REVIEW

Neutrophils: From Inflammatory Bowel Disease to Colitis-Associated Colorectal Cancer

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Abstract: Inflammatory bowel disease (IBD) is a non-specific inflammatory disease of digestive tract, primarily manifesting as ulcerative colitis (UC) and Crohn's disease (CD). The precise etiology of IBD remains elusive. The interplay of genetic factors, environmental influences, and intestinal microbiota contributes to the establishment of an uncontrolled immune environment within the intestine, which can progressively lead to atypical hyperplasia and ultimately to malignancy over a long period. This colorectal malignant tumor that arises from chronic IBD is referred to as colitis-associated colorectal cancer (CAC). Dysregulation in the quantity and functionality of neutrophils plays a significant role in the onset, progression, and recurrence of IBD, as well as in the transition from IBD to CAC. Neutrophils affect the pathophysiology of IBD through various mechanisms, including the production of reactive oxygen species (ROS), degranulation, the release of inflammatory mediators and chemokines, and the formation of neutrophil extracellular traps (NETs). These processes can induce DNA mutations, thereby facilitating the development of colon cancer. Given the incomplete understanding of the disease mechanisms underlying IBD and CAC, effective treatment and prevention strategies remain challenging. Consequently, a comprehensive review of the functional roles of neutrophils in IBD and CAC is essential for advancing our understanding of IBD pathogenesis and identifying potential therapeutic targets.

Keywords: inflammatory bowel disease, colitis-associated colorectal cancer, neutrophil, neutrophil extracellular traps

Introduction

Inflammatory bowel disease (IBD) is a non-specific inflammatory disease of the digestive tract, primarily manifesting as ulcerative colitis (UC) and Crohn's disease (CD). Despite significant advancements in medical science and clinical practice, the precise etiology of IBD remains elusive. The intricate interaction between genetic predispositions and environmental influences contributes to the challenges faced in elucidating the underlying causes of IBD. Additionally, dysregulation of immune responses, damage of the intestinal barrier, and alterations in gut microbiota further complicate the disease's pathophysiology, presenting substantial obstacles to research on IBD's pathological mechanisms. Although IBD is not typically a direct cause of death, it is recognized as a precancerous condition associated with colorectal cancer (CRC), particularly in the case of UC, thereby representing a significant contributor to the incidence of malignant tumors.[1] Colitis-associated colorectal cancer (CAC) is a malignant tumor that arises from chronic IBD. The dysregulation of the immune system is a significant factor contributing to the onset, progression, and recurrence of IBD, and it may also play a role in the transformation of IBD into CAC. Neutrophil infiltration, a critical component of the innate immune response to pathogens, is a prominent pathological characteristic observed during active stage of IBD. Previous studies have indicated that neutrophils can influence the disease trajectory of IBD through mechanisms such as the production of reactive oxygen species (ROS),[2] degranulation,[3–5] the release of inflammatory mediators and chemokines,[6] and the formation of neutrophil extracellular traps (NETs).[7] These processes can induce DNA mutations, thereby facilitating the development of colon cancer. Given that the underlying mechanisms of IBD and CAC remain incompletely understood, effective treatment and prevention strategies are challenging to establish. Current therapeutic options often fail to

adequately halt disease progression and may even exacerbate the condition due to adverse drug effects. Consequently, a comprehensive review of the functional roles of neutrophils in IBD and CAC is essential for advancing our understanding of the pathophysiology of IBD and for identifying novel therapeutic approaches.

From Inflammation to Cancer: IBD and CAC
IBD: An Increasingly Complex Interweave of Genetics, Environment, and Microorganisms

Since the initial documentation of IBD in 1859, its incidence has exhibited a consistent upward trend. Although epidemiological evidence shows that the incidence of IBD in developed countries has stabilized or even declined since the early 21st century, the prevalence remains notably high.[8] Conversely, in a broader spectrum of developing countries, the incidence continues to rise at an alarming rate.[8] As a global health concern, IBD imposes significant burdens on economies and healthcare systems worldwide.[9] A contributing factor to this predicament is the ambiguity surrounding the precise etiology of IBD. Current understanding suggests that no singular cause-whether it be genetic predisposition, immune response, environmental factors, or gut microbiota-can comprehensively account for the disease.

First, genetic susceptibility is a critical factor in the pathophysiology of IBD. The risk of developing IBD is significantly elevated among first-degree relatives, particularly parents.[10] And in more extreme instances, the concordance rate for identical twins with IBD ranges from 20% to 60%.[10] In contrast, the concordance rate for fraternal twins is significantly lower, at approximately 3% to 5%, indicating that genetic factors may substantially influence the onset of IBD.[10] Genome-wide association studies (GWAS) have identified over 250 loci associated with an increased risk of IBD; however, only 38 of these loci are thought to be directly involved in the disease's mechanisms, predominantly linked to inflammatory processes and immune responses.[11,12] The recent Activity-By-Contact (ABC) model has predicted that 43 genes located within enhancers may be implicated in IBD, and CRISPR interference experiments have validated that *PPIF* is closely associated with the disease's pathogenesis, as it encodes cyclophilin D and is involved in mitochondrial activity in macrophages.[13] *NOD2/CARD15* is recognized as a significant susceptibility gene for IBD, with mutations in this gene heightening the risk of IBD among Caucasian populations.[10] This pattern recognition receptor (PRR), which is expressed in Paneth cells, neutrophils, and macrophages, activates the NF-κB signaling pathway upon recognizing bacterial cell wall antigens.[10,14] Additionally, *interleukin-23/ interleukin-23 receptor* (*IL-23/IL-23R*) have been identified as risk factors for IBD across both European and non-European populations.[12] Various immune cells, including T cells, neutrophils, and macrophages, can produce IL-23, which interacts with receptors on intestinal epithelial cells (IECs), thereby influencing intestinal barrier integrity, immune homeostasis, and gut microbiota composition.[15] The inflammatory gene profile associated with IBD overlaps with numerous complex autoimmune and immunodeficiency disorders.[16] Furthermore, the extraintestinal manifestations of ulcerative colitis (UC) and Crohn's disease (CD), such as erythema nodosum, pyoderma gangrenosum, ankylosing spondylitis, and peripheral arthritis with negative rheumatoid factor, suggest a distinct relationship between IBD and immune system dysregulation.[17]

Second, the onset and progression of IBD are significantly influenced by environmental factors. While above evidence underscores the importance of genetic predisposition in the manifestation and advancement of IBD, alterations in genetic composition alone do not adequately account for the pronounced geographical disparities and the rapidly escalating incidence of the disease. This observation suggests that environmental influences and epigenetic factors are also critical in the etiology of IBD. Notably, individuals migrating from regions with lower IBD incidence to those with higher rates experience an increased risk of developing the condition; specifically, the risk escalates by 14% for each decade of younger age at migration, indicating that earlier exposure to high-incidence environments correlates with a heightened risk of IBD.[18] Furthermore, the scientific and technological advancements accompanying industrial transformation appear to have a nuanced relationship with IBD incidence, particularly as urbanization alters lifestyle habits. Epidemiological studies have identified several credible risk factors for IBD, including smoking, antibiotic use, and appendectomy, while factors such as physical activity, breastfeeding, tea consumption, and vitamin D intake are recognized as protective.[19] Additionally, some analyses indicate that smoking exerts differential effects on the risk of

colectomy in UC and CD; specifically, smoking is associated with an increased risk in CD patients, whereas cessation of smoking raises the risk in UC patients.[20,21]

Finally, the aforementioned risk factors associated with IBD are largely connected to the composition of the intestinal microbiota; however, establishing a definitive causal relationship between dysbiosis and IBD remains a challenge.[22] Recent commentary posits that changes in gut microbiota may serve as both a contributing factor and a consequence to IBD.[23] Current observational data, including the efficacy of fecal diversion in alleviating affected intestinal segments in patients with CD, the beneficial effects of antibiotics in treating certain forms of IBD, and the observed reduction in microbial diversity among IBD patients, underscore the significant role of intestinal microorganisms in the pathophysiology of IBD.[22] During IBD, dysregulation of innate immunity, particularly involving neutrophils, leads to structural alterations and a loss of microbial homeostasis. Furthermore, microorganisms can modulate neutrophil expression and function, either directly or indirectly.[24] Additionally, systematic screening associations has indicated that the risk of disease linked to specific genetic variations in IBD may be influenced by microorganisms.[24] Numerous genetic markers associated with IBD, such as *NOD2/CARD15*,[25] *ATG16L*1,[26] and *CARD*9,[27] exhibit intricate interactions with both the immune system and the microbiota.[22,28,29] Intestinal microbes may play a role in the variability of IBD risk genes; for instance, *Faecalibacterium prausnitzii* and *g_Roseburia* have been identified as microorganisms capable of modulating *NOD2* variations in recent observational study of feces from IBD patients.[30] Table 1 presents a compilation of IBD susceptibility genes related to neutrophil function (refers to the comprehensive review conducted by Camille Danne et al[24]) and their interactions with gut microbiota.

The interplay among genetic factors, environmental influences, and intestinal microbiota is intricately linked to the dysfunction of the immune system, contributing to the complexity of IBD. The significant involvement of neutrophils in both the onset and progression of IBD is noteworthy (Figure 1). Recent research has indicated that the IBD-associated

Table 1 IBD Susceptibility Genes Associated with Neutrophils

IBD Susceptibility Gene	Function in Neutrophils	Interactions with Microorganisms	Species
STAT3	Regulating the generation/maturation of neutrophils	Microflora invasion into the lamina propria and activate myeloid *STAT3*-dependent signals	Mice[31]
JAK2		The *JAK2/STAT3* signaling pathway can be inhibited to preserve colon homeostasis and the ecology of gut microbes	Mice[32]
CXCR1/CXCR2	Neutrophil recruitment/migration	The intestinal flora's structure changed as a result of the *Cxcr2* deficiency	Mice[33]
CCL2		Colonic epithelial cells' expression of CCL2 is impacted by LPS produced by bacteria	Mice[34]
CCL7		CCL7 levels in serum are elevated following gut microbiota transplantation	Mice[35]
LSP1		A decrease in *LSP1* levels is correlated with an increase in the abundance of the genus *Fusobacterium*	Human[36]
HGFAC		Not reported	-
MMP9		By downregulating *Mmp9*, *C. butyricum* may provide protection against intestinal damage	Mice[37]
		Mmp9-deficient mice did not exhibit a substantial change in the composition of their fecal microbiota	Mice[38]
HCK		Not reported	-
NOD2	Pathogen recognition and phagocytosis	The favorable qualities of *Bacteroides fragilis* that modulate immunity	Mice[24]
		NOD2 risk allele is associated with decreased abundance of *g_Roseburia* and *F. prausnitzii*	Human[30]
FCGR2A/FCGR3A		Recognition of immune complexes and IgG-sensitized gut microbiota or target cells	Mice[39]

(*Continued*)

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Table 1 (Continued).

IBD Susceptibility Gene	Function in Neutrophils	Interactions with Microorganisms	Species
IL1R2 IL18RAP IL-23/IL-23R	Inflammatory response	Il1r2 gene deficiency resulted in a decrease in the relative content of Actinobacteria and Bacilli in feces The genes Il-18, Il-18r1, and Il-18rap, whose products can form a functional complex and transmit the pro-inflammatory signal of Il-18, were closely related to S. Enteritidis Affecting the intestinal barrier, immune balance, and gut microbiota through receptors in IECs	Mice[40] Chicken[41] Human[12]
LRRK2	Inflammatory response and autophagy	When commensal bacteria activate Nod2 in Paneth cells, LRRK2 is recruited to dense core vesicles, which in turn triggers the release of lysozyme and other antimicrobial peptides Loss of Lrrk2 increased the bacterial richness and altered bacterial community structure	Mice[42] Mice[43]
LITAF	Granules maturation	Inflammatory mediators of Litaf mRNA increase in ileal tissue were considerably suppressed by the microbial metabolic byproduct of secondary bile acid deoxycholic acid	Chicken[44]
PTK2B	Degranulation	Not reported	-
CYBA/CYBB NCF4 IFNGR2	ROS	Epithelial deficiency of Cyba resulted in protection from C. rodentium and L. monocytogenes infection Not reported Not reported	Mice[45] - -
PTAFR ATG16L1	Autophagy	Ptafr and S. Enteritidis were closely associated. Fusobacteriaceae were more prevalent in inflamed ileal tissue from patients homozygous for the ATG16L1 risk gene By lowering goblet cells' release of mucin, the T300A mutation leads to disruption of the gut flora	Chicken[41] Human[46] Mice[26]
CARD9	Apoptosis	The intestinal ecology of Card9-deficient mice was enriched in various fungal species, especially Candida tropicalis	Mice[27]

Abbreviations: ATG16L1, Autophagy related 16 like 1; CARD9, Caspase recruitment domain-containing protein 9; CCL, Chemokine (C-C motif) ligand; CXCR, Chemokine (C-X-C motif) receptor; CYBA/CYBB, Cytochrome b-245 alpha/beta chain; FCGR2A/FCGR3A, Fc gamma receptor 2A/3A; HCK, Hematopoietic cell kinase; HGFAC, Hepatocyte growth factor activator; IFNGR2, Interferon gamma receptor 2; IL, Interleukin; IL1R2, Interleukin 1 receptor 2; IL18RAP, Interleukin 18 receptor accessory protein; JAK2, Janus kinase 2; LRRK2, Lipopolysaccharide-induced tumor necrosis factor-alpha factor; LSP1, Lymphocyte-specific protein 1; MMP9, Matrix metallopeptidase 9; NCF4, Neutrophil cytosolic factor 4; NOD2, Nucleotide-binding oligomerization domain containing 2; PTAFR, Platelet-activating factor receptor; PTK2B, Proline-rich tyrosine kinase 2B; STAT3, Signal transducer and activator of transcription 3.

gene *Card9* is expressed in neutrophils and influences colitis in DSS-induced experimental mice by modulating mitochondrial function.[47] Additionally, *Cxcr2*, a receptor gene responsible for neutrophil chemotaxis, has been shown to alter the composition of the gut microbiota in mice when it is defective.[48,49] The excessive infiltration of neutrophils, recognized as a hallmark of IBD, interacts with these multifaceted factors and plays a critical role in the disease's progression. This review aims to elucidate the role of neutrophils in IBD, while the interactions between neutrophils and intestinal microbiota need to be further explored in the future.

CAC: A Malignant Fruit That Grows in the Chronic Inflammation

Recent advancements in endoscopic technology, coupled with lifestyle modifications and smoking cessation efforts, have contributed to a decline in the incidence of CRC in recent years.[50] However, individuals with a chronic history of IBD remain at an elevated risk for progression to cancer.[51] Chronic inflammation is a significant factor in the initiation and progression of malignant tumors. In the context of CRC, long-standing and recurrent intestinal inflammation associated
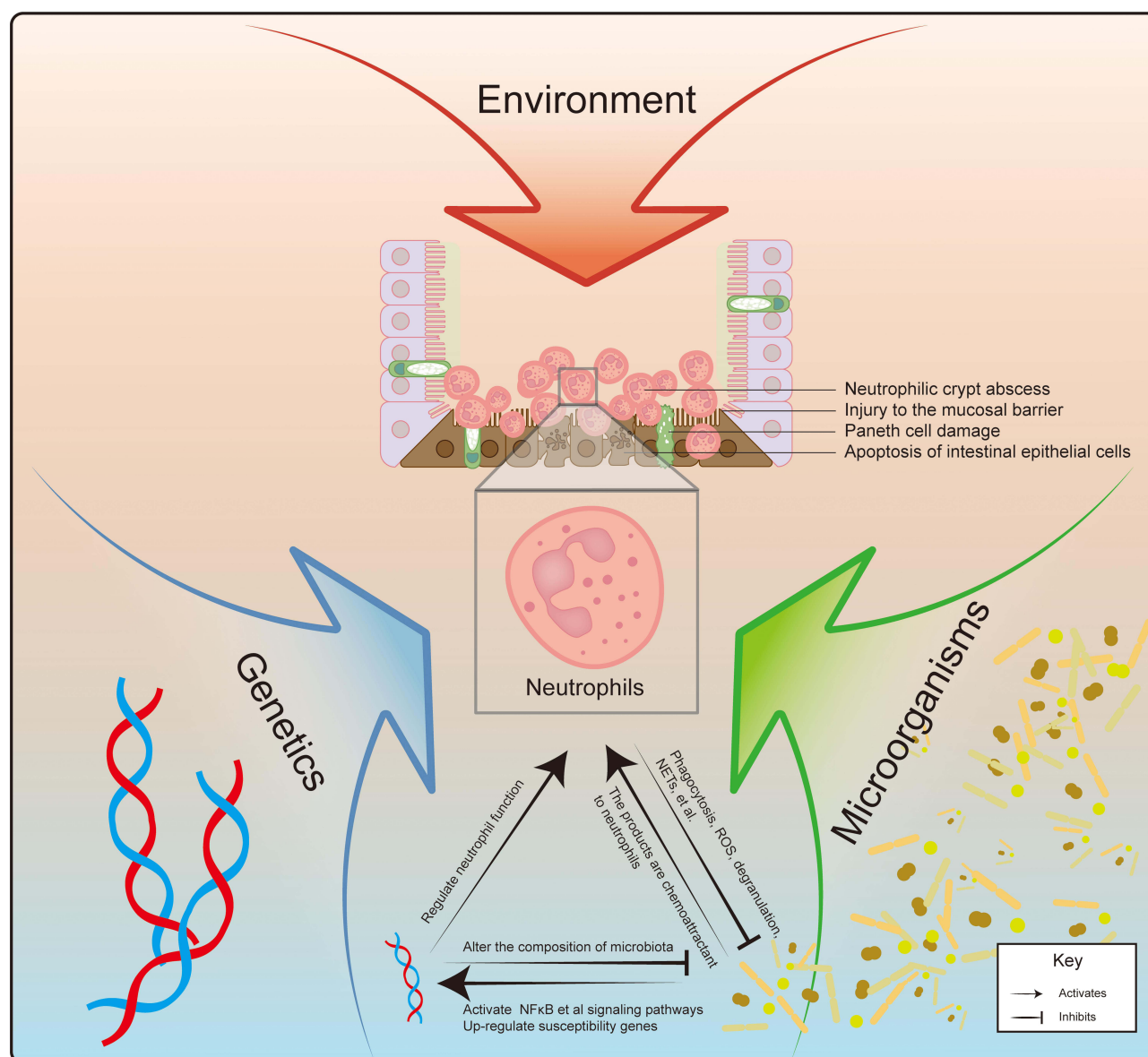
Figure 1 IBD is a multifaceted disorder resulting from a confluence of environmental factors, alterations in gut microbiota, and genetic predisposition. The interplay of these elements leads to the development of intestinal lesions in IBD patients, characterized by Paneth cell injury and apoptosis of IECs, ultimately resulting in mucosal damage and the formation of neutrophilic crypt abscesses. It is likely that the influence of IBD risk gene variants is mediated, at least in part, through their effects on the bacterial microbiota. Modifications in certain IBD susceptibility genes, such as *Cxcr2*, can directly impact the composition of gut flora. Neutrophils serve as critical mediators at the intersection of gut genetics and microbiota. Numerous genes associated with IBD susceptibility are involved in the neutrophil's defense mechanisms against pathogens. Neutrophils play a vital role in limiting microbial dissemination and maintaining microbiota homeostasis. Their production and functional capabilities are regulated both directly and indirectly by microbial factors. Prolonged inflammation leads to significant and sustained neutrophilic infiltration, which alters the intestinal environment, conferring a selective advantage to facultative anaerobic bacteria and promoting the proliferation of *Enterobacteriaceae* within the context of inflammation.[23]

with IBD can lead to atypical hyperplasia, which may subsequently evolve into malignant tumors. The risk of developing CRC in patients with IBD is substantially higher than that observed in the general population.[1,52,53] Furthermore, patients with colorectal cancer associated with IBD exhibit poorer prognoses and higher mortality rates compared to those with sporadic CRC.[54] Notably, long-term UC is particularly prone to progress to CAC, representing a primary cause of mortality among UC patients,[1,55] and effective management of UC can mitigate the risk of CAC.[17] Additionally, individuals with CD face an increased risk of malignancy, particularly those with colonic involvement, who are at a heightened risk for developing CAC.[52] The transition from colitis to colorectal cancer typically spans 16 to 21 years; however, CAC patients with a history of IBD tend to develop malignant tumors approximately 7.7 years earlier than

those with sporadic CRC.[1] Recent research has identified several risk factors for CAC, including extensive involvement of the gastrointestinal tract, low-grade atypical hyperplasia, colonic strictures, primary sclerosing cholangitis, polyps, and a family history of CRC.[56] Conversely, protective factors against CAC include endoscopic surveillance, the use of 5-aminosalicylic acid (5-ASA), and smoking.[56]

In the context of IBD, the prolonged and recurrent nature of the condition can lead to damage to the mucosal membrane and the presence of aberrant white blood cells at the lesion sites, resulting in redox imbalances characterized by an excessive accumulation of ROS. This accumulation not only inflicts direct harm to intestinal microvilli, exacerbating the pathological inflammatory response, but also serves as terminal electron acceptors for anaerobic respiration, thereby facilitating the proliferation of facultative anaerobes.[2,6,57] The abnormal infiltration of neutrophils in IBD appears to heighten the risk of progression to CAC,[58,59] as the ROS released by these cells can induce DNA mutations that contribute to tumorigenesis.[60,61] The transition from colorectal inflammation to cancer follows inflammation-atypical hyperplasia-adenocarcinoma sequence, during which markers associated with DNA double-strand breaks and damage repair progressively increase.[62] In contrast to sporadic CRC, mutations in the p53 gene occur earlier and more readily in normal intestinal tissues affected by CAC,[1] whereas alterations in the APC gene are less frequent and occur later in the progression from IBD to CAC.[51] This distinction underscores the differing mechanisms underlying malignant tumorigenesis in CAC compared to sporadic CRC (Figure 2).

Genetic and epigenetic abnormalities, including chromosome instability (CIN),[63,64] microsatellite instability (MSI),[65,66] DNA hypermethylation,[67,68] DNA glycosylation defects,[69] and aberrant non-coding RNA expression,[70] are closely associated with the development of CAC. Furthermore, the extensive infiltration of dysfunctional immune cells,
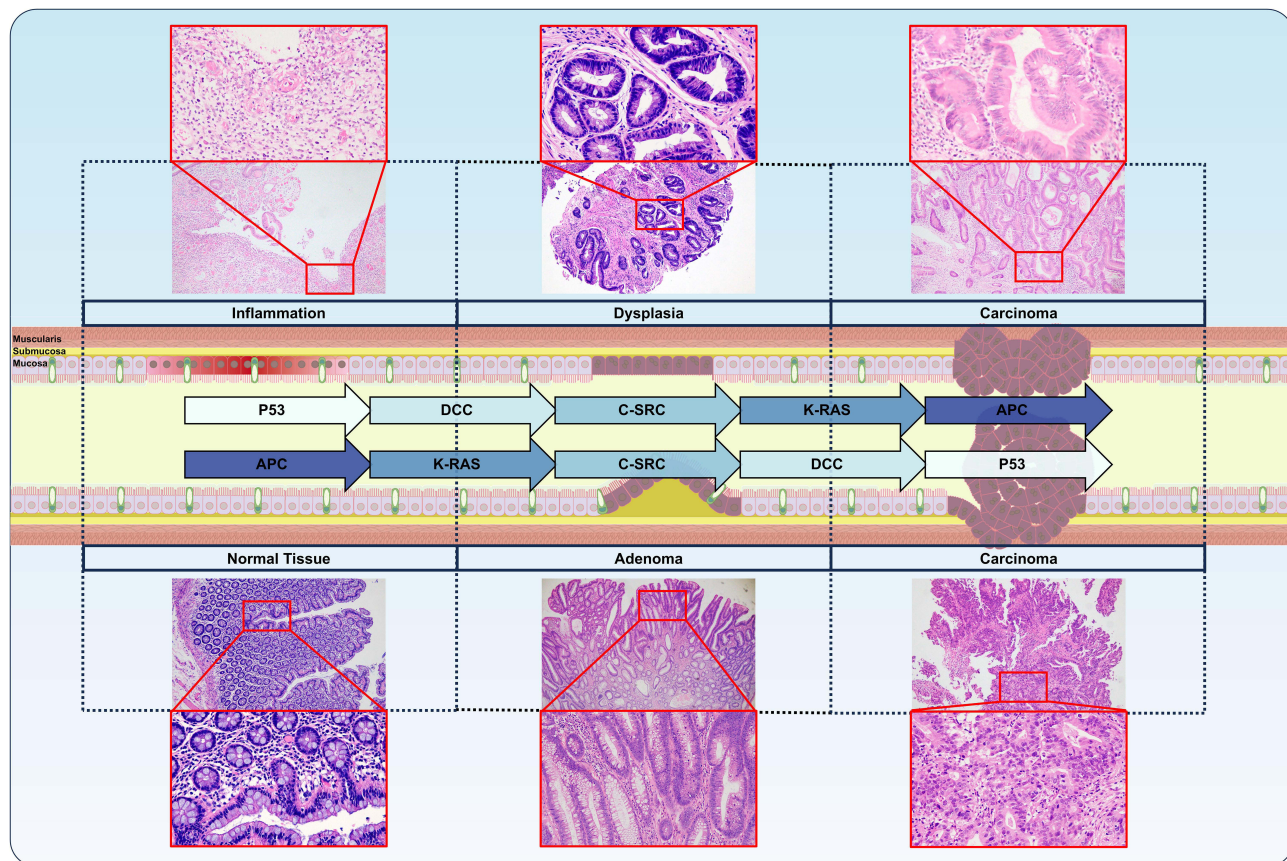

Figure 2 Overview of the variations in tumorigenicity between sporadic CRC and CAC based on IBD. In the inflammation-dysplasia-carcinoma sequence, there is a progressive increase in markers indicative of oxidative damage and DNA double-strand breaks. In the case of CAC, mutations in the p53 gene occur at an earlier stage, while dysfunction of the APC gene is observed at a later stage. Conversely, in sporadic CRC, mutations in the p53 gene arise later, whereas APC gene dysfunction is noted earlier, leading to the formation of a dysplasia-carcinoma sequence.[51] All hematoxylin and eosin (HE) staining images of representative patients included in this article were sourced from the Daping Hospital, Chongqing, China and received approval from the Ethics Committee of the Daping Hospital [Ratification No.: 2024(127)].

along with dysbiosis of intestinal microbiota, can activate nuclear factor κB (NF-κB), a critical factor that exacerbates the disease and facilitates the transition to CAC.[1] Recent studies on pyroptosis have revealed that the stimulator of interferon genes (STING) can collaborate with spleen tyrosine kinase (SYK) to induce pyroptosis in CAC tumor cells within an azoxymethane/dextran sodium sulfate (AOM/DSS)-induced inflammation-cancer transformation model in experimental mice.[71] In addition, pyroptosis results in the release of damage-associated molecular patterns (DAMPs), which promote CAC tumorigenesis through the ERK1/2 signaling pathway.[72]

Moreover, various ways that activate the Wnt/β-Catenin signaling pathway have been implicated in the development of CAC.[73–75] Other molecular mechanisms contributing to the progression of CAC include Toll-like receptors (TLR), the JAK/STAT signaling pathway, the mammalian target of rapamycin complex (mTOR), autophagy, and oxidative stress.[76] As a disease characterized by dysregulated intestinal immunity, IBD is marked by abnormal expression of inflammatory cytokines and the accumulation of immunosuppressive cells within the intestinal milieu, creating an immunosuppressive microenvironment conducive to tumor survival.[67] A recent study identified five differential genes (*AQP9, FCGR3B, GPR109B, PROK2, and S100A12*) in neutrophils from individuals with IBD compared to healthy controls, proposing these genes as biomarkers for the transition from IBD to CAC,[76] thereby establishing a close association between neutrophils and the inflammatory cancer transformation process in IBD.

Neutrophils Regulate IBD and CAC
The Function of Neutrophils

Neutrophils progressively develop bactericidal capabilities throughout their maturation in the bone marrow. Upon entering the bloodstream, these cells, which constitute approximately 60% of the circulating immune cell population, form a critical component of the innate immune system. They play a pivotal role in combating pathogen invasion and initiating inflammatory responses through various mechanisms, including phagocytosis, the production of ROS, degranulation, the formation of NETs, and the recruitment of other immune cells.[6,77] (Figure 3A-C)

Neutrophils possess the ability to identify and engulf pathogens through a diverse array of membrane and intracellular receptors.[79] Following this recognition, they generate superoxide free radicals via respiratory bursts that are facilitated by nicotinamide adenine dinucleotide phosphate (NADPH) oxidase.[80] These superoxide radicals are subsequently converted into hydrogen peroxide and other cytotoxic reactive oxygen species (ROS), which are released within intracellular phagosomes or onto extracellular plasma membranes.[80] Neutrophils also contain a distinct pool of granules that can release various antimicrobial proteins to eliminate pathogens. This release occurs in a specific sequence, beginning with tertiary granules that contain matrix metalloproteinase-9 (MMP9), followed by secondary granules (or special granules) that house lactoferrin, and concluding with primary granules (or azurophilic granules) that contain myeloperoxidase (MPO).[81,82] Furthermore, neutrophils employ NETs as a highly conserved antimicrobial strategy, which involves the formation of an extracellular network composed of DNA and proteins that effectively traps and neutralizes pathogens, thereby preventing their further spread.[7] Upon migration to the site of infection, neutrophils are capable of recruiting various immune cells, including additional neutrophils, to engage in the inflammatory response through the release of a range of cytokines and chemokines.[6] The regulated death of neutrophils is essential for the resolution of inflammation. In addition to apoptosis, neutrophils can modulate the number in the lesion through mechanisms such as necroptosis, necrosis, NETosis, pyroptosis, and phagocytosis, thereby maintaining the homeostasis of the inflammatory response (Figure 3D).[79]

Neutrophils that are isolated via density gradient centrifugation can be categorized into several distinct groups: normal-density neutrophils (NDNs), low-density neutrophils (LDNs), which exhibit either pro-inflammatory or anti-inflammatory characteristics, and tumor-associated neutrophils (TANs), which can further be classified into those with anti-tumor effects (N1 subtype) and those with pro-tumor effects (N2 subtype).[24] Furthermore, polymorphonuclear myeloid-derived suppressor cells (PMN-MDSCs) represent a specialized subset of "neutrophils" found in both tumor and non-tumor conditions, the latter of which encompasses diseases such as systemic lupus erythematosus, multiple sclerosis, rheumatoid arthritis, and IBD. These PMN-MDSCs are often indistinguishable from
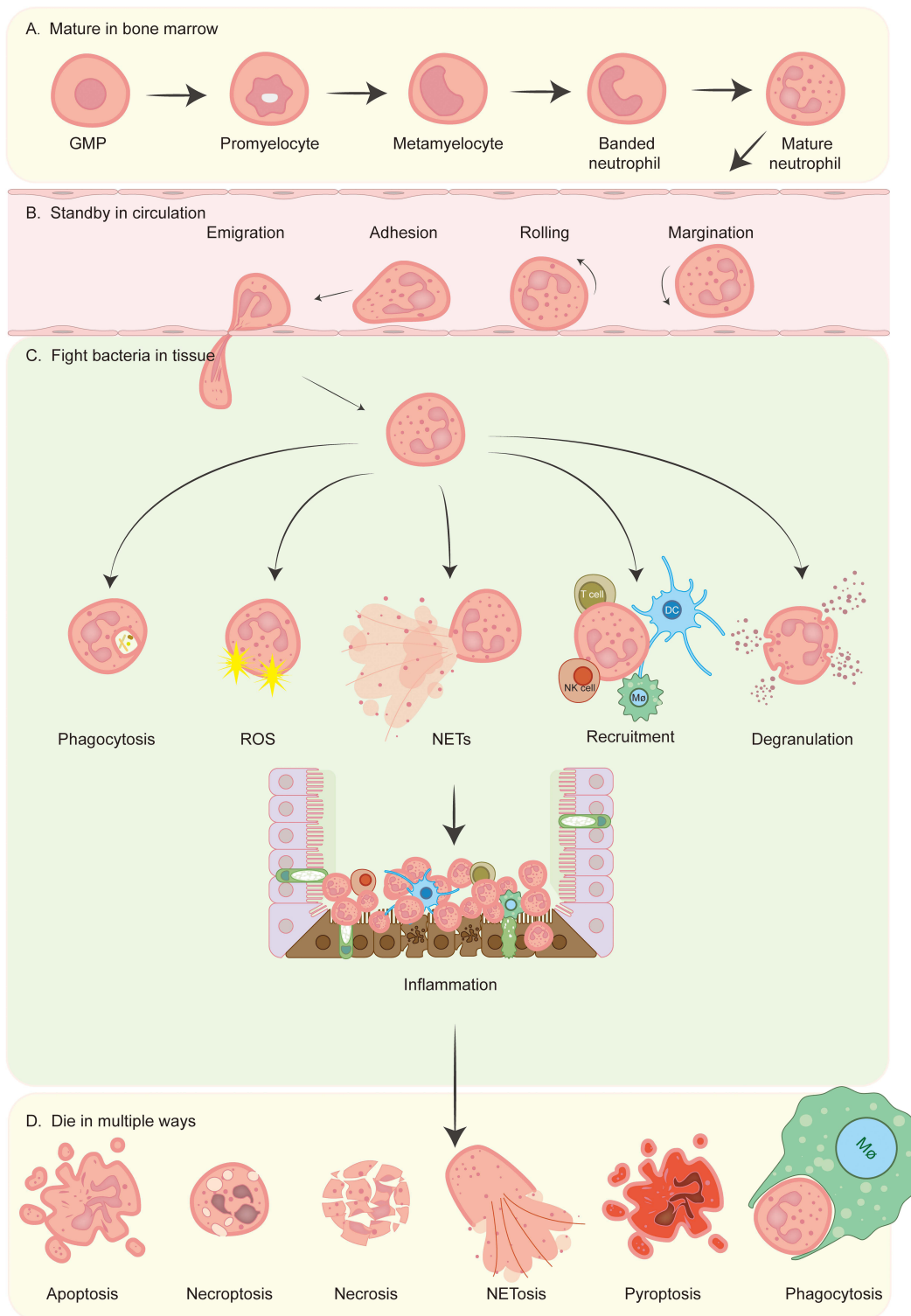
Figure 3 Overview of neutrophil's entire life. (**A**) The differentiation of neutrophils occurs within the bone marrow, where granulocyte-monocyte progenitors (GMPs) are generated from common myeloid progenitors (CMPs), which themselves are derived from hematopoietic stem cells (HSCs). The process of neutrophil generation is regulated by granulocyte-colony stimulating factor (G-CSF) and granulocyte-macrophage-colony stimulating factor (GM-CSF), which guide GMPs through a series of developmental stages, including promyelocyte, myelocyte, metamyelocyte, and band cell, ultimately resulting in the maturation of neutrophils from myeloblasts that then enter the circulatory system.[78] (**B**) Neutrophils present in the bloodstream are activated by chemokines and undergo a series of processes including margination, rolling, adhesion, and migration, prior to exiting the circulatory system. This allows them to accumulate in sites of inflammation through the mechanism of chemotaxis. (**C**) Neutrophils employ various strategies to eliminate pathogenic bacteria at the site of inflammation, including phagocytosis, the production of ROS, the formation of NETs, the recruitment of a diverse array of immune cells (such as dendritic cells (DC), macrophages, T cells, natural killer (NK) cells, and additional neutrophils), and degranulation. (**D**) Neutrophils can undergo cell death through multiple pathways, including apoptosis, necroptosis, necrosis, NETosis, pyroptosis, phagocytosis by macrophages, etc.[79]

conventional neutrophils and possess the ability to inhibit T cells and natural killer (NK) cells through various mechanisms.[83]

The chemotaxis of neutrophils from the bloodstream to localized tissues marks the onset of the inflammatory response. However, inflammation characterized by a predominance of neutrophils may also signify the initiation of chronic inflammatory processes and the potential development of malignant tumors. As research in this area progresses, the role of neutrophils in IBD has become increasingly complex. On one hand, the protective function of neutrophils against intestinal pathogens is significant and cannot be overlooked. Conversely, the abnormal infiltration of neutrophils into intestinal tissues can exacerbate inflammation and contribute to the formation of crypt abscesses. In the context of IBD, the delicate equilibrium that neutrophils strive to maintain is crucial; any disruption of this balance may result in the recurrence or worsening of the disease.

Pathological Mechanism of Neutrophils in IBD

Numerous susceptibility genes associated with IBD are intricately linked to neutrophil functionality, encompassing processes such as pathogen recognition and phagocytosis (*NOD2*), ROS production (*CYBA, CYBB, NCF4, IFNGR2*), mitochondrial-dependent apoptosis (*CARD9*), and autophagy (*ATG16L1*).[24,47] A hallmark of IBD is the excessive infiltration of neutrophils within the intestinal mucosa,[21] which may play a significant role in the disease's pathogenesis.[77,84] Specifically, these aberrantly infiltrated neutrophils contribute to the formation of crypt abscesses, leading to heightened apoptosis of IECs and subsequent impairment of the intestinal barrier[2.] Furthermore, the hyperactivation of neutrophils results in the generation of substantial quantities of ROS, which can rapidly deplete oxygen and nutrients in the surrounding microenvironment, as well as induce lipid peroxidation, thereby compromising the integrity of cellular membranes and organelles.[2,85]

Neutrophil Transepithelial Migration

The onset of intestinal inflammation in IBD prompts IECs to secrete a variety of recruitment signals that facilitate the chemotaxis of neutrophils from the bloodstream to the lamina propria. These signals include cytokines such as IL-8, IL-6, and IL-33, chemokines such as CXCL5, CXCL7, CXCL10, and CCL20, arachidonic acid metabolites including leukotriene B4 (LTB4) and hepoxilin A3 (HXA3), as well as MMPs such as MMP3 and MMP7.[6,86,87] Following this recruitment, neutrophils increase the permeability of the intestinal epithelium by releasing proteolytic enzymes, including neutrophil elastase (NE) and MMPs, thereby facilitating transepithelial migration.[86] This migration serves a dual purpose: it enhances the ability of neutrophils to recognize pathogen antigens and stimulates the immune response; however, it also exacerbates mucosal injury, leading to heightened apoptosis of IECs, which ultimately compromises the integrity of the epithelial barrier.[86] (Figure 4A)

Delayed Apoptosis of Neutrophils

Neutrophils are characterized by a brief half-life of approximately 8 to 12 hours in circulation, which can extend to 1 to 4 days following their migration into tissues.[79] In IBD, the process of neutrophil apoptosis is notably delayed.[92,93] While this prolongation can enhance bactericidal activity, the accumulation of neutrophils poses a heightened risk of damage to normal tissues. The recruitment of neutrophils within the intestines of patients with Crohn's disease (CD) correlates with the severity of the condition,[94] whereas the complete resolution of neutrophils in the intestinal mucosa is associated with improved long-term clinical outcomes in patients with UC.[95] The regulation of neutrophil apoptosis is primarily mediated by integrin receptors.[88] Various cytokines and inflammatory mediators, including IL-1β, IL-6, IL-8, tumor necrosis factor (TNF), interferons (IFN-α, IFN-β, IFN-γ), chemokines such as CXCL1, complement components like C5a, leukotriene B4 (LTB4), granulocyte-macrophage colony-stimulating factor (GM-CSF), and granulocyte colony-stimulating factor (G-CSF) can prolong neutrophil survival by inhibiting apoptosis.[88,89,96] Additionally, factors such as hypoxia, extracellular acidosis, and bacterial product including lipopolysaccharides (LPS), lipoproteins (LP), peptidoglycans (PG), and lipoteichoic acid (LTA) have also been implicated in the delay of neutrophil apoptosis.[88,89] ChemR23 has been linked to drug resistance in IBD immunotherapy; the administration of anti-ChemR23 antibody has been shown to facilitate neutrophil clearance in experimental models of IBD by promoting the transition of pro-inflammatory macrophages (M1)
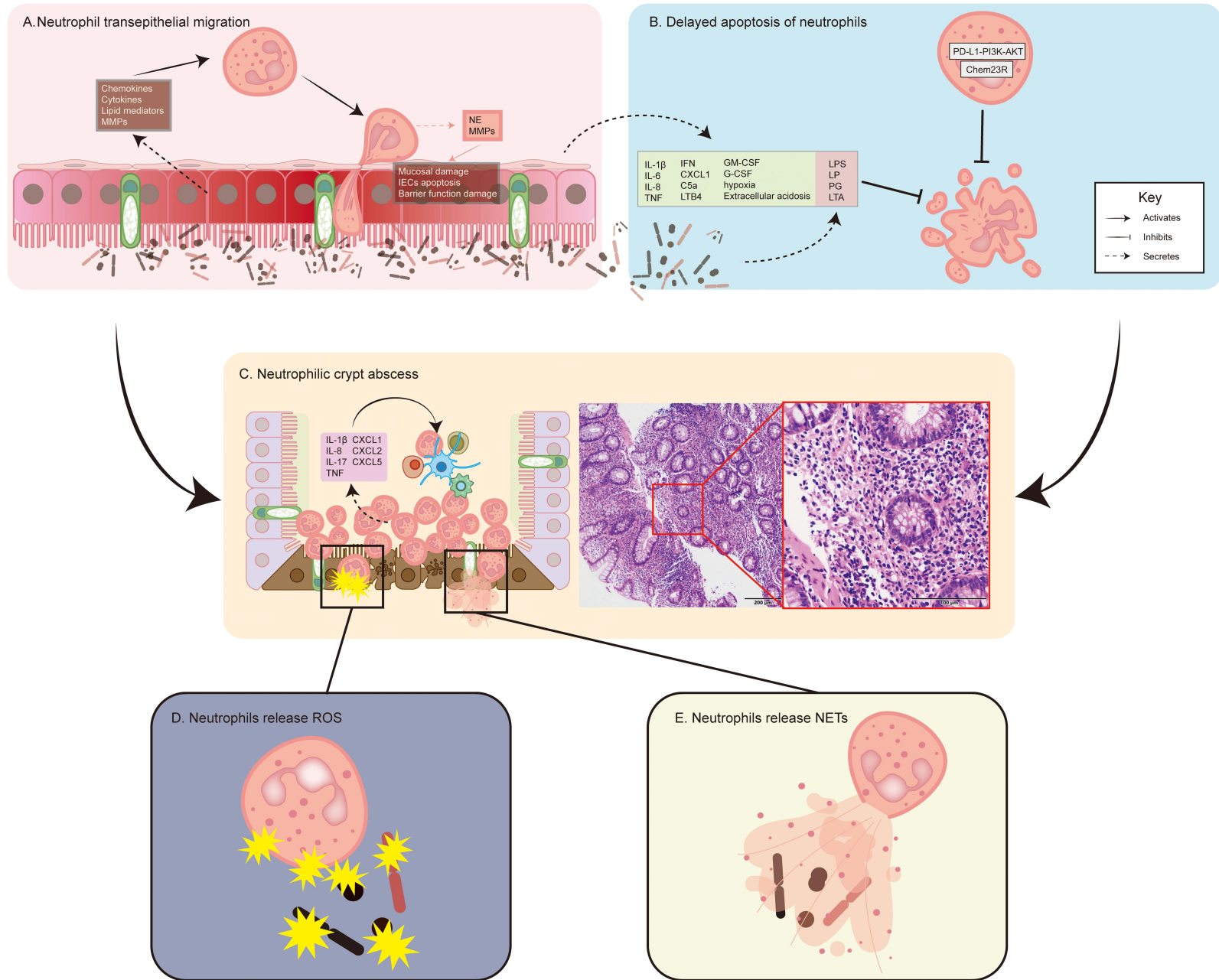
Figure 4 Overview of the pathogenesis of neutrophils in IBD. (**A**) IECs are activated by pathogenic bacteria to release various signaling molecules, including chemokines, cytokines, lipid mediators, and MMPs, which serve to recruit neutrophils to the site of inflammation. This recruitment leads to mucosal damage, apoptosis of IECs, and dysfunction of the intestinal barrier, as neutrophils secrete NE and MMPs that penetrate the intestinal epithelium[86,87] (**B**) The delayed apoptosis of neutrophils may be influenced by several factors, including cytokines, inflammatory mediators, CSF, hypoxic conditions, extracellular acidosis, and LPS, LP, PG, and LTA produced by pathogens.[88,89] Additionally, the ChemR23[90] and PD-L1-PI3K-AKT[91] signaling pathways in neutrophils have been associated with delayed regression. (**C**) The accumulation of neutrophils at the lesion site is a consequence of abnormal aggregation and delayed apoptosis, which ultimately resulting in the formation of a neutrophilic crypt abscess. (**D** and **E**). Neutrophils exhibit dual functionality; they release ROS and NETs that effectively eliminate pathogenic microorganisms. However, excessive inflammation can also result in tissue damage due to the overactivity of these immune responses.

to an anti-inflammatory phenotype (M2).[90] Furthermore, the expression of programmed death-ligand 1 (PD-L1) on neutrophils is upregulated under inflammatory conditions.[97] Recent investigations indicate that the overexpression of PD-L1 in neutrophils, both in humans and mice, can delay apoptosis through the activation of the PI3K-AKT signaling pathway.[91] The extensive infiltration of neutrophils in intestinal lesions, coupled with their delayed apoptosis, contributes to increased neutrophil accumulation and the formation of crypt abscesses, which not only induces local hypoxia but also compromises the integrity of the intestinal barrier, thereby elevating the risk of treatment failure in IBD.[6,21] (Figure 4B)

Neutrophilic Crypt Abscess

Acute inflammation in individuals with IBD is marked by a significant influx of neutrophils into the intestinal mucosa.[21] Delayed apoptosis contributes to the accumulation of neutrophils. Furthermore, neutrophils have the capacity to recruit various immune cells, including monocytes, macrophages, NK cells, DCs, T cells, and additional neutrophils, to the site of inflammation through the secretion of diverse cytokines and chemokines, such as IL-1β, IL-8, IL-17, TNF, CXCL1, CXCL2, and CXCL5, among others.[24] The aggregation of neutrophils within the intestinal environment can damage the integrity of the intestinal epithelial barrier, leading to the formation of crypt abscesses. Proteases released by neutrophils can disrupt cellular junctions, resulting in crypt deformation and the development of abscesses.[24] In contrast to non-IBD intestinal inflammatory conditions, which predominantly feature apoptotic crypt abscesses, the majority of cases of IBD are characterized by neutrophilic crypt abscesses[98] (Figure 4C). Cryptitis and crypt abscesses have become established criteria for the pathological diagnosis and scoring of IBD.[99] Moreover, excessive infiltration of neutrophils is recognized as a contributing factor to the ineffectiveness of IBD treatments.[90]

Neutrophils Release ROS

Neutrophils generate ROS through the action of NADPH oxidase.[100] Furthermore, these immune cells directly influence mitochondrial function via the glycerol 3-phosphate pathway, thereby maintaining mitochondrial polarization and facilitating ROS production.[101] Neutrophils employ respiratory bursts, characterized by the release of ROS, to eliminate pathogens. In the context of IBD, aberrantly activated neutrophils can release excessive amounts of ROS, leading to rapid depletion of oxygen and nutrients in the surrounding environment, as well as inducing lipid peroxidation that compromises cell membranes and organelles.[2] Additionally, extracellular ROS can activate redox-sensitive inflammatory pathways and function as signaling molecules to modulate the inflammatory response.[100] The ROS generated by neutrophils can damage the telomeres of adjacent cells, resulting in increased cellular senescence both in vitro and *ex vivo*.[102] While ROS serves as a crucial mechanism for neutrophils to combat pathogens, chronic inflammation-associated ROS production is linked to an increase in electron receptors (such as nitrates, sulfur oxides, and nitrogen oxides) within the intestines of humans and mice, which may promote the proliferation of facultative anaerobic bacteria and other pathogens.[24] Typically, the levels of intestinal ROS in patients with IBD are elevated compared to those in healthy individuals.[103] However, it has been reported that a reduction in ROS levels due to mutations in the NADPH oxidase gene is associated with refractory Crohn's disease,[104] indicating a need for further investigation into the underlying mechanisms to resolve this apparent contradiction. (Figure 4D)

Neutrophils Release NETs

NETs represent a highly conserved antimicrobial defense mechanism employed by neutrophils, characterized by an extracellular network composed of DNA and proteins that effectively capture and eliminate pathogens, thereby preventing their dissemination[7] (Figure 4E). The proteins found within NETs, such as histones, granule proteins, and various proteases—including the prominent calprotectin S100A8/9—are recognized as significant biomarkers in IBD, constituting approximately 60% of neutrophil cytoplasmic proteins and playing a crucial role in resistance to fungal infections.[7] Under normal physiological conditions, NE and MPO are sequestered within the azurophilic granules of neutrophils.[105] Upon activation, NE translocates to the nucleus from these granules, leading to histone cleavage and subsequent chromatin de-condensation.[105] MPO then binds to chromatin, further facilitating de-condensation, which culminates in cellular rupture and the release of NETs.[105]

The formation of NETs is notably elevated in the intestinal mucosa,[106] feces,[7] and blood[107] of patients with IBD, which cause a positive correlation with disease activity.[108] Furthermore, the stimulation of neutrophils from healthy

individuals with serum derived from patients experiencing active IBD can significantly induce NETs release.[109] CD177$^+$ neutrophils exhibit protective properties in IBD due to their enhanced bactericidal activity, and concurrently producing lower levels of inflammatory mediators such as IL-6, IL-17A, and IFN-γ.[24] In patients with active IBD, there is a marked increase in CD177$^+$ neutrophils within peripheral blood and inflamed mucosa, which are associated with heightened NETs formation.[110] In contrast, CD177-deficient colitis mouse models exhibit more severe colitis, attributed to compromised intestinal barrier function and immune mechanisms.[110] In patients with UC, IL-1β has been shown to modulate NETs formation through an autophagy-dependent mechanism, thereby facilitating NETs generation.[111] Additionally, NETs can induce apoptosis in epithelial cells, compromising the integrity of the intestinal barrier and exacerbating intestinal inflammation in IBD mouse models.[112] In the colon of IBD patients and DSS-induced mice, there is a synchronous increase in the levels of DNase and NETs within the affected areas, alongside the release of NET-associated proteins that damage vascular endothelium.[113] Notably, the concurrent inhibition of high mobility group protein 1 (HMGB1) and DNase I has been shown to significantly reduce the release of NETs-related markers in experimental mouse models.[114] Moreover, hydrogen sulfide may exert anti-inflammatory effects by inhibiting NETs formation and the expression of NF-κB and HMGB1, as demonstrated in rat model of IBD induced by 2,4,6-trinitro-benzenesulfonic acid (TNBS).[115]

NETs have been identified as a factor that elevates the risk of thrombosis in patients with IBD.[107] While NETs serve the purpose of inhibiting the dissemination of pathogens, they also facilitate thrombosis by acting as adhesive structures for platelets, erythrocytes, and various adhesion molecules.[116] Numerous constituents of these structures, such as histones, DNA, NE, and cathepsin G, have the potential to activate platelet function and promote coagulation through the stimulation of both intrinsic and extrinsic coagulation pathways.[116] Patients diagnosed with UC and CD exhibit a threefold increased risk of thromboembolic events compared to healthy individuals.[117] Recent in vitro investigations have demonstrated that LINC00668, present in exosomes, enhances the translocation of NE from cytoplasmic compartments to the nucleus via its interaction with NE, thereby promoting the release of NETs and subsequent thrombosis.[116] Furthermore, the application of DNase I has been shown to diminish disease activity indices and thrombotic events in mouse models of colitis.[107] In conclusion, the release of NETs by neutrophils in the context of IBD contributes to the impairment of the intestinal barrier by inducing apoptosis in IECs, thereby heightening the risk of thrombosis.

Neutrophils are Potential Therapeutic Targets for IBD

In the management of IBD, no definitive pharmacological cure has been identified. The primary objectives of current therapeutic strategies are to alleviate symptoms and prevent disease recurrence.[17] 5-ASA, commonly referred to as mesalamine, is a traditional medication utilized in the treatment of IBD. It functions as a non-steroidal anti-inflammatory agent, mitigating intestinal mucosal inflammation through the inhibition of prostaglandin and leukotriene synthesis. Nevertheless, 5-ASA is not devoid of risks, as patients may experience adverse effects such as abdominal pain, fever, joint pain, and allergic reactions. Clinically, the efficacy of 5-ASA is limited, with an effective response rate of only 65%, and approximately 50% of patients are able to sustain remission, particularly those with severe manifestations of the disease.[118] Furthermore, the effectiveness of 5-ASA in conjunction with biological agents or immunomodulators for maintaining remission in Crohn's disease has yet to be substantiated.[17,52] The use of corticosteroids in patients unresponsive to 5-ASA carries a significant risk of side effects, providing symptomatic relief in only 46% of cases, without contributing to sustained remission or recurrence prevention.[17,119] Endogenous antioxidants present in the gastrointestinal tract have the potential to mitigate mucosal injury, facilitate healing, and reduce ulceration;[2] however, their clinical application in IBD remains limited. Other natural antioxidants, such as resveratrol and curcumin, face challenges including high renal clearance rates, non-specific distribution, and low therapeutic efficacy.[57] For patients exhibiting resistance to 5-ASA or those with severe disease, immunosuppressive or corticosteroid therapies are recommended, with azathioprine being a viable option for preventing IBD recurrence and maintaining remission in corticosteroid-dependent individuals.[17] Nonetheless, these treatments necessitate careful consideration due to the associated risks of infection, long-term medication side effects, and potential serious complications.

Conventional therapies for IBD do not specifically address neutrophils, which play a critical role in the pathogenesis of the condition. Neutrophils are integral to the regulation of intestinal inflammation in IBD.[120] Notably, excessive

Table 2 Some Exploring Neutrophil Targets for IBD Therapy

Drugs	Classes	Mode of Action	Species
LXA4, MaR1, RvE1/D2/D5, Protectin D1	SPM	By encouraging the regression of immune cells, including neutrophils, regress intestinal inflammation	Mice[123]
Cl-amidine, Streptonigrin	PAD4 inhibitors	Inhibit PAD4, DNase I, and citrullinated protein antibodies to target NETs	Mice[124]
Butyrate	Microbial metabolite	Suppresses neutrophil migration and NETs formation	Mice[125]
SM934	Artemisinin analogues	Improves intestinal inflammation by inhibiting immune cells such as neutrophils	Mice[126]
Cyclosporine	Immunosuppressant	Regulates neutrophil function through the SIRT6-HIF-1α-glycolytic axis	In vitro[127]
NAC, 5-ASA	Classic Drugs	Regulates the release of ROS from neutrophils	Mice,[128] In vitro[129]
Nitroxides	MPO inhibitors	Nitroxides display anti-inflammatory and antioxidant activities	Rat[130]

Abbreviations: 5-ASA, 5-amino salicylic acid; LXA4, Lipoxin A4; MaR1, Maresin 1; NAC, N- acetylcysteine; PAD4, peptidylarginine deiminase 4; Rv, Resolvin; SPM, Specialized pro-resolving mediators.

infiltration of neutrophils has been linked to the development of tolerance to anti-TNF therapies and other forms of immunotherapy.[90] The progression of IBD may be mitigated by inhibiting leukocyte migration to the intestine or by utilizing antibodies to antagonize neutrophils in experimental murine models.[6,16] Anti-TNF-α therapy, specifically infliximab, has been employed in the management of IBD. Clinical evidence indicates that this treatment can significantly reduce neutrophil infiltration in the inflamed mucosa of IBD patients and suppress the production of pro-inflammatory mediators, including ROS, calprotectin, IL-8, IL-6, and TNF-α.[121] Neutrophil adsorption therapy has received approval for the treatment of IBD in several countries and has been shown to decrease inflammatory levels and alleviate parenteral symptoms in affected individuals.[122] Table 2 provides a summary of key research focused on targeting neutrophils for IBD treatment, and the need for further clinical trials to validate these findings and assess their therapeutic efficacy.

In the investigation of therapeutic approaches aimed at neutrophils, it is important to note that mere inhibition of these cells may not yield the intended therapeutic outcomes.[23] This is attributable to the essential function of neutrophils in controlling pathogens within the immune system. Consequently, treatments that induce neutrophil deficiency could potentially counteract the intended treatment objectives. Therefore, a more promising avenue for developing treatment strategies for IBD may involve the regulation of hyperactivated neutrophils to facilitate their appropriate resolution, rather than merely diminishing their population.

Neutrophils in the Transformation from IBD to CAC

Chronic inflammation is known to facilitate the renewal of epithelial cells, thereby exerting selective pressure on mutant clones. This phenomenon is associated with an increased propensity for cancer, as it elevates the rate of DNA mutations while simultaneously fostering epigenetic alterations.[131] Inflammatory processes involving neutrophils can disrupt the balance of intestinal microbiota, leading to ecological disturbances that contribute to CAC through the production of reactive metabolites and carcinogens, as well as damage to the epithelial barrier.[132] Neutrophils, as pivotal cells in the inflammatory response, play a significant role in the progression from IBD to CAC.[133] The neutrophil/lymphocyte ratio has emerged as a prognostic marker indicative of poor overall survival in cancer patients.[81] Furthermore, excessive neutrophil infiltration in IBD not only exacerbates inflammation and promotes tumorigenesis through aberrant lipid metabolism[77] but also facilitates cancer development by inducing cellular stagnation and replication errors.[59] Research indicates that patients with UC exhibiting heightened neutrophil infiltration are at an increased risk of developing CAC.[76] The multifaceted roles of neutrophils, including the production of reactive oxygen species (ROS) and neutrophil extracellular traps (NETs), have been implicated in the pathogenesis of colorectal malignancies.

ROS have been shown to facilitate tumor growth and regulate various processes associated with tumor proliferation, including anti-apoptotic mechanisms, epithelial-mesenchymal transition (EMT), and angiogenesis.[134] This regulation

occurs through interactions with several key signaling pathways, such as PI3K/Akt/mTOR, RAS/ERK, JNK/p38, NF-κB, HIF, and Src kinase.[134] In mice model of CAC, the silencing of Glutathione peroxidase 4 (GPX4), an enzyme responsible for the detoxification of ROS, results in increased tumor invasiveness.[61] Additionally, MMP9, a zinc-dependent endopeptidase that targets extracellular matrix proteins, is associated with reduced levels of ROS, diminished DNA damage, and enhanced activation of the mismatch repair pathway in CAC mouse models, thereby inhibiting tumorigenesis via the p53 signaling axis.[135] Furthermore, ROS generated by neutrophils can contribute to cancer metastasis, angiogenesis, and immunosuppression within the tumor microenvironment.[134,136] In chronic inflammatory conditions, neutrophils can induce DNA mutations through the release of ROS, thereby promoting tumor initiation, progression, and metastasis.[60,61,137,138]

NETs are present at elevated levels in tissue and blood samples from patients with CRC,[139] and this elevation is associated with a poor prognosis for individuals undergoing radical resection of CRC.[140] In murine models, the presence of NETs increases in response to LPS induction,[140] and these structures facilitate the capture and transfer of platelet-tumor cell aggregates, thereby contributing to the metastasis of CRC.[141] Additionally, NETs promote tumor growth and metastasis indirectly through mechanisms such as angiogenesis, which is characterized by epithelial-mesenchymal transition (EMT)-related cell migration, degradation of basement membrane proteins mediated by MMPs, and the entrapment of CRC cells.[139]

MPO, a heme peroxidase, is one of the most prevalent proteins found in neutrophils. It is primarily located within the primary granules of these cells and is released following neutrophil activation.[76] Elevated levels of MPO in NETs contribute to oxidative stress in epithelial cells, which in turn aggravates DNA damage and increases the likelihood of mutations.[76] Patients exhibiting high levels of MPO-DNA demonstrate a heightened risk of postoperative infections and a reduced overall survival rate when compared to those with lower MPO-DNA levels.[140] Furthermore, the expression of MPO is significantly greater in the AOM/DSS-induced CAC animal model than in the DSS-induced IBD model.[76]

MDSCs represent a dysfunctional subset of neutrophils in the context of cancer, which poses challenges in differentiating them from conventional neutrophils. MDSCs are widely recognized as significant contributors to the ineffectiveness of immunotherapy across various malignancies.[142] The presence of chronic inflammation leads to the recruitment of numerous immunosuppressive cells, including MDSCs and N2 subtype TANs, thereby establishing an immunosuppressive microenvironment that facilitates tumor survival.[143,144] MDSCs exert their immunosuppressive effects on T cells through the production of ROS-dependent peroxynitrite (ONOO⁻), which further supports tumor viability.[134] Research has demonstrated an increase in MDSC populations in IBD, correlating strongly with the severity of intestinal inflammation.[145,146] In mouse models, the progression from inflammation to cancer in the colon is associated with an accumulation of MDSCs regulated by GM-CSF within the lesions.[147] Notably, the depletion of MDSCs has been shown to mitigate the transition from IBD to CAC in experimental mice.[148] Research indicates that a deficiency in STAT1 results in diminished recruitment of neutrophils and MDSCs during the initial phase of AOM/DSS-induced CAC in murine models, consequently delaying tumorigenesis.[149] Furthermore, the inhibition of neutrophil chemokines has been shown to impede disease progression in CAC model mice. The APE1-NF-κB-CXCL1 signaling pathway in intestinal epithelial cells plays a significant role in modulating the chemotaxis and functionality of neutrophils, thereby exacerbating the progression of IBD.[150] The chemokine CXCL1, which is associated with neutrophil recruitment, has been implicated in promoting CAC by recruiting MDSCs and inducing immunosuppressive mechanisms in mice subjected to AOM/DSS treatment.[151,152] CXCL5, similar to CXCL1, functions as a ligand for CXCR2 and is capable of recruiting neutrophils via its interaction with the CXCR2 receptor, thereby playing a role in the progression of CAC.[133] Furthermore, the inhibition of IL-17 in CAC mouse models results in a reduction of neutrophil recruitment to intestinal tissues, as well as a decrease in the expression of inflammatory mediators and the intestinal signal transducer and activator of transcription (STAT3).[149] This inhibition also leads to diminished expression of arginase-1 (ARG1) and inducible nitric oxide synthase (iNOS) in the colon, both of which are associated with the immunosuppressive functions of MDSCs.[149] Additionally, the intestinal microbiota has been shown to enhance the immunosuppressive capabilities of MDSCs, thereby contributing to the development of CAC.[153]

Recent investigations into the role of neutrophils in CAC have yielded promising findings. The administration of anti-ChemR23 antibody has been shown to inhibit the transformation of IBD to CAC in AOM/DSS-induced mouse models.[90]

Furthermore, CD177^{+} neutrophils have been identified as playing a crucial role in suppressing the tumorigenesis of IECs in mice with IBD, serving as an independent prognostic factor for patients diagnosed with colorectal cancer.[154] Additionally, α-1 antitrypsin (α-1-AT) has demonstrated efficacy in reducing neutrophil populations in CAC mouse model,[155] as well as preventing the progression from IBD to CAC and inhibiting the advancement of established CAC through the inhibition of neutrophil-activated serine protease.[156] Moreover, calcitonin S100a9 has emerged as a significant pro-inflammatory mediator in both acute and chronic inflammatory processes, contributing to persistent inflammation that may lead to carcinogenesis. Targeting S100a9 could potentially mitigate the risk of tumorigenesis in CAC within AOM/DSS-induced mouse models.[54] (Figure 5)

The intricate mechanisms underlying the development of CAC remain inadequately understood, complicating both prevention and treatment strategies. Meta-analysis indicates that 5-ASA may reduce the risk of malignant tumor progression in individuals with IBD.[157–159] Conversely, another analysis suggests that 5-ASA does not effectively halt the progression of CAC.[160] Furthermore, natural antioxidants, including water-soluble vitamins, selenium, and β-carotene, exhibit minimal preventive effects in individuals at high risk for CRC.[1] Although the use of anti-TNF-α monoclonal antibodies in the management of IBD has been shown to mitigate the severity of inflammation,[161] there is a lack of substantial evidence supporting their efficacy in preventing CAC in humans.[1,17] Patients diagnosed with severe IBD accompanied by atypical hyperplasia or malignant tumors require surgical intervention. The associated risks and potential complications of such procedures underscore the critical importance of early intervention in the management of IBD.

Discussion and Prospect

IBD is a multifactorial condition characterized by a dysregulated intestinal immune environment, which arises from the interplay of genetic, environmental, and microbiotic factors. Over time, this dysregulation can lead to atypical hyperplasia and ultimately cancer. While neutrophils are not the sole contributors to IBD, their significance in the pathophysiology of the disease is substantial. Neutrophils function as a double-edged sword in the context of IBD; they play a crucial role in controlling bacterial proliferation, yet an excessive immune response can result in detrimental outcomes. Abnormalities in neutrophil numbers and functions lead to their infiltration into the intestinal mucosa, where they recruit various immune cells, including additional neutrophils, through the release of diverse mediators. This accumulation is exacerbated by resistance to apoptosis, culminating in the formation of crypt abscesses within intestinal lesions. During this process, the integrity of the intestinal epithelial barrier is compromised by ROS, NETs, and proteases released by neutrophils. IBD is characterized by a chronic course punctuated by periods of remission and acute exacerbation.[162] The persistent assault by neutrophils on the intestinal tissue over the disease's progression can ultimately result in the development of irreversible malignancies.

CAC is a multi-stage disease influenced by various cells within the tumor microenvironment. The role of chronic inflammation resulting from IBD is a critical aspect of CAC research that cannot be ignored. A pertinent question arises: at what stage can a disease characterized by persistent intestinal inflammation be classified as malignant? Identifying specific temporal markers to accurately predict and differentiate these stages is a complex challenge. Throughout the progression of CAC, there exists a dynamic interplay between neutrophils (or their various subtypes) and intestinal epithelial or tumor cells. For instance, during acute inflammation, neutrophils migrate from the intestinal mucosa, and in chronic inflammation, neutrophils exhibit resistance to apoptosis, which damage the intestinal epithelial cells while killing the pathogen. Additionally, TANs are prominent during tumorigenesis, NETs are involved in tumor metastasis, and MDSCs are present within the tumor microenvironment. Furthermore, neutrophils engage in intricate interactions with other immune cells and gut microbiota. Consequently, the investigation of neutrophils at specific temporal intervals is insufficient for comprehensively understanding the cell-to-cell interactions that occur during the progression of CAC, and the precise determination of such temporal markers remains unclear.

As previously noted, the transition from IBD to CAC typically spans approximately 20 years, with each episode of relapse and remission in IBD contributing to the dynamics of neutrophil accumulation and regression. Numerous studies have indicated a gradual increase in the risk of CAC correlating with the duration of IBD;[163] however, it is important to recognize that not all individuals with IBD will ultimately progress to CAC. Distinguishing between patients with
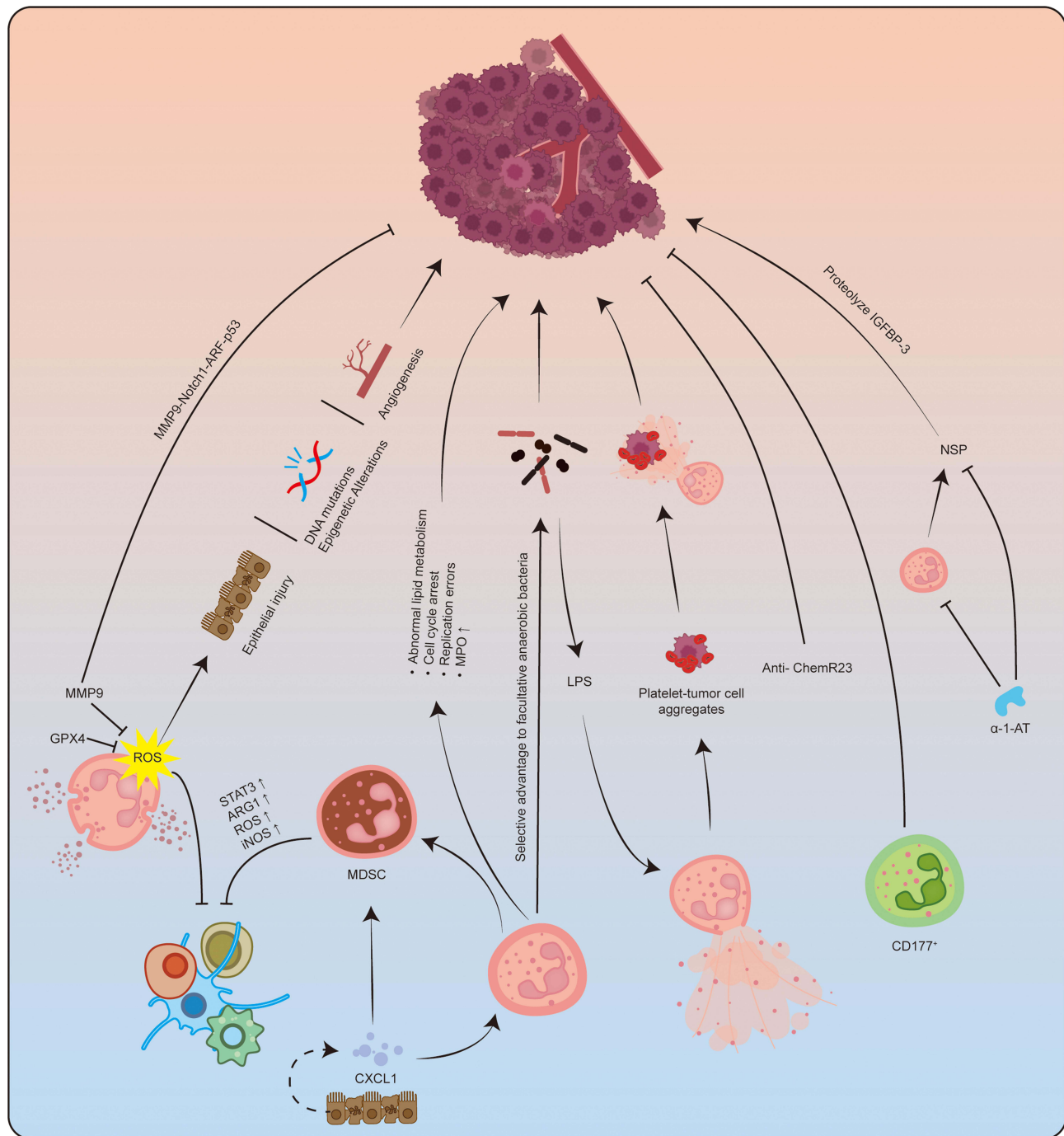
Figure 5 Overview of neutrophils in CAC. Neutrophils play a crucial role in the regulation of the development, progression, and metastasis of CAC through a series of intricate signaling pathways. ROS generated by neutrophils have been implicated in the promotion of CAC through various mechanisms, including the induction of epithelial cell damage, DNA mutations, epigenetic alterations, modulation of angiogenesis and immune suppression. The proteins GPX4 and MMP9 are correlated with diminished levels of ROS. Furthermore, MMP9 has the capacity to inhibit CAC via the MMP9-Notch1-ARF-P53 signaling pathway. Intestinal epithelial and tumor cells secrete neutrophil chemokines, such as CXCL1, which facilitate the increased infiltration of neutrophils and MDSCs. MDSCs contribute to the establishment of an immunosuppressive tumor microenvironment through multiple pathways, thereby enhancing the survival of CAC. Additionally, neutrophils may promote CAC through dysregulated lipid metabolism, which can lead to cell cycle arrest and replication errors, as well as the upregulation of MPO. The bactericidal functions of neutrophils confer a selective advantage to facultative anaerobes. Moreover, bacterial LPS can stimulate neutrophils to release NETs, which have the potential to capture aggregates of platelets and tumor cells, thereby facilitating CAC metastasis. The administration of anti-ChemR23 antibodies has been shown to impede the progression from chronic colitis to colorectal cancer. In murine models of IBD, CD177^{+} neutrophils have been observed to suppress tumorigenesis in intestinal epithelial cells. Additionally, alpha-1 antitrypsin has been demonstrated to decrease neutrophil populations in CAC model mice and to inhibit the transition from IBD to CAC by obstructing the activation of neutrophil serine proteases, thereby preventing the further progression of established CAC.

chronic IBD and those who develop CAC presents a significant challenge, as it remains uncertain whether a certain patients with chronic IBD will inevitably progress to CAC. Variations in genetic predisposition may play a crucial role in the development of CAC, while recurrent episodes of acute inflammation, primarily involving neutrophils, may facilitate tumorigenesis to some extent. A retrospective study may be feasible by analyzing samples of IBD phase from patients with established CAC, but several uncertainties persist. These include the regularity of endoscopic sampling intervals. In instances where samples are collected only during episodes of inflammation recurrence, significant uncertainties arise regarding the potential impact of acute inflammation on chronic inflammatory processes. Specifically, fluctuations in gene expression, immune cell infiltration, and alterations in gut microbiota associated with acute inflammation may confound the underlying chronic inflammation. Moreover, it is noteworthy that a limited number of IBD patients undergo colonoscopy during remission periods between flare-ups, which does not preclude the possibility of DNA damage occurring in the intestinal tissue during remission, potentially leading to dysplasia or malignancy. The dynamics of neutrophil changes within the intestinal tissue during this timeframe remain poorly understood. Additionally, challenges in the clinical study of the progression from IBD to CAC include determining whether samples were consistently obtained from the same anatomical site and whether these samples were adequately preserved over a nearly two-decade span.

Furthermore, the recognized methodology for developing a mouse model of CAC typically involves the administration of the carcinogenic agent AOM in conjunction with the inflammatory agent DSS.[164] Alternative models include those induced by various chemical agents or through genetic modifications.[165] It is important to acknowledge that, while these mouse models are widely regarded as representative of CAC, they still exist significant differences from human IBD and CAC. Additionally, the duration required for the establishment of these models ranges from 10 to 40 weeks.[166,167] The determination of specific time points for research purposes remains a topic of ongoing debate. Inflammatory agents such as DSS can induce acute intestinal inflammation, and the repeated induction of such acute inflammatory responses may lead to sustained chronic inflammation within the murine intestine. During DSS-induced acute inflammation, there is a substantial accumulation of neutrophils, which subsequently diminish following the cessation of the treatment.[150] However, with repeated DSS exposure, neutrophils that exhibit resistance to apoptosis infiltrate the intestinal tissue and differentiate into immunosuppressive subsets. Given that IBD serves as a precursor to CAC, it appears that the role of chronic inflammation in tumorigenesis is more pronounced, as chronic inflammation is associated with the accumulation of DNA damage. Consequently, it is imperative to consider whether and how the influence of acute inflammation on the overall disease should be excluded when collecting samples and analyzing genetic alterations during tumorigenesis. Another critical consideration is animal welfare; the development of the aforementioned mouse model is time-intensive and can result in adverse health effects, including weight loss, diarrhea, and hematochezia, which are detrimental to the well-being of the animals involved.[166]

It seems difficult to answer the question perfectly enough: how neutrophils influence the progression of IBD to CAC. Initially, the relationship between intestinal epithelial or tumor cells and immune cells, such as neutrophils, can be analogously described using the metaphor of seeds and soil. In this analogy, the seed represents the potential for growth, while the soil influences the rate and timing of that growth. Historically, research has predominantly concentrated on the genetic alterations occurring in intestinal epithelial cells as they transition into tumor cells, with comparatively limited investigation into the interactions between these "seeds" and the "soil". Furthermore, CAC is recognized as a multi-stage disease. Chronic inflammation is both a characteristic of IBD and the initiating stage of CAC. Consequently, IBD can be viewed as an integral component of CAC, complicating the ability to distinctly differentiate between the two conditions. The progression of CAC is characterized by a dynamic continuum that includes chronic inflammation, atypical hyperplasia, and ultimately, malignant tumor formation. Within this continuum, it is challenging to pinpoint specific demarcations that separate these stages. Traditional research methodologies often involve the establishment of fixed time intervals for sampling from CAC patients or animal models, which fails to account for the dynamic nature of the disease, particularly the fluctuations associated with the recurrence and resolution of inflammation. This represents a critical gap that necessitates further exploration in contemporary studies.

Lastly, returning to the seed versus soil metaphor, advancements in methodological approaches have significantly enhanced the understanding of the interplay between tumors and immune cells. The evolution from traditional techniques

such as flow cytometry and immunohistochemical staining to more sophisticated methods, including single-cell sequencing, multiplex immunohistochemical staining, and organoid cultures, has the potential to elucidate the intricate relationship between neutrophils, IBD, and CAC. Future research endeavors are anticipated to provide a comprehensive understanding of this complex landscape.

In summary, numerous studies have investigated the impact of neutrophils on IBD; however, their role in CAC remains inadequately understood. The complexity of the disease mechanisms contributes to the incomplete elucidation of the etiology of IBD and its associated malignancies. Nevertheless, neutrophils may offer a novel avenue for clarifying these mechanisms and could emerge as potential targets for the prevention and treatment of both IBD and CAC.

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