Research Advances on Pyroptosis in the Inflammation-Cancer Transition and Disease Progression of Colorectal Cancer: Postprint

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Abstract

Colorectal cancer, as one of the malignant tumors with persistently high incidence and mortality rates worldwide, poses a serious threat to human health. Moreover, the early diagnosis rate of colorectal cancer remains relatively low, with many patients already at middle or advanced stages upon diagnosis, resulting in unsatisfactory therapeutic efficacy and prognosis. However, most current research on colorectal cancer remains confined to the surgical domain, with limited investigation into the underlying cellular and molecular mechanisms. With the deepening understanding of tumor biology, the intimate relationship between inflammation and cancer has been gradually elucidated, and pyroptosis, as a novel form of programmed cell death, has garnered significant attention in tumor immunity and microenvironment regulation. This study systematically reviews the research progress on the inflammation-cancer transition and pyroptosis in colorectal cancer, analyzing the interaction mechanisms between these two processes and the role of pyroptosis in disease progression. The findings reveal that chronic inflammation regulates the transformation of undifferentiated cells into cancer stem cells through cytokines, growth factors, and other mediators, thereby constructing a pro-tumorigenic microenvironment. Pyroptosis, triggered by inflammasome activation and mediated by the caspase family and gasdermin family proteins, can both promote tumor cell death and influence the tumor microenvironment through the release of cytokines such as IL-1β and IL-18, exhibiting a dual role. Targeted strategies against the inflammation-cancer transition and pyroptosis demonstrate therapeutic potential. This study provides a theoretical foundation at the cellular and molecular level for understanding the pathogenesis of colorectal cancer, lays the groundwork for developing precision targeted therapeutic regimens, facilitates the evolution of colorectal cancer treatment from surgery-centered approaches to multi-mechanism combined interventions, and ultimately improves patient prognosis.

Full Text

Preamble

Research Progress on Cell Pyroptosis in Colorectal Cancer Transformation and Disease Development

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Abstract

Colorectal cancer, one of the most prevalent malignancies globally with persistently high incidence and mortality rates, poses a significant threat to human health. Moreover, its early detection rate remains relatively low, with many patients diagnosed at intermediate or advanced stages, resulting in suboptimal treatment outcomes and prognoses. However, current research predominantly focuses on surgical interventions, while studies on cellular and molecular mechanisms remain limited. With deepening research in tumor biology, the close relationship between inflammation and tumors has gradually been revealed. As a novel programmed cell death mechanism, cellular pyroptosis has attracted significant attention in tumor immunity and microenvironment regulation. This study systematically reviews research progress on inflammatory carcinogenesis and cellular pyroptosis in colorectal cancer, analyzing their interaction mechanisms and the role of cellular pyroptosis in disease progression. The findings indicate that chronic inflammation regulates the transformation of undifferentiated cells into cancer stem cells through cytokines and growth factors, thereby constructing a procarcinogenic microenvironment. Cellular pyroptosis, triggered by inflammatory body activation and mediated by caspase family and gasdermin family proteins, exhibits dual effects: it promotes tumor cell death while influencing the tumor microenvironment through the release of cytokines such as IL-1β and IL-18. Targeting strategies for inflammatory carcinogenesis and cellular pyroptosis demonstrate therapeutic potential. This study provides theoretical foundations at the cellular and molecular levels to understand colorectal cancer pathogenesis, lays the groundwork for developing precision-targeted therapies, and facilitates the transition of colorectal cancer treatment from surgery-focused approaches to multi-mechanism combined interventions, ultimately improving patient prognosis.

Keywords: Colorectal cancer; Pyroptosis; Inflammatory cancer transformation; Growth factors; Cell factor

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1.1 Research Status of Colorectal Cancer

Colorectal cancer, as one of the most common malignancies, poses a severe threat to human health. Numerous scholars have investigated its disease characteristics and pathology. Siegel et al. [14] statistically analyzed colorectal cancer data through 2023 and found it has become the second leading cause of cancer death in the United States. The overall incidence shows significant gender disparities: 41.5 per 100,000 in males, 33% higher than in females (31.2 per 100,000). This difference is particularly pronounced across anatomical sites, with significantly higher male incidence in proximal colon and rectal cancers. Regarding age distribution, incidence increases with age across all sites, especially in those over 65; however, individuals under 50 account for 13% of cases, and the 50-64 age group comprises about 32%, indicating that middle-aged populations should not be overlooked. Additionally, incidence, survival, and mortality rates vary by race and region, with highest risk among Native Americans and Alaska Natives and lowest among Asian Americans and Pacific Islanders. Over 50% of cases and deaths are attributable to modifiable risk factors including smoking, unhealthy diet, alcohol consumption, physical inactivity, and overweight [15].

Sedlak et al. [16] revealed that colorectal cancer cells support rapid proliferation through metabolic reprogramming, characterized by dependence on aerobic glycolysis to generate biosynthetic molecules while efficiently acquiring nutrients and eliminating waste. Diet plays a critical role in pathogenesis, with high-fat and high-sugar diets both associated with disease onset. The gut microbiome influences colonic stem cell biology through metabolites; for example, lactic acid-producing bacteria can promote colonic stem cell proliferation by activating integrin signaling pathways, thereby participating in tumorigenesis. In the therapeutic domain, Ciardiello et al. [17] discovered that approximately 20% of colorectal cancer patients have metastasis at initial diagnosis, and 50% of patients with localized lesions eventually progress to metastatic disease. Current metastatic colorectal cancer treatment is based on molecular stratification, with first- and second-line regimens incorporating genetic variation detection

and combined anti-angiogenic drugs with anti-epidermal growth factor receptor (EGFR) agents. Subsequent treatment strategies are formulated based on rat sarcoma viral oncogene homolog (RAS) family, B-type rat sarcoma viral oncogene homolog B1 (B-Raf) mutation status, and microsatellite instability-high/deficient mismatch repair (MSI-H/dMMR) characteristics. For patients showing significant response to first- or second-line chemotherapy combined with cetuximab/panitumumab, EGFR inhibitor rechallenge therapy may be employed. Targeting the EGFR family and its intracellular signaling pathways represents the core of molecular targeted therapy for metastatic colorectal cancer, with Kirsten rat sarcoma viral oncogene homolog (KRAS) and neuroblastoma RAS viral oncogene homolog (NRAS) mutation analysis serving as key criteria for molecular characterization and providing important basis for treatment selection.

Traditional treatment modalities such as surgical resection, chemotherapy, and radiotherapy have remained primary approaches for colorectal cancer patients [8]. However, these conventional methods have inherent limitations: surgical resection may fail to completely eliminate micrometastases, while chemotherapy and radiotherapy can damage normal cells and trigger various side effects [9-10]. With the development of high-throughput sequencing technology, significant progress has been made in tumor genomics research. By analyzing genomic data from colorectal cancer patients, multiple genes and signaling pathways associated with carcinogenesis and progression have been identified [11-12]. Tumor microenvironment research has confirmed that interactions between tumor cells and surrounding cells plus extracellular matrix are crucial for tumor development. Microenvironment factors including inflammatory cell infiltration, fibroblast activation, angiogenesis, and extracellular matrix remodeling all participate in tumor progression [13]. Although therapeutic strategies targeting these factors have been developed, the high heterogeneity and dynamic nature of the tumor microenvironment still limit treatment efficacy.

1.2 Existing Research on Inflammatory Carcinogenesis Mechanisms

Research demonstrates that cancer development is closely associated with inflammation. Afify et al. [18] explored how chronic inflammation promotes cancer development, proposing that cancer tissue growth is driven by cancer stem cells with self-renewal, differentiation, and tumorigenic potential. Under chronic inflammatory conditions, various cytokines and growth factors can stimulate the transformation of undifferentiated cells into cancer stem cells [Figure 1: see original paper]. Cancer can originate from differentiated cells or undifferentiated stem/progenitor cells, with the latter possessing strong plasticity and regenerative capacity. Under conditions such as chronic inflammation, altered levels of cytokines and growth factors can induce the transformation of undifferentiated cells into cancer stem cells. Chronic inflammation accelerates cancer progression by promoting continuous cell proliferation and survival through long-term

exposure to inflammatory mediators. Afify et al. [18] hypothesized that chronic diseases can construct cancer-inducing niches that form microenvironments supporting the emergence of cancer-associated cells, which differ across organs and are provided by cancer cells themselves to maintain survival.

Stevens et al. [19] studied inflammatory carcinogenesis-related cancers and identified inflammatory breast cancer as a rare, highly aggressive subtype. Through multicolor immunofluorescence analysis, they confirmed that CD44+CD24- cells most commonly express phosphorylated signal transducer and activator of transcription 3 (pSTAT3). Combined chromatin immunoprecipitation sequencing (ChIP-seq) and RNA sequencing (RNA-seq) analysis of pSTAT3 revealed that pSTAT3 regulates inflammation, epithelial-mesenchymal transition (EMT), and phosphodiesterase 4A (PDE4A)-related genes in drug-resistant cells. Metabolomic analysis showed elevated cyclic adenosine monophosphate (cAMP) signaling pathways in resistant cells, with cAMP response element-binding protein (CREB) serving as a potential therapeutic target. Bhat et al. [20] proposed that inflammation is a known risk factor for colorectal cancer, constructing an inflammation-rich local environment encompassing tumor cells, endothelial cells, immune cells, cancer-associated fibroblasts, immunosuppressive cells, and secreted growth factors. Through complex interactions, this environment drives colorectal cancer pathogenesis and triggers systemic responses affecting disease outcomes. Abnormally expressed cytokines and chemokines promote metastasis and invasive growth by recruiting immunosuppressive cells, conferring cancer stem cell-like properties, drug resistance, and distant organ pre-metastatic niche formation capabilities upon tumor cells.

Different types of immune cells participate in colorectal cancer inflammation by secreting various cytokines and chemokines, exerting either promotional or inhibitory effects [Figure 2: see original paper]. Th1 cells and M1 macrophages are typically associated with pro-inflammatory responses, while M2 macrophages contribute to inflammation resolution. In colorectal cancer treatment, targeting specific cytokines or their receptors can modulate inflammatory responses to inhibit tumor growth and metastasis [21]. Epithelial-mesenchymal transition represents the core process through which tumor cells acquire migration and invasion capabilities, characterized by loss of cell-cell adhesion and cell-matrix adhesion. Multiple cytokines including tumor necrosis factor α (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6) can trigger epithelial-mesenchhenchymal transition in colorectal cancer cells through different signaling pathways, thereby promoting tumor cell migration and invasion. Systemic inflammation can induce immunosuppression, providing favorable conditions for tumor metastasis [22].

1.3 Research on Pyroptosis and Its Mechanism

Pyroptosis can activate the immune system and influence the tumor microenvironment, exerting either inhibitory or promotional effects on tumor growth. Elias et al. [23] consider pyroptosis a form of programmed cell death mediated by gasdermin family proteins. Initially described as a caspase-1- and

inflammasome-dependent cell death pathway, pyroptosis is characterized by loss of plasma membrane integrity and secretion of cytokines such as IL-1β. Gasdermins form pores that cause plasma membrane rupture, leading to release of cellular contents. During pyroptosis, gasdermin proteins exist in an autoinhibited state in their inactive form, with key regions mediating lipid binding and membrane insertion hidden through interaction between carboxy-terminal and amino-terminal domains. Protease cleavage of the linker region releases the active amino-terminal domain, resulting in pore formation on the cell membrane. Although evidence suggests pyroptosis participates in pathogenesis, its specific role and mechanism require further investigation.

Zhang et al. [24] deeply investigated the mechanism of pyroptosis technology in cancer therapy, discovering that autophagy serves not only as a key regulatory point for cancer cell pyroptosis but also as a self-protective mechanism that weakens therapeutic efficacy. The team successfully developed a novel nano-regulator that can both induce pyroptosis and block autophagy regulatory nodes, thereby achieving precise pyroptosis therapy [Figure 3: see original paper]. The nano-regulator promotes synthesis and accumulation of the photosensitizer protoporphyrin IX in cancer cell mitochondria, directly generating mitochondrial reactive oxygen species and triggering pyroptosis. Autophagy inhibitors generated in situ through palladium-catalyzed bioorthogonal chemical reactions can disrupt pyroptosis checkpoints. Disruption of pyroptosis checkpoints refers to enhancing pyroptosis by inhibiting autophagy. NOD-like receptor family pyrin domain-containing protein 3 (NLRP3) plays a crucial role in apoptosis and can activate caspase-1. Autophagosomes are vesicular structures formed during autophagy that encapsulate and transport intracellular materials to lysosomes. During treatment, bio-mimetic cancer cell membrane coating can be utilized to construct a platform for regulating apoptosis—this coating specifically targets cancer cells while being harmless to normal tissues, thereby achieving efficient and safe anti-tumor therapy.

Some compounds and drugs can activate pyroptosis pathways, becoming potential anti-cancer molecules. Meanwhile, PANoptosis has been identified as a cell death modality combining pyroptosis, apoptosis, and necrosis, mediated by the PANoptosome complex [31]. This process involves inflammatory responses and holds potential application value in tumor therapy.

Inflammasome activation is a prerequisite for caspase-1 and caspase-11 activation [32]. Inflammasomes consist of sensor proteins, adapter proteins, and zymogen forms. When inflammasomes receive signals from pathogen-associated molecular patterns or damage-associated molecular patterns, they trigger caspase activation. The role of caspases in pyroptosis is illustrated in [Figure 5: see original paper].

2.1 Interaction Between Inflammatory Carcinogenesis and Pyroptosis

Pyroptosis is triggered by inflammasome activation and is typically associated with pathogen infection or cell damage, representing a key issue in immune cell cytotoxicity research [25]. Wei et al. [26] discovered that pyroptosis is regulated by various inflammatory caspases. Activated caspases can cleave gasdermin D (GSDMD), releasing its N-terminal domain that binds membrane lipids and penetrates the plasma membrane. Inflammasomes serve as critical regulators of apoptosis, responding to internal and external stimuli such as pathogen-associated molecular patterns. When regulated by inflammasomes, pyroptosis can promote tumor cell death, while released cytokines (such as IL-1, IL-18) can also enhance tumor invasion and metastasis.

Furthermore, Mycobacteria induce macrophage pyroptosis through Mycobacterial secreted protein 12 (EST12) [27]. EST12 can bind to host sensor protein RACK1 to form a complex (EST12-RACK1), which subsequently recruits ubiquitin carboxyl-terminal hydrolase L5 (UCHL5), leading to deubiquitination of NLRP3 protein at lysine 48 (Lys48) and triggering Gasdermin D-induced macrophage pyroptosis with interleukin-1 secretion. Bromodomain-containing protein 4 (Brd4), an important epigenetic transcriptional activator, regulates NAIP-NLRC4 activation in macrophages during Salmonella infection [28]. Brd4 colocalizes with macrophage lineage-determining transcription factor PU.1 and interferon regulatory factor 8 (IRF8) at the neuronal activity-regulated pentraxin (NARP) promoter, promoting its transcription and inducing maturation of caspase-1 and cleavage of Gasdermin D and pro-IL-1β, ultimately promoting infection-mediated inflammatory responses and pyroptosis [29] [Figure 4: see original paper].

Yang et al. [30] found that pyroptosis can be activated through both non-canonical and canonical inflammasome pathways. The non-canonical inflammasome pathway is characterized by caspase-4/5/11-mediated GSDMD cleavage, while the canonical inflammasome pathway features caspase-1-mediated GSDMD cleavage.

2.2 Research Status of Potential Therapeutic Strategies Targeting Inflammatory Carcinogenesis and Pyroptosis

Understanding the mechanism of pyroptosis in colorectal cancer and inflammatory carcinogenesis can facilitate development of novel prevention and treatment strategies. Peng et al. [33] discovered that Gasdermin D is a cytoplasmic effector protein primarily functioning in immune cell pyroptosis. The nuclear localization of Gasdermin D in colorectal cancer differs from its role in pyroptosis—nuclear Gasdermin D promotes apoptosis by regulating its subcellular distribution rather than through pyroptosis-related cleavage. Hypoxia in the tumor microenvironment is a factor for GSDMD nuclear translocation. Under hypoxic conditions, Gasdermin D translocates from the cytoplasm to the nucleus, which

is associated with tumor cell proliferation and apoptosis. Survival curve analysis of colon adenocarcinoma showed no significant difference between high and low Gasdermin D mRNA expression groups. Similarly, rectal adenocarcinoma survival analysis revealed no significant difference between high and low Gasdermin D mRNA expression groups, suggesting that Gasdermin D mRNA expression level may not be a reliable biomarker for predicting prognosis in colorectal cancer patients.

Chen et al. [34] developed a compound therapeutic material named secoisolariciresinol diglucoside (SDG) for treating colorectal cancer with inflammatory transformation. This substance is a lignan extracted from flaxseed with multiple biological activities including anti-cancer properties. SDG induces pyroptosis in colorectal cancer cells by enhancing cleavage of the Gasdermin D protein N-terminal fragment while increasing caspase-1 levels. Additionally, this compound can inhibit human colon cancer cell line HCT116 cell activity, cause cell swelling and bleb formation, producing typical necrotic characteristics. SDG can induce GSDMD-dependent pyroptosis through the ROS/PI3K/AKT/BAX mitochondrial apoptosis pathway, providing a reference for novel applications of SDG in cancer therapy.

Vafaei et al. [35] demonstrated that NLRP3 inflammasome, an important member of the NOD-like receptor (NLR) family, influences tumor development through multiple pathways including immune system function, apoptosis, cell proliferation, and gut microbiota balance. Upon recognition of pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs), NLRP3 inflammasome can be activated, subsequently activating nuclear transcription factor NF- B through primary signal transduction. Persistent activation of NLRP3 inflammasome and its mediated NF- B signaling pathway can induce chronic inflammatory states, a pathological process confirmed to be closely associated with colorectal cancer development. Activated interleukin-1β and interleukin-18 can significantly influence the tumor microenvironment and promote tumor progression by regulating immune responses. Notably, caspase-1 activated by NLRP3 inflammasome can not only promote proteolytic maturation of interleukin-1β and interleukin-18 precursors but also induce pyroptosis, an inflammatory programmed cell death process, leading to massive release of pro-inflammatory cytokines. Research shows that NLRP3 inflammasome-mediated inflammatory cell death through Gasdermin-D is a key mechanism of innate immune response, playing important roles in maintaining intestinal homeostasis, including regulation of intestinal epithelial barrier function and immune responses to gut microbiota [36]. Regarding intervention strategies, small molecule compounds such as andrographolide can inhibit NLRP3 inflammasome activation in macrophages by inducing mitophagy, thereby effectively preventing azoxymethane/dextran sodium sulfate (AOM/DSS)-induced colon cancer in mice [37]. Additionally, the synthetic flavonoid derivative GL-V9 demonstrates excellent anti-inflammatory and anti-tumor effects by inducing autophagy-dependent NLRP3 inflammasome degradation, exerting protective effects against colitis and associated cancer

[38]. Studies have confirmed that inactivated probiotics can also reduce the incidence of NLRP3-mediated colitis and inflammation-associated colon cancer [39]. The mechanism of NLRP3 inflammasome in colorectal cancer is illustrated in [Figure 6: see original paper].

4 Conclusion and Outlook

This study systematically reviewed research progress on inflammatory carcinogenesis and pyroptosis in colorectal cancer, clarifying that chronic inflammation promotes the transformation of undifferentiated cells into cancer stem cells through signaling pathways involving cytokines, growth factors, and NLRP3 inflammasome, providing a suitable microenvironment for tumor growth. Simultaneously, it reveals pyroptosis as an inflammatory programmed death modality that, through regulation by gasdermin family proteins and caspases, participates in tumor cell death and influences the tumor microenvironment via release of interleukin-1β and interleukin-18, offering potential targets for targeted therapy. Furthermore, strategies such as SDG-induced pyroptosis and NLRP3 inflammasome inhibition demonstrate novel therapeutic potential for colorectal cancer, promising more personalized and efficient treatment options for patients.

However, current research has limitations: most mechanistic explorations are based on cellular or animal models, with clinical translation efficacy and safety yet to be validated; the cross-regulatory network between inflammatory carcinogenesis and pyroptosis remains incompletely understood, such as the differential effects of various inflammatory factors on pyroptosis requiring deeper analysis.

Future research should focus on three aspects: First, expand clinical sample validation to promote clinical trials of candidate compounds such as SDG and GL-V9, clarifying their therapeutic value in human colorectal cancer. Second, deepen molecular mechanism research to resolve the dynamic interaction network between inflammatory carcinogenesis and pyroptosis, identifying key regulatory nodes as novel targets. Third, develop specific biomarkers combined with multi-omics technology to improve early diagnosis and prognosis assessment accuracy, and explore combination regimens of pyroptosis inducers with immunotherapy and chemotherapy, providing more comprehensive theoretical support and practical guidance for precision treatment of colorectal cancer.

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