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Review Article

A DNASE1–NET–Eosinophil Axis Linking Helminth Exposure to Protection against Autoimmune Disease

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Abstract

Autoimmune diseases arise from dysregulated innate and adaptive immunity, often driven by persistent inflammation, exposure to self-antigens, and defective immune tolerance. Neutrophil extracellular traps (NETs) play a dual role in host defense and autoimmunity by exposing DNA–protein complexes that activate nucleic acid–sensing receptors. Efficient degradation of extracellular DNA, largely mediated by deoxyribonuclease I (DNase I) encoded by the *DNASE1* gene, is essential for preventing chronic inflammation. Impaired DNase I activity contributes to systemic lupus erythematosus, rheumatoid arthritis, and vasculitis by allowing NET accumulation, autoantibody production, and endothelial damage. Parasitic helminths induce eosinophilia and Th2-skewed responses, which modulate neutrophil activity, neutralize inflammatory mediators such as histamine, and interact with extracellular traps. We hypothesize that helminth-induced eosinophil activation protects against autoimmunity by limiting neutrophil-mediated tissue toxicity, enhancing NET clearance via DNase I, and regulating histamine-driven inflammation**.** In this model, *DNASE1* serves as a central integrator of extracellular DNA metabolism, innate immune sensing, and eosinophil–neutrophil cross-talk. Disruption of this axis predisposes to autoimmunity, whereas helminth-driven modulation restores immune tolerance. This framework provides a testable hypothesis linking extracellular DNA clearance, helminth exposure, and autoimmune disease pathogenesis.

Keywords: Autoimmunity, DNASE1, Neutrophil Extracellular Traps, Eosinophils, Helminth Infection, Immune Tolerance.

INTRODUCTION

The DNASE1 gene, located on human chromosome 16, encodes deoxyribonuclease I (DNase I), a key endonuclease responsible for the degradation of extracellular DNA, including neutrophil extracellular traps (NETs), thereby preventing the accumulation of immunogenic self-DNA and limiting autoimmunity [1]. DNase I is primarily produced in the pancreas and salivary glands and exhibits broad substrate specificity toward both double- and single-stranded DNA [2].

Alterations in DNase activity, rather than structural instability of the enzyme itself, have been documented in inflammatory conditions such as chronic pancreatitis, where inflammatory signaling modulates DNase expression and circulating activity levels [3]. These findings underscore the sensitivity of DNase I–mediated DNA clearance to inflammatory states.

Recombinant human DNase I (dornase alfa; Pulmozyme) is clinically approved for cystic fibrosis, where it reduces mucus viscosity by degrading extracellular DNA. Beyond cystic fibrosis, DNase I has gained increasing attention for its ability to dismantle NETs, which are increasingly implicated in chronic inflammation, fibrosis, and autoimmunity [4].

NETs, DNase I, and Autoimmune Pathogenesis

NETs are web-like chromatin structures extruded by activated neutrophils and decorated with histones, proteases, and citrullinated proteins. While NET formation (NETosis) is an essential antimicrobial defense, excessive formation or defective degradation exposes self-antigens that drive autoantibody production and immune complex formation [5].

Importantly, autoimmunity is not associated with a deficiency of NET formation per se—true NET deficiency results in severe, often fatal infections [6].

Instead, impaired clearance of NETs, frequently due to reduced DNase I activity, is a central pathogenic mechanism in systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and ANCA-associated vasculitis (AAV). Persistent NETs promote endothelial injury, complement activation, and chronic inflammation [7].

DNase I also plays a regulatory role in innate immune sensing. Extracellular DNA derived from NETs or dying cells can activate Toll-like receptor 9 (TLR9) within endosomes, a process tightly regulated by DNase I–mediated DNA degradation [8]. Failure of this regulatory axis amplifies interferon signaling and autoimmunity.

TLR7–NET Axis and Amplification of Inflammation

TLR7 is another nucleic acid–sensing receptor implicated in NET biology. Activation of TLR7 in neutrophils promotes reactive oxygen species (ROS) generation and NETosis, particularly in response to viral and parasitic stimuli. While beneficial in host defense, chronic activation of this pathway contributes to sustained NET formation and tissue damage in diseases such as SLE and osteoarthritis [9].

Thus, an imbalance between NET production (TLR7-driven) and NET clearance (DNase I–dependent) emerges as a critical determinant of autoimmune risk.

Eosinophils, Extracellular Traps, and Immune Modulation

Eosinophils interact directly with NETs and can generate eosinophil extracellular traps (EETs) in allergic and parasitic contexts. EETs consist of DNA and granule proteins and are notably more stable and less susceptible to degradation than NETs, contributing to prolonged inflammatory signaling [10].

At sites of inflammation, eosinophils exert regulatory effects on neutrophils. Although neutrophils bind eosinophil peroxidase (EPO), they reversibly inhibit its enzymatic activity, potentially limiting oxidative tissue damage [11]. More broadly, eosinophils modulate neutrophil recruitment, activation, and differentiation, particularly within type 2 inflammatory environments [12].

Helminths, Eosinophilia, and Immune Tolerance

Parasitic helminths induce robust eosinophilia through a Th2-skewed immune response characterized by IL-5, IL-3, and GM-CSF production. Activated eosinophils degranulate and release cytotoxic proteins to damage and kill parasites [13].

Hookworms (e.g., *Necator americanus* and *Ancylostoma duodenale*) are particularly notable for their ability to modulate host immunity. Epidemiological and experimental data suggest that helminth exposure may confer protection against autoimmune and allergic diseases, a concept central to the “old friends” or hygiene hypothesis [14].

Eosinophil peroxidase (EPO), a key effector molecule released during helminth infection, plays an essential role in parasite killing but also shapes the inflammatory microenvironment by interacting with neutrophils and extracellular DNA [15].

Histamine Regulation and Autoimmune Inflammation

Histamine is increasingly recognized as an immunomodulatory mediator in autoimmunity, influencing T-cell polarization, antigen presentation, and antibody production in diseases such as multiple sclerosis, psoriasis, and rheumatoid arthritis [16].

Eosinophils contribute to immune homeostasis by degrading histamine via histaminase release. While histamine recruits’ eosinophils, these cells in turn limit histamine-driven inflammation, forming a negative feedback loop that constrains tissue damage [17].

Hypothesis

We hypothesize that parasitic helminth exposure protects against autoimmune disease through a coordinated eosinophil-mediated regulatory network that neutralizes neutrophil-driven tissue toxicity, degrades histamine, and indirectly promotes effective clearance of neutrophil extracellular traps via DNase I–dependent mechanisms.

Within this framework, DNASE1 emerges as a central molecular gatekeeper of immune tolerance, linking extracellular DNA clearance, TLR signaling, NET regulation, and eosinophil–neutrophil cross-talk. Disruption of this axis—through reduced DNase I activity, excessive NET formation, or loss of eosinophil-mediated immunoregulation—may predispose individuals to autoimmune disease, whereas helminth-induced eosinophilia restores immune balance and limits autoimmunity.

CONCLUSION

Extracellular DNA and NETs play a central role in the initiation and persistence of autoimmune disease. Defective clearance, often due to reduced DNase I activity, prolongs exposure to self-antigens and amplifies inflammatory signaling. Parasitic helminths offer a natural immunoregulatory context: eosinophil activation, Th2 polarization, and histamine modulation converge to limit neutrophil-mediated tissue damage and promote NET clearance.

We propose that the DNASE1–NET–eosinophil axis represents a critical mechanism linking helminth exposure to protection against autoimmunity. This hypothesis integrates extracellular DNA metabolism, innate immune regulation, and host–

parasite interactions, and suggests that strategies aimed at enhancing DNase I activity, improving NET clearance, or harnessing eosinophil-mediated regulation may offer novel therapeutic avenues for autoimmune disease.

Ethical Approval: This is a hypothesis driven article that does not involved human or animal subjects.

Competing of Interest: Authors declare that they have no conflicts of interest.

Consent to Publish Declaration: Not applicable.

Data Availability: Data sharing does not apply to this article as no datasets were generated or analyzed during the current study.

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