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Mini Review

Immune Tolerance: The Body's Art of Knowing Friend from Foe

Bakalov D, Aguado F, Livonesi E, Sierro J, Langella K
Department of Clinical Immunology, Greece
*** Corresponding Author**: Livonesi E, Department of Clinical Immunology, Greece

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Abstract

Immune tolerance is a fundamental biological process that enables the immune system to protect the body from harmful pathogens while avoiding unnecessary attacks against its own tissues. It is established and maintained through multiple mechanisms operating in primary and secondary lymphoid organs. Central tolerance eliminates or modifies strongly self-reactive lymphocytes during their development, whereas peripheral tolerance controls potentially autoreactive cells that escape central mechanisms. Regulatory T cells, anergy, deletion, immune checkpoints, and mechanisms of immune privilege all contribute to maintaining this delicate balance. Failure of immune tolerance can result in autoimmune diseases, while excessive or inappropriate tolerance may contribute to persistent infections and tumor immune evasion. Understanding immune tolerance has therefore become increasingly important in the development of treatments for autoimmune disorders, transplantation, allergies, and cancer. This article discusses the major mechanisms of immune tolerance, their biological significance, consequences of tolerance failure, and emerging therapeutic approaches aimed at restoring or manipulating immune regulation.

Introduction

The immune system must perform a remarkable balancing act. It needs to recognize and eliminate foreign organisms, abnormal cells, and potentially dangerous substances while simultaneously protecting the body's own healthy tissues. Immune tolerance refers to the collection of mechanisms that prevent the immune system from mounting harmful responses against self-antigens and, in certain circumstances, against otherwise harmless antigens.

Types of Immune Tolerance

Immune tolerance can broadly be divided into central tolerance and peripheral tolerance.

1. Central Tolerance

Central tolerance occurs during the development of lymphocytes in primary lymphoid organs.

For T cells, this process takes place primarily in the thymus. Developing T cells that recognize self-antigens with high affinity may undergo negative selection and apoptosis. Some self-reactive T cells can instead develop into regulatory T cells, which subsequently contribute to immune regulation in peripheral tissues

For B cells, central tolerance occurs mainly in the bone marrow. Strongly self-reactive B cells may be eliminated, undergo receptor editing, or become functionally unresponsive.

Central tolerance is therefore an important first line of defense against autoreactive lymphocytes

2. Peripheral Tolerance

Central tolerance is not completely effective; some self-reactive lymphocytes reach peripheral tissues. Peripheral tolerance provides additional safeguards.

Immune Tolerance and Autoimmune Disease

Autoimmune diseases can arise when mechanisms of self-tolerance become inadequate. Autoreactive lymphocytes may recognize self-antigens and initiate inflammatory responses that damage tissues

Examples of autoimmune diseases include:

- Type 1 diabetes mellitus
- Rheumatoid arthritis
- Systemic lupus erythematosus
- Multiple sclerosis
- Autoimmune thyroid diseases

The mechanisms responsible for loss of tolerance are complex and may involve genetic susceptibility, environmental factors, infections, altered antigen presentation, and abnormal immune regulation

Immune Tolerance in Transplantation

Immune tolerance is also highly relevant to organ and tissue transplantation. The recipient's immune system can recognize donor tissues as foreign and initiate rejection Conventional transplantation strategies often rely on immunosuppressive medications. These drugs can reduce rejection but may also increase susceptibility to infections and other complications Consequently, researchers are investigating immune tolerance-inducing approaches that could allow the recipient to accept a transplanted organ while minimizing generalized immunosuppression. Strategies under investigation include regulatory T-cell therapies, cellular therapies, costimulatory blockade, and approaches designed to promote donor-specific tolerance.

Tolerance, Cancer, and Immune Checkpoints

Immune tolerance is beneficial when it prevents autoimmune damage, but excessive immune inhibition can be problematic in cancer. Tumors can exploit regulatory pathways that normally prevent excessive immune activation.Immune-checkpoint pathways, including PD-1/PD-L1 and CTLA-4, can reduce T-cell activity. Modern cancer immunotherapies can block some of these inhibitory pathways, allowing immune cells to respond more effectively against tumor cells.

However, removing immune checkpoints can also disturb normal tolerance and produce immune-related adverse events, demonstrating the close relationship between immune activation and immune regulation

Conclusion

Immune tolerance is a sophisticated network of mechanisms that allows the immune system to distinguish between harmful threats and the body's own tissues. Central tolerance establishes an early barrier against self-reactive lymphocytes, while peripheral mechanisms provide additional layers of control. Regulatory T cells, anergy, deletion, inhibitory signaling, and other mechanisms work together to maintain immune balance.

Disruption of this balance can contribute to autoimmune disease, whereas excessive immune tolerance can facilitate tumor persistence or chronic infection. Understanding these mechanisms is therefore important not only for explaining immune-system function but also for developing more precise treatments for autoimmune diseases, transplantation, cancer, and other immune-related disorders.

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