ERAD, 2023, Volume 2, Issue 1, pages 5-6

Excellence in Rheumatic & Autoimmune Diseases
ERAD
THE OFFICIAL JOURNAL OF INSTITUTE OF RHEUMATIC AND AUTOIMMUNE DISEASES

Commentary

Ginger, a potential inhibitor of neutrophil extracellular traps (NETs)

Running title: Ginger against NETs

Sotirios G. Tsiogkas*, Dimitrios P. Bogdanos

Department of Rheumatology and Clinical immunology, General University Hospital of Larissa, Faculty of Medicine, School of Health Sciences, University of Thessaly, 41500 Larissa, Greece

*Corresponding Author's e-mail: stsiogkas@gmail.com

Abstract

Neutrophils are a crucial part of the innate immunity. Initial immune responses against pathogens are primarily neutrophil mediated. Neutrophil extracellular traps (NETs) are expelled following neutrophil stimulation. This process, called NETosis, can be highly protective. However, its' non-specific nature results in upregulation of local pro-inflammatory stimuli and often in tissue injury. NETosis has been suggested to participate in the pathogenesis of many immune-mediated diseases, including systemic lupus erythematosus (SLE), rheumatoid arthritis (RA) and psoriasis. Recently, a phytochemical isolated from ginger root was reported to inhibit NETosis and reduce levels of plasma NETs when administered orally to humans and mice.

(Submitted 23 September 2023; accepted 30 September 2023)

Keywords- NETosis; neutrophils; ginger; 6-gingerol

I. INTRODUCTION

Neutrophils are cells specialized to participate in the initial immune response against pathogens[1]. These granulocytes exert their defensive role through phagocytosis, and production of cytokines or reactive oxygen species. In case of neutrophil stimulation, neutrophil extracellular traps (NETs) are expelled[2]. This process, called NETosis is accompanied by release of granule-components and subsequent exertion of anti-microbial functions against bacteria, viruses, and fungi[3]. While its' effect can be highly protective against pathogens, its' non-specific nature results in upregulation of local pro-inflammatory stimuli and potential tissue injury. Interestingly, prolonged NETosis phenomena can mediate breaks in tolerance of adaptive immunity components and lead to autoantibody production[4]. On the other hand, autoantibodies induce NETosis, thus establishing a feed-forward loop[5].

Subsequently NETosis has been suggested to participate in the pathogenesis of many immune-mediated diseases, including systemic lupus erythematosus (SLE)[6], rheumatoid arthritis (RA)[7] and psoriasis[8]. For instance, NETs have been measured increased in circulatory of patients diagnosed with SLE, have been suggested to associate with autoantibody production, and have been aimed as potential targets of new drugs for the disorder. While development of such targeted therapies has been the subject of thorough research[9], there have been reports of natural herbs exhibiting the capacity to attenuate NETosis and combat pro-inflammatory conditions[10].

Recently, researchers suggested that a phytochemical isolated from ginger root, the 6-gingerol, when administered orally to humans and mice inhibited NETosis and reduced levels of plasma NETs[11]. Specifically, neutrophils were isolated from healthy controls and were stimulated using PMA, or anti-RNP complex, or antiphospholipid syndrome IgG. The ginger solution significantly inhibited NETs production in all scenarios. Intriguingly, when ginger supplements were administered orally to a mouse model of antiphospholipid syndrome blood NET levels and thrombi were significantly reduced. Researchers also examined the effect of ginger consumption on a SLE mouse model and found that post-treatment anti-dsDNA and total IgG antibodies were inhibited. Finally, ginger supplements were also consumed by healthy participants. NETosis by ex vivo stimulated cells and blood NET levels were also hindered.

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Interestingly, ginger components have been suggested to inhibit PDE activity[12] and thus reduce immune-mediated cell responses. PDE antagonism leads to accumulation of cAMP intracellularly. PDE4 inhibitors been developed over the last decades and have successfully been used to manage inflammatory-mediated diseases, such as the psoriatic disease[13]. One such example is apremilast which has been FDA-approved for psoriasis and psoriatic arthritis. Whether ginger-mediated inhibition of NETosis both in mice and humans is mainly attributed to this PDE-hampering effect remains to be seen in future research.

II. CONCLUSION

Ginger components seem to effectively restrict the NETs activity. Significantly, observations have now been made in both murine models and humans. Research to assess ginger administration in NET-mediated autoimmune diseases is warranted.

AUTHOR CONTRIBUTIONS

SGT drafted the manuscript. DPB revised the manuscript. The authors approved the final version of the manuscript.

CONFLICT OF INTEREST

All Authors declare no conflict of interest.

References

1. Burn GL, Foti A, Marsman G, Patel DF, Zychlinsky A. The Neutrophil. Immunity. United States; 2021;54:1377–91.
2. Papayannopoulos V. Neutrophil extracellular traps in immunity and disease. Nat Rev Immunol [Internet]. 2018;18:134–47. Available from: https://doi.org/10.1038/nri.2017.105
3. Vorobjeva N V, Chernyak B V. NETosis: Molecular Mechanisms, Role in Physiology and Pathology. Biochemistry (Mosc). United States; 2020;85:1178–90.
4. Gupta S, Kaplan MJ. The role of neutrophils and NETosis in autoimmune and renal diseases. Nat Rev Nephrol. England; 2016;12:402–13.
5. Meng H, Yalavarthi S, Kanthi Y, Mazza LF, Elfline MA, Luke CE, et al. In Vivo Role of Neutrophil Extracellular Traps in Antiphospholipid Antibody-Mediated Venous Thrombosis. Arthritis Rheumatol (Hoboken, NJ). United States; 2017;69:655–67.
6. Salemme R, Peralta LN, Meka SH, Pushpanathan N, Alexander JJ. The Role of NETosis in Systemic Lupus Erythematosus. J Cell Immunol. United States; 2019;1:33–42.
7. Song W, Ye J, Pan N, Tan C, Herrmann M. Neutrophil Extracellular Traps Tied to Rheumatoid Arthritis: Points to Ponder. Front Immunol. 2021;11:1–10.
8. Shao S, Fang H, Dang E, Xue K, Zhang J, Li B, et al. Neutrophil Extracellular Traps Promote Inflammatory Responses in Psoriasis via Activating Epidermal TLR4/IL-36R Crosstalk. Front Immunol. Switzerland; 2019;10:746.
9. Huang J, Hong W, Wan M, Zheng L. Molecular mechanisms and therapeutic target of NETosis in diseases. MedComm. China; 2022;3:e162.
10. Rizvi ZA, Babele P, Sadhu S, Madan U, Tripathy MR, Goswami S, et al. Prophylactic treatment of Glycyrrhiza glabra mitigates COVID-19 pathology through inhibition of pro-inflammatory cytokines in the hamster model and NETosis. Front Immunol. 2022;13:1–19.
11. Ali RA, Minarchick VC, Zahavi M, Rysenga CE, Sturm KA, Hoy CK, et al. Ginger intake suppresses neutrophil extracellular trap formation in autoimmune mice and healthy humans. JCI Insight [Internet]. The American Society for Clinical Investigation; 2023;8. Available from: https://doi.org/10.1172/jci.insight.172011
12. Röhrig T, Pacjuk O, Hernández-Huguet S, Körner J, Scherer K, Richling E. Inhibition of Cyclic Adenosine Monophosphate-Specific Phosphodiesterase by Various Food Plant-Derived Phytotherapeutic Agents. Med (Basel, Switzerland). Switzerland; 2017;4.
13. Papp K, Reich K, Leonardi CL, Kircik L, Chimenti S, Langley RGB, et al. Apremilast, an oral phosphodiesterase 4 (PDE4) inhibitor, in patients with moderate to severe plaque psoriasis: Results of a phase III, randomized, controlled trial (Efficacy and Safety Trial Evaluating the Effects of Apremilast in Psoriasis [ESTEEM] 1). J Am Acad Dermatol. United States; 2015;73:37–49.