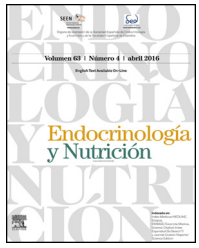
Endocrinol Nutr. 2016;63(8):421–429

Endocrinología y Nutrición

www.elsevier.es/endo



REVIEW ARTICLE

Pathogenesis of thyroid autoimmune disease: the role of cellular mechanisms

Ana Maria Ramos-Leví, Mónica Marazuela*

Department of Endocrinology, Hospital Universitario de la Princesa, Instituto de Investigación Princesa, Universidad Autónoma de Madrid, C/ Diego de León 62, 28006 Madrid, Spain

Received 7 March 2016; accepted 14 April 2016
Available online 24 May 2016

KEYWORDS
Thyroid autoimmunity;
T regulatory cells (Treg);
T helper;
Th17;
Graves' disease;
Hashimoto's thyroiditis

Abstract Hashimoto's thyroiditis (HT) and Graves' disease (GD) are two very common organ-specific autoimmune diseases which are characterized by circulating antibodies and lymphocyte infiltration. Although humoral and cellular mechanisms have been classically considered separately in the pathogenesis of autoimmune thyroid diseases (AITD), recent research suggests a close reciprocal relationship between these two immune pathways. Several B- and T-cell activation pathways through antigen-presenting cells (APCs) and cytokine production lead to specific differentiation of T helper (Th) and T regulatory (Treg) cells. This review will focus on the cellular mechanisms involved in the pathogenesis of AITD. Specifically, it will provide reasons for discarding the traditional simplistic dichotomous view of the T helper type 1 and 2 pathways (Th1/Th2) and will focus on the role of the recently characterized T cells, Treg and Th17 lymphocytes, as well as B lymphocytes and APCs, especially dendritic cells (DCs).

PALABRAS CLAVE
Tiroideas autoinmunitarias;
Células T reguladoras (Tregs);
T helper;
Th17;

Patogenia de la enfermedad tiroidea autoinmune: papel de los mecanismos celulares

Resumen La tiroiditis de Hashimoto y la enfermedad de Graves son 2 enfermedades tiroideas autoinmunitarias muy frecuentes, que se caracterizan por la presencia de autoanticuerpos circulantes e infiltración linfocitaria. Aunque clásicamente se han considerado los mecanismos humorales y celulares de forma independiente, la evidencia actual apoya la existencia de una relación recíproca entre ambas vías de autoinmunidad en la patogenia de la enfermedad tiroidea autoinmune (ETAI). La presentación de antígenos por parte de las células presentadoras de

* Corresponding author.
E-mail address: monica.marazuela@salud.madrid.org (M. Marazuela).

http://dx.doi.org/10.1016/j.endonu.2016.04.003

Enfermedad de Graves;
Tiroiditis de Hashimoto

antígenos y su producción específica de citocinas conduce a una diferenciación de células B y T. El objetivo de este trabajo es revisar los mecanismos celulares implicados en la patogenia de la ETAI. En concreto, se argumentan razones para descartar la visión tradicional, simplista y dicotómica de las vías de las células T helper tipo 1 y 2 (Th1/Th2), y se revisan en detalle las células T recientemente caracterizadas, las células T reguladoras (Tregs) y Th17, así como las células B y las células dendríticas (DC).

Introduction

Hashimoto's thyroiditis (HT) and Graves' disease (GD) are two very common organ-specific autoimmune diseases which are characterized by the presence of circulating thyroid antibodies and infiltration by autoreactive lymphocytes of the thyroid gland, and occasionally the orbit. In this setting, an immunological overlap with other autoimmune diseases and a family history, mainly in females, are frequently found. It has been traditionally thought that HT is mainly mediated by a cellular autoimmune response, with a strong inflammatory infiltrate, which leads to destruction and resultant failure to function of the thyroid gland. On the other hand, GD has mainly been considered to be mediated by a humoral autoimmune response, mainly due to the presence of autoantibodies directed against the thyrotropin receptor (TRAb) which stimulate the growth and function of thyroid follicular cells (TFCs), thus leading to development of goiter and hyperthyroidism. However, as in other autoimmune disorders, humoral and cellular immune mechanisms are closely related and cross-linked in AITD and, once they are triggered, they undergo subsequent feedback circuits which reciprocally amplify and perpetuate one of the responses, while inhibiting the opposite, thus denoting the complex mechanisms involved in the pathogenesis of AITD.[1,2] Moreover, both immune responses have also been reported in the pathogenesis of Graves' orbitopathy, one of the most common extrathyroid manifestations of AITD, which may occur in up to 25% of patients with GD.[3]

Activation of specific pathways for T cell differentiation may depend on the concentration and type of antigen exposure, the nature of the initial antigen-presenting cells (APCs) and, presumably, on still undefined genetic and environmental factors. In this regard, development of experimental models has allowed for increasing understanding of the pathogenesis of AITD. However, a complete understanding of how the complex interaction between genetic susceptibility and environmental factors operates has not been achieved, and further research is needed on why this autoimmune process starts, leading to failure of immunological tolerance at multiple levels.

This review will focus on the cellular mechanisms involved in AITD pathogenesis, specifically the role of the recently characterized T cells, T regulatory (Treg) and T helper (Th) lymphocytes, and also of B lymphocytes and APCs, especially dendritic cells (DCs).

Immune cellular mechanisms in autoimmune diseases: where does it all start?

Maturation of T helper CD4+ lymphocytes occurs in the thymus gland after activation on exposure to specific antigens and cytokines. Normally, activation and proliferation of T cells reacting to self-antigens are previously deleted in the thymus by mechanisms of immune central tolerance. In some individuals, however, autoreactive T cells escape from the controlling immune regulatory mechanisms and may activate, proliferate and differentiate, leading to development of an autoimmune response (Fig. 1).

Differentiated T cells will emerge from the thymus to peripheral lymphoid tissue as mature naïve T cells. Once at the periphery, signals based on response to antigens, co-stimulators and/or specific cytokines result in either activation or downregulation of T cells, which results in different subsets of effector cells (Th1, Th2, and Th17) and a smaller population of Treg.[4] Each specific lymphocyte subtype will have specific markers which will serve as potential identifiers, and each cell type will subsequently secrete specific cytokines, contributing to fulfillment of their specific actions, as will later be explained. In addition, B-cells will be stimulated to produce autoantibodies, while CD4+ T cells will be the major type of lymphocyte infiltrating the specific tissue/organ. We will further discuss these mechanisms and their specific involvement in AITD.

Main actors in thyroid cellular autoimmunity

Antigen-presenting cells and lymphocyte migration to the thyroid gland

APCs, especially DCs, are bone marrow-derived cells of both lymphoid and myeloid stem cell origin that populate all lymphoid organs, as well as almost all non-lymphoid tissues and organs. Human peripheral blood DCs have been classified as conventional DCs (cDCs) and plasmacytoid DCs (pDCs) depending on their specific characteristics.[5] As part of the innate immune system, DCs can rapidly respond to environmental damage and mount a primary immune response, mainly thanks to their potent antigen-presenting capacity for stimulating naïve, memory, and effector T cells[5]. In fact, in order to perform their functions, DCs induce energy and apoptosis of effector lymphocytes, generate Treg cells, and synthesize several cytokines which modulate activation of