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REVIEW

The Role of Pyroptosis in Colorectal Cancer: From Mechanisms to Therapeutic Opportunities

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Abstract: Colorectal cancer is a malignant tumor with high incidence and mortality, which caused more than 1.9 million new cases of colorectal cancer (including anal cancer) and 904,000 deaths in 2022, making colorectal cancer the third-highest incidence and second-highest mortality in cancer worldwide. Conventional treatments including chemotherapy, radiotherapy and surgery have achieved certain results, but there is room for improvement. Pyroptosis is a newly discovered programmed death that induces cell death by cleaving gasdermins through caspase, making the cell form non-selective pores, undergoing cytoplasm flattening caused by plasma membrane leakage and finally leading to death. It can be induced by the following pathways including canonical pathway, non-canonical pathway, apoptotic caspases-mediated pathway and granzymes-mediated pathway. Pyroptosis is often associated with the detection, prognosis, and treatment of colorectal cancer. In canonical pathway, the common inflammasomes including NLRP3, NLRP1, NLRC4, AIM2 and Pyrin are related to the detection and prognosis of colorectal cancer. In terms of the treatment of colorectal cancer, most studies focus on the GSDMD-mediated and GSDME-mediated pyroptosis therapy, while there are relatively few studies on the treatment of colorectal cancer mediated by other gasdermin families, such as GSDMB. The pyroptosis therapy in colorectal cancer involves the drug, natural-occurring substances, chemotherapy, nanotechnology, radiotherapy, virus, and other novel treatments such as photodynamic therapy (PDT). This article explores the mechanisms of pyroptosis and its research on colorectal cancer detection and prognosis, focusing on the research related to pyroptosis and colorectal treatment, and provides an outlook on the future of pyroptosis and colorectal cancer treatment.

Keywords: colorectal cancer, pyroptosis, gasdermin, signaling pathway, treatment

Introduction

Colorectal cancer (CRC) is a common malignant tumor, which caused more than 1.9 million new cases of colorectal cancer (including anal cancer) and 904,000 deaths in 2022, accounting for nearly 1 in 10 cancer cases and deaths.[1] It makes colorectal cancer the third-highest incidence and second-highest mortality in cancer worldwide.[1] In 2025, approximately 107,320 new colon cancer patients and 46,950 new rectal cancer patients are expected to be diagnosed in the United States.[2] Generally, the treatments for colorectal cancer are chemotherapy, radiotherapy and surgery. According to the NCCN Clinical Practice Guidelines in Oncology, common first-line systemic therapies for colon cancer include FOLFOX, CAPEOX, FOLFIRI, Infusional 5-FU/LV and capecitabine, FOLFOXIRI, and bevacizumab. Cetuximab or panitumumab can be used in KRAS/NRAS wild-type disease, while pembrolizumab, nivolumab, and Ipilimumab are commonly used to treat dMMR/MSI-H disease.[3] The treatment of rectal cancer often involves surgery, including local procedures, such as polypectomy, transanal local excision, transanal endoscopic microsurgery, more invasive procedures involving a transabdominal resection, and laparoscopic resection.[4] For most patients with stage II or stage III rectal cancer, combined-modality therapy composed of surgery, concurrent fluoropyrimidine-based chemotherapy with ionizing radiation to the pelvis (chemoradiation), and chemotherapy are recommended.[4] Although much progress has been made in the treatment of colorectal cancer, with a five-year survival rate of 65% in the United States, there is still much room for improvement.[5]

Pyroptosis is a type of programmed cell death, which is mediated by the gasdermin family, making the cell form non-selective pores, undergo cytoplasm flattening caused by plasma membrane leakage and lead to death.[6] The expression

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levels of GSDMD and GSDME in colorectal cancer cells are lower than those in cells of normal tissues.[7,8] Compared with tumors in mice, the silencing of GSDME by methylation is observed in human colorectal cancers. A mouse model with GSDME knocked out can mimic this feature of human colorectal cancers.[9] Nowadays, more and more studies have shown that pyroptosis can be used for the treatment of cancer, such as breast cancer, gastric cancer, lung cancer, and so on.[10] In recent years, there have been many studies using cell pyroptosis to treat colorectal cancer. Distinct from other forms of cell death such as ferroptosis and apoptosis, some drugs, natural substances, and nanotechnologies can induce pyroptosis in colorectal cancer cells, thereby achieving the treatment of colorectal cancer.[9] This article will introduce the relationship between pyroptosis and colorectal cancer, focus on the application of pyroptosis in the treatment of colorectal cancer, and elaborate on the prospects for the future.

The Mechanism of Pyroptosis and Its Research on Colorectal Cancer

Pyroptosis is a kind of programmed cell death, the earliest study of pyroptosis can be traced back to 1986. Friedlander found that anthrax lethal toxin can kill mouse peritoneal macrophages within one hour in vitro system.[11] Nowadays, there is more and more research on pyroptosis, and the mechanism has become clear. Gasdermin, which is a superfamily including gasdermin A/B/C/D(GSDMA/GSDMB/GSDMC/GSDMD), gasdermin E(GSDME)/DFNA5, Pejvakin/DFNB59 in humans, has two conserved domains (except DFNB59), the N-terminal effector domain and the C-terminal inhibitory domain.[12,13] The N-terminal domain is a new type of pore-forming protein.[13] The pore-forming activity of the N-terminal is generally inhibited by binding with C-terminal.[12] For example, in terms of GSDMD, when the caspases or granzymes cleave the gasdermin D, disengaging the N-terminal domain from the C-terminal domain, the pyroptosis begins working and the plasm membrane forms many pores with cell contents passing through them, finally contributing to the cell death.[6,14] GSDMD-N-based pores are nonselective to different ions. Unlike MLKL channel-mediated necroptosis, 10–15 nm pores formed by GSDMD-N should be much larger than MLKL pores, and the pores can disrupt the plasma membrane, inducing cell pyroptosis.[6] That is why gasdermin is called the executioner which executes the death of the cell. In a series of studies on colorectal cancer, a large number of things related to pyroptosis have been found. Pyroptosis can be induced by the following pathways. The pathways and mechanisms of pyroptosis are shown in Table 1.

Canonical Pathway

Inflammasomes are multiprotein complexes, which assemble in the cytosol, reacting to pathogen-associated molecular patterns (PAMPs) and endogenous danger signals (DAMPs). PAMPs are usually produced when microbial infection

Table 1 Pathways and Mechanisms of Pyroptosis

Pathway	Caspase	Mechanism	Reference
Canonical pathway	1	PAMPs and DAMPs stimulate inflammasomes to activate caspase-1 to cleave GSDMD to induce pyroptosis	[6,14,15]
Non-canonical pathway	4/5/11	LPS from Gram-negative bacteria activates caspase-4/5/11 to cleave GSDMD to induce pyroptosis	[16,17]
Apoptotic caspases-mediated pathway	3/8	After chemotherapy, caspase-3 cleaves the GSDME to induce pyroptosis YopJ inhibits TAK1 or IKK kinase to cleave GSDMD to induce pyroptosis during the infection of Yersinia Under hypoxia, TNF-α from macrophage in the presence of GSDMC and nPD-L1 activates caspase-8 to cleave GSDMC to induce pyroptosis	[18–20]
Granzymes-mediated pathway	3	GZMA from cytotoxic lymphocytes can directly cleave and activate GSDMB to induce pyroptosis GZMB can cleave GSDME directly or activate caspase-3 to cleave GSDME indirectly, and then elicit cell pyroptosis	[21,22]

Abbreviations: PAMPs, pathogen-associated molecular patterns; DAMPs, endogenous danger signals; GSDMD, gasdermin D; LPS, lipopolysaccharide; GSDME, gasdermin E; TAK1, TGF-β activated kinase-1; IKK, inhibitor of κB kinase; TNF, tumor necrosis factor; nPD-L1, nuclear programmed death ligand 1; GSDMC, gasdermin C; GZMA, granzyme A; GSDMB, gasdermin B; GZMB, granzyme B.

happens and DAMPs are released from the damaged or dying cell. These complexes consist of a sensor (an NLR protein or an ALR protein), an ASC (an adaptor molecule which is the apoptosis-associated speck-like protein including a CARD), and an effector enzyme (typically pro-caspase-1). When NLR or ALR identify the ligand, the sensor is no longer inhibited and the ASC with its oligomerization potential acts as a large scaffold which takes on the function of recruitment, proximity-mediated autoproteolysis and activation of procaspase-1. The activity of the resulting enzyme, caspase-1, controls the maturation and release of IL-1 and IL-18 which are the pro-inflammatory cytokines and then directs the inflammatory response.[15]

After inflammasome assembly, caspase-1 is activated, inducing the canonical pathway of pyroptosis.[14] Caspase-1 is like a scissor which cleaves the linker between the N-terminal domain and the C-terminal domain of GSDMD. The N-terminal domain releases its activity of inducing pyroptosis after leaving the C-terminal domain.[12] The N-terminal domain binds to membranes containing phosphatidylserine, cardiolipin, or phosphatidylinositol phosphates, forming the oligomeric pores, which induce pyroptosis.[14] GSDMD-N forms non-selective ion-permeable pores, disrupting the plasm membrane, and causing cell death.[6]

The common inflammasomes including NLRP3, NLRP1, NLRC4, AIM2 and Pyrin. They are associated with colorectal cancer in recent studies.

Studies over the past two decades suggest an association between NLRP3 and colorectal cancer. NLRP3 inflammasome can play a role in reducing colitis and inhibiting the tumorigenesis of colitis-associated cancer (CAC).[23] Also, NLRP3 inflammasome is recently found that it can detect the presence of colorectal cancer metastatic growth in the liver and limit the growth of the tumor by using IL-18 to activate natural killer cells, and then triggering FasL-induced apoptosis.[24] Colorectal cancer cells can be induced to death according to the canonical way mediated by NLRP3, but sometimes the signaling pathway can not work because of the silencing of NLRP3 expression in most CRC cell lines. HDAC2 is one of the reasons for this phenomenon. HDAC2-mediated histone deacetylation leads to epigenetic silencing of NLRP3 in CRC. Many chemotherapy drugs are associated with NLRP3-induced cell pyroptosis, so targeting NLRP3 will affect the efficacy of chemotherapy drugs. The latest research shows that Inhibition of HDAC2 can sensitise antitumor therapy through promoting NLRP3/GSDMD-mediated pyroptosis, which provides a new idea in the treatment of colorectal cancer, and combined analysis of HDAC2 and NLRP3 can be used to predict patient survival.[25] In addition, 5-FU, as a traditional chemotherapy drug, tends to induce pyroptosis in colorectal cancer cells with high NLRP3 expression, while it prefers to trigger apoptosis in those with low NLRP3 expression.[25]

NLRP1, as well as NLRP3, can have an impact on reducing CAC tumorigenesis, but NLRP1 attenuates tumorigenesis through non-hematopoietic derived cells, differing from NLRP3, which regulates tumorigenesis through hematopoietic-derived cells.[23,26] As the research revealed, low expression of NLRP1 is common in colorectal cancer, and 5-aza-2-deoxycytidine can enhance the expression of NLRP1 to inhibit colon cancer, suppressing the tumor growth.[27] NLRP1 is an inducer of pyroptosis. Targeting NLRP1 provides new ideas for CRC clinical treatment.

Low expression of NLRC4 correlates with poor prognosis in CRC patients, and increased NLRC4 levels can improve the cancer survival of CRC patients.[28] Just like NLRC4, AIM2 is also low expression in CRC tissues, with poor prognosis in CRC patients. Recent research showed that the BRAF-mutant CRC cell death induced by AIM2 relied on caspase-1, which could induce pyroptosis both in colitis and CAC, providing a new idea in CRC treatment.[29]

Tight junctions are related to epithelial barrier integrity, and Pyrin is beneficial to maintain the integrity of tight junctions by promoting the maturation of IL-18, thereby preserving the epithelial barrier integrity and suppressing colitis and tumorigenesis.[30]

Non-Canonical Pathway

The non-canonical pathway is activated by most Gram-negative bacteria. A recent study has shown that GBP2, a member of guanylate-binding protein, can be recruited into the vacuole of Gram-negative bacteria such as Salmonella-containing vacuole, inducing the rupture of the vacuole, releasing the lipopolysaccharide(LPS) into the cytoplasm, making it be detected by caspase-11.[31] LPS, which is a component of Gram-negative bacteria, can bind to caspase-11, and activate it, making GSDMD split into GSDMD-N and GSDMD-C and form extensive pores, leading to pyroptosis.[16] In humans, caspase-4/5 whose activation can be triggered by LPS is homologous to caspase-11, inducing the cell pyroptosis.[17]

Interestingly, Caspase-11 can not trigger the secretion of IL-1β/IL-18 directly. Caspase-11 is upstream of a canonical NLRP3 inflammasome and it activates NLRP3 by triggering K+ efflux, which induces the activation of caspase-1, leading to the secretion of IL-1β/IL-18.[32] The pannexin-1 channel, which is cleaved and activated by caspase-11 and then induces the release of ATP, plays an important role in this process. The ATP activates the purinergic receptor P2X ligand-gated ion channel (P2X7), and in turn, allows K+ efflux.[33]

LPS has a direct association with the pyroptosis pathway in colorectal cancer.[34] The recent study demonstrates that secretoglobin 3A2, a multi-functional secreted protein, can chaperone LPS to the cytosol, which activates the non-canonical inflammasome pathway when the expression of membranous syndecan 1/heparan sulfate and caspase-4 is high, leading to the pyroptosis in human epithelial-derived colorectal cancer cells.[34] This finding nicely links LPS to the occurrence of pyroptosis.

Besides, LPS, as an inducer of pyroptosis in colorectal cancer cells, has also been used in some related cell experiments. For example, Zhao et al explored the mechanism of resveratrol on LPS/ATP-induced pyroptosis and inflammatory response in HT29 cells. They used LPS combined with ATP to induce pyroptosis of HT29 human colon cancer cells, thus constructing a relevant model and finding that resveratrol inhibited LPS/ATP-induced pyroptosis of HT29 cells.[35] This suggests that LPS has a promising role in constructing a model of pyroptosis in colorectal cancer cells, and demonstrates the inhibitory effect of resveratrol on the occurrence of LPS/ATP-induced pyroptosis in colorectal cancer.

Apoptotic Caspases-Mediated Pathway

Not only caspase-1/4/5/11 but also apoptotic caspases (such as caspase-3/8) have been demonstrated that they can induce pyroptosis, which used to be considered impossible in the past. In colorectal cancer cells, low expression of GSDME switches cell death from pyroptosis to apoptosis. In contrast, overexpression of GSDME facilitates the induction of pyroptosis.[18,36] After chemotherapy, in tumor cells with high GSDME expression, the chemotherapy drugs activate caspase-3. Caspase-3 can cleave the GSDME and produce GSDME-N, which induces pyroptosis. Some chemotherapy drugs, such as decitabine, can reverse GSDME silencing in colorectal cancer cells and promote the conversion of apoptosis to pyroptosis.[18] Moreover, caspase-8 can also trigger pyroptosis during the infection of Yersinia. Yersinia effector protein YopJ, an acetyl transferase, can inhibit TGF-β activated kinase-1 (TAK1) or IKK kinases, and then induce the cleavage of GSDMD, which relies on caspase-8.[19] In addition, triggered by TNF-α in the presence of GSDMC and nPD-L1 activated by hypoxia, caspase-8 can also cleave GSDMC, and generate GSDMC-N, which elicits pyroptosis through forming pores and causing the leakage of liposome.[20]

GSDME is often associated with colorectal cancer cell pyroptosis. Targeting GSDME is relevant to potential clinical treatment. Some chemotherapy drugs can induce pyroptosis in tumor cells, causing cell death. GSDME is the main executor of cell pyroptosis, and targeting GSDME has an impact on the efficacy of chemotherapy drugs.[37] Irinotecan, a kind of chemotherapy drug, is used to treat CRC patients. A recent study shows that GSDME can enhance the pyroptosis of CRC cells and decrease the resistance to irinotecan. Metastasis-associated in colon cancer 1 (MACC1) can inhibit the activation of GSDME and enhance the resistance to irinotecan. CRC cells with high MACC1 expression and low GSDME expression were more resistant to irinotecan, whereas CRC cells with low MACC1 expression and high GSDME expression were less resistant to irinotecan. Therefore, the expression of MACC1 and GSDME can be considered as detection markers to classify colorectal cancer patients into irinotecan resistant and sensitive groups, which can help to confirm the therapeutic strategy for patients.[37]

Granzymes-Mediated Pathway

Granzymes are a family including GZMA, GZMB, GZMH, GZMK, and GZMM in humans, which are essentially serine proteases expressed in cytotoxic T lymphocytes and natural killer cells.[38] A recent study shows that GZMA from cytotoxic lymphocytes can release the pore-forming activity of GSDMB in the manner of cleaving and activating GSDMB, which can give rise to the leakage of liposomes and elicit the cell pyroptosis.[21] GZMB can induce GSDME-mediated pyroptosis in two ways. On the one hand, GZMB can directly cleave GSDME after D270, which is analogous

to caspase-3, inducing cell pyroptosis. On the other hand, GZMB can activate caspase-3 to cleave GSDME, and then elicit cell pyroptosis indirectly.[22]

GZMA induces pyroptosis by cleaving GSDMB, providing new ideas for clinical treatment related to the tumor microenvironment. GZMA released by $CD8^+$TILs can effectively cleave GSDMB within tumor epithelial cells, leading to pyroptosis. At the same time, IFN-γ produced by $CD8^+$TILs can enhance GSDMB expression, further strengthening this cascade reaction. Yang et al found that in colon cancer cells, GSDMB is significantly expressed, and GZMA and IFN-γ are often co-expressed in $CD8^+$TILs. Compared with other $CD8^+$T cell subsets, $GZMA^+IFN\text{-}\gamma^+CD8^+$TILs form stronger interactions with $GSDMB^+CK^+$ cells. GSDMB-mediated pyroptosis releases various intracellular inflammatory factors, such as IL-1β and IL-18, which enhance the local inflammatory response and activate immune cells, including $GZMA^+IFN\text{-}\gamma^+CD8^+$TILs. This activation leads to further stimulation of these $CD8^+$ TILs, prompting them to secrete elevated levels of GZMA and IFN-γ. As a result, their cytotoxic impact on tumor cells is strengthened, and a positive feedback loop is established.[39] These indicate that $GZMA^+IFN\text{-}\gamma^+CD8^+$TILs have a significant effect on the immune microenvironment of colon cancer, which may affect the prognosis of patients by regulating tumor cells expressing GSDMB. The mechanisms of cell pyroptosis are shown in Figure 1.[6,12,14–22,37]

Pyroptosis and the Treatment of Colorectal Cancer

Pyroptosis is related to the treatment of colorectal cancer. The treatment methods and corresponding mechanisms of colorectal cancer are shown in Table 2.

GSDMD-Mediated Pyroptosis Therapy in Colorectal Cancer

Accompanied by medical advances, GSDMD-mediated therapy is gradually being applied to the treatment of colorectal cancer. Several drugs are associated with colorectal cancer treatment. Simvastatin, a kind of statin which can be used to treat cancer, has now been demonstrated to induce cell pyroptosis and inhibit cell proliferation in colon cancer cells through the NLRP3/caspase-1/GSDMD pathway, which may be beneficial in formulating potential therapeutic strategies for colon cancer.

It has been reported that simvastatin significantly inhibits the proliferation of HCT116 and SW620 cells when the concentration of simvastatin is greater than 2 μM. The Cell viability after 48 hours decreased by approximately 20% compared with the control group which was not exposed to simvastatin. Simvastatin can induce the production of ROS in colon cancer cell lines and the release of ROS elicits the production of NLRP3 inflammasome, which may cause the activation of the canonical inflammasome pathway.[40] However, in contrast to simvastatin, Huang Qin decoction, a traditional Chinese medicine formula for the management of colitis, was recently found that it can treat colitis-associated carcinogenesis by repressing the cell pyroptosis and blocking the NLRP3/caspase-1/GSDMD pathway mediated by NFκB. Huang Qin promotes the expression of SLC6A4, and then reduces the levels of serotonin, which blocks the NFκB-mediated NLRP3/caspase1/GSDMD pathway.[41] The development of drugs related to GSDMD-mediated cell pyroptosis deserves further exploration.

Some natural-occurring substances can induce cell pyroptosis, which is helpful in colorectal cancer treatment. Feng et al recently found that Quercetin (Que), a significant flavonoid widely existing in a variety of plants, induces cell pyroptosis in colon cancer through upregulating NEK7 to trigger the NLRP3 inflammasome-GSDMD signaling pathway. NIMA-related kinase 7 (NEK7), a serine-threonine kinase, is down-expressed in colon cancer, which may promote tumor growth and relate to colon cancer progression. Silencing of NEK7 inhibits activation of the NLRP3 inflammasome-GSDMD pathway and attenuates Que-induced pyroptosis in colon cancer cells. NEK7 deficiency accelerates xenograft tumor growth. High expression of NEK7 can suppress colon cancer, and the activation of the NEK7-mediated NLRP3 inflammasome-GSDMD signaling pathway is expected to be a potential therapeutic target for colon cancer. Que, because of its wide occurrence in fruits and vegetables, has far-reaching implications in providing dietary guidelines for colon cancer prevention and treatment.[42] Luteolin (3,4,5,7-tetrahydroxyflavonoid) is also a natural flavonoid which has anticancer properties. HT-29 is a type of colon cell line, and Chen et al demonstrated that luteolin causes HT-29 cell death through the activation of NLRP3/caspase1/GSDMD signaling pathway, thus inducing the cell pyroptosis, which may repress the colon tumor growth. Tumor sizes in mice treated with Luteolin were reported to be reduced by approximately

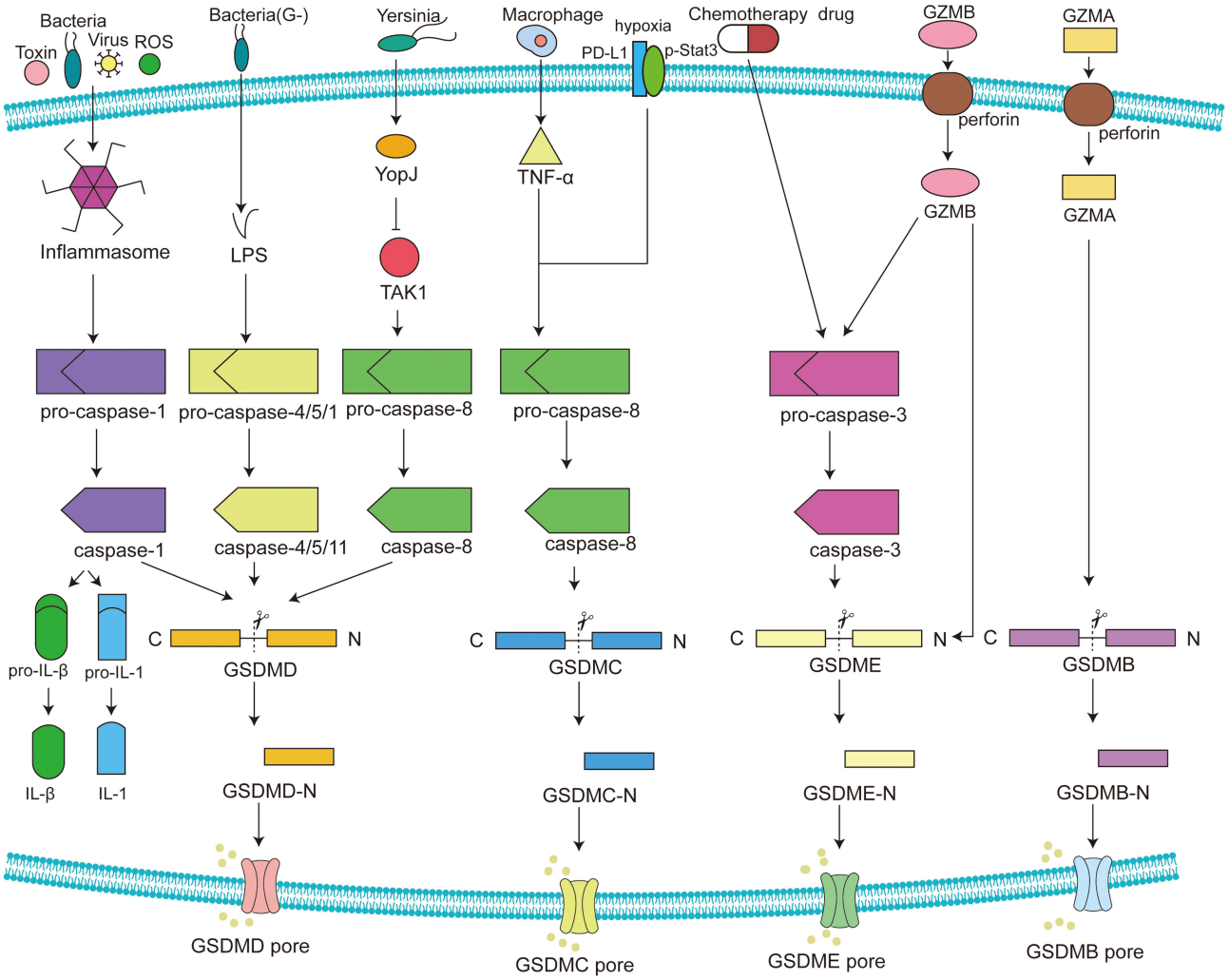

Figure 1 Mechanisms of cell pyroptosis. PAMPs and DAMPs such as toxins, bacteria, viruses, and ROS can stimulate inflammasomes, thereby activating caspase-1, cleaving GSDMD, forming non-selective ion-permeable pores and inducing cell pyroptosis.[6,12,14,15] LPS from Gram-negative bacteria triggers the non-canonical pathway by activating caspase-4/5/11 to cleave GSDMD.[16,17] Apoptotic caspases such as caspase-3 and caspase-8 can also cleave corresponding gasdermin family members to induce cell pyroptosis.[18–20,37] Yersinia effector protein YopJ can inhibit TAK1 or IKK kinases, and then induce the cleavage of GSDMD, which relies on caspase-8.[19] Under hypoxia, p-Stat3 physically interacts with PD-L1 and facilitates its nuclear translocation, enhancing GSDMC gene transcription. Triggered by TNF-α from macrophage in the presence of GSDMC and nPD-L1 activated by hypoxia, caspase-8 can cleave GSDMC to induce pyroptosis.[20] After chemotherapy, caspase-3 can cleave the GSDME and produce GSDME-N to induce pyroptosis.[37] GZMA from cytotoxic lymphocytes can directly cleave and activate GSDMB.[21] GZMB can cleave GSDME directly or activate caspase-3 to cleave GSDME indirectly, and then elicit cell pyroptosis.[22]

Abbreviations: PAMPs, pathogen-associated molecular patterns; DAMPs, endogenous danger signals; ROS, reactive oxygen species; GSDMD, gasdermin D; LPS, lipopolysaccharide; TAK1, TGF-β activated kinase-1; IKK, inhibitor of κB kinase; PD-L1, programmed death ligand 1; GSDMC, gasdermin C; TNF, tumor necrosis factor; nPD-L1, nuclear programmed death ligand 1; GSDME, gasderminE; GZMA, granzyme A; GZMB, granzyme B.

45% compared to the untreated control group.[43] Secoisolariciresinol diglucoside (SDG), a plant lignan derived from flaxseed, has anticancer activity. Chen et al have found that GSDMD is cleaved in SDG-induced pyroptosis by caspase-1 in HCT116 cells which is a type of human CRC cell line. Interestingly, they also found that the PI3K/AKT signaling pathway, which is significant in regulating cancer cell pro-proliferative, antiapoptotic pathways, and differentiation, also plays an important part in SDG-mediated pyroptosis. SDG induces cell pyroptosis and then reduces the growth of CRC in vitro, via inhibiting the PI3K/AKT signaling pathway by increasing intracellular ROS levels.[44] In summary, natural substances have great potential in the treatment of colorectal cancer and deserve more in-depth research. They can guide the direction of dietary combinations and drug development in colorectal cancer treatment, which deserves the attention of researchers.

The first-line treatment drugs for colorectal cancer include capecitabine, oxaliplatin, bevacizumab, etc.[3] Pyroptosis also has applications in chemotherapy and often enhances the chemosensitivity of the drug. Oxaliplatin, also called

Table 2 Treatment Methods and Corresponding Mechanisms of Colorectal Cancer

Strategy	Type	Mechanism	Reference
GSDMD-mediated pyroptosis therapy			
Simvastatin	Drug	NLRP3/caspase-1/GSDMD	[40]
Huang Qin	Drug	NLRP3/caspase-1/GSDMD	[41]
Quercetin	Natural-occurring substance	NLRP3/caspase-1/GSDMD	[42]
Luteolin	Natural-occurring substance	NLRP3/caspase-1/GSDMD	[43]
Secoisolariciresinol diglucoside	Natural-occurring substance	Bax/caspase-1/GSDMD	[44]
LPS	Chemotherapy	Inducing expression of GSDMD	[7]
T22-PE24-H6	Nanotechnology	NLRP3/caspase-1/GSDMD	[45]
T22-DITOX-H6	Nanotechnology	NLRP3/caspase-1/GSDMD OR caspase-11/GSDMD	[46]
GSDME-mediated pyroptosis therapy			
shNrf2	Chemotherapy	ROS/caspase-3/GSDME	[47]
GW4064	Chemotherapy	Bax/caspase-3/GSDME	[48]
Lobaplatin	Chemotherapy	Bax/caspase-3/GSDME	[49]
Radiation	Radiotherapy	Caspase-3/GSDME	[8]
ORFV	Virus	Decreasing ubiquitination on GSDME	[50]
CVB3	Virus	ROS/caspase-3/GSDME	[51]
Gambogic Acid	Natural-occurring substance	Caspase-3/GSDME	[52]
IR700DX-6T-PDT	Photodynamic therapy	ROS/p38/caspase-3/GSDME	[53]
Carbazole-modified chiral Ir(III) complexes	Photodynamic therapy	ROS/caspase-3/GSDME	[54]
Lyso-Ir	Sonodynamic therapy	ROS/caspase-3/GSDME	[55]
Other pyroptosis therapy			
Elraglusib	Immunity	Upregulating the expression of GSDMB	[56]

Abbreviations: GSDMB, gasdermin B; NLRP3, nucleotide-binding oligomerization domain-like receptor pyrin domain-containing3; Bax, Bcl-2-associated X protein; LPS, lipopolysaccharide; Nrf2, nuclear factor erythroid 2-related factor 2; ROS, reactive oxygen species; GSDME, gasdermin E; ORFV, oncolytic parapoxvirus ovis; CVB3, coxsackievirus group B3; GSDMB, gasdermin B.

L-OHP, is a third-generation platinum compound, that has an anti-tumor impact in CRC cells, but intrinsic or acquired resistance to L-OHP often impairs its chemotherapeutic sensitivity, thereby reducing its chemotherapeutic efficacy. LPS plays an important role in enhancing the chemosensitivity of Oxaliplatin in HT29 Cells which is a type of CRC cells via GSDMD-Mediated Pyroptosis. However, LPS itself did not enhance the chemosensitivity of L-OHP. In fact, LPS induces the expression of GSDMD and GSDMD sensitises HT29 cells to L-OHP in vitro and in vivo by eliciting cell pyroptosis, indirectly enhancing the chemosensitivity. However, it is regrettable that the mechanism of GSDMD-mediated chemosensitization is still unclear.[7] Nowadays, the chemosensitivity of chemotherapy drugs due to resistance and other reasons has become a challenge in the treatment of colorectal cancer.[57] Studies related to pyroptosis provide a new idea for it, but a large number of studies are still needed to prove its practicality.

With the advancement of technology, nanotechnology is also widely used in medicine. For example, in lung cancer treatment, Zhu et al designed a biomimetic nanoplatform co-delivering Polyphyllin VI (PPVI) and cisplatin (CDDP), using PPVI's ability to activate NLRP3/GSDMD inflammasome pathway, inhibit glutathione peroxidase 4 (GPX4) via signal transducer and activator of transcription 3 (STAT3) phosphorylation suppression, and induce pyroptosis to enhance CDDP's antitumor effect.[58] In addition, Fe-involved nanostructures are used in photothermal therapy (PTT) due to their ability to generate ROS and trigger ferroptosis, as well as the enhanced photothermal transduction ability of certain organic agents mediated by iron chelation.[59] In colorectal cancer treatment, nanotechnology is also widely applied. Zhang et al encapsulated hemiprotonic phenanthroline-phenanthroline+ into nanomicelle for colorectal cancer therapy.[60] Colon-targeted drug delivery systems using nanotechnology enable more effective treatment of inflammatory bowel disease through diverse approaches, preventing colorectal cancer.[61] Nanotechnology can be used for the induction of

pyroptosis, thus promoting cell death and providing assistance in the treatment of colorectal cancer. T22-PE24-H6 nanotoxin, T22-PE24-H6 therapeutic protein-only nanoparticle that incorporates the exotoxin A from Pseudomonas aeruginosa, can selectively target CRC cells and has great potential to treat CRC.[45] T22-PE24-H6 nanotoxin can induce cell pyroptosis mediated by NLRP3/caspase-1/GSDMD signaling pathway, which differs from most of the chemotherapeutic anticancer drugs which induce pyroptosis mediated by caspase-3/GSDME signaling pathway. T22-PE24-H6 nanotoxin shows a potent CXCR4-dependent cytotoxic effect in CRC cells and can repress the growth and metastasis development of CRC tumor when used at low doses in repeated treatment regimens, without toxicity in non-target organs.[45] T22-DITOX-H6 has higher cytotoxicity compared to T22-PE24-H6. Serna et al found that after injection of T22-DITOX-H6 nanoparticles in a CXCR4+ CRC-CSC (Da13) mouse model, the expression of the pyroptosis markers caspase-11 and NLRP3 was elevated at 48 h, suggesting that the nanoparticles cause cell death by inducing pyroptosis. In their further studies, they found that T22-DITOX-H6 was more potent than 5-FU and was effective on CXCR4+ CRC stem cells that responded poorly to 5-FU or oxaliplatin in vitro and in vivo.[46] Both demonstrate the broad promise of nanotechnology in the treatment of colorectal cancer, not only in terms of its ability to target cancer cells containing specific receptors without exposing them to normal tissue but also in terms of their improved efficacy compared to conventional drugs and their effectiveness in overcoming drug resistance. The mechanism of GSDMD-mediated pyroptosis in colorectal cancer is shown in Figure 2.[7,40–46]

GSDME-Mediated Pyroptosis Therapy in Colorectal Cancer

Like GSDMD, GSDME-mediated pyroptosis is associated with chemotherapy. Nrf2 (Nuclear factor erythroid 2-related factor 2), a classic anti-inflammatory and antioxidant molecule, can inhibit TNF-α production, thereby further inhibiting GSDME activation. Knockdown of Nrf2 results in oxaliplatin-treated CRC cells with higher LDH release and higher expression of GSDME-N that drives cell pyroptosis compared to the non-knockdown cell group. After knocking down Nrf2, the expression of GSDME-N in CRC cells treated with oxaliplatin increased by about 40% compared with the group without knockdown but treated with oxaliplatin. These results suggest that Nrf2 inhibition enhances chemotherapeutic drug-induced cell pyroptosis and improves colorectal cell chemosensitivity.[47] Also related to the chemotherapeutic drug oxaliplatin, GW4064, a synthetic FXR agonist, is synergistic with oxaliplatin in colon cancer cells. GW4064 is not only effective in the treatment of cholestatic liver diseases, metabolic syndrome and alcoholic liver disease, but also beneficial to CRC treatment. GW4064 can enhance the chemosensitivity of CRC to oxaliplatin via pyroptosis mediated by the Bax/caspase-3/GSDME pathway. Combination treatment with oxaliplatin and GW4064 synergistically restore SHP expression, which in turn inhibits the STAT3 signaling pathway, thereby inducing pyroptosis in CRC cells. Combination treatment with oxaliplatin and GW4064 suggests that FXR agonists may be candidates for reversing CRC resistance to STAT3 overactivation and combination therapy with FXR agonists and oxaliplatin has great potential for the future.[48] Therefore, reducing the resistance of chemotherapeutic drugs such as oxaliplatin and improving colorectal cell chemosensitivity through the pyroptosis pathway is a new idea for the effective treatment of colorectal cancer. Also involved with the Bax/caspase-3/GSDME pathway, lobaplatin as a chemotherapeutic drug induces cell pyroptosis. Lobaplatin (chemical formula: C9H18N2O3Pt), a third-generation platinum anti-neoplastic agent, elevates ROS and results in the phosphorylation of JNK. Activated JNK further enhances the translocation of Bax to mitochondria, which activates caspase-3 and cleaves GSDME. GSDME-N finally induces pyroptosis.[49] Chemotherapy related to the pyroptosis pathway has great potential in the treatment of colorectal cancer. However, compared with apoptosis, pyroptosis is a cell death pathway that has been identified in the past decade. There are relatively few studies related to colorectal cancer chemotherapy, and some controversies still exist. Further research is needed to clarify its feasibility in the treatment of colorectal cancer.

Radiotherapy is an important treatment modality for various cancer, while the treatment effect is not very good in CRC.[8] Recently, Tan et al have provided that radiation can induce pyroptosis via the caspase-3/GSDME pathway except in the CRC cells because of the low expression of GSDME in CRC cells. Increased caspase-3 activation but no induction of pyroptosis in CRC cells leads to the occurrence of low radiosensitivity. In conclusion, radiation is toxic to normal tissue cells due to the normal expression of GSDME, while CRC cells, on the contrary, show low radiosensitivity due to the low expression of GSDME. Therefore, reversing GSDME silencing in CRC cells becomes the key to treatment.

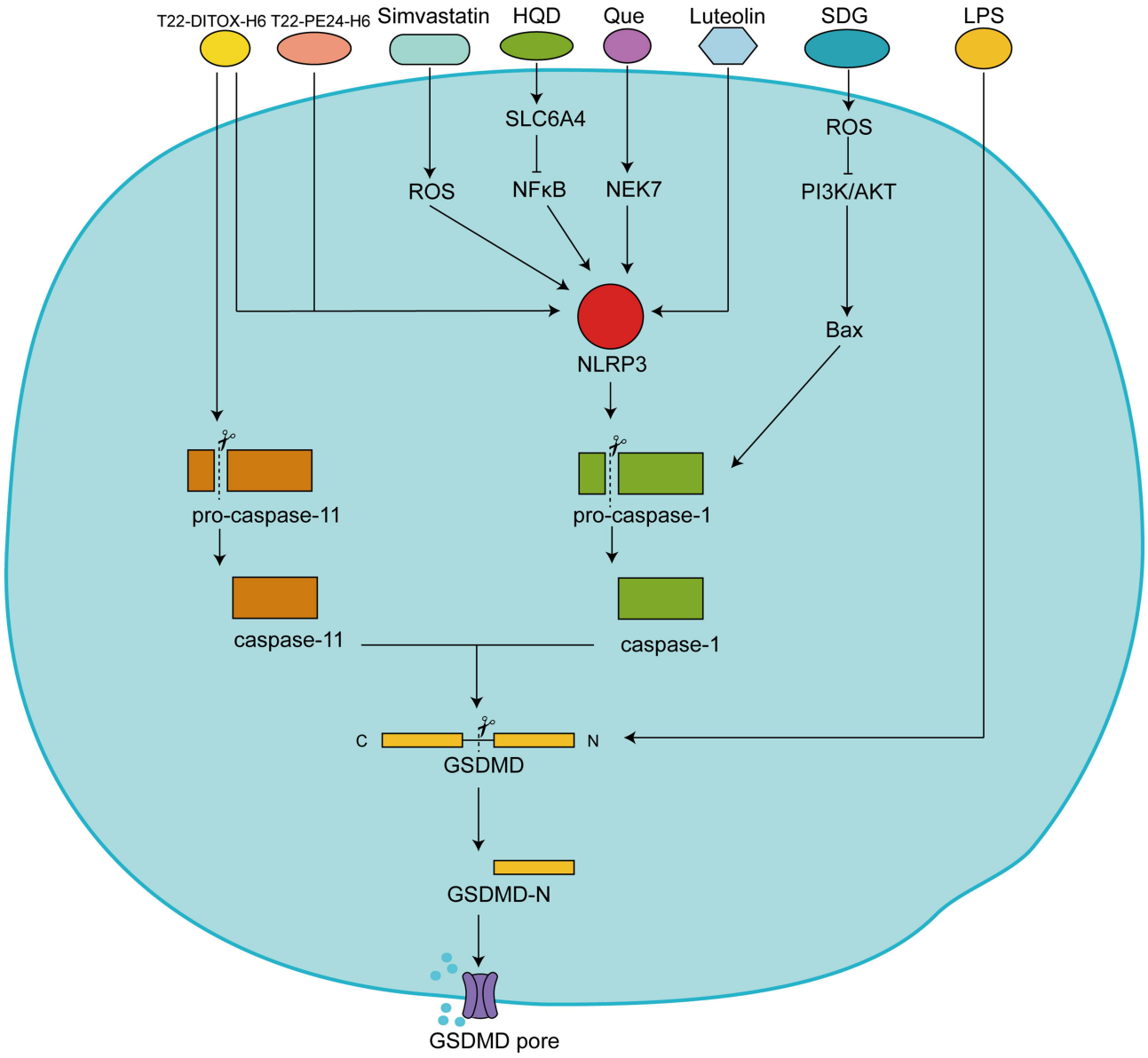

Figure 2 Mechanism of GSDMD-mediated pyroptosis in colorectal cancer. After injection of T22-DITOX-H6 nanoparticles, the expression of pyroptosis markers caspase-11 and NLRP3 increased at 48 h, triggering pyroptosis.[46] T22-PE24-H6 nanotoxin can induce cell pyroptosis mediated by the NLRP3/caspase-1/GSDMD signaling pathway.[45] Simvastatin can induce the production of ROS and the release of ROS elicits the production of NLRP3 inflammasome, which may cause the activation of the NLRP3/caspase-1/GSDMD pathway.[40] HQD promotes SLC6A4 expression and SLC6A4 reduces the levels of serotonin, which blocks the NFκB-mediated NLRP3/caspase-1/GSDMD pathway.[41] Que induces cell pyroptosis in colon cancer through upregulating NEK7 to trigger the NLRP3/caspase-1/GSDMD signaling pathway.[42] Luteolin induces pyroptosis through the activation of NLRP3/caspase-1/GSDMD signaling pathway.[43] SDG induces cell pyroptosis via inhibiting the PI3K/AKT signaling pathway by increasing intracellular ROS levels.[44] LPS induces the expression of GSDMD and GSDMD sensitises HT29 cells to L-OHP in vitro and in vivo by eliciting cell pyroptosis, indirectly enhancing the chemosensitivity.[7]

Abbreviations: NLRP3, nucleotide-binding oligomerization domain-like receptor pyrin domain-containing3; GSDMD, gasdermin D; ROS, reactive oxygen species; HQD, Huang Qin decoction; SLC6A4, solute carrier family 6 member 4; NFκB,nuclear factor kappa B; NEK7, NIMA-related kinase 7; SDG, secoisolariciresinol diglucoside; PI3K, phosphatidylinositol 3-kinase; AKT, otein Kinase B; LPS, lipopolysaccharide; L-OHP, Oxaliplatin.

Radiotherapy combined with decitabine, a hypomethylating agent that can reverse GSDME silencing, may be a feasible treatment method and deserves further study.[8] In summary, radiotherapy used to have a poor therapeutic effect on colorectal cancer, but when the silencing of GSDME in CRC cells is reversed, it will induce cell pyroptosis, thereby improving the therapeutic effect of colorectal cancer. The combination of radiotherapy and drugs has great potential in the treatment of colorectal cancer.

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In addition to causing harm to the human body, viruses also have advantages in medicine, serving as drugs, carriers, etc. Lin et al found that Oncolytic Parapoxvirus ovis (ORFV), a promising oncolytic virus with high immunogenicity and unique immune-stimulating properties, can induce GSDME-mediated pyroptosis in some epithelium-derived tumor cell lines and human colon tumor tissues. ORFV can also pre-stabilize GSDME by decreasing ubiquitination on GSDME, which helps it trigger pyroptosis in tumor cells with low GSDME expression. The dual effects of ORFV demonstrate its great potential in the treatment of CRC.[50] Coxsackievirus Group B3 (CVB3) is an RNA virus with oncolytic activity. It can activate the caspase-3/GSDME pathway by increasing ROS levels, thereby inducing pyroptosis in CRC cells.[51] In short, the virus is a double-edged sword. While viruses are harmful to humans, they are also very useful in medical treatment. Viruses can induce GSDME-mediated pyroptosis, which has some implications for the treatment of colorectal cancer. However, while viruses play a role in treating cancer, whether they will cause harm to the human body, such as causing severe immune responses and causing some sequelae, deserves careful study. Whether it is possible to choose viruses that are less harmful to the human body, or to remove the virulence genes of the virus, and how to exert the function of viral vectors to develop vaccines and drugs are aspects that need to be considered in subsequent research on colorectal cancer treatment options.

Some natural substances can also induce pyroptosis of CRC cells. Gambogic Acid (GA) is the main active ingredient isolated from Gamboge, a brownish resin secreted by Garcinia hanburyi. GA can induce cell pyroptosis through the caspase-3/GSDME pathway. It is worth mentioning that compared with 5-FU, which may cause liver and immunological function damage, GA has excellent anti-cancer activity without causing major organ damage or hepatorenal dysfunction.[52]

Now, there are also some novel therapies to induce GSDME-mediated pyroptosis for the treatment of colorectal cancer. Photodynamic therapy (PDT) has the advantages of specific targeting, spatiotemporal controllability, and extremely low invasiveness. For example, Chen et al developed a lysosome-targeting photosensitizer/photoredox catalyst, which generates ROS upon light irradiation. ROS impair lysosomes, release cathepsin B, and finally induce cellular necrosis or apoptosis.[62] IR700DX-6T, a photosensitizer targeting the mitochondrial translocation protein, can induce cell pyroptosis mediated by the caspase-3/GSDME pathway in CRC cells. IR700DX-6T-PDT produces ROS, which can regulate the p38 signaling pathway. The latter has a regulatory effect on IR700DX-6T-PDT-induced pyroptosis of CRC cells. This suggests that IR700DX-6T-PDT triggers pyroptosis in CRC cells by activating the ROS/p38/caspase-3/GSDME signaling pathway. IR700DX-6T-PDT induces cell pyroptosis, causing tumor cells to secrete cytokines, such as IL-1β and IL-18, triggering immunogenic cell death, activating immune cells such as dendritic cells, macrophages, and natural killer cells, sensitizing MSS-CRC to the immune response of PD-1 blockade, and then inducing CTL infiltration, thereby promotes anti-tumor activities by converting "cold" tumors into "hot" tumors. As mentioned above, decitabine is a commonly used DNA methyltransferase inhibitor that can promote DNA hypomethylation, improve the abnormal methylation of GSDME in CRC cells, and increase GSDME levels. It can enhance the antitumor effect of IR700DX-6T-PDT and PD-1 blockade via combination with them, in the tumors with low endogenous GSDME expression. It is reported that the combined treatment of decitabine, IR700DX-6T-PDT and anti-PD-1 antibody in 4T1 tumor-bearing mice reduced the tumor volume by about 75% on the twelfth day compared with the group treated with decitabine alone.[53] Tao et al synthesized a pair of carbazole-modified chiral Ir(III) complexes (Δ-Ir-Car and Λ-Ir-Car), which can generate abundant ROS under light irradiation and induce the caspase-3/GSDME-mediated pyroptosis pathway. Notably, Δ-Ir-Car exhibits stronger ability to induce pyroptosis under light exposure compared to Λ-Ir-Car, and the mechanism may be attributed to the enhanced internalization of Δ-Ir-Car that promotes cytoplasmic ROS accumulation.[54] In summary, PDT has broad prospects as an emerging treatment method. It can enhance the efficacy of CRC in combination with other drugs and deserves further study. In addition, decitabine has also shown its amazing potential in the combined treatment of CRC tumors. As a drug that can reverse GSDME silencing, it can provide some help for the research of tumor treatment. In addition, sonodynamic therapy (SDT) holds great promise due to its deeper tissue penetrability than phototherapy. Under the action of low-intensity ultrasound, Lyso-Ir, as a sonosensitizer, generates a large amount of ROS, activates the caspase-3/GSDME pathway, and induces pyroptosis in colon cancer cells.[55] The mechanism of GSDME-mediated pyroptosis in colorectal cancer is shown in Figure 3.[8,47–53]

Other Pyroptosis Therapy in Colorectal Cancer

High expression of GSDMB is beneficial to the prognosis of colorectal cancer and helps enhance the sensitivity of colorectal cancer cells to chemotherapeutic drugs. Patients with cytoplasmic or nuclear GSDMB expression in cancer cells tend to benefit more from 5-Fu based chemotherapy. Studies have shown that high expression of GSDMB can increase the sensitivity of

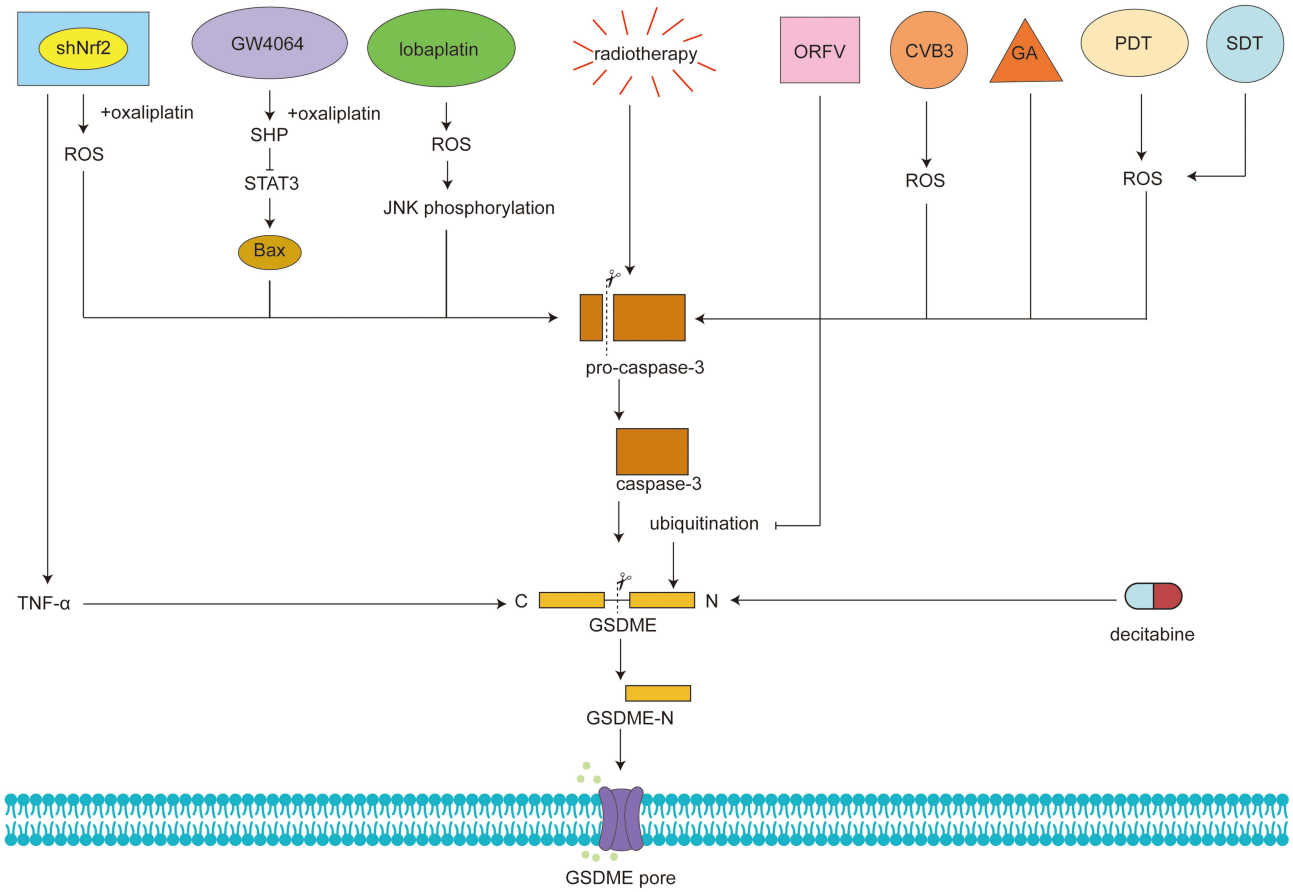

Figure 3 Mechanism of GSDME-mediated pyroptosis in colorectal cancer. Knockdown of Nrf2 leads to more TNF-α production in oxaliplatin-treated CRC cells, which promotes GSDME activation. Knockdown of Nrf2 also promotes pyroptosis mediated by the caspase-3/GSDME pathway by increasing ROS levels.[47] Combination treatment with oxaliplatin and GW4064 synergistically restore SHP expression, which in turn inhibits the STAT3 signaling pathway, thereby inducing pyroptosis mediated by the Bax/caspase-3/GSDME pathway.[48] Lobaplatin elevates ROS and results in the phosphorylation of JNK. Activated JNK further enhances the translocation of Bax to mitochondria, which activates caspase-3 and cleaves GSDME to induce pyroptosis.[49] Radiation can induce pyroptosis via the caspase-3/GSDME pathway, and radiotherapy combined with decitabine can reverse GSDME silencing and help induce pyroptosis.[8] ORFV can pre-stabilize GSDME by decreasing ubiquitination on GSDME, which helps it trigger pyroptosis in tumor cells with low GSDME expression.[50] CVB3 can activate the casp-3/GSDME pathway by increasing ROS levels, thereby inducing pyroptosis in CRC cells.[51] GA can induce cell pyroptosis through the caspase-3/GSDME pathway.[52] PDT and SDT triggers pyroptosis in CRC cells by activating the ROS/caspase-3/GSDME signaling pathway.[53–55]

Abbreviations: Nrf2, nuclear factor erythroid 2-related factor 2; TNF, tumor necrosis factor; GSDME, gasdermin E; ROS, reactive oxygen species; SHP, small heterodimer partner; STAT3, signal transducer and activator of transcription 3; Bax, Bcl-2-associated X protein; JNK, c-Jun N-terminal kinase; ORFV, oncolytic parapoxvirus ovis; CVB3, coxsackievirus group B3; CRC, colorectal cancer; GA, gambogic Acid; PDT, photodynamic therapy; SDT, sonodynamic therapy.

colorectal cancer cells to 5-Fu. It has been reported that in GSDMB overexpressing cells, the IC50 of 5-Fu was 126.9μM, while in control cells was 151.6μM.[63] Glycogen synthase kinase-3 is a serine/threonine kinase associated with the oncogenic process. Its inhibitor elraglusib (9-ING-41) may promote the secretion of IFN-γ in immune cells, thereby upregulating the expression of gasdermin B in CRC cells and enhancing the occurrence of pyroptosis, which still needs further experiments to prove.[56]

Conclusion

Colorectal cancer is a common malignant tumor. Due to its high incidence and high mortality rate, it has gradually attracted people's attention, and various treatment methods have been proposed. Cell pyroptosis, which is associated with the treatment of colorectal cancer includes the canonical pathway, non-canonical pathway, apoptotic caspases-mediated pathway, and granzymes-mediated pathway. These pathways all activate cell pyroptosis by cleaving gasdermin through caspases. GSDMD-mediated pyroptosis for the treatment of colorectal cancer usually involves drugs, natural substances, chemotherapy, and nanotechnology. GSDME-mediated pyroptosis for colorectal cancer treatment usually involves chemotherapy, radiotherapy, viruses, natural substances, and photodynamic therapy. As for the use of the pyroptosis pathways related to GSDMB and GSDMC to treat colorectal cancer, there are relatively few studies. At present, most of the research on the use of pyroptosis to treat colorectal cancer

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is still at the cell experiment level. In the future, on the one hand, we can continue to explore the relevant mechanisms of cell pyroptosis-related signaling pathways in the occurrence and development of colorectal cancer, so as to achieve more precise regulation; on the other hand, we can increase relevant clinical experiments and put the results of basic experiments into clinical practice.

Abbreviations

ALR, AIM2-like receptor; AKT, otein Kinase B; AIM2, absent in melanoma 2; ASC, apoptosis-associated speck-like protein containing a CARD; ATP, adenosine triphosphoric acid; Bax, Bcl-2-associated X protein; CAC, olitis-associated cancer; CAPOX, capecitabine plus oxaliplatin; CDDP,cisplatin; CRC, colorectal cancer; CVB3, coxsackievirus group B3; CXCR4, C-X-C motif chemokine receptor 4; DAMPs, endogenous danger signals; dMMR, deficient mismatch repair; FasL, Fas ligand; FOLFIRI, Fluorouracil with folinic acid and irinotecan; FOLFOX, fluorouracil, leucovorin and oxaliplatin; FOLFOXIRI, 5-fluorouracil, L-leucovorin, oxaliplatin and irinotecan; FXR, farnesoid X receptor; GA, gambogic Acid; GBP2, guanylate-binding protein2; GPX4, glutathione peroxidase 4; GSDMA, gasdermin A; GSDMB, gasdermin B; GSDMC, gasdermin C; GSDMD, gasdermin D; GSDME, gasdermin E; GZMA, granzyme A; GZMB, granzyme B; GZMH, granzyme H; GZMK, granzyme K; GZMM, granzyme M; HDAC2, histone deacetylase 2; IC50, half maximal inhibitory concentration; IL-1, interleukin-1; IL-1β, interleukin-1β; IL-18, interleukin-18; IFN, interferon; IKK, inhibitor of κB kinase; JNK, c-Jun N-terminal kinase; L-OHP, Oxaliplatin; LDH, lactate dehydrogenase; LV, Leucovorin; LPS, lipopolysaccharide; MACC1, metastasis-associated in colon cancer 1; MLKL, mixed lineage kinase domain-like; MSI-H, microsatellite instability-high; MSS, micro-satellite-stable; NEK7, NIMA-related kinase 7; NFκB,nuclear factor kappa B; NCCN, National Comprehensive Cancer Network; NLR, nucleotide-binding domain and leucine-rich-repeat-containing; NLRP1, nucleotide-binding oligomerization domain-like receptor pyrin domain-containing1; NLRP3, nucleotide-binding oligomerization domain-like receptor pyrin domain-containing3; NLRC4, nucleotide-binding oligomerization domain-like receptor caspase recruitment domain-containing 4; nPD-L1, nuclear programmed death ligand 1; Nrf2, nuclear factor erythroid 2-related factor 2; ORFV, oncolytic parapoxvirus ovis; P2X7, P2X purinoreceptor 7; PAMPs, pathogen-associated molecular patterns; PD-1, programmed death 1; PD-L1, programmed death ligand 1; PI3K, phosphatidylinositol 3-kinase; PPVI, Polyphyllin VI; PTT, photothermal therapy; Que, Quercetin; ROS, reactive oxygen species; SDG, secoisolariciresinol diglucoside; SDT, sonodynamic therapy; SHP, small heterodimer partner; SLC6A4, solute carrier family 6 member 4; STAT3, signal transducer and activator of transcription 3; TAK1, TGF-β activated kinase-1; TILs, tumor-infiltrating lymphocytes; TNF, tumor necrosis factor; 5-FU, 5-Fluorouracil.

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Disclosure

The authors declare that they have no conflict of interest in this work.

References

1. Bray F, Laversanne M, Sung H, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2024;74(3):229–263. doi:10.3322/caac.21834
2. Siegel RL, Kratzer TB, Giaquinto AN, Sung H, Jemal A. Cancer statistics, 2025. *CA Cancer J Clin*. 2025;75(1):10–45. doi:10.3322/caac.21871
3. Benson AB, Venook AP, Al-Hawary MM, et al. Colon cancer, version 2.2021, NCCN clinical practice guidelines in oncology. *J Natl Compr Canc Netw*. 2021;19(3):329–359. doi:10.6004/jnccn.2021.0012
4. Benson AB, Venook AP, Al-Hawary MM, et al. Rectal cancer, version 2.2022, NCCN clinical practice guidelines in oncology. *J Natl Compr Canc Netw*. 2022;20(10):1139–1167. doi:10.6004/jnccn.2022.0051
5. Siegel RL, Wagle NS, Cercek A, Smith RA, Jemal A. Colorectal cancer statistics, 2023. *CA Cancer J Clin*. 2023;73(3):233–254. doi:10.3322/caac.21772
6. Chen X, He WT, Hu L, et al. Pyroptosis is driven by non-selective gasdermin-D pore and its morphology is different from MLKL channel-mediated necroptosis. *Cell Res*. 2016;26(9):1007–1020. doi:10.1038/cr.2016.100
7. Wu LS, Liu Y, Wang XW, et al. LPS enhances the chemosensitivity of oxaliplatin in HT29 cells via GSDMD-mediated pyroptosis. *Cancer Manag Res*. 2020;12:10397–10409. doi:10.2147/CMAR.S244374
8. Tan G, Lin C, Huang C, et al. Radiosensitivity of colorectal cancer and radiation-induced gut damages are regulated by gasdermin E. *Cancer Lett*. 2022;529:1–10. doi:10.1016/j.canlet.2021.12.034
9. Croes L, Fransen E, Hylebos M, et al. Determination of the potential tumor-suppressive effects of *Gsdme* in a chemically induced and in a genetically modified intestinal cancer mouse model. *Cancers*. 2019;11(8):1214. doi:10.3390/cancers11081214

10. Wei X, Xie F, Zhou X, et al. Role of pyroptosis in inflammation and cancer. *Cell Mol Immunol*. 2022;19(9):971–992. doi:10.1038/s41423-022-00905-x
11. Friedlander AM. Macrophages are sensitive to anthrax lethal toxin through an acid-dependent process. *J Biol Chem*. 1986;261(16):7123–7126. doi:10.1016/S0021-9258(17)38364-3
12. Shi J, Zhao Y, Wang K, et al. Cleavage of GSDMD by inflammatory caspases determines pyroptotic cell death. *Nature*. 2015;526(7575):660–665. doi:10.1038/nature15514
13. Ding J, Wang K, Liu W, et al. Pore-forming activity and structural autoinhibition of the gasdermin family. Nature. 2016 Jul;535(7610):111-6. doi: 10.1038/nature18590. *Nature*. 2016;540(7631):150. doi:10.1038/nature20106
14. Liu X, Zhang Z, Ruan J, et al. Inflammasome-activated gasdermin D causes pyroptosis by forming membrane pores. *Nature*. 2016;535(7610):1538. doi:10.1038/nature18629
15. Ketelut-Carneiro N, Fitzgerald KA. Inflammasomes. *Curr Biol*. 2020;30(12):R689–R694. doi:10.1016/j.cub.2020.04.065
16. Shi J, Gao W, Shao F. Pyroptosis: gasdermin-mediated programmed necrotic cell death. *Trends Biochem Sci*. 2017;42(4):245–254. doi:10.1016/j.tibs.2016.10.004
17. Shi J, Zhao Y, Wang Y, et al. Inflammatory caspases are innate immune receptors for intracellular LPS. *Nature*. 2014;514(7521):187–192. doi:10.1038/nature13683
18. Wang Y, Gao W, Shi X, et al. Chemotherapy drugs induce pyroptosis through caspase-3 cleavage of a gasdermin. *Nature*. 2017;547(7661):99–103. doi:10.1038/nature22393
19. Orning P, Weng D, Starheim K, et al. Pathogen blockade of TAK1 triggers caspase-8-dependent cleavage of gasdermin D and cell death. *Science*. 2018;362(6418):1064–1069. doi:10.1126/science.aau2818
20. Hou J, Zhao R, Xia W, et al. PD-L1-mediated gasdermin C expression switches apoptosis to pyroptosis in cancer cells and facilitates tumour necrosis. Nat Cell Biol. 2020;22(10):1264-1275. doi: 10.1038/s41556-020-0575-z. *Nat Cell Biol*. 2020;22(11):1396. doi:10.1038/s41556-020-00599-1
21. Zhou Z, He H, Wang K, et al. Granzyme A from cytotoxic lymphocytes cleaves GSDMB to trigger pyroptosis in target cells. *Science*. 2020;368(6494):eaaz7548. doi:10.1126/science.aaz7548
22. Zhang Z, Zhang Y, Xia S, et al. Gasdermin E suppresses tumour growth by activating anti-tumour immunity. *Nature*. 2020;579(7799):415–420. doi:10.1038/s41586-020-2071-9
23. Allen IC, TeKippe EM, Woodford RM, et al. The NLRP3 inflammasome functions as a negative regulator of tumorigenesis during colitis-associated cancer. *J Exp Med*. 2010;207(5):1045–1056. doi:10.1084/jem.20100050
24. Dagenais M, Saleh M. Linking cancer-induced Nlrp3 inflammasome activation to efficient NK cell-mediated immunosurveillance. *Oncoimmunology*. 2016;5(5):e1129484. doi:10.1080/2162402X.2015.1129484
25. Guan X, Liu R, Wang B, et al. Inhibition of HDAC2 sensitises antitumour therapy by promoting NLRP3/GSDMD-mediated pyroptosis in colorectal cancer. *Clin Transl Med*. 2024;14(6):e1692. doi:10.1002/ctm2.1692
26. Williams TM, Leeth RA, Rothschild DE, et al. The NLRP1 inflammasome attenuates colitis and colitis-associated tumorigenesis. *J Immunol*. 2015;194(7):3369–3380. doi:10.4049/jimmunol.1402098
27. Chen C, Wang B, Sun J, et al. DAC can restore expression of NALP1 to suppress tumor growth in colon cancer. *Cell Death Dis*. 2015;6(1):e1602. doi:10.1038/cddis.2014.532
28. Domblides C, Crampton S, Liu H, et al. Human NLRC4 expression promotes cancer survival and associates with type I interferon signaling and immune infiltration. *J Clin Invest*. 2024;134(11):e166085. doi:10.1172/JCI166085
29. Shah S, Qin S, Luo Y, et al. AIM2 inhibits BRAF-mutant colorectal cancer growth in a caspase-1-dependent manner. *Front Cell Dev Biol*. 2021;9:588278. doi:10.3389/fcell.2021.588278
30. Sharma D, Malik A, Guy CS, Karki R, Vogel P, Kanneganti TD. Pyrin inflammasome regulates tight junction integrity to restrict colitis and tumorigenesis. *Gastroenterology*. 2018;154(4):948–964.e8. doi:10.1053/j.gastro.2017.11.276
31. Man SM, Kanneganti TD. Regulation of inflammasome activation. *Immunol Rev*. 2015;265(1):6–21. doi:10.1111/imr.12296
32. Rühl S, Broz P. Caspase-11 activates a canonical NLRP3 inflammasome by promoting K(+) efflux. *Eur J Immunol*. 2015;45(10):2927–2936. doi:10.1002/eji.201545772
33. Yang D, He Y, Muñoz-Planillo R, Liu Q, Núñez G. Caspase-11 requires the pannexin-1 channel and the purinergic P2X7 pore to mediate pyroptosis and endotoxic shock. *Immunity*. 2015;43(5):923–932. doi:10.1016/j.immuni.2015.10.009
34. Yokoyama S, Nakayama S, Xu L, Pilon AL, Kimura S. Secretoglobin 3A2 eliminates human cancer cells through pyroptosis. *Cell Death Discov*. 2021;7(1):12. doi:10.1038/s41420-020-00385-w
35. Zhao P, Ning J, Huang J, Huang X. Mechanism of resveratrol on LPS/ATP-induced pyroptosis and inflammatory response in HT29 cells. *Autoimmunity*. 2024;57(1):2427094. doi:10.1080/08916934.2024.2427094
36. Liu Z, Li Y, Zhu Y, et al. Apoptin induces pyroptosis of colorectal cancer cells via the GSDME-dependent pathway. *Int J Biol Sci*. 2022;18(2):717–730. doi:10.7150/ijbs.64350
37. Cheng MZ, Yang BB, Zhan ZT, et al. MACC1 and gasdermin-E (GSDME) regulate the resistance of colorectal cancer cells to irinotecan. *Biochem Biophys Res Commun*. 2023;671:236–245. doi:10.1016/j.bbrc.2023.06.002
38. Ewen CL, Kane KP, Bleackley RC. A quarter century of granzymes. *Cell Death Differ*. 2012;19(1):28–35. doi:10.1038/cdd.2011.153
39. Yang J, Ding X, Fang Z, et al. Association of CD8+TILs co-expressing granzyme A and interferon-γ with colon cancer cells in the tumor microenvironment. *BMC Cancer*. 2024;24(1):869. doi:10.1186/s12885-024-12605-y
40. Xie W, Peng M, Liu Y, Zhang B, Yi L, Long Y. Simvastatin induces pyroptosis via ROS/caspase-1/GSDMD pathway in colon cancer. *Cell Commun Signal*. 2023;21(1):329. doi:10.1186/s12964-023-01359-y
41. Tao Y, Wang L, Ye X, et al. Huang Qin decoction increases SLC6A4 expression and blocks the NFκB-mediated NLRP3/Caspase1/GSDMD pathway to disrupt colitis-associated carcinogenesis. Funct Integr Genomics. 2024 Mar;24(2):55. doi: 10.1007/s10142-024-01334-x. *Funct Integr Genomics*. 2024;24(3):80. doi:10.1007/s10142-024-01343-w
42. Feng SH, Zhao B, Zhan X, et al. Quercetin-induced pyroptosis in colon cancer through NEK7-mediated NLRP3 inflammasome-GSDMD signaling pathway activation. *Am J Cancer Res*. 2024;14(3):934–958. doi:10.62347/MKAN3550
43. Chen Y, Ma S, Pi D, et al. Luteolin induces pyroptosis in HT-29 cells by activating the Caspase1/Gasdermin D signalling pathway. *Front Pharmacol*. 2022;13:952587. doi:10.3389/fphar.2022.952587

44. Chen T, Wang Z, Zhong J, et al. Secoisolariciresinol diglucoside induces pyroptosis by activating caspase-1 to cleave GSDMD in colorectal cancer cells. *Drug Dev Res*. 2022;83(5):1152–1166. doi:10.1002/ddr.21939
45. Sala R, Rioja-Blanco E, Serna N, et al. GSDMD-dependent pyroptotic induction by a multivalent CXCR4-targeted nanotoxin blocks colorectal cancer metastases. *Drug Deliv*. 2022;29(1):1384–1397. doi:10.1080/10717544.2022.2069302
46. Serna N, Álamo P, Ramesh P, et al. Nanostructured toxins for the selective destruction of drug-resistant human CXCR4+ colorectal cancer stem cells. *J Control Release*. 2020;320:96–104. doi:10.1016/j.jconrel.2020.01.019
47. Huang Y, Yang W, Yang L, et al. Nrf2 inhibition increases sensitivity to chemotherapy of colorectal cancer by promoting ferroptosis and pyroptosis. *Sci Rep*. 2023;13(1):14359. doi:10.1038/s41598-023-41490-x
48. Guo J, Zheng J, Mu M, et al. GW4064 enhances the chemosensitivity of colorectal cancer to oxaliplatin by inducing pyroptosis. *Biochem Biophys Res Commun*. 2021;548:60–66. doi:10.1016/j.bbrc.2021.02.043
49. Yu J, Li S, Qi J, et al. Cleavage of GSDME by caspase-3 determines lobaplatin-induced pyroptosis in colon cancer cells. *Cell Death Dis*. 2019;10(3):193. doi:10.1038/s41419-019-1441-4
50. Lin J, Sun S, Zhao K, et al. Oncolytic parapoxvirus induces gasdermin E-mediated pyroptosis and activates antitumor immunity. *Nat Commun*. 2023;14(1):224. doi:10.1038/s41467-023-35917-2
51. Zhang Y, Xu T, Tian H, et al. Coxsackievirus group B3 has oncolytic activity against colon cancer through gasdermin E-mediated pyroptosis. *Cancers*. 2022;14(24):6206. doi:10.3390/cancers14246206
52. Xu H, Zhang D, Wei R, et al. Gambogic acid induces pyroptosis of colorectal cancer cells through the GSDME-dependent pathway and elicits an antitumor immune response. *Cancers*. 2022;14(22):5505. doi:10.3390/cancers14225505
53. Zhou Y, Zhang W, Wang B, et al. Mitochondria-targeted photodynamic therapy triggers GSDME-mediated pyroptosis and sensitizes anti-PD-1 therapy in colorectal cancer. *J Immunother Cancer*. 2024;12(3):e008054. doi:10.1136/jitc-2023-008054
54. Tao S, Zhao S, Xu K, et al. Carbazole-modified chiral Ir(III) complexes for photodynamic tumor therapy: chirality-driven bioactivity and pyroptosis activation. *Inorg Chem*. 2025;64(31):15980–15992. doi:10.1021/acs.inorgchem.5c02119
55. Guan L, Tao S, Lu X, et al. A lysosome-targeted iridium(III) complex inducing pyroptosis for enhanced sonodynamic therapy of colorectal cancer. *J Med Chem*. 2025;68(13):14008–14018. doi:10.1021/acs.jmedchem.5c01106
56. Huntington KE, Louie AD, Srinivasan PR, et al. GSK-3 inhibitor elraglusib enhances tumor-infiltrating immune cell activation in tumor biopsies and synergizes with anti-PD-L1 in a murine model of colorectal cancer. *Int J Mol Sci*. 2023;24(13):10870. doi:10.3390/ijms241310870
57. Wu QB, Sheng X, Zhang N, Yang MW, Wang F. Role of microRNAs in the resistance of colorectal cancer to chemoradiotherapy. *Mol Clin Oncol*. 2018;8(4):523–527. doi:10.3892/mco.2018.1578
58. Xu Y, Zhang K, Ye Z, et al. Nanomedicine initiates ferroptosis for enhanced lung cancer therapy. *Drug Deliv*. 2025;32(1):2527752. doi:10.1080/10717544.2025.2527752
59. Jiang Z, Jiang Z, Jiang Y, et al. Fe-involved nanostructures act as photothermal transduction agents in cancer photothermal therapy. *Colloids Surf B Biointerfaces*. 2023;228:113438. doi:10.1016/j.colsurfb.2023.113438
60. Zhang Y, Zhao Z, Li J, et al. Treatment of colorectal cancer by anticancer and antibacterial effects of hemiprotonic phenanthroline-phenanthroline^{+} with nanomicelle delivery. *Asian. J Pharm Sci*. 2023;18(3):100801. doi:10.1016/j.ajps.2023.100801
61. Zheng B, Wang L, Yi Y, Yin J, Liang A. Design strategies, advances and future perspectives of colon-targeted delivery systems for the treatment of inflammatory bowel disease. *Asian J Pharm Sci*. 2024;19(4):100943. doi:10.1016/j.ajps.2024.100943
62. Chen Y, Liang C, Kou M, Tang X, Ru J. Lysosome-targeted cyclometalated Ir(III) complexes as photosensitizers/photoredox catalysts for cancer therapy. *Dalton Trans*. 2024;53(28):11836–11849. doi:10.1039/d4dt01345j
63. Sun L, Wang J, Li Y, et al. Correlation of gasdermin B staining patterns with prognosis, progression, and immune response in colorectal cancer. *BMC Cancer*. 2024;24(1):567. doi:10.1186/s12885-024-12326-2