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Immunopathological Role Of Neutrophil Extracellular Traps (Nets) In Rare Autoimmune And Autoinflammatory Diseases: A Scoping Review

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Abstract: Neutrophil extracellular traps (NETs) are an important of the innate immune system that functions to protect the body from pathogens. However, when their formation and clearance processes are disrupted, NETs can contribute to the development of various autoimmune diseases, including rare conditions. Therefore, this study aims to describe the immunopathological role of NETs in rare autoimmune and autoinflammatory diseases through a scoping review approach. A literature search was conducted in the Scopus, PubMed, and Web of Science databases following the PRISMA-ScR guidelines. From a total of 525 identified articles, 10 studies met the inclusion criteria after the selection process and were analyzed further. The results show that the role of NETs can be classified into three main mechanisms. First, enhanced NET formation (enhanced NETosis), triggers the release of autoantigens and the formation of immune complexes. Second, impaired clearance, leads to the accumulation of NETs and prolongs the inflammatory process. Third, the interaction of NETs with other immune system components, including the complement system, which further amplifying the inflammatory response. These three mechanisms are interconnected and form a continuous inflammatory cycle, contributing to tissue damage in rare autoimmune diseases. These findings indicate that NETs represent a potential target for the development of more specific therapies in the future.

Keywords: NETs, rare autoimmune diseasesi, NETosis, inflammation, complement system

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Introduction

Autoimmune and autoinflammatory diseases are groups of disorders caused by dysregulation of the immune system, resulting in inappropriate immune responses against the body's own tissues or persistent inflammation. Recent studies have demonstrated that the innate immune system plays an important role in the pathogenesis of autoimmune and autoinflammatory diseases, particularly through the activity of neutrophils, which are key effector cells in the inflammatory response (Gupta & Kaplan, 2016). One important mechanism involving neutrophils is the formation of neutrophil extracellular traps (NETs). NETs are extracellular structures released by neutrophils to trap and eliminate pathogens. Under physiological conditions, NET formation contributes to host defense.

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However, excessive NET formation (enhanced NETosis) or impaired NET clearance can contribute to autoimmune responses. These abnormalities may promote the exposure of autoantigens, formation of immune complexes, and persistent inflammatory activation (Goel et al., 2021; Odobasic et al., 2016; Yousefi et al., 2020).

NETs also interact with the complement system and other components of the immune system. These interactions can amplify inflammatory responses and contribute to tissue injury. In particular, complement activation and NET formation may reinforce one another, creating a self-sustaining inflammatory cycle that can contribute to disease progression (Yousefi et al., 2020; Goel et al., 2021; Bruschi et al., 2021; Šestan et al., 2023). This mechanism has been extensively investigated in several common autoimmune diseases. However, its role in rare autoimmune and autoinflammatory diseases remains less well characterized (Goel et al., 2021).

Although numerous studies have investigated the role of NETs in autoimmune diseases, the available evidence remains heterogeneous, and an integrated understanding of their immunopathological functions is still limited. Most studies have focused on common autoimmune diseases, resulting in a relative gap in the evidence concerning rare autoimmune and autoinflammatory diseases. Important questions also remain regarding the regulation of NET formation and clearance and their interactions with other immune components, particularly the complement system, in these conditions. This limited and fragmented evidence may hinder a comprehensive assessment of the potential role of NETs as therapeutic targets in rare autoimmune and autoinflammatory diseases.

The objective of this study is to map and characterize the immunopathological role of NETs in rare autoimmune and autoinflammatory diseases through a scoping review. Specifically, this review examines the mechanisms of NET formation and clearance, their interactions with other immune components, including the complement system, and their potential contribution to inflammation and tissue damage in these diseases.

Materials and Methods

Study Design

This study employed a scoping review method to map and summarize the available scientific evidence on the immunopathological role of neutrophil extracellular traps (NETs) in rare autoimmune and autoinflammatory diseases. A scoping review was selected because the topic encompasses heterogeneous evidence across different disease groups, immunopathological mechanisms, and research approaches. This approach allows the identification of major concepts, patterns, and gaps in the existing literature and provides an overview of the development of research on NETs in rare autoimmune and autoinflammatory diseases (Munn et al., 2018). The review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews (PRISMA-ScR) guidelines.

Search Strategy

A comprehensive literature search was conducted in the PubMed, Scopus, and Web of Science databases from January to April 2026. The search was conducted continuously throughout this period. The search strategy combined terms related to NETs with terms related to autoimmune and autoinflammatory diseases using Boolean operators.

The NET-related search terms included "Neutrophil Extracellular Traps," "NETosis," and "NET-associated proteins." These terms were combined with disease-related terms representing rare autoimmune and autoinflammatory conditions, including "Vasculitis," "ANCA-associated vasculitis," "Behcet Disease," "Dermatomyositis," "Polymyositis," "Systemic Sclerosis," "antiphospholipid syndrome," "Still's Disease," "Bullous Pemphigoid," and "Neuromyelitis Optica." Additional terms related to rare autoimmune and autoinflammatory diseases were included where appropriate to improve the sensitivity of the search.

The search strategy was adapted to the indexing system and syntax of each database. The complete search strings, including Boolean operators and database-specific search fields, should be provided in the Supplementary Material to ensure reproducibility.

Eligibility Criteria

Articles were included if they met all of the following criteria: (1) original research studies; (2) published in English; (3) published between 2016 and 2026; (4) involving human participants or human-derived clinical samples; and (5) investigating the role, formation, clearance, or immunological interactions of NETs in rare autoimmune or autoinflammatory diseases.

For the purpose of this review, diseases were considered eligible when they were classified as rare autoimmune or autoinflammatory conditions in the relevant clinical or scientific literature. Disease classification was considered in relation to the specific condition examined in each study rather than solely on the basis of individual clinical manifestations or biomarkers.

Articles were excluded if they were: (1) review articles, editorials, letters, or conference abstracts; (2) animal-only studies; (3) in vitro studies without relevant human clinical or patient-derived data; (4) articles for which the

full text was unavailable; or (5) studies that did not directly address NETs or their immunopathological relevance to the target diseases.

Study Selection

Study selection was conducted in three stages: title screening, abstract screening, and full-text assessment against the predefined eligibility criteria. Two reviewers independently screened the records at each stage to minimize selection bias. Disagreements were resolved through discussion until consensus was reached.

The database search identified 525 records meeting the search criteria. Duplicate records were removed before screening. The remaining records underwent title and abstract screening, followed by full-text assessment of potentially eligible studies. After the screening and eligibility assessment, 10 articles met all inclusion criteria and were included in the final analysis. The study selection process is illustrated in a PRISMA flow diagram.

Data Extraction

Data were extracted into a standardized data-extraction table. The extracted information included author, publication year, disease category, study characteristics, NET-related mechanisms, evidence of enhanced NET formation (NETosis), NET clearance, interactions between NETs and other immune components, complement system involvement, and primary findings.

Data Analysis

The extracted data were analyzed descriptively and organized according to the major immunopathological mechanisms identified across the included studies. Three main analytical categories were used: (1) enhanced NET formation or NETosis, (2) impaired NET clearance, and (3) interactions between NETs and other immune components, particularly the complement system.

The analysis focused on identifying patterns in the contribution of NETs to inflammatory processes, immune dysregulation, and tissue damage across rare autoimmune and autoinflammatory diseases. Differences in disease characteristics, NET-related mechanisms, and interactions with other immune pathways were also considered when synthesizing the evidence.

Result and Discussion

Study Selection

The PRISMA-ScR flow presents the study selection process. The initial database search identified 525 records. After removing duplicate records and screening titles and abstracts, 73 full-text articles were assessed for eligibility. Following full-text assessment, 10 studies met the predefined eligibility criteria and were included in the final scoping review. Studies were excluded at the full-text stage when they did not directly address the role of NETs in the immunopathology of the target rare autoimmune or autoinflammatory diseases, did not provide relevant NET-related findings, or did not meet the other predefined inclusion criteria.

Characteristics of Included Studies

Ten studies published between 2017 and 2023 were included in the review. The studies investigated several rare autoimmune and autoinflammatory diseases, with the largest representation involving antiphospholipid syndrome (APS), adult-onset Still's disease (AOSD), and systemic vasculitides. Other conditions included Behçet's disease and granulomatosis with polyangiitis (GPA).

The included studies predominantly used observational or case-control designs and generally compared patients with healthy controls or other clinically relevant comparison groups. Sample sizes varied substantially, ranging from relatively small case-control groups to larger multicenter cohorts. The studies were conducted in several countries, including the United States, China, Poland, Brazil, Japan, and multinational settings in North America, South America, and Europe. Diagnostic criteria and disease activity assessments also varied according to the specific disease under investigation.

Table 1 summarizes the characteristics of the included studies, including the disease category, study design, sample size, country, diagnostic criteria, and disease activity assessment.

NET-Related Biomarkers and Detection Methods

The included studies evaluated a range of NET-related biomarkers and employed different laboratory methods to assess NET formation, degradation, and NET-associated immune responses. Commonly investigated biomarkers included neutrophil elastase (NE)-DNA complexes, myeloperoxidase (MPO)-DNA complexes, cell-free DNA (cfDNA), citrullinated histone H3 (citH3)-DNA complexes, anti-NET antibodies, and other NET-associated molecular components.

The detection methods included enzyme-linked immunosorbent assay (ELISA), immunofluorescence microscopy, fluorescence-based assays, quantitative polymerase chain reaction (qPCR), DNA-binding assays, and machine learning approaches applied to biomarker profiles. Samples were obtained from plasma, serum, isolated neutrophils, or combinations of these sources.

Table 2 summarizes the NET-related biomarkers, detection methods, sample types, and principal findings reported in the included studies.

Narrative Synthesis of Main Findings

Across the included studies, three major patterns emerged: enhanced NET formation, impaired NET clearance, and interactions between NETs and other immune components, particularly the complement system.

Enhanced NET formation was observed across several disease groups. In AOSD, Wang et al. (2021), Hu et al. (2020), and Jia et al. (2020) reported increased circulating NET-related biomarkers and associations with systemic inflammation, disease activity, organ involvement, or treatment response. Similarly, Perazzio et al. (2017) demonstrated increased NET release in patients with active Behçet's disease, accompanied by increased inflammatory and oxidative responses. In GPA, Surmiak et al. (2023) reported increased NET-related biomarkers during active disease and associations with disease activity.

Impaired NET clearance represented a second major pattern. Studies of APS and systemic vasculitis indicated that reduced NET degradation may contribute to the persistence of extracellular DNA and NET-associated components. Zuo et al. (2020) reported impaired NET degradation in primary APS, which was associated with increased anti-NET antibodies and complement activation. Zuo et al. (2023) similarly identified impaired NET degradation and increased anti-NET antibodies among patients with APS and aPL-positive carriers. Michailidou et al. (2023) also reported increased NET biomarkers and impaired NET degradation across several vasculitis subtypes.

Interactions between NETs and other immune pathways were also evident. In APS, β2-glycoprotein I (β2GPI) was reported to interact with NETs, while increased NET-associated immune responses were linked to complement activation (Kmeťová et al., 2023; Zuo et al., 2020; Zuo et al., 2023). These findings suggest that NET accumulation and impaired degradation may contribute to sustained immune activation through interactions with autoantibodies, autoantigens, and complement pathways.

Several studies also identified potential associations between NET-related biomarkers and clinical disease severity. In AOSD, increased NET signatures were associated with systemic inflammation, organ involvement, and glucocorticoid resistance (Hu et al., 2020; Jia et al., 2020). In Behçet's disease and vasculitis, increased NET formation or impaired NET degradation was associated with disease activity (Perazzio et al., 2017; Surmiak et al., 2023; Michailidou et al., 2023). However, the direction and strength of these associations varied across diseases and study populations.

Overall, the evidence indicates that NET dysregulation may contribute to the immunopathology of rare autoimmune and autoinflammatory diseases through multiple, interconnected mechanisms. Enhanced NET formation, impaired NET clearance, and interactions with autoantibodies and the complement system appear to represent recurring mechanisms across the included studies. Nevertheless, the heterogeneity of diseases, biomarkers, sample types, detection methods, and study designs limits direct comparison between studies and supports the need for further investigation using standardized approaches.

Table 1. Characteristics of Included Studies

No	Author (Year)	Disease	Study Design	Sample Size	Country	Diagnostic Criteria	Disease Activity Assessment
1	Kmeťová et al. (2023)	Antiphospholipid Syndrome (APS)	Observational case-control study	APS patients (n=40); healthy controls (n=20)	United States	Updated Sapporo Criteria	Clinical manifestations (thrombosis and pregnancy loss) and aPL profile
2	Zuo et al. (2023)	APS and aPL-positive carriers	Multicenter observational cohort study	Patients (n=389; APS=308, aPL carriers=81)	Multinational (North America, South America, Europe)	Updated Sapporo Criteria	Clinical manifestations (thrombosis and pregnancy morbidity) and extra-criteria manifestations including brain lesions

3	Surmiak et al. (2023)	Granulomatosis with Polyangiitis (GPA)	Case-control study	GPA patients (n=42; active=21, remission=21); healthy controls (n=21)	Poland	American College of Rheumatology (ACR) 1990 and 2012 Revised Chapel Hill Nomenclature	BVAS and VDI scores
4	Wang et al. (2021)	Adult-onset Still's Disease (AOSD)	Observational case-control study	AOSD patients (n=164); healthy controls (n=305)	China	Yamaguchi criteria	Modified Pouchot's Score
5	Zuo et al. (2020)	Primary Antiphospholipid Syndrome (PAPS)	Case-control study	PAPS (n=76); SLE non-aPL (n=23); VTE non-aPL (n=11); healthy controls (n=44)	United States	Updated Sapporo Criteria	Clinical manifestations (thrombosis and pregnancy loss)
6	Hu et al. (2020)	Adult-onset Still's Disease (AOSD)	Case-control study with machine learning analysis	AOSD patients (n=66); healthy controls (n=40)	China	Yamaguchi criteria	Systemic score based on Pouchot criteria
7	Perazzio et al. (2017)	Behçet's Disease (BD)	Case-control study	BD patients (n=61; active=30, inactive=31); healthy controls (n=30)	Brazil	International Study Group Criteria for Behçet's Disease	Simplified Behçet's Disease Current Activity Form (sBR-BDCAF)
8	Michailidou et al. (2023)	GPA, MPA, TAK, and GCA	Case-control study (VCRC cohort)	Patients (n=310; GPA=123, MPA=61, TAK=58, GCA=68); healthy controls (n=30)	United States and Canada	American College of Rheumatology (ACR) 1990 and 2012 Revised Chapel Hill Nomenclature	BVAS/PGA for AAV and clinical assessment for LVV
9	Jia et al. (2020)	Adult-onset Still's Disease (AOSD)	Case-control study with machine learning analysis	Training cohort: AOSD (n=40), HC (n=24); validation cohort: AOSD (n=26), HC (n=16)	China	Clinical diagnosis based on exclusion of other diseases	Systemic score, laboratory parameters, and organ involvement evaluation
10	Yoshinari et al. (2022)	Microscopic Polyangiitis (MPA)	Observational study with laboratory-clinical correlation	MPA patients (sample size not clearly specified)	Japan	Clinical diagnosis of ANCA-associated vasculitis	Disease activity comparison based on anti-MYL6 antibody presence

Table 2. Summary of NETs Biomarkers, Detection Methods, and Main Findings

No	Author (Year)	Disease	NETs Biomarkers	Detection Method	Sample Type	Main Findings
1	Kmeťová et al. (2023)	APS	β2GPI-DNA complex, NE-DNA complex	ELISA, immunofluorescence, EMSA	Plasma and isolated neutrophils	β2GPI directly binds to NETs. Increased β2GPI-DNA complex is associated with NET formation and autoimmune activation in APS.

2	Zuo et al. (2023)	APS and aPL-positive carriers	Anti-NET IgG, anti-NET IgM, MPO-DNA complex	ELISA, autoantigen microarray, immunofluorescence	Serum	Anti-NET antibodies increased in ~45% of patients and are associated with complement activation, brain white matter lesions, and impaired NET degradation.
3	Surmiak et al. (2023)	GPA		Fluorometry, qPCR, ELISA, phosphoproteomics	Serum and isolated neutrophils	Active GPA phase shows increased NET biomarkers associated with mTOR inhibition, autophagy activation, and higher BVAS scores.
4	Wang et al. (2021)	AOSD	NET-DNA complex, dsDNA	ELISA, PicoGreen assay, immunofluorescence	Plasma and isolated neutrophils	LIR-A3 expression is significantly increased and correlates with circulating NET-DNA levels and systemic inflammation.
5	Zuo et al. (2020)	Primary APS	Anti-NET IgG, anti-NET IgM, NET degradation activity	ELISA, immunofluorescence microscopy, DNase activity assay	Serum and plasma	PAPS patients show impaired NET degradation associated with increased anti-NET antibodies and complement activation.
6	Hu et al. (2020)	AOSD	cfDNA, NE-DNA, MPO-DNA, citH3-DNA	ELISA and machine learning analysis	Plasma	Circulating NET signature predicts severe organ involvement and steroid resistance with high accuracy.
7	Perazzio et al. (2017)	Behçet's Disease	Histone H2A/B, neutrophil elastase, chromatin	Immunofluorescence microscopy	Isolated neutrophils and plasma	NET release is significantly increased during active disease and is associated with elevated sCD40L and ROS production.
8	Michailidou et al. (2023)	GPA, MPA, TAK, GCA	NE-DNA complex, anti-NET IgG, anti-histone antibodies	ELISA and immunofluorescence microscopy	Plasma	Increased NET biomarkers and impaired NET degradation are observed across multiple vasculitis subtypes.
9	Jia et al. (2020)	AOSD	cfDNA, MPO-DNA, NE-DNA, citH3-DNA	ELISA and machine learning analysis	Plasma	Increased NET biomarkers correlate with disease activity, cytokine levels, organ involvement, and glucocorticoid resistance.
10	Yoshinari et al. (2022)	MPA	NET formation and anti-MYL6 antibodies	Fluorescence staining and ELISA	Serum and neutrophils	Anti-MYL6 antibodies inhibit NET formation and are associated with lower disease activity.

The synthesis of 10 studies indicates that NET dysregulation is associated with several rare autoimmune and autoinflammatory diseases. Despite differences in disease characteristics, study populations, biomarkers, and analytical methods, the included studies consistently identified three major patterns: enhanced NET formation (NETosis), impaired NET clearance, and interactions between NETs and other immune components, particularly the complement system. Together, these findings support a potential role for dysregulated NET dynamics in sustaining inflammation and contributing to autoimmune and autoinflammatory processes (Goel et al., 2021; Papayannopoulos, 2018).

Increased NETosis and Inflammatory Activation

Most included studies reported increased NET formation during active disease, particularly in antiphospholipid syndrome (APS), granulomatosis with polyangiitis (GPA), adult-onset Still's disease (AOSD), and Behçet's disease. This increase was reflected by elevated NET-related biomarkers, including MPO-DNA, NE-DNA, citH3-DNA, dsDNA, and other DNA-

protein complexes in patient samples (Surmiak et al., 2023; Wang et al., 2021; Perazzio et al., 2017).

In APS, increased β2GPI-DNA complexes and anti-NET antibodies suggest that NET-associated components may contribute to autoimmune activation. NETs can provide extracellular sources of nuclear and neutrophil-derived antigens that may participate in immune complex formation and sustained immune responses (Kmeťová et al., 2023; Zuo et al., 2020). These findings are consistent with the broader concept that NET-derived material can function as an immunogenic source capable of engaging both innate and adaptive immune pathways (Papayannopoulos, 2018).

In GPA and ANCA-associated vasculitis, increased NET-related biomarkers have been associated with disease activity and BVAS scores. Surmiak et al. (2023) further reported an association between NETosis-related changes and mTOR inhibition and increased neutrophil autophagy in GPA. These findings suggest that NET formation may be regulated by disease-specific intracellular pathways rather than representing a uniform process across all autoimmune and autoinflammatory diseases.

In AOSD, elevated NET-related biomarkers have been associated with systemic inflammation, increased proinflammatory cytokine levels, organ involvement, and treatment response. Hu et al. (2020) and Jia et al. (2020) reported that NET-related biomarker profiles were associated with severe disease manifestations and glucocorticoid resistance. These findings indicate that NET-associated biomarkers may have potential value for disease stratification, although their clinical utility requires validation in larger and independent cohorts.

Across the included studies, NETosis was assessed using different biomarkers and analytical approaches. This methodological heterogeneity limits direct comparison between studies and may partly explain differences in the reported magnitude and clinical associations of NET-related abnormalities. Therefore, the current evidence does not support the use of a single NET biomarker as a standardized clinical measure (Goel et al., 2021).

Impaired NET Degradation and Persistent Inflammation

The included studies also indicate that NET dysregulation may involve impaired clearance in addition to increased NET formation. Evidence from APS and ANCA-associated vasculitis suggests that reduced NET degradation can result in the persistence of extracellular DNA and NET-associated components, potentially prolonging inflammatory and autoimmune responses (Zuo et al., 2020; Michailidou et al., 2023).

In primary APS, increased anti-NET IgG and IgM responses were associated with impaired NET degradation (Zuo et al., 2020). These findings support the concept of dysregulated NET dynamics, in which abnormalities occur at both the formation and clearance stages. Persistent NET material may increase exposure to self-antigens and provide a sustained stimulus for immune activation.

NET clearance may also interact with the complement system. In APS, impaired NET degradation has been associated with complement activation, including changes in complement components and deposition of complement-derived products on NET structures (Leffler et al., 2012; Zuo et al., 2023). These findings suggest a potential reciprocal relationship in which persistent NETs and complement activation may reinforce inflammatory responses.

However, the available evidence remains insufficient to establish whether impaired NET degradation directly drives disease progression. Most available studies are observational and involve relatively small or disease-specific cohorts, which limits causal inference. In addition, differences in NET degradation assays and disease activity measurements make quantitative comparison between studies difficult.

Interaction of NETs with the Immune System and Tissue Damage

The synthesis indicates that NETs interact with multiple components of the immune system, including proinflammatory cytokines, reactive oxygen species (ROS), autoantibodies, and the complement system. These interactions may amplify inflammatory signaling and contribute to persistent tissue injury (Papayannopoulos, 2018; Goel et al., 2021).

In Behçet's disease, increased NET release was associated with elevated sCD40L concentrations and ROS production, suggesting an interaction between NET formation and inflammatory or oxidative pathways (Perazzio et al., 2017). In ANCA-associated vasculitis, increased NET-related biomarkers and impaired NET degradation have also been reported together with anti-NET and anti-histone antibody responses (Michailidou et al., 2023). Rather than describing these antibodies as directly "attacking" NETs, their presence may reflect an immune response to persistent NET-derived material and, in some contexts, may interfere with NET clearance.

The interaction between NETs and complement is particularly relevant to the potential amplification of inflammation. NET formation can expose extracellular DNA, histones, and other molecular components that interact with immune pathways, while complement activation may further promote inflammatory responses. This reciprocal relationship provides a

plausible mechanism through which NET dysregulation could contribute to persistent inflammation and tissue damage (Goel et al., 2021; Papayannopoulos, 2018).

Although core NET-related mechanisms appear to recur across several diseases, their clinical and pathological consequences may differ according to disease-specific immune environments. This variation suggests that NET-targeted interventions may require disease-specific approaches rather than a uniform therapeutic strategy.

Critical Analysis and Research Gaps

The findings support an association between NET dysregulation and the immunopathology of several rare autoimmune and autoinflammatory diseases. However, the current evidence does not establish NETs as a primary cause of disease progression. Most included studies used observational or case-control designs, which are useful for identifying associations but provide limited evidence of causality.

Two major challenges were identified in the current evidence base on Limited study populations and Methodological heterogeneity**.** Rare autoimmune and autoinflammatory diseases are characterized by relatively small patient populations, resulting in limited sample sizes in many of the included studies. Small cohorts reduce statistical power and may limit the generalizability of findings across different populations and disease stages.

Studies used different approaches to assess NET formation and degradation, including ELISA, immunofluorescence, qPCR, DNA-based assays, and other analytical methods. Differences in biomarkers, sample types, laboratory procedures, and outcome definitions complicate direct comparison and prevent the establishment of a standardized NET biomarker for routine clinical use (Goel et al., 2021; Papayannopoulos, 2018).

Longitudinal and translational studies are needed to determine whether NET-related abnormalities precede disease progression, reflect disease activity, or emerge as consequences of ongoing inflammation. Further research should also evaluate whether NET-related biomarkers can improve disease stratification, predict treatment response, or serve as clinically actionable therapeutic targets.

Overall, the available evidence supports NETs as an important component of the immunopathological network in rare autoimmune and autoinflammatory diseases. However, the transition from mechanistic evidence to clinical application requires larger multicenter cohorts, standardized NET measurement protocols, longitudinal designs, and experimental or translational studies that can clarify causal mechanisms and therapeutic relevance.

Conclusion

This scoping review indicates that NET dysregulation is associated with the immunopathology of rare autoimmune and autoinflammatory diseases through three major mechanisms: enhanced NETosis, impaired NET clearance, and interactions with other immune components, particularly the complement system. These mechanisms may collectively contribute to chronic inflammation, autoantigen exposure, and sustained immune activation, thereby contributing to tissue injury across multiple rare autoimmune and autoinflammatory diseases. Across APS, GPA, AOSD, and Behçet's disease, increased NET-related biomarkers were associated with disease activity, systemic inflammation, and organ involvement.

The findings also highlight the need for standardization of NET biomarkers, sample types, and detection methods to improve comparability across studies and support future clinical application. Because the current evidence is predominantly based on observational studies with heterogeneous methodologies and relatively limited sample sizes, longitudinal, translational, and clinical studies are needed to clarify the causal role of NETs and evaluate their potential as diagnostic, prognostic, and therapeutic targets. These efforts may support the development of more specific and evidence-based strategies for the management of rare autoimmune and autoinflammatory diseases.

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