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Progress and perspectives of cellular pyroptosis in digestive tract tumors

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Abstract: *Cellular pyroptosis, a novel mode of cell death in recent years, is triggered by cysteine asparaginase. Distinguished from traditional apoptosis and necrosis, this mode of cell death is characterized by the activation of inflammatory vesicles and the release of inflammatory factors. Its unique mechanism and morphological changes have attracted increasing attention regarding their role in the development and progression of gastrointestinal (GI) tumors. This has provided new insights and potential strategies for tumor prevention and treatment. Among these strategies, intervening in the process of cellular pyroptosis has been considered a promising approach to inhibit tumor growth. This review aims to explore the mechanism of cellular pyroptosis, its role in GI tumors, and its potential applications in therapy.*

Keywords: *cellular pyroptosis, digestive tract tumors, mechanism*

1. Introduction

Cell death plays an important role in an organism's defense against pathogens[1]. However, both morphologically and in terms of the mechanism of occurrence, pyroptosis is distinct from what we know as necrosis and apoptosis[2,3]. Pyroptosis was first described by Friedlander in 1986, when he (Friedlander) observed that peritoneal macrophages in mice were rapidly killed after exposure to anthrax lethal toxin. By 2000 Salmonella-induced cell death was defined as cysteinyl asparaginase-1-dependent necrosis, which was finally formalized and defined as cellular pyroptosis in 2001[3]. The onset of pyroptosis involves both initiation and activation processes[4,5]. It is characterized by an inflammatory response that is dependent on inflammatory cysteoaspartases (caspases) and the gasdermin protein family (GSDMs) that distinguish it from other modes of cell death. After inflammatory vesicles de-activate cysteoaspartase, cysteoaspartase cleaves the GSDM proteins, exposing their N-terminal domains, after which the GSDM proteins bind to cellular lipids to induce the formation of pores in the cell membrane, which releases a large amount of inflammatory factors and triggers cellular focal death[6]. Numerous studies have shown that cellular pyroptosis plays a key role in the development of tumor diseases, and it is essential for the survival and proliferation of tumor cells[7]. It is essential for tumor cell survival and proliferation. Thus the association of focal death with cancer disease makes it a potential target for anti-tumor immunotherapy[8], the aim of this paper is to explore the mechanism of cellular juxtaposition, its role in gastrointestinal tumors and its potential applications.

2. The dual challenge of focal death in immune homeostasis

Cell death and apoptosis are two distinct modes of cell death[9]. Cell pyroptosis is defined as programmed cell death characterized by cell swelling, rupture of the cell membrane, and lysis and leakage of cytoplasmic contents.[10]. In contrast, apoptosis is characterized by cell shrinkage and apoptotic vesicle formation[11]. In addition, focal death is usually associated with an inflammatory response that triggers the release of inflammatory factors, whereas apoptosis usually does not cause a significant inflammatory response. Closely associated with the occurrence of focal death are members of the GSDM protein family[12]. These GSDM proteins are in an inactivated state under normal conditions and their C termini are inhibited. Under specific stimuli, such as infection by pathogenic microorganisms or activation of intracellular inflammatory responses, activated Caspase-1, Caspase-4/5/11, and other proteases can cleave the N-terminus of the GSDM family members, and

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their N-terminal structural domains will result in the formation of a pore in the cell membrane, which will contribute to the swelling of the cell and the release of cytosolic contents, while pro-IL-1β and pro-IL-18 will be cysteine protease cleavage into an activated form, triggering pyroptosis[3]. Pyroptosis has a dual role in the regulation of immune homeostasis. On the one hand, the positive effects of pyroptosis include immunomodulation, cellular repair, and antitumor effects, and the intracellular components released during pyroptosis can be recognized by immune cells as danger signals (DAMPs), which stimulate inflammatory responses and direct relevant immune cells (e.g., macrophages and inflammatory T cells) to reach the damaged area, which helps to remove infected or abnormal cells, thus strengthening the immune response. In addition, pyroptosis not only promotes the activation of intracellular clearance and repair mechanisms to prevent the spread of pathogens or intracellular damage, but also enhances the recognition and killing of tumor cells by the immune response. Together, these functions come together to maintain immune homeostasis[13]. On the other hand, focal death in immune homeostasis may also negatively affect immune regulation. Excessive or inappropriate pyroptosis responses may lead to excessive inflammation and tissue damage[14]. In addition, the cells released by juxtamembryonic deaths may also be used as a source of inflammation. In addition, intracellular components released by juxtamembryonic death may be used as autoantigens, triggering autoimmune responses and leading to the development of autoimmune diseases. Therefore, regulation of the pyroptosis process is important in immune homeostasis to ensure moderate inflammation and immune responses while avoiding excessive destructive inflammation.

3. Molecular mechanisms of cellular pyroptosis

3.1. Normative pathways

The classic pathway of cellular pyroptosis involves the activation of inflammatory cysteine enzymes (especially caspase-1) and the formation of inflammatory vesicles. The following is a breakdown of the steps involved in the classical pathway: Activation of pattern recognition receptors (PRR): PRRs, such as NOD-like receptors (NLR) and AIM2-like receptors (ALR), which are activated in response to stimulation by pathogen-associated molecular patterns (PAMP) or danger-associated molecular patterns (DAMP) released during cellular stress or infection. Inflammatory vesicle formation: PRRs are activated by the recruitment of the bridging protein ASC (apoptosis-associated speck-like protein containing CARD) and caspase-1 in order to form multiprotein complexes. Depending on the specific PRR involved, different types of inflammasomes can be formed. Caspase-1 activation: in inflammasome complexes, pro-caspase-1 undergoes autoproteolytic cleavage to form active caspase-1. The presence of ASC proteins usually facilitates this activation step. Cleavage of pro-inflammatory cytokines: activated caspase-1 then cleaves pro-inflammatory cytokines such as interleukin-1β (IL-1β) and interleukin-18 (IL-18) into their active forms. These cytokines are potent mediators of inflammation and play a crucial role in the immune response. Gasdermin D pore formation: in addition to cleaving cytokines, activated caspase-1 cleaves Gasdermin D (GSDMD), which in turn translocates to the cell membrane to form a pore, leading to cellular swelling and lysis and the release of pro-inflammatory cytokines and danger signals into the extracellular space. Inflammatory response: the release of reactive cytokines and danger signals triggers a strong inflammatory response that attracts immune cells to the site of infection or tissue damage[6,15-17]. Inflammatory response. Overall, the classical pathway of cellular pyroptosis plays a crucial role in host defense against pathogens and in the regulation of inflammation.

3.2. Non-regulated pathways

The non-canonical pathway, also known as the caspase-independent pathway, is distinct from the caspase-1-activated cell death mechanism. Instead, it is triggered by the activation of other cysteoaspartases, such as caspase-4/5 in humans and caspase-11 in mice.These cysteoaspartases can be activated directly by cytoplasmic lipopolysaccharides (LPS) derived from Gram-negative bacteria or other danger signals, and their activation cleaves Gasdermin D (GSDMD) or Gasdermin E (GSDME) proteins, leading to the formation of membrane pores and subsequent release of cytokines and other cellular contents. However, it is important to note that the N-terminus cannot directly promote the activation of inflammatory factors at this time, but rather needs to be activated by the inflammasome pathway consisting of NLRP3, ASC, and caspase-1 to activate pre-caspase-1. This, in turn, initiates the conversion of pro-IL-1β and pro-IL-18 into mature IL-1β and IL-18, ultimately initiating the inflammatory response[6,18].

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3.3. Other cysteine asparaginase pathways

In addition to the cysteoaspartic enzymes we mentioned above, the apoptosis regulator caspase-3/8 has also been shown to induce the onset of pyroptosis, and the specific mechanism can be described as when stimulated by exogenous signals (e.g., TNF-α or chemotherapeutic agents), cysteoaspartic enzyme 3 is activated and cleaves the N-terminal end of the GSDME protein, which induces intracellular inflammatory cascade and ultimately triggers pyroptosis. In earlier studies, it was found that antibiotic chemotherapeutic agents mediated pyroptosis via the caspase-8/GSDMC and GSDME pathways during chemotherapy for breast cancer. In addition, further studies indicated that during the inhibition of lung cancer cell proliferation with TAK8, cysteinyl asparaginase 1 contributes to pyroptosis by modulating the activities of the substrates GSDMD and GSDME[8,19] .

3.4. Granzyme-A/B-mediated pyroptosis pathway

Granzyme is an endogenous protease produced by NK cells and cytotoxic T lymphocytes, which is involved in a variety of intracellular biological processes. granzyme B produced by CAR-T cells induces cellular pyroptosis through the caspase-3/GSDME pathway, in addition, granzyme B directly cleaves GSDME and triggers pyroptosis, resulting in an anti-tumor effect. On the other hand, granzyme A from NK cells and cytotoxic T lymphocytes cleaved GSDMB, leading to cell membrane perforation and mediating cellular pyroptosis to eliminate tumor cells. The above findings reveal that granzymes from different sources regulate pyroptosis through different signaling pathways, especially in immune cell-mediated antitumor immunity[20].The above four mechanisms are shown in Figure 1.

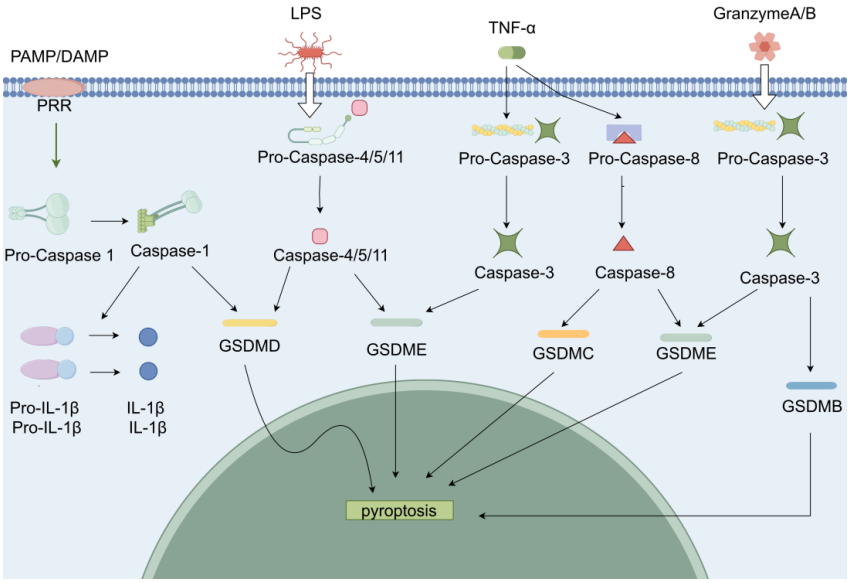

Figure 1: The mechanism and pathway of cell pyroptosis

4. Cellular pyroptosis and digestive tract tumors

4.1. Esophageal Cancer

Focal death-related genes are important in tumor immunity and prognosis[21,22]. Recent studies have shown that dihydroartemisinin (DHA) can trigger focal death by mediating the activation of caspase-8/3[23]. However, further studies on the role of DHA in the treatment of esophageal cancer are needed. Although DHA may have anticancer effects by triggering pyroptosis, more experimental and clinical trials are needed to verify its efficacy and safety before clinical application[23,24]. Cisplatin is a commonly used chemotherapeutic agent for the treatment of several cancers, including esophageal cancer. It induces focal death by activating the Bax-caspase-3/9-GSDME signaling axis, and it also inhibits DNA synthesis and induces DNA damage, thereby inhibiting the growth and proliferation of cancer cells[25]. This finding provides guidance for exploring new therapeutic strategies against esophageal cancer and is expected to improve the efficacy of cisplatin therapy. Although pyrodehydes have potential in anticancer research, the specific mechanism of action in cisplatin treatment of

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esophageal squamous cell carcinoma is still unclear, and more studies are needed to explore and confirm it[26]. The role of chemotherapy resistance in esophageal squamous cell carcinoma Chemotherapeutic resistance has caused great trouble in the treatment of esophageal cancer. Betulinic acid is a naturally occurring compound, and recently J. Chen et al. found that the use of betulinic acid in combination with cisplatin in mice increased the sensitivity of esophageal cancer to cisplatin and may reduce the side effects of cisplatin in patients. This effect was achieved by promoting the expression of ASC and cysteinyl asparagin-1 proteins in TE-1 cells, which in turn mediated the onset of pyroptosis[27]. Although this study was conducted in mice, it offers the possibility of further investigating betulinic acid as a potential anti-esophageal cancer drug. In addition, Wu Mengjiao et al. found that the combination of PLK1 kinase inhibitor and cisplatin in esophageal cancer induced focal death via the BAX / caspase-3 / GSDME pathway, and also improved the chemosensitivity of cisplatin[28]. It is believed that more studies will be conducted in the future to validate the efficacy of this combination therapy and explore its potential in clinical applications.

4.2. Stomach Cancer

It is well known that stomach cancer is in the fourth place in the global ranking of common cancers[29]. Surgery combined with radiotherapy is a promising way to improve the survival rate of gastric cancer patients, but chemotherapy resistance tolerance is still a major challenge affecting the prognosis of gastric cancer at present[30]. The study of Yin J et al. A study by J. Yin et al. showed that GSDME was the only gene in the GSDMs protein family that was associated with the prognosis of gastric cancer when exploring the roles of coagulation-related genes in gastric cancer[31]. BIX enhances the efficacy of chemotherapy by activating GSDME-mediated pyroptosis in gastric cancer cells[30]. Cisplatin is widely used in gastric cancer. Cisplatin is widely used in the first-line treatment of gastric cancer, but long-term use of cisplatin may lead to differentiation of cancer stem cells into different types of gastric cancer cells, which may lead to chemoresistance. This severely limits the efficacy of cisplatin in the treatment of GC. LncRNA ADAMTS9-AS2 is lowly expressed in gastric cancer tissues, while miR-223-3p is overexpressed. The researchers found that the expression of NIRP3, a key protein in the development of focal death, is significantly up-regulated when miR-223-3p is inhibited, which further leads to the development of focal death, and achieves the therapeutic efficacy of inhibiting the proliferation of gastric cancer. Most importantly, the high expression of LncRNA ADAMTS9-AS2 also sensitizes gastric cancer cells that originally showed resistance to cisplatin[32] . Studies have shown that overexpression of lncRNA ADAMTS9-AS2 inhibits gastric cancer development by regulating the miR-223-3p/NLRP3 axis-mediated pyroptosis process[33,34] . In addition, Icariin (ICA), which is mainly found in Epimedium, has multiple biological activities, and the anticancer effects of ICA are associated with the signaling axis between hsa_circ_0003159, miR-223-3p, and NLRP3. In gastric cancer, the use of ICA affects the expression levels of hsa_circ_0003159 and miR-223-3p. ICA upregulates the expression of hsa_circ_0003159 and downregulates the expression of miR-223-3p, which promotes an increase in the expression level of NLRP3. Through this mechanism, ICA can trigger cellular pyroptosis, thereby inhibiting the growth of gastric cancer cells[35] .

4.3. Liver Cancer

Hepatocellular carcinoma is a common malignant tumor, and the search for new therapeutic targets is crucial for improving the long-term prognosis of hepatocellular carcinoma, yet cellular pyroptosis is closely related to the mechanism of hepatocellular carcinoma development[36]. Therapeutic strategies to target cellular pyroptosis can be directed in several directions, and we can induce programmed death of tumor cells by mediating the pyroptosis pathway in tumor cells. For example, some chemicals or corresponding molecularly targeted drugs can induce cellular pyroptosis. Neobava isoflavone is a natural compound, and in the presence of neobava isoflavone, ROS generated in the cell affects the expression level of the mitochondrial outer membrane protein Tom20, which promotes the aggregation of Bax proteins into the mitochondria. Activated Bax proteins cause focal death of hepatocellular carcinoma cells through the caspase-3/GSDME pathway[37]. Alpine isoflavones have also been shown to trigger focal death through the NLRP3/caspase-1 pathway[38]. Similarly, Wanfeng Liang et al. showed that curcumin also has the potential to promote cellular pyroptosis by a mechanism involving increased intracellular ROS production and upregulation of GSDME-N expression[39] . It has been reported that 17β-estradiol (E2) increases the expression levels of NLRP3, ASC (adaptor protein) and caspase-1 and enhances their interactions, thereby enhancing the formation of NLRP3 inflammatory vesicles and triggering cellular cellular cellular death via the ROS signaling pathway[40]. A study by Song et al. demonstrated that Schisandrin B not only reduces HepG2 cell viability and initiates

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apoptosis, but also mediates pyroptosis through the perforin granzyme B/caspase-3/GSDME pathway when transduced by NK cells[41]. Another therapeutic strategy is to reduce the promotion of cellular juxtaposition by inhibiting the inflammatory response and cell proliferation in the hepatocellular carcinoma microenvironment. Dibutyl phthalate is a common plasticizer, and Huo et al. found that long-term exposure to DBP may lead to the development of liver injury and fibrosis. Specifically, DBP induces an inflammatory response and activation of NLRP3 inflammatory vesicles in hepatocytes by activating the p38MAPK and NF-κB pathways. This further triggers an inflammatory response and cellular pyroptosis. Therefore, we conclude that targeting p38MAPK and NF-κB prevents liver fibrosis from further evolving into cirrhosis or hepatocellular carcinoma[42]. Combined treatment of cellular pyroptosis and other therapies: In fact, cellular pyroptosis treatment can also be combined with other therapies, such as radiotherapy, chemotherapy, or immunotherapy. This can enhance the therapeutic effect and reduce the risk of liver cancer progression and metastasis by combining therapeutic strategies. From the above expression we can see that its inhibitory effect on cancer cell proliferation is much greater than its promotional effect, which also provides a potential target for our targeted treatment of hepatocellular carcinoma.

4.4. Colon Cancer

Studies have shown that focal death-related genes (e.g., GSDME) are associated with the treatment and prognosis of colorectal cancer, and that many drugs are able to exert cancer-suppressive effects by inducing focal death through the corresponding signaling axis[43]. Yu et al. found that when colorectal cancer is exposed to lopressor, this antitumor drug triggers the activation of ROS, which further activates the JNK (c-Jun N-terminal kinase) signaling pathway, which promotes the translocation of Bax to the mitochondria, leading to mitochondrial dysfunction and inducing the onset of pyroptosis, it also activates caspase-3 and -9, promoting the apoptosis process through GSDME[44]. The Chen Yiliu et al. found that in colon cancer HT-29 cells, lignans could activate caspase1, cleave GSDMD protein, and then stimulate the downstream onset of pyroptosis[45]. The expression level of NLRP1 is low in normal colorectal cancer cells, but after the use of the antitumor drug DAC (5-azacytidine), its expression can be significantly increased thereby inhibiting cancer cell proliferation[16]. It is certain that pyroptosis is definitely involved in the tumor suppression process, and a large number of studies in the past have found that anticancer drugs such as cisplatin achieve tumor suppression by inducing apoptosis[46]. Thermotherapy has long been used in the diagnosis and treatment of tumors. Thermotherapy has long been used in the diagnosis and treatment of tumors, and a study by Wang et al. found that metal-rich HSP90 nanoinhibitors play an anti-tumor role through oxidative stress-mediated pyroptosis in colon tumor cells[47] . During cancer treatment, patients exhibiting resistance to targeted drugs and the occurrence of adverse events are insurmountable challenges, and activation of STAT3 signaling proteins is an important mechanism for promoting tumor proliferation and the development of chemoresistance. Studies have shown that when oxaliplatin and GW4064 are applied in combination, not only can they induce a synergistic antitumor effect by cutting the GSDME pathway to induce focal death, but more importantly, they can block the STAT3 signaling pathway to enhance the sensitivity of colorectal cancer to oxaliplatin[48] In recent years, it has been found that colorectal cancer metastatic gene In recent years, it has been found that colon cancer metastatic gene (MACC1) is expressed in colon cancer, and in colon cancer with low expression of MACC1, the use of irinotecan not only enhances the cellular pyroptosis by mediating GSDME to promote tumor cell death, but also reduces the resistance of colon tumor cells to irinotecan, which leads to a better therapeutic efficacy [49]. The effect of GSDME on tumor cell death will be better. In the presence of the pro-inflammatory factor interleukin-17A (IL-17A), ROS production is increased, and NLRP3 and cysteine asparaginase-4 are activated to cleave the GSDMD, which in turn triggers mitochondrial dysfunction and cellular death. In addition, IL-17A also has the effect of recruiting CD8+ T cells to infiltrate tumor cells and enhance anti-tumor immunity[50]. Targeting IL-17A-associated pathways may be a potential strategy for treating tumors and modulating immune responses.

4.5. Pancreatic Cancer

Pancreatic cancer is a highly aggressive and fatal disease with limited and ineffective treatment options. Bai et al. demonstrated that focal death-related genes (e.g., GSDMD/GSDME) play an important role in pancreatic cancer, and that predictive models based on these genes are important for pancreatic cancer treatment and prognosis[51,52]. O-glycosylation during post-translational modifications is tightly regulated in normal cells, maintaining normal cellular function and signaling. However, in tumor cells, aberrant O-glycosylation is thought to be a tumor-promoting, growth- and

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migration-promoting factor in pancreatic cancer. Overexpression of GSDME is positively correlated with the malignant behavior of pancreatic cancer and resistance to chemotherapy, and commonly used chemotherapeutic agents such as gemcitabine, irinotecan, 5-fluorouracil, paclitaxel, and cisplatin can exhibit potent antitumor immunity by inducing GSDME-dependent scorched death[53]. The peptide N-acetylgalactosaminyltransferase-6 (GALNT6) is highly expressed in pancreatic ductal adenocarcinomas, and it has been noted that knockdown of GALNT6 leads to increased activation of the NF-κB signaling pathway in pancreatic ductal adenocarcinoma cells as evidenced by an increase in NF-κB phosphorylation. A decrease in glycosylation was also observed, and the above changes combined to achieve the effect of inhibiting tumor cell proliferation[54] . In addition, steroidal saponins are a class of natural compounds, and many of them have potential bioactivities and pharmacological effects. In one study, the steroidal saponins polypodophyllin I (PPI), colchicine III (CCRIS), and parisin V (PSV) were found to show inhibitory effects on the proliferation of PANC-1, AsPC-1, and BxPC-3 cells, which, in turn, led to the occurrence of pyroptosis in pancreatic cancer,. It is noteworthy that PPI, CCRIS, and PSV mediate the onset of focal death through GSDME but not GSDMD[55]. The above demonstrates that the genes involved in pyroptosis can be The above suggests that focal death-related genes can be potential targets for chemotherapeutic agents in the treatment of pancreatic cancer, but further studies are needed to elucidate the specific molecular mechanisms and validate their therapeutic effects.

5. Summary

It is well understood that cellular pyroptosis is an immunogenic form of cell death and that it plays a dual role in tumor development[56]. Especially in anti-tumor therapy, cellular pyroptosis plays a crucial role. In the current study, the GSDMA-E protein family demonstrated antitumor activity in a variety of cancers[3] . Among them, GSDMD is the most popular protein family, while there are other protein families such as GSDMB, GSDMC, and GSDME, which also induce the onset of juxtaposition in response to activation of inflammatory proteases. In tumors, focal death triggers a strong inflammatory response and marked tumor regression. However, the exact mechanism of pyroptosis in anti-tumor has not been thoroughly investigated and still needs to be further explored. It has been demonstrated that in a variety of tumors, the expression of GSDME is silenced, while overexpression of GSDMB exists, and thus may have a dual role in cancer therapy. However, there is still a lack of clear studies on the mechanisms of focal death mediated by GSDMC, GSDME and GSDMB in tumor immunotherapy. In the future, further studies are needed to reveal the mechanisms involved.

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