JURNAL SINTESIS | PENELITIAN SAINS TERAPAN DAN ANALISISNYA
ISSN 2745-9918 dan telah terindeks SINTA 5.
Vol 6 No 2 Tahun 2025

Neutrophil Extracellular Traps as Potential Therapeutic Targets in Systemic Lupus Erythematosus: A Systematic Review of Current Evidence

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ABSTRACT

Introduction: Systemic Lupus Erythematosus (SLE) is an autoimmune disorder in which the immune system becomes increasingly dysregulated, inflamed, and involves multiple organ systems. While Neutrophil Extracellular Traps (NETs) play an essential role in antimicrobial defence, in SLE, they enhance immunopathological damage by driving type I interferon response, autoantibody production, and tissue damage. NETs, due to their unique capability of serving both as disease extraditional and as disease instigators, are a promising target in SLE. **Methods:** The current review is in accordance with PRISMA guidelines and registered in PROSPERO (CRD420251129386). Comprehensive searches were performed in PubMed, ScienceDirect, SpringerLink, and JSTOR, published between 2021 and 2025. Primary research investigating NETs or interventions aimed at them in SLE were included. Articles were excluded for non-originality, focus outside SLE and NETs, and lack of therapeutic focus. Documents were appraised for design, population, sample size, intervention, outcome, and therapeutic relevance for extraction. All retrieved articles underwent duplicate removal, title and abstract screening, and full-text assessment before final inclusion. **Results:** A total of 1.065 articles were initially identified, of which six studies met inclusion criteria. Clinical studies consistently demonstrated elevated NET remnants, impaired NET degradation, and organ-specific deposition associated with lupus nephritis and vascular involvement. Preclinical models showed that PAD4 inhibition, DNase I supplementation, and mitochondrial-targeted antioxidants reduced NET formation, attenuated interferon-driven immune responses, and ameliorated renal and vascular pathology. **Conclusion:** Existing data underscore the role of NETs as critical pathogenic components of SLE and corroborate the possibility of NETs as therapeutic targets. There is, however, an immediate need for bespoke NET assays, active-signed NET biomarker stratification, NET-guided patient stratification, and rigorous clinical trial design.

Keywords: Neutrophil Extracellular Traps, Systemic Lupus Erythematosus, Therapeutic Target

INTRODUCTION

Systemic lupus erythematosus (SLE) is an autoimmune disease with heterogeneous manifestations due to the dysregulation of the innate and adaptive immune systems, causing chronic

inflammation and multi-organ involvement. The distinguishing feature of SLE is the autoantibody response to various nuclear antigens, which leads to immune complex formation and subsequent deposition of these complexes in tissues, causing damage. Approximately, SLE affects 20 to 150 individuals per 100,000 with a disproportionate burden among women, particularly those of childbearing age, and higher prevalence in non-Caucasian populations including Asians, African Americans, and Hispanics (Rees et al., 2017). Improvements in survival have been noted with the use of corticosteroids and immunosuppressants; however, the burden of morbidity remains high due to disease flares, irreversible organ damage, and toxicity from treatments (Fanouriakis et al., 2019).

Neutrophils have received increasing attention as clinically relevant contributors to lupus pathogenesis in the past decade. One function neutrophil appear to have is the creation of neutrophil extracellular traps, or NETs, through a process called NETosis. NETs are traps of chromatin fibres, histones, and antimicrobial proteins that activated neutrophils release to capture and neutralise pathogens (Papayannopoulos, 2018). NETs serve as a host defence mechanism, but paradoxically expose the potential of approfonded autoimmunity by providing a context of enhanced immunogenicity for intracellular autoantigens and perpetuating type I interferon (IFN-I) production, a key pathway in lupus (Knight & Kaplan, 2023).

In SLE, abnormal NETosis is marked by excessive NET formation in conjunction with insufficient NET degradation, causing these structures to persist in the blood and tissues. These NETs are composed of DNA, histones, neutrophil elastase, and myeloperoxidase, all of which are potential autoantigens. Moreover, they stimulate the production of IFN-α from plasmacytoid dendritic cells, which escalates a self-reinforcing cycle of inflammation and autoimmunity. NETs have been identified in the glomerular capillaries in patients with lupus nephritis, one of the most severe forms of SLE, and their presence correlates with the severity of the disease. Furthermore, NETs lead to the destruction of the endothelium and the dysregulation of the blood vessels by the activation of matrix metalloproteinases and thromboinflammation, exacerbating the risk of cardiovascular complications in patients with SLE (Leffler et al., 2022; Hakkim et al., 2017; Carmona et al., 2017).

These findings suggest that NETs are not solely markers of inflammation, but rather active components in the pathogenesis of SLE, making them appealing from a therapeutic perspective. NETs have been targeted using several different approaches. Some of these approaches include the breakdown of extracellular DNA via DNase I, the inhibition of a key NET-forming enzyme, peptidylarginine deiminase 4 (PAD4), and the neutralisation of NET-associated proteins. In lupus murine models, NET formation was reduced, IFN-driven gene expression was suppressed, and glomerulonephritis was attenuated with PAD4 inhibition (Knight et al., 2021). Also, the administration of DNase I has been shown to decrease the load of autoantigen and immune complex deposition. However, clinically applicable doses remain limited owing to safety and pharmacokinetic considerations.

Recent research has investigated the targeting of mitochondrial reactive oxygen species (ROS), crucial incitants of NETosis, alongside enzymatic degradation and PAD4 inhibition, extending further PAD4 inhibition. For example, in murine lupus models, NET formation was attenuated and disease progression improved with the administration of MitoTEMPO, a mitochondrial ROS scavenger, by relieving oxidative stress and perturbing the NETosis pathway (Zhang et al., 2019). Furthermore, therapeutic targeting of TLRs (toll-like receptors) and interferon signalling pathways, both of which act downstream of NET exposure, has shown promise in lupus activity control and immune-mediated tissue damage mitigation (Bangs et al., 2023). These approaches exemplify the shift towards dismantling NETs and targeting upstream molecular illumination and immune amplification loops. The collective insights provided expand the therapeutic scope of SLE beyond direct NET degradation.

Although there is an increasing amount of research that suggests NETs play a role in SLE, the area continues to lack cohesion, with sparse integration of preclinical and clinical data. Comprehensive synthesis analyses are required in the immunopathology of SLE, to assess the therapeutic potential of NET-targeting treatments, and a critical appraisal of the literature will examine NETs as therapeutic targets in SLE with an emphasis on mechanistic pathways, experimental frameworks, and evolving pharmacologic approaches.

METHODS

The review was conducted in a structured manner, strategised along the lines of the PRISMA 2020 statement. A comprehensive protocol outlining the eligibility requirements, search strategy, desired outcomes, and analytic framework was crafted and registered on PROSPERO under the identification number CRD420251129386. Two reviewers independently conducted study selection, data extraction, and quality assessment on a consensus basis.

This systematic review does not involve a single predefined study population because it synthesizes data from previously published research. Each included study contributes its own population as defined by the original investigators. Study selection follows predefined eligibility criteria based on study design, participant characteristics, type of NET-targeted intervention, comparators, and reported outcomes. Only studies meeting these criteria will be included through a systematic and transparent screening process performed independently by two reviewers.

The literature search for systematically included articles was conducted in ScienceDirect, PubMed, and SpringerLink for the years 2021 to 2025. The search employed controlled vocabulary (MeSH) alongside specialised terms related to SLE, NETs, and their therapeutic targeting. Key MeSH terms included ‘Systemic Lupus Erythematosus’ and ‘Neutrophil Extracellular Traps’. The search strategy used the following strings: (“Systemic Lupus Erythematosus” OR “SLE” OR “Lupus”) AND (“Neutrophil Extracellular Traps” OR “NETosis” OR “NETs”) AND (“Therapeutics” OR “therapy” OR “treatment” OR “intervention” OR “PAD4 inhibitor” OR “DNase” OR “NADPH oxidase inhibitor” OR “ROS scavenger” OR “mitochondrial ROS”). Search strings were tailored for each database while maintaining a consistent focus, and reference lists of selected articles and relevant reviews were screened to identify additional studies. Given the variability in study designs, outcome measures, and experimental models, a narrative synthesis was undertaken to integrate findings across clinical, in vivo, and in vitro evidence. Extracted data were tabulated and synthesised descriptively to evaluate the effects of NET-targeted therapies on NET biomarkers, disease activity, and mechanistic pathways in SLE.

RESULT AND DISCUSSION

The systematic search and selection process, summarized in the PRISMA flow diagram (Figure 1), yielded six studies eligible for qualitative synthesis. These comprised both preclinical experimental models and clinical investigations, reflecting the current evidence regarding NETs as potential therapeutic targets in SLE. The review criteria highlight two important points. First, although NETs are increasingly recognized as contributors to lupus pathogenesis, very few studies focus on therapies aimed at modulating NETs. Second, the majority of excluded studies considered NETs only as biomarkers, underscoring a significant research gap and the need for translational studies that move from mechanistic insights to therapeutic applications.

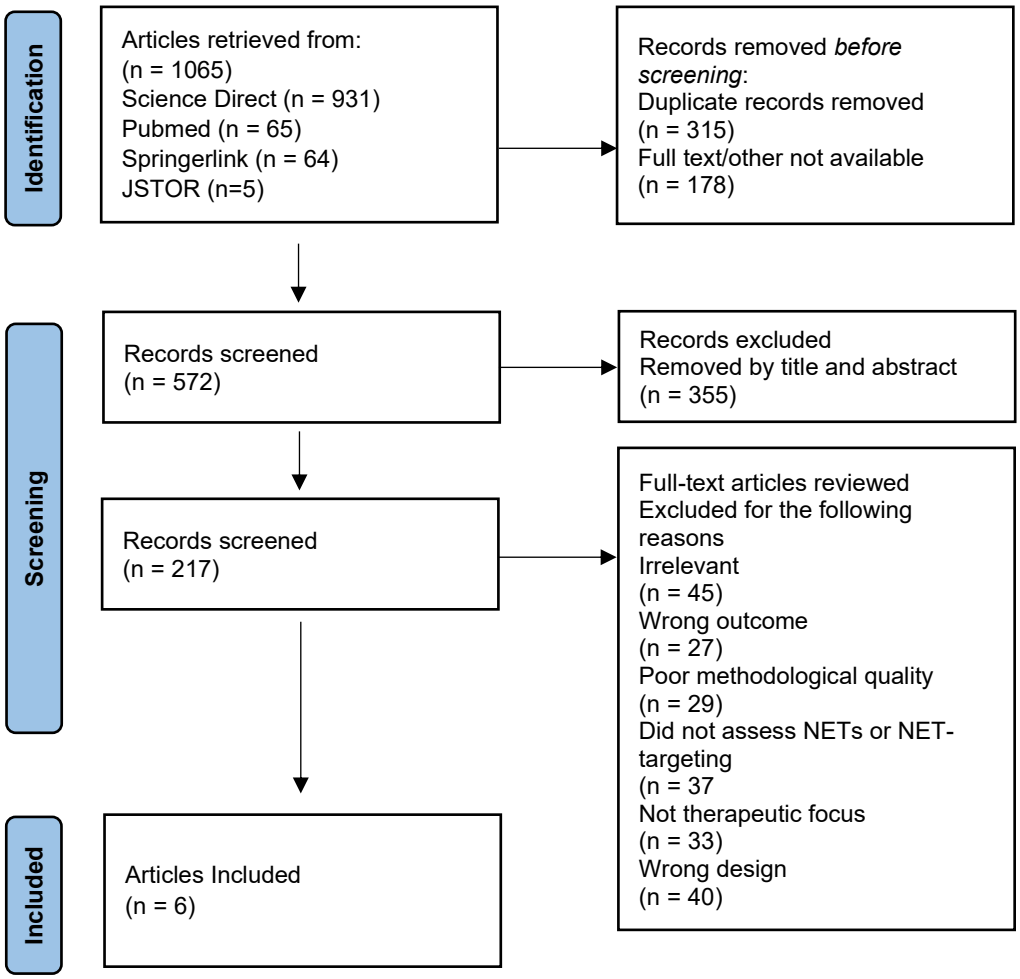

Figure 1. **PRIMA Flowchart**

The included studies comprised both clinical cohorts and experimental preclinical models, providing complementary methodological perspectives on systemic lupus erythematosus (SLE) and the relevance of neutrophil extracellular traps (NETs). Research was conducted across Europe, North America, and Asia, with publication years ranging from 2021 to 2024. Sample sizes varied widely, from controlled experimental groups to clinical cohorts exceeding 100 participants. The analysed populations consisted of individuals diagnosed with SLE, including specific phenotypic subsets such as lupus nephritis and SLE with vascular involvement.

Preclinical investigations employed in vitro neutrophil stimulation to examine mechanisms of NET formation and clearance. Across the studies, NET-related pathways involved oxidative stress, peptidylarginine deiminase 4 (PAD4), impaired extracellular DNA degradation by DNase, and mitochondrial processes leading to oxidised DNA release. Reported therapeutic interventions included PAD4 inhibitors, DNase I administration, and additional NET-modulating strategies aimed at reducing NET burden.

Overall, NET activity consistently correlated with clinical disease severity, including elevated circulating NET remnants, impaired NET degradation, and NET deposition in organs such as the kidneys and vasculature. Modulation of NETs in preclinical models was associated with

improvements in proteinuria, renal pathology, vascular inflammation, and interferon-driven immune activation. These findings highlight NETs not only as biomarkers of disease activity but also as mechanistic drivers of lupus pathogenesis, underscoring their potential as disease-modifying therapeutic targets. For clarity, the main characteristics of the included studies are summarised in Table 1, while NET-focused interventions, outcomes, and therapeutic implications are presented in Table 2.

Table 1. Study Characteristics

No	Author	Population	SLE Phenotype
1	Li, China	SLE patients and healthy controls	General SLE; identified three molecular phenotypes
2	Bertelli, Italy	SLE patients and healthy donors	Lupus Nephritis predominant; pediatric and adult SLE
3	Georgakis, Greece and Sweden	Patients with active SLE; healthy donors as controls.	Active SLE, including lupus nephritis & cutaneous lupus.
4	Henning, Netherlands and Colombia	Patients with incomplete SLE (iSLE), established SLE, and healthy controls.	Mostly low disease activity; subsets included patients with history of cutaneous lupus or lupus nephritis.
5	Liu, Netherlands Russia	100 SLE patients in remission; 22 healthy controls.	Quiescent SLE; subgroups based on renal involvement
6	Fatemi, Iran	17 patients with SLE and 17 healthy controls.	General SLE diagnosis; phenotype specifics not stratified (not focused on organ involvement).

Table 2. NETs-Related Interventions and Outcomes

No	NET-Related Target	Intervention	Outcome Related to NETs	Therapeutic Implication	Key Findings
1	HMGB1, ITGB2, CREB5 (NET-associated biomarkers)	Machine learning and bioinformatics analysis	Diagnostic biomarkers and NET-driven cluster identification	Potential for NET-targeted and stratified treatment	Three NET biomarkers distinguish SLE subgroups and support precision diagnosis
2	NETs stimulate T-bet transcription factor and promote IgG2 class-switch	Ex vivo exposure of naïve B cells to NETs purified from LN patients	Increased IgG2 production and strong T-bet induction in SLE B cells only	Suggests NETosis as a therapeutic target to disrupt pathogenic IgG2 autoantibody production	NETs directly stimulate IgG2 class-switch via T-bet upregulation, contributing to LN pathogenesis
3	IL-33 on NETs; ST2L receptor; neutrophil proteases.	Immune complex–induced NETosis; IL-33/ST2L blockade; protease inhibition.	IL-33 NETs elevated; correlate with disease activity; drive IFN-α production.	IL-33/ST2L and protease pathways as potential therapeutic targets.	IL-33–decorated NETs enhance IFN-α response; protease-processed IL-33 increases NET pathogenicity.
4	Low-density granulocytes (LDGs), circulating NETs (MPO-DNA, cit-H3-DNA, elastase-DNA),	Ex vivo induction of NETosis using patient serum; flow cytometry measurement of LDGs; ELISA for NET complexes.	iSLE and SLE both showed elevated LDGs and increased NET complexes; patient serum induced higher NETosis in healthy neutrophils.	Suggests targeting neutrophil dysfunction or NET formation may help prevent progression from iSLE to SLE.	Neutrophil dysfunction appears early in iSLE, similar to SLE; increased LDGs and NET formation may promote autoimmunity before full disease develops.

	serum-induced NET formation.				
5	Circulating NETs measured as MPO–DNA complexes; oxidative stress assessed via plasma free thiols.	Cross-sectional biomarker assessment; no therapeutic intervention. Plasma NETs and thiol levels compared across clinical subgroups.	NET levels significantly higher in both LN and non-LN vs. healthy controls; no difference between LN and non-LN. NETs inversely correlated with thiols	Reducing oxidative stress may decrease NET formation; antioxidant-based strategies may serve as supportive therapy in SLE.	Elevated NETs persist even during remission; oxidative stress correlates with NET burden; thiols linked to renal function (eGFR). Supports a mechanistic link between ROS-driven NETosis and SLE pathology.
6	SLE-derived NETs affecting neutrophil functions: viability, CD11b expression, oxidative burst.	Neutrophils incubated with isolated NETs from SLE vs. healthy individuals; subsequent assessment of activation markers and cell-death patterns.	SLE NETs reduced neutrophil viability more strongly; increased late apoptosis/necrosis; elevated CD11b expression; enhanced oxidative burst.	Targeting NET-induced inflammatory neutrophil activation may help limit chronic inflammation in SLE.	SLE-derived NETs are more pro-inflammatory than healthy NETs, driving neutrophil activation, promoting inflammatory cell death, and amplifying oxidative signaling.

NETs as Central Mediators in SLE Immunopathology

Neutrophil extracellular traps or NETs are cellular traps released by neutrophils as part of an innate immune response. Activated neutrophils release NETs in the form of fibres that resemble webs made of DNA, histones, and granular proteins such as myeloperoxidase and neutrophil elastase. Despite helping to capture and eliminate pathogens, accumulating evidence shows that NETs and their aberrant formation and clearance are cytoimmune mechanisms in autoimmune diseases, particularly systemic lupus erythematosus (SLE) (Lood et al., 2016). In SLE, NETs serve as a reservoir of immunogenic substances, such as modified autoantigens that shatter tolerance, activating plasmacytoid dendritic cells (pDCs) and autoreactive B cells, sustaining type I interferon (IFN-I) production (Liu et al, 2024).

NETs containing citrullinated histones and oxidised mtDNA have been shown to act as strong innate immune stimulators and amplify the characteristic SLE interferon signature by acting on immune sensors such as Toll-like receptors (TLRs) and other cytosolic DNA sensing pathways (Stabach et al., 2024). NETs are composed of oxidised mtDNA and enriched with other stimuli with interferogenic potential, demonstrating enhanced potential to provoke cellular signalling. Oxidized DNA within NETs primarily originates from nuclear DNA. Thus, the composition of NETs as well as the stimuli and context in which they are produced determines their biological effects. NET-associated components also exert significant interferogenic potential due to their molecular composition. (Wang et al, 2022).

As described in the literature, patients with active SLE demonstrate increased levels of circulating NET remnants, including MPO-DNA complexes, in contrast to healthy controls, as well as impaired NET clearance which causes the immune system to be continuously exposed to immunostimulatory NETs (Shi et al., 2022). Of note, elevated NET markers in these patients are associated with disease activity scores, including SLEDAI, and are especially linked with renal involvement and vasculopathy (Reshetnyak and Nurbaeva, 2023).

The picture is made more complex by the presence of neutrophil subsets, such as low-density granulocytes (LDGs), which are more prevalent in SLE patients, are pro-inflammatory and are likely to undergo NETosis spontaneously, potentially driving inflammation in a given organ (Knight et al., 2013). These cells are known to infiltrate the kidney and skin, where they deposit NETs that locally foster immune complex and complement system activation (Brinkmann et al., 2024).

Beyond the studies included in this review, previous research has shown that NETs may also contribute to vascular inflammation and thrombosis by providing scaffolds for pro-thrombotic molecules such as tissue factor. Although this mechanism was not directly addressed in the analyzed studies, it highlights the broader pathogenic potential of NETs in linking autoimmunity with vascular complications. Additionally, NET-derived antigens can form immune complexes capable of re-activating neutrophils through Fcγ receptor engagement, further amplifying NETosis. This reinforces the concept that NETs are not passive markers of inflammation but active participants in the immunopathology of SLE. Their involvement in multiple pathways from autoantigen exposure to IFN-I amplification and oxidative dysregulation supports NETs as promising therapeutic targets, provided that interventions preserve essential antimicrobial functions (Villanueva et al., 2011; Garcia-Romo et al., 2011).

Mechanisms of NET Formation and Regulatory Failures Relevant to SLE

Neutrophil extracellular traps (NETs) can be released by neutrophils through a process known as NETosis. It can be divided into “suicidal” and “vital” NETosis. Suicidal NETosis is characterised by ROS production through NADPH oxidase, and PAD4 mediated activation leading to histone citrullination and chromatin decondensation (Leffler et al., 20). This method results in cell death and release of chromatin in the form of webs that contain antimicrobial proteins. On the other hand, vital NETosis does not lead to the death of neutrophils which in turn allows the neutrophils to retain some of their effector functions and carry out other cellular activities (Carmona-Rivera et al., 2020).

In the case of systemic lupus erythematosus (SLE), the triggers for NETosis are numerous, such as immune complexes, the engagement of Fcγ receptors, activation of endosomal Toll-like receptors (TLR 7 and TLR 9), as well as fragments of complement C3 and C5, and the cytokines IFN-α and TNF-α (Delgado-Rizo et al., 2017). All of these triggers are directed toward intracellular MAPK, PI3K/Akt, and mTOR signalling pathways responsible for the control of cytoskeletal movements and disintegration of the nuclear envelope (Clark et al., 2017). Within canonical NETosis, PAD4 is prominently active as it catalyses the citrullination of histones that decreases the positive charge of histone proteins and relaxes the association between DNA and histones (Kessenbrock et. Al., 2019). In genetically PAD4-deficient and pharmacologically PAD4-inhibited lupus-prone mouse models, NET release, as well as disease manifestations such as nephritis and vasculopathy, are significantly diminished (Chowdhury et al., 2024). Thus, PAD4 is positioned as a mechanistic “linchpin” and an attractive therapeutic target in the context of SLE-associated NETosis.

The significance of mitochondrial pathways has increased in recent years, especially concerning the mitochondrial ROS (mtROS) and oxidised mtDNA in the context of NETosis (Garcia-Baena et al., 2021). In contrast to nuclear DNA, mtDNA has unmethylated CpG motifs and is more vulnerable to oxidative damage, which strongly activates the cGAS–STING and TLR9 pathways (Wirestam et al., 2022). NETs laden with oxidised mtDNA were demonstrated to strongly instigate type I IFN production in murine and human systems, thus reinforcing the IFN signature in SLE (Leffler et al., 2022).

Insufficient clearance of NETs is another leading pathogenic mechanism in SLE. Genetic variants in nucleases, including DNASE1 and DNASE1L3, alongside neutralising anti-DNase

antibodies, hinder extracellular chromatin degradation, leading to tissue and bloodstream NET stagnation (Hakkim et al., 2021). Sustained NET exposure maintains the chronic inflammatory state by continuously driving autoantigen presentation (Soderberg & Segelmark, 2021). Regulatory NETosis boundaries include sensors for endoplasmic reticulum stress like inositol-requiring enzyme 1 alpha IRE1. IRE1α inhibition of NETosis has been demonstrated to reduce NETs in lupus models, underscoring the intricate interplay of neutrophils signalling crosstalk (Midon et al., 2021).

Moreover, the post-translational modifications (PTMs) of NET components such as oxidation, proteolytic cleavage, and citrullination, change NET components' antigenic properties and their vulnerability to degradation processes (Khandpur et al., 2013). This variety of NET "flavours" suggests that NETs could be of different levels of pathogenicity. Perhaps a form of precise medicine would be needed to identify and target the most relevant NETs in SLE patients. In essence, the rationale describes the need to understand the multiplicity of NETosis pathways and regulatory breakdowns in SLE to enable rational intervention designs. Differentiating pathogenic from physiological NETs provides an opportunity to develop future therapies that could selectively suppress harmful NETosis while maintaining the protective, antimicrobial functions of the NETs (Sangaletti et al., 2012).

NETs and Organ-Specific Pathology: Kidneys, Vasculature, and Beyond

Lupus nephritis (LN) is one of the most severe and prognostically important organ manifestations of systemic lupus erythematosus, and it has an incidence of almost 60% in SLE patients during their disease course (Kaplan & Radic, 2012). Several histopathological studies have shown NETs being deposited in the glomeruli, peritubular capillaries, and interstitial spaces of the kidneys in LN patients, contributing to inflammation and damage of the kidney tissues. These NETs are often found together with immune complexes and complement components, and are therefore thought to be involved in sustaining the inflammation of the glomeruli (Psarras et al., 2020).

NET inhibition focused specifically in the kidneys may change the course of LN's progression, contributing to the idea that NET inhibition may be beneficial. NETs, in a mechanistic fashion, can also injure renal parenchymal cells, such as podocytes, histonically and by releasing proteases like neutrophil elastase and MPO. NETs can also act as a centre for local complement activation, as well as immune complex trapping, which exacerbates the already existing glomerular damage. NETs may also release oxidised mtDNA which is capable of activating local dendritic cells or macrophages, and then locally producing IFN-I, which would lead to inflammation in the area (Kim et al., 2018).

Within the vascular system, NETs serve the dual function of endothelial damage and the scaffold for thrombosis. NET components stimulate endothelial cells to express greater adhesion molecules, less nitric oxide bioavailability, and increased procoagulant activity (Smith & Kaplan, 2015). NETs enhance the tissue factor and von Willebrand factor deposition which leads to platelet adhesion and thrombus consolidation. This is especially important for patients with SLE, as they continue to have significant late mortality due to cardiovascular disease. NETs have also been implicated in the non-renal tissues of patients with lupus. They are found within the dermal-epidermal junctions and interact with keratinocytes to produce pro-inflammatory cytokines, which is implicated in cutaneous lupus (Gupta et al., 2010). In pulmonary lupus, NETs are found within the alveolar spaces and are linked with diffuse alveolar haemorrhage, a potentially deadly complication. In addition, although still not confirmed, neuropsychiatric lupus may pertain to NETs causing microvascular damage to the central nervous system (Pieterse et al., 2018).

The clinical linkages illuminate some of the more practical implications of the findings. There is often an association between elevated circulating NET markers, greater SLEDAI scores,

active nephritis, and certain serological markers, including anti-dsDNA antibodies and hypocomplementaemia. While these associations do not prove causation, the combination of mechanistic animal studies and human biomarker studies presents a compelling rationale for therapeutic intervention (Carmona-Rivera et al., 2020).

Because of the organ-specific diversity of NET-related pathological processes, some therapies might need to be customised. For instance, systemic DNase I therapy might be effective for diffuse NET burden across multiple organ systems, while PAD4 inhibitors may be more effective in reducing renal NET infiltration (Lee et al., 2017). NETs may also have vascular components where infiltration might be best treated with dual-action therapies targeting NET and thrombus formation. This recognition of NETs as active agents of organ damage in SLE pathophysiology shifts the focus from diffuse autoimmune processes to targeted tissue-matrix interactions and emphasises their role in the evolution of tissue-specific disease manifestations and progression (Yousefi et al., 2019).

Therapeutic Strategies Targeting NETs Preclinical Evidence and Translational Prospects

Systemic lupus erythematosus has remained a focus of study for numerous complementary approaches seeking to modify NETs due to their unique strategies on NETs biology. Some of the many approaches are NET enzymatic dissolution, inhibition of NET formation, suppression of upstream NET triggers, and blockade of downstream immune amplification pathways (Lande et al., 2011). NET degradation is best pursued through the action of DNase I or DNASE1L3, which biologics cleave extracellular chromatin, thus reducing the supply of autoantigenic material (Apel et al., 2018).

The preclinical models of systemic administration showed the effect of DNase I which decreases the circulating NETs, immune complexes, and NETs-associated immune complex deposition and renal histopathological alterations. More recent models demonstrate the action of long-acting dual DNASE1/DNASE1L3 biologic which prevents the development and mortality of lupus in several genetic and induced lupus mouse model systems. Although findings are encouraging, other issues like short plasma half-life, anti-DNase autoantibodies and targeting the tissue site remain barriers to their clinical application (Morand et al., 2020; Furie et al., 2019).

Small-molecule PAD4 inhibitors, such as Cl-amidine, function by suppressing histone citrullination and chromatin decondensation, thereby limiting NET release and ameliorating renal and vascular inflammation in lupus-prone mouse models, while retaining key antimicrobial functions of neutrophils. Parallel preclinical approaches involving mitochondria-directed antioxidants, including MitoTEMPO and MitoQ, have demonstrated the capacity to reduce oxidised mtDNA-rich NET formation and attenuate type I interferon responses, ultimately lowering disease activity and organ injury. However, the central role of mitochondrial metabolism in cellular homeostasis introduces important translational considerations, highlighting the need for cautious optimisation before advancing these strategies to clinical evaluation.

Some current treatments for SLE might indirectly influence NET biology. Hydroxychloroquine, for example, mitigates activation of endosomal Toll-like receptors which may, in turn, lessen NET-induced immune activation. Moreover, JAK/STAT inhibitors which attenuate IFN signalling may also mitigate the effects of NETosis. Immunomodulators used in combination with NET-targeted therapies may have enhanced effects. Other approaches being studied include the targeting of higher-order NET triggers like complement activation or Fcγ receptor signalling as well as the monoclonal antibody-mediated neutralisation of NETs components like histones. Such processes strive to alter specific NETs-derived pathological mechanisms while preserving the NETs' function as antimicrobial agents (Strand et al., 2020; Hartl et al., 2022).

Although the therapeutic strategies reviewed here were not directly assessed in the included studies, several of the identified pathogenic NET mechanisms such as IL-33 decorated NETs, elevated LDGs, oxidative stress driven NETosis, and enhanced interferogenic NET activity provide mechanistic rationale for these NET-targeted approaches.

Incorporating these insights into practice will necessitate addressing multiple challenges such as patient diversity, NET measurement variability, and potential impact on immune function. Early clinical trial phases might integrate selective biomarker-guided patient stratification and dynamic NET imaging, along with organ-specific metrics, to improve the identification of patients who stand to benefit from the intervention. Overall, the preclinical evidence is strong for the use of NET modification therapies in SLE, with the caveat that these approaches remain unproven in actual clinical testing. Focused combination of precision targeting, safety, and durability of effect should be prioritised for these next developments (Serpas et al., 2021).

Biomarkers, Measurement Standards, Study Design Gaps, and Future Priorities

The effectiveness of NET-targeting approaches in systemic lupus erythematosus (SLE) for clinical use depends on the existence of reliable and standardised biomarkers. At present, the detection of NETs has remained an issue due to a myriad of NET detection approaches. The analytes measured and the platforms incorporated differ in such a way that it is not possible to eliminate inter-study variability. Some of the predominant NETs detection methods are: MPO–DNA ELISA which measures myeloperoxidase bound to DNA; ELISA for citrullinated histone H3; and NETs imaging via immunofluorescence. The differences among these methods and their use in SLE are anti-DNA serum factors and their sensitivity, specificity, and susceptibility (Jiménez-Alcázar et al., 2017).

NETs in systemic lupus erythematosus (SLE) have largely been investigated through human studies which are either cross-sectional in nature or have small, diverse study groups. Such designs do not allow for the complexity of NET levels and clinical disease activity relationships in clinical disease activity to be inferred. To resolve whether NETs are primarily inflammatory disease drivers or established inflammation markers, large-scale NET studies with longitudinal designs and serial sampling are essential (Zuo et al., 2020). Inflammation-driven studies have the potential to elucidate whether prior clinical flare changes in NET burden, harnessing predictive biomarker functionality. Targeting NETs in randomised controlled trials (RCTs) has been sparse. In the case where the trial is conducted, patient selection based on mechanistic endpoints, biomarker selection, NET burden reduction, IFN signature modulation, and organ-specific clinical outcomes like proteinuria remission in lupus nephritis should be incorporated. RCTs should be designed to allow monitoring for infection due to the possible risk of impaired defence against pathogen harm (Farrera & Fadeel, 2013).

Another emerging area of study is examining the relationships between NETosis and other forms of regulated cell death, including pyroptosis, necroptosis, and ferroptosis. There is the possibility of some shared upstream triggers, collective downstream inflammatory consequences, or both, which broadens the scope of potential combined therapeutic intervention. For instance, the inhibition of lipid peroxidation pathways in ferroptosis might curtail NET formation by reducing some form of structural damage and the subsequent dysfunction of membranes and mitochondria (Leffler et al., 2022).

Future priorities in NET research require definitive delineation of patient subsets and disease states, with particular attention to the documented heterogeneity of NET composition. NETs enriched with oxidised mitochondrial DNA are known to potentiate type I interferon signalling, demonstrating that qualitative NET differences carry clear clinical significance. Identifying such pathogenic NET subtypes will directly inform therapeutic precision and biomarker development. Advancing NET science from bench to bedside additionally demands coordinated efforts toward assay standardisation,

biomarker validation, and the integration of NET-focused endpoints into trial design alongside other inflammatory pathways. These directions, firmly supported by current literature, will refine our understanding of NET-driven pathology in SLE and strengthen the foundation for the effective deployment of NET-targeted therapies (Schrezenmeier & Dörner, 2020; Goel et al., 2022).

This systematic review has several limitations. Much of the evidence on NETs in SLE derives from preclinical studies that may not fully translate to human disease, while existing clinical studies typically small and cross-sectional offer limited ability to infer causality. Heterogeneity in NET detection methods further complicates comparison across studies. In addition, no large-scale randomised trials of NET-targeted therapies exist, and current approaches such as PAD4 inhibition, DNase therapy, and mitochondrial ROS scavengers remain largely experimental with unresolved safety concerns. Progress in this field will require harmonised NET assays, longitudinal studies, composite biomarker panels for patient stratification, and early-phase trials incorporating rigorous safety and pharmacokinetic assessments. Addressing these gaps is essential for advancing NET-targeted strategies toward clinical applicability in SLE.

CONCLUSION

Neutrophil extracellular traps (NETs) have emerged as central mediators in the immunopathogenesis of systemic lupus erythematosus (SLE), linking innate immune activation with autoantigen exposure, type I interferon amplification, and organ-specific injury. Accumulating experimental and translational evidence indicates that dysregulated NET formation and impaired clearance contribute substantially to disease persistence, particularly in lupus nephritis and vascular pathology. Although NET-directed therapies such as PAD4 inhibition, mitochondrial ROS modulation, and enzymatic degradation of extracellular chromatin show compelling efficacy in preclinical models, their clinical applicability remains constrained by biological heterogeneity, assay limitations, and concerns regarding long-term immunocompromise. Moving forward, robust biomarker standardisation, longitudinal cohort studies, and carefully designed early-phase clinical trials will be essential to determine the therapeutic viability of NET modulation. NETs thus represent both an informative biomarker axis and a promising, yet still experimental, therapeutic target in SLE.

ACKNOWLEDGMENTS

The authors would like to express their sincere gratitude to the Institut Ilmu Kesehatan Bhakti Wiyata, Kediri, Indonesia, for institutional support throughout the preparation of this review. We also acknowledge the valuable contributions of colleagues and peers who provided constructive feedback during the development of the research framework. Special appreciation is extended to the database access services that facilitated comprehensive literature retrieval.

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