

Contributions of neutrophils to the adaptive immune response in autoimmune disease

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Author contributions: Both authors contributed to this paper.

Supported by The National Institute of Arthritis and Musculoskeletal and Skin Diseases of the National Institutes of Health (NIAMS-NIH), No. 1R01AR063132.

Conflict-of-interest statement: The authors declare no conflict of interest.

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Received: June 29, 2015

Peer-review started: July 4, 2015

First decision: September 17, 2015

Revised: October 3, 2015

Accepted: November 23, 2015

Article in press: November 25, 2015

Published online: December 12, 2015

Abstract

Neutrophils are granulocytic cytotoxic leukocytes of

the innate immune system that activate during acute inflammation. Neutrophils can also persist beyond the acute phase of inflammation to impact the adaptive immune response during chronic inflammation. In the context of the autoimmune disease, neutrophils modulating T and B cell functions by producing cytokines and chemokines, forming neutrophil extracellular traps, and acting as or priming antigen presentation cells. Thus, neutrophils are actively involved in chronic inflammation and tissue damage in autoimmune disease. Using rheumatoid arthritis as an example, this review focuses on functions of neutrophils in adaptive immunity and the therapeutic potential of these cells in the treatment of autoimmune disease and chronic inflammation.

Key words: Neutrophils; Chronic inflammation; Autoimmune disease; Rheumatoid arthritis; Collagen-induced arthritis

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Core tip: Neutrophils guide the adaptive immune response in persistent inflammation by directly and indirectly interacting with T and B cells. Understanding and manipulating these roles of neutrophils will lead to novel therapeutic approaches to prevent and treat autoimmune diseases, such as rheumatoid arthritis.

Pietrosimone KM, Liu P. Contributions of neutrophils to the adaptive immune response in autoimmune disease. *World J Transl Med* 2015; 4(3): 60-68 Available from: URL: <http://www.wjgnet.com/2220-6132/full/v4/i3/60.htm> DOI: <http://dx.doi.org/10.5528/wjtm.v4.i3.60>

INTRODUCTION

Neutrophils are polymorphonuclear granulocytes comprised of enzyme-containing granules. Neutrophils generate from the bone marrow and account for

50%-70% of circulating leukocytes in humans and 10%-25% in mice^[1,2]. Under acute inflammation, particularly as a result of bacterial infection, neutrophils are the first leukocytes to respond, migrate to the site of inflammation, and kill microorganisms through phagocytosis, degranulation and generation of neutrophil extracellular traps (NETs)^[3-5]. These cells have long been thought of as short-lived cells of the innate immune response.

However, recent research evidence has demonstrated that neutrophils persist beyond acute inflammation to initiate and perpetuate chronic inflammation. The onset of inflammation increases the lifespan of neutrophils in circulation, anywhere from 12 h to several days^[6]. Pro-inflammatory cytokines, such as tumor necrosis factor- α (TNF- α) and interferon- γ , inhibit neutrophil apoptosis^[7]. Neutrophils also change phenotypes as inflammation persists. For instance, Neutrophils isolated from various inflammatory states show altered cell densities in gradient centrifugation^[8,9]. The expression of granulocyte marker CD66b in neutrophils increases in patients with rheumatoid arthritis (RA), and decreases with the treatment by anti-inflammatory glucocorticoids, suggesting neutrophils may alter functions during chronic inflammation^[10]. Glucocorticoids, a class of drugs often prescribed to patients with autoimmune disease, also inhibit apoptosis of neutrophils and increase the neutrophilic production of reactive oxygen species (ROS)^[11].

Tissue-specific autoimmune disease such as RA, multiple sclerosis, and type I diabetes are generated from unknown etiology and impact the quality of life of patients through sustained chronic inflammation driven by innate and adaptive immune responses. Neutrophils bridge the innate and adaptive immune response in autoimmune disease. This review focuses on the functional heterogeneity of neutrophils in autoimmune disease and the contribution of these roles to chronic inflammation, in the context of RA.

RA

RA is an autoimmune disease, in which the body generates antibodies against its own tissues. RA is characterized by tissue-specific autoimmune-mediated chronic inflammation that affects multiple joints and results in destruction of cartilage and bone loss^[12]. Risk factors of RA are multi-dimensional and include genetic defects, infections, and environmental influences^[12].

Population studies of RA estimate that genetics account for about 50% of RA disease susceptibility^[13-15]. The most consistent predictor of susceptibility to RA is the link between specific major histocompatibility (MHC) II-associated alleles of the *DRB1* gene that encode human leukocyte antigen (HLA)-DR4 and the onset of RA^[16]. All of the susceptible alleles encode a conserved amino acid sequences on MHC II^[17]. RA patients with these susceptible HLA-DR4 alleles and subsequent expression of the conserved amino acid sequence on MHC II, develop more autoantibodies associated with

RA-related joint breakdown than patients without these alleles^[18]. Activated antigen-presentation cells (APCs), including dendritic cells and macrophages, upregulate MHC II surface molecule expression, which activates antigen-specific T cells and B cells and initiates the adaptive immune responses in autoimmune disease.

Bacterial infections may trigger the onset of RA. A population-based study in Sweden determined that 45% of inflammatory arthritis patients had an infection prior to the onset of early arthritis^[19]. In Chlamydia-induced reactive arthritis, the microbe primes neutrophils through toll-like receptor signaling, which activates the cell to clear the infection. However, activated neutrophils can also infiltrate the joint and cause chronic inflammation^[20]. Neutrophils may employ the same mechanisms in the onset of RA after an infection. Although many microbial factors have been found in synovial fluid of RA patients, there is no clear agreement that these microbial factors are the causative agents of RA^[21-23].

Environmental factors, such as cigarette smoke, make provoke the development of RA in genetically susceptible populations^[24,25]. Smokers with the HLA-DR shared epitope allele were 3 times more likely to test positive for rheumatoid factor (RF) than non-smokers with HLA-DR shared epitope allele^[25]. Smoking increases the activation and migration of neutrophils^[26,27]. Dysregulated neutrophils as a result of cigarette smoking generate a systemic inflammatory environment that is associated with autoimmune disease, such as RA and systemic lupus erythematosus^[28,29].

Neutrophils account for the majority of inflammatory cells in the synovia of human RA patients, and the joints of collagen-induced arthritis (CIA) mice, a murine model of RA^[30,31]. In both humans and mice, neutrophils accumulate at the pannus-cartilage interface, where much the destruction to both bone and cartilage takes places^[32-34]. Thus, an in-depth understanding of neutrophil function in arthritis is vital to the prevention and treatment of this disease.

Neutrophil identification

The surface marker granulocyte receptor-1 (Gr-1) was previously used to identify neutrophil populations in murine models^[35], as it was thought only mature granulocytes express Gr-1. Later researchers found that Gr-1 antibodies cross-react and bind two Ly-6 family member proteins, Ly6G and Ly6C^[36,37]. While neutrophils express Ly6G, monocytes, memory T cells, and some dendritic cell subsets express Ly6C^[36,38-40]. Studies utilize anti-Gr-1 antibodies to deplete neutrophils and attribute the presence of neutrophils to the ability of cancers cells to acquire metastatic phenotypes^[41,42]. Although neutrophils make up the majority of Gr-1⁺ cells in these studies, the increased metastasis after administration of anti-GR-1 antibodies cannot be attributed solely to neutrophil depletion, as Ly6C⁺ monocyte are also depleted. In CIA, the depletion of neutrophils with anti-GR-1 antibody concluded that neutrophils were necessary for the onset and maintenance of disease,

as this treatment prevented the onset of disease and ameliorated established disease^[31]. Macrophages express Gr-1 and also infiltrate the CIA joint, so this method fails to delineate the roles of neutrophils from macrophages in CIA. Currently, studies utilize antibody clone IA8 to specifically bind Ly6G and deplete neutrophils without an effect on other leukocyte populations^[43].

In general, current murine studies identify neutrophils as CD11b⁺Ly6G⁺Ly6C⁺ cells, and monocytes as CD11b⁺Ly6G⁻Ly6C⁺ cells. Human neutrophils are defined as CD14^{lo/neg}CD15⁺CD16^{hi}CD33⁺CD11b⁺CD15⁺CD66b⁺, and human monocytes are defined as CD14⁺CD16⁺HLA-DR⁺CD66⁻ cells^[44].

Neutrophil effect on T cells

Neutrophils, unlike dendritic cells and macrophages, are not defined as APCs. APCs express antigen to T cells via MHC II molecules and stimulates T cell activation with the aid of co-stimulatory molecules CD80 and CD86. In autoimmunity, autoantigen is presented and antigen-activated T cells quickly expand and migrate to the site of inflammation and induce tissue inflammation through the production of pro-inflammatory cytokines^[45]. In genetically susceptible individuals, the conserved amino acid sequence on MHC II may manipulate the antigen presentation process and cause activation of autoreactive T cells^[46]. In the absence of autoimmune disease, neutrophils isolated from the peripheral blood of healthy controls produce MHC II mRNA, but do not express the cell surface molecule^[47]. Exposure of these healthy neutrophils to synovial fluid from an RA patient elicits surface expression of both MHC II and co-stimulatory molecules^[48]. Contact with T cells induces neutrophilic expression of MHC II and costimulatory molecules^[48]. Since T cells are abundant in the RA joint, neutrophils continually express MHC II and co-stimulatory molecules and act as APCs. This further activates T cells and forms a vicious feedback loop that promotes chronic inflammation and tissue damage in the joints^[48-50]. The continuous activation of T cells in the joint advances joint destruction through the production of pro-inflammatory cytokines and activation of autoreactive B cells^[51,52].

Recently, studies have linked neutrophil functions to Th17 cells. Th17 cells, which produce IL-17, are potent proinflammatory mediators and have been implicated in the pathogenesis of autoimmune disease^[53-56]. IL-17 can induce tissue inflammation by stimulating the recruitment of neutrophils. In the RA joint, IL-17 activates fibroblast-like synoviocytes (FLS), macrophages, and osteoblasts^[53-58]. FLS activation produces the potent neutrophil chemoattractant IL-8^[59,60]. Activation of macrophages produces TNF- α ^[61], and the combination of IL-17 and TNF- α in the joint stimulates synovial endothelial cells to produce more neutrophil chemoattractants^[62,63].

Reciprocally, neutrophils help sustain Th17 cells in the joint through the secretion of Th17 chemokines CCL20 and CCL2^[60]. Human neutrophils purified from the synovial fluid of RA patients express high levels of

these chemokines^[60]. Despite the presence of other chemokines in the joint, Th17 cells preferentially migrate toward CCL20^[64]. Mice that lack the CCL2 receptor (CCR2^{-/-}) develop exacerbated CIA. Furthermore, Th17 and neutrophil populations expand in the lymph nodes and joints of these mice^[65]. Therefore, CCL20 likely plays a more prominent role in Th17 migration than CCL2. The expansion of both neutrophils and Th17 cells in mice with exacerbated arthritis demonstrates the importance of both these cell types to the onset and maintenance of autoimmune arthritis. The reciprocal signaling between Th17 cells and neutrophils causes accumulation and activation of these cells, cultivating an inflammatory microenvironment in the joint^[58,60,66].

Although reducing neutrophils in the joint is beneficial to limit sustained T cell activation, systemic neutropenia can cause infection. Some therapeutics intervene with proinflammatory events that upregulate neutrophils, instead of depleting neutrophil function. A phase II trial that utilizes the anti-IL-17 monoclonal antibody drug, secukinumab, improves symptoms in 46% of RA patients after 16 wk of treatment, and can safely maintain these improvements through week 52^[67,68]. Infection rates of patients on these drugs were 31.9% through week 52. Most infections were mild, but, interestingly, were not associated with neutropenia^[68]. Simultaneously targeting neutrophils may improve IL-17 treatments, as activation of Th17 cells would decrease in addition to just decreasing the IL-17 effector molecule. However, as with many autoimmune therapies, this may leave the patient susceptible to infection.

Neutrophil effect on B cells

One of the major features of autoimmune disease is the presence of autoantibodies in circulation. In RA patients, various autoantibodies against cartilage components, chaperones, enzymes, nuclear proteins, and citrullinated proteins have been identified. However, the clinical significances and pathogenic roles of these antibodies are largely unknown, except for RF, anti-citrullinated protein antibodies (ACPA), and anti-collagen antibodies, which are all associated with joint inflammation^[69-72]. Neutrophils stimulate the activation, proliferation, differentiation, and antibody-production of B cells through the production of the B cell stimulating factor BAFF (also known as BLyS)^[73-75]. Peripheral blood neutrophils from both RA patients and healthy control patients express BAFF as a membrane bound molecule^[76]. However, TNF- α in the RA joint releases surface-bound BAFF from neutrophils and increases the concentration of soluble BAFF^[76]. High levels of soluble BAFF in the serum of RA patients correlates with high concentrations of autoantibodies^[77].

Neutrophils in the joint act on B cells similarly to splenic marginal zone neutrophils, which induce antibody production and immunoglobulin class switching through the production of the B cell stimulants BAFF, APRIL, and IL-21^[78]. These stimulants drive the formation of splenic germinal centers that support the proliferation and

differentiation of B cells. The blockage of BAFF decreases the size and disorganizes splenic germinal centers^[79,80]. Structures similar to splenic germinal centers develop in the synovia of some RA patients^[81]. A therapy that reduces soluble BAFF released from neutrophils may prevent synovial germinal center formation and reduce autoantibody production^[82]. Thus, soluble BAFF from neutrophils plays a critical role in facilitating an environment, both systemically and locally, that activates B cells and perpetuates autoantibody formation.

The release of ROS by neutrophils^[83,84] generates advanced glycation end-products (AGE) through oxidant-induced alteration of the structures of lipids, DNA, and proteins^[83-86]. High levels of AGE in the sera of RA patients correlates with a high disease severity and high levels of inflammation markers^[87]. B cells recognize ROS-modified structures as foreign molecules and produce autoantibodies against these structures^[88,89]. ROS modifies type II collagen, the main structural component in human articular cartilage and induces the production of autoantibodies to ROS-modified collagen^[90-94]. In an *in vitro* study, serum from RA patients could only bind type II collagen after exposure to ROS produced by neutrophils^[95].

Autoantibodies form immune complexes in the joint, which induce neutrophil infiltration and activation through complement-mediated pathways^[96,97]. B cells and neutrophils, therefore, work in concert to maintain inflammation in the RA joint.

Treatment with rituximab, a monoclonal anti-CD20 antibody that depletes B cells, decreases the severity of RA most efficiently in RA patients with high levels of autoantibodies^[98,99]. Some patients experience late-onset neutropenia up to 12 mo following rituximab treatment^[99]. The exact mechanism that causes late-onset neutropenia is not known. One popular hypothesis suggests B cells compete with neutrophils for resources in the developmental niche of the bone marrow as the B cells repopulate after rituximab treatment^[98].

Neutrophils and NET formation

Neutrophils form NETs through a unique model of cell death known as NETosis^[100]. The formation of NETs requires activated neutrophils to lose integrity of intracellular membranes prior to that of the plasma membrane^[101]. In the first steps of NET formation, granules containing cytotoxic antimicrobial proteins decay, and chromatin condenses as the nuclear membrane collapses. The plasma membrane then invaginates, ruptures, and releases NETs comprised of intracellular antimicrobial contents into the extracellular space^[102]. In the context of infection, the antimicrobial proteins trap and kill infiltrating microbes in the extracellular space^[100,103].

NETs release citrullinated histones and proteins into the extracellular space^[104,105]. Citrullination of a protein or histone is a post-translational modification (PTM) that converts arginine residues to citrulline^[104,105]. This process changes the structure and antigenicity

of proteins and histones, as the adaptive immune response can recognize PTM as non-self^[106]. In RA, ACPA are of particular interest as an increase in ACPA correlate with an increased disease severity^[107,108]. An increased propensity for neutrophils to die *via* NETosis correlates with increased levels of ACPA in the serum of RA patients^[105], which suggests NETs are a major source of autoantigen in RA. In fact, proteins extracted NET-induced peripheral blood neutrophils react with sera from RA patients. Sera from RA patients react specifically with citrullinated histone H4^[109].

The discovery of a conserved citrullinated antigen associated with the onset of RA opens up a novel avenue of therapeutic intervention. The enzyme PAD4 controls the citrullination of histone H4^[109]. Interruption of PAD4 function could decrease citrullination of histone H4 and subsequent autoantibody production that is crucial to the development of RA.

NETosis also stimulates FLS to produce the proinflammatory cytokines IL-6, IL-8, and the Th17-associated chemokine CCL20^[105]. Production of IL-6 and IL-8 aid in the polarization of CD4⁺ T cells to Th17 phenotypes, while CCL20 traffics Th17 cells to the site of inflammation. Thus, NET stimulation of FLS shapes a microenvironment favorable to sustained inflammation associated with Th17 cells.

Neutrophils as myeloid-derived suppressor cells

Myeloid-derived suppressor cells (MDSCs) are a heterogeneous group of immature myeloid cells derived from the bone marrow under pathologic conditions that suppress T cell functions^[110]. Murine MDSCs are divided into two subsets based on surface expression of Ly6G and Ly6C; the Ly6G⁺Ly6C⁺CD11b⁺ granulocytic-MDSC (G-MDSC) subset and the Ly6G⁺Ly6C⁺CD11b⁺ monocytic-MDSC (M-MDSC) subset^[111]. The counterparts of M-MDSC subset in humans have been identified as CD11b⁺CD14⁺CD15⁺HLA-DR⁺Lin⁻, while human G-MDSC subset are identified as CD11b⁺CD15⁺CD14⁺HLA-DR⁺Lin⁻^[111] (Table 1). M-MDSCs are immature monocytes that suppress T cell functions through the secretion of inducible nitric oxide synthase (iNOS)^[112-114]. G-MDSCs are neutrophil-like cells that inhibit T cell function through the production of arginase-1^[114].

First described in murine tumor models, MDSCs accumulate in the lymphoid tissues of tumor-bearing mice^[115] and significantly increase in the circulation of cancer patients compared to healthy controls^[116-118]. MDSCs promote tumor growth by inhibiting T-cell mediated immune surveillance and cytotoxic effects on tumor cells^[119]. Recently, evidence indicates MDSCs also contribute to the regulation of autoimmune disease by inhibiting CD4⁺ T cell proliferation and differentiation^[120,121].

Neutrophil-like G-MDSCs are believed to be immunosuppressive in autoimmunity. In the experimental autoimmune encephalomyelitis (EAE) murine model of multiple sclerosis, G-MDSCs express high levels of programmed cell death 1 ligand 1 (PD-L1), a costi-

Table 1 Surface markers used in identification of myeloid-derived suppressor cells

	Human	Mouse
MDSC	CD11b ⁺ CD33 ⁺	CD11b ⁺ Gr-1 ⁺
M-MDSC	CD11b ⁺ CD14 ⁺ CD15 ⁻ HLA-DR ⁻ Lin ⁻	CD11b ⁺ Ly6C ⁺ Ly6G ⁻
G-MDSC	Cd11b ⁺ CD15 ⁺ CD14 ^{lo} HLA-DR ⁻ Lin ⁻	CD11b ⁺ Ly6G ⁺ Ly6C ⁺
Progenitor neutrophil	CD14 ^{lo/neg} CD15 ⁺ CD16 ^{lo/neg}	
Mature neutrophil	CD14 ^{lo/neg} CD15 ⁺ CD16 ^{hi} CD33 ⁺ CD11b ⁺ CD15 ⁺ CD66b ⁺	CD11b ⁺ Ly6G ⁺

MDSC: Myeloid-derived suppressor cell; M-MDSC: Monocytic-MDSC; G-MDSC: Granulocytic-MDSC.

mulatory molecule that negatively regulates T cell proliferation. G-MDSCs inhibit autoantigen-priming of Th1 and Th17 cells in a PD-L1-dependent manner^[122]. In CIA, MDSCs that include mostly neutrophil-like G-MDSCs suppress both T cell proliferation and CD4⁺ T cell differentiation into Th17 cells, mainly through the production of arginase-1^[123]. The depletion of MDSCs increases inflammation and disease severity, while the subsequent adoptive transfer of MDSC ameliorates arthritis^[123]. Furthermore, based on our published^[124] and unpublished data, M-MDSCs as well as G-MDSCs not only suppress T cell functions, but also inhibit B cell proliferation in the context of CIA.

The use of CD11b⁺Gr-1⁺ cells in most functional MDSC studies makes it difficult to confirm G-MDSCs immunosuppressive effects in autoimmune arthritis. Additionally, utilization of Ly6G to recognize G-MDSCs cannot differentiate G-MDSCs from neutrophils. Similar issues exist in human MDSCs, as mature human neutrophils express many of the same surface receptors as G-MDSCs and cannot be distinguished without functional analysis^[125].

Further studies comparing G-MDSC phenotypes vs neutrophil phenotypes are needed to determine the effect of these cells on the adaptive immune response. Current evidence indicates G-MDSCs and neutrophils act in opposing manners on the adaptive immune response^[125]. Uncovering mechanisms that lead to the plasticity of G-MDSCs and neutrophils in autoimmune disease could lead to cell-based therapies that convert pro-inflammatory cells to immunosuppressive cells.

Neutrophils and potential therapeutics

As one of major contributing factors in the establishment of chronic inflammation in RA, neutrophils serve as potential therapeutic targets. Some current therapies for RA interfere with the functions of neutrophils. For example, anti-TNF- α therapies reduce IL-33 receptor expression on neutrophils and subsequently decrease neutrophil migration. Neutrophils from RA patients treated with anti-TNF- α therapies do not respond to IL-33-mediated chemotaxis^[126]. Impaired chemotaxis of neutrophils may lead to a decrease in inflammation and disease severity. The wide array of effector proteins produced by neutrophils, such as BAFF, could also become therapeutic targets for RA.

NETs may serve as a novel therapeutic target for RA and other NET-associated autoimmune diseases. In

addition to targeting enzymes associated with PTM, the use of DNase to breakdown the extracellular DNA and histones associated with NETs has been suggested as a potential therapeutic in NET-associated diseases^[127]. The study of NETs in RA may also reveal currently unknown citrullinated proteins that contribute to RA pathogenesis and could serve as therapeutic targets.

In CIA, the adoptive transfer of MDSCs decrease T and B cell proliferation and decreases the severity of arthritis^[123,124]. The discovery of a mechanism that induces the G-MDSC phenotype from neutrophil-like cells could be crucial for the therapy of autoimmune disease. Manipulation of this mechanism will drive neutrophil-like cells toward an immuno-suppressive MDSC phenotype that impedes the super-active adaptive immune response, and thereby reduces chronic inflammation in autoimmunity. An in-depth understanding of the contributions of the joint microenvironment to the various neutrophil phenotypes, and subsequent neutrophil functions, may aid in the development of neutrophil-based RA therapies.

Similar to many autoimmune therapies, inhibition of neutrophil functions leaves the patients susceptible to infection. For this reason, the inhibition of specific enzymes, such as PAD4, may be a promising therapeutic intervention. If PAD4 can be neutralized, this could curb autoantibody production without completely diminishing the antimicrobial function of neutrophils.

CONCLUSION

Neutrophils are involved in the onset and progression of RA in a complex capacity. Neutrophils engage in several reciprocal signaling events with both B and T cells, which promote a microenvironment conducive to sustained inflammation. The formation of NETs increases the production of ROS and ACPA, which are hallmarks of RA. Neutrophils can act as pro-inflammatory cells influencing chemotaxis and immune cells signaling, but can also have a MDSC phenotype that suppresses the immune response. Since neutrophils affect many aspects of the adaptive immune response and drive chronic inflammation, the disruption of the signals between neutrophils and the adaptive immune response can serve as therapeutic targets for RA.

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P- Reviewer: Saniabadi AR S- Editor: Ji FF L- Editor: A
E- Editor: Wu HL





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