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REVIEW ARTICLE

INVESTIGATING HOW NEUTROPHILS CONTRIBUTE TO THE BODY'S DEFENSE AGAINST INFECTIONS

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ABSTRACT: Neutrophils are essential effector cells of the innate immune system and act as the first line of defense against microbial invaders. At sites of infection, they deploy multiple protective strategies, including phagocytosis, degranulation, production of antimicrobial peptides, and the release of neutrophil extracellular traps (NETs) to capture and neutralize pathogens. While these functions are crucial for host defense, excessive or dysregulated activation can cause tissue injury, chronic inflammation, and immunopathology. This review highlights the multifaceted roles of neutrophils in pathogen clearance, immune regulation, and resolution of inflammation, while also examining how their dysfunction contributes to infectious diseases, autoimmune disorders, and sepsis. Understanding the delicate balance of neutrophil activity offers valuable insights into therapeutic strategies aimed at enhancing host defense while minimizing tissue damage.

Keywords: Neutrophils, Innate immunity, Host defense, Infection, Phagocytosis, NETs, Antimicrobial peptides, Immune regulation, Inflammation, Pathogen clearance, Immune dysfunction, Autoimmunity, Sepsis, Chronic inflammation.

INTRODUCTION:

Neutrophils are the most abundant leukocytes in human circulation and are indispensable components of the innate immune defense system. They respond rapidly to microbial invasion, mobilizing diverse antimicrobial strategies such as phagocytosis, degranulation, secretion of antimicrobial peptides, and NET formation. Beyond their direct pathogen-killing capacity, neutrophils play broader roles in shaping the immune response, regulating inflammation, and interacting with other immune cells like macrophages and dendritic cells.

injury. However, their functional versatility is tightly regulated, as uncontrolled or persistent neutrophil activity can lead to harmful outcomes including chronic inflammation, tissue damage, and autoimmune disease[1]. Ongoing research continues to unravel the molecular mechanisms that govern neutrophil activation, migration, and adaptation to tissue microenvironments. By exploring both their protective and pathological roles, this review emphasizes the therapeutic potential of targeting neutrophil pathways in infectious and inflammatory diseases.

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Current or Ongoing Clinical Trials Targeting Neutrophil Pathways (e.g., PAD4 inhibitors for NETs, CXCR2 blockers for migration).

Blocking Neutrophil Movement (CXCR2/CXCR1 drugs)

Navarixin – tested with an immunotherapy drug (pembrolizumab) in cancer patients. Safe, but did not improve results much.

AZD5069 – tested in lung diseases (like COPD) and in cancer to reduce neutrophil entry into tissues.

Danirixin – studied in flu and COPD patients to see if reducing neutrophils could lessen inflammation.

Reparixin – tested in breast cancer and COVID-19 to stop too many neutrophils from entering tissues.

These drugs can safely lower neutrophil migration, but results were mixed, depending on the disease.

Targeting Neutrophil NETs (DNA traps)

DNase (dornase alfa) – a drug that cuts up the sticky DNA traps. Already used in cystic fibrosis, also tested in COVID-19 and lung diseases. Results are variable.

PAD4 inhibitors (like GSK484, JBI-589) – block the enzyme PAD4, which neutrophils use to make traps[2]. Very promising in lab and animal studies, but not yet tested in people.

NET-targeting is exciting, but right now only DNase is in real human trials; PAD4 blockers are still experimental.

MATERIALS AND METHODOLOGY:

This review compiles a comprehensive analysis of the current literature surrounding the roles of neutrophils in immune defense. A multi-faceted approach was utilized to gather relevant data from peer-reviewed articles, clinical studies, experimental models, and recent reviews on neutrophil biology[3]. The materials and methodologies employed in this review include the following:

Literature Search Approach

A structured search was carried out across academic databases such as PubMed, Scopus, and Google Scholar using keywords including *neutrophils, immune response, pathogen defense, inflammatory responses, NETs,* and other related terms.

Inclusion Criteria

The review focused on peer-reviewed original research articles, clinical studies, and comprehensive reviews. Priority was given to studies addressing the molecular pathways and biological roles of neutrophils in infections, inflammation, autoimmune disorders, and tissue repair.

Data Collection and Integration

Key findings were extracted from the selected studies, with attention to neutrophil activation, cytokine secretion, degranulation, NET formation, phagocytosis, and interactions with other immune system cells.

Experimental Models

Animal studies, primarily using murine models, were reviewed to evaluate neutrophil responses to various pathogens such as bacteria, fungi, and viruses, as well as to inflammatory stimuli and tissue damage. Special focus was placed on neutrophil recruitment and their interactions with other immune cells.

Immunological Techniques

Several immunological techniques were commonly employed to study neutrophil biology.

Flow cytometry was used for analyzing surface markers, cytokine levels, and phagocytosis. Immunofluorescence and immunohistochemistry were applied to detect neutrophil presence and NET formation. Western blotting was used to assess protein expression linked to neutrophil functions, while ELISA allowed for quantification of cytokines and chemokines[4]. Microscopy techniques were utilized to observe neutrophil migration and interactions with pathogens. Additionally, gene expression profiling methods such as RT-PCR and RNA-seq were used to examine changes in gene expression patterns under different conditions.

Data Interpretation

A comparative review of neutrophil responses in various infectious and inflammatory models highlighted the importance of signaling pathways, regulation of neutrophil lifespan, and the resolution of inflammation[5]. Areas identified for further investigation included the need to better understand neutrophil diversity across different tissues, the long-term consequences of persistent neutrophil activation, and their contribution to chronic inflammation and autoimmune diseases

DISCUSSION:

Neutrophils are vital components of the body's initial defense against pathogens, playing an essential role in both immune surveillance and the resolution of infection. Over recent years, our understanding of their functions has grown significantly, revealing that these cells not only perform direct pathogen elimination but also regulate inflammatory responses, influence tissue repair, and coordinate with other immune cells to ensure a balanced immune reaction. Despite the wealth of knowledge gained, the full scope of neutrophil contributions in both health and disease remains an active area of investigation[6].

Activation and Immune Surveillance by Neutrophils

Upon detecting pathogens or damage-associated signals, neutrophils rapidly become activated, undergoing changes such as increased motility, enhanced phagocytic activity, and the release of antimicrobial molecules. These functions are crucial for controlling infections in the early stages. In addition to their direct pathogen-killing functions, neutrophils also contribute to the inflammatory response by secreting cytokines and chemokines, which recruit other immune cells to the site of infection[7]. However, when activated inappropriately or excessively, neutrophils can cause tissue damage and contribute to the chronic inflammation observed in diseases like rheumatoid arthritis and inflammatory bowel disease (IBD). The delicate balance between neutrophil activation and resolution is critical for maintaining health and preventing autoimmune conditions.

Neutrophil Functions: Phagocytosis and NET Formation

One of the hallmark functions of neutrophils is their ability to engulf and destroy invading microorganisms through phagocytosis. This process is particularly effective against bacteria and fungi and is essential for preventing the spread of infection. Additionally, neutrophils utilize another mechanism-neutrophil extracellular trap (NETs)-to ensnare and neutralize pathogens[8]. NETs are composed of DNA and antimicrobial proteins that form extracellular traps around pathogens, preventing their spread. While NETs are highly effective in pathogen elimination, their uncontrolled release can contribute to disease progression in conditions like sepsis, systemic lupus erythematosus (SLE), and thrombosis. Thus, while NETs are an important antimicrobial tool, their dysregulated production can lead to pathological consequences.

Neutrophils in Chronic Inflammation and Autoimmune Disease

In chronic inflammatory diseases and autoimmune conditions, neutrophils can become persistently activated, leading to ongoing tissue damage and inflammation. In these cases, neutrophils shift from being protective to potentially harmful, perpetuating a cycle of immune-mediated damage. The exact mechanisms behind this shift are complex and may involve a combination of cytokine dysregulation, abnormal interactions with the tissue microenvironment, and genetic factors. In autoimmune disorders, neutrophils can exacerbate disease progression by releasing pro-inflammatory mediators that drive tissue damage and exacerbate inflammation. Understanding these mechanisms is crucial for designing effective therapies to modulate neutrophil activity in chronic conditions.

Regulation of Neutrophil Function

Effective neutrophil responses require precise regulation to avoid excessive tissue damage. Several signalling pathways control neutrophil activation, migration, and survival, including those mediated by cytokines, chemokines, and pathogen recognition receptors (e.g., Toll-like receptors). Importantly, neutrophils also play an active role in the resolution of inflammation, either by undergoing programmed cell death (apoptosis) or switching to pro-resolving phenotypes that help restore tissue homeostasis[9]. A breakdown in these regulatory mechanisms can result in unresolved inflammation, tissue injury, and the development of chronic inflammatory diseases or autoimmunity.

Therapeutic Implications

Given their central role in both immune defense and disease, neutrophils are an attractive target for therapeutic interventions. Modulating neutrophil function could potentially treat a wide range of conditions, from bacterial infections and sepsis to autoimmune diseases and chronic inflammation. Strategies that aim to limit neutrophil infiltration into inflamed tissues, inhibit excessive NET formation, or promote the resolution of inflammation without impairing neutrophil function could have significant clinical benefits[10]. However, therapeutic targeting of neutrophils presents a challenge, as it requires selectively modulating their actions to avoid compromising their essential roles in pathogen defense.

Recent advances (2022–2024) in neutrophil research.

Diversity: Neutrophils are not identical; single-cell studies show many subtypes with different roles in infection, cancer, and inflammation.

Swarming: They coordinate in "swarms" using chemical signals like LTB4; interferons can block this.

Reverse migration: After reaching tissues, some neutrophils move back into the blood, helping resolution but sometimes spreading damage.

Suppressive neutrophils (PMN-MDSCs): Special subsets turn off immune responses, especially in cancer; new markers identified.

NETs (Neutrophil Extracellular Traps): Important in clotting, lung disease, and cancer; drugs like DNase, PAD4 inhibitors, and colchicine are being tested.

Trained immunity: Neutrophils can develop a kind of "memory," responding more strongly to repeat infections.

Therapeutics: Drugs blocking neutrophil movement (CXCR2 inhibitors) are in trials, but results are mixed.

CONCLUSION:

Neutrophils are pivotal components of the body's defense machinery, essential for the rapid detection and elimination of pathogens during infection. Their diverse functions, from

phagocytosis and degranulation to the formation of neutrophil extracellular traps (NETs), illustrate their versatility in responding to microbial threats. Beyond their direct antimicrobial actions, neutrophils also play a critical role in shaping the inflammatory environment and guiding the resolution of immune responses. However, while these cells are indispensable for host protection, their dysregulated activity can lead to tissue damage, chronic inflammation, and autoimmune disorders. The delicate balance between their protective and potentially harmful actions underscores the complexity of neutrophil biology.

Emerging insights into the molecular and cellular mechanisms that govern neutrophil function offer promising avenues for therapeutic intervention. By better understanding how neutrophils contribute to both immune defense and pathology, we can identify strategies to modulate their responses—either enhancing their protective capabilities in infection or dampening their harmful effects in chronic inflammation and autoimmune diseases. Ultimately, continued research into neutrophil biology holds the potential to revolutionize the treatment of a wide range of immune-related conditions, leading to more effective, targeted therapies for patients suffering from infections, autoimmune disorders, and inflammatory diseases.

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