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Pyroptosis and its role in cancer

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Abstract

Programmed cell death (PCD) is a form of cell death mediated by specific genes that encode signals. It can balance cell survival and death. Pyroptosis is a type of inflammatory, caspase-dependent PCD mediated by gasdermin proteins, which function in pore formation, cell expansion, and plasma membrane rupture, followed by the release of intracellular contents. Pyroptosis is mediated by caspase-1/3/4/5/11 and is primarily divided into the classical pathway, which is dependent on caspase-1, and the non-classical pathway, which is dependent on caspase-4/5/11. Inflammasomes play a vital role in these processes. The various components of the pyroptosis pathway are related to the occurrence, invasion, and metastasis of tumors. Research on pyroptosis has revealed new options for tumor treatment. This article summarizes the recent research progress on the molecular mechanism of pyroptosis, the relationship between the various components of the pyroptosis pathway and cancer, and the applications and prospects of pyroptosis in anticancer therapy.

INTRODUCTION

The dynamic balance among cell death, proliferation, and differentiation sustains individual development, homeostasis, and pathological processes in humans. Many disease states are associated with cell death. Programmed cell death (PCD) is regulated by specific cellular mechanisms, and some signaling pathways are activated in these

processes (1). Autophagy, apoptosis, and programmed necrosis are the three main types of PCD (2), and together, they may affect the fate of cancer cells. Apoptosis is a type of PCD that involves cell self-destruction controlled by genes. In apoptosis, the cell membrane remains intact, and inflammation usually does not occur (3). Necrosis is a passive cell death process caused by pathological stimuli. The permeability of the cell membrane of necrotic cells increases, which causes the cells to swell and finally break down and release their contents. This leads to an inflammatory reaction (3). Pyroptosis is a form of programmed necrosis, which is PCD induced by gasdermin-mediated.

Pyroptosis was first described in myeloid cells infected by pathogens in 1992 (4-6). It is believed that by clearing intracellular replication niches and improving the defensive responses of the host, pyroptosis plays a vital role in clearing various bacterial and viral infections (7). The activation of pyroptosis may promote cell death and exert anticancer effects (8). Pyroptosis has attracted increased attention because it is related to innate immunity and disease. The research status of the relationship between pyroptosis and various cancers is shown in Figure 1, according to publications in PubMed. Emerging evidence has demonstrated the importance of pyroptosis in cancer. Recently, more and more studies have shown that pyroptosis has become a new research topic in cancer, because it may affect the process of cancer. In this review, we outline the molecular mechanism of pyroptosis and highlight its differences from apoptosis. The importance of the various components of the pyroptosis pathway in cancer and its application prospects in antitumor therapy are also discussed.

THE MECHANISM OF PYROPTOSIS

Pyroptosis is also called gasdermin-mediated PCD. The gasdermin family has regulatory functions in normal cell proliferation and differentiation; it includes gasdermin A (GSDMA), gasdermin B (GSDMB), gasdermin C (GSDMC), gasdermin D (GSDMD), gasdermin E (GSDME) (also known as DFNA5, [Deafness, Autosomal Dominant Nonsyndromic Sensorineural 5]), and DFNB59 (Autosomal Recessive Deafness Type 59 Protein) (9-13). Among them, GSDMD and GSDME have been

extensively studied in pyroptosis. These proteins have inherent necrotic activity in their gasdermin-N domain, which is usually masked by their gasdermin-C domain (14-16). Pyroptosis is activated by various stimuli and inflammatory caspases, which induce the cleavage of proteins in the gasdermin family and release its N-terminal effector and C-terminal inhibitory domains. The necrotic gasdermin-N domain is then transferred to the plasma membrane, forming oligomers (14–19). These oligomers form transmembrane pores that disrupt the osmotic potential, which results in rapid plasma membrane rupture, causing the cells to release their intracellular contents and pro-inflammatory mediators, such as interleukin (IL)-1β and IL-18 (20).

Of the proteins in the gasdermin family, GSDMA, GSDMB, and GSDMC proteins possess a pore-forming gasdermin-N domain. However, they are not cleaved to form functional pores in response to physiological or pathological stimuli (14, 21). Only GSDMD and GSDME are cleaved by caspases between their gasdermin-N and gasdermin-C domains to form membrane pores (11, 14, 21-23). Typically, GSDMD, the downstream effector of inflammasome activation, is cleaved by inflammatory caspases (caspase-1/4/5/11) to induce pyroptosis. However, GSDME is cleaved by an apoptotic caspase (caspase-3), which causes pyroptotic death (14). Different molecular patterns are activated depending on the specific signaling pathway and cell type to induce pyroptosis (24). The role of each component in the gasdermin family is described in Table 1.

Pyroptosis belongs to the inflammatory cell death pathway. According to its activation mechanism, pyroptosis can be divided into the classical pathway, which is dependent on caspase-1, and the non-classical pathway, which is dependent on caspase-4, 5, and 11. These pathways are shown in Figure 2. Both pathways are formed by the cleavage of GSDMD, which forms a free N-terminal peptide; this peptide induces cells to form pores and rupture, which causes the release of cytoplasmic components. Both pathways can simultaneously induce the cleavage of IL-1β and IL-18 precursors to form mature IL-1β and IL-18. The difference between the two is whether caspase-1 is directly activated. (1) The classical pathway of pyroptosis (21, 53): inflammasomes are

multimolecular complexes that contain pattern-recognition receptors (PRRs). The PRR series usually contains Toll-like receptors, intracellular nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs), and absent in melanoma-like receptors. PRRs can recognize pathogen-associated and damage-associated molecular patterns, and can sense the presence of risk factors, such as infection and injury. PRRs can also recruit the adaptor protein containing the caspase recruitment domain (apoptosis-associated speck-like protein containing a caspase recruitment domain [ASC]) and activate caspase-1 through the adaptor protein ASC and pro-caspase-1 binding. On the one hand, the activated caspase-1 cleaves GSDMD to form the GSDMD-N and GSDMD-C domains. The GSDMD-N domain combines with phospholipid proteins on the cell membrane to form holes, after which contents are released, and pyroptosis is induced. On the other hand, the activated caspase-1 cleaves IL-1β and IL-18 precursors to form active IL-1β and IL-18, which are released outside the cell, causing inflammation. (2) Non-classical pathways that depend on caspase-4, 5, and 11 (21, 53). Taking the inflammatory stimulating factor lipopolysaccharide (LPS) as an example, it directly enters the cytoplasm, although not through the receptor, where it activates other caspases, such as caspase-4, 5, and 11, which cleave GSDMD to induce pyroptosis. A new pathway known to cause pyroptosis is caspase-3/GSDME (11, 49). Caspase-3 can be activated by death receptors and mitochondrial pathways. Mature caspase-3 cleaves GSDME to produce GSDME N-fragments. It participates in pore formation in the plasma membrane, resulting in cell swelling and pyroptosis.

THE RELATIONSHIP BETWEEN VARIOUS COMPONENTS IN THE PYROPTOSIS PATHWAY AND CANCER

Pyroptosis is an important natural immune response of the body. It plays a vital role in antagonizing infection and endogenous danger signals. Pyroptosis is widely involved in the occurrence and development of infectious, nervous system-related, and atherosclerotic diseases. In-depth research on pyroptosis has implicated its role in the occurrence, development, and outcome of related diseases and has provided new ideas

for clinical prevention and treatment. In recent years, research interest in pyroptosis has increased significantly as it has successful attracted the attention of scientists and has become a popular research topic. For tumors, pyroptosis is a double-edged sword. On the one hand, as an innate immune mechanism, pyroptosis can inhibit the occurrence and development of tumors. On the other hand, as a mechanism of pro-inflammatory cell death, pyroptosis provides a suitable microenvironment for tumor growth. The key components of the pyroptosis pathway, inflammasomes, gasdermin proteins, and pro-inflammatory cytokines, are all related to tumor occurrence, invasion, and metastasis (54).

GSDMD AND CANCER

Many molecules that participate in the pyroptosis process are closely related to the occurrence and development of lung cancer. Studies have confirmed that the expression level of GSDMD in non-small cell lung cancer is significantly higher than in surrounding lung tissues. Moreover, the GSDMD expression is related to the tumor size, tumor–node–metastasis stage, and high aggressive characteristics (55). In addition, GSDMD is considered to be an independent prognostic marker of lung adenocarcinoma (55). Studies have found that GSDMD in gastric cancer was downregulated and led to the occurrence and spread of this cancer type (56). The low level of GSDMD in gastric cancer cells may be associated with the acceleration of the cell cycle S/G2 transition; GSDMD also inhibits the signal transducer and activator of transcription 3, extracellular signal-regulated kinase (ERK), and phosphatidylinositol 3-kinase/protein kinase B (PI3K/AKT) in gastric cancer. These data indicate the tumor-suppressive effect of GSDMD in gastric cancer. However, whether GSDMD plays a tumor-suppressive or cancer-promoting role in breast and colorectal cancers and other cancers is unknown. Therefore, this will be the focus of future research.

GSDME AND CANCER

In lung cancer, the deletion of the *DFNA5/GSDME* gene promotes drug resistance, whereas the overexpression of *DFNA5/GSDME* can result in increased drug sensitivity (57). Both cisplatin and paclitaxel can induce pyroptosis through caspase-3/GSDME activation. However, in A549 Lung cancer cells, cisplatin is more effective than paclitaxel in triggering pyroptosis (58). According to several studies, the expression of DFNA5/GSDME in hepatocellular carcinoma (HCC) cells was significantly reduced compared to that in normal cells. Furthermore, the upregulation of the *DFNA5/GSDME* expression inhibited cell proliferation, which suggests that *DFNA5/GSDME* may be an anticancer gene (10, 59). Studies have found that GSDME knockout can significantly inhibit breast cancer (BC) cell pyroptosis and reduce the sensitivity of cancer cells to paclitaxel. In addition, GSDME methylation can increase the risk of BC lymph node metastasis, which suggests that GSDME exerts anticancer effects. Recent studies have suggested that chemotherapeutics can convert caspase-3-dependent apoptosis into pyroptosis *via* DFNA5/GSDME, which may be downregulated because of promoter methylation (47). Treatment with decitabine can induce *DFNA5/GSDME* up-regulation in cancer cells, which causes pyroptosis and increases the sensitivity of these cells to chemotherapeutics (11, 60).

NLRP3 (NOD-LIKE RECEPTOR THERMAL PROTEIN DOMAIN ASSOCIATED PROTEIN 3) AND CANCER

Studies have reported that stimulating the formation of NLRP3 inflammasomes in A549 Lung cancer cells with LPS and adenosine triphosphate can activate AKT, ERK1/2, and cyclic adenosine monophosphate response element binding protein. Moreover, it can upregulate the transcription factor Snail and downregulate E-cadherin, which confirms that the NLRP3 inflammasome can promote lung cancer cell proliferation and migration (61). In BC, the production of NLRP3 inflammasomes and IL-1β promote the infiltration of bone marrow cells, such as tumor-associated macrophages and myeloid-derived suppressor cells, which provide an inflammatory microenvironment that promotes BC progression (62). Furthermore, NLRP3 inflammasomes in fibroblasts are

associated with progression and metastasis (63). The NLRP3 inflammasome appears to be an effector that promotes lymphatic system metastasis and BC development (64). Various components involved in pyroptosis are closely related to digestive system tumors. Studies have found that the NLRP3 expression in HCC is significantly downregulated or even absent and that its expression is negatively correlated with the clinical stage and pathological grade. This suggests that the NLRP3 inflammasome participates in developing HCC (65). Furthermore, the NLRP3 inflammasome participates in the innate immune response to cervical cancer, and its expression is widely present in tumor cells (66, 67). The NLRP3 inflammasome activation can be achieved through lysosomal rupture, hemi-ion channels, and reactive oxygen species (ROS). In cervical cancer, the NLRP3 inflammasome is mainly activated by ROS to induce pyroptosis. In most of the cited reports, evidence on the role of NLRP3 in tumors is still in the preliminary stage, and further confirmation is needed to determine the potential therapeutic role of NLRP3 inflammasomes in human malignancies.

IL-18 AND CANCER

IL-18 plays an immunomodulatory role in the occurrence of esophageal squamous cell carcinoma (ESCC) (68, 69). IL-18 can induce $CD8^+$ T cells and natural killer cells to produce interferon-γ, improve anticancer immunity, and inhibit cancer cell proliferation and metastasis (68). Exogenous IL-18 is expected to be a new approach for treating ESCC. In one study, the vascular endothelial growth factor stimulated the production, processing, and secretion of IL-18 in gastric cancer cells. IL-18 promotes cell migration through actin polymerization and tensin down-regulation. Therefore, IL-18 may amplify the angiogenesis, migration, and progression of gastric cancer cells (70, 71). In addition to the angiogenic and invasive properties of IL-18, this cytokine can also induce the expression of protease inhibitor 9 and granzyme B inhibitor in gastric cancer cells, which reduces their sensitivity to lymphocyte-mediated cytotoxicity (72). Recent data indicate that the NLRP3 inflammatory body inhibitor thymoquinone and resveratrol inhibit the metastases of murine melanoma cells by inhibiting the IL-18-

mediated vascular cell adhesion molecule 1 expression and IL-18 secretion (73, 74). Different studies have reported the association between polymorphisms in the IL-18 gene promoter (-137 G >C and -607 C >A) and the development of different human cancers. A meta-analysis showed that the -137 G >C polymorphism is associated with an increased risk of nasopharyngeal carcinoma (NPC) in Asian populations but not in Caucasian populations (75). Another meta-analysis showed that the -607 C >A polymorphism is connected with an increase in the overall cancer risk, especially for esophageal cancer and NPC, in Asian populations (76). Recently, the discovery of IL-18-binding protein (IL-18BP) as a physiological inhibitor of IL-18 has suggested that this cytokine may be an attractive target. Its advantages and disadvantages in treating various diseases are currently being investigated (77, 78). In some types of tumors, the tumor-promoting effect of IL-18 is dominant, and IL-18BP may be beneficial. Therefore, any potential IL-18 treatment should be considered with caution.

IL-1B AND CANCER

IL-1β can promote epithelial–mesenchymal transition (EMT) in ESCC, colorectal carcinoma (CRC), and HCC, and it can promote the migration and invasiveness of cancer cells (79-82). Multiple studies have found that IL-1β is a crucial cytokine related to BC. IL-1β can induce the EMT process in BC, increase tumor malignancy, and increase the resistance of BC to cisplatin by upregulating resistance-related genes. IL-1β can also promote the expression of the oncogene baculoviral inhibitor of apoptosis repeat-containing 3 to decrease the resistance of BC to doxorubicin (82). Moreover, other studies have reported that IL-1β can induce tamoxifen resistance in BC by downregulating estrogen receptor-α (83). In response to the cancer-promoting effect of IL-1β, Tulotta *et al* used anakinra and kanazumab to block the IL-1β signaling pathway. They found that the body's anticancer immunity was enhanced, the number of cancer cells entering the circulation was decreased, and the metastasis of BC was suppressed (79). In the future, it is hoped that antitumor drugs that target IL-1β will become novel cancer therapies.

AIM2 (ABSENT IN MELANOMA 2) AND CANCER

AIM2 is a cytoplasmic sensor that recognizes double-stranded DNA (dsDNA) released during cellular perturbation and pathogenic assault (84). Upon binding to dsDNA, AIM2 assembles a multiprotein complex termed the inflammasome, which drives IL-1β and IL-18 secretion and pyroptosis (85). Several studies observed a decreased AIM2 expression in HCC tissues but not in normal tissues. The AIM2 expression was negatively correlated with tumor progression (86, 87). Additionally, AIM2 deficiency enhanced EMT and fibronectin-1 expression, which may be related to HCC metastasis (86). In human papillomavirus-infected cervical cancer cells, AIM2 can exert a tumor-inhibitory effect by stimulating pyroptosis (88). The AIM2 gene contains a microsatellite instability site, leading to frequent gene mutations in CRC and small intestine cancer (89, 90). Two independent studies have shown that AIM2 can inhibit CRC development (91, 92); AIM2 inhibits the proliferation of colonic stem cells and facilitates cell death by inhibiting the PI3K/AKT signaling pathway (91, 92). In addition, studies have shown that AIM2 inhibits the proliferation of colon cancer cells in the G2/M phase by inducing cell cycle arrest (93). Furthermore, the release of IL-18 mediated by the AIM2 inflammasome triggers the up-regulation of IL-22 binding protein and antimicrobial peptides that regulate intestinal homeostasis (94). A high AIM2 expression is associated with the increased survival rate of patients with Epstein–Barr virus-associated NPC. The function of AIM2 in NPC may involve IL-1β and the recruitment of immunostimulatory neutrophils into tumor masses, which can mediate antitumor activity (95). Depending on cancer, AIM2 plays different roles; for example, AIM2 functions as a tumor suppressor in CRC and HCC but as a tumor promoter in skin carcinoma (96). The AIM2 expression is moderate in skin squamous cell carcinoma, whereas its expression is low or absent in normal skin. The knockdown of AIM2 also leads to the reduced invasiveness of skin squamous cell carcinoma cells. It can inhibit the growth and vascularization of skin squamous cell carcinoma *in vivo* (96). Further

research on AIM2 will help us better understand the role of AIM2 in cancer and to develop new antitumor drugs.

CONCLUSION

Pyroptosis is a type of inflammatory PCD characterized by cell swelling and lysis that is mediated by various inflammasomes, which can discern danger signals and activate the secretion of pro-inflammatory cytokines (such as IL-18 and IL-1β). Pyroptosis can regulate cell proliferation, infiltration, migration, chemotherapy resistance, and other malignant phenotypes through various cell signaling pathways, thereby affecting tumor progression. The various components of the pyroptosis pathway are involved in almost all aspects of tumor development. They play either a tumor-suppressive or a pro-tumorigenic role. Therefore, research on the characteristics and mechanisms of pyroptosis and its relationship with cancer can provide novel ideas and effective drug targets for disease prevention and treatment.