Rev. Biol. Biomed. Sci. 2022-2023 5 (1) 29-42
DOI: 10.31178/rbbs.2022-2023.5.1.4

NETosis in autoimmune diseases with focus on psoriasis

Diana-Antonia Costea[1,2]✉, Monica Neagu[1,2], Carolina Constantin[1], Veronica Lazăr[2], Elena-Georgiana Dobre[1,2]

[1]Department of Immunology, Victor Babes National Institute of Pathology, Bucharest, Romania; [2]Doctoral School of Biology, Faculty of Biology University of Bucharest, 050095 Bucharest, Romania

✉Correspondence to: Diana-Antonia Costea, Department of Immunology, Victor Babes National Institute of Pathology, 99-101 Splaiul Independenței, 050096 Bucharest, Romania. E-mail: diana.costea@s.unibuc.ro

Received: 25 March 2024 / **Revised**: 29 July 2024 / **Accepted**: 19 September 2024 / **Available online**: 31 October 2024

Abstract Neutrophil granulocytes are a key player in host innate immunity and they provide antimicrobial protection also by NETosis, amongst other mechanisms. NETosis involves the formation of intricate web-like structures, composed of DNA-histone complexes and proteins released by activated neutrophils, commonly referred to as *neutrophil extracellular traps* (NETs) with sticky and antimicrobial effects on extracellular pathogens. The dysregulation of neutrophils and NETosis may result in autoimmune diseases, due to the formation of autoantibodies, consequent exaggerated immune stimulation, overexpression of various molecules related to NETosis, and infiltration of cutaneous lesions with neutrophils and other immune cell populations. Furthermore, a neutrophil subpopulation was found to be strongly linked to the pathogenesis of these diseases. The interest in the implications of NETosis in autoimmunity has grown in the past years; researchers found new biomarkers and evaluated therapeutics targeted towards this cell death pathway correlated to psoriasis and autoimmunity. Thus, future studies are needed on this matter in order to increase the quality of life in autoimmune disease patients, as NETosis represents a promising therapeutic target. This review article aimed to thoroughly examine neutrophil functions and their association with NETosis in the context of autoimmune diseases, with a particular focus on psoriasis.

Keywords: psoriasis, NETosis, neutrophil extracellular traps, NETs, autoimmune diseases

Introduction

Neutrophils play an important role in the host's innate immunity as they are the primary line of defense against extracellular microbes and constitute the most abundant cell population in adult peripheral blood (Chiang et al., 2019; Sadeghi et al., 2023). Neutrophils contribute to host protection through the mechanisms of phagocytosis and its steps: ingestion, degranulation, production of reactive oxygen species (ROS) and chemokines. When stimulated by various molecules, neutrophils are able to release neutrophil extracellular traps (NETs) (Chiang et al., 2019; Kvist-Hansen et al., 2021; Mutua and Gershwin 2021; Ding et al., 2022). This process was described for the first time in 2004 by Brinkmann and coworkers; however, the term "NETosis" was coined in 2007 by Steinberg and Grinstein to define the neutrophil cell death that occurs as a result of this newly elucidated mechanism within the innate immune response (Brinkmann et al., 2004; Steinberg and Grinstein 2007). That is, NETosis represents a distinct form of cell death, differing from both apoptosis and necrosis (Chiang et al., 2019; Huang and O'Sullivan 2022). NETosis is divided into four types: vital, suicidal, caspase-dependent and mitochondrial (Huang and O'Sullivan 2022). Despite providing important host protection by disarming or killing bacteria, parasites, fungi and viruses (Delgado-Rizo et al., 2017), neutrophils and NETosis have been recently correlated to multiple autoimmune disorders, such as rheumatoid arthritis, systemic lupus erythematosus, diabetes mellitus, multiple sclerosis and psoriasis (Hu et al., 2016; Neubert et al., 2019; Sadeghi et al., 2023). Psoriasis is a chronic autoimmune inflammatory disease determined by environmental, genetic and immunological factors (Griffiths et al., 2021). In the pathogenesis of psoriasis, the interplay between components of innate and adaptative immunity plays a fundamental role (Surcel et al., 2021a). The IL(interleukin)-23/Th17 axis is crucial in the pathogenesis of psoriasis and provides proof of the interactions between components of innate and adaptative immunity (Schön and Erpenbeck 2018; Wang and Shi 2023). Several cytokines and chemokines contribute to psoriasis inflammatory processes via mechanisms (IL-33–IL-37, CXCR6/CXCL16, CCL20/CCR6 and TLR7–MyD88–DC–CXCL16 axes) in which they interact with specific receptors and immune cells (Furue et al., 2020; Bao et al., 2023; Lu et al., 2023; Tsuji et al., 2023). This disease is characterized by the uncontrolled proliferation of keratinocytes and infiltration of psoriatic lesions with

immune cells (Surcel et al., 2022). The histological hallmark of psoriasis is the Munro's microabscesses in which neutrophils are numerous (Kvist-Hansen et al., 2021; Rodriguez-Rosales et al., 2021; Meng et al., 2022). NETosis was found to be correlated with the severity of psoriasis (Hu et al., 2016). The interest in this link has grown significantly: recent studies shed the light on potential biomarkers and tested current and novel therapies in psoriasis. Therefore, further research on the implications of this cell death process is needed to explore new perspectives for the clinical management of autoimmune diseases. The aim of this article was to provide an overview of the connection between NETosis and autoimmunity, with a specific focus on psoriasis.

Mechanism of NETosis

Neutrophils represent the first line of defense against pathogens (Sadeghi et al., 2023), mainly by phagocytosis, including degranulation and release of a lot of microbicidal factors. Moreover, the activated neutrophils produce ROS and chemokines that promote the recruitment of other immune cells at the infection or inflammatory site (Chiang et al., 2019; Kvist-Hansen et al., 2021; Mutua and Gershwin 2021; Ding et al., 2022). There are two distinct populations of neutrophils separated by gradient centrifugation in Ficoll in human peripheral blood. The first one is represented by polymorphonuclear neutrophils located in the pellet alongside erythrocytes. The low-density granulocytes (LDGs) represent the second population which is found in the peripheral blood mononuclear cell fraction (Czerwińska and Owczarczyk-Saczonek 2022). Low density granulocytes are neutrophils that are released from the bone marrow into the bloodstream before they reach maturity (Skrzeczynska-Moncznik et al., 2020). Interestingly, neutrophils are capable of various forms of programmed cell death, including NETosis and pyroptosis, while also being susceptible to non-programmed cell death through necrosis (Chapple et al., 2023).

Neutrophils are the most numerous cell population of innate immunity in adult peripheral blood (Chiang et al., 2019; Sadeghi et al., 2023). Neutrophil polymorphonuclear leukocytes (neutrophils) are myeloid cells filled with lysosomal granules (which explains the name of granulocytes), housing a potent arsenal of antimicrobial agents. In parallel, current literature underscores the pivotal role of neutrophils in immune processes, including acute and chronic inflammation, and in the modulation of inflammation and wound healing, primarily attributed to the diverse repertoire of surface receptors they express. The comprehensive array of surface receptors encompasses, among others, integrins that facilitate neutrophils' mobilization from the bone marrow into circulation, diapedesis and subsequent tissue infiltration. Neutrophils also express cytokine/chemokine receptors, orchestrating their oriented migration towards infection or tissue injury sites, and priming them for a secondary stimulus. Additionally, neutrophils harbor pattern recognition receptors and Fc- and C3b-receptors, being able of immune phagocytosis and thereby expediting the eradication and clearance of infectious agents or the debridement of compromised tissue (Chapple et al., 2023).

Morphologically, neutrophils possess a multi-lobulated nucleus (Hoffmann and Enk 2016) and a set of several specialized organelles/lysosomes known as granules (Brinkmann and Zychlinsky 2012; Chiang et al., 2019). The granules aid in the neutrophil antimicrobial and pathogen clearance pathways due to the abundance of proteins in their composition (Burn et al., 2021). At least three major neutrophil granule populations (azurophilic, specific, and gelatinase), and a population of secretory vesicles, have been documented. Each subpopulation is defined by a specific set of proteins and a distinctive shape, and it is synthesized at a particular stage of neutrophil maturation (Price et al., 2000). Azurophilic (primary) granules contain mainly toxic mediators such as myeloperoxidase (MPO), neutrophil elastase (NE), defensins, hydrolases, and cathepsins. The secondary and tertiary granules exhibit shared contents, yet their differentiation is facilitated by the distinctive buoyant densities observed during centrifugation on gradient media (Lacy 2006). Specific (secondary) granules contain lactoferrin, collagenase, cytochrome b558, cathelicidins (known as LL-37), nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, alkaline phosphatase. Gelatinase (tertiary) granules incorporate enzymes such as gelatinase, arginase 1, lysozyme, cytochrome b558, collagenase, cathepsins and lectins such as ficolin 1 (Brinkmann and Zychlinsky 2012; Chiang et al., 2019; Czerwińska and Owczarczyk-Saczonek 2022). Finally, secretory vesicles encapsulate extracellular matrix receptors, which are further exposed to the polymorphonuclear leukocyte surface. These receptors activate downstream neutrophil processes and play key roles in rolling, endothelial attachment, basement membrane traversal and diapedesis (Price et al., 2000).

When stimulated by some chemical compounds, inflammatory factors or metabolites, neutrophils can undergo a unique cell death process known as "NETosis" (Ding et al., 2022; Sadeghi et al., 2023). NETosis is the process in which NETs are formed (Meng et al., 2022) and was described for the first time in 2004 by Brinkmann et al. as "structures composed of granule and nuclear constituents that disarm and kill bacteria extracellularly" (Brinkmann et al., 2004).

NETosis is divided into four categories (vital, suicidal, caspase-dependent, mitochondrial), from which the first two constitute the active form of cell death (Huang and O'Sullivan 2022) (Fig. 1).

Vital or non-lytic NETosis occurs within minutes of the interaction with the pathogen (Gram-positive or Gram-negative bacteria) (Hoffmann and Enk 2016; Huang and O'Sullivan 2022). This process results in releasing the NETs without disrupting the nuclear or plasma

membrane, independent of ROS (Sadeghi et al., 2023). Therefore, neutrophils remain viable and maintain their prime functions (phagocytosis, respiratory burst, chemotaxis) (Chiang et al., 2019). Vital NETosis is triggered by detecting the bacterium via TLR (toll-like receptor) 2. The neutrophil uses chemotactic movements to reach the pathogen, followed by nuclear budding and release of DNA-containing vesicles . These vesicles will merge with the cell membrane in order to release the NETs extracellularly (Yipp and Kubes 2013; Huang and O'Sullivan 2022).

In **suicidal or lytic NETosis**, NETs are formed slower (within 2-4 hours) (Chiang et al., 2019), and neutrophils go through a cell death pathway different from apoptosis, necrosis and necroptosis due to the presence of citrullinated histones (Chiang et al., 2019; Huang and O'Sullivan 2022). Lytic NETosis is activated by pathogenic molecules such as lipopolysaccharide (LPS) or viral glycoproteins, cytokines [TNF(tumor necrosis factor)-α, IL-8, the C5a component of the complement system (Huang and O'Sullivan 2022)], and phorbol 12-myristate 13-acetate (Hoffmann and Enk 2016; Huang and O'Sullivan 2022). This pathway is dependent on ROS production (Huang and O'Sullivan, 2022). Phorbol 12-myristate 13-acetate is often used in the research of NETosis as it proves effective in activating the neutrophil respiratory burst by increasing the cytosolic calcium levels (Chiang et al., 2019), therefore promoting the assembly of NADPH oxidase and ROS generation (Sørensen and Borregaard 2016). In suicidal NETosis, peptidyl arginine deiminase 4 (PAD4) catalyzes the conversion of histone 3 (H3) in the neutrophil nucleus to the citrullinated version (Cit-H3), which is the starting point of chromatin decondensation (Sørensen and Borregaard 2016). The oxidative burst mediated by NADPH oxidase promotes the release of granule constituents like NE and MPO (Huang and O'Sullivan 2022). This further promotes chromatin decondensation by cleaving the nuclear histones. In turn, the DNA is separated from the histones and released in the extracellular medium (Sørensen and Borregaard 2016). Neutrophil elastase is also responsible for cleavage of gasdermin D, promoting the formation of pores in the plasma membrane and DNA release (Huang and O'Sullivan 2022). Subsequently, cytoplasmic granular proteins attach to chromatin resulting in the network-*like* structure known as NETs (Sørensen and Borregaard 2016).

Mitochondrial NETosis differs from the "classic" pathway since neutrophils release mitochondrial DNA rather than nuclear DNA. This process, similar to suicidal NETosis, is ROS-dependent and stimulated by C5a and LPS (Sadeghi et al., 2023).

Caspase-dependent NETosis is activated by LPS or whole Gram-negative bacteria, which determine the activation of an enzyme named caspase 11. Caspase 11 is responsible for the cleavage of gasdermin D, a protein responsible for both nuclear and cell membrane pore formation (Huang and O'Sullivan 2022).

NETosis, whether vital or suicidal, is a key player in the antimicrobial protection of the host. This function is believed to be realized via eliminating pathogens by trapping them in the network-*like* structure. Thus, it is safe to assume that neutrophils not only provide host protection by classical intracellular pathways (such as phagocytosis, by trapping the microbes in phagosomes inside the cell) but also by extracellular mechanisms, since the traps are released at the outer face of the plasma membrane (Pinegin et al., 2015). Neutrophil extracellular traps can regulate bacterial infections due to the bactericidal components attached to the chromatin fibers: histones, NE, MPO, lactoferrin, LL-37, gelatinase, proteinase 3, and cathepsin G (Sørensen and Borregaard 2016; Chiang et al., 2019; Mutua and Gershwin 2021). NETs are capable of limiting the growth or eliminating both Gram-positive (*Staphylococcus aureus, Streptococcus pneumoniae, Mycobacterium tuberculosis*) and Gram-negative bacteria (*Escherichia coli, Shigella flexneri, Yersinia pestis*), as well as parasites (*Toxoplasma gondii*, *Plasmodium falciparum*), viruses [Influenza virus, Human Immunodeficiency Virus 1 (HIV-1), Respiratory syncytial virus (RSV)] and microfungi (*Candida albicans, Cryptococcus neoformans, Aspergillus fumigatus*) (Delgado-Rizo et al., 2017).

It is also proved that the other granulocytes are capable of forming and releasing extracellular traps (eosinophil, basophil, mast cell/mastocyte extracellular traps) involved in host defense against pathogens (Czerwińska and Owczarczyk-Saczonek 2022). Besides the protective role, there is more and more evidence of the involvement of NETs in immunopathology (Sadeghi et al., 2023).

NETosis in autoimmunity

Neutrophil extracellular traps play a key role in the pathogenesis and progression of multiple autoimmune diseases (ADs): rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), diabetes mellitus (DM), psoriasis (Ps), multiple sclerosis (MS) (Hu et al., 2016; Neubert et al., 2019; Sadeghi et al., 2023). The importance of NETosis in autoimmunity is highlighted by the formation of autoantibodies targeted towards various NETs constituents (citrullinated peptides, components of the primary granules, double-stranded DNA) that were observed in ADs such as SLE and RA (Vorobjeva 2020).

Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is a chronic autoimmune inflammatory disease characterized by breaking the self-tolerance. It is caused by the exacerbated production of autoantibodies aiming at nuclear proteins and double-stranded DNA. This results in immune complexes buildup and their deposition in certain sites and damage of multiple organs and tissues, for example kidneys, skin and blood vessels (Knight et al., 2012; Hoffmann and Enk 2016; Wang et al., 2023).

Moreover, this promotes the production of NETs and interferon type I (such as IFN-α) by the plasmacytoid dendritic cells (pDCs) (Wang et al., 2023).

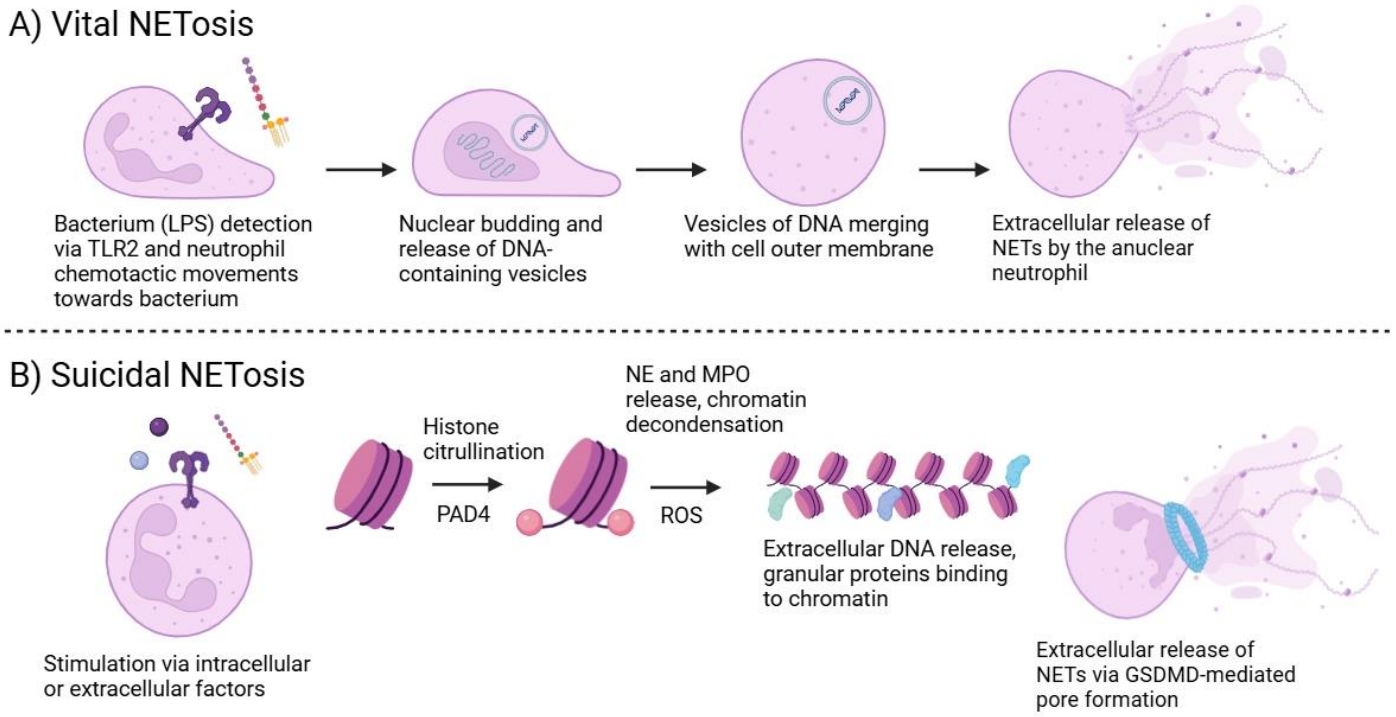

Fig. 1: The vital and suicidal pathways of NETs formation. **A:** Vital NETosis, in which NETs are released without membrane disruption; **B:** Suicidal NETosis, in which neutrophils go through a cell death process in order for NETs to be released. Figure generated with BioRender.com (adapted from Sørensen and Borregaard 2016; Huang and O'Sullivan 2022).

Neutropenia is a particularity of SLE patients, as well as the alteration of neutrophil functions: dysregulated ROS production and phagocytosis, increased apoptosis and NETosis (Sadeghi et al., 2023). A correlation between NETosis and photosensitivity in SLE patients has also been observed (Neubert et al., 2019). Exaggerated production of autoantibodies is caused by the extended exposure to cell debris that act as autoantigens, related to the altered apoptotic mechanisms (Zhu et al., 2022). The imbalance between NET formation and clearance is strongly related to the pathogenesis and severity of SLE (Hoffmann and Enk 2016; Singhal and Kumar 2022; Wang et al., 2023). Neutrophil extracellular traps in lupus patients are not going through the clearance pathways as normal due to high concentrations of LL-37 (Hoffmann and Enk 2016). This defect in the process of NETosis is also linked to the generation of LDGs (Alghamdi et al., 2019). Lood et al. highlighted the role of mitochondrial ROS in stimulating IFN type I release and NETosis in a lupus-*like* disease in murine models (Lood et al., 2016).

Low-density granulocytes represent a neutrophil population with a greater capacity for NETosis and are enriched in the blood of patients with SLE (Delgado-Rizo et al., 2017; Wang et al., 2023). This cell population supports the inflammatory state in SLE by promoting the release of pro-inflammatory cytokines, such as IFN-γ. Low density granulocytes also possess a higher expression of the genes that encode granule constituents (MPO, NE) (Zhu et al., 2022). Plasmacytoid dendritic cells are activated to synthesize IFN-α via releasing LDG intracellular components as high-mobility group box 1, LL37 and α-/β-defensins through NETosis (Delgado-Rizo et al., 2017). The production of IFN type I can be also triggered by the release of oxidized mitochondrial DNA and disrupted NETosis of LDGs (Nakabo et al., 2022; Singhal and Kumar 2022).

The altered self-tolerance in SLE can be linked to post-translational modifications of histones, such as citrullination (Alghamdi et al., 2019). Histones are predominant among the proteins attached to the chromatin strands in the NETs structure. Post-translational modifications represent the addition of various biochemical functional groups to a protein causing an alteration in the chemical structure of an aminoacid or secondary structure of the protein (Knight et al., 2012). Citrullination is a post-translational modification in which arginine is converted to citrulline. Histones citrullinated by the PAD4 enzyme during NET formation can be correlated with loss of self-tolerance in SLE and citrullination is linked to disease severity in SLE (Alghamdi et al., 2019).

Rheumatoid arthritis

Rheumatoid arthritis (RA) is a chronic systemic autoimmune disorder characterized by joint inflammation and bone and cartilage deterioration (Kumar et al., 2018;

Goel and Kaplan 2020), in some cases causing disability (Wigerblad and Kaplan 2023). Risk factors of RA, among which periodontal disease, genetic predisposition and smoking can be counted, have been correlated to NET formation (Goel and Kaplan 2020). The hallmark of RA is the production of autoantibodies against citrullinated protein antigens (ACPAs) (Wang et al., 2023) that are detected in approximately 70% of RA patients (Wigerblad and Kaplan 2023). Autoantibodies against citrullinated protein antigens represent a class of cross-reactive antibodies that specifically recognize proteins or peptides containing citrulline in their structure, thus becoming non-self molecules or autoantigens (Valesini et al., 2015).

Neutrophils in RA patients have a higher ability to release NETs and NETosis is linked to this disease (Wang et al., 2023). This leukocyte population is abundant in synovial fluid in rheumatoid arthritis and is capable of releasing the peptidyl arginine deiminases PAD2 and PAD4 into joints (Zhu et al., 2022). The autoimmune response in RA is triggered by the production of autoantigens. Neutrophil extracellular traps play an important role in this process via histone citrullination due to the overexpressed activity of PAD2 and PAD4 (Delgado-Rizo et al., 2017). Autoantibodies against citrullinated protein antigens recognize the citrullinated histones and, together with pro-inflammatory cytokines (IL-17, TNF-α), contribute to the inflammatory state in RA (Barnado et al., 2016; Wang et al., 2023). These inflammatory mediators stimulate the production of NETs and then activate the synthesis of more ACPAs; consequently, there is a vicious cycle between ACPAs and NETs (Ciesielski et al., 2022). The enzymes PAD2 and PAD4 can also target proteins such as fibronectin, vimentin, fibrinogen, α-enolase, and anti-thrombin (Ciesielski et al., 2022) affecting the coagulation process (Alghamdi et al., 2019). Thus, PAD enzymes catalyze the citrullination of both intra- and extracellular proteins that build up in the joints. The constant exposure to autoantigens results in an altered self-tolerance (Ciesielski et al., 2022). Related to NETosis, neutrophils of RA patients also possess a high expression of NE and MPO (Huang and O'Sullivan 2022). Similar to SLE, LDGs have been tracked in blood samples of RA patients (Sadeghi et al., 2023).

Type 1 diabetes mellitus

Type 1 diabetes mellitus (T1DM) is an autoimmune disorder in which the endocrine system is targeted (Zhu et al., 2022). This disease is defined by the destruction of β-pancreatic isles by autoreactive T-cells that recognize the specific autoantigens exposed via the disruption of β cells (Delgado-Rizo et al., 2017; Sadeghi et al., 2023). Moreover, autoreactive B cells are activated and autoantibodies (insulinoma-associated protein 2 autoantibody, glutamic acid decarboxylase autoantibody, zinc transporter-8 autoantibody) are synthesized (Delgado-Rizo et al., 2017; Zhu et al., 2022), resulting in hyperglycemia (Delgado-Rizo et al., 2017; Vorobjeva 2020). T-cytotoxic cells are fundamental in β-cell disruption by releasing perforins and granzymes. The release of these proteins results in activating the FasL pathway and the synthesis of pro-inflammatory mediators (TNF-α and IFN-γ) (Delgado-Rizo et al., 2017). TNF-α is implicated in promoting NETosis and the release of neutrophil granule constituents, such as cathepsin G, NE, and proteinase 3 (Zhu et al., 2022). High levels of NE and proteinase 3 are evidence of the correlation between NETosis and autoimmunity in patients with T1DM (Delgado-Rizo et al., 2017; Jorch and Kubes 2017). The increased levels of blood sugar stimulate the release of ROS by neutrophils and NETosis, causing an immunological imbalance and microvascular alterations (Kumar et al., 2018; Islam and Takeyama 2023). Delayed wound healing is a particularity of T1DM and high levels of NET constituents (histones, proteinase 3, elastase) have been observed in patients with diabetic foot ulcers (Sadeghi et al., 2023). More biomarkers correlated to NETosis (double-stranded DNA, MPO–DNA complexes) are considered for early detection of T1DM (Vorobjeva 2020).

Multiple sclerosis

Multiple sclerosis (MS) is a chronic disease implicating the central nervous system in which demyelination, neuroinflammation and later motor function impairment and loss of vision occur (Alghamdi et al., 2019; Ciesielski et al., 2022; Sadeghi et al., 2023). An interaction between genetic and environmental factors is considered to play a key role in the pathogenesis of MS (Ciesielski et al., 2022). The demyelination may result from the exaggerated citrullination of myelin basic protein, prompting a failure in maintaining the compact myelin by disrupting the multilayer structure (Huang and O'Sullivan 2022). Myelin basic protein is the predominant protein in the myelin sheath and an important target for citrullination (Alghamdi et al., 2019). This process is catalyzed by PAD2 expressed by oligodendrocytes and results in generating new autoantigens in the myelin sheath, outside the axons (Zhu et al., 2022). In healthy patients, the percentage of citrullination in MBP is 20% but it can reach up to 90% in advanced stages of MS (Alghamdi et al., 2019). Similar to SLE, LDGs are numerous in the peripheral blood of MS patients and can produce NETs (Zhu et al., 2022). Furthermore, neutrophils in MS are abundant, and present a decreased apoptosis and increased degranulation and ROS release (Huang and O'Sullivan 2022).

Psoriasis

Psoriasis (Ps) is a T cell-mediated chronic autoimmune inflammatory disease (Rendon and Schäkel 2019; Surcel et al., 2021b). These clinical manifestations of Ps include skin and joint lesions (Rendon and Schäkel, 2019), as well as extracutaneous co-morbidities, leading to a decrease in patients' quality of life (Surcel et al., 2022),

including depression, anxiety and suicidal ideation (Georgescu et al., 2019; Amin et al., 2020; Grän et al., 2020). Globally, Ps affects over 60 million individuals (Griffiths et al., 2021), regardless of sex (Boehncke and Schön 2015), debuting at a median age of 33 (Griffiths et al., 2021). The incidence is split into two age gaps: 20-30 years and 50-60 years, corresponding to two immunologically and genetically distinct subtypes: early onset, before the age of 40 (75% of cases) and late onset, after the age of 40 (Griffiths et al., 2021). The incidence of Ps is correlated to ethnicity, age, environmental factors and geographical area (Surcel et al., 2022); therefore, it is more common in Caucasians and in developed countries (Gironés Petit et al., 2021).

The etiology of Ps is yet to be determined (Michalek et al., 2016; Georgescu et al., 2019), though it was observed that genetic predisposition, environmental factors and abnormal functioning of the immune system play an important role in Ps disease evolution (Griffiths et al., 2021). Administration of certain drugs (lithium-based or TNF inhibitors, anti-inflammatory drugs) (Lee et al., 2018), neuropsychic stress (Rousset and Halioua 2018), weight gain and obesity (Jensen and Skov 2017), physical stress (radiotherapy and exposure to ultraviolet radiations) (Kamiya et al., 2019), smoking, alcohol consumption (Lee et al., 2018; Grän et al., 2020), infections (*Streptococcus sp*., *Helicobacter pylori*, *S. aureus*, HIV) (Lee et al., 2018) can count among the risk factors. Psoriasis is correlated to other pathologies, such as diabetes mellitus (Grän et al., 2020), cancer (pulmonary cancer, lymphomas, non-melanoma skin cancer) (Loft et al., 2020), cardiovascular diseases (acute myocardial infarction, abdominal aortic aneurysm, coronary artery disease) (Amin et al., 2020; Daugaard et al., 2022), dyslipidemia (Amin et al., 2020), ADs (Daugaard et al., 2022), chronic kidney diseases (Tokuyama and Mabuchi 2020), psoriatic arthritis (Căruntu et al., 2015).

The PASI (Psoriasis Area Severity Index) score represents the gold standard for assessing the severity of psoriatic cutaneous inflammation and reunites the severity and percentage of affected skin areas, and DLQI (Dermatology Life Quality Index) score. There are various therapies depending on the severity of the AD: topical treatments for lighter forms, ultraviolet light therapy for moderate forms, and systemic treatments for severe forms (Raharja et al., 2021). At the moment, biological therapies, such as the fusion protein etanercept or monoclonal antibodies (adalimumab, infliximab and secukinumab) are used for treating methotrexate, cyclosporin or acitretin-resistant severe Ps (Surcel et al., 2019; Raharja et al., 2021).

Even though it has been considered to be a T cell-mediated disease (Grän et al., 2020), innate [macrophages, NK cells, dendritic cells (DCs)], as well as adaptative [T cells (TC)] immunity cells, and non-immune cells (keratinocytes) play a crucial role in Ps pathogenesis (Surcel et al., 2021b). T helper (Th) cells, along with pro-inflammatory cytokines are responsible for supporting the inflammatory state (Surcel et al., 2019).

Histologically, Ps is characterized by an uncontrolled and rapid keratinocyte proliferation and infiltration of psoriatic lesions with DC and TC (Surcel et al., 2022), acanthosis, hyperkeratosis and parakeratosis (Grän et al., 2020). From a clinical point of view, Ps can be pustular and non-pustular (Surcel et al., 2019), and the most common phenotype is *psoriasis vulgaris* (Griffiths et al., 2021). Erythema, induration and desquamation are the main indicators of psoriatic inflammation (Chiang et al., 2019). There have been two phases of Ps pathogenesis described: the initiation of psoriatic events, in which innate immunity (DC, NK cells, macrophages) plays an important role, and maintaining the inflammatory status, mediated by adaptative immunity (Th cells) (Georgescu et al., 2019).

Excessive neutrophil, DC, TC, keratinocyte, fibroblast, mastocyte and melanocyte stimulation is an important cause of the immunological imbalance in Ps (Chiang et al., 2019; Rodriguez-Rosales et al., 2021). In the past years, several immune axes that contribute to the pathogenesis of Ps have been defined. Among those axes, the IL-23/Th17 axis is crucial in the pathogenesis of Ps (Wang and Shi 2023). The IL-17 family comprises of six members (IL-17A to IL-17F), capable of forming active homodimers (Vidal et al., 2021; Brembilla and Boehncke 2023) and five receptors (IL-17RA to IL-17RE) (Baliwag et al., 2015). From this cytokine family, IL-17A, IL-17C and IL-17F play a role in the Ps development by stimulating keratinocytes to release proinflammatory molecules. IL-17A, IL-17C and IL-17F also have a high expression in psoriatic lesions (Blauvelt and Chiricozzi 2018). The interleukins IL-17A and IL-17F have the highest homology level and therefore can easily dimerize resulting in an IL-17A/F heterodimer. The IL-17A glycoprotein is implicated in the pathological processes associated with Ps and can act on non-hematopoietic cells, such as keratinocytes (Lauffer et al., 2020; Vidal et al., 2021). This cytokine can be expressed by cells of both innate and adaptative immunity, but it was observed for the first time in Th17 cells (Vidal et al., 2021). IL-23, a member of the IL-12 cytokine family, is also important for the immunopathogenesis of Ps, as well as other ADs. IL-23 can be released by macrophages, DCs and keratinocytes in psoriatic tissues (Hou et al., 2018; Wang and Shi 2023). Single stranded RNA originating from viruses or NETs is capable of activating TLR8 on the neutrophil surface and therefore stimulating the release of IL-23 by neutrophils. The interaction between IL-23 and IL-23R receptor is responsible for the formation of mast cell extracellular traps, production of IL-17 and differentiation of naive T cell into Th17 and Th1 cells (Wang and Shi 2023).

In the IL23/Th17 axis, dermal DCs are activated by recognizing LL-37-nucleic acid complexes released by damaged keratinocytes. The activated dermal DCs

produce IL-23 that consequently promote activation of Th17 cells and production of IL-17A and other cytokines (Delgado-Rizo et al., 2017; Ogawa et al., 2021). More than that, IL-23 is also effective in stimulating the production of IL-17 by neutrophils (Wang and Shi 2023). IL-17A further triggers the proliferation of keratinocytes, activation of TLR7 and TLR9, and release of other inflammatory molecules like TNF-α, IL-1, IL-6 and IL-8 (Schön et al., 2017; Yamamoto 2020). TNF-α is a pro-inflammatory cytokine produced by immune and non-immune cells. TNF-α regulates keratinocyte function through the interaction with IL-17A in order to modulate cytokine and keratinocyte genes related to Ps (Guo et al., 2023). IL-17A also plays a fundamental role of a pro-angiogenic factor in Ps by stimulating the migration of endothelial cells and the expression of VEGF (vascular endothelial growth factor). IL-17A, together with TNF-α, can stimulate the expression of IL-8, from which the latter two are pro-angiogenic cytokines (Vidal et al., 2021). It is also shown the implications of IL-19 in the IL-23/Th17 axis, linked to Ps severity (Witte et al., 2014). This axis is proof of the interplay between components of innate (DCs) and adaptative (Th17 cells) immunity in Ps (Schön and Erpenbeck 2018).

IL-33–IL-37 axis comprises of other two novel cytokines (IL-33 and IL-37) that play a role in inflammatory diseases via the aryl hydrocarbon receptor (AHR). This axis is in charge of modulating the balance between pro-inflammatory and anti-inflammatory molecules. IL-33 belongs to the IL-1 family and is expressed both in non-immune and immune cells. IL-37 is a member of the IL-1 cytokine family and acts as an anti-inflammatory mediator both intracellularly and extracellularly. It has been observed that the dysregulation of the IL-33–IL-37 axis is caused by increased levels of IL-33 and decreased levels of IL-37 and might play a role in Ps pathogenesis (Tsuji et al., 2023). Furthermore, Zhou et al. demonstrated that IL-33 activates mast cells and promotes early onset of inflammatory responses in a model of imiquimod (IMQ)-induced Ps-*like* dermatitis. IL-33 interacts with mast cells via the IL-33 receptor T1/ST2 (IL-33R) on their surface, stimulating the production of cytokines as IL-1β, IL-6, IL-13 and TNF-α (Zhou et al., 2023).

Chemokines comprise of > 40 proteins with a molecular weight of 8-11 kDa that are classified into several subfamilies (CXC, CC, CX3C) depending on the position of the conserved cysteine residues. Chemokines can be produced by both leukocytes and epithelial cells. In Ps, keratinocytes can synthetize a wide range of chemokines that target immune cells participating to disease pathogenesis: CCL2, CCL5, CCL17, CCL20, CCL22, CCL27, CXCL1, CXCL8, CXCL9, CXCL10, CXCL11, CXCL16 (Singh et al., 2013). CXCR6/CXCL16 axis was found to contribute to the pathogenesis of several ADs, Ps included. C–X–C motif ligand (CXCL) 16 is a chemokine belonging to the CXC subfamily. CXCL16 can facilitate the recruitment and adhesion of numerous immune cells to endothelial and dendritic cells during the progression of ADs. C–X–C motif ligand 16 interacts with the chemokine receptor CXCR6, a G protein-coupled receptor. C–X–C motif ligand 16 is significantly increased in monocytes, keratinocytes and DCs in psoriatic skin compared to normal skin. CD8+ T cells that express CXCR6 have higher percentages in the peripheral blood of patients with Ps. As it follows, the binding of CXCL16 to CXCR6 is vital for the recruitment of CD8+ T cells into psoriatic skin (Bao et al., 2023). The CCL20/CCR6 axis is correlated to psoriatic skin inflammation both in patients and experimental models. This is due to the fact that CCL20, a chemoattractant for Th17 cells expressing CCR6, is released by keratinocytes during Ps evolution (Furue et al., 2020). An original article by Lu et al. demonstrated that TLR7–MyD88–DC–CXCL16 axis plays a significant role in pustular Ps progression in murine experimental models of IMQ-induced Ps. They have observed that the release of CXCL16 by DCs and pro-inflammatory effects of neutrophils can be influenced by TLR7 via the interference with the myeloid differentiation primary response gene 88 (MyD88) signaling pathway. Hence, the TLR7–MyD88–DC–CXCL16 axis might promote migration of neutrophils to lesional skin in pustular Ps by stimulating a pro-inflammatory response (Lu et al., 2023).

In humans, the poly (ADP-ribose) polymerase (PARP) enzymes form a family consisting of 17 members. From this family, PARP1 and PARP2 take part in various biological processes, among which DNA repair, RNA transcription, cell death, oxidative stress and protein translation can be mentioned (Kiss et al., 2020; Antal et al., 2023). Poly (ADP-ribose) polymerase 1 is implicated in skin inflammatory pathways. That fact can be correlated with the PARP1 regulating activity of immune cell differentiation and maturation, as well as the modulating activity of pro-inflammatory transcription factors (Kiss et al., 2020). The inhibition of PARP1 gene has anti-inflammatory effects in Th1- and Th2-mediated diseases. In their experiment, Kiss et al. surprisingly revealed that genetic or pharmacological deletion of PARP1 is in fact exaggerating inflammation in a Th17-mediated disease using a model of IMQ-induced psoriasiform dermatitis (Kiss et al., 2020). In opposition, Antal et al. demonstrated in their study that genetic deletion of PARP2 is anti-inflammatory in IMQ-induced murine Ps -*like* disease (Antal et al., 2023).

Neutrophils can cause psoriatic skin inflammation via numerous mechanisms, such as the production of IL-17, pDCs activation and NETosis (Skrzeczynska-Moncznik et al., 2020). It has been shown that, despite earlier convictions that Th17 cells are the main producers of IL-17, most of this pro-inflammatory cytokine was provided by mastocytes via degranulation or mast cell extracellular traps and neutrophils via NETosis in Ps (Lin et al., 2011; Knight et al., 2012; Pinegin et al., 2015; Hu et al., 2016; Schön et al., 2017). Thus, some similarities between Ps

and SLE have been identified; NETosis, IFN type I, pDC, and cytokines released by Th17 cells participate in the pathogenesis of both diseases (Yamamoto 2020). There is an interrelation between Th17 cells and neutrophils, as Th17 promotes the recruitment of neutrophils in psoriatic microabscesses by stimulating keratinocytes to release cytokines and chemokines such as IL-8 and CCL20 (Li et al., 2020). IL-8 is a cytokine that plays a role in neutrophil chemoattraction (de Alcantara et al., 2021). Results from a recent study by Lambert et al. provided insights on the implications of NETosis in Ps. They outlined a method for activating Th17 and IL-17 release from healthy human peripheral blood mononuclear cells in the context of NETosis. After stimulating peripheral blood mononuclear cells with anti-CD3/CD28 beads, they observed an abundance of Th17 cells in Ps patients carrying a risk variant of the *TRAF3IP2* gene, in the presence of NETs compared to the absence of NETs. *TRAF3IP2* gene encodes Act1, a mediator of Th17 activation (Lambert et al., 2019).

Neutrophils in Ps possess an enhanced capacity to generate NETs, degranulation, phagocytosis and an exaggerated expression of pro-inflammatory cytokines *in vitro*. Neutrophils are plentiful in skin inflammation and blood *in vivo* (Chen et al., 2023). Neutrophils are abundant in Munro's microabscesses (Kvist-Hansen et al., 2021; Rodriguez-Rosales et al., 2021), a Ps histopathological hallmark (Meng et al., 2022), in which they produce pro-inflammatory molecules (IL-6, IL-8 and IL-17) (Mutua and Gershwin 2021). Neutrophil extracellular trap formation was linked to the severity of Ps inflammation and was enhanced in skin lesions and peripheral blood of Ps patients (Hu et al., 2016). Herster et al. identified complexes made out of RNA and antimicrobial peptides related to NETosis, such as LL-37, to be potent activators of pDC and later chronic inflammation in Ps (Herster et al., 2020). Psoriasis, especially the generalized pustular variant, has been recently associated with the deficiency of IL-36 receptor antagonist. Deficiency of IL-36 receptor antagonist is a rare autoinflammatory disease in which loss-of-function mutations in the IL36RN gene play an important role (Hospach et al., 2019). In a study conducted on IMQ-induced Ps in *Il36rn*−/− mice, Watanabe et al. discovered NETosis to be fundamental for the progression of murine Ps-*like* disease, therefore being a potential target for deficiency of IL-36 receptor antagonist therapeutics (Watanabe et al., 2020). Novel biomarkers/mechanisms (LL37, NETosis, anti-LL37 antibodies) were identified in psoriatic arthritis patients (Frasca et al., 2018). The strong correlation between NETosis and psoriatic diseases was further displayed by finding increased levels of MPO-DNA complexes in Ps or psoriatic arthritis patients and correlating it to disease severity (Li et al., 2022).

The crosstalk between neutrophils and keratinocytes is demonstrated by Cao et al. by highlighting the activation of absent-in-melanoma-2 (AIM2) inflammasome in keratinocytes by NETs via the p38-MAPK signaling pathway. Hence, the *in vivo* treatment of IMQ-induced Ps mice with Cl-amidine, a PAD4 inhibitor, ameliorated the Ps-*like* type. The immune responses in keratinocytes were regulated by the synthesis of IFN-γ through the X-linked inhibitor of apoptosis protein (XIAP). This study proposes using the NETs-AIM2 axis as a therapeutic target in Ps as it mediates keratinocyte inflammation (Cao et al., 2023). A previous study emphasized the role of the interaction between neutrophils and keratinocytes in the release of IL-17 by neutrophils in Ps patients (Liu et al., 2022). Another *in vitro* study using human keratinocytes and neutrophils and IMQ mice neutrophils suggests the use of exosomes as candidates for novel therapies in Ps. The exosomes are released by keratinocytes as a means of communication with neutrophils (Jiang et al., 2019).

Low density granulocytes correlate to Ps skin inflammation severity (Teague et al., 2019). Similar to SLE, high levels of LDGs were reported in the peripheral blood of Ps patients compared to healthy subjects. Moreover, compared to polymorphonuclear neutrophils, LDGs showed a greater NE and lower SLPI (secretory leukocyte proteinase inhibitor) staining. These differential staining properties may aid in localizing psoriatic inflammatory sites mediated by LDGs (Skrzeczynska-Moncznik et al., 2020). SLPI is well known for inhibiting serine proteases as human NE (Skrzeczynska-Moncznik et al., 2012). The role of SLPI along with human NE and DNA, as components of NETs, has been demonstrated in psoriatic lesions of patients by observing the stimulation of IFN type I release by pDCs (Skrzeczynska-Moncznik et al., 2012). Mediation of NETosis by SLPI has been also reported (Zabieglo et al., 2015).

Given the current status of Ps as an uncurable disease, current but also novel therapeutic agents have been recently studied (Table 1). Hoffmann et al. tested the potential effects of a "classic" Ps treatment, Fumaderm, a fumaric acid ester-based substance, respectively, against NETs in Ps patient neutrophils. They discovered dimethyl fumarate, a component of this formulation, to be effective *in vitro* against NETosis in a L-glutathione- and ROS-dependent mechanism (Hoffmann et al., 2018). Oral dimethyl fumarate was demonstrated to be effective against high neutrophil counts in Ps patients as well (Morrison et al., 2021). ROS production is high in Ps, and consequently, antioxidants such as cannabidiol were considered in the clinical management of ADs. Due to the antioxidant properties of cannabidiol, it was tested against neutrophils of Ps patients and was found to have considerable anti-NET qualities (Wójcik et al., 2020). Traditional Chinese medicine was also considered in ameliorating Ps symptomatology; Chiang et al. revealed the modulatory effect of Kan-Lu-Hsiao-Tu-Tan on the inflammatory neutrophilic pathways in Ps by blocking ROS production in IMQ-induced murine Ps (Chiang et al., 2020). In an experiment on human skin explants and IMQ mice, Zhang et al. suggested the use of

mesenchymal stem cell exosomes in Ps treatment since it is a potent immunomodulator and it diminishes IL-17 production in NETs (Zhang et al., 2021).

Potential biomarkers and therapeutic targets in Ps have been investigated in the recent years. Several studies highlighted the link between neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, platelet counts and serum uric acid in patients and IMQ Ps-*like* disease in murine models as potent biomarkers of Ps chronic inflammation (Sen et al., 2014; Toprak et al., 2016; Polat et al., 2017; Solak et al., 2017; Herster et al., 2019; Wang et al., 2021). Researchers identified valuable therapeutic targets correlated to NETosis in samples from Ps patients and/or IMQ mice, such as TLR4 (Shao et al., 2019), Src homology-2 domain-containing protein tyrosine phosphatase-2 (Ding et al., 2022), matrix metallopeptidase-9 (Chen et al., 2021) and receptor-interacting protein kinase RIPK1 and RIPK3 (Meng et al., 2022). Furthermore, the significance of PAD4 in NETosis was studied, and developing novel therapies targeting this enzyme may disrupt the Ps-specific interactions between neutrophils, DC, keratinocytes and lymphocytes (Czerwińska et al., 2022).

Table 1: Novel and current therapeutics, biomarkers and therapeutic targets investigated in the past years.

Therapeutic agents		
Therapeutic agent	**Experimental model or sample**	**Reference**
Dimethyl fumarate	Neutrophils from Ps patients	(Hoffmann et al., 2018; Morrison et al., 2021)
Cannabidiol	Neutrophils from Ps patients	(Wójcik et al., 2020)
Kan-Lu-Hsiao-Tu-Tan	Murine experimental models of IMQ-induced Ps	(Chiang et al., 2020)
Mesenchymal stem cell exosomes	Human skin explants and murine experimental models of IMQ-induced Ps	(Zhang et al., 2021)
Biomarkers		
Biomarker	**Experimental model or sample**	**Reference**
NETs – absent-in-melanoma-2 (AIM2) axis	Psoriasis patients and murine experimental models of IMQ-induced Ps	(Cao et al., 2023)
Neutrophil-to-lymphocyte ratio	Psoriasis patients	(Sen et al., 2014; Toprak et al., 2016; Polat et al., 2017; Wang et al., 2021)
Platelet-to-lymphocyte ratio	Psoriasis patients	(Polat et al., 2017; Wang et al., 2021)
Platelet counts	Psoriasis patients and murine experimental models of IMQ-induced Ps	(Herster et al., 2019; Wang et al., 2021)
Serum uric acid	Ps patients	(Solak et al., 2017)
Therapeutic targets		
Therapeutic target	**Experimental model or sample**	**Reference**
Toll-like receptor 4	Psoriasis patients and murine experimental models of IMQ-induced Ps	(Shao et al., 2019)
Src homology-2 domain-containing protein tyrosine phosphatase-2	Experimental models of IMQ-induced Ps	(Ding et al., 2022)
Matrix metallopeptidase-9	Specimens of human psoriatic skin	(Chen et al., 2021)
Receptor-interacting protein kinase RIPK1 and RIPK3	Psoriasis patients	(Meng et al., 2022)
Peptidyl arginine deiminase 4	Psoriasis patients	(Czerwińska et al., 2022)

Conclusions

Neutrophils are the first cell population of innate immunity to reach the infection site when extracellular pathogens attack the host and are capable of eliminating them by various mechanisms, including the formation of NETs. This process, termed "NETosis", represents a distinct form of cell death, different from apoptosis and necroptosis. Despite the potential protective effect, neutrophils, NETosis and molecules related to the process are strongly correlated with the pathogenesis of a variety of autoimmune diseases, among which rheumatoid

arthritis, systemic lupus erythematosus, diabetes mellitus, multiple sclerosis and psoriasis can be counted. In conclusion, the topics covered in this review article include the description of neutrophils, NETosis and their implications in autoimmunity, with an emphasis on the link between this unique cell death process, various axis mediated by cytokines and chemokines and psoriasis, a chronic autoimmune inflammatory disease. Recent studies have previously described biomarkers and novel therapeutics in psoriasis. Therefore, further research into this topic may provide valuable perspectives into the clinical management of autoimmune diseases.

References

Alghamdi M., Alasmari D., Assiri A., Mattar E., Aljaddawi A. A., Alattas S. G., Redwan E. M. 2019. An overview of the intrinsic role of citrullination in autoimmune disorders. *J. Immunol*. 2019, 7592851. doi:10.1155/2019/7592851

Amin M., Lee E. B., Tsai T. F., Wu J. J. 2020. Psoriasis and co-morbidity. *Acta Derm. Venereol. 100*. doi:10.2340/00015555-3387

Antal D., Pór Á., Kovács I., Dull K., Póliska S., Ujlaki G., Demény M. Á., Szöllősi A. G., Kiss B., Szegedi A., Bai P., Szántó M. 2023. PARP2 promotes inflammation in psoriasis by modulating estradiol biosynthesis in keratinocytes. *J. Mol. Med. 101*, 8. doi:10.1007/s00109-023-02338-z

Baliwag J., Barnes D. H., Johnston A. 2015. Cytokines in psoriasis. *Cytokine*. *73*, 2. doi:10.1016/j.cyto.2014.12.014

Bao N., Fu B., Zhong X., Jia S., Ren Z., Wang H., Wang W., Shi H., Li J., Ge F., Chang Q., Gong Y., Liu W., Qiu F., Xu S., Li T. 2023. Role of the CXCR6/CXCL16 axis in autoimmune diseases. *Int. Immunopharmacol*. *21*. doi:10.1016/j.intimp.2023.110530

Barnado A., Crofford L. J., Oates J. C. 2016. At the Bedside: Neutrophil extracellular traps (NETs) as targets for biomarkers and therapies in autoimmune diseases. *J. Leukoc. Biol. 99*, 2. doi:10.1189/jlb.5bt0615-234r

Blauvelt A., Chiricozzi A. 2018. The Immunologic Role of IL-17 in Psoriasis and Psoriatic Arthritis Pathogenesis. *Clin. Rev. Allergy Immunol. 55*, 3. doi:10.1007/s12016-018-8702-3

Boehncke W. H., Schön, M. P. 2015. Psoriasis. *The Lancet. 386*, 9997. doi:10.1016/S0140-6736(14)61909-7

Brembilla N. C., Boehncke W. H. 2023. Revisiting the interleukin 17 family of cytokines in psoriasis: pathogenesis and potential targets for innovative therapies. *Front. Immunol. 14*. doi:10.3389/fimmu.2023.1186455

Brinkmann V., Reichard U., Goosmann C., Fauler B., Uhlemann Y., Weiss D. S., Weinrauch Y., Zychlinsky, A. 2004, Neutrophil Extracellular Traps Kill Bacteria. *Science*. *303*, 5663. doi:10.1126/science.1092385

Brinkmann V., Zychlinsky A. 2012. Neutrophil extracellular traps: Is immunity the second function of chromatin? *J. Cell. Biol*. *198*, 5. doi:10.1083/jcb.201203170

Burn G.L., Foti A., Marsman G., Patel D.F., Zychlinsky A. 2021. The Neutrophil. *Immunity. 54*, 7. doi:10.1016/j.immuni.2021.06.006

Cao T., Yuan X., Fang H., Chen J., Xue K., Li Z., Dang E., Wang G., Shao S.,2023. Neutrophil extracellular traps promote keratinocyte inflammation via AIM2 inflammasome and AIM2-XIAP in psoriasis. *Exp. Dermatol*. *32*, 4. doi:10.1111/exd.14711

Căruntu C., Boda D., Dumitrascu G., Constantin C., Neagu M. 2015. Proteomics focusing on immune markers in psoriatic arthritis. *Biomark. Med. 9*, 6. doi:10.2217/bmm.14.76

Chapple I. L. C., Hirschfeld J., Kantarci A., Wilensky A., Shapira L. 2023. The role of the host—Neutrophil biology. *Periodontol. 2000*. doi:10.1111/prd.12490

Chen J., Bai Y., Xue K., Li Z., Zhu Z., Li Q., Yu C., Li B., Shen S., Qiao P., Li C., Luo Y., Qiao H., Dang E., Yin W., Gudjonsson J. E., Wang G., Shao S. 2023. CREB1-driven CXCR4hi neutrophils promote skin inflammation in mouse models and human patients. *Nat. Commun. 14*, 1. doi:10.1038/s41467-023-41484-3

Chen J., Zhu Z., Li Q., Lin Y., Dang E., Meng H., Sha N., Bai H., Wang G., An S., Shao S. 2021. Neutrophils Enhance Cutaneous Vascular Dilation and Permeability to Aggravate Psoriasis by Releasing Matrix Metallopeptidase 9. *J. Invest. Dermatol. 141*, 4. doi:10.1016/j.jid.2020.07.028

Chiang C. C., Cheng W. J., Korinek M., Lin C. Y., Hwang T. L. 2019. Neutrophils in Psoriasis. *Front. Immunol*. *10*. doi:10.3389/fimmu.2019.02376

Chiang C. C., Cheng W. J., Lin C. Y., Lai K. H., Ju S. C., Lee C., Yang S. H., Hwang T. L. 2020. Kan-Lu-Hsiao-Tu-Tan, a traditional Chinese medicine formula, inhibits human neutrophil activation and ameliorates imiquimod-induced psoriasis-like skin inflammation. *J. Ethnopharmacol*. *246*. doi:10.1016/j.jep.2019.112246

Ciesielski O., Biesiekierska M., Panthu B., Soszyński M., Pirola L., Balcerczyk, A. 2022. Citrullination in the pathology of inflammatory and autoimmune disorders: recent advances and future perspectives. *Cell. Mol. Life Sci.*. *79*, 2. doi:10.1007/s00018-022-04126-3

Czerwińska J., Kasprowicz-Furmańczyk M., Placek W., Owczarczyk-Saczonek A. 2022. Changes in Tumor Necrosis Factor α (TNFα) and Peptidyl Arginine Deiminase 4 (PAD-4) Levels in Serum of General

Treated Psoriatic Patients. *Int. J. Environ. Res. Public Health*. *19*, 14. doi:10.3390/ijerph19148723

Czerwińska J., Owczarczyk-Saczonek A. 2022. The Role of the Neutrophilic Network in the Pathogenesis of Psoriasis. *Int. J. Mol. Sci*. *23*, 3. doi:10.3390/ijms23031840

Daugaard C., Iversen L., Hjuler K. F. 2022. Comorbidity in Adult Psoriasis: Considerations for the Clinician. *Psoriasis: Targets Ther*. *12*. doi:10.2147/ptt.s328572

de Alcantara C. C., Reiche E. M. V., Simão, A. N. C. 2021. Cytokines in psoriasis. *Adv. Clin. Chem. 100*. doi:10.1016/bs.acc.2020.04.004

Delgado-Rizo V., Martínez-Guzmán M. A., Iñiguez-Gutierrez L., García-Orozco A., Alvarado-Navarro A., Fafutis-Morris M. 2017. Neutrophil extracellular traps and its implications in inflammation: An overview. *Front. Immunol. 8,* FEB. doi:10.3389/fimmu.2017.00081

Ding Y., Ouyang Z., Zhang C., Zhu Y., Xu Q., Sun H., Qu J., Sun Y. 2022. Tyrosine phosphatase SHP2 exacerbates psoriasis-like skin inflammation in mice via ERK5-dependent NETosis. *MedComm. 3*, 1. doi:10.1002/mco2.120

Frasca L., Palazzo R., Chimenti M. S., Alivernini S., Tolusso B., Bui L., Botti E., Giunta A., Bianchi L., Petricca L., Auteri S. E., Spadaro F., Fonti G. L., Falchi M., Evangelista A., Marinari B., Pietraforte I., Spinelli F. R., Colasanti, T., … Lande R. 2018. Anti-LL37 antibodies are present in psoriatic arthritis (PsA) patients: New biomarkers in PsA. *Front. Immunol. 9*, SEP. doi:10.3389/fimmu.2018.01936

Furue K., Ito T., Tsuji G., Nakahara T., Furue M. 2020. The CCL20 and CCR6 axis in psoriasis. *Scand. J. Immunol*. *91*, 3. doi:10.1111/sji.12846

Georgescu S. R., Tampa M., Căruntu C., Sarbu M. I., Mitran C. I., Mitran M. I., Matei C., Constantin C., Neagu M. 2019. Advances in understanding the immunological pathways in Psoriasis. *Int. J. Mol. Sci*. *20*, 3. doi:10.3390/ijms20030739

Gironés Petit R., Cano A., Ortiz A., Espina M., Prat J., Muñoz M., Severino P., Souto E. B., García M. L., Pujol M., Sánchez-López E., Slominski A., Albanesi, C. 2021. Psoriasis: From Pathogenesis to Pharmacological and Nano-Technological-Based Therapeutics. *J. Mol. Sci*, *22*. doi:10.3390/ijms22094983

Goel R. R., Kaplan, M. J. 2020. Deadliest catch: Neutrophil extracellular traps in autoimmunity. *Curr. Opin. Rheumatol*. *32*, 1. doi:10.1097/BOR.0000000000000667

Grän F., Kerstan A., Serfling E., Goebeler M., Muhammad K. 2020. Current Developments in the Immunology of Psoriasis. *YJBM*. 3, 97-110.

Guo J., Zhang H., Lin W., Lu L., Su J., Chen X. 2023. Signaling pathways and targeted therapies for psoriasis. *Sıgnal Transduct. Tar*. *8*, 1. doi:10.1038/s41392-023-01655-6

Herster F., Bittner Z., Archer N. K., Dickhöfer S., Eisel D., Eigenbrod T., Knorpp T., Schneiderhan-Marra N., Löffler M. W., Kalbacher H., Vierbuchen T., Heine H., Miller L. S., Hartl D., Freund L., Schäkel K., Heister M., Ghoreschi K., Webe, A. N. R. 2020. Neutrophil extracellular trap-associated RNA and LL37 enable self-amplifying inflammation in psoriasis. *Nat. Commun*. *11*, 1. doi:10.1038/s41467-019-13756-4

Herster F., Bittner Z., Codrea M. C., Archer N. K., Heister M., Löffler M. W., Heumos S., Wegner J., Businger R., Schindler M., Stegner D., Schäkel K., Grabbe S., Ghoreschi K., Miller L. S., Weber, A. N. R. 2019. Platelets aggregate with neutrophils and promote skin pathology in psoriasis. *Front. Immunol.*, *10*, AUG. doi:10.3389/fimmu.2019.01867

Hoffmann J. H. O., Enk, A. H. 2016. Neutrophil extracellular traps in dermatology: Caught in the NET. *J. Dermatol*. *84*, 1. doi: 10.1111/bjd.158391

Hoffmann J. H. O., Schaekel K., Hartl D., Enk A. H., Hadaschik E. N. 2018. Dimethyl fumarate modulates neutrophil extracellular trap formation in a glutathione- and superoxide-dependent manner. *Br. J. Dermatol*. *178*, 1. doi:doi.org/10.1111/bjd.15839

Hospach T., Glowatzki F., Blankenburg F., Conzelmann D., Stirnkorb C., Müllerschön C. S., Von Den Driesch P., Köhler L. M., Rohlfs M., Klein C., Hauck F. 2019. Scoping review of biological treatment of deficiency of interleukin-36 receptor antagonist (DITRA) in children and adolescents. *Pediatric Rheumatol. 17*, 1. doi:10.1186/s12969-019-0338-1

Hou Y., Zhu L., Tian H., Sun H. X., Wang R., Zhang L., Zhao Y. 2018. IL-23-induced macrophage polarization and its pathological roles in mice with imiquimod-induced psoriasis. *Protein and Cell*. *9*, 12. doi:10.1007/s13238-018-0505-z

Hu S. C. S., Yu H. S., Yen F. L., Lin C. L., Chen G. S., Lan C. C. E. 2016. Neutrophil extracellular trap formation is increased in psoriasis and induces human β-defensin-2 production in epidermal keratinocytes. *Sci. Rep. 6*. doi:10.1038/srep31119

Huang S. U. S., O'Sullivan K. M. 2022. The Expanding Role of Extracellular Traps in Inflammation and Autoimmunity: The New Players in Casting Dark Webs. *Int. J. Mol. Sci*. *23*, 7. doi:10.3390/ijms23073793

Islam M. M., Takeyama N. 2023. Role of Neutrophil Extracellular Traps in Health and Disease Pathophysiology: Recent Insights and Advances. *Int. J. Mol. Sci*. *24*, 21. doi:10.3390/ijms242115805

Jensen P., Skov L. 2017. Psoriasis and Obesity. *Dermatology*. *232*, 6. doi:10.1159/000455840

Jiang M., Fang H., Shao S., Dang E., Zhang J., Qiao P., Yang A., Wang G. 2019. Keratinocyte exosomes activate neutrophils and enhance skin inflammation in psoriasis. *FASEB Journal*, *33*, 12. doi:10.1096/fj.201900642R

Jorch S. K., Kubes P. 2017. An emerging role for neutrophil extracellular traps in noninfectious disease. *Nat. Med. 23*, 3. doi:10.1038/nm.4294

Kamiya K., Kishimoto M., Sugai J., Komine M., Ohtsuki M. 2019. Risk factors for the development of psoriasis. *Int. J. Mol. Sci*. *20*, 18. doi:10.3390/ijms20184347

Kiss B., Szántó M., Hegedűs C., Antal D., Szödényi A., Márton J., Méhes G., Virág L., Szegedi A., Bai P. 2020. Poly(ADP-ribose) polymerase-1 depletion enhances the severity of inflammation in an imiquimod-induced model of psoriasis. *Exp. Dermatol*, *29*, 1. doi:10.1111/exd.14061

Knight J. S., Carmona-Rivera C., Kaplan M. J. 2012. Proteins derived from neutrophil extracellular traps may serve as self-antigens and mediate organ damage in autoimmune diseases. *Front. Immunol. 3*, DEC. doi:10.3389/fimmu.2012.00380

Kumar S., Gupta E., Kaushik S., Jyoti A. 2018. Neutrophil Extracellular Traps: Formation and Involvement in Disease Progression. *Iran J. Allergy Asthma Immunol*. 17, 208-220.

Kvist-Hansen A., Kaiser H., Wang X., Krakauer M., Gørtz P.M., McCauley B.D., Zachariae C., Becker C., Hansen P.R., Skov L. 2021. Neutrophil Pathways of Inflammation Characterize the Blood Transcriptomic Signature of Patients with Psoriasis and Cardiovascular Disease. *Int J Mol Sci. 22*, 19. doi:10.3390/ijms221910818.

Lacy P. 2006. Mechanisms of degranulation in neutrophils. *AACI. 2*, 3. doi:10.2310/7480.2006.00012

Lambert S., Hambro C. A., Johnston A., Stuart P. E., Tsoi L. C., Nair R. P., Elder J. T. 2019. Neutrophil Extracellular Traps Induce Human Th17 Cells: Effect of Psoriasis-Associated TRAF3IP2 Genotype. *J. Invest. Dermatol*. *139*, 6. doi:10.1016/j.jid.2018.11.021

Lauffer F., Eyerich K., Boehncke W. H., Asadullah K., Beissert S., Ghoreschi K., Schön M. P. 2020. Cytokines of the IL-17 family in psoriasis. *JDDG.* 18(7), 675–681. *18*, 7. doi: 10.1111/ddg.14124

Lee E.B., Wu K.K., Lee M.P., Bhutani T., Wu J.J. 2018. Psoriasis risk factors and triggers. *Cutis*. 102, 18-20.

Li B., Huang L, Lv P., Li X., Liu G., Chen Y., Wang Z., Qian X., Shen Y., Li Y., Fang W. 2020. The role of Th17 cells in psoriasis. *Immunol. Res. 68*, 5. doi:10.1007/s12026-020-09149-1.

Li B., Li G., Yang X., Song Z., Wang Y., Zhang Z. 2022. NETosis in Psoriatic Arthritis: Serum MPO–DNA Complex Level Correlates With Its Disease Activity. *Front. Immunol.*, *13*. doi:10.3389/fimmu.2022.911347

Lin A. M., Rubin C. J., Khandpur R., Wang J. Y., Riblett M., Yalavarthi S., Villanueva E. C., Shah P., Kaplan M. J., Bruce A. T. 2011. Mast Cells and Neutrophils Release IL-17 through Extracellular Trap Formation in Psoriasis. *J. Immunol*. *187*, 1. doi:10.4049/jimmunol.1100123

Liu X. T., Shi Z. R., Lu S. Y., Hong D., Qiu X. N., Tan G. Z., Xiong H., Guo Q., Wang, L. 2022. Enhanced Migratory Ability of Neutrophils Toward Epidermis Contributes to the Development of Psoriasis via Crosstalk With Keratinocytes by Releasing IL-17A. *Front. Immunol. 13*. doi:10.3389/fimmu.2022.817040

Loft N. D., Vaengebjerg S., Skov, L. 2020. Cancer risk in patients with psoriasis: should we be paying more attention? *Expert. Rev. Clin. Immunol*. *16*, 5. doi:10.1080/1744666X.2020.1754194

Lood C., Blanco L. P., Purmalek M. M., Carmona-Rivera C., De Ravin S. S., Smith C. K., Malech H. L., Ledbetter J. A., Elkon K. B., Kaplan M. J. 2016. Neutrophil extracellular traps enriched in oxidized mitochondrial DNA are interferogenic and contribute to lupus-like disease. *Nat. Med*. *22*, 2. doi:10.1038/nm.4027

Lu J., Zhong X., Guo C., Tang L., Yu N., Peng C., Ding Y., Bao X., Zhou J., Shi Y. 2023. TLR7-MyD88-DC-CXCL16 axis results neutrophil activation to elicit inflammatory response in pustular psoriasis. *Cell Death Dis. 14*, 5. doi:10.1038/s41419-023-05815-y

Griffiths C. E., Armstrong A. W., Gudjonsson J. E., Barker J. N. 2021, Psoriasis. *The Lancet*. *397*, 10281. doi:10.1016/S0140-6736(20)32549-6

Meng X., Guo R., Fan C., Li Y., Liu X. Chen X., Lu L. 2022. RIPK1 downregulation enhances neutrophil extracellular traps in psoriasis. *Postepy Dermatol. Alergol. 39*, 1. doi:10.5114/ADA.2022.113803

Michalek I. M., Loring B., John S. M., World Health Organization. 2016. *Global report on psoriasis*. https://www.who.int/publications/i/item/9789241565189

Morrison P. J., Suhrkamp I., Gerdes S., Mrowietz U. 2021. Oral dimethyl fumarate induces changes within the peripheral neutrophil compartment of patients with psoriasis that are linked with skin improvement. *Br. J. Dermatol. 185*, 3. doi:10.1111/bjd.19899

Mutua V., Gershwin L. J. 2021. A Review of Neutrophil Extracellular Traps (NETs) in Disease: Potential Anti-NETs Therapeutics. *Clin. Rev. Allergy Immunol*. *61*, 2. doi:10.1007/s12016-020-08804-7

Nakabo S., Romo-Tena J., Kaplan M. J. 2022. Neutrophils as Drivers of Immune Dysregulation in Autoimmune Diseases with Skin Manifestations. *J. Invest. Dermatol*. *142*, 3. doi:10.1016/j.jid.2021.04.014

Neubert E., Bach K. M., Busse J., Bogeski I., Schön M. P., Kruss S., Erpenbeck L. 2019. Blue and long-wave ultraviolet light induce in vitro neutrophil extracellular trap (NET) formation. *Front. Immunol. 10*, OCT. doi:10.3389/fimmu.2019.02428

Ogawa Y., Muto Y., Kinoshita M., Shimada S., Kawamura T. 2021. Neutrophil extracellular traps in skin diseases. *Biomedicines*. *9*, 12. doi:10.3390/biomedicines9121888

Pinegin B., Vorobjeva N., Pinegin V. 2015. Neutrophil extracellular traps and their role in the development of

chronic inflammation and autoimmunity. *Autoimmun. Rev*. *14*, 7. doi:10.1016/j.autrev.2015.03.002

Polat M., Bugdayci G., Kaya H., Oğuzman H. 2017. Evaluation of neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio in Turkish patients with chronic plaque psoriasis. *Acta Dermatovenerol. APA*. *26*, 4. doi:10.15570/actaapa.2017.28

Price B., Dennison C., Tschesche H., Elliott E. 2000. Neutrophil tissue inhibitor of matrix metalloproteinases-1 occurs in novel vesicles that do not fuse with the phagosome. *J. Biol. Chem*. *275*, 36. doi:10.1074/jbc.M002263200

Raharja A., Mahil S. K., Barker J. N. 2021. Psoriasis: A brief overview. *JRCPL*. *21*, 3. doi:10.7861/CLINMED.2021-0257

Rendon A., Schäkel K. 2019. Psoriasis pathogenesis and treatment. *Int. J. Mol. Sci. 20,* 6. doi:10.3390/ijms20061475

Rodriguez-Rosales Y. A., Langereis J. D., Gorris M. A. J., van den Reek J. M. P. A., Fasse E., Netea M. G., de Vries I. J. M., Gomez-Muñoz L., van Cranenbroek B., Körber A., Sondermann W., Joosten I., de Jong, E. M. G. J., Koenen H. J. P. M. 2021. Immunomodulatory aged neutrophils are augmented in blood and skin of psoriasis patients. *JACI*. *148*, 4. doi:10.1016/j.jaci.2021.02.041

Rousset L., Halioua B. 2018. Stress and psoriasis. *Int. J. Dermatol*. *57*, 10. doi:10.1111/ijd.14032

Sadeghi M., Dehnavi S., Jamialahmadi T., Johnston T. P., Sahebkar A. 2023. Neutrophil extracellular trap: A key player in the pathogenesis of autoimmune diseases. *Int. Immunopharmacol*. *116*. doi:10.1016/j.intimp.2023.109843

Schön M. P., Broekaert S. M. C., Erpenbeck L. 2017. Sexy again: the renaissance of neutrophils in psoriasis. *Exp. Dermatol*. *26*, 4. doi:10.1111/exd.13067

Schön M. P., Erpenbeck, L. 2018. The interleukin-23/interleukin-17 axis links adaptive and innate immunity in psoriasis. *Front. Immunol. 9*, JUN. doi:10.3389/fimmu.2018.01323

Sen B. B., Rifaioglu E. N., Ekiz O., Inan M. U., Sen T., Sen N. 2014. Neutrophil to lymphocyte ratio as a measure of systemic inflammation in psoriasis. *Cutan. Ocul. Toxicol*. *33*, 3. doi:10.3109/15569527.2013.834498

Shao S., Fang H., Dang E., Xue K., Zhang J., Li B., Qiao H., Cao T., Zhuang Y., Shen S., Zhang T., Qiao P., Li C., Gudjonsson J. E., Wang, G. 2019. Neutrophil extracellular traps promote inflammatory responses in psoriasis via activating epidermal TLR4/IL-36R crosstalk. *Front. Immunol. 10,* APR. doi:10.3389/fimmu.2019.00746

Singh T. P., Lee C. H., Farber J. M. 2013. Chemokine receptors in psoriasis. *Expert Opın. Ther. Tar*. *17*, 12. doi:10.1517/14728222.2013.838220

Singhal A., Kumar S. 2022. Neutrophil and remnant clearance in immunity and inflammation. *Immunology*. *165*, 1. doi:10.1111/imm.13423

Skrzeczynska-Moncznik J., Wlodarczyk A., Zabieglo K., Kapinska-Mrowiecka M., Marewicz E., Dubin A., Potempa J., Cichy J. 2012. Secretory Leukocyte Proteinase Inhibitor-Competent DNA Deposits Are Potent Stimulators of Plasmacytoid Dendritic Cells: Implication for Psoriasis. *J. Immunol*. *189*, 4. doi:10.4049/jimmunol.1103293

Skrzeczynska-Moncznik J., Zabieglo K., Osiecka O., Morytko A., Brzoza P., Drozdz L., Kapinska-Mrowiecka M., Korkmaz B., Pastuszczak M., Kosalka-Wegiel J., Musial J., Cichy, J. 2020. Differences in Staining for Neutrophil Elastase and its Controlling Inhibitor SLPI Reveal Heterogeneity among Neutrophils in Psoriasis. *J. Invest. Dermatol*. *140*, 7. doi:10.1016/j.jid.2019.12.015

Solak B., Dikicier B. S., Erdem T. 2017. Impact of Elevated Serum Uric Acid Levels on Systemic Inflammation in Patients with Psoriasis. *Angiology*. *68*, 3. doi:10.1177/0003319716657980

Sørensen O. E., Borregaard N. 2016. Neutrophil extracellular traps - The dark side of neutrophils. *J. Clın. Invest*. *126*, 5. doi:10.1172/JCI84538

Steinberg B. E., Grinstein S. 2007. Unconventional roles of the NADPH oxidase: signaling, ion homeostasis, and cell death. *Science's STKE. 2007,* 379. doi:10.1126/stke.3792007pe11

Surcel M., Munteanu A., Huică R., Isvoranu G., Parvu I., Constantin C., Bratu O., Căruntu C., Zaharescu I., Sima L., Costache M., Neagu M. 2019. Reinforcing involvement of NK cells in psoriasiform dermatitis animal model. *Exp. Ther. Med*. *18*, 6. doi:10.3892/etm.2019.7967

Surcel M., Munteanu A. N., Isvoranu G., Constantin C., Supeanu T., Bratu O., Alecu M., Neagu M. 2021a. NK cells in psoriasiform dermatitis. from psoriatic site to peripheral blood, through secondary immune organs. *Dermatovenerol* (Buc), 66, 7–16.

Surcel M., Munteanu A., Isvoranu G., Ibram A., Căruntu, C., Constantin C., Neagu M. 2021b. Unconventional therapy with IgY in a psoriatic mouse model targeting gut microbiome. *J. Pers. Med. 11*, 9. doi:10.3390/jpm11090841.

Surcel M., Munteanu A. N., Constantin C., Neagu M. 2022. Immune Markers in Psoriasis. In: Psoriasis. Shahin Aghaei (Ed.), IntechOpen, 1-26. doi:10.5772/intechopen.102567

Teague H. L., Varghese N. J., Tsoi L. C., Dey A. K., Garshick M. S., Silverman J. I., Baumer Y., Harrington, C. L., Stempinski E., Elnabawi Y. A., Dagur P. K., Cui K., Tunc I., Seifuddin F., Joshi A. A., Stansky E., Purmalek M. M., Rodante J. A., Keel, A., … Mehta, N. N. 2019. Neutrophil Subsets, Platelets, and Vascular Disease in Psoriasis. *JACC: Basic to Translational Science*. *4*, 1. doi:10.1016/j.jacbts.2018.10.008

Tokuyama M., Mabuchi T. 2020. New treatment addressing the pathogenesis of psoriasis. *Int. J. Mol. Sci. 21*, 20. doi:10.3390/ijms21207488

Toprak A. E., Ozlu E., Ustunbas T. K., Yalcınkaya E., Sogut S., Karadag A. S. 2016. Neutrophil/lymphocyte ratio, serum endocan, and nesfatin-1 levels in patients with psoriasis vulgaris undergoing phototherapy treatment. *Med. Sci. Monit. 22*. doi:10.12659/MSM.898240

Tsuji G., Yamamura K., Kawamura K., Kido-Nakahara M., Ito T., Nakahara T. 2023. Regulatory Mechanism of the IL-33–IL-37 Axis via Aryl Hydrocarbon Receptor in Atopic Dermatitis and Psoriasis. *Int. J. Mol. Sci*. *24*, 19. doi:10.3390/ijms241914633

Valesini G., Gerardi M. C., Iannuccelli C., Pacucci V. A., Pendolino M., Shoenfeld, Y. 2015. Citrullination and autoimmunity. *Autoimmun. Rev*. *14*, 6. doi:10.1016/j.autrev.2015.01.013

Vidal S., Puig L., Carrascosa-Carrillo J. M., González-Cantero Á., Ruiz-Carrascosa J. C., Velasco-Pastor A. M. 2021. From messengers to receptors in psoriasis: The role of il-17ra in disease and treatment. *Int. J. Mol. Sci*. *22*, 13. doi:10.3390/ijms22136740

Vorobjeva, N. V. 2020. Neutrophil Extracellular Traps: New Aspects. *Moscow Univ. Biol. Sci. Bull*. *75*, 4. doi:10.3103/S0096392520040112

Wang W. M., Wu C., Gao Y. M., Li F., Yu X. L., Jin H. Z. 2021. Neutrophil to lymphocyte ratio, platelet to lymphocyte ratio, and other hematological parameters in psoriasis patients. *BMC Immunology*, *22*, 1. doi:10.1186/s12865-021-00454-4

Wang W., Su J., Yan M., Pan J., Zhang X. 2023. Neutrophil extracellular traps in autoimmune diseases: Analysis of the knowledge map. *Front. Immunol. 14*. doi:10.3389/fimmu.2023.1095421

Wang Z., Shi D. 2023. Research progress on the neutrophil components and their interactions with immune cells in the development of psoriasis. *Skin. Res. Technol*. *29*, 7. doi:10.1111/srt.13404

Wigerblad G., Kaplan M. J. 2023. Neutrophil extracellular traps in systemic autoimmune and autoinflammatory diseases. *Nat. Rev. Immunol*. *23*, 5. doi:10.1038/s41577-022-00787-0

Witte E., Kokolakis G., Witte K., Philipp S., Doecke W. D., Babel N., Wittig B. M., Warszawska K., Kurek A., Erdmann-Keding M., Kunz S., Asadullah K., Kadin M. E., Volk H. D., Sterry W., Wolk K., Sabat R. 2014. IL-19 is a component of the pathogenetic IL-23/IL-17 cascade in psoriasis. *J. Invest. Dermatol. 134*, 11. doi:10.1038/jid.2014.308

Wójcik P., Garley M., Wroński A., Jabłońska E., Skrzydlewska E. 2020. Cannabidiol modifies the formation of NETs in neutrophils of psoriatic patients. *Int. J. Mol. Sci*. *21*, 18. doi:10.3390/ijms21186795

Yamamoto T. 2020. Psoriasis and connective tissue diseases. *Int. J. Mol. Sci*. *21*, 16. doi:10.3390/ijms21165803

Yipp B.G., Kubes P. 2013. NETosis: how vital is it? *Blood. 122*, 16. doi:10.1182/blood-2013-04-457671

Zabieglo K., Majewski P., Majchrzak-Gorecka M., Wlodarczyk A., Grygier B., Zegar A., Kapinska-Mrowiecka M., Naskalska A., Pyrc K., Dubin A., Wahl S. M., Cichy J. 2015. The inhibitory effect of secretory leukocyte protease inhibitor (SLPI) on formation of neutrophil extracellular traps. *J. Leukoc. Biol. 98*, 1. doi:10.1189/jlb.4ab1114-543r

Zhang B., Lai R.C., Sim W.K., Choo A.B.H., Lane E.B., Lim S.K. 2021. Topical Application of Mesenchymal Stem Cell Exosomes Alleviates the Imiquimod Induced Psoriasis-Like Inflammation. *Int. J. Mol. Sci. 22*, 2. doi:10.3390/ijms22020720.

Zhou X., Hu Y., Liu L., Liu L., Chen H., Huan, D., Ju M., Luan C., Chen K., Zhang J. 2023. IL-33-mediated activation of mast cells is involved in the progression of imiquimod-induced psoriasis-like dermatitis. *J. Cell Commun. Signal. 21* 1. doi:10.1186/s12964-023-01075-7

Zhu D., Song W., Jiang Z., Zhou H., Wang S. 2022. Citrullination: A modification important in the pathogenesis of autoimmune diseases. *Clin. Immunol*. *245*. doi:10.1016/j.clim.2022.109134