

REVIEW

The emerging role of neutrophils in autoimmune-associated disorders: effector, predictor, and therapeutic targets

Xiaohong Fu | Heting Liu | Gang Huang | Shuang-Shuang Dai

Department of Biochemistry and Molecular Biology, College of Basic Medical Science, Third Military Medical University (Army Medical University), Chongqing, China

Correspondence

Gang Huang and Shuang-shuang Dai, Department of Biochemistry and Molecular Biology, College of Basic Medical Sciences, Army Medical University, Chongqing 400038, China.
Email: cqhuanggang@aliyun.com and tmmubiodss@aliyun.com

Funding information

National Natural Science Foundation of China, Grant/Award Number: 81771693; Advanced Interdisciplinary Studies Foundation of Basic Medical Science, AMU, Grant/Award Number: 2018JCQY06; Key Support Object of AMU, Grant/Award Number: 410301060133

Abstract

Neutrophils are essential components of the immune system and have vital roles in the pathogenesis of autoimmune disorders. As effector cells, neutrophils promote autoimmune disease by releasing cytokines and chemokines cascades that accompany inflammation, neutrophil extracellular traps (NETs) regulating immune responses through cell–cell interactions. More recent evidence has extended functions of neutrophils. Accumulating evidence implicated neutrophils contribute to tissue damage during a broad range of disorders, involving rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), primary sjögren's syndrome (pSS), multiple sclerosis (MS), crohn's disease (CD), and gout. A variety of studies have reported on the functional role of neutrophils as therapeutic targets in autoimmune diseases. However, challenges and controversies in the field remain. Enhancing our understanding of neutrophils' role in autoimmune disorders may further advance the development of new therapeutic approaches.

KEYWORDS

autoimmune-associated disorders, mechanism, neutrophil, targeted therapy

Abbreviations: AIA, adjuvant-induced arthritis; CCR2, CC-chemokine receptor; CD147, extracellular matrix metalloproteinase inducer; CIA, collagen-induced arthritis; CXCL1/2, CXC-chemokine ligand 1/2; CXCL5, CXC-chemokine ligand 5; CXCL8, CXC-chemokine ligand 8; Gal-9, galectin-9; GTR, glucocorticoid-induced tumor necrosis factor receptor-related protein; IL-17, interleukin-17; IL-6, interleukin-6; JAK, Janus kinase (JAK)-signal transducer and activator of transcription; Mice (mBSA), mice with methylated bovine serum albumin; MPO, myeloperoxidase; Ncf1**mice, Ncf1 (m1J) mutated mice; NCF1-339, a single-nucleotide polymorphism in the NCF1 gene; NE, neutrophil elastase; NET, neutrophil extracellular trap; NOX2, NADPH oxidase 2; PAD4, peptidyl arginine deiminase 4; RIPK1, receptor-interacting protein kinase 1; ROS, reactive oxygen species; SKG mice, a monogenic model of autoimmune arthritis due to altered signal transduction in T cells

1 | INTRODUCTION

Autoimmune diseases are a group of disorders characterized by a failure in self-tolerance to a wide variety of autoantigens.^{1,2} From a clinical perspective, autoimmune inflammation may involve many or even all body organ systems, such as rheumatoid arthritis, systemic lupus erythematosus (SLE) and others (primary sjögren's syndrome [pSS], multiple sclerosis [MS], crohn's disease [CD], and gout).³ The pathogenesis of autoimmunity involves dysfunction of the entire immune system, including neutrophils of innate immune, B and T cells of the adaptive immune, dendritic cells (DCs), and macrophages. Within the various cell types related to autoimmune diseases'

This is an open access article under the terms of the [Creative Commons Attribution](https://creativecommons.org/licenses/by/4.0/) License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

© 2021 The Authors. *MedComm* published by Sichuan International Medical Exchange & Promotion Association (SCIMEA) and John Wiley & Sons Australia, Ltd.

pathogenesis, neutrophils are considered to be essential participants in the occurrence and progression of these diseases.⁴

Neutrophils are the earliest cells gathered at infection or inflammation places and account for around 60% of all leukocytes in the circulation.⁵ Recent reports confirm that the average circulating lifespan of mouse-derived neutrophils extend as long as 12.5 h, while human neutrophils have reached an unprecedented 5.4 days.⁶ The rapid activation of neutrophils and their exponential increase in their lifespan ensure long-term existence in the inflammation site. In the inflammation process of autoimmune diseases, neutrophils “shoot at first sight” and quickly eradicate invading pathogen infections, thereby playing a host defense role and killing pathogens through various strategies. These strategies include phagocytosis,^{7,8} degranulation, reactive oxygen species (ROS) production, and NETosis process. Degranulation refers to the release of granular antimicrobial peptides by neutrophils, such as myeloperoxidase (MPO),⁹ neutrophil elastase (NE), and matrix metalloproteinases (MMPs).^{10,11} In the case of external stimuli, neutrophils quickly produce ROS and promote oxidative burst.¹² Through the NETosis process, neutrophils squeeze out the chromatin network structure and bind to the granular peptides of neutrophil extracellular traps (NETs).^{4,13,14} During inflammation, receptors on neutrophils and vascular endothelial cells regulate the adhesion of neutrophils through complex interaction and control the subsequent migration process from the circulation into tissues.^{15–17} Data from experimental and clinical settings indicate that the function of neutrophils is not only limited to their roles in acute infection. These breakthroughs will change our understanding of the presence or absence of neutrophils.¹⁸

Under the general context of inflammation, neutrophils have been extensively and deeply studied. Ample evidence indicates that neutrophil promotes inflammation and contributes to the pathogenesis of autoimmune diseases.^{19–22} In this study, we have reviewed a large number of relevant literatures and summarized the latest recent advances in neutrophils, focusing on their roles and functions in distinct autoimmune disorders, and their targeted therapies for neutrophil-derived disorders. Furthermore, we hope to draw attention to the modulatory role of neutrophils in autoimmune-associated disorders, which will help us understand the role of neutrophils in autoimmune disorders, and elucidate the etiology, prevention, and treatment of autoimmune disorders.

2 | NEUTROPHILS IN RHEUMATOID ARTHRITIS

2.1 | Role and function

RA is a chronic autoimmune arthropathy mainly characterized by joint damage caused by an inflammatory reaction, which leads to joint dysfunction and disability and seriously affects patient life quality.²³ Neutrophils are abundant in both synovial tissue and fluid, supporting an essential role for these cells in the initiation and progression of RA.^{24,25} The pathogenesis of neutrophils in RA relates to changes in multiple stages, like regulating the functions of other immune cells; acts as APCs by directly interacting with T and B cells; cell–cell interactions; and accelerate the release of proteases and NETs.²⁶

In inflammatory conditions, neutrophil migration may be induced by cytokines through further secreting other cytokines and chemokines. CC-chemokine receptor (CCR2),²⁷ CXC-chemokine ligand 1 (CXCL1),²⁸ CXC-chemokine ligand 5 (CXCL5),^{29,30} CXC-chemokine ligand 8 (CXCL8),³¹ CCL3,³² TNF α ,³³ and IL-1 β ³⁴ are several essential cytokines/chemokines that are recruited by neutrophils. Talbot et al. found that CCR2 has directly participated in the detrimental infiltration of neutrophils into the joints in RA patients.³⁵ It has been well documented that CXCL1 can induce proinflammatory gene expression in synergy with interleukin (IL)-17A and IL-17F.^{36,37} Besides, CXCL5 reported being as crucial as CXCL8, similar to neutrophil chemoattractant in RA synovial fluid, with immuno-neutralization eliminating over 40% of chemotaxis. IL-33 could stimulate activated synovial cells and macrophages to generate cytokines such as TNF α , IL-1 β , CXCL, and CCL3, which will recruit neutrophils to the joint in a cascade manner. Alternatively, IL-33 directly draws neutrophils to the places of inflammation. Both monocyte chemoattractant protein 1 (MCP-1) and IL-8 work for the recruitment of inflammatory cells into the arthritic joint.³⁸ These examples indicate the significance of cytokines/chemokines for recruiting neutrophils into the joints during the acute phase of early RA. In response, these recruited neutrophils polarize and crawl along with the endothelial cells and quickly migrate into inflamed tissues, thereby identifying and engulfing pathogens, such as bacterias, viruses, and fungi and acting as a guardian to defend lifeline.

Notably, the inflammatory microenvironment is the stimulus that allows neutrophils to gain APC-like capabilities. A large number of findings powerfully demonstrate

that neutrophils also serve as APCs by directly interacting with T and B cells, further promoting T-cell activation, migration, and DC maturation. Furthermore, T cells promote the differentiation of neutrophils into APCs.³⁹ In the form of APCs, neutrophils present antigens and activate adaptive immunity. Then, it enhances the expression of plasma membrane receptors (MHC class II antigens) to push more neutrophils to present antigens to T cells.

One of the main characteristics of neutrophils' defensive function is its ability to form NETs. NETs' formation involves activating neutrophils to release their chromatin (DNA and its related histones), carry granzymes and extracellular network structure that can capture and kill extracellular organisms.⁴⁰ Recently it has been reported that the release of NETs represents a new form of neutrophil death (termed NETosis) that is different from apoptosis and necrosis and provides a way for neutrophils at the end of their lifespan to continue to kill pathogens. Interestingly, recent studies have found that neutrophils need autophagy to maintain their normality and fulfill its efficacy,⁴¹ which has been confirmed by enhancing of the autophagy ability in RA patients.⁴²

Neutrophils are the most abundant cell type and detected in RA synovial fluid and synovial tissue. The complex and diverse molecule mechanisms caused by neutrophils have largely contributed to the continuous inflammation and tissue damage of RA synovial joints, and further support the important role of neutrophils in driving the pathogenesis and manifestations of RA.

2.2 | Neutrophil-directed therapy in RA

Currently, wide-ranging used targeted neutrophil therapeutics mainly neutralize specially related cytokines that drive the occurrence of RA. Among them, many cytokines directly affect the function of neutrophils. The effect of targeted therapy depends on the degree of reduction of neutrophil-mediated inflammation. Infliximab (INF), methotrexate (MTX), leflunomide, and glucocorticoids are several common nonbiologic disease-modifying antirheumatic drugs, which are mainly effective by changing neutrophil functionality through various mechanisms.⁴³ For example, INF⁴⁴ suppresses neutrophil chemotaxis and the production of ROS by blocking the priming activation of monocytes on neutrophils. Nowadays, MTX has become a common prescription drug for rheumatoid arthritis. Compared with nonresponders, treatment of RA with MTX alone can reduce the production of neutrophil ROS and supplement system activity in patients with MTX-responder, showing that disease activity (DAS-28) and inflammatory mediators (CRP) decreased. Both i-RA and a-RA patients present

functional alterations in neutrophils and complemented system.⁴⁵ And interestingly, INF and MTX combination therapy reduced the Ca^{2+} concentration significantly by blocking the TRPM2 channel, which makes INF and MTX useful antagonists of neutrophil apoptosis and mitochondrial oxidative stress in RA patients. Also, targeting the cytokines TNF and IL-6 reduced the production of ROS and changed the migration characteristics of neutrophils in RA.⁴⁶

Various experimental treatments mainly target diverse cytokines and their receptors, form extracellular trap of neutrophils, and use neutrophil microparticles to influence the function of neutrophils. During phase 3 and 4 clinical trials, treatment with tocilizumab (TCZ, an inhibitor of IL-6 receptor- α) can reduce the number of neutrophils and the incidence of infection in RA patients.⁴⁷ The down-regulation of peptidyl arginine deiminases (PADs) mediates the effect of igratimod and inhibits the expression of CPs in neutrophils.⁴⁸ Therefore, strategies to inhibit PADs are promising in mouse models.⁴⁹ Filgotinib, as a selective Janus kinase (JAK)-1 inhibitor, has shown initial efficacy and encouraging safety profile in randomized phase IIa trials. Neutrophil exosomes are responsible for the main anti-inflammatory effects in RA, and neutrophil decoy microparticles are being developed into nanotechnology, which can supply local therapy options for certain RA patients. Nanoparticles coated with neutrophil membrane show significant therapeutic effect works by improving joint damage and suppressing the severity of overall arthritis.⁵⁰

3 | NEUTROPHILS IN SYSTEMIC LUPUS ERYTHEMATOSUS

3.1 | Role and function

SLE is a chronic autoimmune disorder, which is mainly characterized by the activation of inflammatory immune cells and the production of proinflammatory autoantibodies, leading to self-attack of organs, tissues, and cells.⁵¹ Neutrophil dysregulation is related to SLE's pathogenesis, abnormal neutrophils fueling inflammatory states by producing disease-inducing cytokines (IL-1 β or BlyS) and becoming a source of many autoantigens in the disease through NETosis.⁵²

In SLE, NET formation causes autoantigens to leak from the uncleared cell debris.⁵³ Then, follicular dendritic cells in the germinal centers of secondary lymphoid tissues present these neo-epitopes to B cells, thereby destroying self-tolerance. Activation of autoreactive B cells and subsequent autoantibodies' production promotes the formation of immune complexes (ICs), which can cause

inflammation reaction and lead to further tissue injury. ICs can also absorb phagocytes and subsequently yield more proinflammatory cytokines. These processes create a vicious circle, leading to continuous inflammation. A great number of autoepitopes of NET proteins that are recognized by autoantibodies produced by patients with SLE can also be removed by proteases. In SLE and non-SLE subjects, the enhancement of NET formation is associated with vascular disease, which may accelerate the construction of coronary plaque and lipoprotein disorders.⁵⁴ NETs can drive macrophages and other cells to release IL-1 and IL-18 through NLRP3 inflammasome or P2X7 purinergic receptors, thereby further exacerbating the inflammatory state of SLE patients.⁵⁵ Fc receptor (FcγR1 or CD64) expression on neutrophils is a potential biomarker of bacterial infections.⁵⁶

Neutrophils ingest more secondary necrotic cells (SNECs), which makes phagocytes NADPH oxidase 2 (NOX2 complex) generate low ROS, resulting in the detrimental inflammatory environment and deteriorated disease status.⁵⁷ Meanwhile, when uncleared apoptotic cells lose their membrane integrity, they present autoantigenic molecules in an inflammatory milieu. Dead cells are insufficiently removed, leading to an autoimmune response against components of the cell's nucleus.

Recent findings indicated that the susceptibility of SLE is related to low production of ROS. NCF1-339 genotype (single-nucleotide polymorphism of NCF1 gene [rs201802880], encoding NADPH oxidase type II subunit NCF1/p47^{phox}) affects the formation of NET, lowering the production of ROS.⁵⁸ ROS production deficiency can lead to excessive IFN response, earlier disease onset, and higher sensitivity to SLE.⁵⁹

Another SLE feature is the elevated level of a pathogenic neutrophil subset, called low-density granulocytes (LDGs).⁶⁰ SLE LDGs display significant transcriptional and epigenetic heterogeneity and comprise two subpopulations of intermediate-mature and immature neutrophils, with different chromatin accessibility and differences in transcription factor motif analysis. Differences in NET formation, oxidized mitochondrial DNA release, chemotaxis, phagocytosis, degranulation, ability to harm the endothelium, and IFN stimulation responses are evident among LDG subsets. Neutrophils can produce type I interferon and can also be used as an antigenic trigger to induce IFNα production.⁵⁹

It has also suggested that differential methylation found on specific genes, and the most prominent feature of SLE is the decreased methylation of genes in the IFN system. Genetic variations in the A20 DUB domain provide a genetic link to citrullination and NETs in SLE.

3.2 | Neutrophil-directed therapy in SLE

According to the meta-analysis, compared with healthy controls, the ratios of neutrophil to lymphocyte (NLR) and platelet to lymphocyte (PLR) of SLE patients are significantly higher and are positively correlated with SLE disease activity index (SLEDAI), suggesting that NLR and PLR can be used as potential biomarkers in SLE management.⁶¹ Besides, NETs are the source of extracellular HMGB1. The expression of HMGB1 in NETs is higher among patients with lupus nephropathy (LN), which is associated with clinical and histopathological characters of active nephritis, suggesting that this alert protein may play a role in the pathophysiology of kidney damage in SLE.⁶²

PAD4 (peptidyl arginine deiminase-4), one of the enzymes that mediate the citrullination of arginine, plays an essential role in the formation of NET after receiving specific type of stimulation. Although the part of PAD4 in the clinical and immunological behavior of mouse SLE is debated,^{63,64} inhibition of PAD4 would have special treatment effects in humans. Therefore, PAD4 may become a potential central drug target through which it could improve NET-induced atherosclerosis.

Light of the ultraviolet-visible (UV-VIS) spectrum will trigger and aggravate the severity of SLE. Avoiding light exposure is a treatment to alleviate the condition because the light-induced NETosis process relies on the production of extracellular ROS caused by riboflavin excitation and its subsequent reaction with tryptophan. Light-induced NETosis required activation of NE and MPO and induced histone citrullination.⁶⁵

L-ascorbic acid-a (HIF-1α inhibitor) or bosentan (an endothelin-1 receptor antagonist) used to lessen the release of NET targeted treatment for neutrophils, revealing that the inhibition of endothelin-1 and HIF-1α could significantly suppress the “pre-NETotic” step of NET formation in human SLE.⁶⁴ Hydroxychloroquine, a disease-modifying antirheumatic drug and a late-stage autophagy inhibitor, is used to prevent plaque formation and increase the survival rate of SLE patients. The NET formation could be targeted by autophagy inhibition with hydroxychloroquine.⁶⁶ Similarly, nocodazole targeting neutrophils in SLE patients could reduce the release of chromatin by interfering with the polymerization of tubulin into microtubules or cytochalasin D (an inhibitor of actin filamentation). M1/70 (an integrin adhesion receptor antibody) pretreatment of neutrophils would reduce the distribution of chromatin to NETs.⁶⁷

4 | OTHERS

In addition to these common disease categories, autoimmune diseases also include some small crowd diseases, including pSS, MS, CD, and gout, etc.⁶⁸ As an essential part of the immune system, neutrophils are dedicated to mobilizing immune defense. Neutrophil dysregulation is a shared mechanism that plays a crucial role in the pathogenesis of these diseases.

4.1 | Neutrophils in pSS

Neutrophils mainly contribute to ROS products during the respiratory burst, which may increase the degree of inflammatory and fibrotic processes, and they participate in the endothelial damage of pSS.⁶⁹ Compared with controls, pSS patients have increased basal neutrophil adhesion, which suggests that blood neutrophils are activated.⁷⁰ However, in those with the recurrent bacterial infection, the adherence of neutrophils in patients significantly decreases, and the opsonic activity of plasma also reduces. In contrast, the contents of neutrophils in intracellular lactoferrin and lysozyme were normal. Correlation analysis found that elevated level of neutrophils and hypoproteinemia in the pSS cohort are significantly associated with lung infections ($p < 0.05$).⁷¹ Neutrophils were increased considerably in the salivary glands of pSS patients and correlated with focus score.⁷² Neutrophil/lymphocyte ratio (NLR) as an inflammation index and red blood cell distribution width (RDW) may prove useful indices to estimate pSS disease activity.⁷³ Neutropenia should be added to various hematological manifestations of pSS, and it may be a presenting feature and an important clue to the diagnosis.

Owing to the complexity of pathogenesis and heterogeneity behind the clinical manifestations, many targeted immunomodulatory therapies for pSS have not shown any benefits in clinical trials. To date, no specific treatment for this disease has been approved. We have made little progress in targeted immunotherapy for pSS, and most of the time, it is still based on empirical therapy. For those patients with pSS, conventional DMARDs or biologics (mostly rituximab) are still mainstream treatment.^{74,75} Clinically, reasonable use of epratuzumab and rituximab based on the patient's condition has shown a certain therapeutic effect. Ianalumab (VAY736), as another medicinal drug for pSS, eliminates pathogenic B cells through directly lysing B cells and breaking BlyS and its receptor signaling pathway, which has remarkably improved the clinical parameters and laboratory index of patients.

4.2 | Neutrophils in MS

Mounting evidence shows the role of neutrophils in MS. For example, neutrophils in the cerebrospinal fluid increased in pediatric MS patients, and MPO (neutrophil product) elevated in serum in MS.⁷⁶ Resting circulating neutrophils begin to sensitize after encountering pathogenic stimuli, which triggers the upregulation of surface receptors and induces chemokine receptor in MS (G-CSF, CXCL1, CXCL8, CXCL5, fMLPR14, TLR215, NE) to increase significantly. Studies have found that neutrophils are related to the level of the cytokine IL-17A (supporting neutrophil activation and recruitment) during the early relapse of MS patients.⁷⁷ Furthermore, neutrophils specifically express the aspartic retroviral-like protease ASPRV1, which increased in the central nervous system during severe cases of MS.⁷⁸ These observations could collectively support that neutrophil activity is a factor that influences MS development and severity.

At present, there are no direct target neutrophil drugs for the treatment of MS, and a very small number can play a therapeutic role by affecting neutrophils. Fingolimod (sphingosine analog) is an immunomodulatory drug that causes a decline in the neutrophil count after consistent dosing.⁷⁹ The immune-suppressive dimethyl fumarate may act to alter neutrophil function.⁸⁰ Cladribine, cyclophosphamide, and mitoxantrone, as cell cycle inhibitors, disrupt DNA synthesis of lymphocytes and other cells, and each reduces the number of neutrophils.^{78,81,82} The deficiency of therapeutic drugs emphasizes further study of the role of neutrophils in MS.

4.3 | Neutrophils in Crohn's disease

CD is a chronic inflammatory disorder that mainly affects gastrointestinal tract.⁸³ In the early stages of CD, a massive influx of neutrophils swallows and kills invading bacteria and fungi and digests foreign organic matters. The innate immune response delays the recruitment of neutrophils to the body's trauma, which has been confirmed in later stages of CD patients. Discovered by whole-exome sequence analysis, neutrophils produce low levels of ROS, and specific changes occurred in genes that regulate glucose metabolism and antimicrobial reactions.⁸⁴ This may be related to the impaired recruitment of neutrophils and killing of bacteria by luminal neutrophils, causing mice to increase their susceptibility to CD disease.⁸⁵

Studies have shown that CD's defect is related to the entry of neutrophils into damaged tissues rather than into the circulation. Therefore, using granulocyte-macrophage colony-stimulating factor (GM-CSF) to increase the

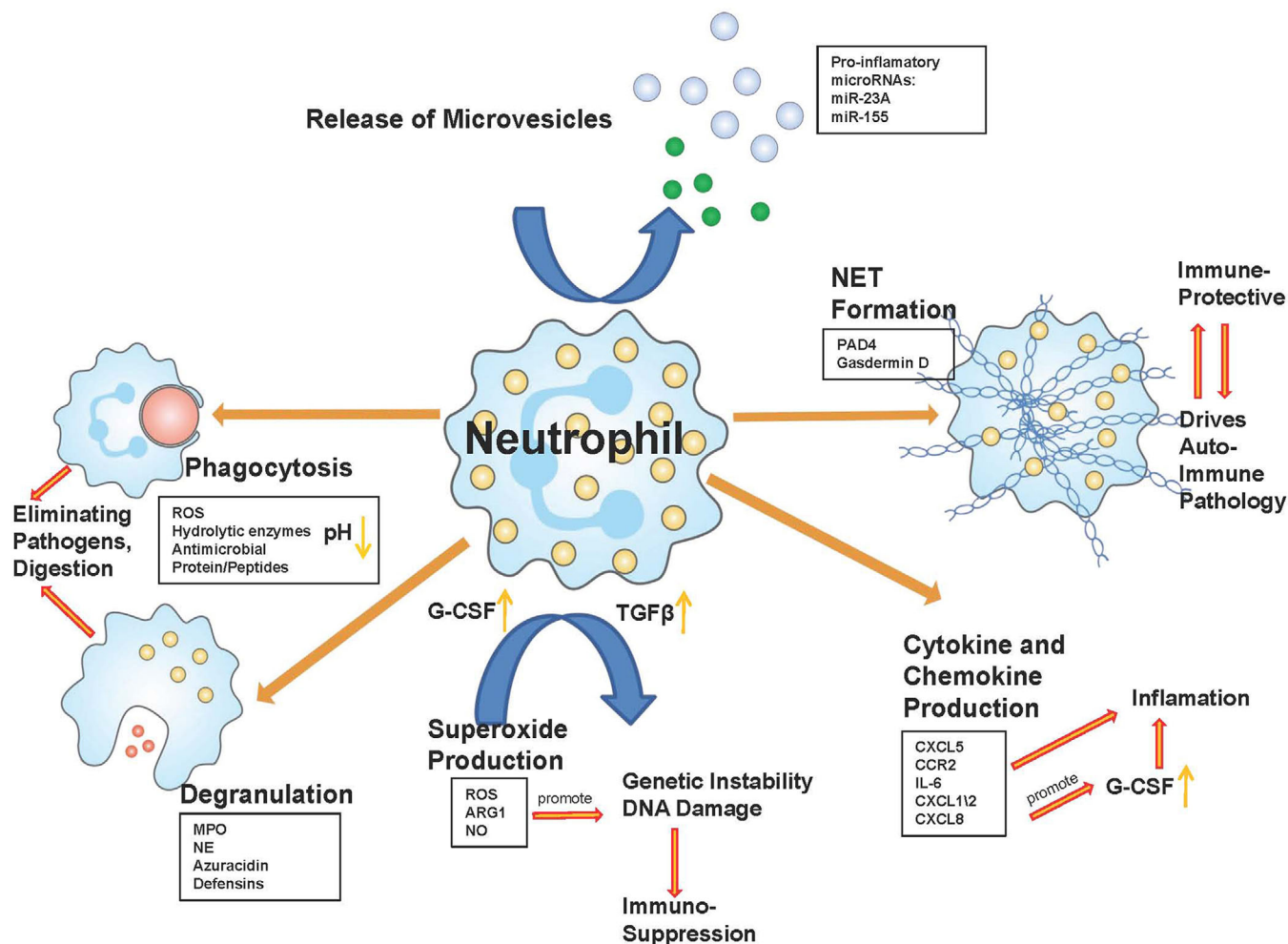


FIGURE 1 The role of neutrophils in autoimmune disorders. Neutrophils are involved in a variety of immune and inflammatory processes, where they can eliminate the invading pathogens through endocytosis and degranulation. They can also drive the immune process or immune suppression by generating reactive oxygen species (ROS), recruiting cytokine and chemokine, and neutrophil extracellular trap (NET) formation

number of circulating neutrophils to treat CD is invalid.^{86,87} Recent evidence shows that IgA has anti-inflammatory properties that can be therapeutically exploited. IgA can induce neutrophil death, which may involve at least in part FcαRI (CD89) and Mac-1 (CD3 and CD11b/CD18) signaling.⁸⁸

4.4 | Neutrophils in gout

Although gout has not been well demonstrated as an autoimmune disease, it has similar clinical symptoms and pathogenesis to some autoimmune diseases. Patients with RA, SLE, and gout suffer from hyperuricemia and reduced amino acid content, which is the purine's precursor. The close correlation between these patients and the purine index has been observed.⁸⁹ Neutrophil granulocytes contain many proinflammatory substances and mechanisms

that enable them to drive local acute immune responses to invade microorganisms or become endogenous inflammatory triggers.⁹⁰ Neutrophil mediated the production of interleukin-1β (IL-1β), which does gouty attacks, causing joint destruction, intense pain, and fever.⁹¹ The regulation of inflammation derived by inflammasome mediated by neutrophil-microvesicles (PMN-Ecto) is a puzzling concept: in the early periods of inflammation, neutrophils infiltrate the peritoneum in response to phosphatidylserine (PS)-positive PMN-Ecto released by C5a.⁹² The precipitation of uric acid causes the inflammation in gout, these crystals mediate the activation of inflammasomes in local immune cells and further lead to the rapid recruitment of neutrophils. During an acute gout attack, this massive influx of neutrophils is accompanied by notoriously clinical inflammatory symptoms.⁹³ Activated neutrophils form NETs, which is found abundantly in gout patients' synovial fluid, and this process is associated with autophagy

TABLE 1 Effector molecules of neutrophils in autoimmune diseases

Diseases	Effector molecules	Functions	Species	References
RA	CCR2	Infiltration of neutrophils into the joints	Mice with adjuvant-induced arthritis (AIA)	27,35
	CXCL5	Citrullinated ENA-78/CXCL5 recruiting monocytes to inflamed joint tissues	Humans and mice with AIA	30
	GITR	Glucocorticoid-induced tumor necrosis factor receptor-related protein (GITR) triggering is required for the development of immune response against CII	Collagen-induced arthritis (CIA)	95
	miR-451	Suppresses neutrophil chemotaxis	Humans and SKG mice	96
	IL-17	Induces hypernociception and neutrophil migration	Mice (mBSA)	97
	IL-17B	Controls immune cell trafficking and neutrophil homeostasis in the inflamed tissues	Humans	36
	CD147	Upregulates calcium-induced chemotaxis, adhesion ability, and invasiveness of human neutrophils	Humans	98
SLE	NCF1-339	Alters formation of neutrophil extracellular traps, high serum interferon activity, and antiphospholipid syndrome	Humans	99
	NCF1-339	Reduces oxidative burst	Humans	58
	NOX2 complex	Produces low ROS	Ncf1**mice	100
	TANK-binding kinase1 (TBK1)	Activates IRF3 and IRF7, leading to IFN-I production and subsequent induction of interferon-stimulated genes (ISGs)	Humans	101
	RIPK1	Decreasing neutrophil death and formation of NETs	Humans	102
	Gal-9	Inhibits TLR7-mediated autoimmunity	Spontaneous murine models of lupus (i.e., BXSB/MpJ and NZB/WF1 mice)	103

and IL-1 β . Studies have shown that a known alternative metabolic fuel β -hydroxybutyrate (BHB) is also an anti-inflammatory molecule and can be used as a treatment for gout.⁹⁰ The main mechanism is that BHB suppresses the NLRP3 inflammasome in neutrophils through reducing the initiation and assembly steps. In turn, it blocks the generation of IL-1 β in mouse and human neutrophils. In most gouty patients, functional activity of neutrophils is impaired due to their lower phagocytic function, which inhibits the body's antioxidant defense capabilities and leads to a chronic sustained pattern of the inflammatory process.

5 | DISCUSSION

Autoimmune diseases involve complex immunity disorders that cause loss of self-tolerance and attack endoge-

nous tissues and cells. Neutrophils acting as instrumental immune cells in the autoimmune disease, infiltrating tissue through immune complex and complement-mediated mechanisms, participating in the release of proteolytic enzymes, and causing tissue damage inflammation.^{3,4,94} However, even though neutrophils are known to be at the center of disease pathogenesis, the mechanism behind this is not fully understood, and targeted drugs have not been studied in detail. In this study, we tried to expand our understanding of the relationship between neutrophils and autoimmune diseases through comprehensive literature reviews. We also reviewed the core functions of neutrophils between innate and adaptive immunity (Figure 1).

Neutrophils participate in the initiation of the inflammatory response through a variety of mechanisms.^{91,92} These mechanisms highlight that neutrophils participate in the pathogenesis of disease in multiple ways, not just by releasing proteases and ROS to induce tissue

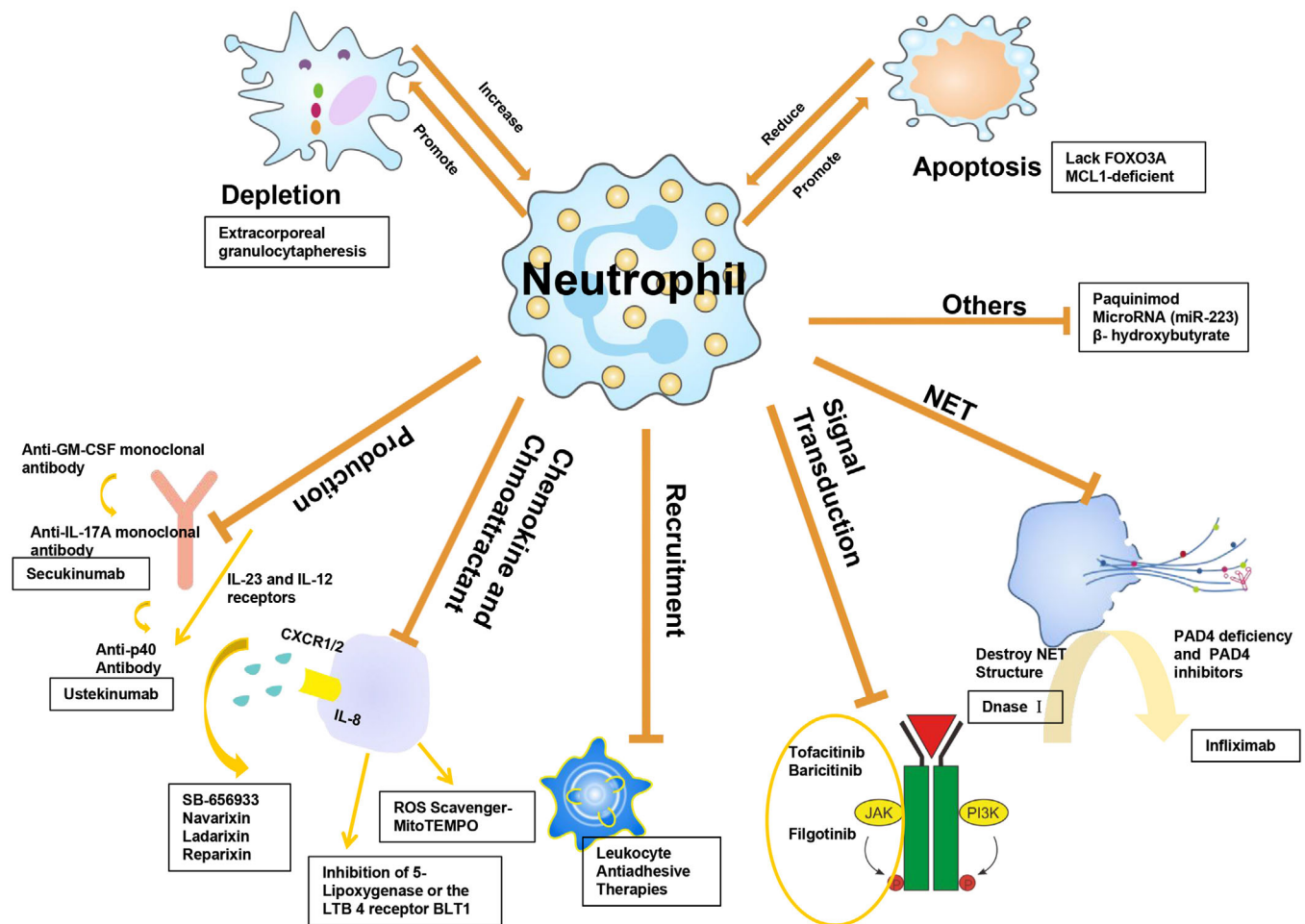


FIGURE 2 The therapeutic strategies of neutrophils in autoimmune disorders. Several aspects of neutrophil biology may be therapeutically targeted, including promotion of depletion and apoptosis, and targeted inhibition of neutrophil production, recruitment of chemokines, signal transduction pathways, and neutrophil extracellular trap (NET) formation, etc. In some cases, increasing depletion or reducing apoptosis is the aim. The boxes indicate representative drugs/strategies

damage. Ample evidence indicated that neutrophil-derived mechanisms not only exacerbate autoimmune diseases but also include cases where neutrophils protect the host from inflammatory tissue damage. Neutrophils exert regulatory function in the overall immune response by direct production of cytokines/chemoattractants and indirect effect between other immune cells (such as MPO and ROS agents) (Table 1). It is also clear that neutrophils are the source of self-antigens in many autoimmune diseases. Studies on a large number of animal models have explained most of this complexity. Improvement of neutrophil-specific gene targeting and interventional approaches will further reveal the complexity. In the past, drug development work always avoided targeting neutrophils, mainly due to concerns about severe infectious complications. As we now know, because of the functional role of neutrophils in the pathogenesis of autoimmune disorders, it is possible to envision the development of drugs that can block the function of neutrophils while

only moderately impairing the host's defenses. Using existing animal models and new ones development to alter the position of neutrophils, which is essential to improve their ability to control autoimmune diseases.

Our current understanding of neutrophil characteristics is limited, and even the detection of marker effects (such as NETosis) is still in its infancy. Nevertheless, with the rapid development of multidimensional and single-cell analysis techniques, it is only a matter of time before this technical problem is solved.¹⁰⁴ Currently, it is being actively studied whether neutrophils, their subgroups, or specific effector functions can be used as biomarkers. The manipulation of neutrophils may help treat autoimmune diseases in the future and even become the basis for new targeted drugs (Figure 2).

Recognizing neutrophils' regulatory roles in autoimmune diseases will encourage us to reconsider the biological significance of neutrophils in physiological and pathological conditions. In addition, based on neutrophils'

ability to regulate autoimmune diseases and the development of more and effective targeted drugs for autoimmune diseases, it may potentially provide new therapies for autoimmune disorders, such as RA, SLE, and other diseases.

ACKNOWLEDGMENTS

Research reported in this publication was supported in part by the National Natural Science Foundation of China (No. 81771693), the Advanced Interdisciplinary Studies Foundation of Basic Medical Science, AMU (No. 2018JCQY06), and the Key Support Object of AMU (No. 410301060133).

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ETHICS STATEMENT

Not applicable.

AUTHOR CONTRIBUTIONS

Xiaohong Fu, Gang Huang, and Shuang-shuang Dai designed the study and wrote the manuscript. Heting Liu contributed to the conception of the study and correction of the manuscript.

DATA AVAILABILITY STATEMENT

No new data were created or analyzed in this review. Data sharing is not applicable to this article.

REFERENCES

1. Duan L, Rao X, Sigdel KR. Regulation of inflammation in autoimmune disease. *J Immunol Res*. 2019;2019:7403796.
2. Perl A. Pathogenesis and spectrum of autoimmunity. *Methods Mol Biol*. 2004;102:1-8.
3. Pietrosimone KM, Liu P. Contributions of neutrophils to the adaptive immune response in autoimmune disease. *World J Transl Med*. 2015;4:60-68.
4. Papayannopoulos V. Neutrophil extracellular traps in immunity and disease. *Nat Rev Immunol*. 2018;18:134-147.
5. Cecchi I, Arias de la Rosa I, Menegatti E, et al. Neutrophils: novel key players in rheumatoid arthritis. current and future therapeutic targets. *Autoimmun Rev*. 2018;17:1138-1149.
6. Bonaventura A, Montecucco F. Inflammation and pericarditis: are neutrophils actors behind the scenes? *J Cell Physiol*. 2019;234:5390-5398.
7. Martin KR, Ohayon D, Witko-Sarsat V. Promoting apoptosis of neutrophils and phagocytosis by macrophages: novel strategies in the resolution of inflammation. *Swiss Med Wkly*. 2015;145:w14056.
8. Jayaprakash K, Demirel I, Khalaf H, Bengtsson T. The role of phagocytosis, oxidative burst and neutrophil extracellular traps in the interaction between neutrophils and the periodontal pathogen *Porphyromonas gingivalis*. *Mol Oral Microbiol*. 2015;30:361-375.
9. Marcinkiewicz J, Walczewska M. Neutrophils as sentinel cells of the immune system: a role of the MPO-halide-system in innate and adaptive immunity. *Curr Med Chem*. 2020;27:2840-2851.
10. Chakrabarti S, Zee JM, Patel KD. Regulation of matrix metalloproteinase-9 (MMP-9) in TNF-stimulated neutrophils: novel pathways for tertiary granule release. *J Leukoc Biol*. 2006;79:214-222.
11. Trentini A, Bellini T, Manfrinato MC, et al. Balanced and unbalanced solutions modulate the release of matrix metalloproteinase-9 (MMP-9) from neutrophils in response to inflammatory stimuli: an in vitro study. *Inflamm Res*. 2014;63:325-328.
12. Marin DP, Bolin AP, Macedo Rde C, Sampaio SC, Otton R. ROS production in neutrophils from alloxan-induced diabetic rats treated in vivo with astaxanthin. *Int Immunopharmacol*. 2011;11:103-109.
13. Fousert E, Toes R, Desai J. Neutrophil extracellular traps (NETs) take the central stage in driving autoimmune responses. *Cells*. 2020;9(4):915.
14. Boeltz S, Amini P, Anders HJ, et al. To NET or not to NET: current opinions and state of the science regarding the formation of neutrophil extracellular traps. *Cell Death Differ*. 2019;26:395-408.
15. Rozman S, Yousefi S, Oberson K, Kaufmann T, Benarafa C, Simon HU. The generation of neutrophils in the bone marrow is controlled by autophagy. *Cell Death Differ*. 2015;22:445-456.
16. Prame Kumar K, Nicholls AJ, Wong CHY. Partners in crime: neutrophils and monocytes/macrophages in inflammation and disease. *Cell Tissue Res*. 2018;371:551-565.
17. Remijsen Q, Vanden Berghe T, Wirawan E, et al. Neutrophil extracellular trap cell death requires both autophagy and superoxide generation. *Cell Res*. 2011;21:290-304.
18. Mocsai A. Diverse novel functions of neutrophils in immunity, inflammation, and beyond. *J Exp Med*. 2013;210:1283-1299.
19. Sideras P, Apostolou E, Stavropoulos A, et al. Activin, neutrophils, and inflammation: just coincidence? *Semin Immunopathol*. 2013;35:481-499.
20. Swirski FK, Robbins CS. Neutrophils usher monocytes into sites of inflammation. *Circ Res*. 2013;112:744-745.
21. Keijsers R, Hendriks AGM, van Erp PEJ, et al. In vivo induction of cutaneous inflammation results in the accumulation of extracellular trap-forming neutrophils expressing RORgammat and IL-17. *J Invest Dermatol*. 2014;134:1276-1284.
22. Gunzer M. Traps and hyper inflammation - new ways that neutrophils promote or hinder survival. *Br J Haematol*. 2014;164:189-199.
23. Burmester GR, Pope JE. Novel treatment strategies in rheumatoid arthritis. *Lancet*. 2017;389:2338-2348.
24. Bach M, Moon J, Moore R, Pan T, Nelson JL, Lood C. A neutrophil activation biomarker panel in prognosis and monitoring of patients with rheumatoid arthritis. *Arthritis Rheumatol*. 2019;72:47-56.
25. Kolaczowska E, Kubes P. Neutrophil recruitment and function in health and inflammation. *Nat Rev Immunol*. 2013;13:159-175.
26. Li Y, Wang W, Yang F, Xu Y, Feng C, Zhao Y. The regulatory roles of neutrophils in adaptive immunity. *Cell Commun Signal*. 2019;17:147.

27. Talbot J, Bianchini FJ, Nascimento DC, et al. CCR2 expression in neutrophils plays a critical role in their migration into the joints in rheumatoid arthritis. *Arthritis Rheumatol.* 2015;67:1751-1759.
28. Conte FD, Barja-Fidalgo C, Verri WA, et al. Endothelins modulate inflammatory reaction in zymosan-induced arthritis: participation of LTB₄, TNF- α , and CXCL-1. *J Leukoc Biol.* 2008;84:652-660.
29. Smith E, McGettrick HM, Stone MA, et al. Duffy antigen receptor for chemokines and CXCL5 are essential for the recruitment of neutrophils in a multicellular model of rheumatoid arthritis synovium. *Arthritis Rheum.* 2008;58:1968-1973.
30. Yoshida K, Korchynskiy O, Tak PP, et al. Citrullination of epithelial neutrophil-activating peptide 78/CXCL5 results in conversion from a non-monocyte-recruiting chemokine to a monocyte-recruiting chemokine. *Arthritis Rheumatol.* 2014;66:2716-2727.
31. Koch AE, Volin MV, Woods JM, et al. Regulation of angiogenesis by the C-X-C chemokines interleukin-8 and epithelial neutrophil activating peptide 78 in the rheumatoid joint. *Arthritis Rheum.* 2001;44:31-40.
32. Auer J, Blass M, Schulze-Koops H, et al. Expression and regulation of CCL18 in synovial fluid neutrophils of patients with rheumatoid arthritis. *Arthritis Res Ther.* 2007;9:R94.
33. Conte Fde P, Barja-Fidalgo C, Verri WA, et al. Endothelins modulate inflammatory reaction in zymosan-induced arthritis: participation of LTB₄, TNF- α , and CXCL-1. *J Leukoc Biol.* 2008;84:652-660.
34. Inaba M, Takahashi T, Kumeda Y, et al. Increased basal phosphorylation of mitogen-activated protein kinases and reduced responsiveness to inflammatory cytokines in neutrophils from patients with rheumatoid arthritis. *Clin Exp Rheumatol.* 2008;26:52-60.
35. Talbot J, Bianchini FJ, Souto FOS, et al. Role of CCR2 expression in neutrophils on development of arthritis. *Immunology.* 2012;137:586-586.
36. Kouri VP, Olkkonen J, Ainola M, et al. Neutrophils produce interleukin-17B in rheumatoid synovial tissue. *Rheumatology (Oxford).* 2014;53:39-47.
37. Gorlino CV, Dave MN, Blas R, et al. Association between levels of synovial anti-citrullinated peptide antibodies and neutrophil response in patients with rheumatoid arthritis. *Eur J Immunol.* 2018;48:1563-1572.
38. An QY, Yan WK, Zhao Y, Yu KQ. Enhanced neutrophil autophagy and increased concentrations of IL-6, IL-8, IL-10 and MCP-1 in rheumatoid arthritis. *Int Immunopharmacol.* 2018;65:119-128.
39. Szodoray P, Nakken B, Barath S, et al. Altered Th17 cells and Th17/regulatory T-cell ratios indicate the subsequent conversion from undifferentiated connective tissue disease to definitive systemic autoimmune disorders. *Hum Immunol.* 2013;74:1510-1518.
40. Brinkmann V, Reichard U, Goosmann C, et al. Neutrophil extracellular traps kill bacteria. *Science.* 2004;303:1532-1535.
41. An Q, Yan W, Zhao Y, Yu K. Enhanced neutrophil autophagy and increased concentrations of IL-6, IL-8, IL-10 and MCP-1 in rheumatoid arthritis. *Int Immunopharmacol.* 2018;65:119-128.
42. Li XH, Yuan K, Zhu QQ, et al. Andrographolide ameliorates rheumatoid arthritis by regulating the apoptosis-NETosis balance of neutrophils. *Int J Mol Sci.* 2019;20:5035.
43. Caramaschi P, Biasi D, Colombatti M, et al. Anti-TNF α therapy in rheumatoid arthritis and autoimmunity. *Rheumatol Int.* 2006;26:209-214.
44. Dain L, Braun-Moscovici Y, Baum E, Nahir AM, Hoffer E. Modification of neutrophil function by plasma of rheumatoid arthritis patients treated with infliximab. *Clin Exp Rheumatol.* 2006;24:38-44.
45. Kaundal U, Khullar A, Leishangthem B, et al. The effect of methotrexate on neutrophil reactive oxygen species and CD177 expression in rheumatoid arthritis. *Clin Exp Rheumatol.* 2020.
46. Hobl EL, Mader RM, Erlacher L, et al. The influence of methotrexate on the gene expression of the proinflammatory cytokine IL-12A in the therapy of rheumatoid arthritis. *Clin Exp Rheumatol.* 2011;29:963-969.
47. Ruiz-Limon P, Ortega R, Arias de la Rosa I, et al. Tocilizumab improves the proatherothrombotic profile of rheumatoid arthritis patients modulating endothelial dysfunction, NETosis, and inflammation. *Transl Res.* 2017;183:87-103.
48. Li B, Li P, Bi L. Iguratimod dose dependently inhibits the expression of citrullinated proteins and peptidylarginine deiminases 2 and 4 in neutrophils from rheumatoid arthritis patients. *Clin Rheumatol.* 2020;39:899-907.
49. Vanhoutte F, Mazur M, Voloshyn O, et al. Efficacy, safety, pharmacokinetics, and pharmacodynamics of filgotinib, a selective JAK-1 inhibitor, after short-term treatment of rheumatoid arthritis: results of two randomized phase IIa trials. *Arthritis Rheumatol.* 2017;69:1949-1959.
50. Zhang Q, Dehaini D, Zhang Y, et al. Neutrophil membrane-coated nanoparticles inhibit synovial inflammation and alleviate joint damage in inflammatory arthritis. *Nat Nanotechnol.* 2018;13(12):1182-1190.
51. Pyne D, Isenberg DA. Autoimmune thyroid disease in systemic lupus erythematosus. *Ann Rheum Dis.* 2002;61:70-72.
52. Salemme R, Peralta LN, Meka SH, Pushpanathan N, Alexander JJ. The role of NETosis in systemic lupus erythematosus. *J Cell Immunol.* 2019;1:33-42.
53. Appelgren D, Dahle C, Knopf J, et al. Active NET formation in libman-sacks endocarditis without antiphospholipid antibodies: a dramatic onset of systemic lupus erythematosus. *Autoimmunity.* 2018;51:310-318.
54. Smith CK, Vivekanandan-Giri A, Tang C, et al. Neutrophil extracellular trap-derived enzymes oxidize high-density lipoprotein: an additional proatherogenic mechanism in systemic lupus erythematosus. *Arthritis Rheumatol.* 2014;66:2532-2544.
55. Kahlenberg JM, Carmona-Rivera C, Smith CK, Kaplan MJ. Neutrophil extracellular trap-associated protein activation of the NLRP3 inflammasome is enhanced in lupus macrophages. *J Immunol.* 2013;190:1217-1226.
56. Ajmani S, Singh H, Chaturvedi S, et al. Utility of neutrophil CD64 and serum TREM-1 in distinguishing bacterial infection from disease flare in SLE and ANCA-associated vasculitis. *Clin Rheumatol.* 2019;38(4):997-1005.
57. Biermann MHC, Boeltz S, Pieterse E, et al. Autoantibodies recognizing secondary NEcrotic cells promote neutrophilic

- phagocytosis and identify patients with systemic lupus erythematosus. *Front Immunol.* 2018;9:989.
58. Olsson LM, Johansson AC, Gullstrand B, et al. A single nucleotide polymorphism in the NCF1 gene leading to reduced oxidative burst is associated with systemic lupus erythematosus. *Ann Rheum Dis.* 2017;76:1607-1613.
 59. Kelkka T, Kienhofer D, Hoffmann M, et al. Reactive oxygen species deficiency induces autoimmunity with type 1 interferon signature. *Antioxid Redox Signal.* 2014;21:2231-2245.
 60. Carmona-Rivera C, Kaplan MJ. Low-density granulocytes: a distinct class of neutrophils in systemic autoimmunity. *Semin Immunopathol.* 2013;35:455-463.
 61. Soliman WM, Sherif NM, Ghanima IM, El-Badawy MA. Neutrophil to lymphocyte and platelet to lymphocyte ratios in systemic lupus erythematosus: relation with disease activity and lupus nephritis. *Reumatol Clin.* 2020;16:255-261.
 62. Whittall-Garcia LP, Torres-Ruiz J, Zentella-Dehesa A, et al. Neutrophil extracellular traps are a source of extracellular HMGB1 in lupus nephritis: associations with clinical and histopathological features. *Lupus.* 2019;28:1549-1557.
 63. Umeda N, Matsumoto I, Kawaguchi H, et al. Prevalence of soluble peptidylarginine deiminase 4 (PAD4) and anti-PAD4 antibodies in autoimmune diseases. *Clin Rheumatol.* 2016;35:1181-1188.
 64. Massarenti L, Enevold C, Damgaard D, Odum N, Nielsen CH, Jacobsen S. Peptidylarginine deiminase-4 gene polymorphisms are associated with systemic lupus erythematosus and lupus nephritis. *Scand J Rheumatol.* 2019;48:133-140.
 65. McGrath H. Ultraviolet-A1 irradiation therapy for systemic lupus erythematosus. *Lupus.* 2017;26:1239-1251.
 66. Frangou E, Chrysanthopoulou A, Mitsios A, et al. REDD1/autophagy pathway promotes thromboinflammation and fibrosis in human systemic lupus erythematosus (SLE) through NETs decorated with tissue factor (TF) and interleukin-17A (IL-17A). *Ann Rheum Dis.* 2019;78:238-248.
 67. Neeli I, Dwivedi N, Khan S, Radic M. Regulation of extracellular chromatin release from neutrophils. *J Innate Immun.* 2009;1:194-201.
 68. Bodil Roth E, Theander E, Londos E, et al. Pathogenesis of autoimmune diseases: antibodies against transglutaminase, peptidylarginine deiminase and protein-bound citrulline in primary Sjögren's syndrome, multiple sclerosis and alzheimer's disease. *Scand J Immunol.* 2008;67:626-631.
 69. Rischmueller M, Tieu J, Lester S. Primary Sjögren's syndrome. *Best Pract Res Clin Rheumatol.* 2016;30:189-220.
 70. Torsteinsdottir I, Gudbjornsson B, Hakansson L. Enhanced neutrophil and eosinophil adhesion in patients with primary Sjögren's syndrome. *Clin Exp Rheumatol.* 1998;16:255-262.
 71. Jin Y, Zhang T, Ye WJ, Zhu XC, Wang LX, Wang XB. Clinical profile and associated factors of pulmonary involvement in primary Sjögren's syndrome. *Med Clin (Barc).* 2019;153:305-311.
 72. Nicaise C, Weichselbaum L, Schandene L, et al. Phagocyte-specific S100A8/A9 is upregulated in primary Sjögren's syndrome and triggers the secretion of pro-inflammatory cytokines in vitro. *Clin Exp Rheumatol.* 2017;35:129-136.
 73. Hui M, Zhao J, Tian Z, et al. Red blood cell distribution width as a potential predictor of survival of pulmonary arterial hypertension associated with primary Sjögren's syndrome: a retrospective cohort study. *Clin Rheumatol.* 2019;38:477-485.
 74. Souza FB, Porfirio GJ, Andriolo BN, Albuquerque JV, Trevisani VF. Rituximab effectiveness and safety for treating primary Sjögren's syndrome (pSS): systematic review and meta-analysis. *PLoS One.* 2016;11:e0150749.
 75. Nocturne G, Cornec D, Seror R, Mariette X. Use of biologics in Sjögren's syndrome. *Rheum Dis Clin North Am.* 2016;42:407-417.
 76. Pulli B, Bure L, Wojtkiewicz GR, et al. Multiple sclerosis: myeloperoxidase immunoradiology improves detection of acute and chronic disease in experimental model. *Radiology.* 2015;275:480-489.
 77. Pelletier M, Maggi L, Micheletti A, et al. Evidence for a cross-talk between human neutrophils and Th17 cells. *Blood.* 2010;115(2):335-343.
 78. Casserly CS, Nantes JC, Hawkins RFW, Vallieres L. Neutrophil perversion in demyelinating autoimmune diseases: mechanisms to medicine. *Autoimmun Rev.* 2017;16:294-307.
 79. Rafiee Zadeh A, Parsa S, Tavoosi N, Farshi M, Masaeli MF. Effect of fingolimod on white blood cell, lymphocyte and neutrophil counts in MS patients. *Am J Clin Exp Immunol.* 2019;8:9-15.
 80. Goldman MD, Dwyer L, Coleman R, Sohn MW, Stuve O. Patient-specific factors modulate leukocyte response in dimethyl fumarate treated MS patients. *PLoS One.* 2020;15:e0228617.
 81. Maniscalco GT, Annunziata M, Ranieri A, et al. Remission of early persistent cladribine-induced neutropenia after filgrastim therapy in a patient with relapsing - remitting multiple sclerosis. *Mult Scler Relat Disord.* 2020;43:102151.
 82. Krishnan C, Kaplin AI, Brodsky RA, et al. Reduction of disease activity and disability with high-dose cyclophosphamide in patients with aggressive multiple sclerosis. *Arch Neurol.* 2008;65:1044-1051.
 83. Csonge V, Jaromi L, Safrany E, et al. Interaction of the major inflammatory bowel disease susceptibility alleles in Crohn's disease patients. *World J Gastroenterol.* 2010;16:176-183.
 84. Denson LA, Jurickova I, Karns R, et al. Clinical and genomic correlates of neutrophil reactive oxygen species production in pediatric patients with Crohn's disease. *Gastroenterology.* 2018;154(8):2097-2110.
 85. Caruso R, Mathes T, Martens EC, et al. A specific gene-microbe interaction drives the development of Crohn's disease-like colitis in mice. *Sci Immunol.* 2019;4(34):eaaw4341.
 86. Weinlage T, Dabritz J, Varga G, Belz M, Foell D. GM-CSF modifies monocytes to develop anti-inflammatory properties that are beneficial in Crohn's disease. *Immunology.* 2012;137:531-531.
 87. Del Valle DM, Torres J, Lafate I, Murray JA, Choung RS, Sato T. Gm-Csf autoantibodies precede the development of Crohn's disease and predict complicated phenotype at diagnosis. *Gastroenterology.* 2020;158:S74.
 88. Viladomiu M, Kivoolowitz C, Abdulhamid A, et al. IgA-coated *E. coli* enriched in Crohn's disease spondyloarthritis promote TH17-dependent inflammation. *Sci Transl Med.* 2017;9(376):eaaf9655.
 89. So AK, Martinon F. Inflammation in gout: mechanisms and therapeutic targets. *Nat Rev Rheumatol.* 2017;13(11):639-647.
 90. Goldberg EL, Asher JL, Molony RD, et al. Beta-hydroxybutyrate deactivates neutrophil NLRP3 inflammasome to relieve gout flares. *Cell Rep.* 2017;18(9):2077-2087.

91. Alberts BM, Bruce C, Basnayake K, Ghezzi P, Davies KA, Mullen LM. Secretion of IL-1 β from monocytes in gout is redox independent. *Front Immunol*. 2019;10:70.
92. Lee KH, Kronbichler A, Park DD, et al. Neutrophil extracellular traps (NETs) in autoimmune diseases: a comprehensive review. *Autoimmun Rev*. 2017;16(11):1160-1173.
93. Maueröder C, Kienhöfer D, Hahn J, et al. How neutrophil extracellular traps orchestrate the local immune response in gout. *J Mol Med (Berl)*. 2015;93(7):727-734.
94. Kraaij T, Tengstrom FC, Kamerling SW, et al. A novel method for high-throughput detection and quantification of neutrophil extracellular traps reveals ROS-independent NET release with immune complexes. *Autoimmun Rev*. 2016;15:577-584.
95. Cuzzocrea S, Ayroldi E, Di Paola R, et al. Role of glucocorticoid-induced TNF receptor family gene (GITR) in collagen-induced arthritis. *FASEB J*. 2005;19:1253-1265.
96. Murata K, Yoshitomi H, Furu M, et al. MicroRNA-451 down-regulates neutrophil chemotaxis via p38 MAPK. *Arthritis Rheumatol*. 2014;66:549-559.
97. Pinto LG, Talbot J, Peres RS, et al. Joint production of IL-22 participates in the initial phase of antigen-induced arthritis through IL-1 β production. *Arthritis Res Ther*. 2015;17:235.
98. Wang CH, Rong MY, Wang L, et al. CD147 up-regulates calcium-induced chemotaxis, adhesion ability and invasiveness of human neutrophils via a TRPM-7-mediated mechanism. *Rheumatology (Oxford)*. 2014;53:2288-2296.
99. Linge P, Arve S, Olsson LM, et al. NCF1-339 polymorphism is associated with altered formation of neutrophil extracellular traps, high serum interferon activity and antiphospholipid syndrome in systemic lupus erythematosus. *Ann Rheum Dis*. 2020;79:254-261.
100. Hahn J, Euler M, Kilgus E, et al. NOX2 mediates quiescent handling of dead cell remnants in phagocytes. *Redox Biol*. 2019;26:101279.
101. Bodewes ILA, Huijser E, van Helden-Meeuwssen CG, et al. TBK1: a key regulator and potential treatment target for interferon positive Sjögren's syndrome, systemic lupus erythematosus and systemic sclerosis. *J Autoimmun*. 2018;91:97-102.
102. Guo R, Tu Y, Xie S, et al. A role for receptor-interacting protein kinase-1 in neutrophil extracellular trap formation in patients with systemic lupus erythematosus: a preliminary study. *Cell Physiol Biochem*. 2018;45:2317-2328.
103. Panda SK, Facchinetti V, Voynova E, et al. Galectin-9 inhibits TLR7-mediated autoimmunity in murine lupus models. *J Clin Invest*. 2018;128:1873-1887.
104. Banerjee S, Biehl A, Gadina M, Hasni S, Schwartz DM. JAK-STAT signaling as a target for inflammatory and autoimmune diseases: current and future prospects. *Drugs*. 2017;77(5):521-546.

How to cite this article: Fu X, Liu H, Huang G, Dai S-S. The emerging role of neutrophils in autoimmune-associated disorders: effector, predictor, and therapeutic targets. *MedComm*. 2021;2:402–413. <https://doi.org/10.1002/mco2.69>