Neutrophil Extracellular Traps in Dermatology and Autoimmune Diseases: A Survey

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Abstract

Neutrophil extracellular traps (NETs) are web-like structures released by neutrophils, playing a pivotal role in immune defense by trapping pathogens. However, their dysregulation is implicated in the pathogenesis of inflammatory and autoimmune diseases, particularly in dermatology. This survey explores the dual role of NETs in immunity and pathology, highlighting their involvement in skin conditions like psoriasis and systemic lupus erythematosus (SLE), where they contribute to chronic inflammation and tissue damage. The survey delves into the mechanisms of NET formation, including NADPH oxidase-dependent and independent pathways, and their triggers, such as reactive oxygen species. It also examines the potential of NETs as diagnostic markers and therapeutic targets, with current research focusing on modulating NET formation and promoting their clearance to mitigate tissue damage. The role of NETs in COVID-19 and their contribution to severe inflammatory responses and thrombotic complications is also discussed. Future research should prioritize understanding the molecular mechanisms of NET dysregulation and developing targeted therapies that balance their protective and pathological roles. By advancing our knowledge of NETs, we can improve therapeutic strategies for managing inflammatory and autoimmune diseases, enhancing patient outcomes and quality of life.

1 Introduction

1.1 Concept of Neutrophil Extracellular Traps (NETs)

Neutrophil extracellular traps (NETs) are complex structures formed by activated neutrophils, composed of chromatin and antimicrobial proteins. These traps function as a defense mechanism, immobilizing and neutralizing pathogens to prevent their spread within the host. NET formation, known as NETosis, occurs via three distinct pathways: classic suicidal NET formation, vital NET formation, and mitochondrial DNA NET formation, each with unique biological implications, particularly in wound healing [1].

Classic suicidal NET formation leads to neutrophil lysis and the release of nuclear chromatin, while vital NET formation allows neutrophils to remain viable, maintaining their phagocytic and chemotactic functions. Mitochondrial DNA NET formation, a less prevalent pathway, involves the release of mitochondrial DNA, underscoring neutrophils' versatility in response to various stimuli [2].

Beyond pathogen capture, NETs modulate the immune response, influencing both innate and adaptive immunity. They activate dendritic cells and stimulate pro-inflammatory cytokine production, amplifying inflammatory responses. Antimicrobial proteins associated with NETs, such as neutrophil elastase and myeloperoxidase, enhance their pathogen-neutralizing capacity [2]. However, dysregulated NET formation can lead to tissue damage and contribute to inflammatory and autoimmune diseases, highlighting their dual role in host defense and tissue injury [1].

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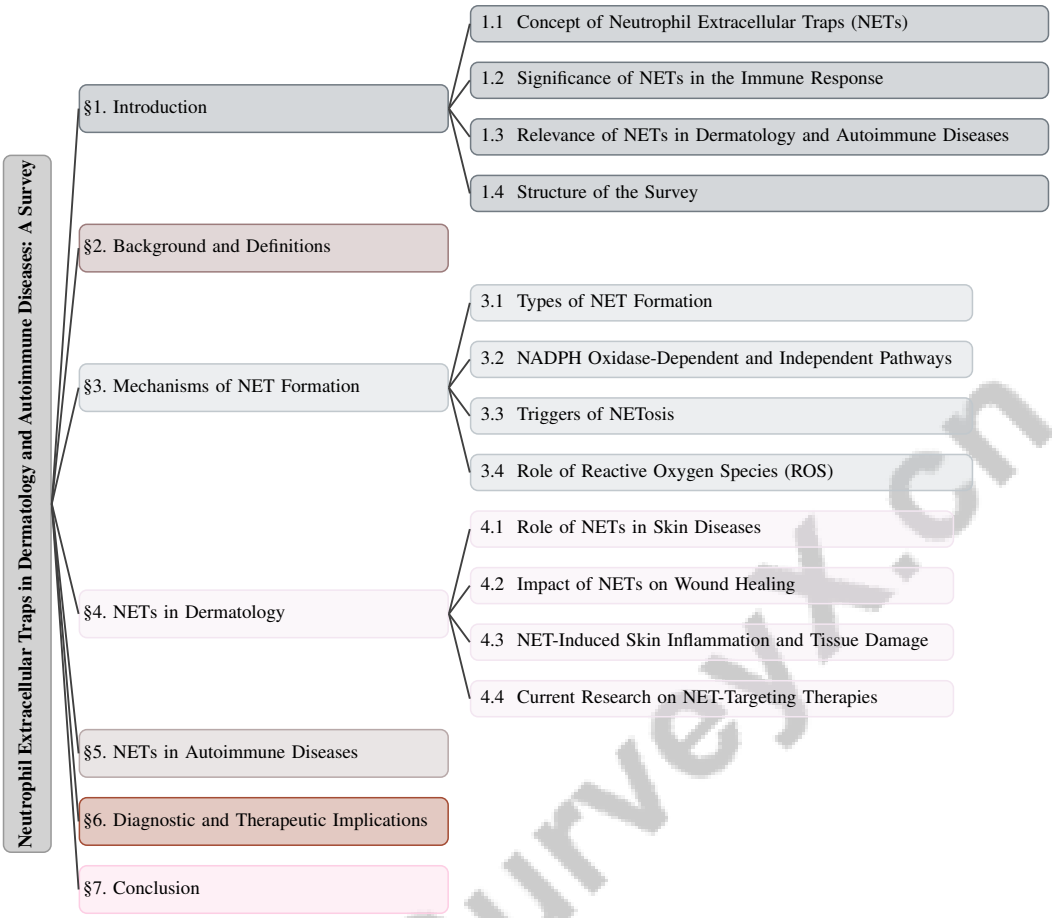

Figure 1: chapter structure

1.2 Significance of NETs in the Immune Response

NETs play a crucial role in the immune system, exhibiting both protective and pathological effects. Primarily, they trap and neutralize pathogens, creating a physical barrier that facilitates clearance by other immune cells, thereby maintaining host integrity against infections [3]. However, NETs also contribute to inflammation and tissue damage, especially when their formation is dysregulated. In severe infections, such as COVID-19, excessive NET formation is associated with exacerbated inflammatory responses and tissue injury [4]. This highlights the complex role of NETs in promoting immune defense while also contributing to pathological conditions.

The activation of neutrophils and subsequent NET release enhance pro-inflammatory functions, potentially leading to collateral tissue damage if not properly regulated. Thus, the balance between the protective and harmful effects of NETs is crucial in determining their overall impact on health and disease [3].

1.3 Relevance of NETs in Dermatology and Autoimmune Diseases

NETs have emerged as significant factors in the pathogenesis of dermatological and autoimmune diseases, extending their role beyond antimicrobial defense. In dermatology, NETs are implicated in skin conditions such as psoriasis and lupus erythematosus, contributing to chronic inflammation and tissue damage. In psoriasis, NETs recruit immune cells and perpetuate inflammatory cycles, exacerbating skin pathology [1]. In systemic lupus erythematosus (SLE), NETs facilitate autoantibody formation by exposing nuclear and cytoplasmic antigens that drive autoimmunity [2].

Dysregulated NET formation is a critical factor in autoimmune disease pathogenesis, stimulating type I interferon production, which amplifies autoimmune responses. This is particularly evident in

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conditions like rheumatoid arthritis and SLE, where excessive NET formation correlates with disease severity [3]. The persistent presence of NETs in tissues not only maintains inflammation but also disrupts immune tolerance, leading to sustained autoimmune activity.

Moreover, NETs are potential biomarkers and therapeutic targets in dermatological and autoimmune diseases. Their presence in the bloodstream and tissues can indicate disease activity and severity, offering valuable diagnostic tools [4]. Therapeutic strategies aimed at modulating NET formation or enhancing their clearance may mitigate tissue damage and improve clinical outcomes for affected patients.

1.4 Structure of the Survey

This survey is structured to provide a comprehensive examination of the role of NETs in dermatology and autoimmune diseases. The **Introduction** elucidates the concept of NETs, their formation, and their dual role in pathogen defense and tissue damage, establishing the foundation for understanding their broader implications in immune responses and relevance to dermatological and autoimmune conditions.

The **Background and Definitions** section explores NET formation mechanisms and biological functions, defining key terms such as NETosis, immunity, pathogenesis, and inflammation. This foundational knowledge is essential for grasping subsequent discussions on NETs' role in disease pathogenesis.

In the section titled , the authors examine the cellular and molecular mechanisms underlying NET formation, distinguishing between NADPH oxidase-dependent and independent pathways, and detailing how various triggers and regulatory pathways contribute to NETosis. The review emphasizes the critical role of reactive oxygen species (ROS) in these processes, illustrating their dual function in promoting antimicrobial defense and potentially exacerbating inflammatory responses, complicating conditions such as wound healing [3, 1].

The section on **NETs in Dermatology** analyzes NET involvement in skin diseases, their impact on wound healing, and their contribution to skin inflammation and tissue damage. It reviews current research on NET-targeting therapies in dermatology, highlighting the therapeutic potential of modulating NET activity.

Subsequently, **NETs in Autoimmune Diseases** discusses NET contributions to autoimmune pathogenesis, examining dysregulation, immunothrombosis, and pro-inflammatory functions. This section also explores the diagnostic and therapeutic implications of NETs in autoimmune disorders.

The survey concludes with a discussion on **Diagnostic and Therapeutic Implications**, evaluating the potential of NETs as diagnostic markers and therapeutic targets. The review analyzes contemporary strategies aimed at targeting NETs, highlighting various pharmacological interventions. It also addresses the significant role of NETs in COVID-19 pathophysiology, detailing their contributions to immunothrombosis and inflammatory responses, as well as their involvement in exacerbating disease severity and complications associated with the virus [3, 4, 1, 2, 5].

Finally, the **Conclusion** summarizes key findings, emphasizing NETs' dual role in immunity and pathology, and discussing the potential for NET-targeted therapies to enhance disease outcomes. The survey identifies critical gaps in current knowledge, underscoring the need for further investigation into NETs' role in dermatological conditions and autoimmune diseases, where excessive NET formation is linked to exacerbated inflammation, impaired wound healing, and the pathogenesis of various inflammatory disorders [3, 2, 1].The following sections are organized as shown in Figure 1.

2 Background and Definitions

2.1 Formation and Biological Functions of NETs

Neutrophil extracellular traps (NETs) are critical components of the immune response, formed through NETosis, resulting in the release of chromatin and antimicrobial proteins. NETosis occurs via classic (suicidal) and vital pathways. Classic NETosis involves neutrophil lysis and nuclear chromatin release, whereas vital NETosis preserves neutrophil viability, allowing continued phagocytic and

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chemotactic functions [2]. This adaptability underscores the complexity of neutrophil responses to diverse pathogenic challenges.

Beyond pathogen entrapment, NETs modulate immune responses by activating dendritic cells and promoting pro-inflammatory cytokine production, which enhances pathogen clearance. However, dysregulated NET formation can lead to tissue damage and contribute to inflammatory and autoimmune diseases [1]. In wound healing, NETs initially defend against microbes but excessive formation can impede healing by exacerbating inflammation [1]. Understanding NETs' dual roles in protection and pathology is crucial for developing therapeutic strategies that leverage their benefits while mitigating harmful effects.

2.2 Role of NETs in the Immune System

NETs enhance neutrophil functions during inflammation by trapping and neutralizing pathogens, aiding in infection containment and clearance by immune cells [3]. They activate dendritic cells and macrophages, promoting pro-inflammatory cytokine production and recruiting immune cells to infection sites [2]. This underscores NETs' role in bridging innate and adaptive immunity.

However, NETs can also contribute to disease pathogenesis, particularly in inflammatory and autoimmune conditions. Dysregulated formation leads to excessive inflammation and tissue damage, as seen in systemic lupus erythematosus and rheumatoid arthritis. Understanding the signaling pathways of NET formation is crucial for therapeutic advancements [2]. Addressing this gap is essential for developing strategies to modulate NET activity, mitigating pathological effects while preserving immune defense roles.

2.3 NETs in Disease Pathogenesis

NETs play a significant role in disease pathogenesis through inflammation and tissue damage. While essential for pathogen defense, dysregulation can exacerbate conditions, particularly in autoimmune diseases where NETs drive autoantibody production and chronic inflammation [4].

In COVID-19, NETs contribute to immunothrombosis and organ damage, with excessive formation correlating with severe inflammatory responses and thrombotic complications [4]. This duality illustrates how protective functions can become detrimental when regulation fails.

NETs also influence cardiovascular disease by promoting endothelial dysfunction and atherosclerotic plaque formation, enhancing thrombus formation through platelet interaction. This highlights their role in disease progression, as they modulate inflammatory responses, which can either enhance antimicrobial defense or contribute to chronic inflammation and impaired wound healing [3, 1].

Understanding NETs' contribution to disease pathogenesis is crucial for developing targeted interventions. Strategies to modulate NET formation or promote clearance could mitigate harmful effects while preserving immune defense roles. Balancing NETs' beneficial and detrimental effects is key to improving clinical outcomes in diseases characterized by excessive inflammation, such as COVID-19 and delayed wound healing [3, 4, 1, 2, 5].

In recent years, the understanding of neutrophil extracellular traps (NETs) has significantly evolved, revealing intricate mechanisms underlying their formation and function. This review aims to elucidate these mechanisms, particularly focusing on the various types of NETosis and the pathways that lead to their formation. As illustrated in Figure 2, the figure categorizes NET formation into three distinct types: classic suicidal NETosis, vital NETosis, and mitochondrial DNA NET formation. Each category is accompanied by a comprehensive overview of the pathways and triggers that initiate these processes. Furthermore, the figure emphasizes the dual role of reactive oxygen species (ROS) in regulating NET formation, highlighting its critical impact on immune responses. By integrating these visual elements with the narrative, we can better appreciate the complexity and significance of NET formation in the immune system.

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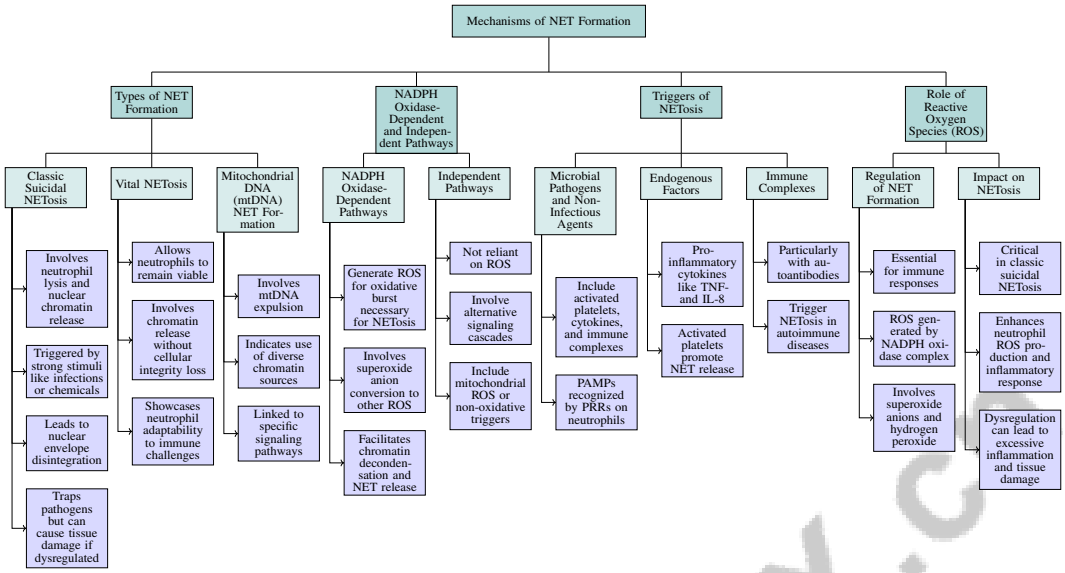

Figure 2: This figure illustrates the mechanisms of NET formation, including the types of NETosis, pathways involved, triggers, and the role of reactive oxygen species (ROS). It categorizes NET formation into classic suicidal NETosis, vital NETosis, and mitochondrial DNA NET formation, detailing the pathways and triggers that initiate these processes. Additionally, it highlights the dual role of ROS in regulating NET formation and its impact on immune responses.

3 Mechanisms of NET Formation

3.1 Types of NET Formation

Neutrophil extracellular traps (NETs) form through chromatin decondensation and antimicrobial protein release, reflecting neutrophils' multifaceted immune roles. This process, initiated by reactive oxygen species (ROS) from NADPH oxidase, is crucial for pathogen capture and immune modulation but can lead to chronic inflammation and is linked to inflammatory and autoimmune diseases and wound healing complications [3, 2, 1]. NET formation occurs via classic suicidal NETosis, vital NETosis, and mitochondrial DNA (mtDNA) NET formation, each representing unique neutrophil responses to stimuli, contributing to defense and pathology. Figure 3 illustrates these three primary types of NET formation, emphasizing the distinct neutrophil responses and their roles in pathogen defense and immune regulation.

Classic suicidal NETosis involves neutrophil lysis and nuclear chromatin release, triggered by strong stimuli like infections or chemicals, leading to nuclear envelope disintegration and mixing of cellular components. This structure traps pathogens but can cause tissue damage if dysregulated [2].

Vital NETosis, in contrast, allows neutrophils to remain viable, performing functions like phagocytosis and chemotaxis. This non-lytic process involves chromatin release without cellular integrity loss, showcasing neutrophil adaptability to immune challenges while preserving functionality [2].

Mitochondrial DNA NET formation, though less common, involves mtDNA expulsion, indicating neutrophils' use of diverse chromatin sources in response to stimuli, suggesting a specialized mtDNA role in immune contexts, linked to specific signaling pathways [2].

Understanding these NET formation types is crucial for developing therapies that modulate NET activity, leveraging protective roles against infections while minimizing detrimental effects, such as exacerbating inflammation and impairing wound healing. By elucidating NETs' dual nature, researchers can balance antimicrobial functions with potential tissue damage, enhancing clinical outcomes in patients with inflammatory diseases [3, 2, 1].

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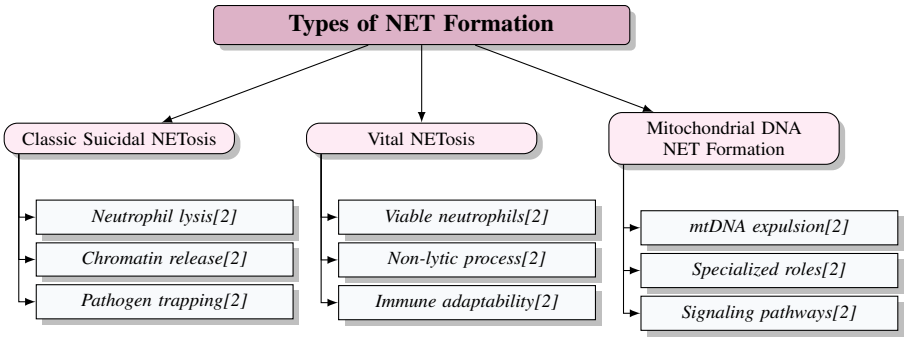

Figure 3: This figure illustrates the three primary types of neutrophil extracellular trap (NET) formation: classic suicidal NETosis, vital NETosis, and mitochondrial DNA NET formation. Each type represents distinct neutrophil responses, highlighting their roles in pathogen defense and immune regulation.

3.2 NADPH Oxidase-Dependent and Independent Pathways

NET formation involves NADPH oxidase-dependent and independent pathways, both crucial for immune responses. NADPH oxidase-dependent pathways generate ROS, initiating the oxidative burst necessary for NETosis, involving superoxide anion conversion to other ROS like hydrogen peroxide and hypochlorous acid, facilitating chromatin decondensation and NET release [2].

Independent pathways, not reliant on ROS, involve alternative signaling cascades, including mitochondrial ROS or non-oxidative triggers. For instance, mtDNA NET formation is an independent pathway, releasing mtDNA in response to stimuli like lipopolysaccharides or cytokines [2].

These pathways reflect neutrophils' adaptability to pathogenic challenges and the need for precise NET formation regulation. Dysregulation can lead to excessive NET production, contributing to tissue damage and exacerbating inflammatory and autoimmune diseases. Understanding these pathways is essential for developing therapies that modulate NET formation, mitigating pathological effects while preserving defense roles [1].

3.3 Triggers of NETosis

NETosis, the process of NET release, is triggered by diverse stimuli, including microbial pathogens and non-infectious agents like activated platelets, cytokines, and immune complexes. Pathogen-associated molecular patterns (PAMPs), such as bacterial lipopolysaccharides (LPS), are recognized by pattern recognition receptors (PRRs) on neutrophils, leading to NET release [3].

Endogenous factors also trigger NET formation; pro-inflammatory cytokines like TNF- and IL-8 stimulate NETosis, with elevated levels observed in inflammatory and autoimmune diseases, linking chronic inflammation to dysregulated NET formation [4]. Activated platelets can also promote NET release through neutrophil receptor interactions [4].

Immune complexes, particularly those with autoantibodies, trigger NETosis. In autoimmune diseases like systemic lupus erythematosus, these complexes activate neutrophils, leading to excessive NET production and contributing to disease pathogenesis [3]. This interplay between NETs and the immune system shows how mechanisms protecting against infections can drive autoimmunity and inflammation.

Understanding NETosis triggers is essential for developing therapies to modulate this process, especially in diseases like COVID-19, where excessive NET formation contributes to immunothrombosis and organ dysfunction. Elucidating NETosis mechanisms, including pro-inflammatory mediators and neutrophil subtypes, can identify therapeutic strategies to mitigate harmful effects [3, 4, 1, 2, 5].

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3.4 Role of Reactive Oxygen Species (ROS)

Reactive oxygen species (ROS) are crucial in regulating NET formation, essential for immune responses. ROS, including superoxide anions and hydrogen peroxide, are generated by the NADPH oxidase complex during the oxidative burst in activated neutrophils [3].

ROS production is critical in classic suicidal NETosis, where the oxidative burst disrupts the nuclear envelope, facilitating chromatin release. This process involves neutrophil elastase and myeloperoxidase activation, translocating to the nucleus and aiding chromatin decondensation [3]. The resulting NETs trap and neutralize pathogens, aiding clearance by immune cells.

Furthermore, exposure to NETs enhances neutrophil ROS production, exocytosis, phagocytosis, and cytokine secretion, creating a feedback loop amplifying the inflammatory response [3]. While crucial for pathogen clearance, dysregulation can lead to excessive inflammation and tissue damage, contributing to inflammatory and autoimmune diseases.

ROS's dual role in enhancing defense while promoting damage underscores the need for precise NET formation regulation, as excessive NETs can exacerbate inflammation and impede healing, especially in prolonged inflammation conditions [2, 1]. Understanding ROS production pathways and their role in NETosis is vital for developing therapies to modulate this process, targeting ROS-generating components to mitigate harmful effects while preserving defense functions.

4 NETs in Dermatology

4.1 Role of NETs in Skin Diseases

Neutrophil extracellular traps (NETs) are pivotal in the pathogenesis of various skin diseases, especially inflammatory and autoimmune disorders. NETs, composed of decondensed chromatin and antimicrobial proteins, are released by activated neutrophils to trap and neutralize pathogens, thus preventing their spread. This process activates proinflammatory functions and modulates immune cells like macrophages and T cells, amplifying inflammation during infections [3, 2]. However, dysregulated NET formation can exacerbate inflammation and tissue damage in skin diseases.

In psoriasis, NETs sustain inflammatory cycles, recruiting and activating immune cells such as dendritic cells and T cells, which intensify the inflammatory response and contribute to the formation of erythematous plaques and scaling [1]. Similarly, in autoimmune diseases like systemic lupus erythematosus (SLE), NETs release nuclear and cytoplasmic antigens during NETosis, facilitating autoantibody formation and sustaining autoimmune responses [2].

As illustrated in Figure 4, which highlights the role of NETs in various skin diseases, these structures are integral to understanding the interplay between inflammation and autoimmunity. The figure emphasizes the importance of comprehending NET regulation and function for therapeutic development, particularly in conditions where their dysregulation leads to chronic inflammation and tissue damage. Conditions like hidradenitis suppurativa and atopic dermatitis exemplify this, where excessive NET production releases cytotoxic molecules, exacerbating injury and hindering inflammation resolution [1]. Understanding the balance between NETs' protective and pathological roles is crucial, as their dysregulation can lead to significant tissue damage and impaired wound healing, particularly in conditions such as COVID-19. Insights into NET regulation and function in skin diseases are essential for developing therapies that mitigate harmful effects while preserving protective roles [3, 2, 5, 1].

4.2 Impact of NETs on Wound Healing

NETs have a dual role in wound healing, facilitating pathogen clearance while potentially impeding tissue repair. They are crucial in the initial immune response at wound sites, trapping and neutralizing pathogens to promote a sterile environment for repair, with antimicrobial proteins like neutrophil elastase and myeloperoxidase being vital [1]. However, excessive NET formation can prolong inflammation, hindering healing, especially in chronic wounds such as those associated with diabetes. Persistent NETs exacerbate tissue damage and delay closure due to cytotoxic molecules like proteases and oxidizing agents that damage surrounding tissue and impede inflammation resolution [1].

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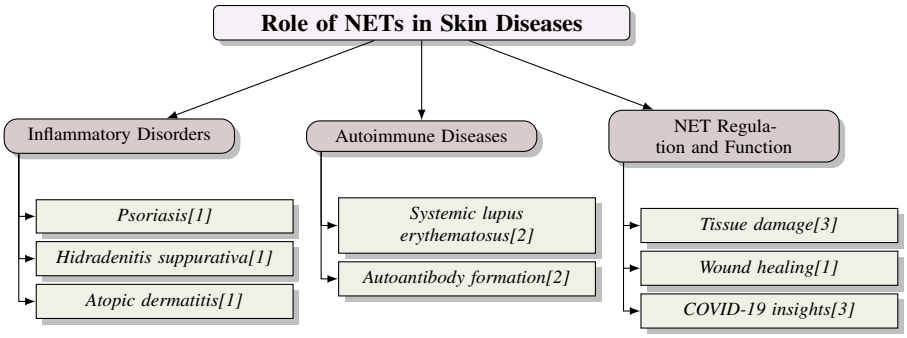

Figure 4: This figure illustrates the role of neutrophil extracellular traps (NETs) in various skin diseases, highlighting their involvement in inflammatory and autoimmune disorders, and emphasizing the importance of understanding NET regulation and function for therapeutic development.

Maintaining a balance between NETs' protective and pathological roles is vital. Understanding their regulation and clearance mechanisms is crucial for developing therapeutic strategies that promote efficient repair while minimizing detrimental effects. Targeting pathways involved in NETosis or enhancing NET clearance may facilitate inflammation resolution and promote healing [1].

4.3 NET-Induced Skin Inflammation and Tissue Damage

NETs mediate inflammatory responses and contribute to tissue damage in various skin conditions. While essential for pathogen defense, dysregulated NET production can lead to excessive inflammation, impair healing, and exacerbate damage, particularly in diabetes and severe infections like COVID-19. Excessive NET formation is linked to prolonged inflammation, disrupting cellular functions, wound architecture, and angiogenesis, contributing to inflammatory and autoimmune diseases [3, 2, 5, 1]. This dual role is evident in chronic inflammatory conditions such as psoriasis and lupus erythematosus.

In psoriasis, NETs contribute to inflammation by releasing chromatin structures with antimicrobial proteins like neutrophil elastase and myeloperoxidase, degrading extracellular matrix components and exacerbating damage [1]. Persistent NETs in lesions lead to continuous immune cell recruitment and activation, sustaining inflammation and disease chronicity [2].

In autoimmune diseases like SLE, NETs expose antigens that trigger autoantibody production [3]. The persistence of these autoantigens forms immune complexes, further driving inflammation and damage. Balancing NETs' protective and pathological roles is critical to mitigating their contribution to chronic inflammatory and autoimmune conditions [1].

Research focuses on developing therapeutic strategies targeting NETs to mitigate harmful effects while preserving protective functions, including pharmacological agents that inhibit formation or promote clearance, offering potential for improving outcomes in dermatological and autoimmune diseases [4]. Understanding mechanisms underlying NET-induced inflammation and damage is crucial for developing effective therapies.

4.4 Current Research on NET-Targeting Therapies

Advances in understanding NETs have spurred interest in developing therapies to modulate their formation and function, particularly in dermatological disorders where excessive formation exacerbates inflammation and impairs healing. Research highlights NETs' dual nature: defending against pathogens while contributing to inflammatory processes. Thus, targeting NETs may improve outcomes in skin-related conditions [3, 2, 1].

In psoriasis, NETs promote keratinocyte activation and immune cell recruitment to lesions [1], prompting exploration of therapies to mitigate inflammation and improve outcomes. One approach uses DNase to degrade extracellular DNA, facilitating NET clearance from inflamed tissues [4].

In SLE, NETs expose antigens, triggering autoantibody production and promoting lupus nephritis [2]. This role has led to investigations into strategies targeting formation or enhancing clearance,

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including agents inhibiting NET-associated enzymes like neutrophil elastase to reduce damage and inflammation [1].

Research also explores targeting signaling pathways in NETosis, such as NADPH oxidase-dependent and independent pathways, to prevent excessive formation and mitigate pro-inflammatory effects. Modulating these pathways could manage dermatological conditions arising from dysregulated activity, addressing inflammation and impaired healing in psoriasis and other disorders, improving outcomes and quality of life [3, 4, 1, 2, 5].

While still in early stages, NET-targeting therapies in dermatology show promise. By reducing excessive formation or enhancing clearance, these therapies could offer a novel approach to treating inflammatory skin diseases, improving outcomes and quality of life. Further research is essential to elucidate mechanisms governing formation, promoting defense while contributing to pathological inflammation. Understanding these mechanisms will aid in developing interventions to mitigate detrimental effects of excessive formation—such as impaired healing and exacerbated inflammation—while preserving crucial functions in pathogen capture and immune modulation. This knowledge is vital for addressing autoimmune diseases and chronic wounds, where dysregulated activity is implicated [3, 2, 1].

5 NETs in Autoimmune Diseases

5.1 Dysregulation of NETs in Autoimmune Diseases

Neutrophil extracellular traps (NETs) are crucial in innate immunity, primarily trapping pathogens. However, their dysregulation significantly contributes to autoimmune diseases like systemic lupus erythematosus (SLE) and rheumatoid arthritis, where excessive NET production leads to chronic inflammation and autoimmunity by exposing nuclear and cytoplasmic antigens, thus facilitating autoantibody generation [4]. The multifactorial mechanisms underlying NET dysregulation involve the overproduction of reactive oxygen species (ROS), which, while essential for NETosis, can lead to uncontrolled NET formation, tissue damage, and sustained inflammatory cycles, particularly problematic in autoimmune diseases where self-antigens become targets [2, 3]. Studies show that NETs expose antigens during autoimmune responses, triggering autoantibody production and disrupting immune tolerance. In SLE, excessive NET formation correlates with immune complex deposition, exacerbating disease severity and complications like nephritis and vasculitis. Understanding these mechanisms is vital for developing therapies that address NET overproduction while preserving their immune defense roles [4].

5.2 NETs and Immunothrombosis

NETs play a pivotal role in immunothrombosis, the interaction between innate immunity and thrombosis, which is particularly relevant in autoimmune diseases. Dysregulated NET formation exacerbates immunothrombosis, contributing to disease pathogenesis by serving as scaffolds for platelet adhesion and aggregation, thereby promoting thrombus formation [4]. The DNA framework of NETs, combined with histones and granular proteins, activates the coagulation cascade, leading to fibrin deposition and thrombus stabilization. In conditions like SLE and rheumatoid arthritis, excessive NET formation is linked to increased thrombosis risk, as NET release causes vascular damage and endothelial activation, creating a pro-thrombotic environment. The interaction between NETs and platelets further amplifies this process, with NETs activating platelets to release pro-coagulant factors, forming dense fibrin networks [3]. The dual role of NETs in host defense and disease pathogenesis necessitates understanding their regulatory mechanisms to develop therapies that mitigate pathological effects while preserving protective functions [2, 1].

5.3 Proinflammatory Functions of NETs

NETs significantly contribute to autoimmune disease pathogenesis through their proinflammatory functions. While primarily a defense mechanism, dysregulated NET formation can lead to excessive inflammation and tissue damage. In diseases like SLE and rheumatoid arthritis, excessive NET formation exacerbates disease severity by enhancing pro-inflammatory responses and sustaining chronic inflammation, resulting in complications and organ dysfunction [4, 3]. NETs expose nuclear and cytoplasmic antigens, triggering autoantibody production and perpetuating autoimmune responses.

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In SLE, NETs contain autoantigens that lead to immune complex formation, causing inflammation and organ damage [4]. Moreover, NETs activate immune cells like dendritic cells, promoting cytokine production and recruiting additional immune cells, creating a cycle of inflammation and damage [2]. Infections like COVID-19 show that excessive NET formation associates with severe inflammatory responses and immunothrombosis, leading to multi-organ failure [4]. ROS are critical in regulating NETosis, essential for NADPH oxidase-dependent pathways, although NETs can also form through NADPH oxidase-independent pathways, highlighting the need for further research into their complex regulation [3].

6 Diagnostic and Therapeutic Implications

6.1 NETs as Diagnostic Markers

Neutrophil extracellular traps (NETs) are pivotal in the pathophysiology of numerous inflammatory and autoimmune diseases, establishing them as potential diagnostic markers. Their presence in biological samples offers insights into inflammatory processes and disease progression in conditions like autoimmune diseases, cardiovascular disorders, and severe infections such as COVID-19. Comprising decondensed chromatin and antimicrobial proteins, NETs bolster immune responses while possibly exacerbating pathological inflammation and tissue damage. Elevated NET levels correlate with disease severity, making them valuable biomarkers for monitoring disease activity and guiding therapeutic interventions [3, 4, 1, 2, 5]. In systemic lupus erythematosus (SLE), increased NET levels during flares highlight their utility for disease monitoring.

Detection of NET components, including cell-free DNA, histones, and neutrophil elastase, serves as a diagnostic tool for identifying active disease or assessing complication risks. High circulating NET levels correlate with increased disease activity in SLE, rheumatoid arthritis, and other autoimmune disorders, suggesting their potential as biomarkers for tracking disease progression and evaluating therapeutic responses. This non-invasive approach enables clinicians to tailor treatment plans and predict patient outcomes more effectively. Furthermore, excessive NET formation can worsen conditions like delayed wound healing and various autoimmune diseases, underscoring their dual role in monitoring and therapeutic interventions [3, 2, 1].

6.2 Therapeutic Targeting of NETs

Therapeutically targeting neutrophil extracellular traps (NETs) offers a promising strategy to alleviate the pathological effects of their dysregulation, particularly in inflammatory and autoimmune diseases. While NETs are critical for pathogen defense, excessive formation or inadequate clearance can exacerbate disease symptoms. Recent research focuses on strategies to modulate NET formation and enhance their clearance, aiming to improve clinical outcomes in chronic inflammation and autoimmunity [1].

A promising approach involves modulating the NADPH oxidase pathway, a key driver of reactive oxygen species (ROS) production and subsequent NETosis. Inhibitors like diphenyleneiodonium (DPI) show potential in reducing ROS production and NET formation. By targeting the oxidative burst that triggers NETosis, these inhibitors may mitigate excessive inflammatory responses and tissue damage associated with dysregulated NET production [2].

Other strategies focus on enhancing NET clearance to prevent their accumulation and associated tissue damage. Enzymes such as DNase I, which degrade the DNA backbone of NETs, have been investigated as therapeutic agents for conditions like systemic lupus erythematosus (SLE), where NET accumulation is implicated in disease pathogenesis [1]. Promoting NET clearance aims to reduce inflammation and improve clinical outcomes in patients with inflammatory and autoimmune diseases.

Developing NET-targeting therapies holds significant promise for treating various inflammatory and autoimmune conditions. By modulating NET formation and clearance, these therapies could address the underlying mechanisms contributing to disease pathogenesis, particularly in cases characterized by excessive inflammation and impaired wound healing. This approach may provide new treatment avenues by mitigating the detrimental effects of excessive NET formation, which exacerbate inflammatory responses and hinder recovery in diseases, including those related to COVID-19 and chronic wounds [3, 4, 1, 2, 5]. Further research is essential to fully understand NETs' complex roles in health

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and disease and to optimize therapeutic strategies that effectively target these structures without compromising their protective functions.

6.3 NETs in COVID-19 and Inflammatory Responses

Neutrophil extracellular traps (NETs) significantly contribute to the pathophysiology of COVID-19, influencing the complex inflammatory responses observed in severe cases. NET formation is a crucial innate immune response designed to trap and neutralize pathogens. However, excessive NET formation in COVID-19 has been linked to severe inflammatory responses, resulting in adverse clinical outcomes such as acute respiratory distress syndrome (ARDS) and thrombotic complications [4].

COVID-19 pathophysiology involves a hyperactive immune response, often termed a "cytokine storm," characterized by excessive pro-inflammatory cytokine release. NETs amplify this inflammatory response, leading to neutrophil infiltration, tissue damage, and impaired gas exchange, thereby worsening respiratory symptoms in COVID-19 patients [4].

Moreover, NETs are implicated in immunothrombosis, marked by microvascular blood clot formation, leading to severe complications such as deep vein thrombosis and pulmonary embolism. In COVID-19 patients, excessive NET formation correlates with increased pro-inflammatory cytokine levels and a heightened risk of thrombotic events [4]. This underscores the urgent need for therapeutic strategies that effectively target NETs to mitigate their pathological effects while preserving their essential roles in host defense.

6.4 Future Directions in NET-Related Therapies

Future research on neutrophil extracellular traps (NETs) should prioritize elucidating their long-term impacts in conditions like COVID-19, where excessive NET formation is linked to severe inflammatory responses and thrombotic complications. Understanding the chronic effects of NETs in post-acute sequelae of COVID-19 could provide insights into persistent symptoms and guide the development of targeted interventions [4]. Additionally, exploring the predictive power of circulating NETs in longitudinal studies could enhance our ability to identify at-risk populations and tailor therapeutic strategies accordingly [5].

Advancements in NET-targeted therapies may involve identifying novel interventions that specifically target dysregulated NETosis while preserving NETs' protective functions. Investigating therapeutic targets to mitigate neutrophil-related lung injury is particularly crucial, given NETs' role in exacerbating respiratory distress in severe COVID-19 cases [5]. Further research should focus on developing pharmacological agents that modulate NET formation and clearance, potentially offering new treatment avenues for various inflammatory and autoimmune conditions.

By investigating NETs' roles in diverse disease processes, the scientific community can enhance understanding of their contributions to disease pathogenesis, particularly in conditions characterized by excessive inflammation and impaired healing, such as COVID-19 and chronic wounds. This research has the potential to inform the development of more effective NET-targeted therapies, ultimately leading to improved patient outcomes by mitigating the detrimental effects of excessive NET formation and enhancing inflammation resolution [3, 4, 1, 2, 5].

7 Conclusion

Neutrophil extracellular traps (NETs) are integral to the immune system, embodying a dual role that encompasses both the defense against pathogens and the potential to incite inflammatory and autoimmune conditions. This survey highlights the intricate balance that NETs maintain between their protective capabilities in pathogen entrapment and their propensity to cause tissue damage and chronic inflammation when regulation fails.

In dermatological contexts, NETs significantly influence conditions such as psoriasis and systemic lupus erythematosus (SLE), where they intensify chronic inflammation and tissue damage. Their presence in skin lesions is associated with the recruitment of immune cells and the continuation of inflammatory cycles, thereby exacerbating skin conditions. In the realm of autoimmune diseases, the

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dysregulation of NET formation is a pivotal element in disease advancement, as NETs can provoke autoantibody production and enhance autoimmune responses.

Exploring therapies that target NETs offers a promising direction for enhancing disease management. Approaches that adjust NET formation or promote their clearance could potentially reduce tissue damage and improve clinical outcomes in inflammatory and autoimmune disorders. The development of pharmacological interventions that focus on specific pathways involved in NETosis, including both NADPH oxidase-dependent and independent mechanisms, may introduce novel therapeutic possibilities for these multifaceted diseases.

Future research endeavors should focus on elucidating the molecular mechanisms that govern NET formation and their roles in disease pathogenesis. It is crucial to investigate the long-term impacts of NETs in conditions such as COVID-19 and to identify new therapeutic targets that can selectively modulate NET activity without compromising their protective functions. By deepening our understanding of NETs in dermatology and autoimmune diseases, the scientific community can advance more effective therapies that enhance patient outcomes and quality of life.

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