

Review

Neutrophils in Intestinal Inflammation: What We Know and What We Could Expect for the Near Future

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Abstract: Neutrophils are short-lived cells that play a crucial role in inflammation. As in other tissues, these polymorphonuclear phagocytes are involved in the intestinal inflammatory response, on the one hand, contributing to the activation and recruitment of other immune cells, but on the other hand, facilitating intestinal mucosa repair by releasing mediators that aid in the resolution of inflammation. Even though these responses are helpful in physiological conditions, excessive recruitment of activated neutrophils in the gut correlates with increased mucosal damage and severe symptoms in patients with inflammatory bowel disease (IBD) and pre-clinical models of colitis. Thus, there is growing interest in controlling their biology to generate novel therapeutic approaches capable of reducing exacerbated intestinal inflammation. However, the beneficial and harmful effects of neutrophils on intestinal inflammation are still controversial. With this review, we summarise and discuss the most updated literature showing how neutrophils (and neutrophil extracellular traps) contribute to developing and resolving intestinal inflammation and their putative use as therapeutic targets.

Keywords: neutrophil; intestinal inflammation; neutrophil extracellular traps



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1. Introduction

Neutrophils are effective antimicrobial cells and the first leukocytes recruited to the site of injury or infection, followed by monocytes, natural killer cells, T cells, B cells, and mast cells [1]. These polymorphonuclear (PMN) phagocytes are the most abundant immune cells in peripheral blood, constituting between 50 and 70% of circulating leukocytes under normal conditions (although this percentage can increase during acute or chronic inflammation) [2]. The bone marrow produces more than 10^{11} neutrophils daily [3], and these cells circulate in the bloodstream only for a few hours due to their relatively short half-life, which is thought to be 6–20 h. However, once neutrophils become activated, their lifespan increases considerably [4], allowing their accumulation in inflamed or wounded tissues.

Classically, neutrophils are characterised by a potent phagocytic activity and a battery of functions (degranulation, reactive oxygen production (ROS), and neutrophil extracellular traps (NETs) formation) directed towards destroying infectious threats. However, that prevailing simplistic view of this cell type has changed over the years due to the advances in in vivo tracking systems and sequencing technologies, among others [5]. Those technologies revealed more complex neutrophil biology that even banned part of well-established dogmas such as their unidirectional migration to peripheral tissues and apoptosis [6]. Nowadays, it is recognised that neutrophils play sophisticated roles during inflammation by releasing cytokines and proteases able to regulate adaptive immune responses. Yet, this cell type is also pivotal for the appropriate resolution of inflammation and tissue repair [4,7,8]. Therefore, prolonged neutrophil activation is damaging and promotes chronic inflammation, and simultaneously, their presence is crucial for precise tissue healing. That

duality must be finely regulated to maintain homeostasis and avoid the occurrence of non-resolving inflammatory responses.

As for many other inflammatory conditions, neutrophils participate in the development and progression of intestinal inflammation. The precise contribution of this cell type to the dysregulation of intestinal homeostasis is still a matter of study. However, as a vital component of the innate immune system, neutrophils are essential for maintaining the balance between immune response and tolerance at the intestinal level. Therefore, in this review, we summarise and discuss the most relevant knowledge related to the role played by neutrophils in the promotion and resolution of inflammation, the participation of NETs in IBD pathophysiology, and the current therapeutic approaches based on neutrophil products.

2. Inflammatory Bowel Disease and a Lack of Treatment Options

IBD, mainly including Crohn's disease (CD) and ulcerative colitis (UC), is a group of immune-mediated disorders of the gastrointestinal tract, defined by a chronic and recurring inflammatory response in the intestinal mucosa. While UC is limited to the colon and presents a continuous inflammation confined to the mucosal layer, CD shows a discontinuous and transmural inflammation that can occur anywhere in the gastrointestinal tract. This disease cannot be cured, and despite the current therapies, a proportion of patients experience relapses and continuous inflammation, which occasionally requires surgical removal of parts of the intestine. Moreover, IBD's young age of onset and the need for long-term treatment result in substantial costs for healthcare systems and society, making this disease an enormous socioeconomic problem worldwide.

The use of biological agents has transformed the treatment of IBD. These drugs dramatically reduced the use of steroids, hospitalisation, and the need for surgery. Despite the great success of these therapeutic approaches, many patients with IBD do not respond adequately to these drugs. For instance, 10–30% of patients with IBD do not respond to anti-TNF therapy, and 20–40% lose effectiveness over time [9]. Moreover, these immunomodulators can blunt physiological immune responses, leading to serious side effects such as infections. As a result, a substantial percentage of patients are treated with expensive compounds and exposed to undesirable side effects without obtaining any therapeutic benefit. Notably, there is room for improvement in the ability of the current IBD therapies to achieve a complete resolution of the inflammation and mucosal healing and therefore, decrease the risk of relapse. Thus, we cannot be content with the current IBD therapeutic armamentarium, and the need for finding new treatments able to boost therapeutic efficacy and diminish the probabilities of adverse events is still a challenge.

3. Neutrophils in IBD Pathophysiology

The involvement of the immune system in the aetiology of IBD has been extensively recognised and demonstrated. Impaired immunity, with the environment, the genetic background, and gut microbiota, is responsible for developing CD and UC [10,11]. Chronic inflammation, by definition, is a dysregulation of the immune response. Consequently, much of the IBD-related research has focused on elucidating the immune mechanisms underlying intestinal inflammation pathogenesis [11,12].

The adaptive immune system is considered to play the most important role in the development of intestinal inflammation. However, at present, it is accepted that the innate immune system is equally necessary for maintaining gut homeostasis [12–14]. The intestine is constantly exposed to foreign antigens, and mononuclear phagocytes such as macrophages and dendritic cells (DCs) are essential for discriminating between harmful and harmless antigens. Therefore, these cells are central in mounting the appropriate immune response to pathogens or tissue damage, but also in favouring tolerance for innocuous dietary products and commensal microbiome. Another critical phagocytic immune cell is the neutrophil. This innate immune system effector is the first line of defence against infection or wounding, being the most rapid leukocyte recruited to the

site of inflammation after these insults. Therefore, neutrophils are vital in protecting intestinal epithelial barrier integrity and the contention of pathogens. Once their tasks are completed, neutrophils undergo apoptosis, and macrophages remove them in a process termed efferocytosis. This process is vital for the resolution of inflammation and recovery of tissue function. However, persistent neutrophil activation, exacerbated infiltration, and low apoptosis rates are commonly observed in IBD, contributing to the chronification of intestinal inflammation.

The role played by neutrophils in IBD is relatively unknown and less studied than for other immune cells. However, the number of studies relating to that topic has increased recently. To date, we know that impaired neutrophil function is pivotal in the induction of gut inflammation. These cells produce high levels of reactive oxygen species (ROS), which cause intestinal epithelial tissue damage [15–17]. Neutrophils can secrete a plethora of cytokines and chemokines that amplify their activation and recruitment (i.e., CXCL1) [18,19] and other innate and adaptive immune responses (i.e., CCL3, CCL4, CCL25) [19,20] within the mucosa. Moreover, these granulocytes can secrete proteases and extracellular traps, which further impair intestinal tissue homeostasis by disrupting the epithelial barrier integrity and by hyperactivating other immune cells [14,15]. In line with this, we cannot deny the enormous contribution of neutrophils and neutrophil-derived products, such as faecal calprotectin (S100A8/S100A9), to IBD clinical practise. This protein is routinely used as an indicator of disease activity in substitution of the classic pro-inflammatory marker C-reactive protein (CRP) [21] (although the utility of more neutrophil-associated biomarkers is being explored [22–25]). Plus, neutrophil infiltration and NETs correlate with disease severity and intestinal damage in patients with IBD [26–29], further corroborating the clinical relevance of this cell type. Functional experiments in CD patients revealed that defective neutrophil activity could be associated with a reduction in the clearance of mucosal bacteria, which would result in an increased immunological response and leukocyte infiltration into the intestine [30]. Altogether, these data highlight the relevance of neutrophils in the development and perpetuation of non-resolving intestinal inflammation.

4. Neutrophils in Intestinal Inflammation

Neutrophils, as essential effectors of the innate immune system, play a role in the pathogenesis of IBD [2,31]. Although the implication of these cells in the control of intestinal inflammation is not entirely known, many studies have demonstrated the participation of neutrophils in the onset and progression of intestinal mucosa damage (Figure 1).

4.1. Neutrophils Participate in the Initiation of Intestinal Inflammation

Although the inflammatory response differs based on the original stimulus and body location, the inflammation induction phase shows common mechanisms that allow for a fast and robust immune response. These universal processes entail a series of modifications, such as enhanced vascular permeability, leukocyte recruitment, and pro-inflammatory cytokine release, directed towards eliminating harmful stimuli [32]. The migration of neutrophils to the intestinal tissue is not entirely understood, but generally involves chemokines (CXCL8, CXCL1) [18,33], complement proteins (C5a) [34], and eicosanoids [35,36]. These polymorphonuclear phagocytes respond to a range of stimuli by releasing factors that regulate the activity and recruitment of other immune cells to inflamed tissues [8,37], which is a hallmark of IBD. Plus, because of their high antibacterial activities and tissue debris clearance capabilities, neutrophils exert collateral tissue damage by releasing ROS, proteases, and the formation of NETs [14,38]. Indeed, the protease inhibition showed positive effects on colitis severity in vivo, reducing neutrophil and macrophage infiltration and the production of pro-inflammatory cytokines [39,40]. Plus, NETs are detected in high amounts in the colons of mice subjected to experimental colitis. NETs promote the impairment of the intestinal barrier integrity and the apoptosis of intestinal epithelial cells [41], favouring the bacterial translocation from the lumen to the mucosa and the initiation of an exacerbated inflammatory response.

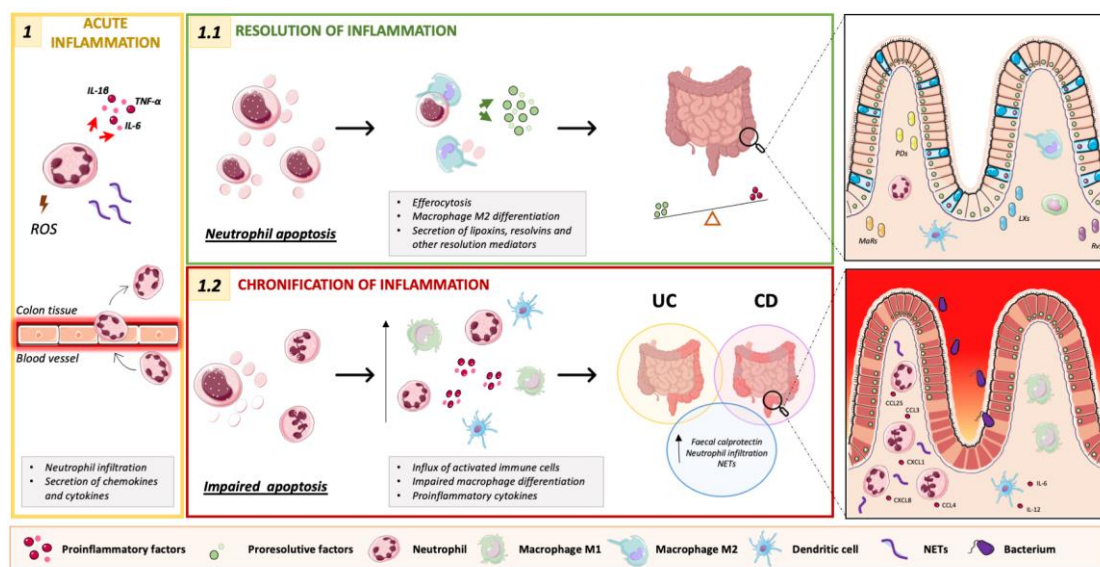


Figure 1. Schematic representation of the functions developed by neutrophils during inflammation. 1. Neutrophils secrete pro-inflammatory mediators during the acute inflammatory response. 1.1. Neutrophil apoptosis and efferocytosis, with the production of pro-resolutive factors, lead to the resolution of inflammation. 1.2. Persistent neutrophil infiltration and low apoptotic rates contribute to the chronification of intestinal inflammation.

Neutrophil depletion experiments have yielded contradictory results in different animal models of IBD. The use of antibodies against neutrophils during dextran sodium sulphate (DSS)-induced colitis, dinitrobenzene sulphonc acid (DNBS) colitis model, or T cell transfer colitis exacerbates disease severity and the infiltration of other inflammatory cells [42,43], suggesting a protective function for these cells during colitis development. In contrast, neutrophils improved colitis symptoms in rats subjected to DSS-induced colitis [44]. In line with this, the depletion of macrophages and dendritic cells (DCs) increases granulocytic inflammation within the intestinal mucosa and presents more severe signs of colitis [45]. However, simultaneous neutrophil elimination using anti-Gr1 antibodies did not aggravate the intestinal inflammation elicited by the lack of both mononuclear phagocytes [45]. The different species, experimental colitis models, and antibodies used might explain the heterogeneity of the outcomes. Moreover, the work of Qualls et al. [45] highlights that the interplay among immune cells in the intestinal mucosa should be considered, adding an extra level of complexity to the study of neutrophil biology during IBD pathogenesis. Plus, it is noteworthy that complete neutrophil depletion might not be the most acceptable strategy to investigate the functions of this cell type during colitis, due to the concomitant impairment of its pro-resolutive and bacterial contention actions. In contrast, approaches aiming to reduce neutrophil hyperactivation and over-accumulation could be more appropriate. In fact, the blockade of CXCR2 alleviates DSS-acute colitis symptoms, and this is thought to be mediated by the reduction in excessive neutrophil recruitment to the colonic lamina propria [46]. Similarly, anti-GM-CSF antibodies caused a significant decrease in neutrophil colonic infiltration (close to control animals) and the restoration of the mucosal integrity during DSS-induced colitis [47]. Collectively, these studies clearly reveal the participation of neutrophils in the development of an aberrant intestinal inflammatory response. Nonetheless, the existence of discrepancies and the relatively unknown role played by neutrophils in the gut urge additional research to fully understand their contribution to the pathogenesis of intestinal inflammation.

4.2. Neutrophils Participate in the Resolution of Intestinal Inflammation

Resolution of inflammation is an active and highly regulated process aiming to restrain excessive inflammation and recover tissue homeostasis. In patients with IBD, relapses

have been linked to defects in this process [48–50]. Therefore, it is crucial to understand the mechanisms underlying the resolution of intestinal inflammation to develop new therapeutic strategies.

Neutrophils are central elements in the resolution of inflammation. The initiation of this process requires the cessation of neutrophil influx and the engulfment of apoptotic neutrophils by macrophages. The efferocytosis of dying granulocytes avoids the amplification of pro-inflammatory signals and induces a macrophage phenotype shift from M1 (pro-inflammatory) to M2 (anti-inflammatory) [51,52]. Apart from that, neutrophils actively participate in tissue repair by releasing factors capable of inducing intestinal tissue healing [7].

4.3. Targeting Neutrophils to Resolve Intestinal Inflammation

4.3.1. Neutrophil Chemotaxis Blockade

Chemokine gradients, among other factors, mediate neutrophil migration to the intestinal tissue. Therefore, the induction of a resolute phase needs to revert those gradients to block the continuous supply of neutrophils to the inflamed tissue.

Apart from their role in remodelling the extracellular matrix (ECM), matrix metalloproteinases (MMPs) are currently known for regulating the availability of certain chemokines. MMP3-treated Caco-2 intestinal epithelial cells present higher CXCL7-dependent neutrophil chemotaxis capacity [53]. Moreover, MMP7^{−/−} mice show accumulation of neutrophils in the submucosa and an impaired transepithelial migration during DSS-induced colitis, which is parallel to a defect in the transmucosal chemokine gradient, suggesting that MMP7 controls the activity or localization of different chemokines [54].

Additional functional experiments using MMP inhibitors or transgenic mice demonstrated the participation of these proteolytic enzymes during intestinal inflammation. However, the specific action of each MMP varies across the numerous members of this protein family. For instance, Mmp-9-deficient mice showed a reduction in the severity of DSS experimental colitis and a reduction in the inflammatory cell infiltrate (including neutrophils) in the colon [55]. In contrast, mice lacking Mmp-2, Mmp-10, or Mmp-19 exhibited the opposite behaviour, showing increased neutrophil infiltration in the colon and aggravated colitis symptoms [56–58]. Moreover, the analysis of the recovery phase, following DSS removal, revealed that Mmp2^{−/−}, Mmp10^{−/−}, and Mmp19^{−/−} mice were unable to resolve colon inflammation adequately [56–58]. Interestingly, that effect was associated with dysregulated neutrophil infiltration during the recovery phase, which in the case of Mmp-19-deficient mice was caused by abnormalities in the cleavage of the chemokine Cx3cl1 [58].

4.3.2. Neutrophil Apoptosis

The apoptosis of accumulated neutrophils in inflamed tissues is essential for restoring tissue homeostasis. Defects in neutrophil apoptosis are commonly associated with immune-mediated diseases [59,60]. Actually, patients with IBD show increased neutrophil survival and delayed apoptosis [61,62]. Neutrophils isolated from an equine model of colitis also presented delayed LPS-induced apoptosis [63], suggesting that the observed increase in neutrophil lifespan may affect the proper resolution of intestinal inflammation. Along with that, different studies involving transgenic mice with altered apoptotic components were performed. Mice deficient in the apoptotic signal trail subjected to DSS-induced colitis display aggravated disease severity and leukocyte infiltration [64]. Plus, mice lacking the apoptotic agonist BH3 interacting domain death agonist (Bid) showed higher persistent weight loss than their wild-type counterparts in the same colitis model [65].

4.3.3. Neutrophil and Specialised Resolving Lipid Mediators

Maresins (MaRs), protectins (PDs), lipoxins (LXs), and resolvins (Rvs) are specialised pro-resolving lipid mediators (SPMs) generated from the metabolism of the arachidonic acid or omega-3 polyunsaturated fatty acids (omega-3-PUFA). These molecules play a

critical role in achieving resolution by decreasing leukocyte activity and promoting tissue repair. PMNs synthesise lipoxin A4, and other SPMs [66–68] that benefit from intestinal inflammation, as was demonstrated in different experimental models of colitis [69–71].

Several studies have linked the activity of SPMs to neutrophils in the context of IBD. MaR1, RvE1, and PD1 reduce PMN infiltration to colon tissue in DSS- and TNBS-treated mice [72–74]. In line with this, the administration of an agonistic monoclonal antibody of the RvE1 receptor (ChemR23) decreases neutrophil infiltration to intestinal tissue during the non-resolutive T cell transfer mouse model [75]. Interestingly, high expression levels of ChemR23 are associated with increased neutrophil infiltration in colon biopsies of patients with IBD [75], suggesting a strong relationship between the activity of the RvE1 receptor and excessive accumulation of neutrophils in the inflamed colon mucosa. Moreover, PD1n-3DPA and RVD5n-3DPA prevent the intestinal damage caused by DSS, and this effect is attributed to the regulation of neutrophil recruitment [76]. A series of in vitro and in vivo experiments demonstrated that both SPMs impaired the adhesion of neutrophils to the endothelium, while other relevant processes in leukocyte trafficking, such as rolling, remained unaffected [76].

5. NETs Overview

In 2004, NETs appeared as a novel innate response of neutrophils to kill bacteria [77]. Extracellular traps are an ancient and conserved defence mechanism [78,79] composed of chromatin fibres, histones, and granular proteins such as calprotectin, neutrophil elastase (NE), myeloperoxidase (MPO), and cathepsin G, among others [80]. Initially, NETs were known for their participation in eradicating pathogens through microbial toxicity or by their immobilisation and subsequent phagocytosis by other immune cells [81], contributing to host protection against infections. However, NET content causes indiscriminate tissue damage and an excessive pro-inflammatory response, which may lead to the development of numerous autoimmune/inflammatory pathologies [82]. Indeed, many studies indicate that the imbalance in the NET production contributes to the activation of different pathogenic pathways in rheumatoid arthritis (RA) [83], systemic lupus erythematosus (SLE) [84], and IBD [29].

5.1. NETs and IBD

The existing literature demonstrates the participation of NETs in the development of inflammatory bowel disease. Circulating levels of NET formation markers such as MPO-DNA complexes are elevated in patients with IBD as compared to healthy volunteers [29]. Additionally, the same group of patients presented with impaired NET degradation ability as controls when exposed to DNase [29]. Similarly, faecal samples from patients with CD and UC showed increased levels of NET-associated proteins [85]. In line with this, preclinical experiments have demonstrated that NETs play a critical role in the pathogenesis of intestinal inflammation. Actually, the degradation of NETs by administering DNase to mice subjected to DSS- or TNBS-induced colitis suppresses the progression of the disease and improves the mucosal damage [29,41].

5.1.1. NET Components and IBD

Myeloperoxidase

Myeloperoxidase is a cationic heme-containing enzyme, mainly found in the azurophil granules of neutrophils, and in the lysosomes of monocytes to a lesser extent. The presence of halides and hydrogen peroxide allows MPO to catalyse the formation of ROS, such as hypochlorous acid (HOCl) [86]. The processes leading to NET formation are not entirely understood and differ considerably depending on the initial stimulant. However, it is generally accepted that MPO and ROS play a critical role in NET formation since patients with MPO-deficient neutrophils fail to form extracellular traps [87]. Furthermore, impaired NET formation in neutrophils from chronic granulomatous disease patients (due to the lack of functional NADPH) reverts after the exogenous administration of HOCl [88].

The involvement of MPO-HOCl in the context of IBD has been extensively studied. MPO levels are increased in both biopsies and stools of patients with IBD [89,90]. MPO levels positively correlate with disease severity [91]. Similarly, preclinical studies have shown that MPO inhibition in mice causes amelioration of clinical and biochemical parameters during DSS-induced colitis, highlighting the importance of MPO activity during the development of intestinal inflammation [92,93].

Protein arginine deiminase-4

Protein arginine deiminase-4 (PAD4) is a hydrolase responsible for catalysing the citrullination or deamination of proteins. PAD4-mediated histone citrullination is critical for NET formation due to that post-translational modification allows chromatin decondensation [94], which could explain why PAD4-deficient neutrophils present impaired NET formation [95].

Several studies have shown a connection between PAD4 activity and the progression of intestinal inflammation. PAD4^{-/-} mice showed abnormal NET formation, and that observation correlated with an improvement in intestinal barrier function during DSS colitis [96]. However, contradictory results revealed worse colitis symptoms and rectal bleeding in PAD4-deficient mice subjected to DSS-induced colitis [97]. Therefore, further studies are required to determine the specific contribution of PAD4 to the maintenance of intestinal mucosa homeostasis.

Neutrophil elastase

Neutrophil elastase is a serine protease stored in neutrophil granules and is one of the most abundant proteins in NETs [98]. During NET formation, NE translocates to the nucleus and along with MPO, degrades specific histones, facilitating the decondensation of chromatin [99].

NE expression is upregulated in UC intestinal tissue [100] and their levels increase with the histopathological score in CD patients [101]. Plus, NE expression can be used as an indicator of the severity of colitis in murine DSS-induced colitis [23]. Additionally, NE hyperactivity caused by the lack of the serine protease inhibitor secretory leukocyte protease inhibitor (SLPI) promotes exacerbated colon inflammation in the same mouse model [39]. Noteworthy, this serine protease may act on the effectiveness of different IBD frontline therapeutic monoclonal antibodies. It has recently been reported that the proteolytic activity of NE degrades, to a different extent, several biological agents currently used for treating patients with IBD [102].

DNA

In addition to the release of different proteins, neutrophils can expel DNA molecules (essentially mitochondrial DNA) during NET formation. This DNA acts as a scaffold for the protein components of the NET, allowing for the proper NET release by neutrophils to combat an infection or tissue damage [103].

As for other components of the NETs, circulating DNA-MPO complexes have increased in UC and CD patients [29,104]. Similarly, extracellular DNA levels in plasma were higher in mice subjected to DSS-induced colitis compared to controls [105], suggesting the participation of this NET component during intestinal inflammation.

5.1.2. Targeting NET' Components in IBD

MPO inhibitors

Targeting the NET component MPO has been explored as a therapeutic approach for alleviating intestinal inflammation symptoms. AZD3241 is a specific inhibitor of extracellular MPO activity. The administration of this compound to DSS-induced colitic mice decreased weight loss and improved both clinical and histological scores [93]. Additionally, the MPO inhibitor 4-methoxy-TEMPO (MetT) demonstrated efficacy in the same animal model. Chami B et al. observed a significant improvement in the histopathological damage after the treatment with MetT in DSS experimental colitis [92]. A disadvantage of using MPO inhibitors is the putative inhibition of the physiological phagocytic capacity of neutrophils and its implications for the host defence against pathogens and tissue damage.

Therefore, theoretically, developing inhibitors that target extracellular MPO appears to be a more suitable approach for translating these results to the human setting.

PAD4 inhibitors

In the context of intestinal inflammation, two PAD4 inhibitors, Cl-amidine and streptonigrin, have been tested. Cl-amidine administration to mice subjected to TNBS-induced colitis reduced the disease activity index and colonic tissue inflammation [106]. This relief in colitis symptoms was accompanied by a decrease in the expression of relevant pro-inflammatory mediators and NET formation [106]. Moreover, Cl-amidine reduces the severity of DSS-induced colitis by suppressing leukocyte activation and preventing the associated DNA damage to colon epithelial cells [107].

Similarly, streptonigrin is a selective inhibitor with high specificity for PAD4 [108]. In mice receiving DSS, this compound reduces weight loss, rectal bleeding, diarrhoea, and general colonic inflammation signs [28]. Furthermore, streptonigrin downregulates the colonic mRNA expression of cytokines and inflammatory genes such as LCN2, IL-1 β , and TNF- α . Interestingly, this PAD4 inhibitor did not present any cytotoxic effects on mice as the intestinal architecture and integrity were not affected by its administration [28]. Altogether, these data suggest that the inhibition of the citrullination activity of PAD4 may be a promising therapeutic strategy for dysregulated colonic inflammation.

NE inhibitors

The viability of different NE inhibitors for the modulation of intestinal mucosal inflammation has been tested in IBD-like animal models. That is the case of alpha-1-antitrypsin (AAT), which attenuates colonic clinical and histological signs of inflammation in mice exposed to DSS. This improvement in disease severity was associated with decreased inflammatory cellular infiltration and reduced release of pro-inflammatory cytokines [109]. Moreover, AAT also accelerates intestinal mucosa repair after DSS withdrawal [109], suggesting that NE inhibition, not only prevents intestinal inflammation but also regulates the recovery of colonic tissue homeostasis. In line with this, transgenic overexpression of elafin, an NE disruptor, protected mice from DSS- and TNBS-induced colitis [110]. Elafin transgenic mice present reduced expression of central pro-inflammatory mediators such as IL6, RANTES, or MIP1 α and improved intestinal barrier integrity [110].

DNases

DNA is one of the principal components of NETs, so its degradation appears as one of the main targets for NET elimination. DNase I is an enzyme responsible for dissolving the DNA strands of NETs, and its suitability to modulate intestinal inflammation has been recently tested. Li T et al. demonstrated that the administration of DNase I to mice subjected to DSS colitis protected against weight loss and tissue damage [29]. Interestingly, the inhibition of NET formation exerted by DNase I decreased macrophage activation and the production of pro-inflammatory cytokines [29], suggesting that NETs DNA degradation might be of particular relevance for generating new treatments for patients with IBD (Figure 2).

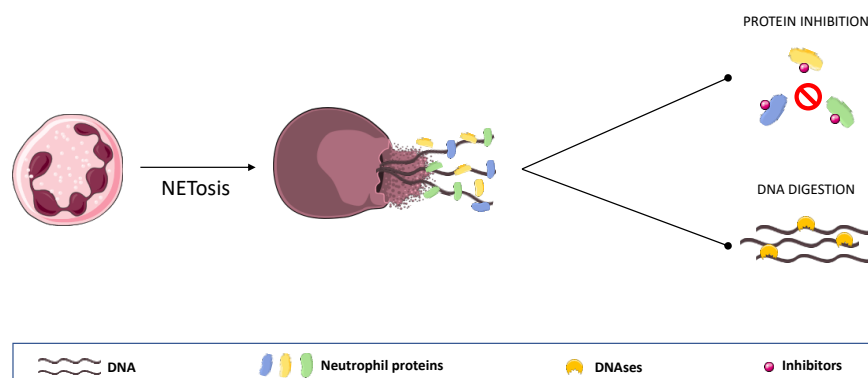


Figure 2. A summary of the different approaches used to block neutrophil extracellular traps formation.

6. Conclusions

Neutrophils are one of the central figures of innate immunity, and based on recent research, this cell type is more relevant to the onset and progression of IBD than initially postulated. Pre-clinical and clinical data unequivocally demonstrate the prominent role played by neutrophils in different aspects of IBD pathophysiology. The complete understanding and regulation of neutrophil biology open the door to developing new drugs for treating IBD. Some of the putative new therapeutic targets to combat intestinal inflammation described above show promising results, particularly in mice colitis models. However, the translation of those approaches to the human setting must entail comprehensive knowledge of how to blockade excessive neutrophil activation while preserving normal neutrophil function, as their complete elimination would also impair the physiological host defence against pathogens and the resolution of inflammation. Therefore, further studies on the cellular and molecular mechanisms controlling neutrophil functions are still necessary.

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