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

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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).

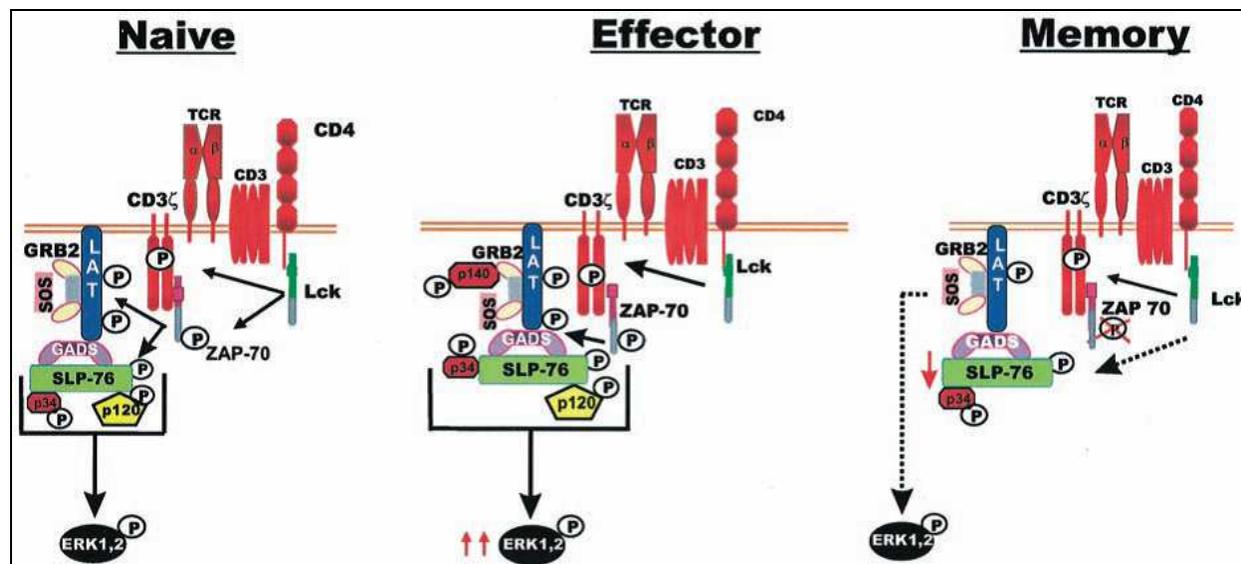


Fig. 1. Representation of T/CD3 cell receptor and signaling pathways and phosphorylation of effector molecules according to the subtype of T lymphocytes (Hussain *et al.*, 2002).

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).

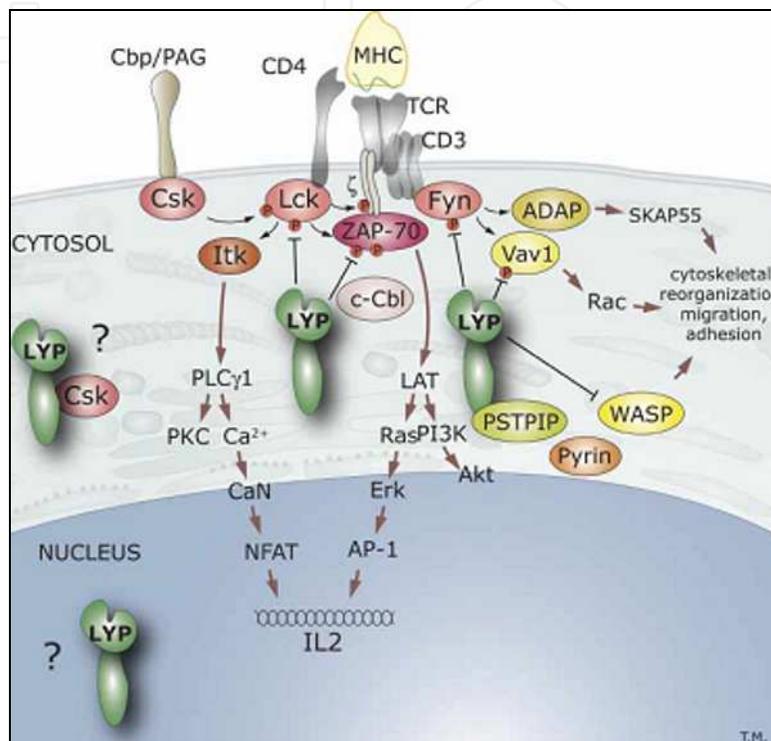


Fig. 2. Possible *loci* of action of protein LYP in signaling of T cell receptor (Vang et al., 2007)

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.

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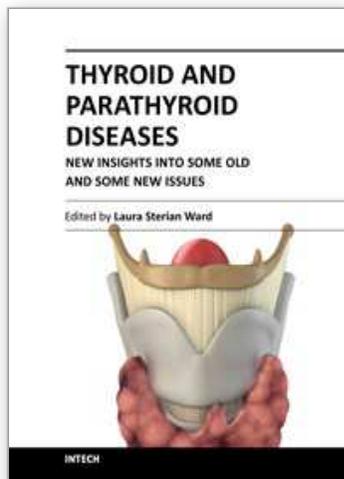
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