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THE MOLECULAR MECHANISM OF PYROPTOSIS AND ITS RELATED DISEASES

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Cells are the basic unit of life, and cell death plays an important role in the body's metabolism, the occurrence and development of diseases. Pyroptosis is a form of programmed cell death. Pyroptosis is significantly different from other cell death methods (such as apoptosis, necrosis, etc.) in morphological characteristics, occurrence mechanism, and mechanism of action. When a cell undergoes pyroptosis, the nucleus condenses to form a pyroptotic body, numerous pores appear in the cell membrane, the cell swells and ruptures, releasing its contents. Caspase family is a homologous and structurally similar proteolytic enzyme in cytoplasm, which selectively recognizes and cleaves peptide bonds behind downstream target aspartic acid residues. Canspase 1,4,5,11 can induce pyroptosis through different pathways. Besides caspases, gasdermin also plays an important role in pyroptosis. Gasdermins (GSDMs) are a family of functionally diverse proteins expressed in a variety of cell types and tissues. The Gasdermin family includes 6 members, of which gasdermin D is the executor of pyroptosis. Upon cleavage by activated capsese, gasdermen D can be divided into N and C segments. Among them, the N fragment can form pores in the cell membrane, leading to cell swelling, rupture, outflow of cytokines and other contents, triggering the body's immune response, and leading to pyroptosis. The occurrence of pyroptosis can be divided into the classical pathway and the non-classical pathway. The classical pathway mainly depends on caspase-1, while the non-canonical pathway depends on the activation of Caspase-4/5/11. In addition, there are uncommon Caspase-3/8-mediated pathway and Granzyme-mediated pathway. As a way of cell death, pyroptosis is inextricably linked to disease. Inflammasomes and cytokines produced in the process of pyroptosis can trigger an inflammatory response in the body, and an excessive inflammatory response can lead to diseases, such as infectious diseases, neurological diseases, and tumors. In infectious diseases, pyroptosis is closely related to the infection of a variety of bacteria, fungi and viruses, and PAMPs and LPS can be recognized by corresponding inflammasomes and caspases, respectively, and activate the downstream pyroptotic pathways. Pathogen infection is the main way to induce pyroptosis. In cardiovascular diseases, a high-fat environment can induce an increase in reactive oxygen species (ROS), trigger endothelial cell pyroptosis, and exacerbate the development of atherosclerosis (AS). In the nervous system, cell death is involved in the pathogenesis of the progression of degenerative diseases of the central nervous system, such as Alzheimer's disease (AD), Parkinson's disease (PD), and stroke. In terms of tumors, pyroptosis can inhibit the occurrence and development of tumors, and at the same time, as a pro-inflammatory death, pyroptosis can form a microenvironment suitable for tumor cell growth, thereby promoting tumor growth.

Key words: *molecular mechanism, pyroptosis, disease.*

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Introduction. Cells are the basic unit of life, and the metabolism of the body is often accompanied by the occurrence of cell death. Cell death plays a key role in the development of the body, the maintenance of homeostasis and the occurrence and development of diseases. The modes of cell death are mainly divided into passive cell death and active cell death. Passive cell death is a self-protection mechanism produced by cells when they are stressed, injured or infected by pathogenic microorganisms. In this process, inflammation is produced, so it is also called inflammatory death. Typical passive cell death has cell coke. apoptosis and cell necrosis (Dutta et al., 2012). Active cell death mainly refers to the cell self-regulation process produced by organisms in order to regulate the number of cells, promote morphogenesis, and remove harmful or abnormal cells, mainly including apoptosis and autophagic death, both of which are cell behavior regulated by genes (Rogers et al., 2017; Tsuboyama et al., 2016).

Pyroptosis is a newly discovered way of cellular program death in recent years. It is the body's primary non-specific defense mechanism. It has an irreplaceable role in preventing external pathogen invasion and sensing endogenous danger signals(W. Xu and Huang, 2022). This article reviews the discovery and nomenclature, morphological and molecular features, molecular mechanisms and pyroptosis-related diseases of pyroptosis in recent years.

The discovery and naming of pyroptosis. Pyroptosis was initially proposed in 2001 by Cookson and Brennan to describe proinflammatory programmed necrosis that occurs

in *Salmonella*-infected macrophages in a caspase-1-dependent manner (Riedl and Shi, 2004). The term "pyropto-sis" comes from the Greek roots pyro, which means "fire" or "fever," and ptosis to denote a falling. The combination of the two words reflects the inflammatory nature of this method of cell death (Walle and Lamkanfi, 2016). However, how the activation of inflammatory caspase causes cell pyrolysis has not been answered. It was not until the publication of two independent research results in 2015 that this question was initially answered (Shi et al., 2014; Shi et al., 2015). They all found that gasdermin D (GSDMD) is a substrate of inflammatory caspase, which causes pyrolysis by forming small holes in the cell membrane after lysis (Shi et al., 2017). Therefore, pyroptosis is defined as gasdermin family-mediated programmed cell necrosis.Shao, et al found pyrolysis can also be caused by the activation of caspase-4/5/11 by Lipopolysaccharide (LPS) in the cytoplasm. The activated caspase-4/5/11 will eventually induce pyrolysis through the cleavage of gasdermin family proteins (J. Li et al., 2022). Therefore they defined pyroptosis as Gasdermin family-mediated programmed cell necrosis (Shi et al., 2015).

Morphological and molecular features of pyroptosis. Morphological features of pyroptosis. Pyroptosis is morphologically characterized by both cell necrosis and apoptosis. When cells undergo pyroptosis, the nucleus is condensed, chromatin DNA is randomly fragmented and degraded, the cells are swollen in a circular shape, and multiple vesicular protrusions are formed. Numerous pores appear on the surface, causing the cell membrane to lose its integrity (F. Wang et al., 2018). Blister-like protrusions are similar in size to apoptotic bodies and are called pyroptotic bodies. The formation of pores in the cell membrane is mainly a non-ion-selective channelformed by GSDMD (Sannino et al., 2018).

The cell membrane loses the ability to regulate the entry and exit of substances, the cell loses the balance of internal and external ions, osmotic swelling occurs and the membrane ruptures, releasing active substances such as cell contents, stimulating the body's immune response, recruiting more inflammatory cells, and expanding the inflammatory response (Jorgensen et al., 2017; Vanden Berghe et al., 2016).

Molecular features of pyroptosis Caspase family. Caspase family is a homologous and structurally similar proteolytic enzyme in cytoplasm, which selectively recognizes and cleaves peptide bonds behind downstream target aspartic acid residues. In normal cells,caspase protein usually exists in the inactive pro-caspase state, and only after hydrolysis of amino acid sequence into active caspase can play its role. So far, 15 caspases have been identified in mammals, 13 caspases in humans and 11 caspases in mice (Eckhart et al., 2008). According to the differences in structure and function, caspase can be divided into apoptotic and inflammatory types. Among them, Apoptosis caspase includes caspase-2/3/6/7/8/9/10, represented by caspase3, which is related to apoptosis. But it was found that caspase-3 also can induce pyroptosis by cleaving gasdermin E(GSDME) (Yupeng Wang et al., 2017). Moreover, caspase-8 which is related to apoptosis can also straightly cleave GSDMD to induce pyroptosis (Demarco et al., 2020). Inflammatory caspases include caspase-1/4/5/11/1213/14, which mediate inflammatory responses (Bergsbaken et al., 2009; Yazdi et al., 2010). Activation of inflammatory caspase-1 and caspase-4/5/11 ultimately leads to cell apoptosis.

Gasdermin family. Gasdermins(GSDMs) are a family of functionally diverse proteins expressed in a variety of cell types and tissues (Aglietti and Dueber, 2017; Kovacs and Miao, 2017). The earlier identified GSDMs in the gastrointestinal tract and dermis were named "gas-dermin"(Tamura et al., 2007). 6 GSDMs were found in humans and 10 GSDMz were found in mice. GSDMs consists of Gasdermin A (GSDMA), Gasdermin B (GSDMB), Gasdermin C (GSDMC), Gasdermin D (GSDMD), Gasdermin E (GSDME) and Pejvakin (PJVK).

GSDMA and GSDMB are mainly expressed in esophagus and intestinal cells, and are associated with hair loss, asthma and inflammatory diseases (Das et al., 2016; Saeki et al., 2009). Human GSDMC protein is expressed in epithelial cells of stomach, esophagus and spleen, and is inhibited in cancer cells such as gastric cancer, and its biological function is still under study (Ruan, 2019).

GSDMD and GSDME are widely expressed in different cell tissues. GSDMD is the executioner of pyroptosis due to its ability to form membrane pores (Feng et al., 2018). GSDMD can be specifically activated by inflammatory Caspase-1, 4, 5, 11, and cleaved into GSDMD-N (p30 fragment) and GSDMD-C (p20 fragment). GSDMD-C exists in the cytoplasm, and GSDMD-N has lipophilic and can binds specifically to phosphatidylinositol on the inside of the cell membrane and cardiolipin on the outside of the bacterial plasma membrane, oligomerizes in the membrane and forms a pore with a diameter of 10–16 nm (Zhao et al., 2018). The pore secretes a substrate of smaller diameter, eventually causing the membrane to rupture and releasing the entire cell contents (Evavold et al., 2018). When stimulated by chemotherapy drugs, tumor necrosis factor and virus infection, GSDME can be activated by caspase-3 of apoptotic signaling pathway to punch holes in cell membranes and transform the cells that should undergo apoptosis into pyroptosis (Y. Wang et al., 2018; X. Zhang and Zhang, 2018).

Usually GSDME is expressed at a high level in normal cells, while cancer cells undergo epigenetic modifications such as DNA methylation and histones, and most of them are in the state of GSDME inhibited expression or low-level expression(Yu and He, 2017). Pyroptosis of normal cells expressing GSDME may be one of the reasons for the toxic side effects of conventional chemotherapy drugs.

The mechanism of pyroptosis. The occurrence of pyroptosis can be divided into two ways: caspase-1-dependent and non-caspase-1-dependent(Ji et al., 2021). The way of cell death that depends on caspase-1 is called classical pathway pyrolysis, while the way of cell death that is not dependent on caspase-1 is caused by human caspase-4 and -5 or Caspase-11 induction in mice is called non-classical pathway pyrolysis. The morphological characteristics of pyrolysis in the classical pathway and the non-classical pathway are similar.

Both pathways cause the release of IL-1beta and IL-18, which are involved in inflammasome activation. IL-1beta induces tissue inflammation, vasodilation, and extravasation of immune cells, and also plays a role in adaptive immune responses(Slaats et al., 2016). IL-18 can promote the production of interferon-γ by Th1 cells, Natural killer(NK) cells and cytotoxic T cells, promote the development and maturation of Th2 cells, and enhance local inflammatory response(Wu et al., 2022).

Canonical pathway. Canonical pyroptosis is mediated by inflammasome assembly with GSDMD cleavage and IL-1β and IL-18 release(Frank et al., 2019; Xia et al., 2019). Inflammasomes are multimolecular complexes that are activated when the host becomes resistant to microbial infection.

When pathogens invade host cells, specific pattern recognition receptors (pattern recognition receptors, PRRs) on the cell surface or inside recognize pathogen-related molecular patterns (PAMPs) structure and endogenous risk-associated molecular patterns (DAMPs) (Broz, 2015). Pattern recognition receptors bind to specific ligands, and then combine with other proteins to form inflammasomes. If the Nod-liker Recptor Protein 3(NLRP3) inflammasome is activated, its ligands can stimulate eukaryotic cells to generate reactive oxygen species (ROS) and damage lysosomes to release lysosomal proteases to mediate NLRP3 activation (Grootjans et al., 2017). Activated NLRP3 converts biologically inactive pro-caspase-1 into active caspase-1. The caustic executive protein GSDMD is cleaved by activated caspase-1 at the Asp275 site, forming a 31 kDa N-terminus (N-GSDMD) and. a 22 kDa C-terminus (C-GSDMD) (Shi et al., 2015). N-GSDMD penetrates the cell membrane to form non-selective pores, resulting in cell swelling and pyroptosis (X. Chen et al., 2016; Sborgi et al., 2016). At the same time, caspase-1 also cleaves the precursors of IL-1β and IL-18 into mature IL1β and IL-18, which are released through the pores formed by GSDMD, leading to pyroptosis (He et al., 2015; Kayagaki et al., 2015).

Non-canonical pathway. Non-classical pyroptosis is activated by the activation of Caspase-4/5/11 as the premise pathway, mainly through the direct binding of the inflammatory Caspase-4/5/11 protein precursor to the LPS in the cytoplasm to assemble and trigger cell pyroptosis (Jorgensen and Miao, 2015). When pathogenic microorganisms infect host cells, PRRs located in the cytoplasm are recognized and bound to corresponding ligands, assembled to form multi-protein complexes in the cytoplasm, and activate inflammatory Caspase-4/5/11 to further cleave GSDMD protein to the cell membrane Punch holes to promote the occurrence of pyroptosis (Ji et al., 2021). At the same time, the inflammasome acts on downstream molecules to promote the release of mature and ruptured cell membranes such as inflammatory cytokines (such as IL-1β, IL-18, etc.), chemokines, and adhesion molecules to the outside of the cell, recruiting and activating more inflammatory cells. trigger an inflammatory response (Martinon and Tschopp, 2004).

In addition, Pannexin-1 is found to be another key protein in mediating pyroptosis in the non-classical pathway induced by caspase-11 (Yang et al., 2015). Upon stimulation with LPS, activated caspase-11 can specifically cleave and modify Pannexin-1, elicited intracellular ATP release and thereby induce pyroptosis mediated by the ion channel P2X7 receptor (Yang et al., 2015).

Caspase-3/8-mediated pathway. Members of the gasdermins protein family are highly conserved in structure. With the exception of DFNB59, all gasdermins contain C-terminal and N-terminal domains, the N-terminal being the executor of pyroptosis (Ding et al., 2016). Caspase-3 has long been considered as an important marker of apoptosis. Recently, Wang et al. Found that caspase-3 can affect and activate gsdme and promote the occurrence of focal death. In tumor cell lines with high expression of gsdme, chemotherapeutic drugs can induce the activation of Caspase-3 and cleave gsdme. The generated gsdme-n can punch holes in the cell membrane and cause the scorch death of tumor cells (Hyman and Yuan, 2012). Sarhan et al. Reported that caspase-8 can cleave gsdmd and mediate cell death during the inhibit ion of TGF-β-activated kinase 1(TAK1) by pathogenic Yersinia through effector YopJ(Chavarría-Smith and Vance, 2015; Orning et al., 2018). TNF-mediated apoptosis is converted to pyroptosis by PD-L1 in breast cancer cells. Under hypoxic conditions, the nuclear translocation of programmed death-ligand 1(PD-L1)is promoted by p-Stat3, which together enhance GSDMC transcription. Under the stimulation of tumor necrosis factor-α(TNF-α), Caspase-8 specifically cleaved GSDMC to generate N-GSDMC, and formed pores in the cell membrane to induce pyroptosis (Hou et al., 2020).

Granzyme-mediated pathway. Recently, Shao,etc, found for the first time that gasdermin can perform the perforation function through serine protease gzma hydrolysis at non ASP sites, and proved the cell death induced by cytotoxic lymphocytes as focal death (Mehta et al., 2013). This discovery rewrites the conclusion that focal death can only be activated by caspase. The serine protease granzyme A in cytotoxic lymphocytes (such as CTLs, NK cells, etc.) can enter the target cells through perforin, and the target cells can be induced to scorch by hydrolyzing lys229 / lys244 sites of gasderminb (gsdmb) molecules (Zhiwei Zhou et al., 2020). GSDMB has tissue-specific expression and is highly expressed in digestive system epithelial cell-derived tumor cells. Induction of focal death by gsdmb will enhance antitumor immunity and will become a potential target for the treatment of these tumors (Mehta et al., 2013).

Pyroptosis and diseases. Inflammatory bodies formed during pyroptosis can stimulate tumor cell pyroptosis and decrease tumor cell growth. The accumulation of inflammatory bodies, on the other hand, can create a favorable milieu for tumor cell growth (Demkow, 2021). GSDMD activation causes the release of inflammatory cytokines such IL-1 and IL-18, which activate immune cells, chemokines, cytokines, and adhesion molecules, so amplifying the inflammatory response (Liu et al., 2016). Il-1 β is an endogenous heat source that promotes fever, vasodilation, chemotactic migration of leukocytes, cytokine increase and hyperalgesia. Its unregulated discharge causes autoimmune disorders to develop(periodic syndrome, Mediterranean fever) (Feng et al., 2018). By boosting the production of IFN-γ, Il-18 causes

inflammation. It is a well-known antibacterial inflammatory cytokine that causes T cells and macrophages to become activated. At the same time, excessive pyrotopia activation can result in a significant number of cell death, tissue damage, organ failure, and even autoimmune inflammation, septic shock, or tumor, resulting in irreversible body harm (Jorgensen and Miao, 2015; Poli et al., 2015).

Pyroptosis and Infectious diseases. Pyroptosis is closely associated with multiple bacterial, fungal and viral infections In the pyroptotic pathway, PAMPs and LPS can be recognized by the corresponding inflammasomes and caspases, respectively, and activate the downstream pyroptotic pathway. Therefore, pathogen infection is the main way to induce pyroptosis. Pyroptosis has been found in Shigella, anthrax, tuberculosis, Brucella infection and bacillary dysentery (Banerjee et al., 2017; Zheng et al., 2016). Pyroptosis functions as a host defense mechanism when a pathogen infects the body, activating the innate immune system to fight infections (Gong et al., 2020). When cells are infected by Salmonella, the activation of caspase-1 will lead to the production of inflammatory factors, cell membrane damage, and even cell rupture, which is beneficial to the removal of intracellular bacteria(Gong et al., 2020). When Shigella infectes cells, it rapidly invades the intestinal mucosa quickly, cause inflammatory reaction, and eventually result in bacterial dysentery (Tien et al., 2006). In Lei et al.'s studyin the pathogenesis of enterovirus 71, the enterovirus protease 3C was found to cleave gasdermin D (Lei et al., 2017). The cleavage site is distinct from the caspase-induced cleavage site and physiologically inactivates the N-terminal fragment, thereby disabling the downstream pyroptosis pathway.

Enterovirus 71 escapes the resistance mechanism of the host cellular immune system by directly disrupting key factors in the pyroptosis pathway, providing anew perspective for reassessing pathogen resistance to host pyroptosis

Pyroptosis and Cardiovascular diseases. Atherosclerosis is a chronic progressive disease characterized by lipid accumulation and inflammatory cell infiltration (Benjamin et al., 2017). Many factors such as hyperlipidemia, hyperglycemia and smoking can promote the progression of As (Y. Zhang et al., 2018).

High fat environment can induce the increase of reactive oxygen species (ROS), trigger endothelial cell scorch death and downstream inflammatory waterfall, and aggravate the development of As. It can also promote the expression of AIM2, GSDMD-N and other genes in smooth muscle cells, increase the area of plaque and the number of dead cells in mice by inducing the scorch death of smooth muscle cells, and increase the instability of plaque (Pan et al., 2018).

Oxidized low density lipoprotein (ox-LDL) has a strong as promoting effect. It can induce endothelial cell death through ERS/ASKI axis or miR-125a-5p expression (Hang et al., 2020; Zeng et al., 2019). While ox-LDL induces macrophage focal death, it promotes the occurrence of cell focal death by limiting autophagy, and promotes the formation of necrotic nuclei and plaque instability (Zhenfeng Zhou et al., 2020).

High density lipoprotein (HDL) can play an anti as role, but when combined with chronic inflammatory diseases, it can be oxidized and modified to promote oxidation and inflammation. Oxidized HDL can induce NLRP3 mediated cell scorch death in macrophages, thereby promoting the progression of as plaque (Ji et al., 2021).

Pyroptosis and Central nervous system disease. Studies have shown that cell death is involved in the pathogenesis of central nervous system degenerative diseases progress, such as Alzheimer's disease (AD), Parkinson's disease(PD) and stroke(Zhiwei Zhou et al., 2020; Liu et al., 2016). The pathological features of AD are synaptic loss, neuronal death and extracellular neuroinflammatory plaques β- Amyloid- β, A β), which can interfere with the function of membrane and cause the outflow of K + from neurons. Low K concentration can activate nlrp1 and cause cell pyroptosis (Tan et al., 2014).

Pyroptosis activated by the PD-causing protein α-synuclein is closely related to the development of PD-induced neuroinflammation (Hu et al., 2022). Normally, aggregated α-synuclein can be released from impaired neurons and recognized by Toll-like receptors on microglia to activate the NF-B pathway and the NLRP3 inflammasome, thereby inducing microglia Pyroptosis and neuroinflammation(S. Wang et al., 2019).

Inflammation activated by inflammasome and pyroptosis is closely related to stroke pathology (Barrington et al., 2017). Increased expression of NLRP3, NLRP1, caspase-1, IL-1β and IL-18 was observed in brain samples from stroke patients(D Fann et al., 2013). Activation of the NLRP3/caspase-1/GSDMD pathway induces microglia and astrocyte pyroptosis in a mouse model of middle cerebral artery occlusion (MCAO) (P. Xu et al., 2019; Zhou et al., 2019). In addition, absent in melanoma 2 (AIM2) and NOD-like receptor containing 4(NLRC4) inflammasomes in microglia and NLRP6 and NLRP2 inflammasomes in astrocytes have been shown to activate GSDMD-mediated pyroptosis and inflammation, leading to models of ischemic brain injury damaged neuronal cells (Kim et al., 2020; Q. Li et al., 2020).

The role of Pyroptosis in Tumors. Pyroptosis can affect the occurrence and progression of tumor, which regulates the proliferation, invasion and metastasis of tumor cells through some non-coding RNA and other molecules.

Studies have found that inflammatory bodies can also exist in tumor cells, and these bodies can promote and inhibit tumor growth (L. C. Chen et al., 2012; Dinarello, 2010). Because inflammatory corpuscles are the key molecules that guide caspase-1 in cell focal death, it may be an important node between tumor cells and pyroptosis. Different tumors involve different inflammatory bodies. For example, NLRP3 widely exists in tumor cells (H. Zhang et al., 2018), and related tumors include nasopharyngeal carcinoma, colorectal cancer, and lung adenocarcinoma (Ungerbäck et al., 2012; Yanli Wang et al., 2016). In addition, liver cancer is also associated with aim2 inflammatory bodies (Ma et al., 2016). Although it can be inferred that cell death is related to tumor, the relationship between them is relatively complex. Studies have shown that cell death can inhibit the occurrence and development of tumor, but on the other hand, cell death can promote inflammatory death and form a microenvironment suitable for the growth of tumor

cells, so as to promote the growth of tumor (Brostjan and Oehler, 2020).

Pyroptosis and lung cancer. Lung cancer is the most common cancer in the world and one of the leading causes of death (Hong et al., 2015; Sun et al., 2019). In non-small cell lung cancer(NSCLC), GSDMD was found to be elevated (Gao et al., 2018). Furthermore, a high level of GSDMD aided tumor spread and predicted a poor outcome in lung adenocarcinoma(LUAD) patients. Activation of the pyroptotic signaling pathway (NLRP3/caspase1) promoted apoptosis but not pyroptosis in GSDMD-deficient tumor cells. Furthermore, inhibiting tumor proliferation by inhibiting the epidermal growth factor receptor/ Protein Kinase B(EGFR/Akt) signaling pathway in nonsmall-cell lung cancer(NSCLC) was achieved by silencing GSDMD (Peng et al., 2019). Xi et al. reported in 2019 that GSDMD colocalized with GzmB near immunological synapses, and that a deficiency in GSDMD reduced CD8+ T cell cytolytic capabilities, suggesting that GSDMD is required for tumor cell immune response (Xi et al., 2019). GSDME is found in a variety of molecular subtypes of lung cancer. In A549, PC9, or NCI-H3122 cells, GSDME or caspase-3 reduction drastically decreased GSDME-dependent pyroptosis (Lu et al., 2018). Both paclitaxel and cisplatin were shown to trigger apoptosis in A549 cells by Zhang et al., however some of the dying cells had a morphology that was very similar to pyroptosis (C.-c. Zhang et al., 2019).

Pyroptosis and gastric cancer. Gastric cancer is a cancer that starts in the cells of the stomach and has a poor prognosis and a high mortality rate (Graham, 2015; Wei et al., 2020). GSDMA was found to be a tumor suppressor gene in gastric cancer (Saeki et al., 2009), but it was also found to be overexpressed in some gastric cancer cells, suggesting that it could operate as an oncogene. GSDMB was found to be strongly expressed in the majority of malignant tissue samples but not in the majority of normal gastric tissues, suggesting that it may be linked to invasion (Komiyama et al., 2010). On the other hand, GSDMC was shown to be downregulated in gastric cancer, suggesting that it may act as a tumor suppressor. Wang et al. found that GSDMD can inhibit extracellular-signal-regulated kinase1/2(ERK1/2), Signal transducer and activator of transcription 3(STAT3) and phosphatidylinositol-3-kinase/Protein Kinase B(PI3K/AKT) in gastric cancer (GC) cells, thereby reducing the expression of Cyclin A2 and Cyclin DependentKinase (CDK2). Therefore, the reduction of GSDMD expression in GC cells increases the expression of Cyclin/CDK complex as a substance that regulates cell cycle, promotes the transition from S phase to G2 phase, and accelerates GC cell proliferation (W. J. Wang et al., 2018). Chemotherapeutic medicines were discovered to cause pyroptosis rather than apoptosis in gastric cancer cells with high GSDME expression. The stomach cancer cell lines that had been treated with 5-fluorouracil (5-FU) looked to go into pyroptosis (Y. Wang et al., 2018).

Pyroptosis and breast cancer. GSDMB overexpression was linked to tumor growth in breast malignancies, and overexpression predicted a poor response to HER-2 targeted treatment (Hergueta-Redondo et al., 2014). This suggests that GSDMB could be a new tumor prognostic marker. Furthermore, high GSDMC levels have been linked to a poor prognosis in breast cancer patients (Hou et al., 2020). Antibiotics such as doxorubicin, daunorubicin, actinomycin D, and epirubicin have been shown to increase the expression of nuclear PD-L1 and GSDMC and facilitate caspase-8 activation, resulting in pyroptotic death in breast cancer cells (Hou et al., 2020). Pizato et al. found that compared with untreated breast cancer cells, caspase-1 was activated,-gasdermin D was cleaved,IL-1β secretion was enhanced, and high mobility group protein B1(HMGB1) was secreted in breast cancer cells treated with docosahexaenoic acid (DHA). It is proved that DHA can induce pyrosis in breast cancer cells (Pizato et al., 2018). GSDME expression was shown to be low in various malignancies, and low levels of GSDME were also linked to poor breast cancer patient survival (Op de Beeck et al., 2012). The P2X7 signaling pathway has been linked to cancer (Burnstock and Verkhratsky, 2010; Fu et al., 2009). Ivermectin regulates the sensitivity of extracellular ATP and HMGB1 by mediating P2X4/P2X7-gated Pannexin-1 channel, and activates caspase-1 to induce apoptosis and pyroptosis (Draganov et al., 2015).

Conclusion. Pyoptosis has been clarified as an inflammatory and planned mode of cell death, but there are still some questions to be answered, such as what function other members of the gasdermin family play in pyroptosis.

Pyroptosis plays an important role in the maintenance of normal physiological function and morphology of tissues. At the same time, it is also involved in the occurrence of severe pathological damage and the development of clinical diseases, especially in tumor.

More and more researches focus on the phenomenon of pyroptosis in tumors, and the current research mainly focuses on the compounds or molecules activating inflammasomes such as NLRP1/3, NLRC4, and AIM2 and promoting cell pyroptosis. They have the potential to become new drugs for treating tumors. However, we do not fully understand the mechanism that these molecules affect tumor cell pyroptosis. Future research towards elucidating the mechanism of pyroptosis will help us improve our understanding of tumor cell pyroptosis and help develop anti-tumor drugs based on pyroptosis.

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Молекулярний механізм піроптозу та пов’язаних з ним захворювань

Основною структурною одиницею будови живих організмів є клітина, яка відіграє важливу роль у метаболічних процесах, виникненні та розвитку захворювань. Піроптоз – це захисний механізм вродженого імунітету, що унеможливлює розмноження внутрішньоклітинних патогенів. Піроптоз є формою запрограмованої некротичної загибелі клітини. За піроптозу, на відміну від інших процесів, а саме апоптозу та некрозу, в результаті активації каспази відбувається порушення цілісності плазматичної мембрани. Даний процес

має особливості і відрізняється механізмом виникнення та морфологічними характеристиками процесу. Коли клітина піддається піроптозу, ядро конденсується з утворенням піроптотичного тіла. У клітинній мембрані з'являються численні пори, клітина набухає і розривається, вивільняючи свій вміст. Каспаза є гомологічним і протеолітичним ферментом у цитоплазмі клітин, який вибірково розпізнає та розщеплює пептидні зв'язки. Каспаза може індукувати різні механізми розвитку піроптозу. Крім того, газдермін також відіграє важливу роль у процесі піроптозу. Газдерміни – це функціонально різноманітні білки, що експресуються в різних типах клітин і тканин. Гасдерміни представлені 6 видами білків. Після розщеплення газдерміни можна розділити на фрагменти N і C. N-фрагмент може спричинює процес утворення пор в клітинній мембрані, що призводить до набряку клітини, розриву, відтоку цитокінів та іншого вмісту, запускаючи процес імунної відповіді організму та спричинюючи процес піроптозу. Процес виникнення піроптозу розрізняють на класичний шлях і некласичний. Класичний процес в основному залежить від каспази-1, тоді як некласичний – від активації каспази-4/5/11. Як спосіб загибелі клітин, піроптоз нерозривно пов'язаний із захворюваннями. Інфламасоми та цитокіни, що утворюються в процесі піроптозу, можуть викликати запальну реакцію в організмі, що може призвести до прояву інфекційних, неврологічних та онкологічних захворювань. За інфекційних захворювань піроптоз тісно пов'язаний з інфекційними процесами, етіологічним чинником яких є бактерії, мікроскопічні гриби та віруси. Патогени ідентифікуються специфічними білками (інфламасомами та каспазами) і, відповідно, і в клітинах організму активізуються піроптичні процеси. Збудники інфекційних захворювань є основним етіологічним фактором індукції піроптозу. При серцево-судинних захворюваннях високий вміст жиру може викликати збільшення активних форм кисню, що спричинює піроптоз ендотеліальних клітин, а також активізує процес розвитку атеросклерозу та інсульту. Піроптоз нервових клітин бере участь у патогенезі прогресування дегенеративних захворювань центральної нервової системи, таких як хвороба Альцгеймера та хвороба Паркінсона. Піроптоз може як пригнічувати появу пухлин, так і створювати оптимальні умови для їх росту і розвитку.

Ключові слова: *молекулярний механізм, піроптоз, захворювання*