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Review

Neutrophils and arthritis: Role in disease and pharmacological perspectives

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ABSTRACT

The inflammatory response in the joint can induce an intense accumulation of leukocytes in the tissue that frequently results in severe local damage and loss of function. Neutrophils are essential cells to combat many pathogens, but their arsenal can contribute or aggravate articular inflammation. Here we summarized some aspects of neutrophil biology, their role in inflammation and indicated how the modulation of neutrophil functions could be useful for the treatment of different forms of arthritis.

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1. Introduction

Rheumatic diseases, represented by varied forms of arthritis and other musculoskeletal disorders, affect millions of people around the world and are currently one of the most studied diseases in many centers of research [1]. There are variable and well-established models to study different types of arthritis, most of them in mice, which give us valuable information about the mechanisms that regulate the production of mediators of inflammation,

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cellular infiltration in the joint and tissue damage and dysfunction. Furthermore, these proof-of-concept models are useful for preclinical studies during the development of new anti-inflammatory and anti-rheumatic drugs [2]. However, although useful, these models do not represent the authentic pathogenesis in humans, which can cause failures during translational studies. Thus, there are many challenges for the study of arthritis, especially on basic research, and being conscious of the limitation of arthritis models is only the first step for a better interpretation of the findings.

Neutrophils are crucial cells that have significant roles in virtually all inflammatory diseases, ranging from acute, chronic, autoimmune, infectious, and non-infectious conditions [3]. The most known effector functions of neutrophils are related to their role in innate immunity since different chemoattractants quickly recruit neutrophils from the bloodstream. However, recent research points out neutrophils as active cells during adaptive immunity, facilitating the recruitment and activation of antigen-presenting cells or due to a direct interaction with T cells [4,5].

Neutrophils have an arsenal of antimicrobial molecules that are essential to combat several microorganisms. In this regard, the neutropenia or malfunctioning of neutrophils is associated with the development of opportunistic infectious diseases. On the other hand, several of the neutrophil-derived molecules that are crucial for the control of pathogens are detrimental to the host tissue. Especially in autoimmune and autoinflammatory disorders, the accumulation of neutrophils causes tissue damage and dysfunction, sometimes irreversible [4]. Thus, the development of compounds that interfere on neutrophil biology is useful for the treatment of many inflammatory diseases. Particularly in rheumatology, the infiltration of neutrophils is directly associated with the worsening of the clinical condition, including cartilage and bone destruction and pain in the different forms of arthritis [6]. Here, we explored the recent findings in the field of neutrophil biology, its association with arthritis and possible pharmacological approaches focusing on the biology of neutrophils.

2. Neutrophil biology

Neutrophils represent one of the most important effector cells during innate immune response. The mechanisms by which neutrophils deal with infection and their contribution to tissue damage are discussed below in separated sections. In humans, these cells represent the most abundant leukocytes in the blood, a variable that changes considerably among the species [7]. Importantly, there is a rapid mobilization of stored neutrophils from the bone marrow to the circulation during infectious/inflammatory conditions [8,9]. Independent on the species, neutrophils quickly migrate from blood to the tissue under different chemoattractants during inflammation, where they have an important role in the control of infections and contribute to tissue repair. During the maturation of neutrophils, much of their arsenal of molecules filled different types of granules, including primary or azurophilic, secondary or specific, and tertiary or gelatinase. Section 2.2 addresses the content of each granule in detail (killing mechanisms of neutrophils in host defense) [for review see 10,11]. Adult humans produce billions of neutrophils daily mainly by the actions of the cytokine Granulocyte-Colony Stimulating Factor (G-CSF) on progenitor stem cells. In fact, the infusion of G-CSF is clinically used to increase the neutrophil count in the peripheral blood of patients undergoing myelosuppressive chemotherapy for acute myeloid leukemia or severe chronic neutropenia [12]. Currently, a paradigm in the field of neutrophil biology is its lifespan, considered short when compared to other leukocytes. Using *in vivo* labeling neutrophils, Pillay and colleagues found that human neutrophils present a lifespan of 5.4 days on circulation while mouse neutrophils survive up to 12.5 h in physiologic conditions [13].

Some studies indicate that there is a heterogeneous population of neutrophils that could represent different phenotypes of these cells during an inflammatory response. Those variations depend on their morphology, cell surface markers, secreted molecules and density [for reviewnd see 14]. However, these subsets of neutrophils could be only a natural variation during their lifespan, considering the immature, mature and aged neutrophils and according to their state of activation. *In vitro* studies suggest that aged neutrophils decrease their ability to migrate and produce less pro-inflammatory molecules [15]. However, it was recently demonstrated that aged neutrophils in circulation display pro-inflammatory activity in mice [16]. Interestingly, neutrophil aging depends on the microbiota, since microbiota-depleted mice have reduced the circulation of aged neutrophils. Moreover, the decrease of a commensal population by the treatment with antibiotics ameliorates organ damage in mouse models of inflammation [16].

Senescent neutrophils express high levels of CXCR4 (the ligand CXCL12 is highly expressed by bone marrow stromal cells), a process that is essential for the home back to the bone marrow where the apoptotic neutrophils are phagocytosed by macrophages, ending their life cycle [9] (Fig. 1). *In vitro*, peripheral blood human neutrophils increase their expression of CXCR4 around 3 h at 37 °C, an event that anticipates the apoptosis [17]. Importantly, there is an established concept that the apoptosis of neutrophils on inflammatory milieu is an important signal for the resolution of inflammation. The induction of neutrophil apoptosis by administration of H_2O_2 leads to the resolution of joint inflammation in antigen-induced arthritis in mice [18]. Mechanistically, the efferocytosis of apoptotic neutrophils by macrophages changes the profile of lipid mediators produced by these last cells, leading to the production of molecules with anti-inflammatory and pro-resolution properties, so-called specialized pro-resolving mediators (SPM) [for review see 19] (Fig. 1).

In addition to the neutrophil function in innate immunity, recent evidence points out their significant contribution to an adequate activation of adaptive immune response. Stored molecules in neutrophils, such as myeloperoxidase and proteinase-3, are potential autoantigens in some diseases and can lead to the development of anti-neutrophil cytoplasmic autoantibodies (ANCA) that mediate the chronic inflammation of some vasculitis [20]. Moreover, some studies demonstrate that neutrophils can express MHC-II, the co-stimulatory molecules CD86, CD40, and CCR7, a chemokine receptor that enables cells to migrate toward lymph node through lymphatic vessels, acting as antigen presenting cells. These conditions support the idea of the existence of neutrophil-like antigen-presenting cells, suggesting that they could have a strong relationship with T cells [21–24]. On the other hand, TLR-activated neutrophils cross-talk with NK cells by promoting their activation, which, in turn, drive the maturation of dendritic cells for a proper antigen presentation to T cells [25]. Moreover, the previous migration of neutrophils could facilitate the infiltration of T cells toward the site of infection. In a mouse model of Influenza virus infection, the early migrated neutrophils to trachea create a trail of CXCL12 in the tissue that attract $CD8^+$ T lymphocytes locally, crucial cells to deal with this disease [5]. These findings strength the multirole of neutrophils in immunity, suggesting neutrophils may differentiate into different subsets defined by distinct phenotypic and functional profiles depending on the disease, a so-called neutrophils plasticity [26]. Altogether, deepening on the basic knowledge of neutrophil biology will certainly help the better understanding of the pathogenesis of several diseases and will favor the optimization of future treatments.