels of IL-1 and IL-18 pro-inflammatory mediators. Chen et al. demonstrated that NLRP1 expression was associated with tumor progression in colon cancer [98,91].

Tang et al. showed that NLRP3 and caspase-1 inflammasome pathways participate in the development of colorectal cancer [92]. FL118 induces pyroptosis in colorectal cancer cells by activating NLRP3-ASC-Caspase-1-IL-18 and IL-1 signaling pathways [92]. Previous research demonstrated that mRNA and protein expression of NLRP3 and Caspase-1 was downregulated in colon cancer patients, indicating a relationship between pyroptosis and colon cancer [92]. GSDMC expression is downregulated in colorectal tumors [73]. Additionally, the decreased expression levels of GSDMC may promote the proliferation and development of tumor cells. GSDMC has the potential to open up a new therapeutic window for treating and regulating colorectal cancer in the near future [73]. Wu et al. demonstrated a significant correlation between GSDMD expression levels in human colorectal cancer (CRC) tissues and a poor prognosis in CRC patients. LPS, but not TNF-, induced pyroptosis in HT29 cells by promoting GSDMD and GSDMD-N membrane translocation and increasing chemosensitivity in response to L-OHP. Additionally, the overexpression of GSDMD in HT29 cells decreased cell survival and resulted in cell death. Reduced GSDMD expression is associated with a poor prognosis in CRC, and LPS-induced pyroptosis may increase the anticancer activity of L-anti-cancer Ohp by activating the GSDMD signaling pathway, hence suppressing CRC carcinogenesis. Our findings lay the foundation for future exploitation of GSDMD as a predictive biomarker and a feasible target for colorectal cancer treatment [93]. Recent research indicates that GSDME may be a potential biomarker for the detection of colorectal cancers [94]. Additional research is required to reveal the underlying mechanism of GSDME-mediated pyroptotic cell death in colorectal cancer.

4.1.4. Lung cancer

According to a recent study, pyroptosis mediated by GSDMD is critical to the genesis and progression of lung cancer (LC) [95]. GSDMD deficiency has been shown to significantly slow tumor development. Reduced epidermal growth factor receptor signaling, increased caspase-3 breakdown, and accelerated apoptosis in GSDMD-silenced NSCLC cells result in the suppression of tumor growth in transplanted animals. Stimulation of NLRP3/caspase-1 signaling induces apoptosis rather than pyroptosis in tumor cells lacking GSDMD [95]. GSDMD knockdown inhibits cell growth in NSCLC by promoting apoptosis and inhibiting the EGFR/Akt pathway. High GSDMD expression has been associated with aggressive characteristics such as larger tumors and advanced tumor-node-metastatic stages [96]. Surprisingly, high expression level of GSDMD in lung adenocarcinoma (LAD) resulted in a worse prognosis (SCC) when compared with that for squamous cell carcinoma [96]. Lu et al. demonstrated that knockdown of DFNAS/GSDME causes caspase-3-activated cells to flip from apoptosis to pyroptosis, thus confirming that the expression level of DFNAS/GSDME regulates the death mode of caspase-3-activated cells. LC, the deletion of the DFNAS/GSDME genes increases resistance to drugs, whereas overexpression of DFNAS/GSDME enhances drug sensitivity [97]. According to Hoechst33342/PI staining, flow cytometry analysis, and loss real-time live-cell imaging analysis, the downregulation of inflammasome components promotes the progression of NSCLC in A549 and H1299 cell lines [98]. A previous study discovered increased NLRP3, ASC, Caspase-1, IL-1, IL-18, and GSDMD mRNA and protein expression in A549 and H1299. Therefore, inhibiting the ROS/NF-κB/NLRP3/GSDMD signaling axis promotes NSCLS progression by downregulating caspase-mediated pyroptosis. According to Liu
et al., the upregulation of IncRNA-XIST may promote the development of NSCLC by inhibiting pyroptotic cell death mediated by the miR-335/SOD2/ROS/NLRP3 signaling pathway, thus implying that NLRP3 inflammasome-mediated pyroptosis provides new insight and knowledge on the pathogenesis and development of lung cancer [39].

4.1.5. Cervical cancer

Cervical cancer is linked to infection with a DNA virus called human papillomavirus (HPV) in more than 90% of cases [100]. HPV transforms infective cervical cells into cancer cells by integrating the viral DNA and evading host antiviral immunity [101]. SIRT1 (Sir–tuin 1) is the mammalian ortholog of silent information regulatory 2 (Sir2), and it has been established that SIRT1 regulates cell death by deacetylating the NF–B subunit RelA/p65 [102]. SIRT1 is overexpressed in HPV-infected cervical cancer cells as compared to normal cervical cancer cells, and it contributes to cancer cell development and proliferation [103]. SIRT1 expression in cervical cancer cells suppresses NF–B–induced transcription of absent in melanoma 2 (AIM2) genes by disrupting the mRNA of the AIM2 gene transcription factor RelB. SIRT1 knockdown, on the other hand, increased RelB stability and activated AIM2 inflammasome-related genes, resulting in AIM2 inflammasome-regulated pyroptosis [104]. AIM2 is a receptor that recognizes cytosolic double-stranded DNAs (dsDNA), including HPV, and forms a large supramolecular complex with ASC to activate caspase-1-induced pyroptosis [33]. Additionally, extracellular vesicles transport AIM2 inflammasomes and AIM2 inflammasome-regulated pyroptosis between cells [104]. These data suggest that pyroptosis induced by the AIM2 inflammasome contributes to the development of CC. Yang et al. established that the protein expression levels of caspase-1, GSDMD, and NLRP3 were reduced in human and mouse tumor tissues and cell lines [105]. In a previous study, researchers used the GSDMD siRNA lentivirus to transfect endometrial cancer cells to investigate the potential role of the GSDMD protein molecule in pyroptosis-regulated cell death [105]. GSDMD knockdown induced pyroptosis in endometrial cancer tissues and cell lines derived from xenograft mice. Additionally, increased expression levels of caspase-1, GSDMD, and NLRP3 decreased tumor weight and volume [105]. Overexpression of miR-214, which targets the NLRP3 inflammasome in CCs, may activate pyroptosis-signaling pathways. Cervical cancer patients have decreased levels of miR-214, NLRP3, and caspase-1. Pyroptosis can be induced in CC cells by upregulating miR-214 and increasing NLRP3 inflammasome expression [106]. Tong and colleagues identified the miR-145/GSDMD signaling pathway as a key mediator of tanshinone II’s action on HeLa cells [30]. Thus, CC formation requires the miR-145/GSDMD signaling pathway. Additionally, the miR-145/GSDMD signaling axis may be a target for CC treatment, and there is a relationship between miR-145 and pyroptosis, which provides fresh insights into the pathophysiology of CC and potential preventative medicine for its treatment and regulation [32]. As a result, additional research is necessary to elucidate the critical role of pyroptosis-dependent cell death in CC.

4.1.6. Ovarian cancer

Recent research has examined the role of the IncRNA GAS5 in ovarian cancer suppression. The IncRNA GAS5 induces apoptosis and pyroptosis in ovarian cancer cells and thus acts as a tumor suppressor. Overexpression of IncRNA GAS5 was associated with caspase-1 activation, which increased the expression levels of IL-18 and IL-1β in a time-dependent manner, whereas IncRNA GAS5 knockdown decreased the expression level of these factors [107]. IncRNA GAS5 influenced inflammasome development and triggered an inflammatory response by disrupting the glucocorticoid receptor (GR), which is distributed throughout the body and is required for the regulation of genes involved in growth, metastasis, and the immune system [107,100]. Liang et al. suggested that decreased GSDME-dependent pyroptosis is a key factor in OC progression [109]. Additionally, Qiao and colleagues found that GSDMD/caspase-4 expression was downregulated in epithelial ovarian cancer (EOC) cell lines such as Ho8910PM, A2780, and Ho8910 [110]. They used alpha-NETA to induce pyroptosis in those cell lines and produced a variety of microbubbles [110]. Alpha-NETA increased the expression of pyroptosis-related proteins in EOC cells, including caspase-4 and GSDMD [110]. Caspase-4 and GSDMD knockdown significantly reduced alpha-NETA cell invasion activity in EOC cells, thus indicating that alpha-NETA activated pyroptosis signaling pathways [110]. Luborsky et al. reported that the mRNA and protein expression levels of NLRP3, Caspase-1, IL1, and IL18 were significantly decreased in ovarian cancers, indicating that pyroptosis plays a critical role in the progression of OC [111]. HOTTIP, an IncRNA, is an important regulator in multiple cancers, including OC. Tan et al. recently demonstrated an increase in HOTTIP expression in OC tissue samples and cell lines [112]. In this study, the authors revealed that silencing HOTTIP inhibited cell growth and NLRP1 inflammasome-mediated pyroptosis. Additionally, HOTTIP increased AKT2 expression by inhibiting the ASK1/JNK signaling pathway and negatively regulating miR-148a-3p. Further rescue experiments revealed that the upregulation of AKT2 and downregulation of miR-148a-3p expression in OC cells mitigated the effects of HOTTIP downregulation [112]. These findings suggest a novel pyroptosis-related mechanism through which HOTTIP contributes to the development of OC, suggesting that HOTTIP may be therapeutic target.

4.1.7. Breast cancer

Breast cancer is a complex, heterogeneous illness with a diverse histological characteristics and clinical manifestations [113]. Pizato et al. demonstrated that a reduction in GSDMD-regulated pyroptosis contributes significantly to BC progression [114]. Decreased caspase-1, GSDMD, HMGB1, and IL-1 expression was also found to increase BC cell proliferation and expansion. Cytoplasm and membrane hole development were also observed in BC cells. Guo and colleagues discovered that retinoic acid-inducible gene (RIG-I) signaling induces pyroptosis in ER + BC cells by activating the caspase-3, caspase-1, and GSDMD signaling pathways [113]. The formation of a cellular membrane pore in BC cells results in lysosomal damage and generation of reactive oxygen species (ROS) [115]. The formation of a cellular membrane pore in BC cells results in lysosomal damage and generation of ROS [114]. According to Wu and colleagues, IL-1β expression was significantly elevated during the development and progression of breast neoplasms, and variations in IL-18 and IL-1β have been associated with breast tumor progression [116]. Increased GSDMB expression levels have been associated with shorter survival and higher rates of metastasis in BC [117]. Hergueta and colleagues found that GSDMB enhanced invasion and metastasis in BC cells [117]. As a result, GSDMD may be considered a robust biomarker for monitoring the prognosis of BC. The expression of DFNA5/GSDME (formerly known as ICERE-1) is elevated in ER-negative cell lines, which promotes BC-specific carcinogenesis of hormone-unresponsiveness. Kim et al. reported that DFNA5 methylation is associated with lymph node metastases in human BC [78]. Reduced DFNA5/GSDME expression levels in MCF-7 cells are also sensitive to paclitaxel treatment, as shown in a new study. Additionally, Masuda et al. revealed that p53 may induce DFNA5/GSDME expression through
Metformin is a biguanide derivative commonly used to treat type 2 diabetes and can inhibit cancer proliferation. Many retrospective data and experimental studies have shown that metformin has antineoplastic activity. However, the specific mechanisms are unknown [127]. Through in vitro and in vivo, Wang et al. demonstrated that metformin might promote GSDMD-induced pyroptosis of esophageal squamous cell carcinoma (ESCC) by targeting the miR-497/proline-, glutamic acid-, and leucine-rich protein-1 (PELP1) axis [128]. Another study suggested that metformin can be an alternative treatment for chemo- and radiotherapy-resistant ESCC or other malignancies with similar pyroptosis pathways [129].

4.2. Triggering pyroptosis in tumors for therapeutic purposes

4.2.1. Metformin. A recent study revealed that eukaryotic elongation factor-2 kinase (eEF-2K), a negative regulator of protein synthesis, plays a significant role in DOXO-induced pyroptosis of human melanoma cells [122]. The silencing of eEF-2K increases pyroptosis and enhances the sensitivity of melanoma cells to doxorubicin. Therefore, targeting eEF-2K may enhance the anti-tumor efficacy of doxorubicin, providing a novel insight into tumor chemotherapy [122].

4.2.1.2. Doxorubicin. A recent study revealed that eukaryotic elongation factor-2 kinase (eEF-2K), a negative regulator of protein synthesis, plays a significant role in DOXO-induced pyroptosis of human melanoma cells [122]. The silencing of eEF-2K increases pyroptosis and enhances the sensitivity of melanoma cells to doxorubicin. Therefore, targeting eEF-2K may enhance the anti-tumor efficacy of doxorubicin, providing a novel insight into tumor chemotherapy [122].

4.2.1.3. Lobaplatin. Yu et al. revealed that lobaplatin (LPT) can reduce the viability of HT-29 and HCT116 colon cells in a dose-dependent manner. Moreover, HT-29 and HCT116 cells show microscopic features of cell enlargement, huge bubbles from the plasma membrane, and many pores in the membrane after lobaplatin treatment, as revealed by transmission electron microscopy (TEM) [129]. Mechanistically, lobaplatin elevates the level of ROS and c-Jun N-terminal kinase (JNK) phosphorylation. Activated JNK triggers caspase-3/9 cleavage and GSDME-dependent pyroptosis in colon cancer cells by recruiting Bax to mitochondria, thereby promoting the release of cytochrome c into the cytosol and leading to GSDME-dependent pyroptosis [129]. Lobaplatin eliminates colon cancer cells via GSDME-dependent pyroptosis and thus can be used as an anticancer drug [129].

4.2.1.4. Paclitaxel and cisplatin. Paclitaxel and cisplatin activate caspase-3 and GSDME in A549 lung cancer cells to induce pyroptosis. Cisplatin has a stronger promoting effect on pyroptosis than paclitaxel. Similarly, cisplatin triggers stronger caspase-3 activation and production of the N-terminal segment of GSDME than paclitaxel [130]. These findings show that cisplatin can induce higher pyroptosis of A549 cells as compared to paclitaxel, indicating that cisplatin may have additional benefits on lung malignancies with high GSDME expression [130].

4.2.1.5. 5-Fluorouracil. Treatment with 5-fluorouracil causes the production of cleaved caspase-3 and accumulation of the N-terminal segment of GSDME in gastric cancer cells, leading to pyroptosis [62]. CRISPR-Cas9-mediated deletion of GSDME transforms 5-fluorouracil-induced pyroptosis into apoptosis, suggesting that GSDME might transform 5-fluorouracil-induced caspase-3-dependent apoptosis into pyroptosis in gastric cancer cells [62].

4.2.1.6. Others. Other pyroptosis-related chemicals have also been investigated. For instance, Chalcone derivative-8 with the α,β-unsaturated-ketone unit inhibits the proliferation of NCI-H460 cancer cell lines. Zhu et al. reported that these derivatives trigger GSDME-mediated pyroptosis. Moreover, N-substituted EF24 analog 13d decreases xenograft tumor development by inhibiting cell viability, arresting cell cycle in the G2/M phase, promoting cell apoptosis, and inhibiting cell viability. Compound 13d can also cause pyroptosis due to the suppression of the nuclear transcription factor-κB (NF-κB) and caspase-3 signaling pathways in lung cancer [132]. L61H10 is a unique-binding regional intron-1 of DFNA5 [79]. p-63 is a member of the p53 family that promotes DFNA5 expression, indicating that it is a novel transcriptional member of the p53 family [118]. Wu et al. demonstrated that the expression of caspase-1, IL-1β, and GSDMD proteins was positively correlated in BC tissues, which was consistent with the development of the caustic death pathway [119]. Overexpression of IL-1β and NLRP3 in the breast tumor microenvironment has been associated with the accumulation of MDSCs and TAMs. An in silico meta-analysis of caspase-1, NLRP3, and IL-1β revealed the expression levels of these factors was correlated with longer overall survival of BC. NLRP3 demonstrated a favorable association with survival across all molecular subtypes in the TCGA BC dataset. The levels of NLRP3 and IL-1β in TAM are associated with survival, lymph node invasion, and metastasis in patients with HER2+ BC. This indicates that pyroptosis has a positive impact on the progression, invasion, and metastasis of BC. There is an urgent need for additional experimental research into the pathophysiology of pyroptosis.

4.1.8. Skin cancer

Miguchi et al. showed that the expression level of GSDMC was lower in malignant melanoma cells, possibly due to cancer cell invasion and metastasis [73]. A previous study also showed that DFNA5/GSDME expression was significantly higher in the nonresistant MeWo cell line than in the etoposide-resistant MeWo ETO 1 cell line [120]. Furthermore, DFNA5/GSDME knockdown increased etoposide resistance in etoposide-resistant melanoma cells, whereas DFNA5/GSDME upregulation improved etoposide sensitivity, implying that low expression of DFNA5 is associated with increased etoposide resistance in melanoma cells [121].

Eukaryotic elongation factor-2 kinase (eEF-2K) regulates protein synthesis to trigger autophagy and pyroptosis in tumor cells [122]. Yu et al. recently reported that eEF-2K signaling is crucial in pyroptosis of doxorubicin-stimulated human MCs [122]. These findings demonstrate that GSDME-dependent pyroptosis is crucial in melanoma.

4.1.9. Other cancers

The expression of mammalian STE20-like kinase 1 (MST1) is reduced in pancreatic ductal adenocarcinoma (PDAC) cells. However, restoration of MST1 expression increases PDAC cell death and suppresses PDAC cell proliferation, migration, and invasion through ROS-driven pyroptosis [123]. Recently, it was found that microRNA (miRNA) is associated with pyroptosis in certain cancers [124]. miRNA-214 reduces glioma cell proliferation and migration by altering the caspase-3 pathway [125]. Moreover, Kay et al. showed that the NAIP-NLR4 inflammasome contributes to the development and progression of glioma [126].

4.2. Triggering pyroptosis in tumors for therapeutic purposes

4.2.1. Chemotherapeutic drugs

4.2.1.1. Metformin. Metformin is a biguanide derivative commonly used to treat type 2 diabetes and can inhibit cancer proliferation. Many retrospective data and experimental studies have shown that metformin has antineoplastic activity. However, the specific mechanisms are unknown [127]. Through in vitro and in vivo, Wang et al. demonstrated that metformin might promote GSDMD-induced pyroptosis of esophageal squamous cell carcinoma (ESCC) by targeting the miR-497/proline-, glutamic acid-, and leucine-rich protein-1 (PELP1) axis [128]. Another study suggested that metformin can be an alternative treatment for chemo- and radiotherapy-resistant ESCC or other malignancies with similar pyroptosis pathways [129].
Due to the increased expression of NLRP3, caspase-1, and IL-1, squamous cell carcinoma (OSCC) cells, thus limiting their migration. A recent study showed that anthocyanins can lower the viability of OSCC cells, thus increasing GSDMD protein expression, indicating that anthocyanin induces its anti-cancer effect through pyroptosis induction [135]. Furthermore, GSDME inhibition in malignant cells induces pyroptosis [135].

4.2.1.7. Alpha-NETA. Alpha-NETA is a reversible choline acetylcholine-transferase inhibitor. A recent study showed that alpha-NETA can activate GSDMD/caspase-4-induced pyroptosis, thus inhibiting EOC cell growth [110], consistent with the results of in vivo tests. Pyroptosis induction may be induce a therapeutic effect for OC treatment [110].

4.2.1.8. PLK1 inhibitors. A previous study showed that PLK1 inhibitors can enhance ESCC cell sensitivity to cisplatin (CP) by suppressing the DNA damage repair mechanism and enhancing the Bax/Caspase-3/GSDME signaling pathway-dependent pyroptosis [60]. Therefore, PLK1 inhibitors are promising therapeutic agents for ESCC-targeted treatment, especially when combined with CP [60].

4.2.1.9. Decitabine (DAC). Fan et al. developed a decitabine (DAC) and nano-drug combination therapy for generating pyroptosis in malignant cells by targeting epigenetics [135]. DAC pretreatment demethylated the DNAl5 gene in malignant cells of tumor-bearing mice. The researchers used a tumor-specific nanoliposome loaded with CP (Lipo-DPP) to activate caspase-3 and pyroptosis in tumor cells. Decitabine combined with chemotherapeutic nanodrugs induced pyroptosis of tumor cells through epigenetics, thus enhancing the immunological impact of chemotherapy [135]. Furthermore, GSDME inhibition in malignant cells induces pyroptosis [135].

4.2.1.10. Anthocyanidins (ANTH). Anthocyanidins (ANTH) are natural colorants belonging to the flavonoid family. They have attracted much attention because of their anticancer properties [136]. A recent research study showed that anthocyanins can lower the viability of oral squamous cell carcinoma (OSCC) cells, thus limiting their migration and invasion. Anthocyanins can lead to pyroptosis activation in OSCC due to the increased expression of NLRP3, caspase-1, and IL-1β. Furthermore, western blot assay revealed that anthocyanin can increase GSDMD protein expression, indicating that anthocyanin induces its anti-cancer effect through pyroptosis induction. A recent study showed that anthocyanins can lower the viability of OSCC cells, thus limiting their migration and invasion. Anthocyanins can lead to pyroptosis activation in OSCC due to increased expression of NLRP3, caspase-1, and IL-1β. Western blotting assay showed that anthocyanin can increase GSDMD protein expression, indicating that anthocyanin induces its anticancer effect through pyroptosis induction [137]. However, caspase-1 inhibitors can reduce anthocyanin-activated pyroptosis, while increasing cell survival, migration, and invasion rates [137].

4.2.1.11. Galanin. Yang et al. discovered that galanin treatment increased the N-terminal fragment of GSDME in a dose-dependent manner. They also showed that GSDME knockdown can exacerbate nuclear DNA damage in glioblastoma multiforme cells, thus implying that pyroptosis may influence the extent of apoptosis after galanin treatment [138].

4.2.1.12. Omega-3 fatty acids. Numerous research studies have demonstrated that omega-3 fatty acids can control inflammation and exhibit anti-cancer properties [139]. The omega-3 fatty acid docosahexaenoic acid (DHA) can cause cancer cell death because of its anticancer properties [140]. Pizato et al. explored the potential inhibitory effect of DHA on triple-negative breast cancer cells and the underlying molecular pathways. They discovered that DHA increases caspase-1 and GSDMD activation, increases IL-1 production, and translocates human high mobility group box 1 (HMGB1) to the cytoplasm to form holes in the membrane in breast cancer cells [114].
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study showed that GSDME knockdown in GSDME-expressing tumors enhances tumor development. However, ectopic expression in GSDME-repressed tumors decreases tumor growth in mice through killer cytotoxic lymphocytes. However, this suppression does not occur in perforin-deficient or killer lymphocyte-depleted animals. GSDME expression increases the quantity and activity of tumor-infiltrating natural killer and CD8+ T lymphocytes, and their ability to phagocytose tumor cells through tumor-associated macrophages. Killer-cell granzyme B promotes caspase-independent pyroptosis in target cells by directly cleaving GSDME at the same location as caspase 3. GSDME proteins that are not soluble or have pore defects cannot suppress tumor development. Consequently, tumor GSDME functions as a tumor suppressor by increasing antitumor immunity through pyroptosis induction [151]. However, Gao Tan showed that HMGB1, a proinflammatory factor secreted by GSDME-mediated pyrototic epithelial cells, promotes colorectal cancer growth through the ERK1/2 pathway [152]. Furthermore, Liu discovered that pyroptosis-released components from tumor cells can stimulate pyroptosis in macrophages resulting in cytokine release and cytokine release syndrome (CRS) [153]. These findings show that pyroptosis mediates the tumoricidal effects of certain inhibitors or cytolytic immune cells. Pyroptosis-induced release of inflammatory factors may either induce anti-tumor immunity, promote tumor growth, or generate inflammatory cascades. Therefore, the relationship between pyroptosis and anti-tumor immunity should be assessed.

A previous study showed that human umbilical cord mesenchymal stem cells release substances that trigger MCF7 cell pyroptosis. The substances can also significantly alter the expression of NLRP1 and CAPS4 and the pathways associated with inflammation [154]. Colunga et al. discovered that calpain, caspase-7, and caspase-3 activation in many malignant melanoma cells inoculated with the herpes simplex virus type 2 (HSV-2) mutant PK (HSV-2 mutant PK) can increase the oncolytic impact of PK. The PK can also increase expression level of heat shock proteins, such as Beclin-1 and H11/Hsp B8. The corresponding immunohistochemical results also revealed that TNF-α activated and participates in the formation of the NLRP3 inflammasome-mediated by caspase-1, thus inducing apoptosis and pyroptosis [155]. Zhou et al. indicated that increased ROS may oxidize Tom20, an outer mitochondrial membrane protein, after iron therapy, thereby allowing Bax recruitment to mitochondria and accelerating caspase-3/ GSDME-mediated pyroptosis. Iron triggers ROS to promote DFNA5/ GSDME-dependent pyroptosis and selectively enhances DFNA5/ GSDME expression in melanoma cells. Therefore, it may be a promising therapy for melanoma. Iron supplements can enhance the anticancer function of clinical ROS-induced medicines and suppress the proliferation and spread of xenografted melanoma cells via DFNA5/ GSDME-dependent pyroptosis [156].

5. CONCLUSIONS AND PERSPECTIVES

Pyroptosis, a caspase-dependent cell death, causes pore formation, cell swelling, rupture of the plasma membrane, and release of all intracellular contents. This paper discusses the molecular mechanisms of pyroptosis to generate ideas for developing therapeutic strategies for disease treatment. A number of studies have shown that tumor cells undergo pyroptosis in vivo, suggesting a potential role for pyroptosis in the regulation of tumorigenesis. Previous studies have extensively investigated approaches for promoting apoptosis of cancer cells as a strategy to eliminate malignant cells. However, this approach is hampered by the revelation that tumor cells have mechanisms of evading apoptosis. Based on theories of inflammation—cancer transformation and chronic inflammation-induced cell carcinogenesis, pyroptosis, as a pro-inflammatory mode of death, can create a microenvironment suitable for tumor cell growth. The role of pyroptosis in cancer is an extremely complex issue. This review argues that it should be discussed in different cancer periods according to the characteristics of cancer occurrence and development. At the stage of cancer occurrence, the current evidence points out that pyroptosis promotes cancer more than it inhibits cancer. For example, it promotes cancer occurrence by promoting the release of IL-1, IL-18, or NLRP inflammatory bodies, which can be confirmed in gastric cancer and liver cancer. It should be noted that the pathway of pyroptosis-induced cancer may be different in different cancers, which needs further exploration. However, interestingly, we also found that the decrease of pyroptosis could promote the development of cancer in the process of cancer progression. For example, in gastric cancer, the downregulation of GSDMD was significantly positively correlated with the proliferation of cancer cells, or the decrease of NLRP3 inflammasome could promote the development of liver cancer, including the decrease in caspase-1 and IL-1 expression in HCC tissues. This conclusion can also be more or less evident in other cancers (such as lung cancer and cervical cancer). Throughout the whole process, the research of the Gasdermin family is also a very promising issue, such as the possibility of GSDMD and GSDME as biomarkers in colorectal cancer, and GSDML, a member of the Gasdermin family with future research prospects.

In cancer treatment, pyroptosis provides us with some potential new targets, such as HOTTIP. For the existing drugs, the study of pyroptosis also helps us make better use of existing drugs for anticancer treatment. Immunotherapy is a hot research direction in the field of cancer treatment. As mentioned above, we look forward to more studies on immunotherapy related to pyroptosis in the future.

In conclusion, there is growing evidence that tumor pyroptosis has antitumor and protumor roles. Failure of cancer therapy is largely caused by resistance to apoptosis. Focusing on answering the question “What Role Does Pyroptosis Play in Cancer?” will help to improve cancer diagnosis and treatment.

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AUTHORS’ CONTRIBUTIONS

CLZ contributed to the guidance of this review and gave the final approval of the version to be published; CH drafted the manuscript; and JL prepared the figures. All authors read and approved the final manuscript.

CONSENT FOR PUBLICATION

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