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Review

The role of pyroptosis in gastrointestinal cancer and immune responses to intestinal microbial infection

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ABSTRACT

Pyroptosis, a type of inflammatory programmed cell death, is mediated by multiple inflammasomes which can recognize danger signals and activate the secretion of pro-inflammatory cytokines like IL-18[1] and IL-1β[2]. It can induce cancer cell death within the gastrointestinal tract. NLRs[3], AIM2[4], GSDM[5] family play important roles in pyroptosis signaling pathways in intestinal cancer such as gastric cancer, colitis-associated colorectal cancer and esophageal cancer, *etc*. Furthermore, several inflammasomes are elucidated to be involved in mucosal innate immune responses and modulate specific enteric pathogens infection. Precise modulation of inflammasome activation and exploration of potential diagnostic markers can contribute to the diagnosis, prevention and treatment of intestinal tumors and inflammatory or infectious disorders in human patients in the near future.

1. Introduction

Cell death is a critical pathway of self-destruction to keep homeostatic balance *in vivo*, including apoptosis, autophagy, oncosis and pyroptosis [1]. As a type of non-inflammatory programmed cell death (PCD), apoptosis can be induced by either extrinsic or intrinsic factors [1–3]. Caspase-2, -3, -6, -7, -8, -9 are known as the apoptotic caspases [4–12]. Pyroptosis is inherently a type of inflammatory programmed cell death mediated by various inflammasomes, a multi-protein platform which facilitate caspase-1 activation, and typically activate the release of pro-inflammatory cytokines such as interleukin (IL) -18 and IL-1β *in vitro* [1,2,7,8,10,13–18]. Therefore, it is called caspase-1-dependent PCD as well [5,19–21], another process of cellular self-destruction which is totally distinct from apoptosis among characteristics, mechanisms and outcomes [4,6,22].

Pyroptosis can mostly be initiated by microbial infections, e.g. *Salmonella, Francisella, Mycobacterium* and *Legionella* [1,23]. Indeed, the regulation of pyroptosis exists between pathogens and the host [1]. Recent studies have indicated that inflammasomes could maintain intestinal homeostasis and defense the gastrointestinal (GI) tract from invasive pathogens. Otherwise its dysregulation might result in GI disorders such as inflammatory bowel disease and cancer [14]. Clearly, inflammasomes play an emerging role in the regulation of gut microbiota and promotion of the integrity of intestinal epithelium and immune surveillance [14]. Pyroptosis also induces tumor cell death. Cancer is currently a leading cause of increasing mortality [24]. Investigating and understanding the inflammasome signaling pathways assist us to explore therapeutics approaches to bacteria-triggered gut inflammation and a variety of GI tumors, *e.g.* gastric cancer (GC), colitis-associated colorectal cancer (CAC) and esophageal cancer, *etc*. Accurate regulation of inflammasome stimulation paves the way for treatment targets for colitis and GI tumors.

2. Features and mechanisms of pyroptosis

2.1. The characteristics of pyroptosis

The most obvious disparity between pyroptosis and apoptosis is that pyroptosis arouses inflammation while apoptosis does not [25,26]. In particular, characteristics such as plasma membrane rupture, rapid pore formation, cytoplasmic swelling, osmotic cell lysis, release of pro-inflammatory cellular cytokines and DNA cleavage are observed in

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[1] Interleukin (IL) -18.
[2] Interleukin (IL) -1β.
[3] NOD-like receptors
[4] absent in melanoma 2-like receptors
[5] gasdermin

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Table 1
Differences between several forms of programmed cell death

	Pyroptosis	Apoptosis	Necrosis	Autophagy
Obvious Characteristic	Inflammatory cell death	Non-inflammatory cell death		
Inducing Factors	Pathological stimulation	Gene regulation under physiological conditions	Severe injury, pathological leisions	Nutrition deficiency, hormone induction
Cellular Morphology	Cytomorphosis, cell inflation	Shrinkage	Cytomorphosis, cell inflation	Vacuole
DNA	Random degradation, cleavage	Degradation to 180-200bp or integral multiple fragments	Random degradation	Random degradation
Plasma membrane	Rupture	Intact	Rupture	Intact
Organelles	Deformation	Intact	Deformation, swelling	Absorbed by autophagosome and digested by lysosome

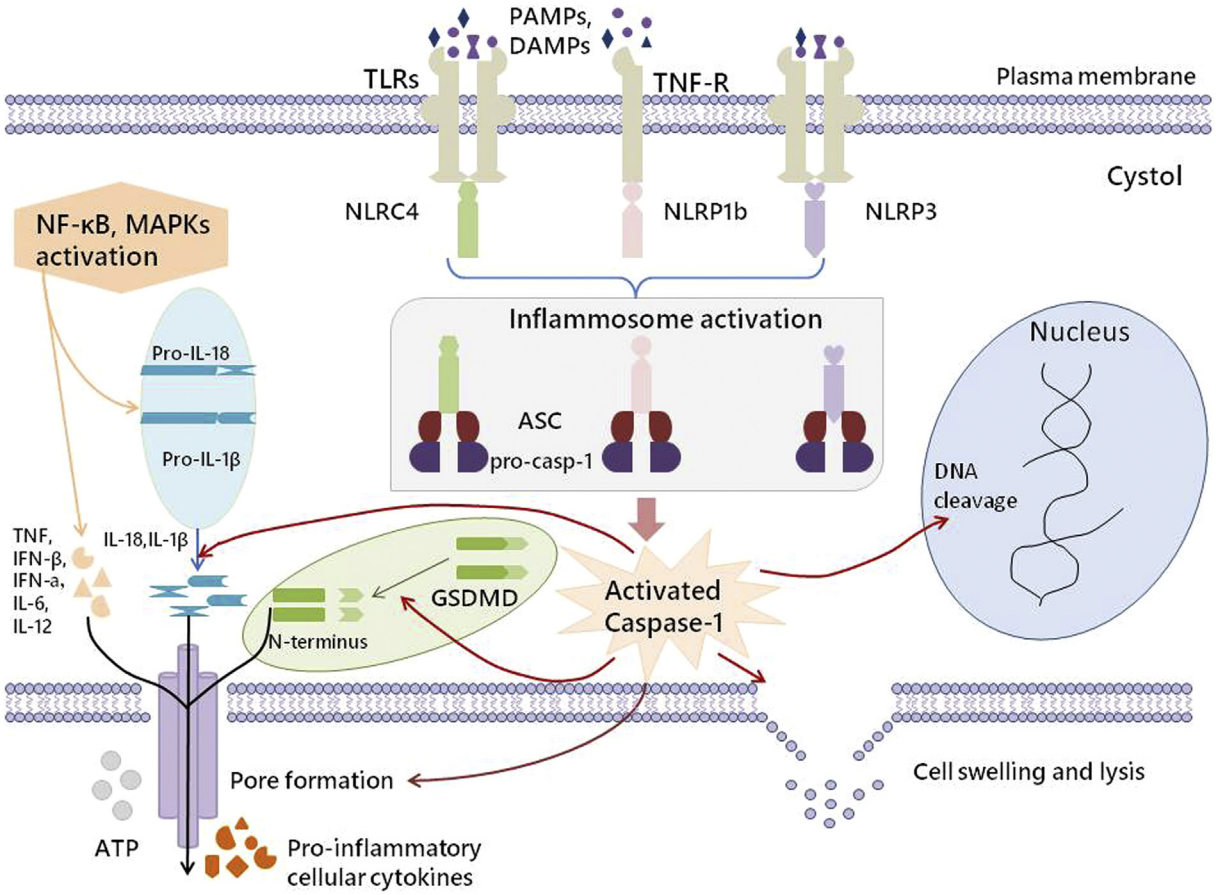

Fig. 1. Characteristics and brief mechanism of pyroptosis.
Plasma membrane rupture, pore formation, cell swelling, osmotic cell lysis, release of pro-inflammatory cellular cytokines and DNA cleavage occur in pyroptosis, which is mediated by the activation of caspase-1. Caspase-1 activation requires NLRs that are consisted of a PYD domain or CARD domain to interact with the PYD or CARD domain of caspase-1, either dependently or independently of ASC. The activated caspase-1 drives cleavage of the the executioner molecule GSDMD, both of which allow the conversion of pro-forms of IL-18 and IL-1β into their biologically active forms. PAMP: pathogen-associated molecular patterns; DAMP: damage-associated molecular patterns; TLR: Toll-like receptors; TNF: tumour necrosis factor; NF-κB: nuclear factor-κB; MAPK: mitogen-activated protein kinase; IFN: interferon; GSDMD: gasdermin-D; ASC: apoptosis-associated speck-like protein

pyroptosis [1,27–30]. Caspase-1 is the enzyme that mediates this inflammatory process of cell death [1]. It converts the inactive pro-forms of IL-18 and IL-1β into mature inflammatory cytokines which are subsequently secreted during pyroptosis [31] (Table 1). The chromosomal DNA cleavage, induced by an unidentified caspase-1-activated nuclease, differs from nuclear fragmentatation observed in apoptosis. It is another form of nuclear condensation distinct from that in apoptosis due to the maintenance of nuclear integrity [1,6,22,32](Fig. 1). Hence, the shortage or pharmacologic silence of caspase-1 prevents the host from inflammation, implying that caspase-1 is a promising molecular target in inflammasome-mediated disorders.

2.2. Inflammosomes

Pattern-recognition receptors (PRRs) are known to defend against microbial colonization and infection [33]. Researches also verified its regulating role in intestinal epithelial integrity and repair [34]. Thus, it is not difficult to conclude that PRR dysregulation could lead to pathologic disorders within the GI tract including cancer [33]. Certain families of PRRs containing in the inflammasomes including NOD-like receptors (NLRs) and the absent in melanoma 2-like receptors (AIM2) can detect intracellular and extracellular danger signals [1,35–37]. The NLRs nucleotide-binding oligomerization domain-containing protein 1 (NOD1) and NOD2 initiate a cascade accompanied by ligand

recognition which yields inflammatory cytokines [38]. Similarly, the signaling cascade triggered by Toll-like receptors (TLRs) also results in inflammatory cytokines production, *e.g.* pro-IL-1β, IL-6, IL-8, IL-12, tumour necrosis factor (TNF), interferon-α (IFN-α), IFN-β, *etc* [39]. Caspase-1 is then activated by NLRs and TLRs recognition and transfers these inactive precursors into mature inflammatory cytokines during pyroptosis [36,37](Fig. 1).

Caspase-1-activating NLRs can recognize multiple signals released by the cognate host cells or diverse microbial pathogens. In order to respond to these stimuli, the host produce secondary factors to bind the NLR protein, NLRP3 (NACHT, LRR and PYD domains-containing protein 3), NLRP1b and NLRC4 (NLR family CARD domain-containing protein 4), which are all required for caspase-1 activation [40–43]. Particularly, NLRP3 responds to lipopolysaccharide (LPS), nucleic acids, ATP, urate crystals, pore-forming toxins [44], silica [45], asbestos [46], *etc*. These microbial molecules trigger NLRP3 expression indirectly via TLR ligands [45–48]. NLRP3 then facilitate the generation of inflammasome, a multi-protein complex that contains caspase-1, allowing complex activation [49]. NLRC4-dependent-caspase-1-activation can be induced by some Gram-negative microbes, *e.g. Pseudomonas aeruginosa*, *Legionella pneumophila* and *Salmonella typhimurium*, *etc*. According to their mutant analyses, cytosolic flagellin is indicated to activate NLRC4 as it provides microbial motality [50–52]. Recently, PrgJ, a component of the type III secretion system of *Salmonella*, can activate NLRC4 as well [53]. Additionally, the presence of NLR family apoptosis inhibitory protein (NAIP5), another NLR family protein, is suggested to associate with NLRC4 in an inflammasome complex [14]. The NLRP1b inflammasome responds to *Bacillus anthracis* lethal toxin which can cleave host mitogen-activated protein kinases (MAPKs) [54]. NLRP1b mediated caspase-1 activation requires proteolytic activity of the lethal toxin [11], in a two-step mechanism which is verified *in vitro*. Bacterial muramyl dipeptide stimulates conformational change of NLRP1, allowing it to attach nucleotide and oligomerize with caspase-1 [55]. However, it still remains to be investigated thoroughly the specific pathway of NLRP1 conformational recognition and oligomerization. Of all the mechanisms leading to pyroptosis, NLRP3 is one of the major caspase-1-activating NLRs. It then stimulates the local aggregation of pro-caspase-1, induces its hydrolysis into caspase-1, and converts the inactive pro-forms of IL-18 and IL-1β into mature IL-18 and IL-1β, That is so called pyroptosis [56](Fig. 1).

Apart from assembled NLRP1, NLRP3 and NLRC4, another known major component of inflammasome is the AIM-2-like receptors (ALRs) [3,57]. The DNA sensor AIM2, mediates caspase-1-dependent PCD via sequence-independent recognition of the intracellular-delivered double-stranded DNA (dsDNA) [58–61]. The activated AIM2 further triggers linear ubiquitination and polymerization of the N-terminal pyrin domain (PYD) of inflammasome adaptor apoptosis-associated speck-like protein (ASC) [62–65].

The AIM2 and NLRs inflammasomes signaling pathways eventually lead to pyroptosis that is partly mediated by the caspase substrate Gasdermin-D (GSDMD) [17,18]. Hence, pyroptosis is also defined as gasdermin (GSDM)-mediated programmed necrosis [28]. Caspase-1 is commonly recognized as initiator caspase, while GSDMD acts as the executioner molecule. The active caspase-1 as well as caspase-4, -5, -11 binds to the cleavage site of GSDMD. N-terminal and C-terminal subunits are released, insert into the membrane and result in pyroptosis [17,18,66,67] (Fig. 1). Members of GSDM family except for GSDME share the gasdermin-N domains that perforate membranes [66–69]. Their expressions are known to be predominantly localized in the epithelium of the skin and GI tract [70]. They show tissue-specific and linear features in their expression within the GI tract. In the esophagus and stomach, *GSDMA*, *GSDMC*, and *GSDMD* cluster genes are weekly expressed and considered as tumor inhibitors whereas *GSDMB* genes are overexpressed and identified as oncogenes [71]. In the small intestine, strong expressions of *GSDMD* genes are detected [70], while *GSDMC* genes show predominant expressions in the colon [70]. Furthermore, *GSDME* acts as a tumor suppressor in colorectal cancer (CRC) cell lines [72]. Interestingly, expressions of *GSDMD and GSDMC* are strictly modulated along the proximal–distal axis [70,73]. GSDMD may possibly be deemed as a prospective biomarker in the diagnosis and prognosis of CRC as it was proved to be inversely related to tumor metastases in CRC patients. Ma et al. showed that the AUC of GSDMD reaches 0.767 with sensitivity of 88.2% [74]. lncRNA RP1-85F18.6 was found to inhibit pyroptosis of CRC cells by modulating ΔNp63. GSDMD expression is downregulated in CRC cells mainly via the GSDMD-N domain [28]. Therefore, through silencing lncRNA RP1-85F18.6, GSDMD-N domain cleavage is increased, and pyroptosis of CRC cells is activated by inducing ΔNp63 expression [74].

3. The role of pyroptosis in gastric cancer

GC is one of the most common malignant tumor, and with its increasing incidence, it has been listed as a worldwide principal health issue [75–77]. GC is a multifactorial disease with low overall survival rate, high susceptibility of relapse and poor prognosis [78–80]. Importantly, recent studies have implicated the effects of Gsdm family in the mechanism of pathogenesis and chemotherapy underlying GC, highlighting the clinical relevance of low or refrained expression of Gsdm in gene-targeted therapeutic approaches for gastric malignant disorders.

3.1. GSDMD regulation in gastric cancer cell proliferation

GSDMD, the common executor of pyroptosis, has been confirmed by recent studies to be associated with GC. Its decreased expression is shown to induce cancer cell proliferation [81]. *In vitro,* both GSDMD mRNA and protein levels were markedly downregulated in GC cell lines and clinical GC tissues. *In vivo,* nude mice with BGC 823/GSDMD cells injection developed a smaller size and lower weight of tumor than those with BGC 823/Vector cells injection [81]. Importantly, these studies simply verify that low expressions of GSDMD can promote GC tumorigenesis. To further discuss the mechanism, Wang and Chen et al. found that GSDMD possibly inhibited proliferation by cell cycle arrest, which suppressed the S to G2/M phase transition in BGC 823/GSDMD cell lines. Also as shown in Western blotting, the expressions of CDK2 and Cyclin A2 were decreased when GSDMD expression level was upregulated [81]. The activation of such signaling pathways as signal transducers of transcription 3 (STAT3), extracellular signal regulated kinase (ERK) and phosphatidylinositol 3 kinase/protein kinase B (PI3K/AKT) signaling pathways were revealed to take part in GSDMD down-regulation in gastric carcinogenesis [81]. Although the potential mechanism of GSDMD in GC still requires thorough investigation, GSDMD is believed to prevent GC cells from proliferation. Thus it provides us a new perspective that GSDMD can be proved to be both diagnostic marker and treatment strategy for GC.

3.2. GSDME cleavage in gastric cancer chemotherapy

Caspase-3 was constantly considered to be an indicator of apoptosis. Chemotherapeutic drugs were known to destroy tumor cells by inducing caspase-3-mediated apoptosis. Two recent studies from China successively proposed that caspase-3 mediated activation and cleavage of GSDME was able to switch apoptosis to pyroptosis in cancer cells in response to chemotherapy [82]. It is absolutely a subversive finding that transforms our understanding of PCD.

GSDME, also called DFNA5 (deafness, autosomal dominant 5), is discovered to function in hearing impairment [83,84], which has recently been found to be a tumor suppressor and potential candidate for epigenetic therapy in melanoma cancer and GI tumors [72,80,84–87]. Wang and Gao et al. noted that the cleavage of GSDME mediated by caspase-3 stimulated pyroptosis in tumor cells after they were treated with chemotherapy [82]. However, some tumor cells express little

GSDME [72,80,88]. It is suggested that decitabine could reverse GSDME silence and thus induce cellular sensitization to chemotherapy drugs [72,80]. Therefore, decitabine are encouraged to be employed in combination with other chemotherapy drugs in hematological tumor. Meanwhile, normal tissues equally undergo caspase-3 activation of GSDME-dependent pyroptosis after chemotherapy. Thus, GSDME-mediated pyroptosis exhibit an effect in the toxicity of chemotherapy [82]. This finding highlights that tumor cells might downregulate GSDME to escape cell death, which offer new insights into chemotherapy resistance.

Wang and Yin et al. further investigated that particularly in GC, cells with high expression of GSDME undergo the switch from caspase-3 dependent apoptotis to pyroptosis induced by chemotherapeutic drugs. After they treated GC cell lines SGC-7901 and MKN-45 with 5-FU, they found the swelling cells, large bubbles from the plasma membrane, released LDH, decreased cell viability and elevated percentage of PI and APC Annexin-V double positive cells [24]. All the above features resembled pyroptosis induced by GSDMD [72]. Moreover, it was proved that the cleavage of GSDME was induced by 5-FU in GC cells by measuring the protein level. The knockdown of caspase-3 rather than caspase-1 and caspase-7 in SGC-7901 by siRNA markedly suppressed GSDME cleavage, suggesting that caspase-3 contributes to the cleavage of GSDME [24]. They used the CRISPR-Cas9 technology which ultimately confirmed that GSDME switched 5-FU-induced apoptosis to pyroptosis.

4. Pyroptosis in colitis-associated colorectal cancer and immune responses to colonic microbial infection

Globally, CRC is the leading cause of cancer-related death [14,89]. As colitis is one of the predisposing factors in CRC, around 5% of CRC is composed of CAC. Inflammasomes play a critical role in colon carcinogenesis by preventing the host against inflammation and bacterial pathogens [14,90]. Loss of caspase-1 gene expression can lead to susceptibility of colitis-induced tumorigenesis *in vivo* [91]. A number of analysis have pointed out that the expressions level of such inflammasome components as *NALP1*, *NLRP3*, *NLRC3, NLRC4* and *AIM2* are reduced in CAC mice models [92–94]. Collectively, we predict these inflammasomes as promising targets for colon cancer treatment in the future.

4.1. The role of inflammasomes in colitis-associated colorectal cancer

4.1.1. NALP1

As one of the proteins in the inflammasome, NALP1 (nucleotide-binding oligomerization domain-like receptor family, pyrin domain-containing 1) also plays a critical role in pyroptosis associated with cancers [95,96]. The data from Chen et al. confirmed that the expression level of NALP1 mRNA was observed significantly decreased in the human CRC tissues compared with normal and para-carcinoma tissues. They proceeded to find out that CRC patients with higher NALP1 expression level in paracancerous tissues exhibited longer survival time in the study. The elevated expressions of NALP1 detected by qRT-PCR, western blot after treatment of an antitumor drug 5-aza-2-deoxycytidine in both CRC cell lines and animal models imply that DAC can inhibit the tumor progression in CRC partly by restoring NALP1 expression [95]. Implications from these data suggest that higher NALP1 expression levels in tumor and para-tumoral tissues correlate with lower risk of metastasis, longer survival and better clinical outcomes of colon cancer patients. Therefore, upregulation of NALP1 expression deserves further attention as new insights into CRC therapy.

4.1.2. NLRP3

Zaki et al. and Allen et al. both reported that NLRP3 and caspase-1-deficient mice were more inclined to tumorigenesis in the AOM/DSS model of CAC, as a result of a defect in STAT1 activation and IL-18 production. In their further investigation, additional provision of IL-18 could mitigate the severe epithelial inflammation and hyperplasia in NLRP3-deficient mice [97]. The result that polyps grew more rapidly in mice lacking IL-18 or IL-18R also proved the protective role of upstream IL-18 in colitis-associated oncogenesis [97,98]. Also, NLRP3 plays a role in the negative regulation of metastatic colon tumor growth in the liver by stimulation of NK cells activity mediated by IL-18 [99]. However, the mechanism of NLRP3 protection from CAC remains unknown, which is partly associated with its maintainence in intestinal epithelial barrier integrity [93,94]. In addition, the absence of MyD88 (myeloiddifferentiationfactor88), a factor in the downstream of IL-18 signaling lead to tumor induction in the AOM/DSS mice model [98]. On the other side, several studies contrarily demonstrated that *NLRP3*$-/-$ and *IL-18*$-/-$ mice were protected mice from colitis-related carcinogenesis [100–104], partly owing to different microbial composition [105]. Taken together, further evaluation of NLRP3 downregulation offers a new perspective for the treatment and monitoring of CAC patients.

4.1.3. NLRC4

It is still controversial whether NLRC4 inflammasome plays an important role in CAC development since studies have drawn contradictory conclusions. Hu et al. found more tumors in the AOM/DSS mice model lacking NLRC4 and suggested NLRC4 as a potential tumor suppressing inflammasome [91]. They observed upregulated epithelial proliferation and apoptosis inhibition with NLRC4 deficiency in advanced cancer [91]. In their studies, cancer suppression effects of NLRC4 in the epithelial compartment imply that Nlrc4 signaling mainly function within intestinal epithelium [91,106]. Carvalho et al. also highlighted that NLRC4 functioned as a negative regulator in DSS-induced colitis [107]. In contrast, Allen et al. proposed that NLRC4 was unable to affect CAC carcinogenesis [108]. NAIPs are capable of activating NLRP4 [50,53,109]. Interestingly, absence of NAIPs1-6 in colon epithelial cells results in increased tumorigenesis during AOM exposure [110]. However, NAIP1-6-deficient mice were prevented from DSS-induced colitis [110]. Hence, the exact mechanism of the NAIP-NLRC4 axis remains further research in colitis and CAC.

4.1.4. NLRP6

Similar to NLRP3, NLRP6 deficiency functions in the restriction of colitis and CRC development as well. The inflammasome NLRP6 contribution to intestinal inflammation and tumorigenesis suppression is determined by its abundant expression in the epithelium of human small intestine [111], particularly in the goblet cells and enterocytes [112]. Normand et al. observed that NLRP6 was expressed by the myofibroblasts in the stem cell niches. By comparing gene expressions in NLRP6 and wildtype (WT) mice, they implicated that colon cancer was likely to occur as critical signaling pathways in epithelial stem cell proliferation and transference were potentially dysregulated in *NLRP6*$-/-$ mice, *e.g.* Wnt and Notch pathways [112]. IL-18 release promotion mediated by NLRP6 was also indicated in monocytes to avoid DSS-induced colitis [113]. NLRP6 activation can be regulated by bacterial metabolites such as taurine, spermin and histidine [114]. Other mechanisms of NLRP6 anti-cancer effect involve colonic microenvironment moderation and epithelial STAT-3 activation [115].

4.1.5. AIM2

Researches demonstrated that AIM2 could restrain intestinal inflammation and inhibit the cancer progression [92,116,117]. In the mice models of CAC, such as *Apcmin/+*(117)and AOM-DSS mice [116,117], colitis aggravated, polyps grew and tumor burden increased in $Aim2^{-/-}$ mice [116,117]. They observed a decreased expression level of AIM2 in colon cancer cell lines [118–121]. Indeed, some research groups suggested that AIM2 predominantly functions independently of inflammasome activation within the non-hematopoietic compartment [116,117,122], while others not [123]. The former

Table 2
Major studies of inflammatory cell death in colorectal pathologies

Inflammasomes	Experimental Models	Study (author, year)	Major Findings
NLRC4	DSS colitis	Carvalho FA, et al. 2012 [110]	NLRC4 protected the intestine from inflammatory diseases.
	AOM-DSS	Hu B, et al. 2010 [94]	NLRC4 mediated increased colonic inflammation-induces tumorigenesis through epithelial cell regulation.
		Allen IC et al. 2010	There were no differences found in progression or outcome in colitis.
	AOM-induced CRC	Allam R et al. 2015 [113]	NLRC4 was not necessary in the protection of NAIPs from colonic carcinogen exposure.
NLRP6	AOM-DSS DSS colitis	Normand S, et al. 2011 [115]	NLRP6 prevented the epithelial injury, and decelerated inflammation-induced tumor growth in the colon.
	AOM-DSS	Hu B, et al. 2013 [118]	*Nlrp6*$^{-/-}$mice were more susceptible to inflammation-induced CRC formation.
	DSS colitis	Seregin SS, et al. 2017 [116]	NLRP6-dependent TNFα release in inflammatory monocytes promoted the intestinal epithelial barrier function.
AIM2	DSS colitis	Wilson JE, et al. 2015 [120]	*Aim2*$^{-/-}$ mice had greater tumor burden
		Man SM, et al. 2015 [119]	*Aim2*$^{-/-}$ mice were inclined to develop colorectal tomor, in which gut bacteria also played a role.
		Hu S, et al. 2015 [126]	Transplantation of germ-free mice with *Aim2*-deficient mice colonic microbiota were more likely to develop colitis.

AOM, axozymethane; DSS, dextran sodium sulfate.

groups indicate the role of AIM2 rely on its control of cell proliferation by downregulating the activation of kinase AKT [116,117]. The AKT pathway prohibition can be expected as potential target. Overexpression of AIM2 was validated to inhibit cancer cells proliferation as cell cycle was delayed [122], whereas stem cells of *Aim2*$^{-/-}$ mice proliferated rapidly in comparison with WT stem cells [116,117]. Studies indicate the possible usage of suppressive oligodeoxynucleotidesor pyrin-containing proteins to suppress AIM2 inflammasome activity help prevent colonic inflammation [124–126]. Another interesting fact refers to the positive role of AIM2 in prevention of microbial dysbiosis [13,123]. Man et al. showed a notable distinction of bacterial diversity and composition between *Aim2*$^{-/-}$ and WT mice [116]. These data underline the synergy between AIM2 inflammasome and microbiota diminishes susceptibility to colitis and tumorigenesis. More studies confirmed this result through fecal transplantation and all found that the gut microbiota from *Aim2*$^{-/-}$ mice substantially increased tumorigenesis in WT mice [123] (Table 2).

4.1.6. LXRs

Liver X receptors (LXRs) are implicated as a potential target in cancer therapy [127]. Meanwhile, a study from France revealed that LXR agonist stimulation of LXRβ (or NR1H2) could specifically trigger pyroptotic cell death and thus reduce tumor growth in CRC by NLRP3 inflammasome-mediated inflammatory cell death both *in vitro* and *in vivo* [128]. LXRβ, a nuclear receptor with differential cytoplasmic localizations in CRC cells rather than normal colon mucosa cells [129], allowed this process of LXR ligand-induced pyroptosis, which requires the release of ATP via pannexin 1 channel that directly interacts with LXRβ [128]. Since several researches have already elucidate the function of LXR ligands in cancer therapy, these data unveil their characteristic of specific cytotoxicity in tumor cells. It provides us a potential therapeutic strategy in colon cancer with less adverse effects on normal cells. However, there is still much work to be done about its clinical application.

4.1.7. Other inflammasomes in CAC

Nlrp1b, as one of the paralogs of *NLRP1* gene, forms an inflammasome platform in response to bacterial toxin [54,130] and controls CAC progression [131]. *NLRP1b*-deficient mice become more sensitive to DSS-induced colitis and AOM-DSS- induced colon carcinogenesis [131], which is primarily owing to NLRP1b regulation of microbiota, IL-1β and IL-18 supplementation, epithelial barrier impairment, and cell death stimulation [131]. Similarly, NLRP12 is identifed as a protective inflammasome in inflammation and colitis-associated tumorigenesis [132,133].Enhanced NF-κB and MAPK signaling within the non-hematopoietic compartment rather than hematopoietic cells is involved in the deficiency of NLRP12 expression [132,134,135]. Further study tried to find out the exact relationship among gut microbiota, immunity and NLRP12 in the oncogenesis suppression [133].

4.2. The function of pyroptosis in immune responses to colonic microbial infection

Pyroptosis can also be induced by a variety of invading pathogens, and several inflammasomes appear to protect the host against microorganisms and intestinal inflammation via their PRRs recognization [1,23]. Besides, inflammasomes are proved to be significant in removal of infected cells and guard against enteric pathogens' intraepithelial proliferation, thus promoting the integrity of intestinal epithelium barrier, otherwise dysbiosis might occur [14]. The intestinal barrier, mainly functioned via shedding of epithelial cells, is a crucial shelter between the host and invading bacteria [136]. When bacterial ligands bind to NAIP members of the inflammasomes [137], pyroptosis will be induced. Also, either apoptosis or pyroptosis may induce epithelial cell shedding to eliminate pathogenic microbes, e.g. *Citrobacter*, *Shigella*, and *Salmonella,* whereas these bacteria can conversely prevent shedding via their effector proteins such as OspE [138,139]. In innate immunity, bacteria like *Bifidobacterium breve* reduces TNFα-induced cell shedding via NOD2-dependent mechanism in dendritic cells, monocytes/macrophages, and epithelial cells [140,141]. To reinforce gut barrier function, such mucosa-associated microbes as *Lactobacillus* can drive IL-17 and IL-22-producing cells that is modulated by IL-6 and IL-23, *e.g.* group 3 innate lymphoid cells (ILC3s) and T helper 17 (Th17) cells, in Peyer's patch DCs dependent on Mincle-Syk axis. This kind of detection will thus prevent inflammation, limit bacterial translocation and maintain host-microbiota mutualism [142]. Recently, one of the bacterial metabolites called Urolithin A (UroA) and its synthetic analogue (UAS03) can intensify gut barrier function by upregulating tight junction proteins. Stimulation of aryl hydrocarbon receptor (AhR)- nuclear factor erythroid 2–related factor 2 (Nrf2) as well as inflammation mitigation plays a pivotal role. In this way, prospective therapy of intestinal diseases related to barrier dysfunction, *e.g.* severe colitis, alcohol liver diseases and CRC, can be focused on the oral administration of UroA/ UAS03, as revealed by Singh, et al. IBD [143]. Drugs targeted on the inhibition of T3SS effector virulence of many enteric microbes have been taken into account. For instance, compounds like salicylidene acylhydrazides are designed to obstruct T3SS needle complex assembly [144–146].

The mucosal immune system can modulate colon bacteria via inflammasome pathway which ultimately leads to decreased cytokines level [147]. Elinav et al. described a reconstructed colonic microbiota constitution depending on the expression disruption of the ASC or

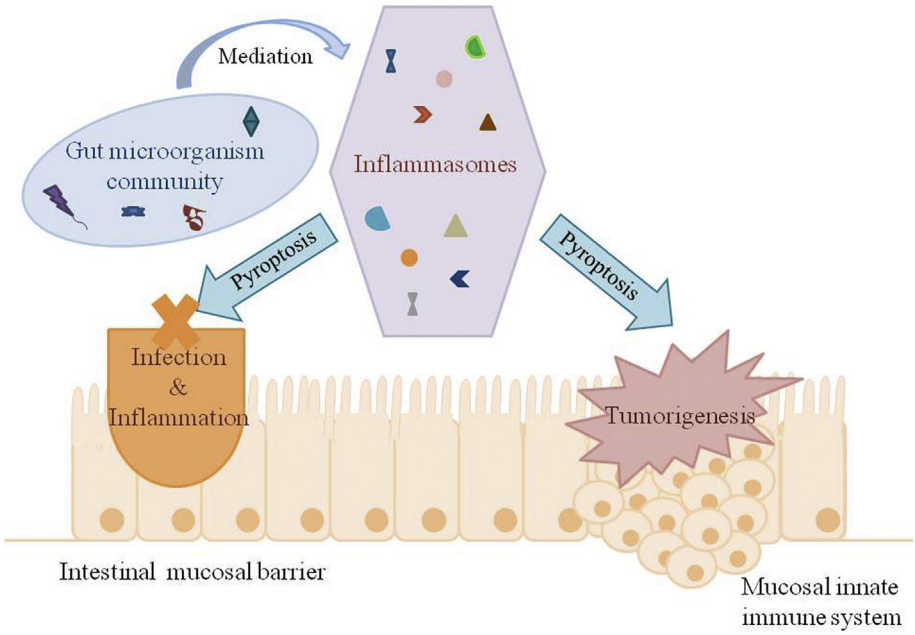

Fig. 2. Concise relationship among pyroptosis, gut microbiota community and intestinal mucosal innate immune system.
The enteric pathogens infected intestinal epithelial cells, damage the integrity of intestinal epithelium, and alter gut microbiota community. Inflammasomes are involved in mucosal innate immune responses and modulate specific enteric pathogens infection.

NLRP6, which is highly assembled in the gut epithelium compartment [148]. Deficiency of either NLRP6 or ASC in mice models result in severe DSS colitis in relation to altered gut microbiota community characterized by markedly overgrowth of phyla *Bacteroidetes* (*Prevotellaceae*) via reduced cytokine IL-18 production [147]. Another study focused on caspase-11, also highly expressed in colon, of which deficiency obviously reduced the representation of *Prevotella* and enhanced the morbidity mice of DSS-induced colitis. Demon et al. highlights that this inflammasome pathway is caspase-1 owing to the caspase-11 function of pyroptosis initiation which leads to caspase-1 stimulation and subsequent release of IL-18 and IL-1β [147].

Pyroptosis plays a pivotal role in restraint of microbial pathogens growth directly or indirectly initially via activation of pattern recognition receptors (PRRs), including Pathogen-Associated Molecular Patterns (PAMPs) and Damage-Associated Molecular Patterns (DAMPs), like lipopolysaccharide (LPS), flagellin, or lipoprotein. PRRs trigger specific mechanisms associated with inflammasomes and immune system to eliminate these pathogens from the host [149]. Recently, a caspase-11-dependent macrophage pyroptosis, independently of caspase-1activation, is stimulated in dealing with the invasion of Gram-negative bacteria that endode type III secretion system (T3SS) and type IV secretion system (T4SS) or induce vacuolar lysis [73,150] [151]. Cytosolic lipid A motif of LPS of Gram-negative bacteria activates caspase-11, leading to novel pyroptosis signaling pathways and release of IL-1α which mediates neutrophil recruitment [152]. Besides, caspase-11 induced by LPS also triggers NLRP3-dependent caspase-1 activation and classical secretion of IL-1β and IL-18 [153,154]. Both of the caspase-11 and caspase-11 mediated inflammasomes collaboratively act on the sensing and clearance of pathogens, which however, can be resisted or prohibited by 'intelligent' bacteria [155]. The functional T3SS-dependent effector proteins, exoenzyme S (ExoS), and ExoU, which are expressed by *P. aeruginosa* restrain inflammasome activation probably by regulation of host cell cytoskeleton dynamics and phospholipase A2 activity respectively [156]. T3SS effector protein OspC3 of *Shigella flexneri* inhibits caspase-4-dependent pyroptosis (caspase-4, a homolog of caspase-11) and escape of immune surveillance [157,158]. Hence, multiple evasion strategies that microbial pathogens adopted to suppress inflammasome activation indicate the importance of caspase-11 as a regulator. Caspase-11 is able to restrict pathogenic *Legionella pneumophila* infection within macrophages *in vitro* and *in vivo* by means of its enzymatic activity in innate immune response. By inducing the fusion of *L. pneumophila*-containing vacuole with lysosomes subsequent to F-actin polymerization, active caspase-11 boosts phagosome-lysosome fusion and thus inhibits *L. pneumophila* growth independently of caspase-1 [159]. Studies has indicated the multiple contributions of caspase-11 to pyroptosis stimulation under *L. pneumophila* infection. The canonical caspase-1-dependent inflammasome pathways of which host protection against *L. pneumophila* when it invades the cytosol can cause the secretion of IL-18, IL-1β and IL-1α, and promotes NLRP3-dependent caspase-1 activation [160]. Caspase-11 and a non-canonical inflammasome activation can be triggered by *L. pneumophila* cytosolic LPS, and thus contributes to pyroptosis [154,161]. This is probably ascribed to the translocation and expression of flagellin through T4SS into cytosol. Interestingly, the host tries to initiate innate immune system to defense against over-replication of *L. pneumophila*. Also, the growth of *L. pneumophila* is restricted via autophagic pathways since the less expression of autophagy component ATG5, the more *L. pneumophila* replicates in A/J macrophages [162]. The activity of autophagosomes requests caspase-1 and inflammasomes, *e.g.* NAIP5, NLRC4 [163]. Some Gram-negative genus, *e.g. Yersinia* and *Aeromonas* with T3SS exert their virulence by modulating pyroptosis or apoptosis [164]. In host immune responses to bacterial invasion, activation of such signaling pathways as NF-κB and MAPK induce the expression of proinflammatory cytokines like IL-12,-18 via the effectors of T3SS, T2SS or T6SS in both genus [165]. For instance, studies showed the T3SS effector, *Yersinia* outer membrane protein J (YopJ) impeded NF-κB and MAPK signaling via acetyltransferase and deubiquitinase, and finally activated apoptosis [166,167]. However, another protein, YopK regulated caspase-1-dependent pyroptosis in a certain species [168]. Also, T3SS effectors *Aeromonas hydrophila* AexU protein and other effectors of secretion systems like T2SS and T6SS of *Aeromonas*, namely Act 2, Hcp, targeted NF-κB signaling [169,170]. Pallett et al. elucidated that in mice colons, the T3SS effector protein of *C. rodentium*, $NleF_{CR}$ suppressed the release of mature IL-18 at initial stages of *C. rodentium* infection and hindered neutrophil influx *in vivo* mediated by caspase-11 [171]. The caspase-11-IL-18 axis is thus modulated by enteric bacteria in response to innate immune system. In addition, in comparison with WT mice, the $Nlrc4^{-/-}$ mice infected with *C. rodentium* exibited more severe gut inflammation, which reflects strengthened host immune innate responses. The expression of NLRC4 helps defend against *C. rodentium*-induced colonic damage [172]. Like Shigella, the T3SS effector protein of EPEC, $NleF_{EPEC}$ restrains IL-18 excretion *in vitro* in a human caspase-4-dependent

manner. $NleF_{EPEC}$ directly binds to caspase-4 subunits p10 and p20 and thus inhibits caspase-4 activation in IECs [171]. Interestingly, the clearance of distinct pathogens dependent on IL-1β, IL-18 in pyroptosis varies due to the targeted cell types and relevant virulence policies.

5. Implications for pyroptosis in esophageal cancer

Esophageal inflammation or reflux esophagitis can induce squamous epithelium to be gradually replaced by columnar epithelium [75]. This is commonly defined as Barrett's esophagus, which plays an important role in the development of esophageal cancer. It is reported high levels of proinflammatory cytokines in biopsies of Barrett's esophageal epithelium, especially IL-1β [78]. Nadatani et al. found that LPS produced by predominant Gram-negative bacteria in patients with Barrett's esophagus upregulated the TLR4 signaling. It enhanced the secretion level of IL-8 and TNF-α in Barrett's cells [173–175]. After treating Barrett's cells with LPS, elevated expressions of NLRP3 and caspase-1 activity were observed in the study owing to the increased ROS production activated by LPS [176]. Thus, it is obvious that the esophageal bacteria induce NLRP3 and thus result in pyroptosis in Barrett's esophagus. Nonetheless, the specific role and mechanism of pyroptosis in esophageal carcinoma is less known yet.

6. Concluding remarks

Collectively, as a type of inflammatory programmed cell death, pyroptosis is capable of inducing cell death in a majority of intestinal cancers. The decreased expression level of certain inflammasome components in CAC are indicated in several studies. The down-regulation of inflammosomes mediate GC cell proliferation and thus offer us insights into promising therapeutics targets and strategies for chemotherapy resistance. Exploring potential diagnostic markers can contribute to early detection of GI cancer. Moreover, the enteric pathogens infected IEC, damage the integrity of intestinal epithelium, alter gut microbiota community and disrupt mucosal innate immune system (Fig. 2). Based on previous findings, we can infer that therapeutic target on specific inflammasomes and precise modulation of their activation might restrain bacteria-triggered gut inflammation. However, the specific mechanisms of pyroptosis in these intestinal infection and malignant tumors remain partly unclear yet. More experiments and clinical trials are required before its clinical practice in the future.

Declarations of interest

None

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