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CELLULAR AND MOLECULAR GASTROENTEROLOGY AND HEPATOLOGY

REVIEW

Neutrophils as Components of Mucosal Homeostasis

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SUMMARY

There is recent appreciation that neutrophils contribute significantly more to innate immunity than just their function in battling infection. It is now clear that neutrophils can influence tissue metabolism, the composition of the microbiome, and communication between cell types through the release of microparticles. This article highlights the role of neutrophils in both homeostasis and pathology in mucosal surfaces.

Inflammatory responses in the intestinal mucosa inevitably result in the recruitment of neutrophils (polymorphonuclear leukocytes [PMNs]). Epithelial cells that line the mucosa play an integral role in the recruitment, maintenance, and clearance of PMNs at sites of inflammation. The consequences of such PMN–epithelial interactions often determine tissue responses and, ultimately, organ function. For this reason, there is significant interest in understanding how PMNs function in the mucosa during inflammation. Recent studies have shown that PMNs play a more significant role in molding of the immune response than previously thought. Here, we review the recent literature regarding the contribution of PMNs to the development and resolution of inflammation, with an emphasis on the role of the tissue microenvironment and pathways for promoting epithelial restitution. These studies highlight the complex nature of inflammatory pathways and provide important insight into the difficulties of treating mucosal inflammation. *(Cell Mol Gastroenterol Hepatol 2017;4:329–337; http://dx.doi.org/10.1016/j.jcmgh.2017.07.001)*

Keywords: Epithelium; Microbiota; Inflammation; Hypoxia-Inducible Factor; Metabolism.

A primary function of the intestinal mucosa is to provide a selective barrier to the outside. The potential for infection by pathogenic organisms and the necessity to communicate with commensal microorganisms exist on the same surfaces. In this regard, tissue healing after injury occurs in conjunction with the constant flux of new antigenic material and requires that the mucosal immune system appropriately dampen inflammatory and immunologic reactions to harmless ingested antigens. The overlying epithelium plays an important role in coordinating both inflammation and resolution. The epithelium lies juxtaposed to the mucosal immune system and lines the entire gastrointestinal (GI) tract. Covering a surface area of approximately 300 m^2, the human adult intestinal epithelium consists of a monolayer of cells with intercellular tight junctions, a complex 3-dimensional structure, and a thick mucous gel layer that provides a dynamic and regulated barrier to the flux of the luminal contents to the lamina propria.[1,2] It is widely understood that the GI tract exists in a state of low-grade inflammation. Such a state results from the constant processing of luminal antigenic material and the priming of the mucosal immune system for rapid and effective responses to antigens or microbes that may penetrate the barrier.[3]

The presence of polymorphonuclear leukocytes (PMNs) at sites of tissue injury and infection has long been recognized as a hallmark of mucosal inflammation.[4] It increasingly has become appreciated that the presence of PMNs at sites of injury do not necessarily prove causation to tissue damage, and, in fact, a number of studies now suggest that PMNs provide important cues that promote inflammatory resolution and a return to mucosal homeostasis. In this review, we discuss recent literature regarding the role of microbiota in the recruitment of PMNs to the mucosal surface, the critical role of PMNs in oxygen metabolism, and implicating PMNs in promoting homeostasis in the mucosa.

Microbiota Promote PMN Recruitment into the Mucosa

The mammalian GI tract plays host to trillions of bacteria, viruses, and fungi, collectively termed the *microbiota*. A finely balanced mutualism exists within the intestinal mucosa, in that microbes are essential for intestinal health but also can be involved in inflammation and pathologic damage.[5] Because PMNs provide the first line of defense to infection, PMNs frequently interact with the commensal microbiome. In general, PMNs do not initiate inflammation in these interactions with commensal microbes. In past

Abbreviations used in this paper: **ATP, adenosine triphosphatase; CGD, chronic granulomatous disease; DMOG, dimethyloxalylglycine; GI, gastrointestinal; HIF, hypoxia-inducible factor; IBD, inflammatory bowel disease; ICAM-1, intracellular adhesion molecule-1; IL, interleukin; NADPH, reduced nicotinamide adenine dinucleotide phosphate; PHD, prolyl-hydroxylase; PMN, polymorphonuclear leukocyte; SIRPα, signal-regulatory protein-α.**

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2352-345X
http://dx.doi.org/10.1016/j.jcmgh.2017.07.001

years it increasingly has been evident that the microbiome significantly impacts the development and activation of the immune system, including PMNs.

Circulating neutrophils increase within days after birth in human neonates. In a study of antibiotic treatment of pregnant mice, neonatal pups born to these mice developed a reduced number and altered composition of microbes as compared with mice not treated with antibiotics.[6] This microbial shift correlated with reduced numbers of neutrophils, fewer Ly6G+ cells in the bone marrow, and decreased circulating granulocyte colony-stimulating factor. This relative neutropenia was similar in germ-free mice. Prior work had identified interleukin (IL)17 as a key regulator of granulocyte colony-stimulating factor and granulocytosis.[7,8] Indeed, IL17-producing cells were reduced in these antibiotic-treated and germ-free mice. The IL17 production was not dependent on the adaptive immune system because RAG-deficient mice had persistent IL17 production and neutrophil recruitment. The neutropenia associated with antibiotic therapy in these mice resulted in increased susceptibility to sepsis, arguing for a protective role for microbiota-stimulated PMN production and recruitment. This neutropenia was reversed with reconstitution of normal microbiome after antibiotic therapy.

Beyond bacterial load and composition, specific bacteria have been shown to change PMN populations. Segmented filamentous bacteria, for example, have been shown to induce IL17- and CXCR2- (PMN receptor for IL8) dependent recruitment of neutrophils[9] (Figure 1). Segmented filamentous bacteria are spore-forming, gram-positive, filamentous bacteria ranging between 1 and 2 μm in diameter and as long as 80 μm in length that colonize the intestine of mice at the time of weaning.[10] Unlike the IL17-dependent PMN recruitment in the prior neonatal study, the IL17 production was dependent on the adaptive immune system because PMN recruitment was not appreciated in RAG-deficient mice. In neutrophil-depleted mice with filamentous bacterial colonization, bacterial expansion and IL17-producing cells were increased, suggesting a negative feedback of neutrophils on IL17 production. Other studies have had similar findings that germ-free and antibiotic-treated mice have decreased neutrophilic response to peritoneal inflammation.[11] Recruitment in this experimental model was MyD88-dependent. Another study identified that reconstitution of PMN number in germ-free mice can be achieved by serum transfer from mice with a conventional microbiome, suggesting that a soluble factor (eg, IL17) is integral to PMN recruitment.[12] These studies contribute to the conflicting data regarding whether IL17 is more pathogenic or protective in the GI tract. These data speak to the importance of IL17 to recruitment of PMNs necessary to fight infections. Other studies point to the pathogenic, proinflammatory role of this cytokine, particularly IL17F, in the GI tract in diseases such as inflammatory bowel disease (IBD).[13]

There are likely to be differences between various mucosal surfaces with regard to the contribution of PMNs to mucosal homeostasis. A comparison of the GI tract and the lung for instance, suggests that the role of PMNs on tissue function may be different. This particular aspect has been shown convincingly in vivo. The depletion of circulating PMNs using anti-Gr1 antibodies resulted in the exacerbation of symptoms in a number of different murine colitis models, strongly implicating PMNs as a central protective factor in ongoing inflammation.[14] By contrast, the depletion of PMNs in acute lung injury models appears to have an anti-inflammatory effect[15] and severe disease has been associated strongly with the presence of PMNs, driving the argument that PMNs play a key role in acute lung injury.[16] It is notable that this idea has been revisited to suggest that PMNs can be eliminated effectively through mucociliary clearance

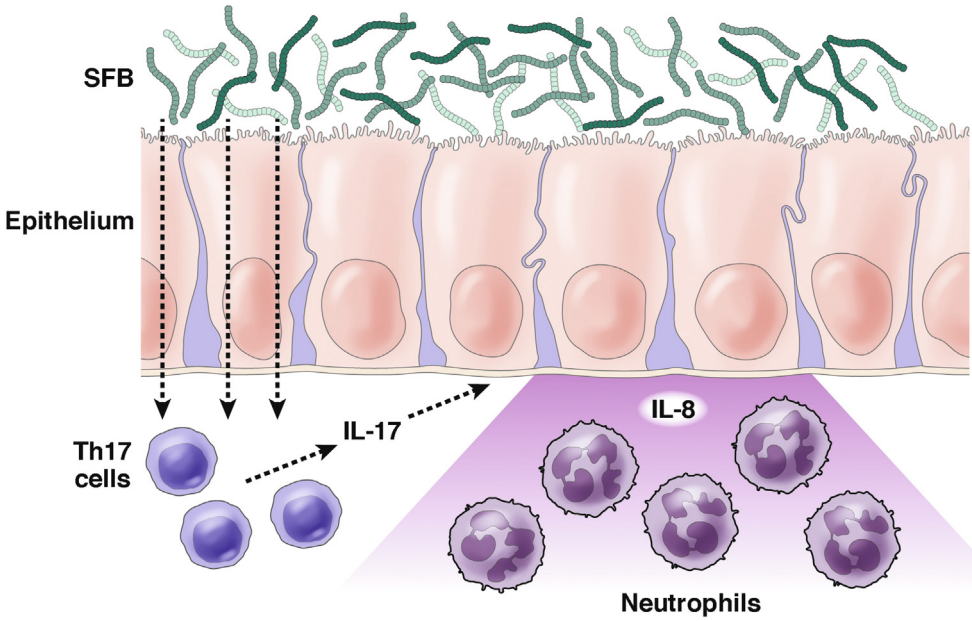

Figure 1. Selective components of the microbiome influence PMN recruitment to the mucosa. The luminal microbiota, including segmented filamentous bacteria (SFB), provide signals (eg, IL23 production from multiple cell types) that drive the accumulation of Th17 cells in the lamina propria. In turn, Th17 cells secrete IL17, which activates the release of chemokines from epithelial cells to promote the accumulation of PMNs at tissue sites.