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Neutrophil Extracellular Traps in Psoriasis: Mechanisms and Emerging Insights

Yiru Chen

School of Basic Medical Science, Naval Medical University, Shanghai, China
2560308710@qq.com

Abstract. Psoriasis is a well-known inflammatory skin disease characterized by recurring disease flare-ups and excessive proliferation of epidermal cells induced by immune system dysfunction. The disease arises from the synergistic impact of genetic predisposition, dysregulated immune responses and environmental factors. Rather than merely defined by structure, neutrophil extracellular traps (NETs) are regarded as a specific response of activated neutrophils, in which chromatin is released to the extracellular space along with antimicrobial proteins. Though originally regarded as a function for defense against invasion by pathogens, increasing evidence suggests that NET formation also impinges on inflammatory aggravation. In psoriasis, NETs formation is increasingly becoming recognized as an active role player in disease development and progression. In this review, we describe the regulation of NETs production and focus on how these structures can intersect with immune responses to affect the inflammatory microenvironment of psoriatic skin in order to direct future mechanistic research and therapeutic interventions.

Keywords: Neutrophil extracellular traps, Immune cells, Psoriasis

1. Introduction

Psoriasis represents an immune-mediated disorder of the skin, a disorder in which aberrant inflammatory signaling results in hyperplasia of the epidermis, accumulation of immune cells and loss of normal barrier function. Growing evidence now indicates that psoriasis is an outcome of a multifactorial pathogenic process, involving predisposition owing to inherited factors, induced by external stimuli, and development of immune response abnormalities, among which immune-mediated inflammatory responses play the most important role [1]. Upon activation, neutrophils undergo a specialized process by extracellular expulsion of chromatin-bound protein complexes, which was described as NETosis and involves histones and numerous granular factors [2]. At first, NETs were considered to be a vital host defense reaction to invading pathogens, exerting antimicrobial effects by sequestering and inactivating them. However, emergent studies indicate that aberrant NETs generation leads to tissue injury and persistent inflammation, because it boosts immune cell activation and facilitates cytokine-mediated signaling, thereby contributing to various types of autoimmune and chronic inflammatory diseases [3].

In psoriasis, NETs have been widely present in both lesion skin and peripheral blood, and their variations mirror the progress of disease [4]. NETs-related factors, such as chromatin and protein

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factors, are immune stimulation signals that induce activation of macrophage and keratinocytes and consequently promote the cytokine-induced inflammation such as TNF-α, IL-1β, IL-17 and IL-23, forming an amplification loop to promote inflammation and keratinocyte proliferation [5]. Meanwhile, NETs can further amplify inflammation by activating inflammasome and raising DMAPs, promoting the local NE production of local tissues and other immune cell subsets at the level of tissue involvement, sustaining a positive feedback of inflammation [6]. Based on these findings, NETs play a dual role in psoriasis, affecting disease development while also offering promising avenues for the therapeutic development. An overview is presented here of the regulatory mechanisms driving NETs formation and their contributions to the immune–inflammatory milieu of psoriasis and provide views on avenues for future mechanistic investigation and targeting of therapies.

2. Overview of the formation and biological functions of neutrophil extracellular traps

2.1. Mechanisms of NETs formation

NETs formation is another specific response of neutrophils to infection or inflammatory triggers, in which chromatin located in extracellular structures in the presence of proteins is released; this process is generally referred to as NETosis. Depending on the underlying regulatory pathways, NETosis can be classified into two different types, referred to as the classical and non-classical NETosis. Classical NETosis relies generally on the NADPH oxidase-mediated ROS production. ROS are important upstream signals that activate PAD4-mediated histone modification, allowing chromatin decondensation. At the same time, the structural degradation of nuclear and plasma membrane allows the chromatin–protein components to be extruded in the extracellular space, forming the NETs.

Non-classical NETosis, by contrast, is shorter in activation time and does not result in cell death. In this pathway, chromatin is extruded extracellularly by vesicular transport whereas cell membrane integrity is maintained and the neutrophil cell remans capable of performing some cell functions. The process includes production of mitochondrial ROS and calcium signaling mechanisms [2]. In addition, various types of inflammatory stimuli are also shown to elicit NETs formation and have different relevance to many pathologies [7].

2.2. Core components of NETs

NETs are a highly organized extracellular web that is mainly composed of decondensed chromatin and various granular proteins from neutrophils. DNA and the attached histones constitute the backbone of NETs. In addition to their structural role, histones also have intrinsic bactericidal activity. Protein composition, the structures associated with NETs, mainly contain several granular proteins from neutrophils, such as NE and myeloperoxidase (MPO), lactoferrin and antimicrobial peptides. Granular proteins not only keep the structural integrity of NETs but also have their bactericidal and immunoregulation effects after their secretion out [8]. Among them, NE and MPO are able to enter the nucleus and help to mediate chromatin remodeling and are crucial in the regulation of NETosis. The 'DNA–protein complex' structure of NETs concentrates various bactericidal substances locally and aids in promoting the adhesive property and structural stability of NETs, improving the pathogen-trapping ability of NETs [9].

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2.3. Physiological functions of NETs

NETs were first identified as an important constituent of host defense against invading pathogens. NETs ensnare bacteria, fungi or viruses by forming extracellular mesh-like structures and kill them through the actions of embedded antimicrobial proteins, thereby limiting propagation of the infection. Furthermore, NETs serve to limit propagation of the pathogen by establishing extracellular barriers to confine microbe infection to restricted areas.

Unlike their antimicrobial activity, NETs formation has an influence in regulating different aspects of immune response. Components exposed as part of NETs formation (extracellular DNA and associated proteins) are immune stimulus elements that activate macrophages and dendritic cells and induce pro-inflammatory cytokine production. In addition, NETs modify adaptive immunity by controlling T cell differentiation and function, acting as an important bridge between innate and adaptive immunity [9]. Overall, NETs have both protective and immune-regulatory roles in the immune system, involved in antimicrobial defense and affecting the immune activity.

2.4. Pathological roles of NETs

Although NETs have an important role in antimicrobial defense, uncontrolled or pathological NETs production will upset normal tissue homeostasis and promote pathological processes. First, NETs contain abundant histones and proteolytic enzymes, all of which are toxic and able to directly damage vascular endothelial cells and the surrounding tissues, thereby causing inflammatory responses and aggravating tissue injury. Second, NETs also work as DAMPs that trigger a series of immune responses and cytokine activities, leading to a continual feedback mechanism of inflammation. In various autoimmune diseases, NETs expose autoantigens, to induce autoantibody production and trigger immune reactions.

Moreover, NETs also interact with different immune cell populations and enhance the proliferation and activation of inflammatory cells, thereby sustaining chronic inflammatory responses. In psoriasis, elevated levels of NETs exacerbate disease status and are involved in sustaining and exacerbating inflammatory responses [10].

3. Central role of NETs in the inflammatory microenvironment of psoriatic skin

Increasing data strongly suggest that NETs are involved in building a complex inflammatory environment through their interaction with cytokines, adaptive immunity and vascular endothelial cells, thereby contributing to the establishment and progression of psoriasis.

3.1. Interaction between NETs and inflammatory cytokines in psoriatic lesions

3.1.1. Promotion of NETs formation by the IL-23/IL-17 axis

In psoriasis, the IL-23/IL-17 signaling pathway is central to disease-related immune responses and contributes to the regulation of NETs generation. IL-23 drives Th17 cells proliferation and related immune cells expansion and activation, boosting IL-17 production, which in turn amplifies the inflammatory response and is of upregulating neutrophil recruitment and activation [11]. As one pro-inflammatory cytokine, IL-17 is not only capable of affecting keratinocytes to induce the release of chemokines to guide neutrophil infiltration into lesional skin but also can directly trigger NETs formation by neutrophils [12]. Notably, neutrophils in psoriatic lesions perform not only functions as

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effector cells but also constitute an important provider of IL-17. Neutrophils can produce IL-17 when generating NETs, thus aggravating local inflammatory responses.

In addition, the release of NETs activates keratinocytes and dendritic cells, inducing IL-23 production and sustaining a self-amplifying interaction of IL-23, IL-17 and NETs. This self-amplifying circuit is thought to contribute to the maintenance of chronic inflammation in psoriasis [13].

3.1.2. Pro-inflammatory effects of proteolytic enzymes released by NETs

NETs contain a large number of proteolytic enzymes and oxidative enzymes, such as NE and MPO, both of which are involved in inflammation occurring in psoriatic microenvironment. NE participates in degradation of extracellular matrix and disrupts tissue barriers, allowing inflammatory cells to penetrate and enhance keratinocytes activation. In contrast, MPO leads to oxidative stress and induces accumulation of inflammatory factors to lead to aggravated tissue injury. These enzymes play a certain role in NETs formation too. NE and MPO also participate in chromatin decondensation during NETosis, which promotes the release of NETs and leads to an inflammatory cascade. Clinical studies have detected high levels of NETs-related complex in patients with psoriasis, which are correlated with worsening of the symptoms and are supportive of their role in the promotion of inflammation [4].

3.2. NETs as a source of autoantigens driving adaptive immune responses

3.2.1. NET–DNA/LL-37 complexes and activation of plasmacytoid dendritic cells

Aside from amplifying inflammatory cascades, NETs can act as the source of autoantigens triggering the adaptive immune response. In psoriasis, NETs-derived extracellular DNA binds to LL-37 to form a functional DNA–peptide structure. DNA–peptide assemblies of this kind are potent immunogenic platforms and are recognized by plasmacytoid dendritic cells (pDCs).

Evidence suggests that LL-3 or similar peptides augment nucleic acid stability, and assist in internalization into the pDCs, trigger TLR9-dependent pathways activating type I IFN secretion, with IFN-α being one of the secreted products [14]. A release of IFN-α represents a key early event of the immune response of psoriasis by inducing myeloid DC maturation and their capacity to act as antigen-presenting cells, thereby triggering subsequent T cell activation. Accordingly, NETs-associated DNA/LL-37 assemblies are considered as relevant components mediating the innate and adaptive responses and regulating early stages of disease development.

3.2.2. Activation of t cells, particularly Th17 cells, by NETs-associated antigens

NETs contain large amounts of DNA, histones, various granular proteins, which can act as autoantigens, be processed by antigen-presenting cells and promote the activation of T cells. NETs-derived antigens can be shown to induce differentiation of $CD4^+$ T cells to Th17 and increase IL-17 levels to enhance inflammation [15]. In addition, NETs can produce the DAMPs to activate dendritic cells and macrophages to enhance expression of cytokines, such as IL-1β, IL-6 and IL-23. The expression of secreted cytokines provides the conditions required to enhance differentiation of Th17 cells. It can thus be understood as a loop between neutrophils and T cells and further accelerates and maintains chronic inflammation in psoriasis [16].

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3.2.3. Interaction between NETs and vascular endothelial cells in promoting angiogenesis in psoriasis

Emerging evidence has shown that NETs play a role in regulating endothelial cell function and vascular structure. DNA–protein assemblies released from NETs act on endothelial cells to induce the upregulation of adhesion molecule and inflammatory mediator expression, leading to leukocyte adhesion and transmigration of endothelial cells. Aside from these effectors, proteolytic enzymes and inflammatory molecules in NETs promote endothelial cell proliferation and migration and also enhance the activation of angiogenesis-related signaling pathways.

In psoriatic lesions, NETs act synergistically with inflammatory cytokines to induce further angiogenesis and support permanent infiltration of inflammatory cells. Experimental studies in animal models demonstrate that inhibition of NETs formation could significantly attenuate inflammatory activity and vascular changes of psoriasis-like skin lesions, highlighting NETs' contribution to pathological vascular changes [17].

4. Therapeutic strategies targeting NETs in psoriasis

Recent studies of the contribution of NETs to psoriasis have opened the door to treating psoriasis by inhibition of NETs. Current approaches to manipulate NETs formation may occur indirectly by affecting the inflammatory signaling pathways or directly by interference with NETosis and promoting NETs degradation in situ, and would hence be therapeutically beneficial.

4.1. Effects of current therapeutic agents on NETs formation

4.1.1. Regulatory effects of biologics targeting IL-17 and IL-23

Targeting IL-23/IL-17 signaling pathway with biologics is a major strategy of treating moderate-to-severe psoriasis and can shape the dynamics of NETs. Blocking IL-17/IL-23 signaling pathway greatly reduces inflammation and constrains the accumulation of immune cells in the psoriatic skin lesions [18].

Therapeutic antibodies blocking IL-17 or IL-23 can inhibit the function of cytokines and reduce the recruitment and activation of neutrophils, thus indirectly limiting the occurrence of NETosis[19]. Besides, IL-17 blockers also suppress the neutrophil-mediated inflammatory reactions; however, they may also impair the host antimicrobial defenses and cause a 'double-edged sword' effect in regulation of NETs [20]. Although therapeutically effective, there are some subsets of patients that show limited effects or recurrence of their disease, indicating that the NETs-related pathways may not be completely inhibited in all cases.

4.1.2. Potential effects of small-molecule agents

In recent years, small-molecule targeted therapies have become a focus for treating psoriasis. Phosphodiesterase 4 (PDE4) inhibitors inhibit the production of inflammatory cytokines by modulating intracellular cAMP levels, thus indirectly inhibiting the activation of neutrophils and NETs formation [21]. Janus kinase (JAK) inhibitors exert their effect by targeting the JAK–STAT cascade to suppress the production of multiple pro-inflammatory cytokines, which, in turn, reduce inflammatory responses and may affect NETosis. Agents of this class also exert pleiotropic immunomodulatory actions and are known to reduce NETs-induced inflammation via multiple pathways [22]. However, few studies on the direct effect of small-molecule drugs on NETs are

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currently available, and their specific mechanisms of action and clinical relevance need further clarification.

4.2. Development of novel NETs-targeted therapeutic strategies

4.2.1. Inhibitors of NETs formation

Controlling the critical steps of NETosis is now a promising direction. Peptidyl arginine deiminase 4 (PAD4) is essential for modifying histones and chromatin relaxations, and PAD4 inhibitors are interesting new targets for limiting NETs formation. Indeed, experimental studies have demonstrated that inhibiting PAD4 activity reduces greatly the NETs release and alleviates inflammation [23]. In addition, other agents, such as chloroquine, have been shown to suppress lysosome activities and block Toll-like receptors signaling pathways to reduce the NETs formation and limits the production of inflammatory cytokines and chemokines. These possibilities are of therapeutic application in autoimmune diseases [24].

4.2.2. Therapeutic potential of NETs-degrading enzymes

NETs are mainly formed from extracellular DNA, so enzymatic degradation of DNA is a direct and easy strategy for NETs clearance. DNase I can degrade extracellular DNA to break up the NETs structure and weaken the pro-inflammatory activity of NETs. In animal models, DNase I administration could effectively reduce inflammation and tissue damage, suggesting its feasibility in the treatment of psoriasis [25]. However, DNase I clinical application is limited because of its disadvantages including poor stability and short half-life. More researches are needed to explore DNase I's efficacy and safety in psoriasis.

5. Conclusion

NETs, an innate immunity player, are critical for host defense against infections. Beyond bacteria clearance, NETs are also crucial components of many inflammatory and autoimmune diseases. In psoriasis, NETs exist in lesional skin and in blood, and they are associated with psoriasis activity. Their pro-inflammatory activity results from associations with the IL-23/IL-17 pathway, triggering of immune cells that supply the autoantigens, and promoting angiogenesis. The current available psoriasis treatments focus on inflammation and indirectly modulate NETs. Targeting NETs is promising but also important to strike a balance between therapy for a disease and defense against microbial infection. Further research is needed to elucidate their functioning and to find precise and safe ways to address them for individualization of treatment of psoriasis.

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