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Review Article

NETosis in Autoimmune Diseases

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Neutrophils are the major antimicrobial cells of the innate immune system, which are recruited rapidly to the sites of infection and provide the primary defense against pathogens. Recent evidence suggests that neutrophils undergo a distinct cell death mechanism called NETosis, which not only contributes to the host defense, but also leads to severe pathological immune responses in cases of dysregulation. Here, we review the general features of NETosis as well as the generation of autoantigens and damage-associated molecular patterns by NETosis in autoimmune diseases. This review discusses the pathogenic role of NETosis in rheumatoid arthritis and systemic lupus erythematosus, where neutrophils may play a key role in the pathogenesis of these diseases, and suggest the possibility of neutrophil extracellular traps as biomarkers and therapeutic targets for the treatment of autoimmune diseases. **(J Rheum Dis 2016;23:82-87)**

Key Words. Neutrophil extracellular traps, NETosis, Citrullination, Damage-associated molecular patterns, Autoimmune diseases

INTRODUCTION

Neutrophils are the most abundant leukocytes in mammals and form a crucial part of the innate immune system as a first line of defense against pathogens [1]. Upon infection, they are rapidly recruited to the sites of infection or inflammation by chemoattractants and inflammatory cytokines, which are secreted by tissue-resident macrophages and other sentinel cells [2]. In response to these molecules, neutrophils invade the infected tissues and play critical roles for clearance of the infection and recruitment of other immune cells. They possess multiple defense mechanisms, including phagocytosis, nicotinamide adenine dinucleotide phosphate (NADPH)-dependent oxidative burst, and degranulation of antimicrobial proteins to handle the infection and inflammation [3]. In 2004, it was reported that neutrophils have a distinct host defense mechanism to trap and kill pathogens, which are so called neutrophil extracellular traps (NETs) [4]. The release of NETs is a specialized form of neutrophil death, termed NETosis, which is distinct from apoptosis and necrosis [5]. This unique feature of neutrophils contributes to host defense, but also chronic inflammation and autoimmune diseases resulting from detrimental bystander damage. Here we focus on the generation of autoantigens and damage associated molecular patterns (DAMPs) by NETosis. This review will provide an overview of the contribution of NETosis to the pathogenesis of autoimmune diseases, such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). The involvement of NETosis in other diseases including antiphospholipid syndrome (APS), anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis, and cancer are discussed elsewhere [2,6].

MAIN SUBJECTS

NETosis

NETosis is a form of cell death unique to neutrophils that releases NETs, web-like structures of chromatin fiber and additional proteins. NETs are composed of decondensed chromatin with histones and various antimic-

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robial proteins such as neutrophil elastase (NE), myeloperoxidase (MPO), and cathepsin G [4,5]. Most of NET-associated proteins are of granular origin with several nuclear and cytoplasmic origins (Table 1) [7-10]. NETs serve as a physical barrier to prevent microbial dissemination by capturing and killing pathogens and increase the local concentration of antimicrobial effectors [11]. However, recent evidence suggests that NETs also have detrimental effects in autoimmune diseases by providing autoantigens and contributing to tissue damaging inflammation.

NETosis can be initiated by diverse stimuli that can be broadly classified into microbes, microbe products, host factors, and others (Table 2) [3,12,13]. Neutrophil activation in response to these factors is mediated by a multi-step signaling cascade. First, binding of one of the above factors to its receptors on neutrophils induces calcium influx. Elevated calcium leads to protein kinase C (PKC)

Table 1. Neutrophil extracellular trap-associated proteins [7-10]

Cellular localization	Protein name
Granules	Azurocidin
	Bactericidal/permeability-increasing protein (BPI)
	Cathelicidin/LL37
	Cathepsin G
	Defensins 1 and 3
	Gelatinase B/matrix metalloproteinase 9
	Gelatinase-associated lipocalin
	Lactotransferrin
	Lysozyme C
	Myeloperoxidase (MPO)
	Neutrophil elastase (NE)
	Proteinase 3 (PR3)
Nucleus	Histone H2A
	Histone H2B
	a) Histone H2B
	b) H2B-like histone
	Histone H3
	Histone H4
	Myeloid nuclear differentiation antigen
Cytoplasm	S100A8 (component of calprotectin)
	S100A9 (component of calprotectin)
	S100A12
Cytoskeleton	Actin (β and/or γ)
	α-actinin (1 and/or 4)
	Cytokeratin-10
	Myosin-9
	Plastin-2
Peroxisomes	Catalase
Glycolytic enzymes	α-enolase
	Transketolase

Table 2. NETosis inducers [3,12,13]

Microbes	
	Aspergillus fumigates, Aspergillus nidulans
	Candida albicans, Candida glabrata
	Cryptococcus gattii, Cryptococcus neoformans
	Eimeria bovis
	Enterococcus faecalis
	Escherichia coli
	Helicobacter pylori
	HIV-1
	Influenza A virus
	Klebsiella pneumoniae
	Lactococcus lactis
	Leishmania amazonensis, Leishmania donovani
	Listeria monocytogenes
	Mannheimia haemolytica
	Mycobacterium tuberculosis
	Pseudomonas aeruginosa
	Salmonella enteric
	Serratia marcescens
	Shigella flexneri
	Staphylococcus aureus
	Streptococcus (group A), *Streptococcus dysgalactiae, Streptococcus pneumonia*
	Toxoplasma gondii
	Yersinia enterocolitica
Microbe products	
	Glucose oxidase
	Lipophosphoglycan (LPG)
	Lipopolysaccharide (LPS)
Host factors	
	Anti-neutrophil antibodies
	GM-CSF + C5a
	HMGB1
	IL-8
	Immune complexes
	MIP-2
	Platelet activating factor (PAF)
	TNF
Others	
	Calcium ionophore (ionomycin)
	Hydrogen peroxide (H_2O_2)
	Monosodium urate (MSU) crystals
	Nitric oxide (NO)
	Phorbol myristate acetate (PMA)

C5a: complement 5a, GM-CSF: granulocyte macrophage colony stimulating factor, HIV: human immunodeficiency virus, HMGB1: high mobility group box 1, IL-8: interleukin 8, MIP-2: macrophage inflammatory protein 2, TNF: tumor necrosis factor.

activation and phosphorylation of $gp91^{phox}$ (NOX2) by PKC allows the cytosolic and membrane-bound subunits of NADPH oxidase to assemble into a functional complex to produce reactive oxygen species (ROS) and nitric oxide (NO) [14,15]. For this reason, the most frequently used compound to induce in vitro NETosis is phorbol myristate acetate (PMA), a synthetic activator of the PKC family of enzymes [16].

The intracellular signaling induces several morphological changes in nuclear structure and granular membranes [5]. Initially, activated neutrophil undergoes chromatin decondensation and loses its characteristic multi-lobular structure of the nucleus. During NETosis, NE, a neutrophil-specific protease, is transferred from azurophilic granules to the nucleus and participates in histone modification and chromatin unfolding by degrading histone H1. In the next step, both nuclear and granular membranes disintegrate and additional granular proteins including MPO associate with chromatin. Eventually, the cell membrane ruptures and fully functional NETs are released from the cell (Figure 1) [3-5].

Citrullination and NETosis

Protein citrullination is a post-translational modification of peptidyl arginine to citrulline, which is mediated by peptidylarginine deiminase (PAD) family of enzymes. During NETosis, activation of NADPH oxidase is followed by activation of PAD4, which converts positively charged arginines in histones to neutral citrullines, thereby weakening the binding of histones to DNA and contributing to histone decondensation [17,18]. Histone citrullination by PAD4 is a prominent posttranslational modification in NETs and drives the major morphologic changes in NETosis [17,19,20]. Inhibition of PAD4 by Cl-amidine, a PAD inhibitor, disables NET formation [17] and neutrophils from mice deficient in PAD4 display impaired NETosis [20,21]. However, the implication of PAD4 in NETosis may be dependent on the stimulus. It has been reported that PMA induces NETosis without apparent activation of PAD4 and detectable histone citrullination [22]. It seems likely that PMA is qualitatively different from more physiologic stimuli to induce NETosis, because inflammatory and infection-related stimuli induce both histone citrullination and NETosis [22,23]. It is worthy to note that PAD4 is regulated by specific isoforms of PKC. While PMA activates PKC α, an inhibitor of PAD4, many other stimuli including calcium ionophores activate PKC ζ, an inducer of PAD4 [2,22]. Therefore, differential engagement of PKC isoforms induces differential histone citrullination by regulating PAD4 activation during NETosis.

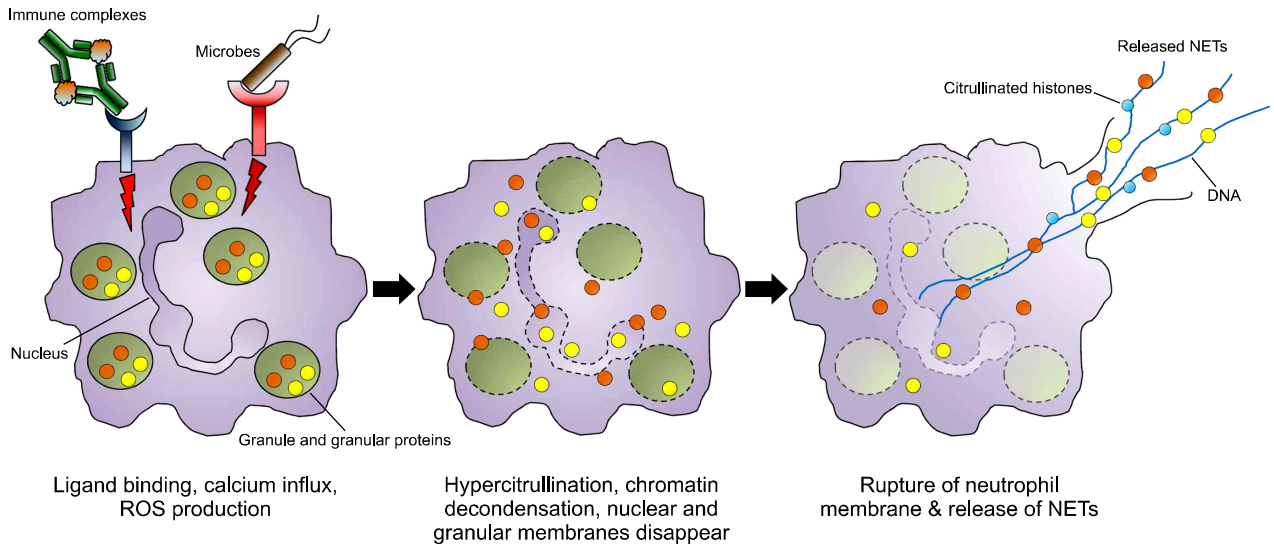

Figure 1. NETosis. NETosis is initiated by binding of ligands such as immune complexes and microbes to their receptors on neutrophils, followed by calcium influx and reactive oxygen species (ROS) production. The intracellular signaling induces histone citrullination, chromatin decondensation, and disintegration of nuclear and granular membranes, which enables granular proteins to translocate to the nucleus. Subsequently, granular and cytoplasmic proteins are mixed with the chromatin. Finally, the neutrophil membrane ruptures and fully functional web-like neutrophil extracellular traps (NETs) are released.

DAMPs and NETs

DAMPs are endogenous danger molecules released at the site of tissue damage under conditions of cell stress or tissue injury, which can initiate and perpetuate a non-infectious inflammatory response by activating the innate immune system [24]. DAMPs include intracellular proteins, such as histones, high-mobility group box 1 (HMGB1), and heat-shock proteins (HSPs), and purine metabolites, such as adenosine triphosphate (ATP) and uric acid, and mitochondrial components, such as formyl peptides and mitochondrial DNA [25]. Recognition of these DAMPs by pattern recognition receptors (PRRs) in innate immune system such as toll-like receptors (TLRs) and inflammasomes, induces inflammatory response [26]. Although DAMPs normally induce inflammatory responses to mediate host defense, they have also been implicated in multiple diseases including RA, atherosclerosis, sepsis, and cancer. [25,26].

NETs are composed of deleterious substances including histones and HMGB1, and these NET-derived DAMPs, in turn, can induce NETosis [27-29]. It has been reported that HMGB1 and histones released by injured hepatocytes stimulate NETosis through TLR4 and TLR9, and the development of NETs subsequently exacerbates inflammatory liver injury [27]. In addition, citrullinated histones and their immune complexes function as DAMPs, and citrullinated histone-containing immune complexes induce NETosis [30]. Therefore, tissue damage initiates the release of DAMPs which activate neutrophils to form NETs and, in turn, this NET formation generates additional DAMPs to exacerbate inflammatory responses through this vicious cycle.

NETosis in rheumatoid arthritis

RA is a systemic autoimmune disease associated with chronic inflammation, mainly in the synovial joints, resulting in joint damage and loss of function [31]. The excessive and prolonged activation of the innate immune system contributes to the pathogenesis of autoimmune diseases including RA by establishing chronic inflammatory response. NETosis is a potent defense mechanism of neutrophils to protect human from invading pathogens [4]. However, dysregulation or defects of NETosis can lead to severe pathological consequences. Aberrant NETosis or impaired clearance of NETs plays a role in contributing to inflammation and tissue damage in autoimmune diseases [2]. NETs may promote production of autoantibodies by providing a source of citrullinated autoantigens, thereby stimulating inflammatory responses in RA. Neutrophils from RA patients have displayed significantly enhanced NETosis, compared to neutrophils from healthy controls, and NET-releasing neutrophils have been shown to infiltrate RA synovial tissue [7]. Furthermore, RA sera and immunoglobulin (Ig) fractions from RA patients with high levels of anti-citrullinated protein antibody (ACPA) significantly induced NETosis and this effect was recapitulated when neutrophils were exposed to inflammatory cytokines interleukin-17A and tumor necrosis factor (TNF). More importantly, NETs augmented inflammatory responses and citrullinated autoantigens implicated in RA pathogenesis were externalized during NETosis. Citrullinated autoantigens can be produced by active extracellular PADs in RA which are released during neutrophil cell death [32]. Further support for the pathogenic role of NETosis in RA has also been reported. Citrullinated histones derived from NETosis reacted with ACPA-positive RA IgG and the immune complexes containing citrullinated histones activated macrophage to produce inflammatory cytokines and propagated NETosis [30]. These results suggest that accelerated NETosis perpetuates pathogenic mechanisms in RA.

NETosis in systemic lupus erythematosus

NETosis is also involved in SLE by providing a source of autoantigens and inducing inflammatory responses. SLE is a severe autoimmune disease that affects skin and multiple organs, including kidney, lung, heart, and brain. It is characterized by autoantibodies to DNA, histones, ribonucleoproteins (RNPs) such as Ro and La, and ANCA antigens that are all NET components [2,33]. Recent evidence suggests that NETosis is associated with SLE. It has been reported that the clearance of NETs by serum endonuclease deoxyribonuclease I (DNase I) is essential for the progression of this disease. NET degradation was impaired in a subset of SLE patients due to the presence of DNase I inhibitors and anti-NET antibodies which prevent the access of DNase I to NETs [34]. In addition, SLE patients who have impaired NET degradation were at higher risk of developing nephritis. Further investigation has revealed that a low-density granulocyte subset expanded in SLE patients is prone to NETosis, and netting neutrophils infiltrate affected skin and kidneys, where they expose immunostimulatory molecules such as LL37 and dsDNA [35]. Furthermore, immune complexes that include the antimicrobial peptide LL37, human neu-

trophil peptide (HNP), and self-DNA, which are released during NETosis, activated plasmacytoid dendritic cells (pDCs) via TLR9 leading to interferon-α (IFN-α) production [29,36]. The released IFN-α further activates pDCs by priming neutrophils to autoantibodies that induce NETosis. A recent study highlights the importance of NETs enriched in oxidized mitochondrial DNA in the pathogenesis of SLE [37]. Ribonucleoprotein immune complexes induce oxidized mitochondrial DNA release that elicits interferon-induced gene expression, and mitochondrial reactive oxygen species (ROS) scavengers suppress lupus-like disease in vivo [37].

NETs as biomarkers and potential therapeutic targets

NETs may be useful biomarkers for NET-driven autoimmune diseases. For example, decreased NET degradation is associated with clinical manifestations in SLE [38]. Decreased NET degradation even preceded an increase in SLE Disease Activity Index (SLEDAI) score and proteinuria. Therefore, these results suggest that NET degradation can be used as a biomarker for predicting and assessing disease activity and renal involvement in SLE. However, this measurement only detects the relative changes of NETs among samples. Furthermore, the clinical heterogeneity of SLE may limit the usefulness of NETs as biomarkers for SLE. Future studies will need to establish standard and validated methods for measuring NETs as biomarkers for autoimmune diseases.

The inhibition of NET formation could be a potential therapeutic target for the treatment of autoimmune diseases. Treatment of ROS scavengers such as N-acetyl-cysteine (NAC) and MitoTEMPO blocks NET formation and suppresses SLE [6,37]. In addition, antimalarials and DNase I may target NETs to reduce disease activity in SLE [6], and PAD inhibitors which target citrullination and NETs modulate disease activity in collagen induced arthritis and murine lupus [6,39]. Therefore, NETs may provide potential therapeutic targets to treat autoimmune diseases.

CONCLUSION

Since the discovery of NETosis, it has come into the spotlight because of its potential pathogenic role in autoimmune diseases. NETs play a key role in host defense by trapping and killing microbes if they are released and cleared at the right place and time, otherwise dysregulation of the formation and clearance of NETs has detrimental effects by providing autoantigens and DAMPs. Although much progress has been made in recent years, it is still unclear why NETs from different stimuli are distinct, and why autoantibodies against NETs found in each autoimmune disease are unique. For example, the autoantibodies detected in RA patients are ACPA and rheumatoid factor (RF), whereas anti-nuclear antibodies (ANA), such as anti-dsDNA antibody, are the major autoantibodies found in SLE patients. In addition, NETosis induced by sterile inflammatory mediators such as immune complexes and TNF, which are involved in autoimmune diseases, is distinct from NETosis induced by microbial exposure. A better understanding of the molecular mechanisms regulating the release and clearance of NETs, and downstream signaling pathways that induce NETosis may allow for the development of new biomarkers and therapeutics for autoimmune diseases.

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CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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