Human major histocompatibility complex and thyroid dysfunction in hepatitis C carries

Complexo de histocompatibilidade maior humano e disfunção tireoidiana em portadores de hepatite C

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Abstract

The major histocompatibility complex (MHC) is a multigenice family of receptors which are crucial in antigen presentation, mediation, and initiation of the cellular immune response. An association exists between certain MHC polymorphisms and autoimmune thyroid disease in animals and humans. Hepatitis C virus (HCV) infection the treatment of hepatitis C with interferon-α (IFN-α)have been shown to be associated with increased incidence of thyroid dysfunction. IFN-α has been the basis for the treatment of HCV infection identified as an immunomodulatory cytokine that induces T-lymphocyte activation and expression of MHC molecules. It becomes evident therefore that the MHC- class I and MHC- class II antigens are central to the host immune response and thus are ideal candidate genes to investigate for associations with HCV infection. Autoimmune thyroid diseases are characterized by increased, rather than decreased expression, of MHC- class II antigen. Furthermore, work in animals suggests that the increased production of thyroid antibody and expression of MHC- class I and MHC- class II antigen are associated. This study will approach the relation between MHC and thyroid dysfunction in HCV infection carries.
Key Words: Major histocompatibility complex. Hepatitis C. Interferon-alpha. Thyroid dysfunction. Autoimmunity.

Resumo

O complexo de histocompatibilidade maior (CHM) é uma família multigênica de receptores que são cruciais na apresentação de antígenos, mediação e início da resposta imune celular. Existe uma associação entre determinados polimorfismos do CHM e a doença auto-imune da tireóide em animais e humanos. Foi demonstrado que o vírus da hepatite C (HCV) e o tratamento da hepatite C crônica com interferon-α (IFN-α) estão associados ao aumento da incidência de disfunção da tireóide. O IFN-α tem sido a base para o tratamento da infecção pelo HCV, tendo sido identificado como uma citocina imunomoduladora que induz a ativação de linfócitos T e a expressão de moléculas de CHM. Torna-se evidente, portanto, que antígenos CHM- classe I e CHM-classe II são fundamentais para a resposta imune do hospedeiro e, portanto, são candidatos a genes ideais para investigar as associações com infecção pelo HCV. Doenças auto-imunes da tireóide são caracterizadas por aumento da expressão de antígenos CHM-classe II. Além disso, pesquisas em animais sugerem que o aumento da produção de anticorpos antitireoidianos e a expressão de antígenos CHM-classe I e MHC-classe II estão associados. Este estudo abordará a relação entre o CHM e disfunção tireoidiana em portadores de infecção pelo HCV.
Palavras-chave: Complexo de histocompatibilidade maior. Hepatite C. Interferon-alfa. Disfunção da tireóide. Auto-imunidade.

INTRODUCTION

The human leukocyte antigen system (HLA) is the name of the major histocompatibility complex (MHC) in humans. The MHC is a multigene family of receptors which are crucial in antigen presentation, mediation, and initiation of the cellular immune response, and are found in the region of chromosome 6p21 with sites involved in peptide binding form binding pockets that are collectively termed the peptide-binding region. Since the HLA region contains many immune response genes, and has been shown to be highly polymorphic, it logically became the first candidate genetic region to be studied for association with thyroid dysfunction, as well as for association with other autoimmune diseases. The MHC is highly variable from individual to individual, and segregates in families in a mendelian codominant fashion. [1]

Discovery of MHC helped in the understanding of how T-lymphocytes recognize antigens on viruses, and has been shown to be associated with spontaneous resolution of viremia following hepatitis C virus (HCV) infection. The interferon-α (IFN-α) has been the basis for the treatment of HCV infection has been identified as an immunomodulatory cytokine that induces T-lymphocyte activation and expression of MHC molecules.

An association exists between certain MHC polymorphisms and autoimmune thyroid disease in animals and humans. The target cells in several organ

specific autoimmune diseases have been shown to express MHC class II (MHC-II) aberrantly and this expression may have allowed presentation of such cell specific surface antigens to potentially autoreactive T helper lymphocytes. Previous studies in vitro findings that reovirus enhances the expression of MHC class I (MHC-I) molecules in cultured human thyroid follicular cells through induction of IFN-α, and aberrant expression of MHC-II antigens is associated with autoimmune thyroid disease. [2]

HCV infection has been shown to be associated with increased incidence of thyroid dysfunction, moreover, IFN-α therapy of chronic HCV infection is associated with the thyroid dysfunction. IFN-α induces MHC-II expression and probably CD40 expression on thyrocytes and, beside MHC-II, the IFN-α also induces MHC-I expression on thyrocytes by way of interleukin-2 and chemokines. Becomes evident therefore that the MHC- I and MHC-II antigens are central to the host immune response and thus are ideal candidate genes to investigate for associations with HCV infection. [3,4]

This study will address the relation between MHC and thyroid dysfunction in HCV infection carries.

Human Major Histocompatibility Complex

The HLA is the name of the MHC in humans, and corresponds to complex group of genes on a single chromosome that codes the MHC antigens. The classical MHC is divided into 3 sub-regions, class II (centromeric), class I, and class III (telomeric). The MHC-I or MHC-II molecules are those cell surface glycoproteins that actually perform the binding and recognition steps, while other genes that map to the MHC-I or MHC-II regions may contribute to antigen-processing and presentation functions in other distinct ways. The overall structures of the class I and II MHC molecules are comparable [5]. The genes in the class III region encode complement components which are involved in the induction of inflammatory responses and damages to pathogens via proteolytic cleavages of glycoproteins.

The major function of the MHC molecules is to facilitate the display of unique molecular fragments on the surface of cells in an arrangement that permits their recognition by immune effectors such as T-lymphocytes.

The MHC has received much attention in the fields of evolutionary and conservation biology because of its potential implications in many biological processes. The MHC-I molecules function primarily as the targets of the cellular immune response, whereas the MHC-II molecules regulate both the humoral and cellular immune responses.

·MHC class I

MHC-I molecules are heterodimers of a class I heavy chain and β_2-microglobulin, which display peptides derived from proteins degraded in the cytosol

on the cell surface and thus facilitate the recognition of intracellular antigens by circulating cytotoxic CD8+ T cells with $\alpha\beta$ T-cell receptors [6] (Figure 1).
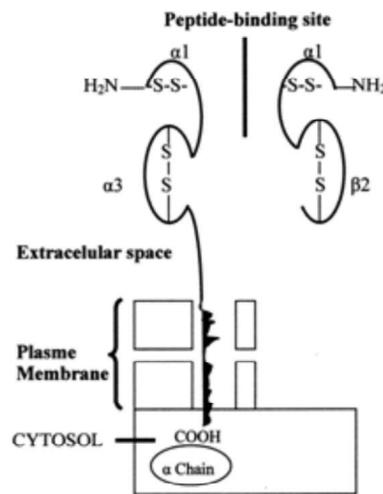

Figure 1 - Schematic structure of MHC-I molecule

This peptide–MHC interaction not only contributes to the stability of the heterodimer on the cell surface, but forms the basis for its function, as complexes of intracellular pathogen derived peptides with MHC are the ligands for cytolytic $\alpha\beta$ T-cells. Thus MHC-I is expressed on the surface of most nucleated cells in the body, where it presents antigens derived from cytosolic proteins. MHC is a set of high lypolymorphic integral membrane glycoproteins consisting of two non-covalently associated polypeptides of M_r 45,000 and M_r 12,000. The M_r 45,000 heavy chain has been shown to contain all of the structural polymorphism associated with class I antigens and is therefore responsible for the serologically defined polymorphism of HLA-A, -B, and -C antigens. The peptide ligands are derived from pathogenic organisms or from endogenous proteins and can form complexes with HLA class I molecules due to sufficient binding affinity for the binding cleft of the HLA molecule. These peptide ligands, in context with HLA class I, are presented on the cell surface and recognized by appropriate cytotoxic CD8+ T cells. MHC-I molecules are expressed on the nuclear cells and load protease-generated peptides to CD8^{+} T-lymphocytes.

MHC-I genes encode proteins that are expressed on the surface of nearly all nucleated cells in the body. Peptides displayed on the cell surface by MHC-I are generated by proteolytic processing of protein-antigens in the cytoplasm. Initially, antigens are degraded by the 26S proteasome, most probably following ubiquitination. These peptides are degraded by the proteasome complex in the cytosol and then are actively

translocated into the lumen of the endoplasmic reticulum by the transporters associated with antigen processing (TAP), a heterodimer constituted by the TAP1 and TAP2 subunits. [7]

Growing evidence indicates that these immune functions are only the tip of the icebergs, and that MHC-I proteins also perform crucial roles outside the immune system.

·MHC class II

The MHC- II molecules are highly polymorphic membrane glycoproteins that bind peptide fragments of proteins and display these peptides for recognition by CD4^{+} T cells. MHC-II genes are expressed primarily on specialized antigen-presenting cells such as macrophages, B lymphocytes, and dendritic cells. The MHC-II molecules must bind a large number of different peptides to guarantee T cell-mediated immunity to the universe of foreign antigens. The MHC-II peptides are derived from endosomes and are cleaved by nonspecific enzymes and, the binding of a peptide to a particular class II allele is nevertheless specific. Activated macrophages also increase expression of MHC-II and adhesion molecules, resulting in more effective antigen presentation to T helper cells.

Synthesis of the classical MHC-II molecules takes place in the endoplasmic reticulum where they bind to the invariant chain (Ii) molecule at the peptide-binding domain. Ii molecules act as chaperones directing the classical MHC-II molecules to the endocytic pathway and prevent the peptide grooves from binding with self-molecules. The non-classical MHC-II molecules HLA-DM and HLA-DO mediate the removal of invariant chain peptide and the loading of the antigens onto the groove of the classical MHC-II molecule, which is then transferred to the cell surface where it interacts with CD4+ T cells to regulate the adaptive immune responses against invading pathogens. [8]

Transcription of MHC-II is regulated by promoter elements, which consist of conserved upstream sequences called the S, X, and Y boxes and downstream sequences, which in the DRA promoter, include an octamer-binding site. The MHC-II protein consists of two amino acid chains, called α and β, encoded by MHC-II A and MHC-II B genes, respectively. DNA sequences of the MHC-II α and β chain extracellular domains are modified as follows: a T cell epitope is covalently attached to the extracellular domain of the MHC-II β chain by insertion directly following the signal peptide. Leucine zippers are fused to the COOH-terminus of the extracellular domains of α and β chains to promote heterodi-merization and a His-tag and biotinylation signal is attached to the MHC-II α and β chain respectively for subsequent purification and tetramer formation. Several highly conserved promoter DNA elements that control MHC- II gene transcription, as well
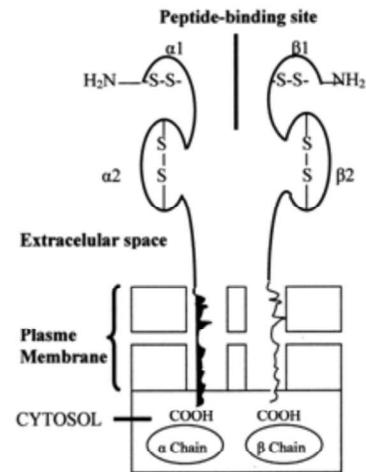

Figure 2 - Schematic structure of MHC-II molecule

as potential transacting factors with which they interact, have been identified [9] (Figure 2).

The MHC-II region is of particular interest because very many of the <"40 genes included are specifically involved in antigen processing and presentation to the T-cell receptors. The class II region shows evidence of rapid adaptive duplications and deletions as well as allele and haplotype polymorphism within and between human and mouse species.

The constitutive expression of MHC-II molecules is restricted to antigen-presenting cells and, only a limited number of cell types express MHC-II molecules which include cells of the monocyte-macrophage lineage, dendritic cells and B lymphocytes. Previous studies showed that MHC-II gene expression is regulated by epigenetic mechanisms. For example, the MHC-II transactivator and the regulatory factor X proteins serve as focal points for recruiting histone modifying enzymes to MHC-II promoters. Much of understanding on the transcriptional control of MHC-II gene expression has been derived from studies with cells obtained from patients with a MHC-II deficiency, also referred to as bare lymphocyte syndrome. [10]

The regulation transport from lysosomes to the plasma membrane has specifically been described for MHC-II molecules. Therefore MHC-II may be an ideal marker to study the nature of transport vesicles mediating retrograde transport from lysosomes.

In summary MHC- II are expressed only by antigen-presenting cells, and encode cell surface proteins with a peptide-binding region that bind and present self and foreign peptides to CD4 T-cells, to trigger the immune response.

Human Major Histocompatibility Complex and Hepatitis C

Exposure to a virus-infected cell can cause the antigen-specific T lymphocytes to differentiate into

cytotoxic effector T cells, which can lyse virus infected or virally transformed cells. These cytotoxic T cells are specific not only for the viral antigen but also for self major histocompatibility antigens and will lyse virus-infected cells only if these cells also express the correct MHC gene products.

MHC-I and MHC- II antigens are central to the host immune response and thus are ideal candidate genes to investigate for associations with HCV infection. The various stages of HCV infection evolution have been found to be associated with the MHC.

Previous studies demonstrated that killer cell immunoglobulin-like receptor genes and MHC-I and MHC-II loci helped determining the clinical outcome of HCV infection. Several other studies have examined the association of MHC alleles with the progression or resolution of liver disease, and DQB1*0401 and DRB1*0405 were more prevalent among patients who developed chronic liver disease, and HLA-DRB1*0701 has been shown to be associated with persistence in patients who were homogeneous in terms of gender, source of infection (genotype 1b) and ethnicity. [11]

The study of a class MHC-II restricted immunodominant molecule within the non-structural 3protein region of HCV has identified a highly significant variation that correlated with escape from CD4+ T cell responses. Cytotoxic T lymphocytes recognize peptide fragments of cellular or viral proteins in the form of short peptides comprising amino acids presented in association with MHC-I molecules on the surface of infected cells. [12]

Variation within a viral epitope can lead to a total or partial loss of functional recognition by cytotoxic T lymphocytes. Substitutions occurring at key anchor residues may alter peptide affinity for MHC-I molecules and thereby interfere with antigen presentation and effector T-cell mediated clearance of infected cells.

The effects of HCV proteins on MHC-I restricted antigen presentation are not widely studied and most of the findings are related to MHC-II restricted antigen presentation. HCV alters antigen-presentation capacities of professional antigen-presenting cells, thereby contributing to the persistence of virally infected cells, and the most prominent effects were observed on MHC-II restricted antigen presentation and dendritic cells functions. The associations between the human MHC and sustained virological response have been found in HCV infected patients, indicating that the various immunogenetic backgrounds of chronic HCV infection patients are related to the differences in the course of the disease. [1]

Visualization of HCV specific T cells ex vivo using MHC-I tetramers has demonstrated that HCV-specific CD8+ T cells are severely impaired in function in chronically infected individuals, as demonstrated by the lack of proliferation and cytokine production in response to specific antigen stimulation. Generation of HCV-specific CD4+ T cells occurs after stimulation by MHC-II/viral peptide complexes and facilitates the induction of HCV-specific CD8+ T-cell responses and optimal antibody production. CD8+ T cells recognize and attack infected cells expressing viral peptides in the context of MHC-I surface molecules.

Human hepatocyte expression of MHC-I has been well documented as low to absent in vivo. The ability of hepatocytes to act as good targets for CD8+ T-cells is crucial for the clearance of heptotrophic viral infections. Central to the success of the CD8+ T-cells responses is the recognition of infected cells through TCR-MHC-I interactions. The low or absent levels of MHC-I on hepatocytes have be described in vivo and could potentially contribute to the failure of the CD8+ T-cells response to clear HCV. [13]

The IFN-α has been the basis for the treatment of HCV, and the major effect of IFN is their modulation of antigens of the MHC. All IFN induce an increase in surface expression of MHC-I antigens. IFN-α is known to induce the up-regulation of MHC-I on many cell types including hepatocytes. Moreover, IFN-α represents a major component of the current HCV infection treatment, as well as being expressed by cells upon viral infection as part of the innate cellular response. [13]

Recent studies suggest that type I IFN have an impact on adaptive immunity by regulating MHC-I antigen expression, stimulating dendritic cell maturation, and increasing the function of the natural killer cells. IFN-α has been identified as an immunomodulatory cytokine that induces T-lymphocyte activation and expression of MHC molecules. However the reports by studies investigating MHC polymorphisms and response to IFN-based therapy have been largely inconsistent and, the studies themselves are characterized by considerable heterogeneity arising from factors such as differences in ethnic composition, genes evaluated and genotyping method. [1]

Major histocompatibility complex and thyroid dysfunction in hepatitis C

Many of the human thyroid diseases appear to be autoimmune diseases, and the roles of the MHC cell surface molecules in the etiology of these diseases have been examined extensively.

The MHC is one of the most important regions of the genome with respect to immunity to pathogens, autoimmunity and transplantation. It contains clusters of genes that are critical for innate and adaptive immune function, including antigen processing and presentation as well as the complement system. MHC genes are under tight regulatory control and mis-regulation of their expression gives rise to a range of diseases.

The pathogenesis of IFN associated autoimmunity included induction of MHC and other molecules as well as the modulation of lymphocyte

functions. The expression of MHC- II molecules on thyrocytes has been demonstrated in autoimmune thyroid diseases. There a relationship with cytokine production and MHC system. MHC-II genes may play a role in the clearance of, and susceptibility to HCV infection, and may influence the development of different phenotypes of thyroid disorders. [14]

The cytokines enhance the expression of MHC-I and MHC-II molecules on thyrocytes. INF gamma increases thyrocyte expression of MHC-II molecules, theoretically enhancing antigen presentation, and IFN-α induces MHC-II expression and probably CD40 expression on thyrocytes [3]. Beside MHC-II, IFN also induces MHC-I expression on thyrocytes by way of interleukin -2 and chemokines [4], adding to the inflammatory response and the thyroiditis. Cytokines can affect thyrocyte growth, signal transduction, iodine organification, hormone release and thyroglobulin production.Therefore cytokines may contribute to the development of thyroid dysfunction through direct actions on thyrocytes.

Current practice guidelines recommend that individuals with HCV infection be treated with IFN-α plus ribavirin. The treatment with IFN-α for HCV infection is associated the etiology of thyroid disorders, especially thyroid autoimmune disorders, and has been asserted on the grounds of epidemiological. The exogenous IFN-α is believed to stimulate lymphocyte, macrophage and neutrophil function as well as increasing cytokine and chemokine concentrations, especially, interleukin-6. IFN-α induces MHCII expression and probably CD40 expression on thyrocytes, and the latter results in an increased T-cell activation of the CD40 signalling pathway within the thyroid gland. [3]

Administration of INF-α, used in the treatment of HCV infection, is most commonly associated with hypothyroidism. Hyperthyroidism, sometimes followed by hypothyroidism (reminiscent of subacute thyroiditis), has also been described following INF-α therapy. Thyroid dysfunction appears to occur more often in patients who had anti-thyroid peroxidase antibodies prior to the initiation of cytokine therapy and is often permanent.[15]

·Major histocompatibility complex and Hyperthyroidism

The term hyperthyroidism refers to any condition in which there is too much thyroid hormone in the body. Grave's disease (GD) is the commonest form of hyperthyroidism. It is mediated by an antibody directed against the thyroid-stimulating hormone (TSH) receptor on the thyroid cells, which acts as an agonist for TSH, thus stimulating the thyroid cells to hyperactivity (Figure 3).

Several studies of the MHC-HLA complex locus located at chromosome 6p21.3 have shown a well defined relationship to susceptibility to autoimmune
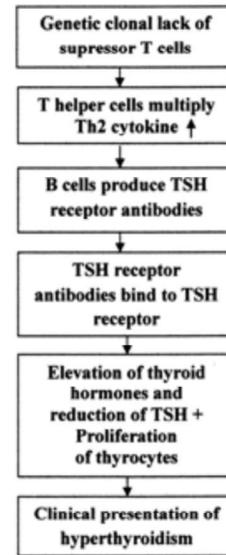

Figure 3 - Physiopathology of hyperthyroidism

thyroid disease within specific ethnic groups. The regulation of HLA class I molecules on thyroid cells, including HLA-B and HLA-C molecules, has been demonstrated in response to immune cell infiltration of the thyroid gland, which may be one of the earliest features of autoimmune attack in GD. MHC-I molecules could be playing a greater role than MHC-II molecules in GD for a number of reasons. MHC-I molecules bind and present internally derived peptides including viral or bacterial antigens which may be linked to disease initiation through molecular mimicry. [15]

IFN gamma is a likely modulator of MHC-II expression in the thyroid but other signals like TSH seem to influence its action. Several case-control studies have demonstrated an association of MHC-II alleles with GD, and linkage analysis has confirmed this association.

Association of the MHC-II encoded HLA-DRB1-DQA1-DQB1-DR3 haplotype with GD has been known for several years. HLA-DR3 is associated with DG in whites. HLA-DQA1 is associated in some populations, especially for men. However, the overall contribution of MHC genes to GD has been estimated to be only 10–20% of the inherited susceptibility. Other MHC-II antigens, including death receptor antigen, have been shown to be aberrantly expressed by both thyroid follicular cells and activated lymphocytes in patients with GD. Previous work on GD has emphasized the capacity of MHC-II expressing thyroid follicular cells to present antigen to auto-reactive T cells, which infiltrate the affected tissue. [16]

Iodide therapy in GD is a well recognized treatment, and high concentration of iodide suppresses thyroid hormone secretion. Iodide has been reported to decrease MHC-I and MHC-II gene expression in rat FRTL-5 thyrocytes, human thyrocytes, and GD in vivo. The

studies suggest that the therapeutic action of iodide in GD is associated with decreased MHC gene expression that this action is a direct effect of high concentrations of iodide on the thyroid cells, and that altered MHC gene expression in the target tissue may well be associated with the development or perpetuation of GD.

Type I IFN modulate the immunoregulatory system, these cytokines may precipitate autoimmune disorders. Hyperthyroidism has been reported in patients treated with IFN-α for HCV infection. IFN-α is also known to suppress the expression of MHC-II antigens in thyroid cells, and the CD40 expression on thyrocytes in situ compared to normal thyrocytes. Moreover, IFN increases the expression of the MHC-I antigen on thyroid epithelial cells, activating cytotoxic T cells by way of interleukin-2 and chemokines. The result is inflammation leading to tissue damage and hypothyroidism or GD. [4]

In GD, IFN is thought to induce or modulate switching of the T-cell response to TH2. This, in turn, stimulates B cell proliferation and differentiation under the influence of interleukin-6 and increase CD40 overexpression, resulting in an increase in TSH stimulating immunoglobulin, simulating GD. [3]

In summary MHC have been associated with GD in several populations of distinct ethnic background and there is increasing evidence supporting an association between GD and HLA-DRB1-DQA1-DQB1-DR3 haplotype.

·Major histocompatibility complex and Hypothyroidism

For an adequate thyroid hormones production, it is important that the hypothalamic-pituitary-thyroid axis be maintained whole so as to ensure the sequence of activities of the hypothalamic releasing hormone over the pituitary gland, producing TSH, which in turn acts on the thyroid, producing thyroid hormones. Deficiencies in these stages lead to tertiary (hypothalamic), secondary (pituitary) or primary (thyroid) hypothyroidism.

Hypothyroidism results of deficiency in the production or in the activity of thyroid hormone from the thyroid gland, being iatrogenic destruction of the gland and autoimmune thyroiditis represent the most common causes of adult primary hypothyroidism in iodine-sufficient areas, and other causes are surgical removal of the thyroid gland, thyroid gland ablation with radioactive iodine, external irradiation, a biosynthetic defect in iodine organification, replacement of the thyroid gland by tumor, and drugs such as lithium or IFN (Figure 4). [17]

Thyroid hormones may be lowered by a variety of different mechanisms, but true primary immune-mediated hypothyroidism is usually characterized by the presence of autoantibodies. Further support for the sharing of autoimmune loci between related disorders comes from association of polymorphism of the
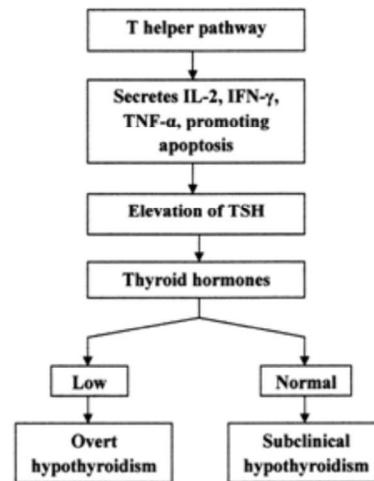

Figure 4 - Physiopathology of hypothyroidism

cytotoxic T lymphocyte associated-4 gene with autoimmune hypothyroidism.

The presence of hypothyroidism in chronically HCV-infected individuals, either under treatment or not, has been well documented, and the data suggest that MHC may influence your development.

Increased expression of MHC-I genes and aberrant expression of MHC-II genes in thyroid epithelial cells is associated with autoimmune hypothyroidism. There has also been a resurgence of interest in antigen presentation by "nonprofessional" cells, a phenomenon first recognized in autoimmune thyroid disease in which thyrocytes were observed to "aberrantly" express MHC class II molecules and to function as antigen-presenting cells. [18]

Long term IFN-α therapy is frequently associated with side effects which affect the thyroid gland such as hypothyroidism, because the IFN increase the expression of both MHC-I and MHC-II molecules.

Major histocompatibility complex and Hashimoto's thyroiditis

Evidence indicates that there is a strong genetic component that predisposes individuals to autoimmunity. The autoimmune thyroid disease (ATD) is a multifactorial disease with a significant genetic and environmental component. Genetic susceptibility in combination with external factors is believed to initiate the autoimmune response to thyroid antigens. The pathogenesis of ATD is known to be associated with autoimmune processes against various constituents of thyroid tissues, including cell membranes, receptors, and enzymes. ATD encompasses two entities: autoimmune thyroiditis represented by Hashimoto's thyroiditis (HT), and autoimmune hyperthyroidism represented by GD previously discussed.

The primary genes linked to autoimmunity are those of the MHC. MHC-II molecule, play a role in presenting antigen to the immune system and thus participate in immune and autoimmune responses. The expression of MHC-II molecules on thyrocytes has been demonstrated, and it has been reported that HLADR and DQ subgroups were associated with HT. [19]

The development of the autoimmune failure of the thyroid is a multistep process, requiring several genetic and environmental abnormalities to converge before full blown disease develops. At the onset of disease, MHC-II positive antigen-presenting cells, particularly dendritic cells, and different subclasses of macrophages, accumulate in the thyroid. The mechanisms, whereby auto reactive T cells escape deletion and anergy, and become activated, remain uncertain. There is evidence that the thyroid cell itself, by "aberrantly" expressing MHC molecules, can play the role of "non-professional" antigen-presenting cells and present disease-initiating antigen directly to the T cells, and elevated interferon levels lead to aberrant MHC antigen expression by thyrocytes provoking an autoimmune response and the development of antithyroid antibodies. Beside MHC-II, IFN-α also induces MHC-I expression on thyrocytes by way of interleukin-2 and chemokines, adding to the inflammatory response and the thyroiditis. [4] Indeed, in thyroid sections from patients with either HT, MHC-II positive thyrocytes were found immediately adjacent to aggregates of IFN-α positive lymphocytes, suggesting that MHC-II expression by the thyrocytes was secondary to the release of IFN-α by the infiltrating T cells. [20]

FINAL REMARKS

MHC-I and MHC-II antigens are central to the host immune response and thus are ideal candidate genes to investigate for associations with HCV. MHC-I molecules may present HCV epitopes to cytotoxic T cells, resulting in a protective immune response.

Some patients with chronic hepatitis C experience thyroid problems, and thyroid dysfunction may also be a side effect of IFN-based treatment. One of the cardinal effects of IFN-α is to increase MHC-I antigen expression on cells but suppress the expression of MHC-II antigen. Indeed, IFN-α was shown to increase the expression of MHC-I antigens on thyrocytes. Over-expression of MHC-I antigens is associated with activation of cytotoxic T cells, and thus can lead to tissue damage and inflammatory response.

Autoimmune thyroid diseases are characterized by increased rather than decreased expression of MHC-II antigen. Furthermore, work in animals suggests that the increased production of thyroid antibody and expression of MHC-I and MHC-II antigen are dissociated.

Aberrant expression of MHC-II molecules by thyrocytes is a characteristic finding in thyroid autoimmune diseases such as HT, GD and focal thyroiditis. It is generally accepted that in established thyroid autoimmunity MHC-II expression on thyrocytes is secondary to thyroid inflammation rather than being a primary event.

Support evidence for the view that MHC-II expression on thyrocytes may be due to local release of IFN in these diseases where of IFN containing lymphocytes adjacent to MHC-II expressing thyrocytes in thyroids with autoimmune diseases.

Competing interests: The authors declare that they have no conflict interests.

REFERENCES

1. RHODES, S. L. et al. Associations between the human MHC and sustained virologic response in the treatment of chronic hepatitis C virus infection. **Genes Immun.**, Basingstoke, v. 9, n. 4, p. 328-33, June. 2008

2. MONTANI, V. et al. Regulation of major histocompatibility class II gene expression in FRTL-5 thyrocytes: opposite effects of interferon and methimazole. **Endocrinology.**, Baltimore, v. 139, n. 1, p. 290-302, Jan. 1998.

3. RIDGWAY, E. C.; TOMER, Y.; MCLACHLAN, S. M. Update in thyroidology. **J. Clin. Endocrinol. Metab**., Philadelphia, v. 92, n. 10, p. 3755-3761, Oct. 2007.

4. LLOYD, A. R. et al. Host and viral factors in the immunopathogenesis of primary hepatitis C virus infection. **Immunol. Cell Biol.**, Adelaide, v. 85, n. 1, p. 24-32, Jan. 2007.

5. STROMINGER, J. L. Structure class I and class II HLA antigens. **Br. Med. Bull.**, London, v. 43, n. 1, p. 81-93, 1987.

6. GERMAIN, R. N.; MARGULIES, D. H. The biochemistry and cell biology of antigen processing and presentation. **An. Rev. Immunol.**, Palo Alto, v. 11, p. 403-50, 1993.

7. KLOETZEL, P. M.; OSSENDORP, F. Proteasome and peptidase function in MHCclass-I-mediated antigen presentation. **Curr. Opin. Immunol**., Philadelphia, v. 16, n. 1, p. 76-81, Feb. 2004.

8. KUMANOVICS, A.; TAKADA, T.; LINDAHL, K. F. Genomic organization of the mammalian MHC. **An. Rev. Immunol.**, Palo Alto, v. 21, p. 629-657, Apr. 2003.

9. CLINICHER, L. H.; KARA, C. Sequences and factors: a guide to MHC class II transcription. **An. Rev. Immunol.**, Palo Alto, v. 10, p. 13-19, Apr. 1992.

10. Reith W, Mach B. The bare lymphocyte syndrome and the regulation of MHC expression. **An. Rev. Immunol.**, Palo Alto, v. 19, p. 331-373, Apr. 2001.

11. FANNING, L. J.et al. HLA class II genes determine the natural variance of hepatitis C viral load. **Hepatology (Baltim.).**, Baltimore, v. 33, n. 1, p. 224-230, 2001.

12. RÖTZSCHKE, O. et al. Isolation and analysis of naturally processed viral peptides as recognized by cytotoxic T cells. **Nature (Lond.).**, London, v. 348, p. 252-254, Nov. 1990.

13. WILLBERG, C. B. et al. Protection of hepatocytes from cytotoxic T cell mediated killing by interferon-alpha. **PLos ONE.**, San Francisco, v. 2, n. 8, p. 791, Aug. 2007.

14. AZOCAR, J.; CLAVIJO, O. P.; YUNIS, E. J. MHC class II genes in HCV viral clearance of hepatitis C infected Hispanic patients. **Hum. Immunol.**, New York, v. 64, n. 1, p. 99-102, Jan. 2003.

15. ALBERT, L. J.; INMAN, R. D. Molecular mimicry and autoimmunity. **N. Engl. J. Med.**, Boston, v. 341, n. 27, p. 2068–2074, Dec. 1999.

16. GRUBECK-LOEBENSTEIN, B. et al. Pathogenetic relevance of HLA class II expressing thyroid follicular cells in nontoxic Goiter and in Graves' disease. **Clin. Invest.**, Berlin, v. 81, n. 5, p. 1608-1614, May. 1988.

17. VANDERPUMP, M. P. et al. The incidence of thyroid disorders in the community: a twenty-year follow-up of the Whickham Survey. **Clin. Endocrinol.**, Oxford, v. 43, n. 1, p. 55-58, July. 1995.

18. BOTTAZZO, G. F. et al. Role of aberrant HLA-DR expression and antigen presentation in induction of endocrine autoimmunity. **Lancet.**, London, v. 2, n. 8359, p. 1115-1118, Nov. 1983.

19. WANG, F. W. et al. HLA and hypertrophic Hashimoto's thyroiditis in Shanghai Chinese. **Tissue Antigens.**, Copenhagen, v. 32, p. 235-236, 1988.

20. HAMILTON, F. et al. Spatial correlation between thyroid epithelial cells expressing class II MHC molecules and interferon-gammacontaining lymphocytes in human thyroid autoimmune disease. **Clin. Exp. Immunol.**, London, v. 83, n. 1, p. 64-68, Jan. 1991.