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Immunopathogenesis of Autoimmune Thyroid Diseases: A Molecular Perspective

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Introduction

Autoimmune Thyroid Diseases (AITDs) are the most prevalent organ-specific autoimmune disorders, encompassing Primarily Hashimoto's Thyroiditis (HT) and Graves ' disease (GD). These conditions arise from a breakdown in self-tolerance that leads to the immune system targeting thyroid antigens. HT is characterized by progressive thyroid destruction, often resulting in hypothyroidism, while GD manifests as hyperthyroidism due to the production of stimulatory autoantibodies against the Thyroid-Stimulating Hormone Receptor (TSHR). The pathogenesis of AITDs involves a complex interplay between genetic susceptibility, environmental triggers and immune dysregulation. Genes encoding HLA molecules, immune checkpoint proteins, cytokines and thyroid-specific proteins are implicated in disease development. Polymorphisms in CTLA4, PTPN22, FOXP3 and IL2RA have been associated with increased risk. Environmental factors such as iodine intake, infections, stress and smoking may trigger disease onset in genetically predisposed individuals. Central to the immune pathology is the aberrant activation of autoreactive CD4+ T cells, followed by B-cell activation and autoantibody production. The thyroid gland itself participates in disease perpetuation through expression of MHC class II molecules and secretion of pro-inflammatory cytokines. Recent advances in immunogenomics and single-cell transcriptomics have shed light on the specific immune cell populations and molecular pathways involved. Understanding the molecular underpinnings of AITDs is essential not only for elucidating disease mechanisms but also for identifying biomarkers and developing targeted immunotherapies. This perspective provides a molecular overview of the immunopathogenesis of autoimmune thyroid diseases, integrating recent insights from genetics, immunology and systems biology [1].

Description

The immunopathogenesis of AITDs begins with the loss of immune tolerance to thyroid-specific antigens such as Thyroglobulin (Tg), Thyroid Peroxidase (TPO) and TSHR. Central tolerance is compromised during thymic selection, allowing autoreactive T cells to escape into the periphery. Peripheral tolerance mechanisms, including regulatory T cells (Tregs), anergy and deletion, are often insufficient or dysfunctional in individuals with AITD. A critical step in the initiation of autoimmunity is the presentation of thyroid antigens by Antigen-Presenting Cells (APCs) to naïve CD4+ T cells. This interaction is enhanced in the presence of danger signals and inflammatory cytokines, leading to T-cell activation, differentiation and migration to the thyroid gland. In Hashimoto's thyroiditis, Th1 and Th17 cells predominate, producing IFN-γ and IL-17 that mediate thyroid follicular cell apoptosis. In contrast, Graves' disease is characterized by a Th2-biased response, promoting B-cell maturation and autoantibody production. Notably, T follicular helper (Tfh) cells are crucial in supporting the formation of ectopic germinal centers in the thyroid, where affinity maturation of autoreactive B cells occurs. These B cells produce high-affinity autoantibodies, including anti-TPO, anti-Tg and anti-TSHR antibodies, the latter being stimulatory in GD and blocking or neutral in HT. The thyroid epithelium is not a passive target; it contributes to immune activation by expressing HLA-DR molecules and producing chemokines that recruit immune cells. The cumulative effect is chronic inflammation, tissue remodeling and progressive thyroid dysfunction [2].

Genetic predisposition to AITD is supported by familial clustering and twin studies. Genome-Wide Association Studies (GWAS) have identified susceptibility loci shared with other autoimmune diseases, reflecting common immunogenetic mechanisms. The HLA-DR3 and DR5 haplotypes are strongly associated with GD and HT, respectively. Non-HLA genes such as CTLA4, which encodes an inhibitory receptor on T cells and PTPN22, a phosphatase involved in T-cell receptor signaling, are also key contributors. FOXP3 mutations or polymorphisms can impair Treg function, leading to inadequate suppression of autoreactive cells. Additionally, variants in cytokine genes like IL2RA, IL21 and TNFA influence T-cell differentiation and immune homeostasis. Epigenetic mechanisms including DNA methylation, histone modifications and microRNA expression modulate gene expression in immune and thyroid cells, bridging environmental influences with genetic susceptibility. For example, excessive iodine intake may epigenetically enhance antigen presentation or thyroid antigen expression, thus contributing to disease onset. Furthermore, viral infections, particularly with Epstein-Barr virus or hepatitis C, have been proposed as environmental triggers that induce bystander activation or molecular mimicry. Smoking and psychological stress have been linked to GD exacerbations, possibly through immune modulation or sympathetic nervous system activation. These multifactorial influences underscore the complexity of AITD pathogenesis and highlight the need for integrative research approaches [3].

Recent advances in single-cell sequencing, flow cytometry and transcriptomic profiling have provided unprecedented resolution of the immune landscape in AITDs. Infiltrates in the thyroid gland include not only classical Th1 and Th2 cells but also memory T cells, cytotoxic T lymphocytes, innate lymphoid cells and dendritic cells. Regulatory T cells, although present, often exhibit impaired suppressive function. B-cell subsets include both naive and class-switched memory cells, many of which contribute to local autoantibody production. Importantly, the discovery of Tertiary Lymphoid Structures (TLS) in the thyroid tissue of AITD patients has redefined our understanding of chronic autoimmunity. TLS resemble secondary lymphoid organs in architecture and function, supporting antigen presentation, T–B cell interaction and affinity maturation. Molecular profiling of thyroid tissue has revealed overexpression of genes involved in type I interferon signaling, antigen processing and oxidative stress. These findings support a model where local thyroidal immune dysregulation drives autoimmunity independent of systemic immune cues. Moreover, checkpoint molecules such as PD-1, TIM-3 and LAG-3 are altered in expression, suggesting a state of T-cell exhaustion or dysregulation that may prevent resolution of inflammation. These insights pave the way for novel diagnostic markers and potential therapeutic targets, such as modulating Tfh cells, restoring Treg function or inhibiting TLS formation [4].

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Therapeutic approaches in AITDs have traditionally focused on managing thyroid hormone levels through levothyroxine replacement in HT or antithyroid drugs in GD. However, these treatments do not address the underlying autoimmune process. With advances in molecular immunology, new therapeutic strategies are being explored. Monoclonal antibodies targeting B cells (e.g., rituximab) or immune checkpoints (e.g., CTLA4-Ig) have shown promise in clinical trials but remain limited in routine use due to safety and cost considerations. Small-molecule inhibitors of kinases involved in immune cell signaling, tolerogenic vaccines using thyroid antigens and microbiome modulation are areas of active investigation. Another emerging field is precision immunotherapy, where treatment is tailored based on the patient's immunological profile, genetic background and disease phenotype. Biomarkers such as cytokine signatures, gene polymorphisms or antibody titers may help stratify patients who are likely to benefit from immunomodulation. Importantly, early identification of at-risk individuals through genetic or serological screening may enable preventive strategies. Public health interventions such as iodine intake regulation and stress management could also reduce AITD incidence in high-risk populations. As our molecular understanding deepens the future of AITD management will likely shift toward immunological modulation, disease interception and personalized care [5].

Conclusion

In conclusion, autoimmune thyroid diseases are multifaceted disorders arising from a convergence of genetic, environmental and immunological factors. At the molecular level, dysregulation of immune tolerance, altered T- and B-cell responses and local thyroidal immune activation contribute to disease pathogenesis. Advances in immunogenomics, cellular profiling and translational immunology have significantly enhanced our understanding of AITDs and opened avenues for innovative diagnostics and targeted therapies. While current treatments focus primarily on correcting hormonal imbalances, future strategies will likely involve immune-modifying interventions aimed at restoring tolerance and preventing progression. A comprehensive molecular perspective not only informs clinical management but also sets the foundation for precision medicine in thyroid autoimmunity.

Acknowledgement

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Conflict of Interest

None.

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