

We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,900

Open access books available

186,000

International authors and editors

200M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com



Immune Profile and Signal Transduction of T-Cell Receptor in Autoimmune Thyroid Diseases

Adriano Namó Cury

*Endocrinology and Metabolism Unit of Santa Casa São Paulo, São Paulo
Brazil*

1. Introduction

Autoimmune thyroiditis is of great importance because of its prevalence in global population and represents an organ-specific immune dysfunction whose pathophysiological stages have not yet been fully elucidated. It is well accepted that, as in other autoimmune diseases, there is loss of tolerance to auto-antigens (such as thyroperoxidase or thyroglobulin) with subsequent abnormal lymphocyte activation fostering aggression to thyroid tissue.

From the autoimmune dysfunction, especially in Hashimoto's thyroiditis (HT), the thyrocyte may undergo apoptosis by the FAS-mediated in CD4 + and CD8 + mechanism, or by downregulation of anti-apoptotic protein expression such as Bcl-2 (Mitsiades, Poulaki et al., 1998; Fountoulakis, Vartholomatos et al., 2008). In the HT, lymphocytic infiltrate is intense with formation of germinal centers and destruction of thyroid follicles by chronic inflammation through the natural killer cells (NK) and cytotoxicity induced by auto-antibodies.

In Hashimoto's thyroiditis, chronic inflammation and apoptosis are accepted as a mechanism of the disease and resultant hypothyroidism. It is noteworthy that presence of lymphocytic infiltrate alone does not necessarily induce hypothyroidism (Martin, Colonel et al., 2004) but induces immune dysfunction of T cells response due to genetic and environmental predisposition in different populations and ethnic groups.

T cell and B cell immune dysfunction with production of autoantibodies, cytotoxic cell death, in addition to the previously mentioned apoptosis is the classical model of thyrocytes and thyroid follicle destruction. But recently described as non-classic mechanism and not related to cell death, but to the chronic inflammatory process by inhibiting the thyroid function mediated by inflammatory cytokines TNF- α and INF- γ based upon T cell dysfunction, even without a lymphocytic infiltrate, but by exposure *per se* to inflammatory cytokines (Caturegli, Hejazi et al., 2000; Kimura, Kimura et al., 2005).

Differently, within the group of autoimmune thyroid diseases, Graves' disease (GD) occurs in a unique situation in autoimmunity, with dysfunction in T and B cells, however producing an autoantibody IgG, with great affinity to specific regions of the TSH (TSH-R)

receptor that determines hyperfunction, hypertrophy of the thyroid follicle, abnormal dynamics of activation, or even blockade of TSH-R and hyperthyroidism itself (Hadj-Kacem, Rebuffat et al., 2009). Production of TRAb stimulator and sometimes blocker is an expression of the break of tolerance to TSH-R specific epitopes with biological effect similar to TSH, yet with longer lasting and slower signaling to thyrocytes.

Exposure of TSH-R subunit-A seems to be responsible for generating the TRAb stimulator, which generates an atypical biological signal to the thyroid cells which respond with activation of the intracellular machinery, hypertrophy, and hypersecretion (Rapoport and McLachlan 2007). In GD the inflammatory infiltrate is less intense when compared to HT, and the phenomenon of apoptosis is less pronounced due to probable protection by soluble FAS (sFas), interfering with the classic mechanism of apoptosis FAS-FASL (Feldkamp, Pascher et al., 2001; Fountoulakis, Vartholomatos et al., 2008) or by upregulation of anti-apoptotic proteins in thyrocytes such as Bcl-2, Bcl-xL and cFLIP (Stassi, Di Liberto et al., 2000).

Comprehension of cell phenotype, dynamics of lymphocyte activation in the break of immune tolerance and its correlation with immunoregulator genes is mandatory to understand the etiology and development mechanism of autoimmune thyroid diseases. Moreover, for the attempt to elucidate the pathways of cellular and humoral dysfunctions that determine the route leading to HT or GD.

2. Immunity and T cells

2.1 Inflammatory response in autoimmune thyroid diseases

Immune behavior of autoimmune thyroid diseases lies in the characterization of the concept of breaking the mechanism of tolerance to self antigens, activation and differentiation of cell clones in charge (T-cell subtypes) of the amplification and execution of inflammatory response in thyroid tissue and dynamics of lymphocyte receptors in HT or GD. Differentiation and amplification of the inflammatory response in different types of T cells plays an essential role in the pathogenesis of the disease.

The understanding of cell phenotype, dynamics of lymphocytes activation in the break of immune tolerance and its correlation with immunoregulator genes is mandatory for the etiology and development mechanism of autoimmune thyroid diseases. Or even for the attempt to elucidate the pathways of cellular and humoral dysfunctions that rule the path leading to HT or GD.

The CD4 + T helper lymphocytes (Th) can be classified into at least three subtypes, Th1, Th2 and Th17 in accordance with a profile of cytokine production (Abbas, Murphy et al., 1996; Mosmann and Sad 1996). In HT the Th1 cell response prevails with predominant production of IFN- γ , IL-2 and TNF- β (Fisfalen, Palmer et al., 1997; Fisfalen, Soltani et al., 1997; Watanabe, Yamamoto et al., 2002). The Th2 humoral response pertains to GD with production of cytokines IL-4, IL-5, IL-6, IL-10 and IL-13 and suppression of INF- γ (Yano, Sone et al., 1995; Abbas Murphy et al., 1996; Fisfalen, Palmer et al., 1997; Fisfalen, Soltani et al., 1997).

Th17 lymphocytes were recently described and specific studies on thyroid autoimmune diseases are scarce. T cells that differentiate to Th17 subtypes secrete IL-17, IL-17F, IL-21

and IL-22 (Wilson, Boniface et al., 2007) playing an important role in chronic inflammatory diseases such as asthma (Traves and Donnelly 2008) or systemic lupus erythematosus (Garrett-Sinha, John et al., 2008). IL-17 has potent proinflammatory action of chemotaxis, with chemokine synthesis and stimulus of cell proliferation (Weaver, Hatton et al., 2007).

Proportion of Th17 lymphocytes in patients with GD was first described by Nanba *et al.*, whose main finding was a higher rate of Th17, on the peripheral blood of patients with GD without treatment with anti-thyroid drugs when compared to patients with GD in remission (Nanba, Watanabe et al., 2009). Study of the profile of Th17 lymphocytes in Hashimoto's thyroiditis according to Figueroa-Vera *et al.*, (Figueroa-Vega, Alfonso-Perez et al., 2010) discloses a higher expression of the RORC2 gene responsible for differentiation of the Th17 phenotype, in addition to the sheer number of Th17 lymphocytes in peripheral blood and thyroid tissue of patients with HT, however without significant results in those with GD.

2.2 Loss of tolerance and natural regulatory T cells

Autoimmunity occurs mainly by loss of tolerance to auto-antigens from the perpetuation of autoreactive T cells and pathogenic for their cellular targets. Didactically, it can be understood that the stages of loss of tolerance occur in two moments: (1) failure of central tolerance and (2) peripheral. Initially, the correct reading of non-auto-antigens and no formation of autoreactive cells is known as clonal selection theory or negative selection when autoreactive lymphocytes are deleted at the initial stages of cell differentiation in the thymus (Burnet 1959). Evasion of cell clones from the negative central selection, autoreactive lymphocytes to the periphery may or may not be activated and trigger the process of autoimmune disease, however according to the genetic and environmental interaction. There is a break in the state of anergy or antigenic ignorance, with clonal activation and expansion that will then initiate the autoimmune and inflammatory process (Green, Droin et al., 2003).

This cellular mechanism is known as intrinsic cellular mechanism of peripheral tolerance (Schwartz 2005). The extrinsic cellular mechanism of tolerance is carried out by regulatory T cells CD4 + CD25 + natural (Treg) that exist because of the expression of Forkhead Box Protein 3 (Foxp3), Treg are responsible for suppression of immune response of auto-reactive clones (Sakaguchi, Yamaguchi et al., 2008) and control amplification of the inflammatory response. Failure in negative central and peripheral selection promotes clonal expansion with differentiation of autoreactive cell subtypes, which according to the genetic and environmental triggers differentiate into T cells to produce inflammatory cytokines inducing inflammation and cell destruction.

It is believed that failure of the negative selection process could not *per se* trigger autoimmunity. Perpetuation of pathogenic autoreactive cells associated with a lesser expression and differentiation of Tregs would be another condition for autoimmunity development. It was shown that CD4+ CD25 + cells may experimentally prevent development of autoimmune thyroiditis (Gangi, Vasu et al., 2005; Vergini, Li et al., 2005). As the proportion and function of Tregs seems altered in the ATD when analyzing peripheral and cells of the thyroid ambient itself without the ability to downmodulate the autoimmune

response in the thyroid environment (Marazuela, Garcia-Lopez et al., 2006), or even suffer increased apoptosis in the thyroid environment (Nakano, Watanabe et al., 2007) a significant event considering that regulatory action of Treg cells modulates and inhibits inflammatory immune response Th1, Th2 and Th17.

Therefore, the evasion of autoreactive cells, the reduced presence of Tregs, the non-control of inflammatory response, in the genetic context and environmental factor, the predominance of phenotypes Th1, Th2 or even Th17 characterizes autoimmune thyroid disease. Hashimoto's thyroiditis with typical Th1 response and cell infiltrate by thyroid tissue and thyrocyte apoptosis.

In GD, product of a more humoral response Th2, lesser lymphocytic infiltrate and specific failures for TSHR that generate, presumably the only autoimmune condition that promotes hyperplasia, with a lesser degree of apoptosis and IgG by affinity for TSHR. The Th17 response might possibly be involved in HT or GD. However studies encompass a limited number of patients and primarily use peripheral blood to isolate lymphocytes, while study of lymphocytes from the thyroid is scarce, since indications for surgery for patients with GD or HT are less frequent nowadays.

3. Immunoregulator genes

The autoimmune thyroid diseases (ATD), such as Hashimoto's thyroiditis and Graves' disease are found in the general population and have an estimated prevalence of 5% (Ban, Davies et al., 2003). Pathogenesis of ATD especially that of GD is brought about by complex interaction between environmental and genetic factors. Genetics of predisposition for ATD involve HLA (human leukocyte antigen) system genes and specific genes that affect any step of the immune response regulation, i.e. activation and suppression of T cells and consequent modulation of B-cells.

Besides genes of the MHC class II system such as HLA-DR3 and DQA1 * 0501 on chromosome 6p21 (Yanagawa, Manglabruks et al., 1993; Zamani, Spaepen et al., 2000; Maciel, Rodrigues et al., 2001), on chromosome 2q33, we found the *loci* of genes involved in the regulation of T lymphocytes: CD28, CTLA4 and ICOS in which, specifically polymorphisms of the cytotoxic T lymphocyte antigen-4 (CTLA-4) are associated to various autoimmune diseases (Chistiakov and Turakulov 2003; Vaidya and Pearce 2004).

Allelic variants of the CTLA-4 gene with potential effect on functional modulation of the T cell were shown as single-nucleotide polymorphism (SNP) + 49 A> G in exon 1, which seems to modify both the structure and protein expression of CTLA-4 [7]. In 2003, Ueda *et al.*, identified the SNP +6230 G> A in the stop codon of gene CTLA-4 (CT60) associating it to higher risk for GD, HT and type 1 diabetes (DM1) due to expression of different isoforms of mRNA gene CTLA-4 (Ueda, Howson et al., 2003).

In case-control studies during the last decade, polymorphism +49 A> G of CTLA4 gene exon 1 was associated with autoimmune diseases, such as GD, DM1, HT, rheumatoid arthritis, autoimmune Addison's disease, multiple sclerosis (Yanagawa, Hidaka et al., 1995; Nistico, Buzzetti et al., 1996; Kotsa, Watson et al., 1997; Yanagawa, Taniyama et al., 1997; Awata, Kurihara et al., 1998; Fukazawa, Yanagawa et al., 1999; Heward, Allahabadia et al., 1999; Vaidya, Imrie et al., 2000; Ueda, Howson et al., 2003; Blomhoff, Lie et al., 2004; Young-Min

and Vaidya 2004; Kavvoura, Akamizu et al., 2007). and in familial studies was associated with GD in Caucasian, Japanese, Chinese and Korean populations (Heward, Allahabadia et al., 1999; Vaidya, Imrie et al., 1999).

Proteins CD28 and CTLA4 are costimulatory molecules found on the surface of T cells that bind to the family of B7 receptors expressed on antigen presenting cells (APC) (Reiser and Staderker 1996). Immune response relies on the generation of two signals: the first, from the interaction of antigenic peptides with receptors on T cells in the context of MHC and the second signal (costimulatory) that activates, enhances and promotes T cell proliferation by production of cytokines (such as IL-2), where complex CD28/B7 functions as a positive regulator of T cells, and the CTLA4/B7 expressed exclusively in activated T lymphocytes, provides an inhibitory signal, required to limit proliferation of T cells and regulates the autoimmune response (Oosterwegel, Greenwald et al., 1999; Sharpe and Abbas 2006).

4. Polymorphisms, functional impact on the T cell and transduction of TCR

The polymorphism +49 A> G (rs231775) of gene CTLA-4, which promotes the exchange of amino acid threonine for alanine at position 17, has emerged as the natural candidate, among polymorphisms of CTLA-4 gene, because of the ability to promote functional changes of protein CTLA-4. Kouki *et al.*, (Kouki, Sawai et al., 2000) showed a higher frequency of genotype GG or AG at position 49 of the CTLA-4 gene in GD patients, and lesser control over proliferation and clonal expansion of T cells. Whereas Maurer *et al* (Maurer, Loserth et al., 2002) found differences in the pool of intracellular CTLA-4 protein, prompting imbalance in the expression and competition between CTLA-4 and CD28 on the surface of T cells, possibly modifying the suppression of T cells and generating larger quantities of inflammatory cytokines.

The CT60 polymorphism (rs30807243) seems to determine a distinct expression of mRNA isoforms through alternative splicing, with a lesser expression of soluble CTLA-4 (sCTLA-4) in relation to the total length isoform of CTLA-4 (*fl*CTLA-4) (Ueda, Howson et al., 2003). The correlation between immune-cell genotype and phenotype was demonstrated by presence of susceptibility allele G or allele A of protection, to specific subtypes of T cells in healthy controls, and the quantitative variations of the type CD4 + CD25 + cells called regulatory T cells (Treg) (Atabani, Thio et al., 2005).

Other studies have shown an association between the SNP at exon 2 of CTLA-4 gene in mice, and a new variant of the protein called ligand independent of CTLA-4 (liCTLA-4) (Wicker, Chamberlain et al., 2004), that also has a significant inhibitor function on T cell response when binding and dephosphorylating the T cell receptor (TCR).

Expression of the isoform liCTLA-4 seems to be greater in regulatory and memory T cells (Vijayakrishnan, Slavik et al., 2004), a possible association between the gene CTLA-4 (its isoforms) and immune response after antigen presentation by APC and T cell activation as from the T cell receptor. As such, genetic variations in the CTLA-4 gene region play an important role in T cell signaling and therefore in its function and proliferation of T cells. Different genotypes may determine different phenotypes and probable predisposition to autoimmunity by loss of negative selection mechanisms (central and peripheral immune system dysfunction) and a distinct pattern of CD4 + T cells.

The possibility of analyzing the actions of protein CTLA-4 (and its isoforms) and its correlation with the type of activated T cell (either the memory/effector or naive cell) as well as the profile of tyrosine residues phosphorylation and activity of protein kinases in the intracellular environment (Maier, Anderson et al., 2007) may explain how the genetic profile influences immune response and promotes autoimmune thyroid disease for different clinical or subclinical poles as in HT and GD.

The expression of surface molecules, phenotype, discloses the history of antigenic exposure (Appay, Dunbar et al., 2002) or indicates the functional capacity of each cell subtype (Rufer, Zippelius et al., 2003). Naive or memory / effector cells are pointed out by presence or absence of CD45RA, naive cells are mainly CD4 + CCR7 + CD45RA^{high}, memory cells CD4⁺ CCR7 + CD45RA^{low} and effector cells CD4 + CCR7-CD45RA^{low} (Amyes, McMichael et al., 2005).

During the antigen presentation process, costimulation and clonal expansion of the different populations of T lymphocytes, memory, effector or naive cells use the same pathway on the cell surface by means of the TCR/CD3 complex (Farber 2000), however with different properties in activation of the immune response. Naive cells are hyper-responsive to antigenic and non- antigenic stimuli, with increased susceptibility to apoptosis, while memory cells activated by slower kinetics, and are hyporesponsive to stimulation of the TCR and less susceptible to apoptosis (Hussain, Anderson et al., 2002).

In all T cell lines and their cellular clones, the same mechanism of signal transduction linked to the TCR was identified (Germain and Stefanova 1999), exhibiting phosphorylation of tyrosine residues in the subunits linked to the TCR/CD3 (ζ , ϵ , δ , γ) by the family proteins tyrosine kinase p56 lck (Iwashima, Irving et al., 1994).

Phosphorylation of the CD3 ζ subunit brings about activation and recruitment of other tyrosine kinases such as ZAP-70 that phosphorylate multiple molecules like SLP-76 (Bubeck Wardenburg, Fu et al., 1996) and ligand for activation of the T cell (LAT) (Zhang, Sloan-Lancaster et al., 1998) that associated with Grb2 and GADS (Liu, Fang et al., 1999) activate according to messengers Ras/Erk MAP kinases and activation or suppression of intracytoplasmic events, such as activation of enzymes, modulation of transcription genes, synthesis of inflammatory cytokines, mobilization of intracellular calcium or induction of cell proliferation or cell apoptosis (Wange and Samelson 1996) (figure 1).

Therefore, the antigen-specific response can be well characterized by specific intracellular markers of phosphorylation and development of antibodies for specific epitopes of cytoplasmic proteins (Rosette, Werlen et al., 2001). The phenotypic correlation of T cell subtypes and pattern of TCR/CD3 ζ phosphorylation with allelic variants of CTLA-4 (CT60 SNP) gene was recently demonstrated by Maier *et al.*, (Maier, Anderson et al., 2007), with a different signaling pattern of CD4 + T cells according to presence of allele G.

Polymorphism (rs2476601) of gene PTPN22 (protein tyrosine phosphatase nonreceptor 22) on chromosome 1p13 responsible for the expression of protein tyrosine-specific phosphatase (LYP), with a suppressive and regulatory function of post- TCR phosphorylation are associated with autoimmune diseases such as GD, DM1 and to polyglandular autoimmune conditions (Bottini, Musumeci et al., 2004; Velaga, Wilson et al., 2004; Skorka, Bednarczuk et al., 2005; Dultz, Matheis et al., 2009). The exchange of nucleotide C by T at position 1858

(C1859T) causes at codon 620, the exchange of amino acid arginine by tryptophan and possible changes in signaling and dephosphorylation post-TCR of family kinases through protein LYP (LYP*W620) (Bottini, Musumeci et al., 2004).

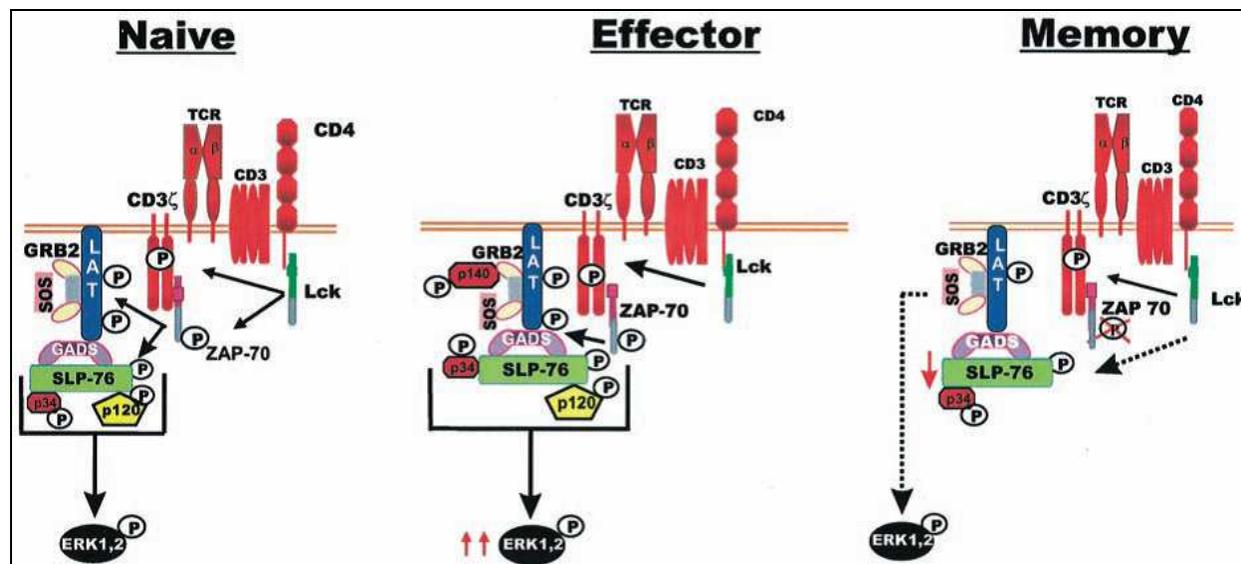


Fig. 1. Representation of T/CD3 cell receptor and signaling pathways and phosphorylation of effector molecules according to the subtype of T lymphocytes (Hussain *et al.*, 2002).

The main function of LYP protein would be to downregulate T cells through TCR signaling, by direct effect on dephosphorylation of the protein kinases Lck and Fyn, from complex TCR ζ /CD3 and ZAP70 protein among others (Figure 2) (Cloutier and Veillette 1999; Gyorloff-Wingren, Saxena et al., 1999; Wu, Katrekar et al., 2006). It is noteworthy that, according to the genotype of PTPN22 and the two alleles of LYP (LYP * W620 or LYP * R620), a distinct TCR signaling takes place (Vang, Congia et al., 2005).

The LYP * W620 of "predisposition" (CT or TT genotype of PTPN22) leads to a gain of function, proteins Lck dephosphorylation, TCR ζ much more efficiently than LYP * R620 (CC genotype of PTPN22), with less mobilization of intracellular calcium or transactivation of the IL-2 gene (Vang, Congia et al., 2005). That is, predisposition alleles (LYP * W620) activate phosphatases leading to suppression of TCR better than CC homozygotes (LYP * R620 / * R620 LYP), possibly by binding to a larger number of intracellular proteins in TCR signaling than LYP * R620 (Vang, Miletic et al., 2007).

As such LYP * W620 shows gain of function based upon the allelic variation of gene PTPN22 C1859T and possibly predisposes to autoimmune diseases by suppressing the TCR signaling in a much more potent way during thymic development, resulting in loss of negative selection and survival of a greater number of self-reactive cells (Vang, Miletic et al., 2007). Whether they can or not also jeopardize selection of T cells CD4 + CD25 + (Treg), if lineages of T cells are committed in accordance to expression of protein LYP, nevertheless remain scarcely known.

The ATD are a group of autoimmune diseases of poorly understood pathophysiology considering the determinant type of inflammatory response (Th1 or Th2) in the target organ,

inducing apoptosis or hyperstimulation and a heterogeneous clinical condition. Thus, different cell phenotypes and immune response may take place when patients with ATD are compared to the population with no autoimmune diseases. There are few studies of autoimmune diseases that have studied the pattern of intracellular signaling of T lymphocytes and possible dysfunctions in T cell activation and immune response, except in rheumatic diseases such as systemic lupus erythematosus (Pang, Setoyama et al., 2002).

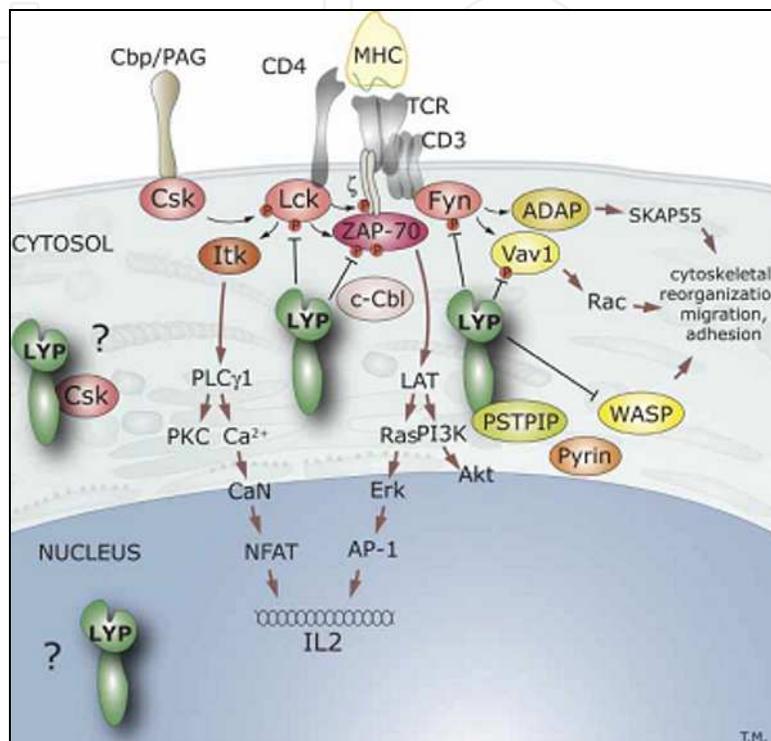


Fig. 2. Possible *loci* of action of protein LYP in signaling of T cell receptor (Vang et al., 2007)

5. Conclusions

Therefore, the main conclusions of this chapter, that is to say correlation of CT60 polymorphism +49 A > G and of the PTPN22 gene with differences in T cell subtypes and intracellular signaling in memory and naive T cells has been established for patients with ATD. But the transduction of TCR activation need to be elucidated in GD a HT. Comparison of immunophenotyping and phosphorylation of TCR, cells in the periphery and of the thyroid environment may answer some questions about genetic profile and predominant phenotype in HT and GD.

Study of CD4 + cell subtypes has extended their association with other thyroid diseases are important, such as the association of Treg and aggressiveness of papillary thyroid carcinoma (French, Weber et al., 2010) was recently published, involving ATD in a different way and impact. Considering that frequency and existence of CD4+CD25+ has already been associated to a worse prognosis in breast adenocarcinoma and lymphomas (Carreras, Lopez-Guillermo et al., 2006; Gobert, Treilleux et al., 2009).

Therefore, study of the microenvironment as well as dynamics of TCR activation and association with specific genotypes might also contribute to a better association between

clinical endocrinology and the main genetic and biochemical markers of autoimmune thyroid diseases. As well as the actual evolution of subclinical and clinical phases, therapeutic response in GD and new predictors of remission or relapse, or even the varying presentation of HT, duration of progression to hypothyroidism, and variations on antibodies and different epitopes, glandular volume and texture at ultrasound as well as association with autoimmune polyglandular syndrome or frequency in different ethnic groups.

6. References

- Abbas, A. K., K. M. Murphy, et al., (1996). "Functional diversity of helper T lymphocytes." *Nature* 383(6603): 787-793.
- Amyes, E., A. J. McMichael, et al., (2005). "Human CD4+ T cells are predominantly distributed among six phenotypically and functionally distinct subsets." *J Immunol* 175(9): 5765-5773.
- Appay, V., P. R. Dunbar, et al., (2002). "Memory CD8+ T cells vary in differentiation phenotype in different persistent virus infections." *Nat Med* 8(4): 379-385.
- Atabani, S. F., C. L. Thio, et al., (2005). "Association of CTLA4 polymorphism with regulatory T cell frequency." *Eur J Immunol* 35(7): 2157-2162.
- Awata, T., S. Kurihara, et al., (1998). "Association of CTLA-4 gene A-G polymorphism (IDDM12 locus) with acute-onset and insulin-depleted IDDM as well as autoimmune thyroid disease (Graves' disease and Hashimoto's thyroiditis) in the Japanese population." *Diabetes* 47(1): 128-129.
- Ban, Y., T. F. Davies, et al., (2003). "Analysis of the CTLA-4, CD28, and inducible costimulator (ICOS) genes in autoimmune thyroid disease." *Genes Immun* 4(8): 586-593.
- Blomhoff, A., B. A. Lie, et al., (2004). "Polymorphisms in the cytotoxic T lymphocyte antigen-4 gene region confer susceptibility to Addison's disease." *J Clin Endocrinol Metab* 89(7): 3474-3476.
- Bottini, N., L. Musumeci, et al., (2004). "A functional variant of lymphoid tyrosine phosphatase is associated with type I diabetes." *Nat Genet* 36(4): 337-338.
- Bubeck-Wardenburg, J., C. Fu, et al., (1996). "Phosphorylation of SLP-76 by the ZAP-70 protein-tyrosine kinase is required for T-cell receptor function." *J Biol Chem* 271(33): 19641-19644.
- Burnet, M. (1959). "Auto-immune disease. I. Modern immunological concepts." *British medical journal* 2(5153): 645-650.
- Carreras, J., A. Lopez-Guillermo, et al., (2006). "High numbers of tumor-infiltrating FOXP3-positive regulatory T cells are associated with improved overall survival in follicular lymphoma." *Blood* 108(9): 2957-2964.
- Caturegli, P., M. Hejazi, et al., (2000). "Hypothyroidism in transgenic mice expressing IFN-gamma in the thyroid." *Proceedings of the National Academy of Sciences of the United States of America* 97(4): 1719-1724.
- Chistiakov, D. A. and R. I. Turakulov (2003). "CTLA-4 and its role in autoimmune thyroid disease." *J Mol Endocrinol* 31(1): 21-36.

- Cloutier, J. F. and A. Veillette (1999). "Cooperative inhibition of T-cell antigen receptor signaling by a complex between a kinase and a phosphatase." *J Exp Med* 189(1): 111-121.
- Dultz, G., N. Matheis, et al., (2009). "The protein tyrosine phosphatase non-receptor type 22 C1858T polymorphism is a joint susceptibility locus for immunthyroiditis and autoimmune diabetes." *Thyroid* 19(2): 143-148.
- Farber, D. L. (2000). "T cell memory: heterogeneity and mechanisms." *Clin Immunol* 95(3): 173-181.
- Feldkamp, J., E. Pascher, et al., (2001). "Soluble Fas is increased in hyperthyroidism independent of the underlying thyroid disease." *The Journal of clinical endocrinology and metabolism* 86(9): 4250-4253.
- Figuerola-Vega, N., M. Alfonso-Perez, et al., (2010). "Increased circulating pro-inflammatory cytokines and Th17 lymphocytes in Hashimoto's thyroiditis." *The Journal of clinical endocrinology and metabolism* 95(2): 953-962.
- Fisfalen, M. E., E. M. Palmer, et al., (1997). "Thyrotropin-receptor and thyroid peroxidase-specific T cell clones and their cytokine profile in autoimmune thyroid disease." *The Journal of clinical endocrinology and metabolism* 82(11): 3655-3663.
- Fisfalen, M. E., K. Soltani, et al., (1997). "Evaluating the role of Th0 and Th1 clones in autoimmune thyroid disease by use of Hu-SCID chimeras." *Clinical immunology and immunopathology* 85(3): 253-264.
- Fountoulakis, S., G. Vartholomatos, et al., (2008). "Differential expression of Fas system apoptotic molecules in peripheral lymphocytes from patients with Graves' disease and Hashimoto's thyroiditis." *European journal of endocrinology / European Federation of Endocrine Societies* 158(6): 853-859.
- French, J. D., Z. J. Weber, et al., (2010). "Tumor-associated lymphocytes and increased FoxP3+ regulatory T cell frequency correlate with more aggressive papillary thyroid cancer." *The Journal of clinical endocrinology and metabolism* 95(5): 2325-2333.
- Fukazawa, T., T. Yanagawa, et al., (1999). "CTLA-4 gene polymorphism may modulate disease in Japanese multiple sclerosis patients." *J Neurol Sci* 171(1): 49-55.
- Gangi, E., C. Vasu, et al., (2005). "IL-10-producing CD4+CD25+ regulatory T cells play a critical role in granulocyte-macrophage colony-stimulating factor-induced suppression of experimental autoimmune thyroiditis." *Journal of immunology* 174(11): 7006-7013.
- Garrett-Sinha, L. A., S. John, et al., (2008). "IL-17 and the Th17 lineage in systemic lupus erythematosus." *Current opinion in rheumatology* 20(5): 519-525.
- Germain, R. N. and I. Stefanova (1999). "The dynamics of T cell receptor signaling: complex orchestration and the key roles of tempo and cooperation." *Annu Rev Immunol* 17: 467-522.
- Gjorloff-Wingren, A., M. Saxena, et al., (1999). "Characterization of TCR-induced receptor-proximal signaling events negatively regulated by the protein tyrosine phosphatase PEP." *Eur J Immunol* 29(12): 3845-3854.

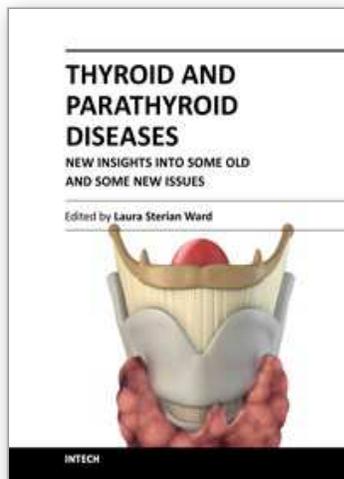
- Gobert, M., I. Treilleux, et al., (2009). "Regulatory T cells recruited through CCL22/CCR4 are selectively activated in lymphoid infiltrates surrounding primary breast tumors and lead to an adverse clinical outcome." *Cancer research* 69(5): 2000-2009.
- Green, D. R., N. Droin, et al., (2003). "Activation-induced cell death in T cells." *Immunological reviews* 193: 70-81.
- Hadj-Kacem, H., S. Rebuffat, et al., (2009). "Autoimmune thyroid diseases: genetic susceptibility of thyroid-specific genes and thyroid autoantigens contributions." *International journal of immunogenetics* 36(2): 85-96.
- Heward, J. M., A. Allahabadi, et al., (1999). "The development of Graves' disease and the CTLA-4 gene on chromosome 2q33." *J Clin Endocrinol Metab* 84(7): 2398-2401.
- Hussain, S. F., C. F. Anderson, et al., (2002). "Differential SLP-76 expression and TCR-mediated signaling in effector and memory CD4 T cells." *J Immunol* 168(4): 1557-1565.
- Iwashima, M., B. A. Irving, et al., (1994). "Sequential interactions of the TCR with two distinct cytoplasmic tyrosine kinases." *Science* 263(5150): 1136-1139.
- Kavvoura, F. K., T. Akamizu, et al., (2007). "Cytotoxic T-lymphocyte associated antigen 4 gene polymorphisms and autoimmune thyroid disease: a meta-analysis." *J Clin Endocrinol Metab* 92(8): 3162-3170.
- Kimura, H., M. Kimura, et al., (2005). "Increased thyroidal fat and goitrous hypothyroidism induced by interferon-gamma." *International journal of experimental pathology* 86(2): 97-106.
- Kotsa, K., P. F. Watson, et al., (1997). "A CTLA-4 gene polymorphism is associated with both Graves disease and autoimmune hypothyroidism." *Clin Endocrinol (Oxf)* 46(5): 551-554.
- Kouki, T., Y. Sawai, et al., (2000). "CTLA-4 gene polymorphism at position 49 in exon 1 reduces the inhibitory function of CTLA-4 and contributes to the pathogenesis of Graves' disease." *J Immunol* 165(11): 6606-6611.
- Liu, S. K., N. Fang, et al., (1999). "The hematopoietic-specific adaptor protein gads functions in T-cell signaling via interactions with the SLP-76 and LAT adaptors." *Curr Biol* 9(2): 67-75.
- Maciel, L. M., S. S. Rodrigues, et al., (2001). "Association of the HLA-DRB1*0301 and HLA-DQA1*0501 alleles with Graves' disease in a population representing the gene contribution from several ethnic backgrounds." *Thyroid* 11(1): 31-35.
- Maier, L. M., D. E. Anderson, et al., (2007). "Allelic variant in CTLA4 alters T cell phosphorylation patterns." *Proc Natl Acad Sci U S A* 104(47): 18607-18612.
- Marazuela, M., M. A. Garcia-Lopez, et al., (2006). "Regulatory T cells in human autoimmune thyroid disease." *The Journal of clinical endocrinology and metabolism* 91(9): 3639-3646.
- Martin, A. P., E. C. Coronel, et al., (2004). "A novel model for lymphocytic infiltration of the thyroid gland generated by transgenic expression of the CC chemokine CCL21." *Journal of immunology* 173(8): 4791-4798.
- Maurer, M., S. Loserth, et al., (2002). "A polymorphism in the human cytotoxic T-lymphocyte antigen 4 (CTLA4) gene (exon 1 +49) alters T-cell activation." *Immunogenetics* 54(1): 1-8.

- Mitsiades, N., V. Poulaki, et al., (1998). "Fas/Fas ligand up-regulation and Bcl-2 down-regulation may be significant in the pathogenesis of Hashimoto's thyroiditis." *The Journal of clinical endocrinology and metabolism* 83(6): 2199-2203.
- Mosmann, T. R. and S. Sad (1996). "The expanding universe of T-cell subsets: Th1, Th2 and more." *Immunology today* 17(3): 138-146.
- Nakano, A., M. Watanabe, et al., (2007). "Apoptosis-induced decrease of intrathyroidal CD4(+)CD25(+) regulatory T cells in autoimmune thyroid diseases." *Thyroid : official journal of the American Thyroid Association* 17(1): 25-31.
- Nanba, T., M. Watanabe, et al., (2009). "Increases of the Th1/Th2 cell ratio in severe Hashimoto's disease and in the proportion of Th17 cells in intractable Graves' disease." *Thyroid: official journal of the American Thyroid Association* 19(5): 495-501.
- Nistico, L., R. Buzzetti, et al., (1996). "The CTLA-4 gene region of chromosome 2q33 is linked to, and associated with, type 1 diabetes. Belgian Diabetes Registry." *Hum Mol Genet* 5(7): 1075-1080.
- Oosterwegel, M. A., R. J. Greenwald, et al., (1999). "CTLA-4 and T cell activation." *Curr Opin Immunol* 11(3): 294-300.
- Pang, M., Y. Setoyama, et al., (2002). "Defective expression and tyrosine phosphorylation of the T cell receptor zeta chain in peripheral blood T cells from systemic lupus erythematosus patients." *Clin Exp Immunol* 129(1): 160-168.
- Rapoport, B. and S. M. McLachlan (2007). "The thyrotropin receptor in Graves' disease." *Thyroid: official journal of the American Thyroid Association* 17(10): 911-922.
- Reiser, H. and M. J. Stadecker (1996). "Costimulatory B7 molecules in the pathogenesis of infectious and autoimmune diseases." *N Engl J Med* 335(18): 1369-1377.
- Rosette, C., G. Werlen, et al., (2001). "The impact of duration versus extent of TCR occupancy on T cell activation: a revision of the kinetic proofreading model." *Immunity* 15(1): 59-70.
- Rufer, N., A. Zippelius, et al., (2003). "Ex vivo characterization of human CD8+ T subsets with distinct replicative history and partial effector functions." *Blood* 102(5): 1779-1787.
- Sakaguchi, S., T. Yamaguchi, et al., (2008). "Regulatory T cells and immune tolerance." *Cell* 133(5): 775-787.
- Schwartz, R. H. (2005). "Natural regulatory T cells and self-tolerance." *Nature immunology* 6(4): 327-330.
- Sharpe, A. H. and A. K. Abbas (2006). "T-cell costimulation--biology, therapeutic potential, and challenges." *N Engl J Med* 355(10): 973-975.
- Skorka, A., T. Bednarczuk, et al., (2005). "Lymphoid tyrosine phosphatase (PTPN22/LYP) variant and Graves' disease in a Polish population: association and gene dose-dependent correlation with age of onset." *Clin Endocrinol (Oxf)* 62(6): 679-682.
- Stassi, G., D. Di Liberto, et al., (2000). "Control of target cell survival in thyroid autoimmunity by T helper cytokines via regulation of apoptotic proteins." *Nature immunology* 1(6): 483-488.
- Traves, S. L. and L. E. Donnelly (2008). "Th17 cells in airway diseases." *Current molecular medicine* 8(5): 416-426.

- Ueda, H., J. M. Howson, et al., (2003). "Association of the T-cell regulatory gene CTLA4 with susceptibility to autoimmune disease." *Nature* 423(6939): 506-511.
- Vaidya, B., H. Imrie, et al., (2000). "Association analysis of the cytotoxic T lymphocyte antigen-4 (CTLA-4) and autoimmune regulator-1 (AIRE-1) genes in sporadic autoimmune Addison's disease." *J Clin Endocrinol Metab* 85(2): 688-691.
- Vaidya, B., H. Imrie, et al., (1999). "The cytotoxic T lymphocyte antigen-4 is a major Graves' disease locus." *Hum Mol Genet* 8(7): 1195-1199.
- Vaidya, B. and S. Pearce (2004). "The emerging role of the CTLA-4 gene in autoimmune endocrinopathies." *Eur J Endocrinol* 150(5): 619-626.
- Vang, T., M. Congia, et al., (2005). "Autoimmune-associated lymphoid tyrosine phosphatase is a gain-of-function variant." *Nat Genet* 37(12): 1317-1319.
- Vang, T., A. V. Miletic, et al., (2007). "Protein tyrosine phosphatase PTPN22 in human autoimmunity." *Autoimmunity* 40(6): 453-461.
- Velaga, M. R., V. Wilson, et al., (2004). "The codon 620 tryptophan allele of the lymphoid tyrosine phosphatase (LYP) gene is a major determinant of Graves' disease." *J Clin Endocrinol Metab* 89(11): 5862-5865.
- Verginis, P., H. S. Li, et al., (2005). "Tolerogenic semimature dendritic cells suppress experimental autoimmune thyroiditis by activation of thyroglobulin-specific CD4+CD25+ T cells." *Journal of immunology* 174(11): 7433-7439.
- Vijayakrishnan, L., J. M. Slavik, et al., (2004). "An autoimmune disease-associated CTLA-4 splice variant lacking the B7 binding domain signals negatively in T cells." *Immunity* 20(5): 563-575.
- Wange, R. L. and L. E. Samelson (1996). "Complex complexes: signaling at the TCR." *Immunity* 5(3): 197-205.
- Watanabe, M., N. Yamamoto, et al., (2002). "Independent involvement of CD8+ CD25+ cells and thyroid autoantibodies in disease severity of Hashimoto's disease." *Thyroid : official journal of the American Thyroid Association* 12(9): 801-808.
- Weaver, C. T., R. D. Hatton, et al., (2007). "IL-17 family cytokines and the expanding diversity of effector T cell lineages." *Annual review of immunology* 25: 821-852.
- Wicker, L. S., G. Chamberlain, et al., (2004). "Fine mapping, gene content, comparative sequencing, and expression analyses support Ctl4 and Nramp1 as candidates for Idd5.1 and Idd5.2 in the nonobese diabetic mouse." *J Immunol* 173(1): 164-173.
- Wilson, N. J., K. Boniface, et al., (2007). "Development, cytokine profile and function of human interleukin 17-producing helper T cells." *Nature immunology* 8(9): 950-957.
- Wu, J., A. Katrekar, et al., (2006). "Identification of substrates of human protein-tyrosine phosphatase PTPN22." *J Biol Chem* 281(16): 11002-11010.
- Yanagawa, T., Y. Hidaka, et al., (1995). "CTLA-4 gene polymorphism associated with Graves' disease in a Caucasian population." *J Clin Endocrinol Metab* 80(1): 41-45.
- Yanagawa, T., A. Manglabruks, et al., (1993). "Human histocompatibility leukocyte antigen-DQA1*0501 allele associated with genetic susceptibility to Graves' disease in a Caucasian population." *J Clin Endocrinol Metab* 76(6): 1569-1574.
- Yanagawa, T., M. Taniyama, et al., (1997). "CTLA4 gene polymorphism confers susceptibility to Graves' disease in Japanese." *Thyroid* 7(6): 843-846.

- Yano, S., S. Sone, et al., (1995). "Differential effects of anti-inflammatory cytokines (IL-4, IL-10 and IL-13) on tumoricidal and chemotactic properties of human monocytes induced by monocyte chemotactic and activating factor." *Journal of leukocyte biology* 57(2): 303-309.
- Young-Min, S. and B. Vaidya (2004). "CTLA4 exon 1 polymorphism, rheumatoid arthritis and autoimmune endocrinopathy." *Clin Rheumatol* 23(6): 568-569.
- Zamani, M., M. Spaepen, et al., (2000). "Primary role of the HLA class II DRB1*0301 allele in Graves disease." *Am J Med Genet* 95(5): 432-437.
- Zhang, W., J. Sloan-Lancaster, et al., (1998). "LAT: the ZAP-70 tyrosine kinase substrate that links T cell receptor to cellular activation." *Cell* 92(1): 83-92.

IntechOpen



Thyroid and Parathyroid Diseases - New Insights into Some Old and Some New Issues

Edited by Dr. Laura Ward

ISBN 978-953-51-0221-2

Hard cover, 318 pages

Publisher InTech

Published online 07, March, 2012

Published in print edition March, 2012

This book was designed to meet the requirements of all who wish to acquire profound knowledge of basic, clinical, psychiatric and laboratory concepts as well as surgical techniques regarding thyroid and parathyroid glands. It was divided into three main sections: 1. Evaluating the Thyroid Gland and its Diseases includes basic and clinical information on the most novel and quivering issues in the area. 2. Psychiatric Disturbances Associated to Thyroid Diseases addresses common psychiatric disturbances commonly encountered in the clinical practice. 3. Treatment of Thyroid and Parathyroid Diseases discusses the management of thyroid and parathyroid diseases including new technologies.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Adriano Namó Cury (2012). Immune Profile and Signal Transduction of T-Cell Receptor in Autoimmune Thyroid Diseases, *Thyroid and Parathyroid Diseases - New Insights into Some Old and Some New Issues*, Dr. Laura Ward (Ed.), ISBN: 978-953-51-0221-2, InTech, Available from:

<http://www.intechopen.com/books/thyroid-and-parathyroid-diseases-new-insights-into-some-old-and-some-new-issues/cellular-immune-profile-and-tyrosine-phosphorylation-of-the-t-cell-receptor-and-allelic-variants-of->

INTECH
open science | open minds

InTech Europe

University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China

Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

© 2012 The Author(s). Licensee IntechOpen. This is an open access article distributed under the terms of the [Creative Commons Attribution 3.0 License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

IntechOpen

IntechOpen