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Immune and regulatory functions of neutrophils in inflammatory bone loss

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ABSTRACT

Although historically viewed as merely anti-microbial effectors in acute infection or injury, neutrophils are now appreciated to be functionally versatile with critical roles also in chronic inflammation. Periodontitis, a chronic inflammatory disease that destroys the tooth-supporting gums and bone, is particularly affected by alterations in neutrophil numbers or function, as revealed by observations in monogenic disorders and relevant mouse models. Besides being a significant debilitating disease and health burden in its own right, periodontitis is thus an attractive model to dissect uncharted neutrophil-associated (patho)physiological pathways. Here, we summarize recent evidence that neutrophils can contribute to inflammatory bone loss not only through the typical bystander injury dogma but intriguingly also through their absence from the affected tissue, where they normally perform important immunomodulatory functions. Moreover, we discuss recent advances in the interactions of neutrophils with the vascular endothelium and – upon extravasation – with bacteria, and how the dysregulation of these interactions leads to inflammatory tissue damage. Overall, neutrophils have both protective and destructive roles in periodontitis, as they are involved in both the maintenance of periodontal tissue homeostasis and the induction of inflammatory bone loss. This highlights the importance of developing approaches that promote or sustain a fine balance between homeostatic immunity and inflammatory pathology.

1. Introduction

Neutrophils are relatively short-lived, terminally differentiated white blood cells that are endowed with capacity for swift recruitment to sites of infection or tissue injury and potent microbicidal mechanisms [1–3]. Huge numbers of neutrophils [4] are produced in and released from the bone marrow (BM) into the circulation at a rate of 10^{11} neutrophils per day under steady-state conditions [5]. Circulating neutrophils migrate to extravascular sites (*e.g.*, in the skin, gut, lungs, or gingiva) in response to tissue infection or injury *via* the leukocyte adhesion cascade, a sequence of low- and high-affinity adhesive interactions between the neutrophils and the endothelium [6–8]. The first step involves transient rolling interactions, mediated by the binding of endothelial cell surface molecules (P- or E-selectin) to their glycoprotein ligands on neutrophils. This rolling-dependent braking down of neutrophils is followed by their firm adhesion on the endothelium and subsequent intraluminal crawling to identify appropriate sites for transendothelial migration. Firm adhesion and crawling are primarily mediated by β_2-integrins (heterodimers with a unique CD11 subunit and a common CD18 subunit) through interactions with their endothelial counter-receptors, such as ICAM-1 and ICAM-2. Specifically, lymphocyte function-associated antigen-1 (LFA-1; CD11a/CD18) and macrophage-1 antigen (Mac-1; CD11b/CD18) mediate, respectively, firm adhesion and crawling [6,7,9].

As there is a fine balance between the protective and potentially destructive effects of neutrophils, their production, trafficking, and clearance are tightly regulated by several homeostatic mechanisms operating in the BM, intravascularly, or peripheral tissues [10–12].

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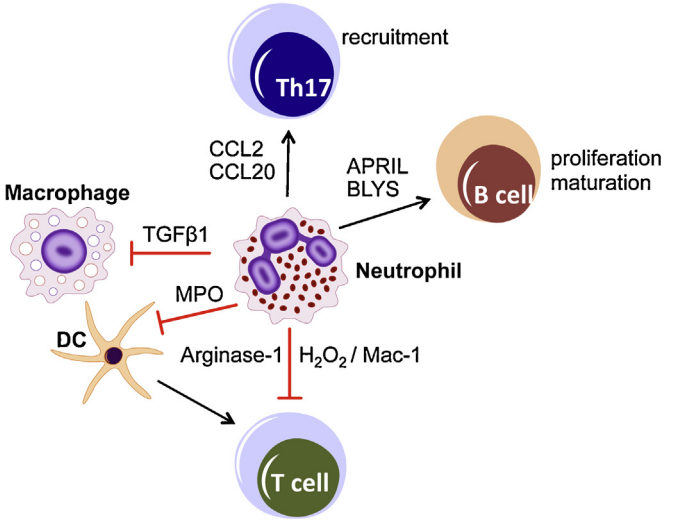

Fig. 1. Neutrophil cross-talk with other leukocyte types. Whereas the recruitment and activation of neutrophils has long been known to be regulated by chemokines and cytokines secreted by both tissue stromal and resident leukocytes, neutrophils are now appreciated for their *de novo* biosynthetic capacity. They can produce and release immunoregulatory molecules that can activate or suppress other leukocyte types, thereby exacerbating or controlling inflammation depending on context. A few examples with potential relevance to periodontal disease are given. Neutrophils release CCL2 and CCL20 and recruit Th17 cells to sites of inflammation. By secreting BLyS and APRIL, neutrophils promote the proliferation and maturation of B cells into plasma cells. Neutrophils can potentially suppress T cell activation by releasing arginase-1 (depletes arginine required for T cell activation) or by delivering H_2O_2 into the immunological synapse in a Mac-1 integrin-dependent manner. Neutrophils can also indirectly suppress T cell activation through a myeloperoxidase-dependent mechanism that inhibits dendritic cell (DC) function. Neutrophil-derived TGFβ1 can promote resolution of inflammation by suppressing macrophage inflammatory responses.

In mice and humans, the granulocyte colony-stimulating factor (G-CSF) is the major regulator of both granulopoiesis and neutrophil release from the BM [13,14]. Interleukin (IL)-17 (also known as IL-17A) promotes granulopoiesis and orchestrates neutrophil recruitment by up-regulating G-CSF and chemokines [10,15] and/or down-regulating endogenous inhibitors of the leukocyte adhesion cascade [16,17].

Although neutrophils have been traditionally viewed as merely anti-microbial effectors in the context of acute infection and inflammation, accumulating evidence suggests that neutrophils are functionally versatile and perform hitherto unanticipated functions, including engagement in regulatory crosstalk with both innate and adaptive immune leukocytes [7,18–20] (Fig. 1). In addition to their classical antimicrobial and cytotoxic mechanisms (release of reactive oxygen species, antimicrobial peptides such as α-defensins and cathelicidin, and proteases such as elastase, cathepsin G or matrix metalloproteinases), neutrophils are now appreciated for a notable *de novo* biosynthetic capacity for C–X–C and C–C chemokines, cytokines with proinflammatory, anti-inflammatory, or immunoregulatory properties, as well as angiogenic and fibrogenic factors [18,21]. This previously underappreciated biosynthetic ability of neutrophils contributes to their crosstalk with tissue resident cells and other leukocytes. For instance, by releasing CCL2 and CCL20, neutrophils can recruit IL-17-producing CD4+T helper cells (Th17) to sites of inflammation [22], whereas by secreting B-lymphocyte stimulator (BLyS) and a proliferation-inducing ligand (APRIL), neutrophils can enhance survival, proliferation, and maturation of B cells into plasma cells [23,24]. Moreover, neutrophil-derived transforming growth factor β1 (TGFβ1) downregulates inflammatory responses by macrophages [25]. Evidence for subsets of neutrophils that perform regulatory functions [26] and for the polarization of tumor-associated neutrophils to phenotypes with antitumor or protumorigenic activity [27] suggests that the neutrophil population may not be as homogeneous as traditionally thought, but may display substantial diversity and functional plasticity (reviewed in refs. [3,18,27–31]).

Therefore, besides hallmarking acute inflammation, neutrophils are now increasingly acknowledged as important players in chronic inflammatory or aging-related disorders, including psoriasis, rheumatoid arthritis, atherosclerosis, inflammatory bowel disease, cancer, diabetes, and periodontitis [18,32–36]. This review discusses emerging new concepts on the role of neutrophils in infection and inflammation using periodontitis as a paradigm. Periodontitis is an oral inflammatory disease that leads to the destruction of the alveolar bone and other tissues that surround and support the teeth, such as periodontal ligament and gingiva, collectively known as the periodontium [37]. Moreover, periodontitis is associated with increased risk of certain systemic disorders, such as atherosclerosis and rheumatoid arthritis [38]. Periodontitis is an attractive study model of neutrophil–microbe interactions for two important reasons. First, the disease is readily accessible for obtaining host cells and tissue as well as microbial samples directly from specific microenvironments in the mouth, thus facilitating the conduct of longitudinal studies. For instance, the microorganisms studied are those that can be recovered directly from diseased periodontal pockets rather than those that have flowed through the ecosystem [39]. Second, periodontal tissue homeostasis and health is particularly sensitive to neutrophil defects affecting their numbers or function, as shown by clinical studies in patients with monogenic neutrophil disorders and experiments in relevant mouse models, discussed below [16,40–48]. Neutrophil infiltration and immunopathology is a hallmark also in common forms of periodontal disease [36,49,50].

2. Concepts derived from the study of rare monogenic diseases

Rare diseases (defined as affecting ≤1 in 1250 individuals) represent an important medical and social issue, cumulatively affecting 25 million patients in North America alone [51]. Importantly, the investigation of rare monogenic diseases is not relevant only to the treatment of patients with these specific disorders. These rare maladies constitute in fact real-life models to understand human biological pathways and obtain critical mechanistic insights into common diseases [46,52–54]. For instance, the study of leukocyte adhesion deficiency (LAD) has led to a better understanding of neutrophil biology and of mechanisms that control periodontal immunity and tissue homeostasis [46,47,55].

2.1. Leukocyte adhesion deficiency type I

LAD constitutes a group of inherited disorders that impede the normal extravasation of circulating neutrophils and hence their recruitment to peripheral tissues [42,56]. The underlying genetic defects involve defective expression or function of β_2 integrins or related adhesion molecules. LAD type I (LAD-I) is caused by deficiency in β_2 integrins, LAD-II involves defective glycosylation of selectin ligands, and LAD-III is due to dysfunction of signaling molecules required for integrin activation [55]. The most common LAD type is LAD-I, an autosomal recessive immunodeficiency arising from mutations in the *ITGB2* gene that encodes for the common β_2-integrin subunit CD18 [42,56]. Neutrophils are absent or only scarcely found in extravascular sites in LAD-I patients, who have increased blood neutrophil counts (neutrophilia), suffer from frequent infections at mucosal or skin surfaces, and develop aggressive periodontitis in childhood [41,47,56,57].

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