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The role of neutrophils in autoimmune diseases

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ABSTRACT

Though chronic autoimmune disorders such as rheumatoid arthritis or systemic lupus erythematosus affect a significant percentage of the human population and strongly diminish the quality of life and life expectancy in Western societies, the molecular pathomechanisms of those diseases are still poorly understood, hindering the development of novel treatment strategies. Autoimmune diseases are thought to be caused by disturbed recognition of foreign and self antigens, leading to the emergence of autoreactive T-cells (so-called immunization phase). Those autoreactive T-cells then trigger the second (so-called effector) phase of the disease which is characterized by immune-mediated damage to host tissues. For a long time, neutrophils have mainly been neglected as potential players of the development of autoimmune diseases. However, a significant amount of new experimental data now indicates that neutrophils likely play an important role in both the immunization and the effector phase of autoimmune diseases. Here we review the current literature on the role of neutrophils in autoimmune diseases with special emphasis on rheumatoid arthritis, systemic lupus erythematosus, autoimmune vasculitides and blistering skin diseases. We also discuss the role of neutrophil cell surface receptors (e.g. integrins, Fc-receptors or chemokine receptors) and intracellular signal transduction pathways (e.g. Syk and other tyrosine kinases) in the pathogenesis of autoimmune inflammation. Though many of the results discussed in this review were obtained using animal models, additional data indicate that those mechanisms likely also contribute to human pathology. Taken together, neutrophils should be considered as one of the important cell types in autoimmune disease pathogenesis and they may also prove to be suitable targets of the pharmacological control of those diseases in the future.

1. Introduction

Neutrophils (also known as polymorphonuclear leukocytes or PMNs) are the most abundant circulating leukocytes in humans. Their primary role is to provide the first line of defense against bacterial and fungal pathogens, as indicated by the severe bacterial and fungal infections during reduction of neutrophil numbers (neutropenia) or when neutrophils are unable to fulfil their antimicrobial functions. The latter situation is exemplified by two human genetic disorders, chronic granulomatous disease (CGD) caused by a genetic defect of the NADPH oxidase [1] and leukocyte adhesion deficiency (LAD), characterized by defective neutrophil adhesion and extravasation due to defective adhesion molecule (integrin or selectin) expression or function [2]. Neutrophils are equipped with an arsenal of antimicrobial proteins including reactive oxygen species-producing enzymes, chelators of vitamins and trace elements and enzymes capable of degrading microbial proteins or cell wall components. That weaponry may not only be detrimental for microbes but it can also damage components of the host tissues. Indeed, improper activation of neutrophils is thought to be a significant component of several disease pathogenesis with immune-mediated damage to host tissues.

Autoimmune diseases are characterized by defective discrimination of self and non-self molecules, leading to inappropriate recognition of host tissues as foreign structures, and concomitant immune attack against host organs. The pathogenesis of autoimmune diseases can generally be divided into a first, "immunization" phase characterized by the emergence of autoreactive T-lymphocytes. Those T-cells then trigger a secondary response ("effector" or "tissue destruction" phase) by activating various other cell types (B-cells, cytotoxic T-cells, NK-cells, neutrophils, macrophages, osteoclasts, fibroblasts, etc.) that damage the host tissue. The activation of those effector cells by the autoreactive T-cells can be mediated by a number of routes including autoantibody production, cytokine networks or direct cell–cell contacts. In several cases, the mechanisms linking the immunization and effector

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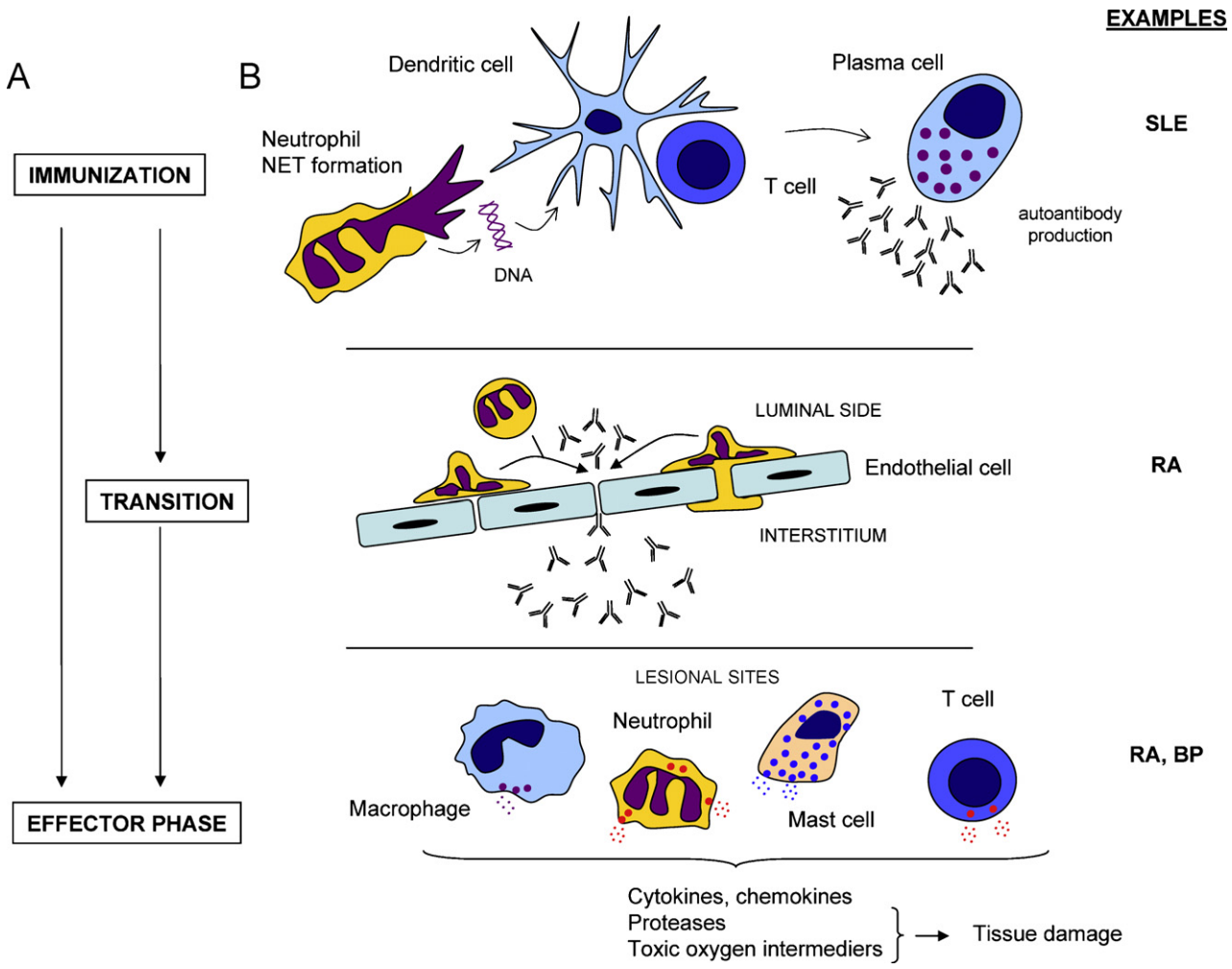

Fig. 1. Participation of neutrophils in different phases of autoimmune diseases. (A) Different phases of autoimmune diseases. (B) Neutrophils are able to contribute to several phases of autoimmune diseases. They can participate in the immunization phase by releasing the autoantigen through NET formation in SLE, seem to be important in the initiation of autoantibody deposition in autoimmune arthritis and form an important effector cell compartment at lesional sites. Abbreviations: SLE, Systemic lupus erythematosus; RA, Rheumatoid arthritis; BP, Bullous pemphigoid.

phases are so complex that they deserve to be considered a third, "transition" phase (Fig. 1A).

While neutrophils are present in high numbers at the sites of autoimmune damage, their role in autoimmune disease pathogenesis has mainly been neglected for a long time [3,4]. This was likely due to the perception of neutrophils as terminally differentiated, short-lived immune cells; the lack of appropriate approaches of molecular manipulation of neutrophils; and our inability to test the role of those cells in a given disease pathomechanism. More recent studies, however, indicate that neutrophils are capable of performing a large number of functions critical for the autoimmune disease process, including antigen presentation, regulation of the activity of other cell types, direct tissue damage, etc. It is increasingly evident that neutrophils are able to participate in each phases of autoimmune diseases (immunization, transition and effector phases). For example, neutrophils can expose/release autoantigens when activated (e.g. in autoimmune vasculitis), when dying by apoptosis, or during formation of neutrophil extracellular traps (NETs). They can also contribute to tissue deposition of autoantibodies or, as an effector cell type, they can induce tissue damage themselves (Fig. 1B). These mechanisms will be discussed in more detail later in this review.

The use of antibody-mediated depletion and genetic deletion of neutrophils, as well as the generation of neutrophil-specific genetic alterations in conditional knockout animals has allowed us to very precisely test the role of neutrophils in autoimmune disease mechanisms in live experimental animals.

In this paper, we review our current knowledge on the role of neutrophils in human autoimmune diseases and in vivo models of those diseases in experimental animals, and discuss how (through what receptors and signaling pathways) neutrophils may participate in the autoimmune disease process. An overall summary of the diseases to be discussed and the evidence supporting the role of neutrophils in their pathogenesis is provided in Table 1.

2. Overview of neutrophil function

Neutrophils play a pivotal role in antimicrobial host defense (primarily in innate immunity) by recognizing microorganisms through their various receptor systems and forming one of the first lines of defense against the invading microbes. Neutrophils originate from the bone marrow where they develop from the common myeloid progenitor cells through the myeloblast–promyelocyte–myelocyte–metamyelocyte pathway [4]. After being released from the bone marrow, neutrophils circulate in vessels until being attracted to tissues by chemotactic signals (e.g. formyl peptides, lipid mediators and chemokines) (Fig. 2A). When activated, these cells target their massive weaponry against the invading microbes. Neutrophils contain four different exocytic compartments (namely