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REVIEW

From Inflammasomes to Pyroptosis: Molecular Mechanisms in Chronic Intestinal Diseases — Opportunity or Challenge?

Jintao Fang[1,*], Weihan Zhu[1,*], Dian Yu[1], Lujian Zhu[2], Haorui Zha[1], Jingyi Tang[3], Yujia Li[1], Xiaxin Zhu[1], Ting Zhao[1], Wei Zhang[1,4]

[1]The Second Clinical Medical College, Zhejiang Chinese Medical University, Hangzhou, 310000, People's Republic of China; [2]Department of Infectious Diseases, Jinhua Municipal Central Hospital, Jinhua, 321000, People's Republic of China; [3]Lanxi Hospital of Traditional Chinese Medicine, Jinhua, Zhejiang, 321100, People's Republic of China; [4]Department of Gastrointestinal Surgery, The Second Affiliated Hospital of Zhejiang Chinese Medical University, Hangzhou, 310000, People's Republic of China

*These authors contributed equally to this work

Correspondence: Wei Zhang, Department of Gastrointestinal Surgery, The Second Affiliated Hospital of Zhejiang Chinese Medical University, Hangzhou, 310000, People's Republic of China, Email zhangweils1968@163.com

Abstract: Pyroptosis is a unique form of programmed cell death characterized by intense inflammation. It involves the activation of Gasdermin proteins, which form membrane pores, leading to rapid cell rupture and the release of inflammatory molecules. Unlike other types of cell death, pyroptosis has distinct activation mechanisms and plays a complex role in chronic intestinal diseases, including inflammatory bowel disease, intestinal fibrosis, chronic infectious enteritis, and colorectal cancer. This review comprehensively examines how pyroptosis influences disease development and progression while exploring the therapeutic potential of targeting pyroptosis-related pathways. Moreover, the complex interplay between gut microbiota and pyroptosis is summarized, highlighting its critical role in the pathogenesis of chronic intestinal disorders. A deeper understanding of pyroptosis-related mechanisms in these diseases may provide valuable insights for future research and contribute to the development of innovative therapeutic strategies in gastroenterology.

Keywords: pyroptosis, chronic intestinal diseases, inflammasomes, gasdermin proteins, cell death

Introduction

Pyroptosis is a form of programmed necrotic cell death characterized by intense inflammatory responses.[1–4] It is triggered by intracellular infections caused by bacteria, viruses, fungi, and protozoa in response to pathogen-associated or damage-associated molecular patterns (PAMPs or DAMPs).[5,6] While pyroptosis plays a key role in host defense by eliminating infected cells, excessive inflammatory responses can contribute to severe pathological conditions, such as multi-organ dysfunction.[7] Pyroptosis can be activated via both inflammasome-dependent and non-inflammasome-dependent pathways, with the former being more extensively studied. The classic inflammasome-dependent pathway begins with recognizing pathogenic microorganisms or intracellular damage signals by pattern-recognition receptors (PRRs) (Figure 1). Upon activation, PRRs interact with pro-caspase-1 and the adaptor protein ASC (apoptosis-associated speck-like protein containing a CARD), forming a multiprotein inflammasome complex.[8] This inflammasome plays a central role in pyroptosis, facilitating caspase-1 activation.[9] Once activated, caspase-1 undergoes auto-cleavage into its CARD domain and P20/P10 subunits, which oligomerize into a tetramer. This tetramer cleaves Gasdermin D (GSDMD) and processes pro-interleukin (IL)-1β and pro-IL-18 into their active forms, IL-1β and IL-18. GSDMD serves as a key mediator of pyroptosis.[10] Upon cleavage, its N-terminal domain forms pores in the plasma membrane, leading to membrane rupture and the release of intracellular contents along with pro-inflammatory cytokines.[11,12] While this mechanism effectively combats infections, it can also exacerbate inflammatory damage in various disease contexts.[13]

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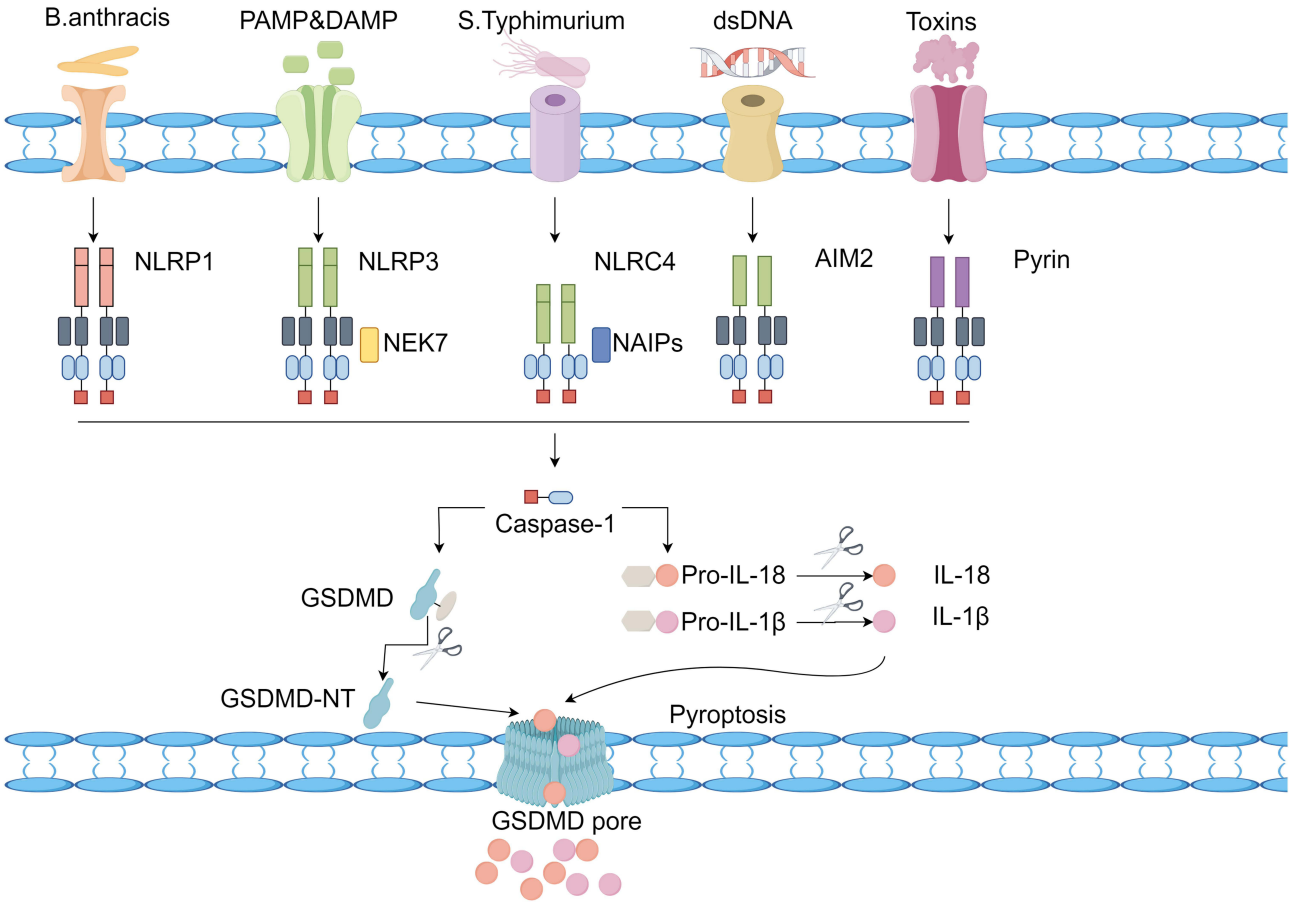

Figure 1 The classic activation mechanism of pyroptosis: caspase-1-dependent. By Figdraw.

On the other hand, the non-classical pyroptosis pathway involves caspase-4 and 5 in humans or caspase-11 in mice, which directly detect intracellular signals, bypassing the inflammasome complex.[8,14] Unlike caspase-1, caspase-11 does not process pro-IL-1β or pro-IL-18 into their mature forms.[15]

Recent research has highlighted the significant roles of Gasdermin protein isoforms in chronic intestinal diseases, particularly Gasdermin B (GSDMB) and Gasdermin C (GSDMC). GSDMB exists in multiple isoforms with distinct functions, and certain variants can induce pyroptosis when cleaved by proteases such as Granzyme A. This cleavage releases N-terminal fragments that promote membrane lysis and drive inflammatory responses, associating GSDMB with inflammatory bowel disease (IBD) and colorectal cancer (CRC).[16] Meanwhile, GSDMC, expressed in intestinal epithelial cells, is regulated by type 2 cytokines such as IL-4 and IL-13. Targeting Gasdermin isoforms presents promising therapeutic strategies for chronic intestinal diseases: enhancing pro-pyroptotic GSDMB isoforms may strengthen immune responses against pathogens while reducing CRC tumorigenesis, whereas inhibiting non-pyroptotic variants could mitigate excessive inflammation in IBD. Understanding post-translational modifications and cleavage mechanisms of these proteins may lead to novel interventions that selectively regulate their activity.[17]

Inflammasomes are essential cytoplasmic multiprotein complexes that detect host threats by recognizing PAMPs, DAMPs, homeostasis-altering molecular processes (HAMPs), or effector-triggered immunity (ETI).[18] They play a pivotal role in pyroptosis by managing inflammatory responses to infections and tissue damage, promoting the release of IL-1β and IL-18.[18] Typical inflammasomes consist of three main components: 1) PRRs, which serve as the sensors of PAMPs and DAMPs and are essential for inflammasome assembly. 2) ASC, which is activated and undergoes oligomerization and recruitment upon detecting inflammatory ligands, serving as a bridge between sensor proteins and effector proteins, forming the scaffold for inflammasome assembly.[19] 3) Effector proteins, primarily represented by inflammatory caspases such as Caspase-1, essential for inflammasome

function.[20] Pyroptosis is one of several regulated cell death mechanisms, alongside apoptosis and necroptosis, each with distinct pathways, outcomes, and inflammatory implications. Pyroptosis is a rapid inflammatory response to infection or cellular stress, contrasting with apoptosis, which is a controlled, non-inflammatory process. Necroptosis acts as an alternative pathway when apoptosis fails, sharing some characteristics with pyroptosis but distinct in its regulatory mechanisms and triggers. Necroptosis is often a backup mechanism activated when apoptosis is inhibited and is mediated by receptor-interacting protein kinases (RIPK1 and RIPK3), leading to MLKL activation.[21,22]

Recent research has highlighted pyroptosis as a key regulator of intestinal homeostasis and inflammation in chronic diseases.[23] Chronic intestinal diseases, such as IBD, irritable bowel syndrome (IBS),[24] celiac disease (CeD),[25] chronic infectious enteritis, and intestinal fibrosis,[26] are increasingly recognized as significant global public health concerns due to their rising prevalence and associated mortality rates.[27] Given its crucial role in both immune defense and pathological inflammation, this review aims to provide a comprehensive overview of the molecular mechanisms underlying pyroptosis in chronic intestinal diseases (Figure 2). By examining its dual roles in both defense and pathology, this review sheds

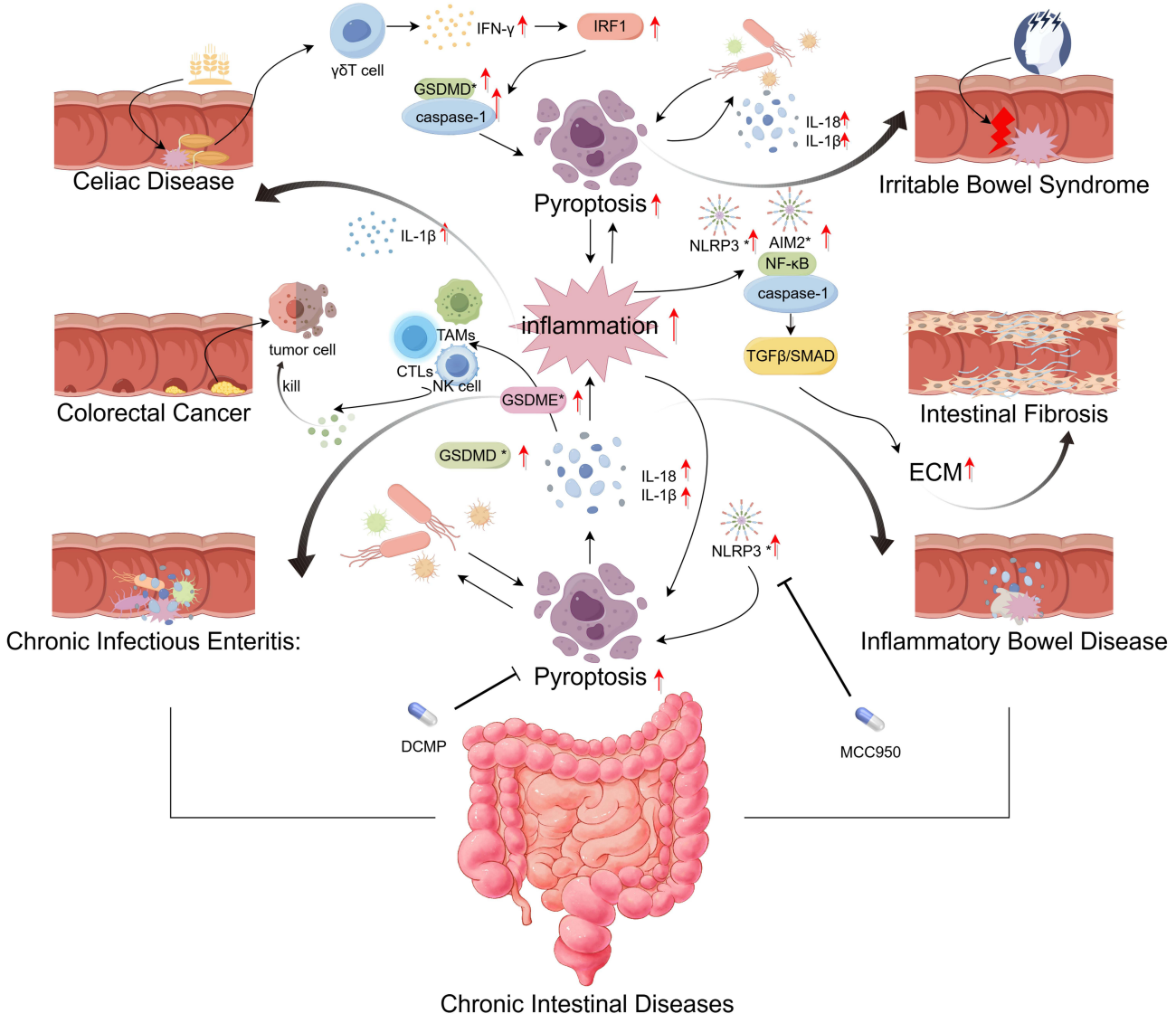

Figure 2 Pyroptosis in chronic intestinal diseases. By Figdraw.

Note: Pyroptosis has been implicated in a variety of chronic intestinal diseases, including inflammatory bowel disease, irritable bowel syndrome, celiac disease, chronic infectious enteritis, intestinal fibrosis, and colorectal cancer. The potential therapeutic molecular targets are marked with*.

Abbreviations: ECM, extracellular matrix; CTLs, cytotoxic T lymphocytes; NK, natural killer; TAMs, tumor-associated macrophages; IRF1, interferon regulatory factor 1; DCMP,dxms@cum@ppadt@pss; GSDME, gasdermin e; GSDMD, gasdermin d.

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light on the multifaceted nature of pyroptosis and its implications for future research and clinical advancements in gastroenterology.

Pyroptosis in IBD

IBD, which includes Crohn's disease (CD) and ulcerative colitis (UC),[28,29] is a chronic, non-specific inflammatory disorder of the gastrointestinal tract.[30,31] The etiology of IBD is multifactorial and not yet fully understood. However, it is widely recognized that environmental factors, genetic predisposition, and gut microbiome dysbiosis interact to disrupt intestinal immunity, compromise the mucosal barrier, and trigger chronic inflammation and tissue damage.[32,33] Pyroptosis plays a key role in IBD progression, with excessive activation observed in the intestinal tissues of IBD patients.

This dysregulated pyroptotic response contributes to chronic inflammation by amplifying damage signals and intensifying local immune responses, perpetuating a cycle of persistent inflammation that exacerbates the disease.[34] Emerging evidence suggests that pyroptosis is not only a major driver of intestinal injury but also a key factor in tissue repair, fibrosis, and long-term complications such as CRC.[23]

Several studies have reported elevated expression of inflammasomes in the intestines of IBD patients, leading to excessive pyroptosis and exacerbating intestinal damage.[35] Research has demonstrated that NOD-like receptor protein 3 (NLRP3)-deficient mice show significantly reduced pyroptosis in colonic tissues, alleviating IBD severity and delaying disease onset.[36] This finding highlights the NLRP3 inflammasome as a crucial mediator in both the development and potential treatment of colitis. Furthermore, Gasdermin family proteins, such as GSDMB, Gasdermin D (GADMD), and Gasdermin E (GSDME), which are critical in executing pyroptosis, strongly correlate with IBD severity, making them promising therapeutic targets.[37] Recent advances in therapeutic strategies include the development of oral pyroptosis inhibitors, which specifically target intestinal lesions.[34,38] These inhibitors hold great potential for reducing inflammation, preventing excessive pyroptosis, and preserving intestinal integrity, offering new avenues for IBD management.

Pyroptosis in Intestinal Fibrosis

Intestinal fibrosis is a severe complication of chronic gastrointestinal diseases, including IBD, which encompasses CD and UC, as well as conditions such as ulcerative jejunitis and radiation enteritis.[39] This pathological condition results in bowel narrowing, structural alterations, and functional impairment, significantly reducing patients' quality of life.[40] Intestinal fibrosis is closely associated with chronic inflammation and is influenced by factors such as cellular damage, recruitment of inflammatory cells, and the production of transforming growth factor-beta (TGF-β).[41] Recent studies have revealed a positive correlation between fibrosis, pyroptosis, and inflammasomes.[42,43] Key upstream activators of the TGF-β/Sma-Mad related protein (SMAD) pathway, such as caspase-1, NLRP3, and nuclear factor kappa B (NF-κB), have been identified, with TGFβ emerging as a potential anti-fibrotic target. Activation of inflammasomes, including NLRP3 and absent in melanoma 2 (AIM2), has been implicated in fibrosis progression.[44] The NLRP3 inhibitor MCC950 has demonstrated significant anti-fibrotic effects in preclinical studies.[45] During chronic inflammation, macrophages and lymphocytes are recruited to affected tissues, where they undergo pyroptosis. This process releases inflammatory factors, activates the TGF-β signaling pathway, increases extracellular matrix (ECM) synthesis, and indirectly promotes intestinal fibrosis.[46] GSDMD-dependent macrophage pyroptosis has been shown to intensify the inflammatory response in the intestinal mucosa, contributing to local cell death and fibrosis progression.[47,48] Furthermore, GSDME has emerged as a novel therapeutic target for fibrosis prevention and treatment.[49] In vitro studies using intestinal epithelial cell models have highlighted a strong association between pyroptosis and intestinal fibrosis. As the understanding of pyroptosis mechanisms deepens, researchers are actively exploring anti-fibrotic strategies targeting pyroptosis pathways, including inhibitors of NLRP3 inflammasomes and caspase-1, which have demonstrated promise in preclinical models.[50] While studies on pyroptosis and fibrosis have focused on other organs, such as the liver,[51] kidneys,[52] and lungs,[53] further investigation is necessary to fully elucidate its role in intestinal fibrosis. Targeting pyroptosis could offer novel therapeutic opportunities for managing intestinal fibrosis and improving outcomes for patients with chronic gastrointestinal diseases.

Pyroptosis in CeD

CeD is a chronic autoimmune disorder of the small intestine triggered by gluten ingestion in genetically susceptible individuals.[54] This condition affects approximately 1% of the global population.[55] In CeD, DAMPs released during inflammatory cell death are thought to initiate mucosal damage and contribute to the persistence of chronic disease. Pyroptosis, a pro-inflammatory form of programmed cell death, is believed to play a significant role in the pathophysiology of CeD by driving inflammation and tissue damage. Elevated caspase-1, IL-1β, and GSDMD levels have been observed in the duodenal tissues of CeD patients, suggesting active pyroptosis.[56] In genetically predisposed individuals, gluten consumption induces an influx of γδT cells into the duodenal mucosa. These cells produce high levels of interferon-γ, which upregulates interferon regulatory factor 1 (IRF1) expression and enhances GSDMD expression in intestinal epithelial cells, priming them for a "pre-pyroptotic" state. These cells undergo pyroptosis following gluten exposure, leading to villous atrophy in the duodenum and subsequent nutrient malabsorption.[57] During pyroptosis, the release of intracellular contents into the extracellular space can be misinterpreted by the immune system as foreign antigens, thereby triggering an autoimmune response. This process is important in the pathogenesis of CeD[58] and may also contribute to further damage in the small intestine. Furthermore, CeD is frequently associated with other autoimmune disorders, such as thyroid diseases and type 1 diabetes, where pyroptosis is also thought to play a significant role.[59] The association between pyroptosis and CeD highlights its broader relevance in autoimmune diseases. Future research should aim to elucidate the precise molecular mechanisms underlying pyroptosis in CeD and explore targeted therapeutic strategies to mitigate inflammation and intestinal damage.

Pyroptosis in Diverticulitis

Diverticulitis is a chronic inflammatory condition of the colon associated with diverticular disease.[60] It is characterized by inflammation or infection of diverticula—pouches formed within the wall of the large intestine. The recurrence of diverticulitis is unpredictable and often results in persistent gastrointestinal symptoms.[61] The pathogenesis of diverticulitis is closely associated with an imbalance in the gut microbiota and inflammation of the intestinal wall. A complex positive feedback loop exists between the inflammatory response in diverticulitis and pyroptosis. Research suggests that the composition of the gut microbiota significantly influences both the formation of diverticula and the subsequent inflammatory response.[62] During episodes of diverticulitis, infection by gut microbes can trigger pyroptosis, a pro-inflammatory form of programmed cell death. This process leads to cellular destruction and the release of cytokines, which amplify the immune response. The resulting inflammatory cascade exacerbates intestinal inflammation and contributes to disease progression.[63]

Some studies suggest that acute diverticulitis may lead to subsequent IBS-like symptoms, although the mechanisms underlying this transition remain poorly understood. Furthermore, the role of pyroptosis in diverticulitis has not been extensively investigated. Further research is needed to address this gap and determine how pyroptosis influences disease progression, recurrence, and symptomatology.

Pyroptosis in IBS

IBS is a common chronic functional gastrointestinal disorder characterized by recurrent abdominal pain or discomfort and altered bowel habits.[64] It affects approximately 5% to 10% of the global population.[24,65] Although the exact causes and pathophysiological mechanisms of IBS remain unclear, it is widely believed that a combination of factors, such as gut microbiota, immune responses, gastrointestinal motility, and psychological influences, contribute to its development. Psychological factors play an important role in IBS, with evidence indicating that conditions such as anxiety may exacerbate pyroptosis, potentially worsening IBS symptoms.[66,67] Excessive pyroptosis has been implicated in altering the gut microbiota composition, leading to microbial dysbiosis. This dysbiosis can activate inflammasome, further driving pyroptosis and creating a feedback loop that intensifies IBS symptoms.[68,69] Moreover, dysregulation of inflammasomes may contribute to abnormal immune responses and gut inflammation in IBS. Studies have shown that pyroptosis can also compromise the integrity of intestinal epithelial cells by increasing intestinal permeability, allowing harmful substances to enter the gut and trigger inflammation. The release of cytokines such as IL-1β and IL-18 during pyroptosis has been

associated with intestinal discomfort and pain.[64] Moreover, infectious gastroenteritis is recognized as a significant risk factor for the onset of IBS.[70] Such infections can induce pyroptosis, increasing inflammatory responses and subsequently disrupting gut function.[71,72] Current research has provided preliminary insights into the association between pyroptosis and IBS. However, inconsistencies remain regarding the specific role of pyroptosis in IBS pathogenesis. This highlights the need for further targeted studies to clarify the relationship between pyroptosis, gut microbiota, and IBS. Investigating this association could pave the way for innovative therapeutic approaches. Modulating pyroptosis pathways may help alleviate IBS symptoms, and interventions targeting pyroptosis—such as anti-inflammatory drugs or agents that regulate gut microbiota—offer promising new perspectives for IBS treatment.

Pyroptosis in Chronic Infectious Enteritis

Pyroptosis plays a significant role in the progression of chronic infectious enteritis.[73] Research indicates that patients with chronic infectious enteritis show elevated inflammasome activity in the gut, leading to increased pyroptosis. This process serves both as a defense mechanism against persistent infection and an adaptive response to gut microbial dysbiosis. Pyroptosis may affect the progression of chronic infectious enteritis through several mechanisms: 1) Inhibition of Pathogen Replication: Infected intestinal epithelial cells undergoing pyroptosis can release inflammatory factors that improve local immune responses, directly eliminate infected cells, and inhibit bacterial replication and spread within the gut. This mechanism helps to control infection and modulate inflammation.[74] 2) Modulation of Gut Microbiota: Pyroptosis can alter the composition of the gut microbiota, which in turn affects immune responses.[1] A balanced microbiota competes with pathogens, reducing inflammation and preventing persistent infections.[3] 3) Pyroptosis contributes to gut self-repair mechanisms. The clearance of damaged cells creates space for new cell regeneration, facilitating tissue healing. However, excessive pyroptosis can lead to excessive inflammation, worsening enteritis symptoms.[75] However, excessive pyroptosis can exacerbate inflammation, worsening enteritis symptoms.[76] Studies have shown that gut microbial infections can induce pyroptosis, which clears infected cells and intensifies local inflammation.[77] The interaction between microbial infection and pyroptosis is considered a key factor in the pathogenesis of chronic infectious enteritis.[23,73] Some bacteria, such as Helicobacter pylori,[78] can evade host immune surveillance by inducing pyroptosis. This allows them to maintain chronic inflammation within the host,[79] leading to gut tissue damage and gastrointestinal dysfunction.[80] The Gasdermin family, particularly GSDMD, plays a key role in defending intestinal epithelial cells against bacterial infections and regulating intestinal inflammation.

The colonic mucus layer serves as both a habitat for symbiotic bacteria and a physical barrier against pathogens such as E. coli. In intestinal epithelial cells, GSDMD deficiency leads to reduced mucus secretion, loss of the mucus layer, and significant changes in the spatial distribution and composition of the gut microbiota.[81] GSDMD-deficient mice are more susceptible to gut pathogen infections, highlighting the importance of GSDMD in maintaining gut integrity. In chronic infectious enteritis, pyroptosis triggers local inflammatory responses and may impact systemic immune status. Caspase-driven damage signals activate various inflammatory pathways, contributing to chronic infectious enteritis.[23] Persistent pathogen stimulation and immune activation make pyroptosis a defining feature of the disease. Chronic inflammation, coupled with ongoing tissue regeneration, can impair gut barrier function and promote microbial dysbiosis. This dysbiosis, in turn, exacerbates inflammation and may lead to severe complications such as intestinal perforation and sepsis. Thus, understanding the mechanisms of pyroptosis offers valuable insights into the pathogenesis of chronic infectious enteritis and related inflammatory conditions.

Pyroptosis in CRC

CRC is a complex disease with high incidence and mortality rates, influenced by genetic, environmental, and immune factors. It is the third most common cancer globally, driven by aging populations and deteriorating environmental conditions.[82] CRC often develops in conjunction with other inflammatory intestinal disorders.[83] Recent studies have shown that pyroptosis plays a dual role in CRC, inhibiting tumor cell growth and metastasis and potentially promoting tumor progression through chronic inflammation.[84,85] In the tumor microenvironment (TME), pyroptosis significantly impacts immune regulation by releasing IL-1β and IL-18, which increase the interaction between innate and adaptive immunity.[86] This process recruits immune cells, such as natural killer (NK) cells and cytotoxic T lymphocytes (CTLs), to the tumor site, thereby boosting tumor immune surveillance.[87] Moreover, tumor-associated macrophages (TAMs) can also induce pyroptosis in CRC cells via the secretion of

pro-inflammatory factors, though, in some cases, this may paradoxically support tumor survival and proliferation.[88] Moreover, in CRC patients, pyroptosis-related genes (PRGs) are strongly correlated with disease prognosis.[85,88] One key pyroptosis protein in CRC is GSDME. The methylation status of GSDME is emerging as a potential biomarker for CRC, offering opportunities for early diagnosis and disease monitoring.[84] Genetic, mutational, and environmental factors influence the expression of human inflammasome signaling and pyroptosis-related genes, which in turn regulate inflammasome activation. In CRC cells, caspase-3 activation cleaves GSDME, releasing an N-terminal fragment that forms membrane pores, triggering pyroptosis. While GSDME is typically expressed in various cell types, it is often silenced in tumor cells. However, GSDME expression can shift tumor cells from apoptosis induced by tumor necrosis factor-alpha (TNF-α) and cycloheximide to pyroptosis.[89] The absence of pyroptosis-related proteins in tumor cells, such as GSDME, is associated with decreased levels of perforin and granzyme B, as well as reduced infiltration of NK cells and CTLs in the TME. This suggests that a lack of pyroptosis can change the immune landscape and impact tumor progression.[8] Furthermore, single nucleotide polymorphisms in the NLRP3 gene have been associated with decreased survival rates in invasive CRC patients.[90] Research highlights the role of pyroptosis-related genes, including NLRP3, AIM2, and Gasdermin M5 (GSDM5), in the pyroptosis signaling pathways of various cancers, such as gastric cancer, colitis-associated CRC, and esophageal cancer. Inflammasomes, key regulators of mucosal innate immune responses, influence intestinal pathogen infections and inflammation-driven tumorigenesis.[91] Deficiency in NLRP3 inflammasomes can impair NK cell IL-18 signaling pathways, promoting CRC cell growth and metastasis. Mice lacking NLRP3 or caspase-1 show increased susceptibility to inflammation-induced colon tumors.[92] Similarly, mice deficient in Asc and caspase-1 are more prone to colitis and colitis-associated cancer,[93] demonstrating the protective role of inflammasome in CRC-related inflammation models. From a therapeutic perspective, certain Food and Drug Administration-approved chemotherapeutic drugs and natural compounds have been shown to induce pyroptosis in tumor cells. For instance, 5-fluorouracil (5-FU)[94] and programmed death-ligand 1 (PD-L1)[2] inhibitors enhance drug efficacy and reduce resistance by promoting pyroptosis by activating caspase-3 and caspase-1. Moreover, translocator protein (TSPO)-targeted photodynamic therapy (PDT) has shown promise in inhibiting CRC progression by inducing pyroptosis via photosensitizers that generate reactive oxygen species under specific light wavelengths.[95] Emerging advancements in nanotechnology[96] and gene editing[97,98] are being tailored to patient-specific genetic profiles and tumor characteristics to improve treatment outcomes. Overall, pyroptosis is critical in the onset and progression of CRC, representing a promising therapeutic target. Further research into the mechanisms of pyroptosis and its clinical applications is expected to improve CRC prognosis and provide novel treatment strategies.

Connection Between Gut Microbiota and Pyroptosis

The gut microbiota, a diverse microbial community within the gastrointestinal tract, plays a crucial role in host health and disease. Its composition is intricately associated with pyroptosis. Dysbiosis, or an imbalance in gut microbiota, can lead to the production of abnormal metabolic products that modulate inflammation and pyroptosis.[99] Certain beneficial microbes, such as specific strains of Lactobacilli and Bifidobacteria, can inhibit inflammasome activation and reduce pyroptosis by producing metabolites like short-chain fatty acids.[100] However, some pathogenic bacteria, such as toxin-producing Clostridium perfringens, can trigger pyroptosis by activating the NLRP3 inflammasome, compromising the integrity of the gut barrier and exacerbating inflammation.[101,102] Pyroptosis plays a direct role in shaping the diversity and composition of the gut microbiota and is closely associated with inflammasomes in gut pathology. For example, the nucleotide-binding domain and leucine-rich repeat protein 6 (NLRP6) inflammasome significantly influence gut microbiota composition, epithelial cell function, and susceptibility to gastrointestinal inflammation, infections, and tumors.[103] The NLRP3 inflammasome has been shown to impact oxidative stress by altering the gut microbiota, specifically targeting bacteria such as Bacteroidetes and Lactobacillus species, including Lactobacillus reuteri.[104] Similarly, the AIM2 inflammasome helps regulate the gut microbiota and prevent dysbiosis and inflammation by managing the IL-18/IL-22BP/IL-22 and signal transducer and activator of transcription 3 (STAT3) pathways, along with the expression of specific antimicrobial peptides.[105] This complex interplay between pyroptosis and gut microbiota is especially relevant in chronic intestinal diseases such as IBD and CRC.[37] In IBD, pyroptosis is significantly elevated, leading to gut microbiota imbalances, extensive epithelial cell death, gut barrier destruction, and a perpetuating cycle of inflammation. Studies in animal models have shown that the nucleotide-binding domain, leucine-rich repeat, and pyrin domain-containing protein

1 (NLRP1) inflammasome exacerbates colitis through interactions with commensal microbes, reducing populations of butyrate-producing bacteria via IL-18-induced antimicrobial peptides. This disruption further compromises gut barrier function and perpetuates inflammation.[106] In CRC, pyroptosis plays a dual role in both anti-tumor immunity and tumor progression. On the one hand, inducing pyroptosis in CRC cells can inhibit tumor growth by increasing immune surveillance. On the other hand, chronic inflammatory responses within the TME may support tumor progression. Fusobacterium nucleatum, a bacterium associated with CRC, has been shown to affect CASP6 expression, which is linked to resistance to 5-FU chemotherapy. This suggests that microbial interactions may affect CRC progression through mechanisms involving pyroptosis. Therefore, understanding the complex feedback loops between pyroptosis and the gut microbiota is essential for elucidating the pathogenesis of chronic intestinal diseases.

Conclusion and Future Research Perspectives

As research on pyroptosis in chronic intestinal diseases advances, the development of diagnostic and therapeutic strategies targeting pyroptosis has become a growing priority. This review provides a comprehensive analysis of pyroptosis across multiple chronic intestinal diseases, emphasizing its dual role in both host defense and inflammation. This review incorporates the latest findings on pyroptosis mechanisms, particularly the roles of inflammasomes and Gasdermin proteins, exploring the complex interaction between pyroptosis and gut microbiota and highlighting how dysbiosis can modulate inflammation. Moreover, it discussed the potential of targeting pyroptosis as a therapeutic strategy and recent advancements in pyroptosis inhibitors, which could revolutionize disease management.

Recent research has focused on various preclinical intervention strategies to modulate pyroptosis as a therapeutic target in chronic intestinal diseases, such as small-molecule inhibitors targeting components of the NLRP3 inflammasome, herbal medicine inhibiting NLRP3 activation, and targeting Gasdermin proteins.[14] While preclinical studies have shown promise, clinical trials specifically investigating these interventions in chronic intestinal conditions are still emerging. Ongoing studies on NLRP3 inflammasome inhibitors may provide insights into their efficacy in treating IBD and related disorders.[107] However, comprehensive clinical data remain limited, requiring further research.

Despite the comprehensive overview of pyroptosis and its role in chronic intestinal diseases, several challenges remain. First, much of the current understanding is based on preclinical studies with limited clinical validation. More extensive clinical research is needed to fully elucidate the therapeutic potential of targeting pyroptosis. Second, the interaction between pyroptosis and gut microbiota is highly complex, and the precise contributions of specific microbial species to pyroptosis-driven pathology require further investigation. Lastly, while the manuscript provides insights into potential therapeutic strategies, the feasibility, specificity, and long-term safety of these interventions in clinical settings have not been fully evaluated.

Future research should focus on developing novel treatments that target inflammasomes or the Gasdermin family of proteins to reduce inflammation in chronic intestinal conditions. For instance, selectively inducing pyroptosis in CRC cells while sparing normal cells could enhance anti-tumor immune responses and improve the efficacy of existing cancer therapies.[23] However, the potential limitations of targeting pyroptosis must be carefully considered. The role of pyroptosis in chronic intestinal diseases is intertwined with immune responses and gut microbiota, and its impact extends across various cell types and molecular pathways, making it challenging to target specifically without impacting other physiological processes. Targeting pyroptosis non-specifically could inadvertently impair immune defense mechanisms against infections or cancer. Furthermore, therapeutic responses may vary due to genetic factors and individual microbiome compositions, requiring personalized treatment approaches. Therefore, a deeper understanding of pyroptosis is important for developing innovative diagnostic tools and therapeutic strategies that minimize adverse effects while maximizing clinical benefits. Continued efforts in this field hold the potential to open new therapeutic avenues, ultimately improving the management of chronic intestinal diseases and CRC.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests in this work.

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