Review

Neutrophil Influence on Adaptive Immunity

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Neutrophil–T cell crosstalk in inflammatory bowel disease

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Abstract

Neutrophils are the most abundant leucocytes in human blood, promptly recruited to the site of tissue injury, where they orchestrate inflammation and tissue repair. The multifaceted functions of neutrophils have been more appreciated during the recent decade, and these cells are now recognized as sophisticated and essential players in infection, cancer and chronic inflammatory diseases. Consequently, our understanding of the role of neutrophils in inflammatory bowel disease (IBD), their immune responses and their ability to shape adaptive immunity in the gut have been recognized. Here, current knowledge on neutrophil responses in IBD and their capacity to influence T cells are summarized with an emphasis on the role of these cells in human disease.

Keywords

CD, human, IBD, IL-22, IL-23, LL-37, mucosal immunology, neutrophils, T cells, Th17, UC

Abbreviations: 6-MP, Mercaptopurine; AHR, Aryl hydrocarbon receptor; CD, Crohn’s disease; CGD, chronic granulomatous disease; DSS, dextran sodium sulphate; EEN, total enteral nutrition; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte–macrophage colony-stimulating factor; IBD, inflammatory bowel disease; IFN-γ, Interferon-γ; IL, interleukin; LL-37, Cathelicidin; MHC, major histocompatibility complex; MPO, myeloperoxidase; NETs, neutrophil extracellular traps; RORγt, retinoic acid receptor-related orphan receptor gamma-t; ROS, reactive oxygen species; STAT3, signal transducer and activator of transcription 3; Th, T helper; TLR, Toll-like receptor; TNBS, Trinitro-benzene sulphonic acid; TNF, tumour necrosis factor; UC, ulcerative colitis.

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INTRODUCTION TO INFLAMMATORY BOWEL DISEASE

Inflammatory bowel disease (IBD) is a progressive non-curative disorder of the gastrointestinal tract subdivided into two major subtypes, Crohn’s disease (CD) and ulcerative colitis (UC). The onset of IBD usually occurs in young adults, but approximately 25% of all patients with IBD are diagnosed during childhood [1,2]. The current view of IBD pathogenesis is complex and stems from studies on human genetics, microbiome research and immunology. The multifactorial disease mechanisms involve genetic susceptibility and environmental factors that lead to a dysregulated commensal ecosystem and misguided immune responses in the gut. Indeed, a critical role for the immune system in perpetuating IBD can be seen from current treatment options that aim at limiting/dampening inflammation. These include steroids, total enteral nutrition (EEN), immunomodulatory drugs (methotrexate, 6-MP) and biological therapies. Although biological drugs targeting TNF (etanercept, infliximab, adalimumab, certolizumab pegol and golimumab), T cells (vedolizumab, α4β7 inhibitor) and IL-23 (ustekinumab) have revolutionized treatment of IBD [3], up to 40% of patients do not respond to anti-TNF therapy, or it loses efficacy with time [4]. IBD subtype, severity and clinical response are determined using a global approach including clinical examination, endoscopy, radiology, histopathologic review and laboratory tests. One of the key non-invasive laboratory tests of intestinal inflammation is faecal calprotectin [5]. Calprotectin is a protein abundant in neutrophils, and its levels have been related to a variety of clinical IBD characteristics and aspects [5–12]. In addition, neutrophils and their localization in the gut are important for assessment of histological IBD severity through clinical scoring systems [13]. New insights into neutrophil biology, their heterogeneity and plasticity in contexts stretching from tissue homeostasis to inflammation depict them as sophisticated cellular immune response mediators [14,15]. In this review, the neutrophil influence on adaptive immunity through interactions with T cells, and in particular Th17 cells, neutrophil antigen-presenting capacities, and their role in IL-23 driven inflammation will be covered focusing on human IBD (Figure 1).

**FIGURE 1** Human neutrophil–T cell crosstalk in IBD. Neutrophil recruitment from the blood to the intestine is promoted through the CXCR1/CXCR2/IL-8 axis. Neutrophil responses in IBD are illustrated with a focus on their possible influence on Th17 differentiation and maintenance through LL-37 and IL-23, respectively. Furthermore, neutrophils exhibit bactericidal activity through production of ROS, MPO and NETs, as well as contribute to production of Th17 cytokines, such as IL-22, and alterations in these functions may disrupt homeostasis. Finally, neutrophils might be able to directly interact with T cells through presentation of antigens on MHC class II.
INTIMATE CROSSTALK BETWEEN NEUTROPHILS AND T CELLS IN IBD

Among the many aspects of neutrophil and T-cell biology, the ability of both neutrophils and T cells to infiltrate the intestine during homeostasis and inflammation is of particular importance for IBD. It is evident from studies performed in a non-IBD context that neutrophils and T cells crosstalk [16], and their conversation is not one of the lonesome kind: stromal cells in the microenvironment respond to T-cell-derived IL-17 with induction of factors such as IL-8, G-CSF or GM-CSF, crucial for neutrophil recruitment and survival [17–20]. Except for Th17 cells that are effector CD4* T cells named after their ability to produce of IL-17, also other types of T cells, such as γδT cells, mucosal associated invariant T cells, CD1d-restricted NKT cells and subsets of CD8* T cells, are able to produce IL-17 [21]. Although neutrophils cannot directly respond to IL-17 due to the lack of its receptor, Th17 cells can directly interact with human neutrophils through IL-17-independent mechanisms via production of GM-CSF, TNF and IFN-γ [22]. Moreover, it has also been demonstrated that human neutrophils cultured with IFN-γ and lipopolysaccharide induced migration of Th17 cells in a CCL2- and CCL20-dependent manner [22]. Interestingly, in a reciprocal chemotactic relationship, the Th17 cells produced IL-8 leading to neutrophil migration [22]. In line with these reports, in colonic tissue from children with the newly diagnosed treatment-naïve IBD, the highest expression of IL-8 and its receptors CXCR1 and CXCR2 (found on neutrophils) was detected in patients with severe disease and levels of these receptors were correlated with expression of their ligand IL-8 [23]. This suggests an IL-8/CXCR1/CXCR2-dependent influx of neutrophils into the intestine during IBD. In addition, a higher frequency of IL-8* cells was found in lamina propria of patients with IBD compared with controls, while epithelial IL-8 levels remained unaltered [23]. But what was the identity of those IL-8* cells in colonic lamina propria of patients with IBD possibly having the capacity to contribute to neutrophil recruitment? Evidence of T cells themselves being major producers of IL-8 in IBD is scarce [24], and recent studies employing broader sequencing techniques point to stromal and myeloid sources of IL-8 in both UC and CD [25–27]. In fact, isolated colonic human fibroblasts have the capacity to respond to IL-17 and T-cell-derived IL-22 with elevated levels of neutrophil chemo-attractants [28–30]. Corroborating a role for T cells in recruitment of neutrophils, work done in a mouse model of trinitro-benzene sulphonic acid (TNBS) colitis suggested that T cells regulate recruitment of neutrophils to the intestine [31]. However, although a direct T-cell effect on neutrophil recruitment was proposed, indirect T-cell-mediated mechanisms involving stroma or myeloid cells were not addressed and, thus, not ruled out.

Apart from the chemotactic relationship between T cells and neutrophils that may be direct or indirect as discussed above, it has recently been suggested that neutrophils are able to facilitate Th17 differentiation in secondary lymphoid organs through production of the antimicrobial peptide cathelicidin (also known as LL-37) [32]. Cathelicidin is found in secondary granules of neutrophils and in neutrophil extracellular traps (NETs), which are extracellular, web-like chromatin structures, not only important in protection against infection, but also implicated in immune-mediated conditions. In this study, cathelicidin was shown to potentiate AHR and RORγt expression and SMAD2/3 and STAT3 phosphorylation in Th17 cells [32]. Moreover, the authors demonstrated that cathelicidin directed T cells from a Th1 to a Th17 phenotype and it further protected Th17 cells, but not Th1 cells, from apoptosis [32]. Although this mechanism was shown for neutrophils and T cells in secondary lymphoid organs, a similar mode of action may be relevant also for the inflamed gut where neutrophil degranulation and formation of NETs is evident [33]. Indeed, higher cathelicidin levels were detected in UC and CD intestinal biopsies [34]. In addition, serum levels of cathelicidin were elevated in children with IBD [35] and have been further related to disease activity and indicated risk for intestinal strictures in adults with CD [36].

Although work done in recent years has shed some insights into intestinal neutrophil influx mediated by T cells, as well as neutrophil capacity to influence Th17 differentiation, future studies should address these interactions in a wide range of clinical IBD contexts. Investigating neutrophils and T cell simultaneously, and with a strategy employing single-cell sequencing and proteomic approaches, given the preproduced neutrophil granular content, will likely be both important and rewarding for future study design.

NEUTROPHILS AND ANTIGEN PRESENTATION

Antigen presentation to T cells is an important step in maintenance and activation of adaptive immunity, and neutrophils are able to orchestrate this process by directly presenting antigen to T cells [37,38]. In a mouse model of chronic gut inflammation, colonic neutrophils isolated from lamina propria were able to induce proliferation of antigen-specific CD4* T helper cells, in both antigen- and MHC class II (MHC-II)-dependent manners [39]. In addition, colonic neutrophils expressed higher surface levels of the costimulatory molecule CD86 and of MHC-II in inflamed mucosa and showed elevated synergistic cytokine production when co-cultured with T cells [39]. This suggests that neutrophils infiltrating the intestine can present antigens to T cells, as well as maintain a cytokine-rich local microenvironment perpetuating inflammatory response in the colon. Thus, while there is
precedent to suggest a role for neutrophil antigen presentation to T cells in driving colonic inflammation in mice, little is known on neutrophil antigen-presenting capacities in the secondary lymphoid organs and at the mucosal barriers in patients with IBD. However, in a human non-IBD context, the neutrophil capacity to present antigens and induce proliferation of antigen-specific memory CD4+ T cells has also been demonstrated [37,40]. In more detail, this process was MHC-II-dependent [37] and neutrophils also had the potential to migrate to lymph nodes via CCR7 [40]. In addition, neutrophil antigen-presenting capacities and phenotypes have been explored in multiple clinical contexts, such as in allergy [41], parasitic skin infection [42], rheumatoid arthritis [43], and cancer [44]. Taken together, there is reason to believe that neutrophils contribute to activation and maintenance of adaptive responses in human IBD also through a direct antigen presentation to T cells, but confirmatory studies will be needed to address this in clinical IBD contexts (Figure 1).

**IL-23 SIGNALLING IN NEUTROPHILS AND T CELLS**

IL-23 is a heterodimeric cytokine consisting of a unique p19 subunit pairing with p40, the latter also being shared with IL-12. IL-12 and IL-23 have divergent functions in shaping T-cell immunity: while IL-12 regulates the differentiation of naïve T cells into Th1 cells producing IFN-γ, IL-23 is essential for maintenance of Th17 cells producing IL-17A and IL-22 [45,46]. In IBD, the IL-23 receptor [47], as well as members of IL-23 and IL-12 signalling pathways, is well-established IBD risk gene [48]. Furthermore, the p40 subunit is successfully targeted in the clinic with monoclonal antibodies [3]. While the importance of IL-23-mediated production of IL-17A and IL-22 by T cells is well defined in driving T-cell-dependent animal models of colitis [46,49–51], other sources of IL-17A and IL-22 have also been described. Indeed, IL-22- and/or IL-17A-expressing neutrophils have been reported in a variety of tissue contexts during inflammation both in humans and in mice [52–60]. With respect to the intestine, both neutrophils and IL-22 had a protective effect against disease in a microbiota antigen-specific T-cell-mediated colitis model, although a causal relationship between IL-22-producing neutrophils and protection against inflammation was not formally shown [60]. Mechanistically, it was suggested that IL-23 stimulated the expression of IL-23R, AHR, RORC and IL-17A/IL-22 in neutrophils and that this occurred in a mTOR-dependent manner [60]. In a dextran sodium sulphate (DSS)-induced mouse model of acute colitis, a protective role of IL-22-producing neutrophils has been demonstrated [57]. In more detail, the IL-22 production was potentiated by TNF, and IL-22-producing neutrophils targeted colonic epithelium to augment production of protective antimicrobial peptides [57] (Figure 1).

With regard to neutrophil heterogeneity and different states, in a study focusing on human neutrophils in IBD, IL-22 mRNA expression was higher in a subset of CD177+ neutrophils, and these neutrophils were subsequently found at higher frequencies both in peripheral blood and in colonic lamina propria in patients with UC and CD, compared to controls [61]. In addition to IL-22 expression, the CD177+ neutrophils also exhibited increased bactericidal activity through producing higher levels of reactive oxygen species (ROS), myeloperoxidase (MPO), NETs and antimicrobial peptides, but lower levels of proinflammatory cytokines, such as IL-17A, IFN-γ and IL-6. A protective effect against inflammation of this particular neutrophil population was further suggested in a DSS colitis model, where depletion of CD177-expressing cells aggravated intestinal disease [61]. It could thus be concluded that CD177+ neutrophils may play a protective role in IBD through increased bactericidal activity and production of IL-22. Of note, human neutrophil capacity to produce IL-17 has been debated and issues regarding the specificity of commercially available antibodies recognizing IL-17 and IL-17 family member cytokines in human neutrophils have been raised [62], emphasizing the necessity of confirmatory studies including multiple detection techniques on different levels ranging from mRNA to protein. Furthermore, attention to accuracy when comparing results from different contextual frameworks (e.g. species, tissues, diseases and experimental setups) is also needed in this context. An intriguing question regarding the induction of IL-17A and IL-22, both in T cells and in neutrophils themselves, is the cellular source of their upstream regulator IL-23. While the general and most established notion would be antigen-presenting cells, such as dendritic cells or macrophages [63–65], as the dominant cellular source of IL-23, it was recently suggested that neutrophils were the main source of IL-23 in the newly diagnosed treatment-naïve children with IBD [23]. Other human studies have also shown that bacteria-derived neutrophil-activating proteins induced the production and/or secretion of IL-23/IL-12 [66,67]. Moreover, it has been demonstrated that TLR8-dependent human neutrophil production of IL-23 was potentiated by TNF and that supernatants from TLR8-stimulated neutrophils promoted naïve T-cell differentiation into Th17 cells [68]. Collectively, this may suggest that neutrophils not only contribute to production of IL-22 and IL-17A, but that they may also be able to regulate their induction through IL-23, both in T-cell-dependent and in an autocrine manner. Future research is warranted to define the significance of neutrophil contributions to IL-23, IL-22 and IL-17 family cytokines in IBD, where the neutrophil capacity to induce and contribute to Th17 responses should be addressed both at early stages of disease development and in advanced IBD settings. Different
strategies may be needed to target IL-23 signalling pathway dependent on the cellular context/stage/status of disease.

LESSONS LEARNT ON INTESTINAL NEUTROPHIL BIOLOGY FROM MONOGENETIC IBD

Advances in whole-genome sequencing have facilitated studies of immunodeficiencies and IBD-like conditions that affect a proportion of young children with very-early-onset IBD. In those cases, a single gene causing immunopathology can often be identified and explained by functional responses in immune or non-immune cells. Indeed, neutrophil defect-causing mutations have been associated with IBD-like manifestations, and by studying these rare conditions, we might gain novel insights into IBD pathogenesis. The neutrophil defects includes, but are not limited to, chronic granulomatous disease (CGD) (**CYBB, CYBA, NCF1, NCF2 and NCF4**), glycogen storage disease type Ib (**SLC37A4**), congenital neutropenia (**G6PC3**) and leucocyte adhesion deficiency type 1 (**ITGB2**) (reviewed in Ref. [69]). These disorders may present with neutropenia, functional defects in phagocytic ROS production and defective granulocyte chemotaxis, resulting in intestinal manifestations that phenotypically resemble CD, with or without granuloma formation. Indeed, immunological assessment, including immunotyping of T-cell subsets and analysis of neutrophil oxidative burst capacity, is part of routine clinical care when monogenetic IBD is suspected [70].

As not all forms of neutropenia have been related to IBD-like disease, it is reasonable to speculate that functional neutrophils, even at low numbers, are able to elicit their protective effects preventing intestinal inflammation [71]. Interestingly, possible secondary effects on T-cell subsets, including altered regulatory T-cell frequencies, have been noted in CGD and other immunodeficiencies primarily presenting with granulocyte defects [72–74]. Of note, ROS-dependent induction of T regulatory cells by macrophages has been described in animal models and humans [75]. Indeed, while human neutrophils are capable of inducing suppressive T cells during pregnancy [76] and of inhibiting T-cell proliferation during systemic response [77], whether and how neutrophils regulate suppressive T-cell functions in human IBD remains to be further defined (Figure 1).

FUTURE PERSPECTIVE

It is an exciting time period for research on neutrophil–T-cell crosstalk in IBD. Mechanistic insights from animal models and emerging human studies have recently contributed significantly to our understanding of the neutrophil role in intestinal inflammation, as well as to their capacity to influence adaptive immunity. Depletion of neutrophils using different experimental setups, models and species leads to different outcomes with respect to pathogenicity and protection in intestinal inflammation (discussed in Ref. [78,79]). This phenomenon is perhaps not surprising in the light of the multifaceted functions of neutrophils and their intricate relationship with T cells. It should also not be overlooked that these two cells function in concert with other cell types in their microenvironment, where microbiota and its interplay with the immune system are of key importance for understanding of the spectrum from homeostasis to inflammation in the gut. Looking forward, more specific neutrophil targeting in mice [80] will be essential to further dissect neutrophil–T-cell interactions in models of IBD. Moreover, the intervention with different functional aspects of neutrophils and their crosstalk with T cells, rather than complete elimination of cells that are as crucial in maintaining intestinal homeostasis as neutrophils are, may present a more straightforward therapeutic strategy. Of note, recent broad sequencing efforts dissecting the intestinal immunological landscape in both UC [25] and CD [26] did unfortunately not include neutrophils, and this represents an exciting knowledge gap to be filled by future work. Studies designed to address distinct clinical aspects of IBD focusing on neutrophil–T-cell interactions using high-dimensional technologies at single-cell resolution, and paying attention to different neutrophil states, which may be highly heterogeneous and developmental context-dependent [16,81], will be important to build a basis for development of next-generation therapeutic strategies targeting neutrophil functions in IBD and other chronic inflammatory conditions.

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CONFLICT OF INTERESTS

The author declares no competing interests.

AUTHOR CONTRIBUTION

EK conceptualized the work and wrote the article.

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