CMJ. 2025;47(4): 1-2.

Cumhuriyet Medical Journal

| cmj.cumhuriyet.edu.tr | Founded: 2004 Available online, ISSN:1305-0028 Publisher: Sivas Cumhuriyet Üniversitesi

The Confluence of Autoinflammation, Autoimmunity, and Peripheral Immune Tolerance: A New Chapter in Immunological Harmony

Ali Şahin [1,a,*]

[1] *Department of Rheumatology, Sivas Cumhuriyet University, Sivas, Türkiye*

**Corresponding author*

Editorial

History

Received: 03/12/2025
AccepteD: 19/12/2025

Copyright

This work is licensed under Creative Commons Attribution 4.0 International License

ABSTRACT

The 2025 Nobel Prize in Physiology or Medicine celebrated the discovery of mechanisms of peripheral immune tolerance, completing the immunological spectrum that spans autoinflammation and autoimmunity. This editorial contextualizes the award within decades of research illustrating how regulatory T cells (Tregs) and other tolerance mechanisms uphold self-integrity while sustaining host defense. Recent discoveries regarding transcriptional regulation, T-cell plasticity, and tumor immunology underscore the importance of immune balance in both health and disease.

***Keywords*:** Peripheral immune tolerance, Regulatory T cells, Autoimmunity, Immune homeostasis, Foxp3–Ikzf1 axis

Otoinflamasyon, Otoimmünite ve Periferal İmmün Toleransın Keşismesi: İmmünolojik Ahenkte Yeni Bir Bölüm

Editoryal

Süreç

Geliş: 03/12/2025
Kabul: 19/12/2025

Telif Hakkı

Bu Çalışma Creative Commons Atıf 4.0 Uluslararası Lisansı Kapsamında Lisanslanmıştır.

ÖZ

Fizyoloji veya tıp alanında 2025 Nobel ödülü otoinflamasyon ve otoimmüniteyi kapsayan immünolojik spektrumu tamamlayan periferal immün tolerans mekanizmalarının keşfini kutladı. Bu editöryal on yıllarca süren bir çalışmanın ödülü olan bu araştırmada regülatör T hücreler (Treg) ve öteki immün tolerans mekanizmalarının konak savunması devam ederken öz bütünlüğünün nasıl olduğunu ele almaktadır. Transkripsiyonel regülasyon, T hücre plastisise ve tümör imünolojisini ilgilendiren son çalışmalar sağlıkta ve hastalıkta immün dengenin öneminin altını çizmektedir.

Anahtar Kelimeler: Periferal immün tolerans, Regülatör T hücreler, Otoimmünite, İmmün homeostaz, Foxp3–Ikzf1 aksı

[a] alisahin@cumhuriyet.edu.tr *0000-0003-0743-5288*

How to Cite: Şahin A. The Confluence of Autoinflammation, Autoimmunity, and Peripheral Immune Tolerance: A New Chapter in Immunological Harmony, Cumhuriyet Medical Journal. 2025;47(4): 1-2.

Immunology has long been characterized by paradox. Autoinflammation signifies the impulsive hyperreactivity of the innate immune system, while autoimmunity denotes the misdirected precision of adaptive immunity. The acknowledgment of peripheral immune tolerance mechanisms, awarded the 2025 Nobel Prize, finalizes this conceptual triangle, elucidating the immune system's distinction between vigilance and self-harm.

Regulatory T cells are at the center of this balance. This is based on early research that showed how they keep effector responses in check and stop autoimmune disease.[1] The emergence of Type 1 regulatory T cells (Tr1) introduces complexity to this framework; by modulating cytokine environments and attenuating pathological inflammation, Tr1 cells provide an additional layer of tolerance beyond classical Foxp3$^+$ Tregs.[2] Mechanistic advancements persist in elucidating the enforcement of tolerance. The Ikzf1 Foxp3 transcriptional partnership inhibits gene expression programs that would otherwise facilitate unregulated immunity, establishing a direct connection between transcriptional regulation and immune suppression.[3]

Tumor immunology underscores the dual nature of

tolerance: tumor-infiltrating Tregs inhibit antitumor immunity, serving as protectors of self and as targets for immunotherapy.[4] Recent research indicating that platelet factor 4 can shift the equilibrium towards TH1-Treg polarization underscores the dynamic and context-sensitive nature of immune tolerance mechanisms.[5] The 2025 Nobel Prize recognizes not only a molecular discovery but also an intellectual synthesis.

Immune homeostasis is not a fixed state; it changes based on the environment, the tissue it is in, and the plasticity of the cells. From autoinflammation to autoimmunity and now peripheral tolerance, immunity is shown to be a system that is not just for fighting, but also for knowing when to back off.

References

1. Sakaguchi S, Mikami N, Wing JB, Tanaka A, Ichiyama K, Ohkura N. Regulatory T Cells and Human Disease. *Annu Rev Immunol*. 2020;38:541-566. doi: 10.1146/annurev-immunol-042718-041717.
2. Zeng H, Zhang R, Jin B, Chen L. Type 1 regulatory T cells: a new mechanism of peripheral immune tolerance. *Cell Mol Immunol*. 2015;12(5):566-71. doi: 10.1038/cmi.2015.44.
3. Ichiyama K, Long J, Kobayashi Y, Horita Y, Kinoshita T, Nakamura Y, Kominami C, Georgopoulos K, Sakaguchi S. Transcription factor Ikzf1 associates with Foxp3 to repress gene expression in Treg cells and limit autoimmunity and anti-tumor immunity. *Immunity*. 2024;57(9):2043-2060.e10. doi: 10.1016/j.immuni.2024.07.010.
4. Tay C, Tanaka A, Sakaguchi S. Tumor-infiltrating regulatory T cells as targets of cancer immunotherapy. *Cancer Cell*. 2023;41(3):450-465. doi: 10.1016/j.ccell.2023.02.014.
5. Kuratani A, Okamoto M, Kishida K, Okuzaki D, Sasai M, Sakaguchi S, Arase H, Yamamoto M. Platelet factor 4-induced TH1-Treg polarization suppresses antitumor immunity. *Science*. 2024;386(6724):eadn8608. doi: 10.1126/science.adn8608.