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Dual role of CD177 + neutrophils in inflammatory bowel disease: a review

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Abstract

Inflammatory bowel disease (IBD) represents a group of recurrent chronic inflammatory disorders associated with autoimmune dysregulation, typically characterized by neutrophil infiltration and mucosal inflammatory lesions. Neutrophils, as the earliest immune cells to arrive at inflamed tissues, play a dual role in the onset and progression of mucosal inflammation in IBD. Most of these cells specifically express CD177, a molecule increasingly recognized for its critical role in the pathogenesis of IBD. Under IBD-related inflammatory stimuli, CD177 is highly expressed on neutrophils and promotes their migration. CD177 + neutrophils activate bactericidal and barrier-protective functions at IBD mucosal inflammation sites and regulate the release of inflammatory mediators highly correlated with the severity of inflammation in IBD patients, thus playing a dual role. However, mitigating the detrimental effects of neutrophils in inflammatory bowel disease remains a challenge. Based on these data, we have summarized recent articles on the role of neutrophils in intestinal inflammation, with a particular emphasis on CD177, which mediates the recruitment, transepithelial migration, and activation of neutrophils, as well as their functional consequences. A better understanding of CD177 + neutrophils may contribute to the development of novel therapeutic targets to selectively modulate the protective role of this class of cells in IBD.

Keywords CD177, Neutrophils, Inflammatory bowel disease, Platelet endothelial cell adhesion molecule-1, β2 integrins

Introduction

CD177, also known as human neutrophil antigen (HNA-2), polycythemia vera-1, and NB1 glycoprotein, is polymorphic and was first discovered in 1971 in the blood of neonates with alloimmune neutropenia [1–3]. It is considered the second specific antigen of human neutrophils [3]. CD177 (molecular weight: 56–62 kDa) primarily resides on the plasma membrane and is linked through glycosylphosphatidylinositol and neutrophil secondary granules [4, 5]. Notably, it is exclusively expressed on neutrophils, exhibiting a bimodal expression pattern, and based on its expression, neutrophils can be divided into two subgroups: CD177 + and CD177 − [6]. Although CD177 + and CD177 − neutrophils are similar in subgroup morphology and cytoplasmic granules, they exhibit significant differences in gene expression and functionality (Table 1) [7]. In the general population, variance in CD177 expression relates to carbohydrate and lipid biosynthesis and glycoprotein metabolism [8]. In patients with inflammatory diseases, the absence of CD177 leads to reduced neutrophil recruitment in the early stages of disease and impacts neutrophil immune functions early in inflammation [9]. Specifically in inflammatory bowel disease (IBD), the expression of CD177 is closely linked to its bactericidal activity, mucosal barrier repair abilities, and inflammatory response [10, 11].

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Table 1 Difference between CD177+ and CD177− neutrophil subsets

	CD177+ Neutrophils	CD177− Neutrophils	References
Healthy population	95–97%	3–5%	[5, 7]
Life and number	Long/many	Short/few	[9, 12, 76]
Expression and migration under stimulation	Increased/accelerated	No change	[6, 9]

IBD is a class of autoimmune diseases closely linked to environmental factors, genetic predisposition, and gut microbiota. IBD is thought to primarily arise from dysbiosis and resulting immune dysfunctions and is classified into remission and active phases. Pathologically, it is characterized by neutrophil infiltration and epithelial mucosal damage [13, 14]. During active phases, IBD patients exhibit more complex symptoms, gastrointestinal dysfunction, and severe mucosal inflammation compared to those in remission. Neutrophils serve as a "double-edged sword" in this context; while their excessive infiltration exacerbates inflammation, their reduction can impair immune responses, aggravating the condition [15, 16].

The functional heterogeneity of neutrophils is associated with surface receptor expression, such that different neutrophil subtypes play diverse roles in IBD [17]. However, the pro-inflammatory and anti-inflammatory roles of neutrophils in IBD are still under debate. Initially thought to be involved only in adhesion and migration, recent studies have highlighted that CD177 expression on neutrophils correlates with the progression and duration of inflammatory diseases [18]. In particular, CD177 is implicated in neutrophil activation and the regulation of inflammatory responses in conditions such as allergic asthma and sepsis, where its overexpression can exacerbate inflammation [19, 20]. Transcriptional analysis of whole blood from patients with IBD has shown that *CD177* is the most significantly altered gene, correlating positively with the degree of endoscopic activity and could reflect the degree of inflammation in patients [21].

Overall, as a surface molecule, CD177 regulates neutrophil-mediated inflammatory responses and exhibits complex immunoregulatory functions through its expression in various tissues and organs [22]. However, the specific expression and mechanisms of action of CD177 in different organs and tissues are not yet fully understood. Further research into the functions and regulatory mechanisms of CD177 is essential for a deeper understanding of its roles in health and disease, particularly in the regulation of immune responses and inflammatory processes. This review focuses on the expression of CD177 on neutrophils and its role in IBD. The article elaborates on how CD177 facilitates neutrophil migration and mediates immune responses within the inflammatory milieu of IBD. The review underscores the pivotal role of CD177 in the progression of inflammation and explores its potential as a biomarker for disease prediction and diagnosis. These findings not only deepen our understanding of CD177's function but also anticipate its application in enhancing more effective and personalized treatment strategies aimed at improving therapeutic outcomes for patients with IBD.

CD177 expression

Physiological heterogeneity of CD177 expression

CD177 is a high-frequency antigen expressed on subpopulations of neutrophils in the peripheral blood of approximately 97% of healthy individuals [7]. Flow cytometry is typically used to measure CD177 expression, revealing a bimodal expression pattern whereby CD177-positive individuals contain both CD177 + and CD177 − neutrophil subpopulations [23]. Beyond flow cytometry, modern techniques analyzing hPLN, a CD177-binding peptide, can specifically target the CD177-positive population of neutrophils in both humans and mice to determine their relative abundance [24].

The proportion of CD177 + neutrophils varies from 0 to 100%, with an average of 45–65%, while no neutrophils in CD177-negative individuals express CD177 [23, 25]. The percentage of CD177 + neutrophils varies among individuals but is generally higher in females than in males, in younger individuals than in older individuals, and in pregnant women [7, 26]. In CD177-positive individuals, the proportion of CD177 + neutrophils typically remains stable over time [4].

Based on the differential levels of CD177 expression on the cell membrane, CD177 + neutrophils can be further subdivided into low-CD177- and high-CD177-expressing subgroups [27]. CD177 + neutrophils can form high-affinity complexes with proteinase 3 (PR3), resulting in CD177/PR3-high and -low neutrophil subpopulations, which remain unchanged throughout one's life [28]. Moreover, Ly6G is a neutrophil surface marker used to identify CD177 + neutrophils in mice [29]. Recently, Lin and colleagues utilized single-cell RNA sequencing to thoroughly analyze Ly6G + neutrophils isolated from mice, identifying subpopulations with high, medium, and low Ly6G + expression [30].This finding was also validated in human neutrophils, demonstrating the existence

of similar neutrophil subpopulations in both mice and humans. The identification of these subpopulations, particularly CD177 + neutrophils, aids in further understanding the potential dual roles—protective and pathological—these cells may play in IBD, offering potential targets for targeted therapies.

Pathological heterogeneity of CD177 expression in different tissues

In-depth studies have revealed that the expression and role of CD177 vary in different tissues and organs under various conditions. Under physiological conditions, CD177 is expressed at low levels in the duodenum, kidneys, and vagina; moderately in the esophagus, liver, and spleen; and highly in the colon, rectum, mammary glands, cervix, appendix, and bone marrow, maintaining homeostatic balance [22]. Similarly, under pathological conditions, CD177 expression and the number of CD177 + neutrophils vary among different organs and tissues. For example, CD177 expression and CD177 + neutrophil levels are significantly reduced in colon, breast, and cervical cancer tissues, with expression closely related to the patients' anti-cancer responses and prognoses, suggesting that CD177 may inhibit tumor progression by affecting cancer-related or immune-related pathways [22, 31, 32].

Furthermore, CD177 expression and the number of CD177 + neutrophils are high in inflammatory diseases such as gastritis, pancreatitis, and anti-neutrophil cytoplasmic antibody (ANCA)-associated systemic vasculitis, with CD177 expression closely related to pro-inflammatory responses and adverse patient outcomes [28, 33, 34]. For example, the degree of mucosal inflammation in gastritis positively correlates with CD177 expression, and patients infected with *Helicobacter pylori* exhibit higher CD177 expression and mucosal inflammation scores than uninfected individuals [34]. CD177 levels in neutrophils from patients with acute pancreatitis are significantly elevated and correlate positively with C-reactive protein levels and disease severity, with studies showing that recombinant human CD177 can exert protective effects by inhibiting the formation of neutrophil extracellular traps (NETs) [33]. In ANCA vasculitis, anti-ANCA antibodies function similarly to anti-CD177 antibodies, with CD177 expression positively correlating with the severity of the patient's condition [28].

These findings suggest that CD177 expression is not only related to inflammatory diseases characterized by neutrophil dysfunction but also closely linked to neutrophil infiltration at inflammation sites. Beyond tumors and inflammatory diseases, Aladily et al. found that CD177 expression in patients with clonal bone marrow diseases reflect the maturation stage of neutrophils in the peripheral blood and bone marrow, with the least mature neutrophils not expressing CD177, indicating bone marrow dysplasia [35].

Mechanisms influencing CD177 expression

Research into the mechanisms underlying low or absent CD177 expression has been extensive. Studies by Lin et al. found that mice lacking translocating chain-associating membrane protein (TRAM) have enhanced resistance to sepsis and less tissue damage [36]. Previous research confirmed that the TRAM signaling pathway influences the production of neutrophils with low CD177 expression by activating Src family kinases (SFK), thereby increasing the number of neutrophils with high and medium CD177 expression, suggesting that knockout of TRAM promotes the production of CD177-low expressing neutrophils [37]. On the other hand, the myeloid cell trigger receptor-1 (TREM-1) is a factor that promotes the release of inflammatory mediators. Studies by Seo et al. found that after using anti-TREM-1 (α-TREM-1), CD177 expression increased on neutrophils without TREM-1 knockout, while no change in CD177 expression was observed on neutrophils with TREM-1 knockout, indicating that the expression of TREM-1 promotes the generation of CD177-low neutrophils [11]. These findings emphasize that multiple pathways exist in the body to maintain low CD177 expression on neutrophils, and different signaling pathways influence CD177 expression, highlighting its complex regulatory mechanisms. Therefore, understanding these pathways and their interactions is crucial for elucidating the regulatory mechanisms of CD177 expression and could provide new research directions for the treatment of future inflammatory and immune-related diseases.

CD177 is a polymorphic gene that needs to undergo transcription and translation to become a protein; thus, the absence of CD177 may be related to single nucleotide polymorphisms (SNPs), gene sequence abnormalities, and protein processing anomalies [38]. Initially, the deletion of the *CD177* gene was thought to be due to the insertion of base pairs causing incorrect splicing, forming a stop codon [39]. However, subsequent researchers could not confirm this result in their cohort and found it related to the CD177 pseudogene (*CD177P1*), SNPs, and gene mutations [40]. A study by Wu et al. showed that when exon 7 of *CD177* is entirely provided by *CD177P1*, it results in a non-functional CD177 phenotype [41]. Later studies revealed new nonsense SNPs (SNP c.787A > T and c.1291G > A) [23], both associated with the non-functional CD177 phenotype [42, 43]. In summary, SNPs form premature stop codons, subsequently affecting protein synthesis and leading to the deletion of the *CD177* gene.

High CD177 expression in IBD

While exploring the relationship between CD177 expression and IBD, researchers observed that dextran sulfate sodium (DSS)-induced IBD wild-type mice showed significantly higher CD177 + neutrophil expression than IBD *CD177*-knockout mice, with the latter exhibiting more severe intestinal mucosal inflammation and higher disease scores [8]. Furthermore, past research found that granulocyte colony-stimulating factor promotes mucosal healing in IBD by enhancing CD177 expression, increasing the number of CD177 + neutrophils, and activating neutrophil functions [44, 45].

Under normal conditions, CD177, produced through transcription and translation, is located in secondary granules and vesicles and is transferred to the neutrophil membrane upon stimulation by appropriate mediators [46, 47]. When neutrophils mature and enter circulation, the transcription of proteins stored in secondary granules is suppressed [48]. Nowak et al. conducted genetic analyses on patients with IBD and observed a significant overexpression of *CD177* compared to healthy controls [10]. Thus, the high expression of CD177 in IBD is regulated by inflammatory inducers, neutrophil maturity, and different stages of CD177 production. Additionally, bacterial stimulants and inflammatory mediators released during active IBD can stimulate neutrophil recruitment at IBD intestinal mucosa, leading to a significant increase in the percentage of CD177-high neutrophils in peripheral blood and intestinal mucosa [8]. These results suggest that CD177 + neutrophils have a migratory advantage in IBD, and the mechanisms involved require further clarification.

Migratory advantage of CD177 + neutrophils

The migratory advantage of CD177 + neutrophils make CD177 a key target molecule for reducing neutrophil aggregation at sites of inflammation in IBD [6]. Stimulated by inflammatory mediators, neutrophils adhere firmly to activated endothelium and undergo a series of trans-endothelial and -epithelial migrations to reach the site of inflammation and exert their immune functions [49]. In mice, the homolog of human CD177, Ly6G, significantly enhances the recruitment of neutrophils to inflamed tissues (Table 2) [50]. However, CD177 is a glycosylphosphatidylinositol (GPI) -anchored protein lacking a transmembrane domain and requires binding with other molecules to mediate signal transduction [18]. Studies have shown that in mice with DSS-induced IBD, the expression of migration-related proteins, such as selectins, integrins, and adhesion molecules, is significantly increased compared to that in control mice [51, 52]. These findings suggest that released mediators promote the binding of CD177 on the neutrophil surface with other molecules, thereby mediating additional rapid migration pathways for CD177 + neutrophils.

Table 2 Homology of CD177 and Ly6G

CD177/Ly6G		References
Gene	Ly-6 superfamily	[12]
Type of protein	GPI-anchored	[4, 53]
Alleles	2	[34]
Cellular expression	Neutrophils	[4]
Anti-CD177/Ly6G Ab	Neutropenia	[54, 55]

CD177 interaction with β2 integrins

B2 integrins, particularly Mac-1 (also known as CD11b/CD18), exist in a non-activated state in the circulation and are adhesion molecules that co-localize with CD177 on the neutrophil membrane, mediating neutrophil adhesion, migration, and recruitment [56]. Confocal imaging-supported immunoprecipitation and binding studies confirm the physical association between CD177 and β2 integrins [57]. In inflammatory diseases, CD177 mediates the initial adhesion of neutrophils to the vascular wall, followed by their passage through endothelial and epithelial barriers, ultimately reaching the site of inflammation [18]. Studies have shown that in mouse models of IBD, the use of β2 integrin inhibitors can block most neutrophil migration and alleviate inflammation [58]. The activation of β2 integrins also promotes neutrophil adhesion and inhibits migration, indicating that β2 integrins and their ligands play a crucial role in neutrophil migration [59]. However, clinical trials have shown very limited effects of these inhibitors on inflammatory and autoimmune diseases. There is still a lack of direct experiments exploring the interaction between CD177 and β2 integrins, with only indirect evidence describing the impact of their interaction on neutrophil adhesion, migration, and recruitment.

In chemical-induced mouse models of IBD, blocking the adhesion of neutrophils can reduce their migratory capacity, leading to acute disease flares and even mortality [16]. Only cells transfected with β2 integrins can adhere to immobilized CD177 protein, and antibodies against CD177 and β2 integrins can inhibit this adhesion [57]. Moreover, Wang et al. found that in animal experiments, anti-Ly6G antibodies could inhibit the chemotactic migration of neutrophils to inflamed lungs but did not affect neutrophil migration in β2 integrin-deficient mice [55]. This indicates that although CD177 and Ly6G share structural and functional similarities and both interact with β2 integrins to promote neutrophil migration, antibodies against CD177 and Ly6G separately

regulate the levels of β2 integrins to inhibit the migration of CD177 + neutrophils [18, 59].

Further experiments have shown that anti-CD177 antibodies promote the fixation and release of CD177 + neutrophils by activating β2 integrin-mediated signaling pathways, thereby inhibiting neutrophil migration [18]. Mitogen-activated protein kinase lies downstream of β2 integrins and can inhibit neutrophil migration. Previous studies have confirmed that the activation of extracellular signal-regulated kinase (ERK) enhances the activity of G protein-coupled receptor kinases, leading to receptor binding inhibition and signal termination [60]. This receptor desensitization also reduces the number of potentially active receptors on the cell surface, thereby reducing the internal signals generated by chemotactic factors [61]. Accordingly, using the ERK inhibitor U0126 diminishes the inhibitory effect of anti-CD177 antibodies on neutrophil migration [18]. Recent studies have shown that the expression of β2 integrins increases neutrophil adhesion and reduces integrin internalization, leading to downstream Src and ERK phosphorylation, thereby weakening ERK-mediated chemotactic factor signaling and consequently fixing neutrophils and inhibiting the migration of CD177 + neutrophils [59].

CD177 interaction with PECAM-1

Platelet endothelial cell adhesion molecule-1 (PECAM-1; also known as CD31) is an adhesion molecule primarily located at the junctions between endothelial cells and plays a crucial role in the migration of neutrophils through these junctions during the development of IBD [62]. This role primarily involves homophilic interactions between PECAM-1 molecules and heterophilic interactions between PECAM-1 and CD177, participating in the interactions between neutrophils and endothelial cells, with the heterophilic interactions being more pronounced [63, 64]. Under the stimulation of chemotactic factors, the interaction between CD177 and PECAM-1 increases, thereby promoting the migration of CD177 + neutrophils. Monoclonal antibodies against CD177 and PECAM-1 can inhibit this migratory advantage [65, 66]. These studies suggest that CD177 promotes transendothelial migration of CD177 + neutrophils and recruits them to exert immune effects at sites of inflammation by binding to PECAM-1.

Bayat et al. demonstrated that treatment with anti-PECAM-1 antibodies significantly reduces the migration of CD177 + neutrophils compared to that of CD177 − neutrophils [67]. However, another study reported that after treatment with anti-PECAM-1 antibodies, CD177 + neutrophils still accumulated at cellular junctions, indicating that the antibodies block the transmembrane migration following β2 integrin-mediated tight adhesion [66]. This interaction is mediated by the membrane-proximal domain 6 of PECAM-1, which initiates signaling pathways under divalent cation conditions, promoting the degradation of vascular endothelial cadherin at endothelial junctions and weakening the stability of the endothelial barrier, thereby facilitating the transendothelial migration of CD177 + neutrophils [63, 67]. Given the homology between human CD177 and mouse Ly6G, both of which interact with PECAM-1, these results suggest that the heterophilic interaction between CD177 and PECAM-1, by enhancing adhesion between neutrophils and endothelial cells, plays a critical role in transmembrane migration in inflammatory diseases.

PR3, a serine protease released by activated neutrophils, is located in the granules of neutrophils. It promotes neutrophil migration by attaching to the neutrophil plasma membrane through CD177 [68]. When neutrophils from individuals positive and negative for CD177 are stimulated by the chemotactic peptide fMLF, CD177 + cells show a marked increase in surface PR3 activity, indicating PR3's involvement in the migration of CD177 + neutrophils [69]. Further investigation revealed that the heterophilic interaction between CD177 and PECAM-1 could anchor PR3 at cellular junctions. This interaction, by regulating vascular integrity and permeability, participates in the migration of CD177 + neutrophils [70].

Interaction of CD177 with other immune cells

As CD177 + neutrophils migrate extensively and accumulate excessively in inflammatory tissues in IBD, they can directly cause damage to and death of epithelial cells, disrupt the intestinal mucosal barrier, and induce stress in intestinal epithelial cells. This leads to the upregulation of matrix metalloproteinases (MMPs) and the release of higher levels of interleukin (IL)-8 and tumor necrosis factor-alpha (TNF-α), mediating the further migration of CD177 + neutrophils from the lamina propria to the epithelium and promoting their accumulation in the inflamed mucosa [71]. Neutrophil migration and activation are positively correlated with the expression of *CD177*. Overly activated Ly6G + neutrophils release large amounts of interferon-γ and IL-17A, similar to findings in allergic asthma, promoting neutrophil migration [72]. This release of inflammatory and chemotactic factors occurs due to the interaction between CD177-overexpressing neutrophils and other immune cells. CD177-overexpressing neutrophils directly adhere to and signal through receptors and molecules on the surface of CD4 + T cells, affecting their function and thus promoting the release of interferon-γ [73]. Dendritic cell (DC) natural killer lectin group receptor-1, an anti-inflammatory molecule produced by DCs, normally maintains

tissue balance through interactions with neutrophils [74]. However, the excessive accumulation of CD177 + neutrophils disrupts this balance, leading to an overwhelming inflammatory response. The abundant release of inflammatory factors reduces the number of regulatory T cells (Treg cells), inhibits their immunoregulatory function, and causes an imbalance in the Treg/Th17 cell ratio, thereby reducing levels of anti-inflammatory factors (such as IL-10 and transforming growth factor-β) and increasing levels of pro-inflammatory factors (such as IL-17 and TNF-α) [75]. These findings indicate that CD177 on neutrophils, through interactions with surface molecules on other immune cells, induces the excessive activation and migration of neutrophils and the release of a large amount of inflammatory factors in IBD.

Furthermore, CD177 plays a potential key role in regulating the migration of human neutrophils through cell activation pathways. Its expression in neutrophils is associated with cell adhesion and migration, relevant to cell positioning and movement during inflammation [18]. In IBD, CD177 on neutrophils, through interactions with other cell surface molecules, activates signaling pathways. Resulting interactions with intracellular signaling molecules thereby regulate cell functions and immune responses. CD177 also participates in inflammation-related signaling pathways, affecting the generation and regulation of inflammatory signals [76]. Inflammation causes immune cells to migrate across membranes and infiltrate inflamed tissues, and CD177 expression, by affecting this process, impacts the onset and progression of IBD [77]. Therefore, regulating the interactions and functional conditions of CD177 with its binding molecules can modulate migration-related signaling pathways, control the migration of neutrophils, and regulate the infiltration of neutrophils at IBD inflammation sites, thereby modulating immune intensity in the IBD mucosal inflammation area.

Dual role of CD177 + neutrophils in IBD

IBD is a complex autoimmune disease with a pathogenesis involving multiple factors, including genetics, immune anomalies, microbial dysbiosis, impaired mucosal barriers, and the infiltration and release of inflammatory mediators by immune cells [78]. T cells, B cells, macrophages, DCs, and Tregs are the main immune cells involved in IBD, playing crucial roles in regulating the immune system and the onset of inflammatory responses [78]. The main strategy for alleviating IBD involves the use of immunosuppressive drugs that reduce inflammation and maintain disease stability, but long-term use can compromise immune function and increase the risk of infection [73]. To avoid the adverse effects of immunosuppressants, more clinicians and researchers are focusing on research targeting immune-related genes for the treatment of IBD. Currently, drugs targeting *CD177* expression on neutrophils have improved several autoimmune diseases, such as sepsis, biliary obstruction, and anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis [79–81].

Neutrophils are the most important and abundant cells in innate immunity and play a critical role in maintaining intestinal function balance after transmembrane migration to the intestinal mucosal lamina propria [77, 82]. Concurrently, neutrophils regulate signaling pathways and interact with macrophages and intestinal epithelial cells in the inflamed intestinal mucosa, influencing the release of immune regulatory molecules and modulating the body's immune response [11]. The inflammatory state of IBD is closely related to the diversity and stability of the intestinal microbiota. Dysfunctional or overly robust neutrophil function can lead to abnormal immune activity, further disrupting the homeostasis of the intestinal microbiota [83]. An increase in CD177 expression on neutrophils has been observed in various immune diseases, with recent discoveries highlighting its significant role in IBD. However, different researchers have reported varying findings and insights regarding its specific function in IBD.

Positive role of CD177 + neutrophils in IBD

TREM-1 on neutrophils can react with anti-TREM-1 agonistic antibodies to produce higher levels of CD177 + neutrophils. This process promotes mucosal repair and reduces the release of inflammatory mediators, contributing to the improvement of intestinal mucosal inflammation in patients with IBD [11]. Intestinal epithelial lymphocytes (IELs), a stable class of immune cells in the intestinal mucosa, together with neutrophils, form the body's first line of pathogen defense. This defense mechanism maintains intestinal homeostasis and plays an immune defense role, where the accumulation of TCRγδ + CD8aa + IELs is closely related to intestinal barrier integrity [84]. Chen et al. discovered that using anti-Ly6G antibodies in DSS-induced IBD mice significantly reduced the number of CD177 + neutrophils and markedly upregulated pro-inflammatory TCRγδ + CD8aa + IELs, thereby exacerbating intestinal mucosal inflammation [53]. Dimethyl fumarate (DMF), a derivative of the intestinal microbiota, inhibits the activation of TCRγδ + CD8aa + IELs induced by gasdermin D, suppressing intestinal inflammation. Recent scRNA-seq studies have revealed dysbiosis in the microbiota of CD177-negative IBD mice and reduced levels of DMF [53]. These findings not only demonstrate the positive role of CD177 in IBD but also the effects of DMF, which correlates positively with CD177 expression in regulating

the intestinal microbiota. This also provides a new perspective for understanding the role of CD177 in the development of IBD and for developing treatment strategies. These animal studies indicate that CD177 + neutrophils can mediate related signaling pathways to reduce the release of pro-inflammatory mediators, playing a protective role in IBD.

Recent discoveries have shown that at IBD inflammation sites, intestinal mucosal and tissue damage are exacerbated in *CD177*-knockout mice, suggesting a protective role of CD177 + neutrophils in IBD [53]. RNA sequencing analysis of CD177 + and CD177 − neutrophils extracted from the peripheral blood of patients with IBD and healthy individuals revealed significant differences in gene expression, which relates to their potential roles in immune regulation [8]. In vitro experiments further validated that compared to CD177 − neutrophils, CD177 + neutrophils produce larger amounts of ROS, antimicrobial peptides, and NETs [8]. Therefore, they exert a stronger antimicrobial effect and protect the intestines from microbial infections at IBD inflammation sites, consistent with previous findings in acute pancreatitis studies [33, 85]. Moreover, CD177 + neutrophils secrete large amounts of IL-22, which can induce the expression of antimicrobial proteins Reg3β and Reg3γ by phosphorylating the transcription factor STAT3 in colon epithelial cells, enhancing bactericidal activity. It also reduces mucosal permeability, promotes epithelial cell proliferation and migration, repairs the IBD epithelial mucosal barrier, and maintains intestinal epithelial homeostasis [86].

Negative role of CD177 + neutrophils in IBD

The development of IBD is closely related to the excessive activation of the immune system, and the excessive recruitment of CD177 + neutrophils can lead to the overactivation of immune responses, further damaging inflamed tissues. TRAM is a signaling molecule that promotes the production of CD177-high neutrophils, and studies have found that inhibiting TRAM signaling significantly alleviates damage and inflammation in IBD mucosa [37]. This result contradicts previous findings, indicating its involvement in immune responses. CD177 plays a vital role in immune regulation, and using immunohistochemistry and quantitative reverse transcription-polymerase chain reaction to analyze neutrophils isolated from IBD active patients revealed a significant increase in CD177 at both mRNA and protein levels, correlating positively with inflammation severity, consistent with previous studies on patients with septic shock [87]. These findings suggest that CD177 enhances immune responses by over-activating immune cell activity, thereby participating in the pathological process of IBD.

Damage to the intestinal mucosal epithelial barrier and worsening dysbiosis of the intestinal microbiota are key factors leading to tissue damage and exacerbated inflammation in IBD. As the disease progresses, a large number of CD177 + neutrophils preferentially pass through the intestinal mucosal barrier, disrupting connective proteins such as β-catenin and E-cadherin, thereby damaging intestinal mucosal integrity [88]. Damage to the intestinal mucosal barrier increases its permeability and reduces the resistance of the epithelial barrier, leading to a significant shift in the intestinal microbiota, thereby exacerbating the degree of dysbiosis in inflamed tissues [89]. Under LPS stimulation, the abnormally activated degranulation of CD177 + neutrophils exacerbates the inflammatory response. The excessive release of ROS can damage cell membranes and activate redox-sensitive inflammatory pathways, impairing epithelial cell integrity and their tight junction functions [90]. The excessive accumulation of NETs in the inflamed mucosa in IBD can induce epithelial cell death through apoptosis and bacterial translocation, as well as promote the production of inflammatory mediators such as TNF-α by activating the ERK1/2 signaling pathway, exacerbating inflammation in IBD [91]. Further research has found that high levels of TNF-α promote macrophages to secrete excessive pro-inflammatory cytokines and exacerbate inflammation by destabilizing the ubiquitin-like protein PHD and the ring finger domain 1 [92]. Besides their bactericidal action, activated neutrophils can release α-defensins, calprotectin, and other mediators, recruiting T cells and DCs to the sites of inflammation in IBD, thus participating in the pathogenesis of the disease [93]. Dectin-1 signaling in neutrophils plays a crucial role in this process, stimulating macrophages and DCs to release pro-inflammatory cytokines, which in turn amplify the inflammatory response, thereby worsening damage to the intestinal mucosa [94].

In the early stages of IBD, dysbiosis of the intestinal microbiota triggers an infection that activates the body's immune system, leading to the early involvement of CD177 + neutrophils in inflammatory immune regulation. These cells regulate signaling pathways to reduce the release of inflammatory stimuli and decrease the severity of inflammation. Additionally, IL-22 persistently repairs epithelial cells, thereby reconstructing the patient's mucosal barrier and alleviating the severity of the condition [95]. Thus, in the early stages of IBD, targeting CD177 + neutrophils to enhance their expression and migration abilities can effectively alleviate inflammation and repair the epithelial barrier. However, during the active phase of IBD, as the infiltration of neutrophils increases and their immune actions intensify, further tissue damage and inflammation occur [71]. In this context,

the deleterious effects of neutrophils gradually outweigh their beneficial roles, worsening the patient's condition. These mechanisms illustrate the dual role of neutrophils in the pathological process of IBD, participating in immune defense while also triggering excessive inflammatory responses, thus influencing disease progression. An in-depth study of the specific mechanisms of neutrophils in IBD will aid in better understanding and developing interventions for the disease. By controlling the migration of CD177 + neutrophils, the infiltration of neutrophils at IBD inflammatory sites can be regulated, balancing their immune and barrier repair functions to achieve better therapeutic outcomes.

CD177 as a diagnostic marker

The pathogenesis of IBD is closely related to the active state and infiltration level of neutrophils, the overactivation or suppression of which can cause immune system anomalies and promote disease progression. CD11b/CD18, ROS, and CD177 are markers on the surface of neutrophils, directly or indirectly involved in their adhesion, migration, and activation [56, 96]. Compared to CD11b/18 and ROS, CD177, as a marker of neutrophil activation, participates in entire neutrophil activities, including adhesion, migration, activation, and interaction with other immune cells, significantly affecting neutrophil function and infiltration and thus influencing the development of IBD [11, 18]. Recent studies have shown that CD177 expression and the percentage of CD177 + neutrophils are significantly positively correlated with the Crohn's disease activity index and mayo score, both of which reflect the inflammatory severity of IBD and its progressive conditions [8, 97]. Therefore, CD177 stands out among neutrophil markers for assessing the severity of IBD.

CD177, a novel podoplanin receptor, regulates human cancer-associated fibroblast physiology, implicating its role in cancer pathology and patient prognosis [98]. High CD177 expression can indicate poor prognosis in ovarian and pancreatic cancers while representing a good prognosis in breast and lung cancers, which is related to the tumor microenvironment [31, 99]. Immunohistochemical analysis of advanced gastric cancer samples has shown that high *CD177* expression is associated with good prognosis and is the gold standard for predicting survival rates [100]. Colorectal cancer, a severe complication of IBD and one of the most common malignancies globally, is closely related to the degree of disease and infiltration of immune cells in the tumor microenvironment [101]. Studies have found that CD177 + neutrophils inhibit cancer cell occurrence in colorectal cancer and are also an independent prognostic indicator for patients [102].

As the most predominant immune cells, neutrophils can also serve as predictive markers for various autoimmune diseases, especially in combination with CD177. Patients with chronic and acute liver failure related to immune anomalies show significantly higher CD177 protein expression than healthy adults, associated with poor prognosis [103]. Follow-up studies have found decreased CD177 protein levels in patients recovered from COVID-19, while levels remain high in deceased patients, serving as a marker for critical patients and indicating disease progression [104].Moreover, the severity of biliary atresia is also related to neutrophil activation, with CD177 overexpression indicating higher interferon stimulation and degranulation, damaging bile duct epithelial cells, and promoting inflammation in biliary atresia [105]. In a prospective study, peripheral blood CD177 + neutrophils were identified as an early diagnostic marker for biliary atresia, showing significantly higher diagnostic accuracy than traditional markers like serum γ-glutamyl transferase in obstructive biliary diseases [106].

CD177 expression not only facilitates protective immune responses but also contributes to the pathologic process of chronic inflammation and tissue damage. It is involved in the recruitment and activation of neutrophils, crucial for resisting intestinal pathogens and promoting mucosal healing. However, excessive or uncontrolled CD177 activation can lead to severe inflammation and immune dysregulation, exacerbating disease severity. Thus, CD177 also serves as a diagnostic marker for hematologic diseases (such as polycythemia vera) and autoimmune disorders (such as granulomatosis with polyangiitis) [64, 107]. CD177 expression and the presence of anti-CD177 antibodies can provide valuable diagnostic and prognostic information. Nonetheless, the heterogeneity in CD177 expression among individuals poses challenges for its use as a diagnostic marker. For instance, a small subset of individuals naturally do not express CD177, complicating the interpretation of pathologic mechanisms and outcomes. Therefore, establishing standardized reference ranges and diagnostic criteria for CD177 expression is crucial for its widespread clinical application, considering variations in laboratory techniques and population differences. To enhance the diagnostic utility of CD177, further research into its regulatory mechanisms and roles in various diseases is necessary, and large-scale clinical studies are needed to validate the effectiveness of CD177 as a diagnostic marker across different populations and disease contexts.

Conclusion

In summary, the expression of CD177 in the peripheral blood and inflamed mucosa, as well as the percentage of CD177 + neutrophils, are significantly in patients with IBD than in individuals without IBD. In the initial stages of IBD, the body recruits CD177 + neutrophils to the site of inflammation as a defense mechanisms, where they play a role in bactericidal activity and barrier protection (Fig. 1). As the infiltration of CD177 + neutrophils, macrophages, and CD4 + T cells increases over time, the release of a large number of chemokines induces the recruitment of more immune cells to the inflamed mucosa, triggering an excessive immune response and further exacerbating inflammation in IBD. The expression of CD177 and the migration rate of CD177 + cells are positively correlated with stimulants such as LPS and inflammatory

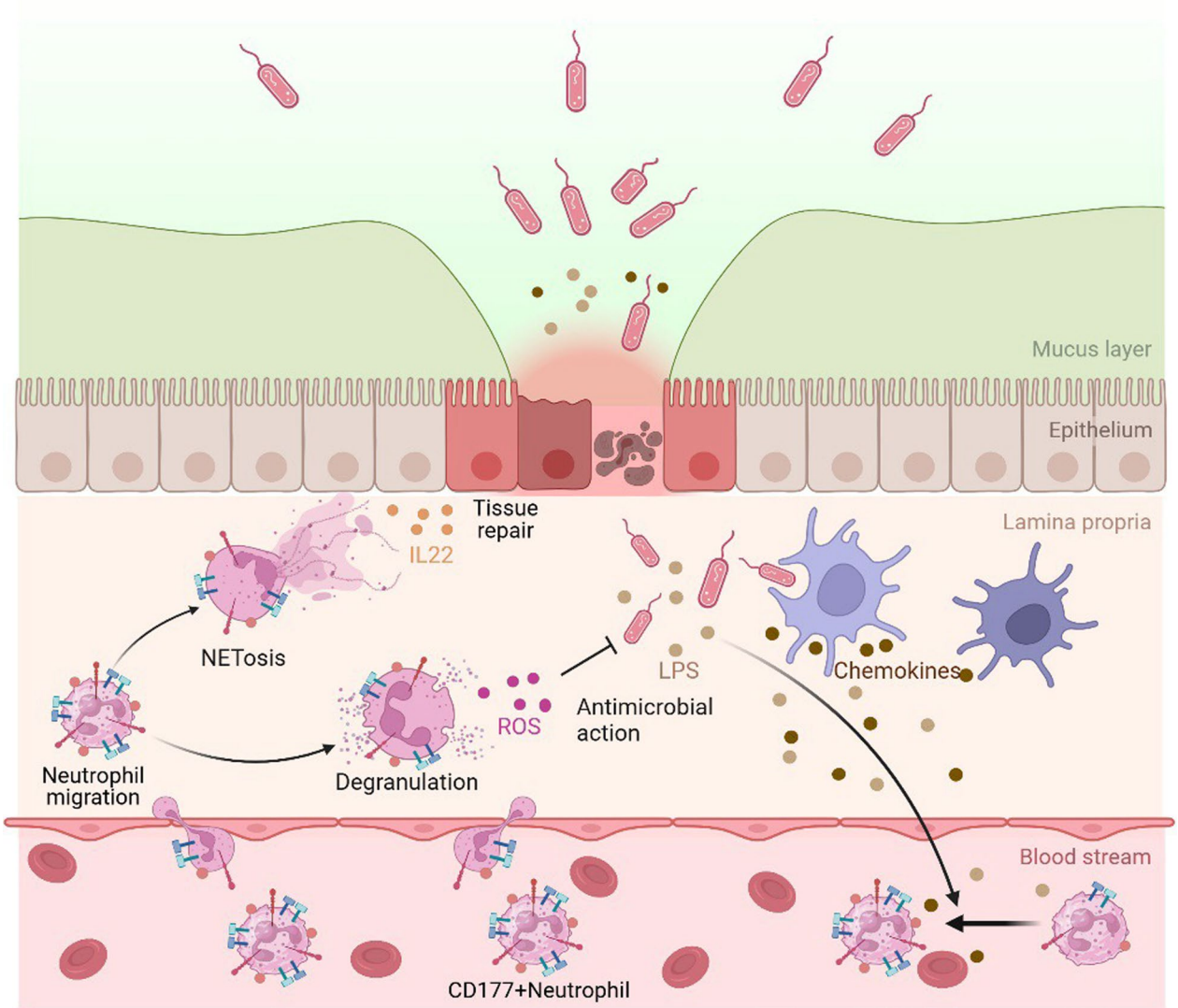

Fig. 1 CD177 + neutrophils play a protective role in IBD by releasing a range of cytokines. In the early stages of inflammatory bowel disease onset, LPS (released by bacteria) and chemotactic factors (released by immune cells) enter the bloodstream, elevating CD177 expression on the surface of neutrophils, as well as its binding molecules, PR3 and PECAM-1. The interaction between these molecules and CD177 facilitates CD177 + neutrophil migration. Upon reaching the inflammatory sites, CD177 + neutrophils are rapidly activated and exert positive effects, including (1) the release of bactericidal substances: CD177 + neutrophils release ROS and NETs to eliminate bacteria; (2) the release of IL-22: CD177 + neutrophils release IL-22 to restore the intestinal mucosal barrier, preventing bacterial invasion; and (3) anti-inflammatory action: CD177 + neutrophils play an anti-inflammatory role. These combined effects reduce bacterial invasion and inhibit the release of chemotactic factors, reducing neutrophil infiltration at the inflammatory site and improving the patient's inflammatory condition

mediators, jointly determining the percentage of CD177 + neutrophils in the inflamed mucosa of IBD.

The primary treatment approach for IBD involves reducing inflammation and promoting mucosal healing, typically by decreasing the infiltration of neutrophils at sites of inflammation. However, an excessive reduction in neutrophils can worsen the patient's condition [16]. The experimental introduction of CD177 on neutrophils revealed a relationship between CD177 expression and the severity of IBD inflammation [53]. Based on this and its dual role in IBD, CD177 could become a new target for IBD treatment, warranting active research into the expression of CD177 on neutrophils, the migration of CD177 + cells, and their mechanisms of action. By modulating the expression or activity of CD177, new pathways for regulating immune responses and inflammation intensity can be provided, offering new strategies for treating IBD. However, the functions of CD177 are not yet fully understood, and there is a lack of related clinical studies on IBD. Utilizing the homology between Ly6G in mice and CD177 in humans, studies on the mechanisms of CD177 + neutrophils in mice and related drugs are being conducted. Comprehensive studies of these drugs will better elucidate their interactions with CD177 and its related signaling pathways, providing a scientific basis for developing innovative treatment strategies. This in-depth understanding is expected to bring more effective and personalized treatment options for IBD patients.

Abbreviations

IBD	Inflammatory bowel disease
PR3	Proteinase 3
TRAM	Translocating chain-associating membrane protein
DC	Dendritic cells
TREM-1	Triggering receptor expressed on myeloid cell 1
SNP	Single nucleotide polymorphism
ERK	Extracellular signal-regulated kinase
PECAM-1	Platelet endothelial cell adhesion molecule-1
IL-8	Interleukin-8
TNF-α	Tumor necrosis factor alpha
ANCA	Anti-neutrophil cytoplasmic antibody
IELs	Intestinal intraepithelial lymphocytes
LPS	Lipopolysaccharide
NETs	Neutrophil extracellular traps
Treg cells	Regulatory T cells
ROS	Reactive oxygen species

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CL-Z and JK-L wrote the original draft.HL-C and WW-Z wrote and edited the review. XL-M and TY-S prepared the tables and figures. All authors contributed to the article and approved the submitted version.

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