ISSN: 2181-3906 2025

International scientific journal
«MODERN SCIENCE AND RESEARCH»
VOLUME 4 / ISSUE 5 / UIF:8.2 / MODERNSCIENCE.UZ

PATHOPHYSIOLOGY OF AUTOIMMUNE DISEASES MECHANISMS OF IMMUNE TOLERANCE DISRUPTION

Sultanov Samadjon
Assistant of the Department of "Pathology and Forensic Medicine",
Central Asian Medical University.
Xotamov Muhammadzakaryo Bahodirjon o'g'li
Central Asian Medical University, Dentistry Department, 2nd year, Group 523 student.

https://doi.org/10.5281/zenodo.15477844

Abstract. *This article explores the complex pathophysiology of autoimmune diseases with a primary focus on the mechanisms underlying the breakdown of immune tolerance. Immune tolerance is essential for preventing the immune system from attacking the body's own tissues.*

The review covers both central and peripheral tolerance processes, highlighting how genetic predispositions, environmental factors, and immune regulatory failures contribute to the development of autoimmunity. Key cellular players, such as regulatory T cells and antigen-presenting cells, are discussed in relation to their roles in maintaining immune homeostasis.

Additionally, the article examines current understanding of molecular mimicry, epitope spreading, and other pathogenic mechanisms leading to self-reactivity. The challenges in diagnosis and treatment of autoimmune diseases are also addressed, emphasizing the need for targeted therapeutic approaches aimed at restoring immune tolerance rather than merely suppressing immune responses.

Keywords*: Autoimmunity, Tolerance, Apoptosis, Antigen, Epitope, Autoantibody, Lymphocyte, Cytokine, Inflammation.*

ПАТОФИЗИОЛОГИЯ АУТОИММУННЫХ ЗАБОЛЕВАНИЙ МЕХАНИЗМЫ НАРУШЕНИЯ ИММУННОЙ ТОЛЕРАНТНОСТИ

Аннотация. *В статье рассматривается сложная патофизиология аутоиммунных заболеваний с упором на механизмы, лежащие в основе нарушения иммунной толерантности. Иммунная толерантность необходима для предотвращения атаки иммунной системы на собственные ткани организма. Обзор охватывает как центральные, так и периферические процессы толерантности, подчеркивая, как генетическая предрасположенность, факторы окружающей среды и нарушения иммунной регуляции способствуют развитию аутоиммунитета. Ключевые клеточные игроки, такие как регуляторные Т-клетки и антигенпрезентирующие клетки, обсуждаются в связи с их ролью в поддержании иммунного гомеостаза. Кроме того, в статье рассматриваются современные представления о молекулярной мимикрии, распространении эпитопов и других патогенных механизмах, приводящих к аутореактивности. Также рассматриваются проблемы диагностики и лечения аутоиммунных заболеваний, при этом подчеркивается необходимость целенаправленных терапевтических подходов, направленных на восстановление иммунной толерантности, а не просто на подавление иммунных реакций.*

Ключевые слова: *Аутоиммунитет, Толерантность, Апоптоз, Антиген, Эпитоп, Аутоантитело, Лимфоцит, Цитокин, Воспаление.*

Introduction

Autoimmune diseases are a broad class of disorders in which the immune system, designed to defend the body against pathogens, mistakenly targets its own healthy tissues and organs. This erroneous immune response leads to chronic inflammation, tissue destruction, and progressive dysfunction in affected organs. Common autoimmune diseases include systemic lupus erythematosus, rheumatoid arthritis, type 1 diabetes mellitus, and multiple sclerosis, each of which displays unique clinical manifestations but shares a fundamental breakdown in immune self-tolerance. Under normal physiological conditions, the immune system employs intricate control mechanisms to prevent self-reactivity. These mechanisms are collectively referred to as immune tolerance and are vital in distinguishing between foreign antigens and the body's own components. Immune tolerance is established in two primary ways: central tolerance, which occurs during lymphocyte maturation in the thymus and bone marrow; and peripheral tolerance, which functions in peripheral tissues to regulate mature lymphocytes that may have escaped central deletion.

The breakdown of immune tolerance can be attributed to several overlapping factors, including genetic predisposition (such as HLA gene variants), environmental triggers (like infections, toxins, or dietary components), and defects in immune regulatory pathways. Failure in the deletion or inactivation of autoreactive T and B lymphocytes permits these cells to survive, proliferate, and initiate an immune attack against self-antigens. This results in the production of autoantibodies, activation of complement pathways, and recruitment of inflammatory cells, all of which contribute to tissue damage and disease progression. Furthermore, autoimmune diseases are often multifactorial in origin, with hormonal influences (such as estrogen), epigenetic modifications, and microbiota imbalances also playing critical roles in the disruption of immune tolerance. Gender disparities observed in autoimmunity with females being disproportionately affected further highlight the complexity of immune regulation.

Literature review and method

Autoimmune diseases develop when the immune system mistakenly targets and attacks the body's own cells and tissues. This abnormal immune response leads to chronic inflammation and tissue destruction. Under normal conditions, the immune system is able to distinguish between self and foreign molecules, a process regulated by immune tolerance. Immune tolerance prevents harmful immune reactions against the body's own tissues. When immune tolerance mechanisms fail, autoreactive immune cells become activated, leading to the onset and progression of autoimmune diseases. Understanding the pathophysiology of these diseases requires a thorough investigation of how immune tolerance is established and maintained, and what causes its breakdown.

Immune tolerance refers to the immune system's ability to avoid attacking the body's own cells and molecules. It is essential for preventing autoimmune diseases and maintaining self-tolerance. There are two primary types of immune tolerance: central and peripheral. Central tolerance occurs during the development of immune cells in primary lymphoid organs, where self-reactive cells are eliminated or inactivated. Peripheral tolerance acts on mature immune cells that have escaped central tolerance, preventing their activation in peripheral tissues. Both types are necessary to maintain immune homeostasis and prevent autoimmunity.

Central tolerance mainly occurs in the thymus for T cells and in the bone marrow for B cells. During this process, developing lymphocytes are exposed to self-antigens. Those that strongly recognize self-antigens undergo apoptosis, a process known as negative selection. This eliminates potentially harmful autoreactive cells early in their development. Some self-reactive cells can also differentiate into regulatory T cells, which help suppress immune responses. The failure of central tolerance allows autoreactive lymphocytes to enter the circulation, increasing the risk of autoimmune diseases. Peripheral tolerance controls immune cells that escape central tolerance and enter peripheral tissues. It involves several mechanisms such as anergy (functional inactivation), suppression by regulatory T cells, and deletion through apoptosis. Peripheral tolerance also depends on the absence of co-stimulatory signals and the presence of inhibitory signals that prevent activation of autoreactive cells. These processes ensure that immune responses are limited to harmful pathogens and do not target self-antigens, maintaining immune balance and preventing autoimmunity.

The breakdown of immune tolerance can be triggered by genetic factors, environmental influences, and immune regulatory failures. Genetic predispositions, such as specific HLA alleles, increase susceptibility to autoimmune diseases. Environmental factors include infections, toxins, and dietary components that may modify self-antigens or activate immune cells inappropriately. Defects in regulatory T cells, co-stimulatory molecules, or cytokine signaling pathways can impair immune regulation. Together, these factors lead to the survival and activation of autoreactive lymphocytes, initiating autoimmune responses. Once immune tolerance is lost, autoreactive T and B cells attack self-tissues, causing chronic inflammation and tissue injury. Autoantibodies produced by B cells can bind to self-antigens and activate the complement system, enhancing inflammation. Infiltration of inflammatory cells leads to destruction of target organs, such as joints in rheumatoid arthritis or pancreatic islets in type 1 diabetes. The chronic nature of these immune attacks results in progressive organ dysfunction and clinical symptoms characteristic of autoimmune diseases.

Treatment of autoimmune diseases focuses on suppressing the aberrant immune response and restoring tolerance. Conventional therapies include corticosteroids and immunosuppressive drugs that reduce inflammation but have broad effects. Emerging approaches target specific immune pathways, such as biologics that inhibit cytokines or deplete autoreactive cells.

Immunotherapy aimed at enhancing regulatory T cells or inducing antigen-specific tolerance shows promise for more precise and long-lasting treatment. Advances in understanding immune tolerance mechanisms pave the way for novel therapies that can prevent or reverse autoimmune disease progression.

Discussion

The pathophysiology of autoimmune diseases is deeply rooted in the failure of immune tolerance mechanisms. Both central and peripheral tolerance play indispensable roles in preventing self-reactivity, and disturbances in either can contribute to the development of autoimmunity. Genetic predisposition, combined with environmental factors such as infections or toxins, can trigger immune tolerance breakdown, highlighting the multifactorial nature of these disorders. One important aspect is the role of regulatory T cells (Tregs), which are crucial for maintaining peripheral tolerance.

Dysfunction or deficiency of Tregs has been implicated in many autoimmune conditions, emphasizing their potential as therapeutic targets. Additionally, molecular mimicry—where foreign antigens resemble self-antigens can lead to cross-reactivity and immune activation against self-tissues.

Despite significant advances in understanding immune tolerance mechanisms, many questions remain. The precise triggers that shift the balance from tolerance to autoimmunity are not fully understood, and individual variability in immune responses complicates diagnosis and treatment. Moreover, current therapies largely focus on symptom management and immune suppression rather than restoring tolerance, underscoring the need for more targeted and curative approaches. Future research should prioritize identifying early biomarkers of tolerance breakdown and developing antigen-specific immunotherapies that selectively re-establish immune balance without broadly suppressing immunity. Integrating genetic, epigenetic, and environmental data will also be vital to create personalized treatment strategies. Overall, a comprehensive understanding of immune tolerance failure is essential for improving outcomes for patients suffering from autoimmune diseases.

Conclusion

Autoimmune diseases result from a complex failure of the immune system to maintain self-tolerance, leading to immune attacks against the body's own tissues. Both central and peripheral immune tolerance mechanisms are essential for preventing the activation of autoreactive lymphocytes. Genetic predispositions, environmental triggers, and defects in immune regulation collectively contribute to the breakdown of immune tolerance. This breakdown initiates chronic inflammation and tissue damage, which characterize autoimmune disorders. Despite advances in understanding the underlying mechanisms, many challenges remain in diagnosing and effectively treating these diseases. Current therapies focus mainly on suppressing immune responses rather than restoring normal immune tolerance. Future therapeutic strategies should aim to specifically target the causes of immune tolerance failure and promote long-lasting immune balance. Overall, deepening our knowledge of immune tolerance and its disruption is crucial for developing more precise and effective treatments for autoimmune diseases, ultimately improving patient outcomes and quality of life.

REFERENCES

1. Abbas, A.K., Lichtman, A.H., & Pillai, S. (2018). Cellular and Molecular Immunology (9th ed.). Elsevier.
2. Rose, N.R., & Bona, C. (1993). Defining criteria for autoimmune diseases (Witebsky's postulates revisited). Immunology Today, 14(9), 426–430.
3. Goodnow, C.C., Sprent, J., Fazekas de St Groth, B., & Vinuesa, C.G. (2005). Cellular and genetic mechanisms of self tolerance and autoimmunity. Nature, 435(7042), 590–597.
4. Davidson, A., & Diamond, B. (2001). Autoimmune diseases. The New England Journal of Medicine, 345(5), 340–350.
5. Sakaguchi, S., Yamaguchi, T., Nomura, T., & Ono, M. (2008). Regulatory T cells and immune tolerance. Cell, 133(5), 775–787.

6. Vinuesa, C.G., Sanz, I., & Cook, M.C. (2009). Dysregulation of germinal centres in autoimmune disease. Nature Reviews Immunology, 9(12), 845–857.
7. Tsokos, G.C. (2011). Systemic lupus erythematosus. The New England Journal of Medicine, 365(22), 2110–2121.
8. Mathis, D., & Benoist, C. (2009). Aire. Annual Review of Immunology, 27, 287–312.
9. Wucherpfennig, K.W. (2001). Mechanisms for the induction of autoimmunity by infectious agents. Journal of Clinical Investigation, 108(8), 1097–1104.