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Letter to the Editor

NETosis in Autoimmunity: Cell-Mediated vs. Ab-Mediated

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Dear Editor-in-Chief

Among the diverse mechanisms contributing to the pathogenesis of autoimmune diseases, NETosis, a specialized form of cell death exhibited by neutrophils, plays a critical role. Neutrophil extracellular traps (NETs) are web-like structures of DNA, histones, and granular proteins that trap and neutralize pathogens. However, excessive or dysregulated NETosis can promote autoimmunity by exposing intracellular antigens and perpetuating inflammation (1).

Cell-mediated NETosis

Various stimuli, including infections, cytokines, and activated platelets initiate cell-mediated NETosis. This form of NETosis involves the activation of signaling pathways that culminate in the release of NETs. The key steps include the activation of protein kinase C (PKC), the generation of reactive oxygen species (ROS) by Nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, and the translocation of neutrophil elastase and myeloperoxidase (MPO) into the nucleus, leading to chromatin decondensation and the release of NETs (2).

Macrophages, upon activation, release pro-inflammatory cytokines such as interleukin-1β (IL-1β) and tumor necrosis factor-alpha (TNF-α), which can enhance NETosis (3). Furthermore, macrophages can phagocytose NETs, leading to the production of additional inflammatory mediators that contribute to chronic inflammation in autoimmune diseases (1). The components of NETs can act as danger-associated molecular patterns (DAMPs) that activate macrophages through pattern recognition receptors such as toll-like receptors (TLRs). This activation leads to the production of cytokines and chemokines that further recruit and activate other immune cells, perpetuating inflammation (4).

T lymphocytes, particularly CD4+T helper cells, influence NETosis through the secretion of cytokines such as interferon-gamma (IFN-γ), which can potentiate NET formation by neutrophils. Additionally, the interaction between T cells and neutrophils can lead to the activation of the inflammasome pathway in neutrophils, promoting NETosis. This cross-talk between neutrophils and T cells creates a feedback loop that amplifies the inflammatory response and sustains autoimmune processes (5). In T1D, inflammatory cytokines released by macrophages and T cells enhance NET formation, leading to the release of autoantigens that exacerbate T cell-mediated destruction of β-cells (6). Cell-mediated NETosis also contributes to MS etiology. Activated central nervous system macrophages and T lymphocytes release cytokines that induce NETosis, causing demyelination. Damaged neurons and NETs emit myelin antigens that activate autoreactive T cells, boosting MS's autoimmune response (7).

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The presence of NETs in autoimmune diseases, such as systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA), underscores their pathogenic potential. In SLE, the release of NETs exposes nuclear antigens, such as DNA and histones, which can trigger the production of autoantibodies. Additionally, the pro-inflammatory components of NETs can perpetuate the inflammatory cascade by activating dendritic cells and promoting the production of pro-inflammatory cytokines, such as IL-6 and TNF-α(2).

Antibody-Mediated NETosis

In antibody-mediated NETosis, immunological complexes (ICs) activate neutrophil Fc receptors to release NETs. This process is important in autoantibody-rich autoimmune diseases. In SLE, anti-dsDNA antibodies can form ICs with NET-derived DNA, promoting NETosis and the autoimmune response (Fig. 1). Recent investigations have shown that antineutrophil cytoplasmic antibodies (ANCA) can promote NETosis and cause endothelial damage and vascular inflammation, contributing to vasculitis. ICs and neutrophils illustrate the vicious cycle of NETosis and autoimmunity, where NETs provide autoantigens that induce pathogenic autoantibodies (8, 9).

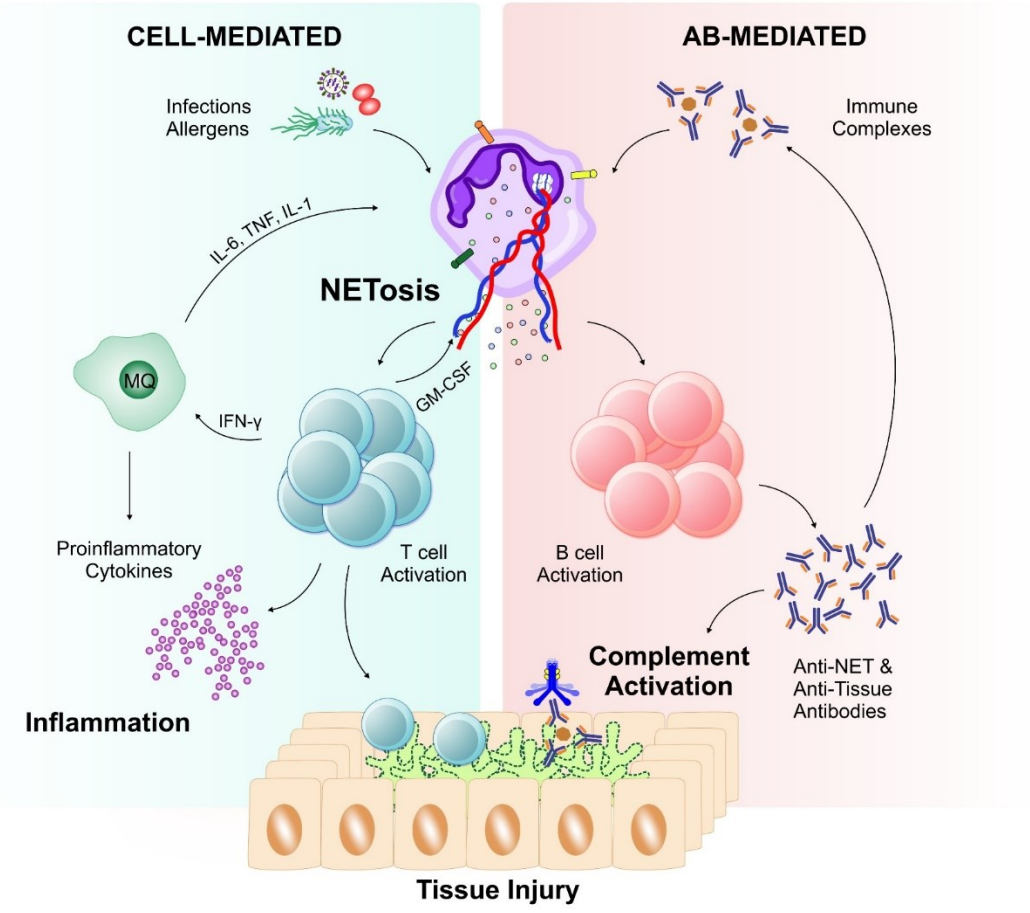

Fig. 1: Cell- and Ab-mediated formation of NETosis in autoimmune disease

While antibody-mediated NETosis is less prominent in T1D compared to diseases like SLE, the presence of islet autoantibodies suggests that ICs may contribute to disease progression. Autoantibodies targeting β-cell antigens could potentially promoting further NETosis and inflammation.

Antibody-mediated NETosis is also relevant in MS, particularly in the context of ICs containing myelin-specific antibodies. These ICs can engage Fc receptors on neutrophils, promoting NETosis and amplifying inflammation. The presence of antibodies against myelin oligodendrocyte glycoprotein (MOG) in some MS patients highlights the potential role of antibody-mediated NETosis in disease progression (6, 7).

Similarities

Both cell-mediated and antibody-mediated NETosis share common features, including the propagation of inflammation and the exposure of autoantigens, which are central to the pathogenesis of autoimmune diseases. Moreover, both forms of NETosis can amplify the autoimmune response by promoting the activation of antigen-presenting cells and the production of pro-inflammatory cytokines (9).

Differences

Despite their similarities, cell-mediated and antibody-mediated NETosis differ in their initiation and propagation mechanisms. Infectious and inflammatory stimuli primarily trigger cell-mediated NETosis, whereas ICs formed by autoantibodies drive antibody-mediated NETosis. The distinct pathways involved in these processes suggest potential therapeutic targets for modulating NETosis in autoimmune diseases (8).

Conflict of interest

The authors declare no competing interests.

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