REVIEW ARTICLE

IMMUNOGENETIC FACTORS IN AUTOIMMUNE THYROID DISEASES: CENTRAL ROLE OF HLA IN DISEASE SUSCEPTIBILITY

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ABSTRACT

Autoimmune thyroid diseases (AITDs), including Graves' disease (GD) and Hashimoto's thyroiditis (HT), represent the most common organ-specific autoimmune disorders worldwide. Their development results from a complex interaction between genetic susceptibility and environmental triggers. Among genetic determinants, human leukocyte antigen (HLA) genes located within the major histocompatibility complex (MHC) are of primary importance. Specific HLA class II polymorphisms influence antigen presentation, T-cell activation, and tolerance breakdown. This article reviews the immunogenetic basis of AITD with emphasis on HLA structure, functional polymorphisms, molecular mechanisms of susceptibility, and available population data, highlighting the need for further investigation in the Albanian population.

FAKTORËT IMUNOGJENETIKË NË SËMUNDJET AUTOIMUNE TË GJËNDRËS TIROIDE: ROLI KYÇ I HLA NË NDJESHMËRINË NDAJ SËMUNDJES

ABSTRAKT

Sëmundjet autoimune të tiroides (AITD), përfshirë sëmundjen e Graves (GD) dhe tiroiditin Hashimoto (HT), përfaqësojnë çrregullimet autoimune organ specifike më të shpeshta në nivel global. Zhvillimi i tyre është rezultat i një ndërveprimi kompleks ndërmjet predispozitës gjenetike dhe faktorëve mjedisorë nxitës. Ndër determinantët gjenetikë, gjenet e antigjenit leukocitar human (HLA), të lokalizuara në kompleksin kryesor të histokompatibilitetit (MHC), kanë rëndësi parësore. Polimorfizmat specifike të HLA të klasës II ndikojnë në prezantimin e

antigjeneve, aktivizimin e qelizave T dhe prishjen e mekanizmave të tolerancës imune. Ky artikull rishikon bazën imunogjenetike të AITD, me theks në strukturën e HLA, polimorfizmat funksionale, mekanizmat molekularë të ndjeshmërisë ndaj sëmundjes dhe të dhënat e disponueshme në popullata të ndryshme, duke theksuar nevojën për studime në popullatën shqiptare.

INTRODUCTION

Autoimmune thyroid diseases affect approximately 2–5% of the general population, with a significantly higher prevalence among women, ranging from 5–15% (1). The two principal clinical entities are Graves' disease (GD), characterized by hyperthyroidism due to stimulating autoantibodies against the thyroid-stimulating hormone receptor (TSHR), and Hashimoto's thyroiditis (HT), characterized by progressive autoimmune destruction of thyroid tissue leading to hypothyroidism.

Although GD and HT manifest with opposing thyroid functional states, they share fundamental immunopathological mechanisms. Both diseases involve lymphocytic infiltration of the thyroid gland, breakdown of immune tolerance, and production of thyroid-specific autoantibodies such as anti-thyroglobulin (TgAb), anti-thyroid peroxidase (TPOAb), and, in GD, anti-TSHR antibodies (2,3). These shared mechanisms suggest overlapping genetic predispositions with disease-specific modifiers.

This article represents a narrative review focused on the immunogenetic mechanisms involved in autoimmune thyroid diseases, with particular emphasis on HLA-related susceptibility. Literature was selected through a non-systematic search of PubMed, Scopus, and Google Scholar databases using keywords including "autoimmune thyroid disease", "Hashimoto thyroiditis", "Graves disease", "HLA", "MHC", and "immunogenetics". Priority was given to original studies, review articles, and landmark publications addressing HLA associations and molecular mechanisms of disease susceptibility.

Genetic Contribution to Autoimmune Thyroid Diseases

The role of genetic predisposition in AITD has been strongly supported by familial aggregation studies. Approximately 33% of siblings of patients with GD or HT develop AITD, and up to

56% of siblings produce thyroid autoantibodies (4). Such findings indicate that genetic susceptibility extends beyond overt clinical disease to subclinical autoimmunity.

Twin studies provide further compelling evidence. Concordance rates are significantly higher in monozygotic (MZ) twins compared with dizygotic (DZ) twins. For GD, concordance reaches approximately 35% in MZ twins versus 3% in DZ twins. For HT, concordance has been reported at 55% in MZ twins and nearly 0% in DZ twins (4). These data clearly demonstrate a strong heritable component, while incomplete concordance underscores the contribution of environmental triggers.

Multiple susceptibility genes have been implicated in AITD, including immune regulatory genes (e.g., CTLA-4, PTPN22, CD40) and thyroid-specific genes (e.g., thyroglobulin). However, among all genetic factors, the HLA region remains the most consistently associated locus.

The Major Histocompatibility Complex (MHC)

The major histocompatibility complex (MHC) is located on the short arm of chromosome 6 (6p21) (5). It is the most gene-dense and polymorphic region of the human genome and is divided into three functional subregions: class I, class II, and class III (6).

Class I MHC Molecules

HLA class I molecules consist of an α (heavy) chain associated with β2-microglobulin. The heavy chain contains two peptide-binding domains (α1 and α2), an immunoglobulin-like domain (α3), a transmembrane segment, and a cytoplasmic tail. It is encoded by the HLA-A, HLA-B, and HLA-C loci.

Class I molecules present endogenous peptides to CD8+ cytotoxic T lymphocytes, which eliminate infected or abnormal cells. Non-classical class I molecules include HLA-E, -F, and -G, as well as pseudogenes (5,7).

Class II MHC Molecules

Class II molecules are particularly relevant to autoimmune disease. They are normally expressed on professional antigen-presenting cells (APCs), including B cells, macrophages, dendritic cells, Langerhans cells, thymic epithelial cells, and activated T cells. They consist of α and β chains,

each containing a peptide-binding domain, an immunoglobulin-like domain, and a transmembrane region.

These molecules are encoded by genes within the HLA-DP, HLA-DQ, and HLA-DR regions. CD4+ T helper cells recognize peptides presented by class II molecules and orchestrate adaptive immune responses (7).

Importantly, class II genes exhibit marked polymorphism, particularly within peptide-binding regions. Variability in amino acid composition directly affects peptide-binding specificity and stability, making these genes central determinants of autoimmune susceptibility.

Class III Region

The class III region encodes molecules involved in inflammatory responses, including complement components (C2, C4, factor B), tumor necrosis factor-α (TNF-α), lymphotoxin, and several heat-shock proteins (7). Although not directly involved in antigen presentation, these molecules contribute to immune regulation and inflammation.

HLA and Susceptibility to Autoimmune Thyroid Disease

Because the HLA region contains numerous immune response genes and exhibits high polymorphism, it was the first candidate region investigated in AITD.

T cells recognize antigenic peptides only when presented by specific HLA molecules (8). Different HLA alleles bind distinct peptide repertoires with varying affinities. If an HLA molecule efficiently binds a thyroid autoantigen, it may present it to autoreactive T cells that have escaped central or peripheral tolerance (5,9). This interaction represents a critical step in the initiation of autoimmune thyroid disease.

HLA Associations in Graves' Disease

In Caucasian populations, susceptibility to GD is strongly associated with HLA-DR3 and the linked allele HLA-DQA1*0501 (10–12). Further molecular analysis identified arginine at position 74 (Arg74) in the HLA-DRβ1 chain as a key determinant (13).

Position 74 lies within pocket 4 (P4) of the peptide-binding groove. Replacement of a neutral amino acid (alanine or glutamine) with positively charged arginine alters the three-dimensional

configuration of the binding pocket. Structural modeling studies demonstrate that this substitution modifies peptide-binding characteristics and influences T-cell activation (13).

Functional studies have shown that HLA-DR3 preferentially binds immunodominant peptides derived from the TSH receptor. Additionally, interaction between DRβ1-Arg74 and a thyroglobulin gene variant confers an odds ratio exceeding 16, suggesting synergistic genetic and biochemical interactions during disease initiation (14).

HLA Associations in Hashimoto's Thyroiditis

In HT, susceptibility has been associated with HLA-DR3, HLA-DR5, HLA-DR4, and HLA-DQw7 (DQB1*0301) (15–17). Although overlap exists between GD and HT, the strength and pattern of associations differ, indicating partially distinct immunogenetic mechanisms.

Evidence from Type 1 diabetes mellitus

Insights into structural-functional mechanisms of HLA susceptibility are well illustrated by Type 1 diabetes mellitus. In this disease, aspartic acid at position 57 of the HLA-DQ β-chain plays a pivotal role (18–20).

Absence of Asp57 alters the charge and structure of the peptide-binding groove, allowing insulin peptides to bind more effectively and be presented to autoreactive T cells. Presence of Asp57, in contrast, stabilizes the groove and reduces pathogenic peptide binding (19,20). This example demonstrates how a single amino acid substitution can significantly influence autoimmune risk.

A similar structural principle likely applies to HLA-DRβ1 Arg74 in GD.

Intrathyroidal Antigen Presentation and Local Immune Activation

For thyroid autoimmunity to develop, autoantigens must be presented locally within the thyroid gland or its draining lymph nodes. In GD and HT, thyroid epithelial cells (thyrocytes) aberrantly express HLA class II molecules (21).

This abnormal expression enables thyrocytes to function as facultative APCs, directly presenting thyroid autoantigens to CD4+ T cells. However, effective T-cell activation requires both antigen presentation and co-stimulatory signaling. CD40 expression on thyrocytes may provide this additional signal, contributing to sustained immune activation and disease progression (22).

Thus, autoimmune thyroid disease likely results from the convergence of genetic susceptibility, structural HLA determinants, local antigen presentation, and co-stimulatory signaling.

HLA Distribution in the Albanian Population

Data regarding HLA allele distribution in the Albanian population remain limited, despite the recognized importance of HLA polymorphisms in autoimmune diseases. In 2009, Sulcebe et al. analyzed HLA allele and haplotype frequencies in 160 healthy unrelated Albanian individuals and demonstrated that the Albanian population shares several immunogenetic characteristics with other southeastern European populations, while also presenting specific haplotypic patterns (17).

The most frequent HLA-A-B-DRB1 haplotypes identified included A02-B18-DRB111, A02-B51-DRB116, and A01-B08-DRB103. Some of these haplotypes contain alleles previously implicated in susceptibility to autoimmune conditions, including autoimmune thyroid diseases in other ethnic groups. However, no studies to date have specifically investigated the relationship between HLA polymorphisms and Graves' disease or Hashimoto's thyroiditis in Albanian patients.

The six most frequent HLA-A-B-DRB1 haplotypes were:

- A02-B18-DRB111 (5.60%)
- A02-B51-DRB116 (4.74%)
- A01-B08-DRB103 (3.48%)
- A24-B35-DRB111 (2.77%)
- A02-B51-DRB113 (2.21%)
- A24-B35-DRB114 (1.89%)

This lack of national data represents an important gap in the current understanding of autoimmune thyroid disease susceptibility within the Albanian population. Since HLA associations often vary significantly among ethnic and geographic populations, findings derived from Caucasian, Asian, or other European cohorts cannot necessarily be extrapolated directly to Albanian individuals. Population-specific immunogenetic studies are therefore essential to

determine whether known susceptibility alleles such as HLA-DR3, HLA-DR5, DQA1*0501, or specific amino acid polymorphisms including DRβ1-Arg74 are similarly associated with disease risk in Albania.

Furthermore, characterization of HLA profiles in Albanian patients with autoimmune thyroid diseases could contribute to improved understanding of disease heterogeneity, familial clustering, antibody production, and potentially different clinical phenotypes. Such studies may also provide the basis for future personalized approaches in risk stratification, early diagnosis, and targeted immunological monitoring.

Given the increasing prevalence of autoimmune diseases and the current absence of local immunogenetic data, further multicenter studies involving Albanian patients with Graves' disease and Hashimoto's thyroiditis are strongly warranted.

CONCLUSION

Autoimmune thyroid diseases arise from complex interactions between genetic predisposition and environmental factors. Among genetic determinants, HLA class II polymorphisms play a central role by regulating antigen presentation and T-cell activation. Specific amino acid substitutions within the peptide-binding groove can alter peptide affinity and influence autoimmune risk.

Understanding these immunogenetic mechanisms in diverse populations, including Albania, may provide valuable insights into disease susceptibility, pathogenesis, and potential strategies for personalized risk assessment and early intervention.

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