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REVIEW

Research progress on the effect of pyroptosis on the occurrence, development, invasion and metastasis of colorectal cancer

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Abstract

Pyroptosis is a type of programmed cell death mediated by gasdermines (GSDMs). The N-terminal domain of GSDMs forms pores in the plasma membrane, causing cell membrane rupture and the release of cell contents, leading to an inflammatory response and mediating pyrodeath. Pyroptosis plays an important role in inflammatory diseases and malignant tumors. With the further study of pyroptosis, an increasing number of studies have shown that the pyroptosis pathway can regulate the tumor microenvironment and antitumor immunity of colorectal cancer and is closely related to the occurrence, development, treatment and prognosis of colorectal cancer. This review aimed to explore the molecular mechanism of pyroptosis and the role of pyroptosis in the occurrence, development, treatment and prognosis of colorectal cancer (CRC) and to provide ideas for the clinical diagnosis and treatment of CRC.

Key Words: Cell pyroptosis; Tumor metastasis; Colorectal cancer; Clinical diagnosis; Review

Core Tip: Pyroptosis plays an important role in inflammatory diseases and malignant tumors. With the further study of pyroptosis, an increasing number of studies have shown that the pyroptosis pathway can regulate the tumor microenvironment and antitumor immunity of colorectal cancer and is closely related to the occurrence, development, treatment and prognosis of colorectal cancer. This review aimed to explore the molecular mechanism of pyroptosis and the role of pyroptosis in the occurrence, development, treatment and prognosis of colorectal cancer (CRC) and to provide ideas for the clinical diagnosis and treatment of CRC.

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INTRODUCTION

Colorectal cancer (CRC) is a gastrointestinal malignancy. According to China's cancer statistics report in 2023, the incidence and mortality of colorectal cancer rank third and fifth, respectively, among all malignant tumors[1-5]. Pyroptosis is a type of programmed cell death that can be divided into typical and atypical pathways according to the pathways involved in inflammasome formation. The typical pathway is triggered by inflammasome assembly and promotes the activation of cysteinyl aspartate specific protein-1 (caspase-1), which then promotes the cleavage of the effector protein gasdermin D (GSDMD)[6-8]. In the nonclassical pathway, Caspase-4/5/11 directly cleaves GSDMD without assembling the inflammasome. Caspase-1 converts pro-interleukin (IL)-1β and pro-IL-18 to IL-1β and IL-18 through its proinflammatory activity[9]. By recruiting and activating exocellular inflammatory factors, immune cells induce the synthesis of inflammatory factors, adhesion factors and chemokines, thereby amplifying the inflammatory response. In addition to Caspase-1, Caspase-4/5/11, granzyme A (GZMA) and granzyme B (GZMB) may also cause pyroptosis. Recent studies[10-15] have shown that pyroptosis plays an important role in the occurrence, development and metastasis of cancer and affects therapeutic outcomes by affecting the infiltration of immune cells[16-18]. Therefore, extensive research is needed to elucidate the molecular mechanism underlying the relationship between pyrodeath and CRC (Figure 1).

THE SIGNALING PATHWAY OF PYRODEATH

Caspase-1-dependent pathway

Typically, pyroptosis is mediated by Caspase-1, and the key step is the recruitment and activation of Caspase-1[19]. For example, in the NOD-like receptor thermal protein domain associated protein 3 (NLRP3) inflammasome, when the NLRP3 protein is exposed to pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs), the NLRP3 protein contains a caspase recruitment domain, an associated speck-like protein containing a caspase recruitment domain (ASC) and Caspase-1, and is assembled into the NLRP3 inflammasome[20]. NLRP3 inflammasome assembly activates precaspase-1, which not only mediates the maturation and secretion of IL-1β and IL-18 but also directly cleaves GSDMD to produce GSDMD-N[21-25]. Subsequently, GSDMD-N binds to phosphatidylinositol, phosphatidylic acid, and phosphatidylserine on the inner surface of the membrane through membrane-lipid interactions and forms oligopolymer pores (GSDMS pores) with inner diameters of 10 nm to 20 nm in the lipid bilayer, ultimately leading to cell pyrosis[26-30]. At the same time, small holes in the plasma membrane cause the connection between the inner and outer membranes to form nonselective membrane channels, resulting in the outflow of K + ions, causing the ion concentration on both sides of the plasma membrane to be unbalanced, and the solute to enter the cell, resulting in cell swelling and eventually cell death[31-34].

Caspase-4/5/11 pathway

Like in the classical pyro pathway, the protein involved in the nonclassical pyro pathway is also GSDMD; the difference is that the nonclassical pyro pathway is directly recognized by caspase-11 (mouse) and caspase-4/5 (human) combined with lipopolysaccharide in the cell wall of gram-negative bacteria. Lipopolysaccharide (LPS) and activate their own protease activity[35-38]. After activation, Caspase-4/5/11 directly cleaves GSDMD into the C segment and N-terminal segment and forms cell membrane pores *via* the oligomerization of GSDMD-N[39-41]. This pyrodeath mediated by Caspase-4/5/11-GSDMD is called nonclassical pyroptosis and is a process independent of Caspase-1[42-44].

Other activation pathways

In addition to the classical and nonclassical pyroptosis pathways mentioned above, other signaling pathways can also induce pyroptosis[45]. When intracellular GSDME expression is high, Caspase-3 cleaves GSDME to induce pyroptosis, while when GSDME expression is low or absent, apoptosis occurs. Recent studies[46-50] have shown that the aminoprotease GZMA can enter target cells *via* perforin and induce pyrodeath in target cells through Lys229/Lys244 of

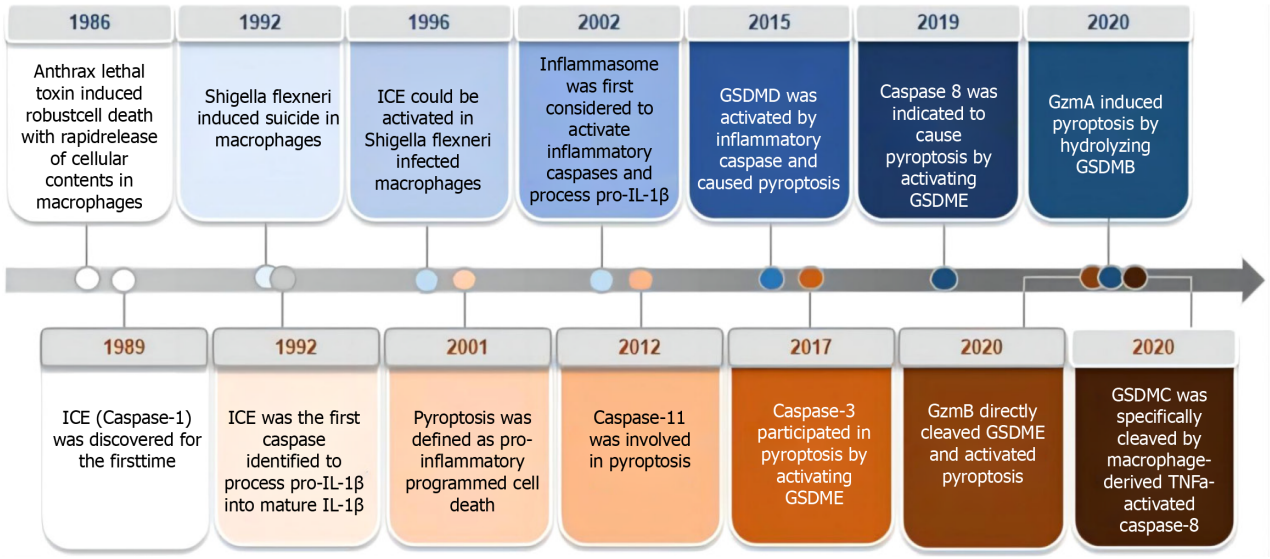

Figure 1 Summary of the timeline of research and reports on pyroptosis. ICE: Caspase-1; IL: Interleukin; GSDMD: Gasdermin D; TNF: Tumor Necrosis Factor. Citation: The authors have obtained the permission for figure using from the BioRender.com (Supplementary material)[203].

gasdermin B (GSDMB), contradicting the conclusion that pyroptosis can be activated only by caspases.

GSDM family proteins are the key substrates of pyroptosis

DFNA5 and Pejvakin (PJVK, also known as DFNB59)[51-54]. With the exception of PJVK, all Gasdermin proteins have a dual-domain structure: A C-terminal effect domain and an N-terminal inhibition domain[55]. The N-terminal domain of GSDMD is lipophilic and can bind to phosphatidylinositol phosphate and phosphatidylinositol, which allows the cell membrane to form nonspecific pores that lead to pyrodeath by releasing cell contents[56-58].

GSDMD is widely expressed in a variety of cells and tissues and is a common substrate protein for mouse Caspase-11 and human Caspase-4/5. GSDMD has 487 amino acids with a relative molecular mass of 53 × 10^3 and consists of a 30 × 10^3 N-terminal domain and a 22 × 10^3 C-terminal domain. In general, the C-terminus of GSDMD is connected to the N-terminal domain by a long ring, leaving GSDMD in a self-inhibitory state, while GSDMD can be cleaved by Caspase-1/11 into two independent domains in a state of activation of the cell pyro pathway, where the N-terminus is inserted into the plasma membrane to induce pyroptosis (Figure 2). Therefore, GSDMD has become an important target for pyroptosis intervention.

THE RELATIONSHIP BETWEEN PYRODEATH AND THE OCCURRENCE AND DEVELOPMENT OF COLORECTAL CANCER

The GSDM family

GSDMC-induced pyroptosis plays a role in colorectal cancer, and GSDMC is significantly upregulated in CRC patients. GSDMD deficiency promotes the development of CRC, possibly through reduced pyroptosis caused by the downregulation of interferon-γ and transcriptional activator 1 signaling[59-62]. In addition, GSDMD expression is significantly downregulated in human CRC tissues, and patients with high GSDMD expression in CRC tissues have a decreased risk of distant metastasis[63-67]. GSDMD is involved in the proliferation, invasion, scorch death and metastasis of colorectal cancer cells and inhibits the occurrence and development of tumors[68-70]. Studies[71-75] have shown that GSDME plays a key role in the progression of colorectal cancer, and GSDME methylation can be used as a potential specific marker and a meaningful prognostic biomarker for patients with colorectal cancer. These findings suggest that colorectal cancer cells may inhibit their proliferation through Caspase-3/GSDME-mediated pyroptosis. In addition, GSDME-mediated pyroptosis promoted the development of colitis-associated colorectal cancer but not in xenograft models[76-78].

The NLRP inflammasome

These findings show that CRC risk is associated with the NLR in CRC tissues and/or cell lines, providing preliminary evidence for the involvement of the NLR in CRC development. In addition, a study revealed that NLRP5, also known as MATER, is not expressed in normal colon tissue but is expressed in colon cancer tissue and cell lines[79]. The NLRP1, NLRP3, and NLRP12 inflammasomes are negative regulators of intestinal tumorigenesis[80]. Studies[81-84] have confirmed that human colorectal tumor tissues express lower levels of NALP1 than surrounding tumor tissues and are associated with patient survival and tumor metastasis[85]. Increasing the expression of NALP1 improved the survival rate of the mice. NLRP3 deficiency significantly increased mortality in mice with acute DSS-induced colitis, and the incidence of CRC tended to increase in NLRP3-deficient mice[86-90]. The NLRP3-/- receptor of immune cells that express

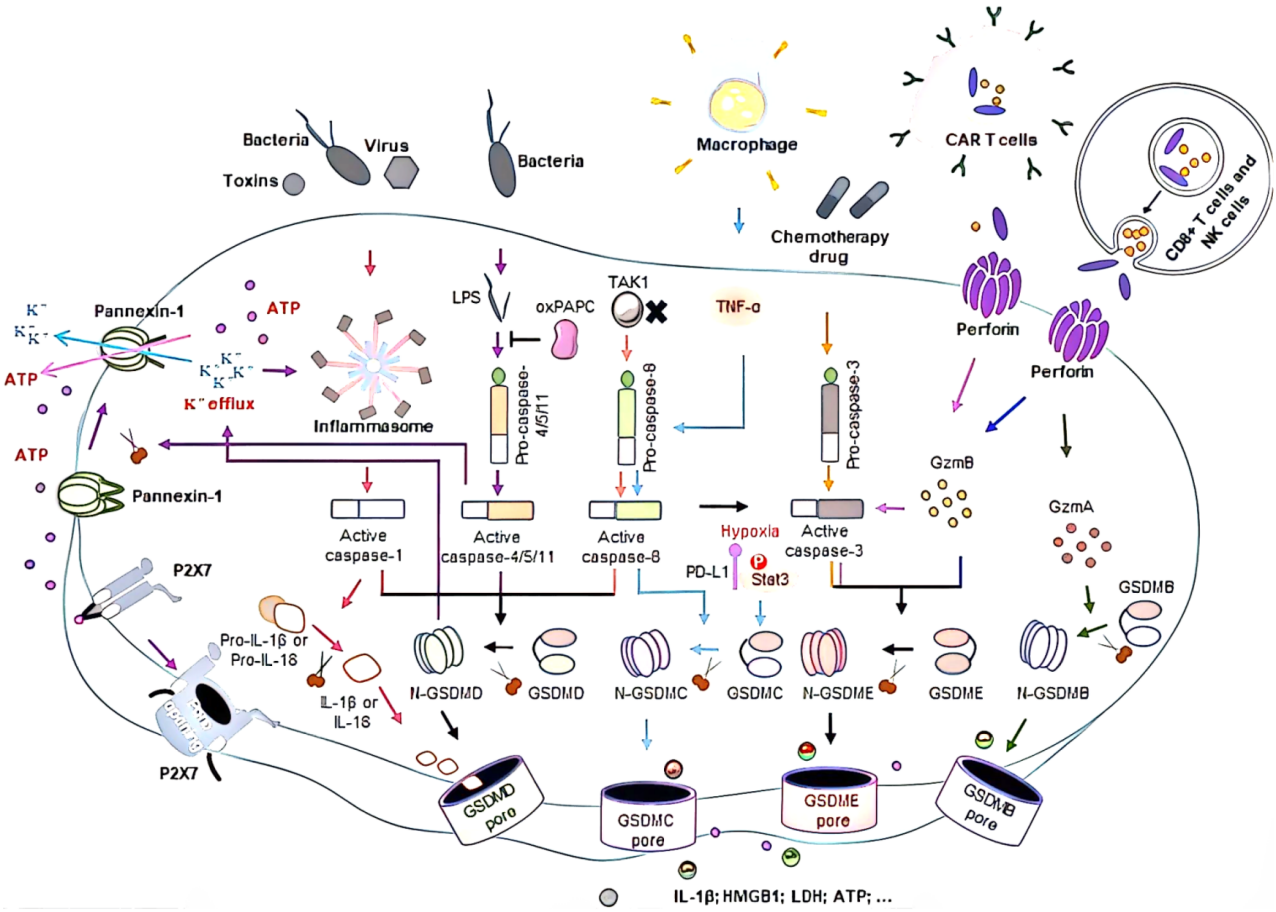

Figure 2 The role and summary of pyroptosis related signaling pathway in tumor. GSDM: Gasdermines; TNF: Tumor necrosis factor. Citation: The authors have obtained the permission for figure using from the BioRender.com (Supplementary material)[203].

NLRP3 can prevent tumor development[91-95]. Nlrp12-deficient mice are highly sensitive to colon inflammation and tumorigenesis and exhibit increased production of inflammatory cytokines, chemokines, and tumor necrosis factors. Further studies showed that NLRP12 deficiency in mice led to the activation of nuclear factor kappa-B (NF-κB) and extracellular signal-regulated kinase (ERK) in macrophages. This can promote the development of colitis or colon cancer [96-100].

The above evidence suggests that the NLRP inflammasome plays a key role in the prevention of colorectal cancer and can serve as a potential biomarker of the tumor microenvironment.

Inflammatory cytokines

IL-18 can stimulate epithelial cell regeneration and induce antitumor responses mediated by T cells and natural killer cells. IL-18 administration reduces AOM/DSS-induced inflammation and tumorigenesis in CasP1-deficient mice[101-104]. Conversely, other studies have shown that IL-18 deletion is protective against AOM/DSS-induced colitis and CRC [105]. While IL-18 directly prevents inflammation-driven carcinogenesis, it also downregulates soluble IL-22-binding proteins that neutralize IL-22, thereby indirectly enhancing the carcinogenic effect of IL-22.

IL-1β has traditionally been considered a proinflammatory and procancer factor. However, recent studies[106-108] have shown that L-1 plays a dual role in CRC. In a mouse model of colitis-associated cancer, inhibition of the NLRP3 inflammasome reduced tumor expansion, which was associated with reduced levels of IL-1β and IL-18 at the tumor site [109]. The underlying mechanism of the dual role of IL-1β in CRC has recently been well understood. A study investigated the effect of IL-1 signaling on different cell types in the CRC microenvironment. Analysis of epithelial-specific IL-1R1 deletions showed that the proliferation of early CRC tumors was slowed and that NF-κB activation was reduced. T-cell-specific ablation of IL-1R1 similarly reduced tumor-induced inflammation in IL-17- and IL-22-dependent tumors, thereby reducing the progression of CRC[110]. However, related studies have shown that IL-1β plays the opposite role through ZEB1 activation, thereby promoting the dryness and invasion of colon cancer cells. Therefore, the dual role of IL-1β needs to be carefully considered when developing anticancer therapies that inhibit IL-1β (Figure 3).

Relationship between pyrodeath and colorectal cancer treatment

Pyroptosis-related factors are important prognostic indicators of CRC. Recent studies[111-115] have shown that genes associated with pyroptosis play an important role in assessing the prognosis of patients with CRC. The mRNA expression of Caspase-9 is downregulated in colorectal cancer tissues, poorly differentiated tumors exhibit decreased Caspase-9

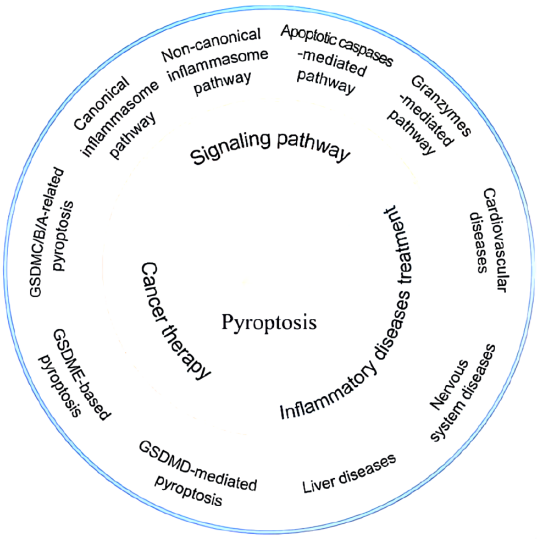

Figure 3 Summary of pyroptosis related pathways. GSDM: Gasdermines.

mRNA expression, and Caspase-9 mRNA expression can be used as an independent prognostic factor in stage II colorectal cancer patients[116]. Localization of GSDMD in the cytoplasm *in vivo* indicates a good clinical prognosis for CRC patients, while nuclear displacement of GSDMD is associated with a poor prognosis[117-120]. Nuclear GSDMD (but not cytoplasmic GSDMD) inhibits cell growth and promotes pyrodeath in cancer. Hypoxia in the TME causes mild or moderate nuclear displacement of GSDMD *in vivo*[121]. Pyroptosis-related genes in CRC patients included CAS P3, CHMP2A, CHMP2B, CHMP3, CHMP4C, CHMP6, CHMP7, GSDME, HMGB1, IL1A, IRF2, and TP63, and the above 12 pyrodeath-related genes were associated with immune cell infiltration[122-125]. These results indicate that pyroptosis plays an important role in the tumor immune microenvironment[126]. Similarly, 13 apoptosis-related genes, AIM2, CASP1, CASP5, CASP6, CASP8, CASP9, ELANE, GPX4, GSDMD, NLRP7, NOD2, PJVK, and PRKACA, have been shown to be associated with the prognosis of CRC patients[127-130].

Long noncoding RNAs (lncRNAs) are associated with CRC. Recent studies have shown that lncRNAs associated with pyroptosis play a role in the prognosis of CRC patients[131-133]. miR-21-5p also plays an important role in the prognosis of CRC patients. The overexpression of miR-21-5p resulted in the release of various inflammatory factors, including IL-1β and IL-18, and the mRNA associated with pyroptosis was significantly upregulated. In addition, overexpression of miR-21-5p, a downstream factor, leads to downregulation of growth factor beta-induced protein (TGFBI), which leads to pyroptosis[134]. Chen *et al*[132] reported that four lncRNAs associated with pyroptosis, namely, ELNF1-AS1, PCAT6, TNRC6C-AS1 and ZEB1-AS1, could be used as biomarkers to accurately predict the prognosis of CRC patients (Figure 4). Some studies showed that 8 lncRNAs associated with pyroptosis, Z99289.2, FENDRR, CCDC144NL-ASL, TEX41, MNX1-AS1, NKILA, LINC02798, and LINC02381, have potential roles in the response to treatment and prognosis in CRC patients[135-138].

The pyroptosis pathway is a potential target for colorectal cancer drug development

Pyroptosis may be an important therapeutic target for cancer treatment. Studies have shown that arsenic trioxide (ATO) and ascorbic acid jointly upregulate the expression of Caspase-1 and promote inflammasome formation, thereby inducing pyroptosis in CRC cells[139]. Moreover, ATO inhibited the growth of CRC cells by inhibiting telomerase activation and inducing Caspase-3-dependent apoptosis[140]. The antitumor drug 5-aza-2′-deoxycytidine (DAC) is a DNA methylation inhibitor that treats CRC by upregulating the expression of NLRP1. After CRC cells were treated with DAC, the expression level of the inflammasome NLRP1 increased both *in vivo* and *in vitro*, suggesting that DAC inhibits the growth of colon cancer by inducing pyroptosis. In addition, DAC increased the expression of miR-133b and triggered the apoptosis of CRC cells[141]. Therefore, pyroptosis may be targeted for CRC treatment by ATO and DAC. LPS in the outer membrane of gram-negative bacteria increased the sensitivity of CRC to oxaliplatin and increased antitumor activity by inducing GSDMD-mediated pyrodeath in HT-29 cells. Loplatin induces pyroptosis by activating Caspase-3 and GSDME, thereby eliminating CRC cells. The camptothecin (CPT) analog FL118 inhibits CRC growth and metastasis by inducing NLRP3/caspase-1-mediated pyrodeath in SW48 and HT129 cells[142].

Two small molecule inhibitors, BI2536 and CPT, were further confirmed to induce GSDME-mediated pyrodeath *via* caspase-3-dependent apoptosis, demonstrating anticolorectal cancer activity *in vitro* and *in vivo*. Some studies[143-145] have shown that the forkhead box p2 gene (FOXP2) acts as a tumor inhibitor. FOXP2 can promote the activation of Caspase-1 to enhance cell pyrodeath. In a mouse model of colitis-associated tumors, FOXP2 was downregulated in colitis and tumor tissue, and CRC patients with low FOXP2 expression had lower survival rates. Further study indicated that knockdown of FOXP2 promoted the expression of proliferating cell nuclear antigen (PCNA) and cyclin D1 and downregulated the expression of Caspase family proteins and GSDMD. A recent study[146] showed that tumor cells are sensitive to apoptosis induced by alpha-ketoglutaric acid (αKG) in an acidic environment. αKG enhances reactive oxygen species levels and activates Caspase-8 to lyse GSDMC, thus providing a theoretical basis for the use of αKG as a new treatment

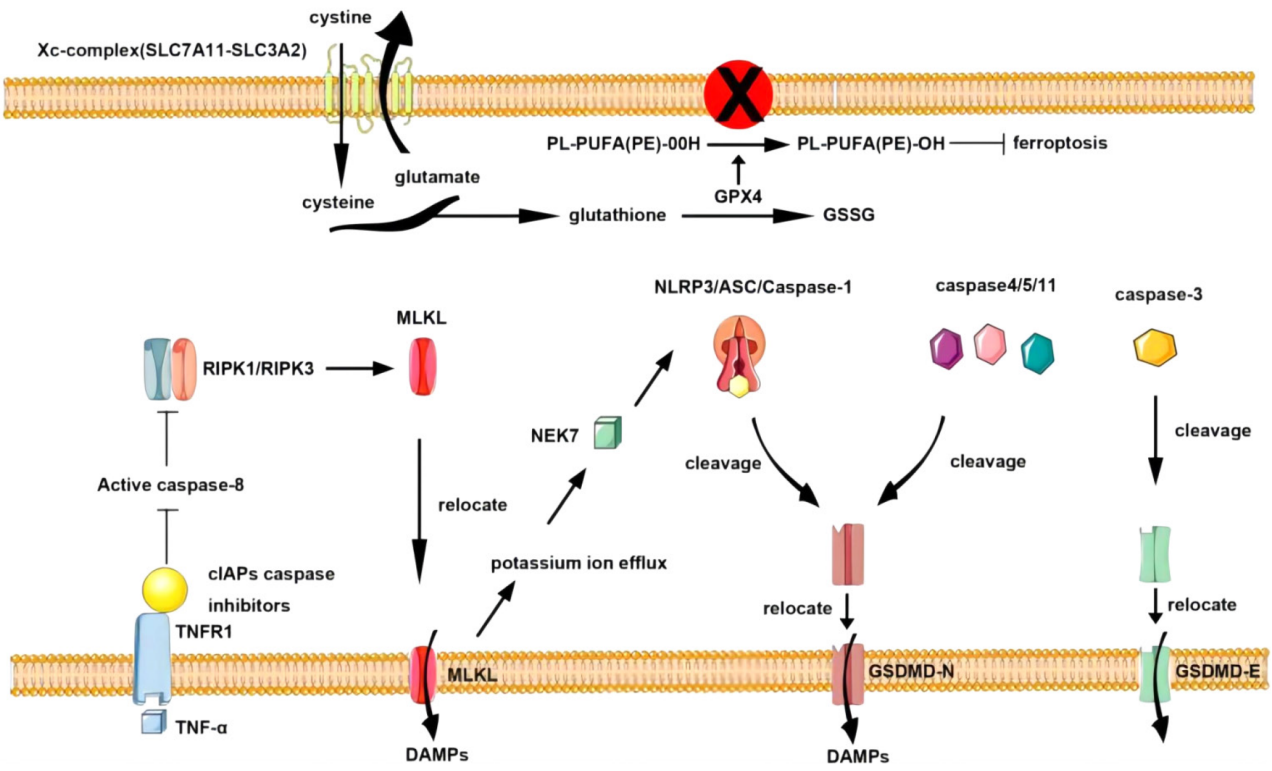

Figure 4 Pyroptosis is a process by which specific receptors on the surface of colorectal cancer. GSSG: Oxidized glutathione; MLKL: Mixed lineage kinase domain-like; DAMP: Damage-associated molecular patterns; GPX: Glutathione peroxidase; TNF: Tumor necrosis factor. Citation: The authors have obtained the permission for figure using from the BioRender.com (Supplementary material)[203].

strategy for CRC through the induction of GSDMC-mediated pyrodeath (Figure 5).

RELATIONSHIPS BETWEEN PYROPTOSIS AND THE OCCURRENCE, DEVELOPMENT, INVASION AND METASTASIS OF CRC

The GSDM family includes GSDMD, GSDME, GSDMC, and GSDMB in the gastrointestinal tract and is associated with a variety of gastrointestinal tumors[147-150]. Pyroptosis in CRC can be divided into three categories: (1) Different levels of GSDMs affect the occurrence and development of CRC; (2) GSDMs mediate pyroptosis to affect the TME; and (3) GSDMs can be used as target effectors for antitumor therapy.

Pyroptosis and the occurrence and development of CRC

Gsdms-mediated pyrogen death acts as a double-edged sword in the development of tumors and can either promote the occurrence of tumors or suppress tumors through tumor immunity, depending on the tumor environment in which the cells are located[151-154]. In nontumor cells, GSDMS-mediated pyroptosis may promote tumor development through chronic inflammatory stimulation, while in tumor cells, antitumor immune responses may predominate[155]. GSTM family proteins are downstream effector molecules of the inflammasome that play a role in the occurrence of CRC by mediating pyroptosis[156-158]. Changes in gut microbes and inflammasome activation can promote or inhibit the development of CRC. On the one hand, microbial stimulation can promote the proteolytic shear NT domain of GSDM, the formation of pores and the release of inflammatory factors to produce pyrodeath, and pyrodeath of tumor cells can inhibit the growth of CRC[159]. On the other hand, the inflammatory factors released by porous GSDM stimulate immune cells, which can increase the clearance of tumor cells, establish tolerance, and promote the tumor microenvironment.

GSDMD is the first member of the GSDM family to be extensively studied as an executor of pyroptosis. It is expressed in most tumors and affects tumor progression and prognosis[160-162]. Studies[163-165] have shown that the lncRNA RP1-85F18.6 can regulate the Np63 signaling pathway, induce the proliferation and invasion of CRC cells, disrupt the cell cycle, and inhibit the death and apoptosis of CRC cells. However, the lncRNA RP1-85F18.6 promoted the pyro-death of CRC cells after GSDMD knockdown[166]. This finding suggested that GSDMD may be a benign prognostic factor for CRC. Pinitrol diglucoside (SDG) induced pyroptosis in CRC cells by activating the BAX-Caspase-1-GSDMD pathway through the ROS/PI3K/AKT signaling pathway and significantly inhibited tumor growth in a HCT116 nude mouse model[167]. In addition, LPS enhances the antitumor activity of oxaliplatin in HT29 cells by activating GSDMD expression through a nonclassical pathway, thus inhibiting the growth of HT29 cells and promoting cell death. This study

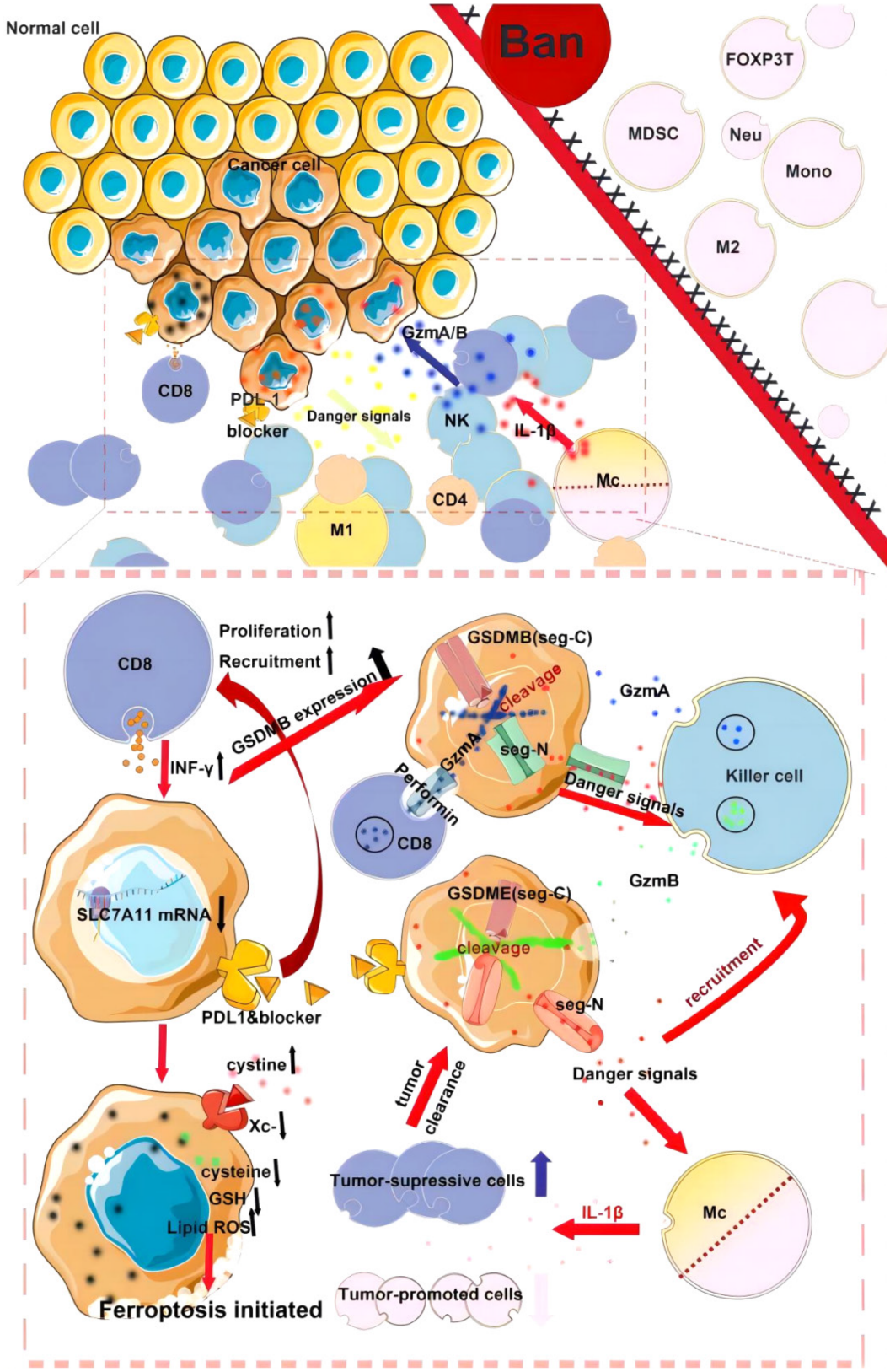

Figure 5 Pyroptosis induces immune cells in the colorectal cancer microenvironment. MDSC: Myeloid-derived suppressor cells. Citation: The authors have obtained the permission for figure using from the BioRender.com (Supplementary material)[203].

also analyzed the relationship between GSDMD expression and overall survival in 244 CRC patients, and immunohistochemical analysis revealed that the overall survival of patients with high GSDMD expression was significantly greater than that of patients with low GSDMD expression, indicating that compared with that of normal cells, the expression of GSDMD in CRC cells is reduced and is associated with poor prognosis in CRC patients. Studies[168-170] have shown that GSDMD mediates pyroptosis and the release of the inflammatory factors IL-1β and IL-18, which can inhibit the prolif-

eration of tumor cells, to induce an immune response in colorectal adenocarcinoma. In conclusion, GSDMD may regulate the pyrodeath of CRC cells through different signaling pathways, inflammatory stimulation pathways and antitumor immunity pathways, which are closely related to the progression and prognosis of CRC, and high expression of GSDMD may be a prognostic factor for CRC[171].

GSDME usually acts as a cancer suppressor in CRC. Gene promoter hypermethylation is involved in the development and progression of cancer, and abnormal CpG island methylation of gene promoters is a common change in human CRC [172-174]. GSDME gene methylation was reported in 29 (34%) of 85 CRC patients, and methylation was significantly associated with lymphatic invasion and TNM stage, suggesting that GSDME gene methylation may play a role in the development of CRC. Recent studies[175-178] have shown that the expression of the lncRNA paraventular assembly transcript 1 (NEAT1) is upregulated in the ionizing radiation response and that the downregulated expression of miR-448 enhances the expression of GSDME and induces pyroptosis in CRC cells[179]. These results indicated that NEAT1/miR-448 could affect the pyrodeath and viability of CRC cells by regulating the expression of GSDME. Liu *et al*[175] used apopsin to activate Caspase-3 and Caspase-9 through the mitochondrial pathway to induce pyrodeath in GSDME cells, which significantly reduced tumor growth in an HCT-116 mouse tumor model. However, some studies have shown that GSDME mediates the release of intracellular HMGB1 through the ERK1/2 pathway, which promotes the progression of colitis-related colorectal cancer in mice. It is possible that pyroptosis causes the release of a large number of intracellular DAMPs (such as HMGB1, IL-1β, IL-18 and other inflammatory cytokines) that trigger chronic inflammation, thus promoting the development of chronic inflammation-related tumors[180]. Therefore, by inhibiting GSDME-mediated pyroptosis or reducing the release of intracellular HMGB1, the occurrence of colitis-associated CRC can be reduced. GSDME may regulate the pyroptosis of colorectal cancer cells according to pathological status, expression level and inflammatory factor stimulation[181-184].

GSDMC is mainly expressed in the gastrointestinal tract and skin. GSDMC converts apoptosis to necrosis *via* the action of tumor necrosis factor (TNF)[185]. In hypoxia, PD-L1 functions as a nonimmune checkpoint, generates nuclear translocation, and enhances the gene transcription of GSDMC. Caspase-8- and TNF-α-mediated cleavage of GSDMC causes pyroptosis, which promotes tumor development. Some studies[186-190] have shown that both the mRNA and protein levels of GSDMC are high in CRC tissues. Inhibition of GSDMC expression significantly reduced the proliferation and tumorigenesis of CRC cell lines *in vivo* and *in vitro*, while overexpression of GSDMC promoted the proliferation of CRC cells. These results suggest that GSDMC can act as an oncogene in the development of CRC. Therefore, the antitumor or protumor effects of GSDMC may depend on the degree to which pyroptosis is induced.

There are few studies on GSDMB in CRC, and its role is still unclear[191]. The GZMA-mediated cleavage of GSDMB enhances the expression of GSDMB in mouse CRC cells and thus promotes the clearance of mouse tumor cells[192]. These results suggest that GSDMB-mediated pyroptosis may promote the occurrence of CRC. Therefore, the occurrence and development of CRC cells can be affected by the pyrogenic pathway or the different expression levels of GSDMs, indicating that GSDMs may be potential tumor markers for CRC[193-195]. However, the specific mechanism regulating CRC progression is currently unclear and lacks clinical verification, and further research is still needed.

Pyroptosis and the CRC tumor microenvironment

The TME includes immune cells, stromal cells, blood vessels, the extracellular matrix and extracellular vesicles[196]. The TME is crucial for the occurrence and development of CRC, can promote the formation and progression of CRC blood vessels, and can also predict the prognosis of CRC patients by calculating the infiltration of immune cells[197-200]. Pyroptosis, a highly immunogenic form of cell death, induces local inflammation accompanied by the recruitment of a large number of tumor-infiltrating lymphocytes (TILs) and macrophages, further amplifying the inflammatory response, thereby relieving immunosuppression in the TME and inducing a systemic immune response. Some studies[201,202] have shown that pyroptosis induced by GSDMs can regulate the antitumor immune response generated by the TME. Downregulation of GSDMD reduced the cytolytic ability of CD8 + T cells, indicating that GSDMD is necessary for the optimal CTL response against tumor cells and has antitumor activity. Pyroptosis mediated by GSDMs plays a dual role in regulating the TME. On the one hand, the inflammatory response associated with pyroptosis can induce normal cells to become cancerous and provide an appropriate TME for tumors to promote the growth of tumor cells. On the other hand, pyroptosis can be used as a cytotoxic lymphocyte killing mechanism. Increasing the number and function of TILs and the phagocytosis of macrophages can enhance the antitumor immune response and inhibit tumor development. GZMB can directly cleave GSDME by activating Caspase-3 to activate target cells to cause scorch death, which can increase the antitumor function of CD8 + T lymphocytes and NK cells in tumors, affect the tumor microenvironment and recruitment of immune cells, and inhibit the growth of tumor cells. A recent study analyzed the correlation between GSDMD expression and immune invasion in pancarcinoma tissues, and in rectal adenocarcinoma, GSDMD expression was positively correlated with NK cells and CD8 + T cells and negatively correlated with CD4 + T cells. In addition, a study analyzed the relationship between different sublocalization levels of GSDMD and the TME in 178 CRC patients, and the results showed that the cytoplasmic expression of GSDMD was correlated with the proliferation of CD3 + lymphocytes, while the membrane expression of GSDMD was positively correlated with CD68 + macrophages and CD8 + lymphocytes. The nuclear expression of GSDMD was negatively correlated with CD68 + macrophages and CD8 + lymphocytes. Recent research has shown that in a mouse model of colon cancer, oncolytic paraviruses stabilize GSDME by reducing the ubiquitination of GSDME, initiating pyrodeath, recruiting more cytotoxic lymphocytes, reshaping the TME, turning "cold" tumors into "hot" tumors, and activating antitumor immunity (Figure 6). At present, there are few studies on pyroptosis and the CRC microenvironment, but their relationship is worthy of further study.

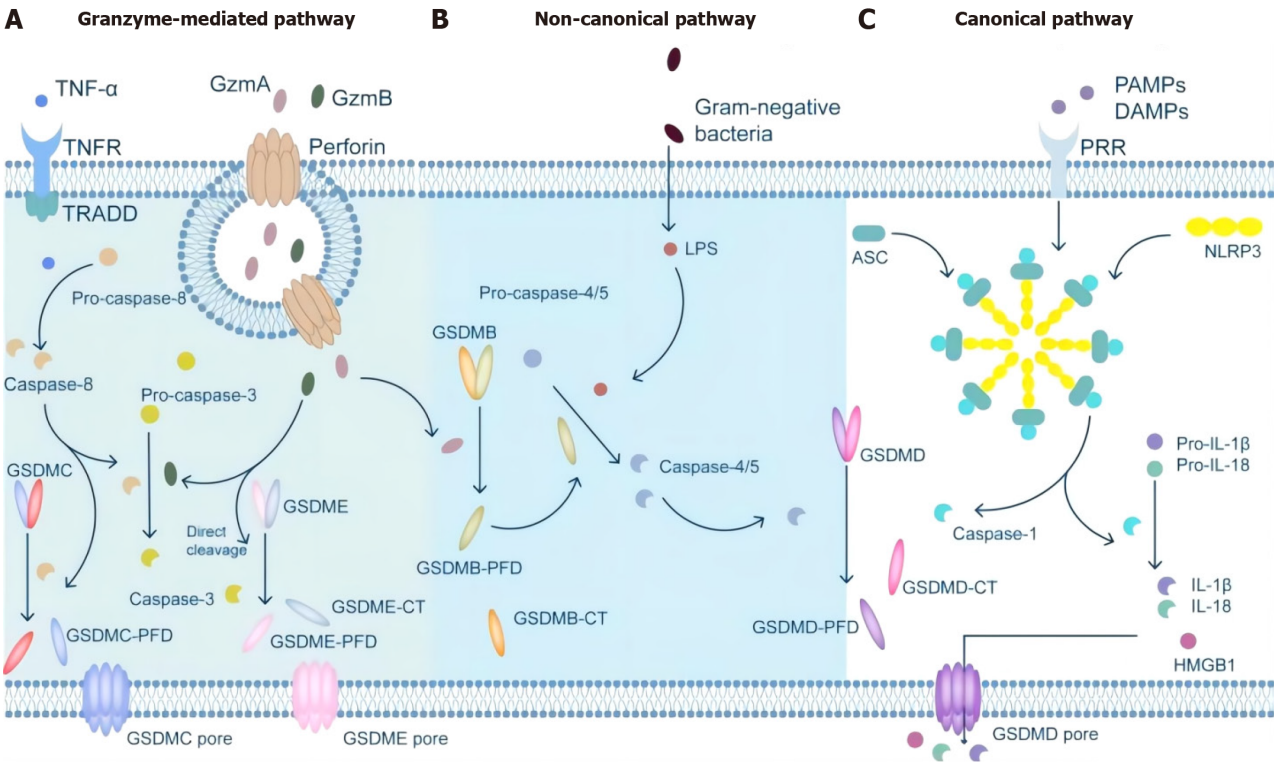

Figure 6 Pyroptosis and the colorectal cancer tumor microenvironment. A: Granzyme-mediated pathway; B: Non-canonical pathway; C: Canonical pathway. NLRP: Nucleotide-binding oligomerization domain (NOD)-like receptor family, pyrin domain-containing protein; DAMP: Damage-associated molecular pattern; TNF: Tumor necrosis factor; TRADD: Tumor necrosis factor receptor type 1-associated death domain protein; ASC: Apoptosis-associated speck-like protein containing a CARD; PAMP: Pathogen-associated molecular pattern; IL: Interleukin. Citation: The authors have obtained the permission for figure using from the BioRender.com (Supplementary material)[203].

Pyroptosis and its therapeutic effect on CRC

Chemotherapy, radiotherapy and immunotherapy can induce the death of tumor cells, thereby enhancing local and systemic antitumor immune functions. In recent years, immunotherapy has attracted much attention for the treatment of CRC. Immunotherapy is a therapeutic method for restoring normal antitumor immunity by restarting and maintaining the tumor immune cycle to control and eliminate tumors. It can not only activate the immune system against tumors but also affect the tumor microenvironment. Pyroptosis is a highly inflammatory and lytic form of programmed cell death that involves the production of a large number of new antigens, stimulation of the systemic immune response, and inhibition of tumor progression. Some studies have shown that neither blocking the PD-1/PD-L1 pathway nor inducing transient pyroptosis can inhibit the growth of 4T-1 tumors alone, but the combination of the two has a strong inhibitory effect on tumor growth, indicating that immunotherapy agents and drugs that cause pyroptosis can synergistically and effectively clear tumors. In addition, in mouse colon cancer cells, upregulation of GSDMB expression did not affect tumor growth in immunoactive mice, but it could enhance the ability of anti-PD-1 antibodies to block immune checkpoints, thus playing a role in inhibiting tumor growth. In the future treatment of CRC patients, we may be able to achieve synergistic effects through GSDM-mediated pyrodeath and immune checkpoint inhibitors to improve the effectiveness of immunotherapy.

GSDMD and GSDME are the most common apoptosis-related proteins in cancer research and play important roles in the pathogenesis and treatment of cancer. In the treatment of CRC, many chemotherapy drugs can clear tumor cells by inducing apoptosis, and with the use of drugs, tumor cells exhibit apoptosis resistance and drug tolerance. An increasing number of studies have shown that many chemotherapy drugs induce GSDMD and GSDME to pyroath tumor cells through various cell signaling pathways. Therefore, the use of chemotherapeutic agents that induce the pyroptotic death of tumor cells may be a new antitumor treatment strategy for overcoming apoptosis resistance.

LPS-induced pyroptosis promoted the expression of GSDMD in CRC cells and increased the chemical sensitivity of HT29 cells to oxaliplatin, thus enhancing the antitumor effect of these cells. In addition, the relationship between the sublocalization of different GSDMD molecules and the prognosis of CRC patients and reported that high cytoplasmic GSDMD expression is an independent favorable indicator of prognosis and can improve the efficacy of chemotherapy in CRC patients. Studies have shown that multivalent CXCR4-targeted nanotoxins (T22-PE24-H6) induce GSDMD-mediated pyroptosis, thereby inhibiting the metastasis of CRC cells. Nanotoxins mediate the pyroptosis of CRC cells through the Caspase-1/GSDMD pathway, have strong antitumor effects and can effectively overcome the apoptotic resistance associated with chemotherapy resistance and metastatic CRC tumors. Therefore, the use of some drugs to regulate the expression level of GSDMD or induce the death of tumor cells through the Caspase-1/GSDMD pathway may provide a new strategy for the treatment of CRC.

In recent years, the Caspase-3/GSDME signaling pathway has been shown to be related to the chemotherapy and antitumor immunity of CRC. Activation of Caspase-3 by chemotherapeutic agents to inhibit GSDME can transform the mitochondrial apoptosis pathway into pyroptosis. In addition, GSDme-NT can also enhance the activation of Caspase-3 and play a positive feedback role in self-amplification. Further cutting of full-length GSDME can promote the transformation of Caspase-3-mediated apoptotic cells to pyroptotic cells through the Caspase-3/GSDME pathway, activate the body's antitumor immune system, effectively inhibit the proliferation and metastasis of tumors, and improve the efficacy of chemotherapeutic drugs. TNF-α + CHX and ABT-263 (Navitoclax) chemotherapy drugs induced the apoptosis and pyrodeath of colon cancer cells through the BAK/BAX-Caspase-3-GSDME pathway and that GSDME-CT palmitoylation promoted chemotherapy-induced pyrodeath. The palmitoacylation inhibitor 2-bromopalmitate (2-BP) inhibited palmitoacylation and chemotherapy-induced pyrodeath in GSDME-CT, but total cell death did not change, indicating that 2-BP can transform pyrodeath into apoptosis, providing a new target for realizing the transformation between chemotherapy-induced pyrodeath and apoptosis. Chemotherapy drugs such as platinum can increase the level of phosphorylated ROS/JNK, activate the Bax mitochondrial apoptosis pathway to activate Caspase-3 and -9, and then cleave GSDME to mediate the pyroptosis of colon cancer cells, suggesting that GSDME pyroptosis may be a potential mechanism by which lobacplatin clears CRC tumor cells. Therefore, the selection of appropriate chemotherapy drugs for CRC treatment can activate the Caspase-3/GSDME pathway to induce pyroptosis, which can effectively clear tumor cells, increase sensitivity to chemotherapy drugs, and target tumor cell pyrodeath to overcome the apoptotic resistance of tumor cells and activate the body's antitumor immune system, providing new insights for CRC antitumor therapy. However, the application of the activated pyroptosis pathway in the treatment of CRC patients' needs further clinical validation.

CONCLUSION

Current research on CRC, a new type of programmed cell death, is still lacking, and there are still many unanswered questions, such as how to promote CRC tumor cell pyrodeath and avoid normal cell pyrodeath to inhibit the occurrence and development of CRC. How to reduce the death of CRC tumor cells to increase chemotherapy drug sensitivity and avoid adverse reactions and how to balance pyroptosis in CRC and antitumor immunity are important questions. Notably, pyroptosis can reshape the TME, transform "cold" tumors into "hot" tumors, and may improve the response to immune checkpoint inhibitors, which has great potential for antitumor therapy. However, most of the current studies on the correlation between pyroptosis regulation of CRC development and the TME have been conducted in cell and animal models and lack relevant clinical validation. Therefore, in-depth studies on the specific mechanism and biological role of pyroptosis regulation in CRC can identify new targets for CRC treatment and aid in the development of effective molecular targeted drugs for the clinical treatment of CRC.

FOOTNOTES

Author contributions: Wang X wrote the manuscript; Yin QH, Wan LL, Sun RL, and Wang G collected the data; Gu JF and Tang DC guided the study; and all authors reviewed, edited, and approved the final manuscript and revised it critically for important intellectual content, gave final approval of the version to be published, and agreed to be accountable for all aspects of the work. Gu JF and Tang DC contributed equally to this work as co-corresponding authors. The reasons for designating Gu JF and Tang DC as co-corresponding authors are the supervisors and principals of this study.

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