

Thyroid Disorders: Mechanisms and Molecular Characterization

Gisele Marques Alvarenga^{1#}, Elane Barboza da Silva¹, Márcia Elaine Braga de Menezes¹, Rafael Perseguini Del Sarto¹ and Aline Maria Araújo Martins^{2,3*#}¹UDF – Centro Universitário do Distrito Federal, Setor de Edifícios Públicos Sul, Eq 704/904, Conj. A - Asa Sul, Brasília - DF, 70390-045, Brazil²Brazilian Center for Protein Research, Department of Cell Biology, University of Brasilia, UNB – DF, Brazil³Liver Transplantation Center, HUWC / Federal University of Ceara - UFC, Brazil

#These authors contribute equally to this work

***Corresponding author:** Dr. Aline M A Martins, Brazilian Center for Protein Research, Department of Cell Biology, University of Brasilia, UNB – DF, Brazil, Tel: +55 61 8186 9696; E-mail: alinemartins@ufc.br**Received date:** March 11, 2016; **Accepted date:** May 03, 2016; **Published date:** May 10, 2016**Copyright:** © 2016 Alvarenga GM, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution and reproduction in any medium, provided the original author and source are credited.

Abstract

Since Dailey et al. first described the possible correlation between inflammation caused by autoimmune diseases and thyroid cancers in 1955, the majority of the events involving these two conditions have not been clearly elucidated, and this association is still very controversial in the literature. Chronic inflammation predisposes the organism to cell proliferation reactions, cytokines secretion and other phenomena that influence rearrangements and mutations in thyroid follicular cells. Thus, is possible that in thyroid autoimmune phenotypes, the same mechanistic forces occur, mainly by the similarity of molecular events that affect both diseases. The large quantity of pro-inflammatory substances secreted within thyroid milieu in a chronic autoimmune condition, and the imbalance between anti and pro-apoptotic effectors, result in thyroid cells transformation, reducing thyroid hormones synthesis. Key important events regarding chronic inflammation momentum are those driving PTC carcinogenesis and its deregulation of the MAPK signaling pathway, causing rearrangements of RET/PTC, TRKA and mutation points in RAS and BRAF. In this review, we highlight the most relevant molecular events on thyroid disorders, giving an especial attention to mechanisms that drive molecular protagonists.

Keywords: Thyroid disorders; Hashimoto's thyroiditis; Thyroid cancers

Introduction

The thyroid is an endodermal endocrine gland [1-4], macroscopically characterized by a loose connective tissue capsule from where septae run into the gland, dividing it into lobes and lobules [4,5]. Its function is to synthesize and store thyroxine (T4) and triiodothyronine (T3) and calcitonin hormones, controlling body metabolism [4,6]. This gland consists of thousands of thyroid follicles, vesicular endocrine glands coated by simple cuboidal epithelium and C cells (or parafollicular cells) [4,5,7]. The cavity of the follicles contains a gelatinous substance called colloid [4,8].

Among the diseases that occur in the thyroid, the most commonly diagnosed is the Hashimoto's Thyroiditis (HT) - an autoimmune disease - and different types of thyroid cancer [9-12].

Hashimoto's Thyroiditis (HT)

Hashimoto's Thyroiditis (HT) was first described by Hashimoto in 1912 [13]. HT is an autoimmune disease caused by the production of anti-thyroid antibodies that results in chronic inflammation of the thyroid, which ultimately leads to the destruction of the gland, compromising its functionality [14].

In this condition, it is observed a widespread infiltration of eosinophils and lymphocytes that causes parenchymal alterations and progressive loss of follicular cells, which leads to thyroid tissue replacement and fibrosis [15]. These events result in fibrotic phenotype and parenchyma atrophy [16-19].

As the HT causes loss of epithelial cells, a replacement by fibrotic tissue takes place as a phenotypic result from the tissue remodeling, as well as a proliferation of autoreactive CD4 + T helper cells. These tissue disruptions of the thyroid architecture result in a phenotype of progressive hypothyroidism, increasing functionality loss [16].

There are cytological abnormalities in HT, as nodules proliferation and changes in cell nucleus similar to those occurring in papillary thyroid carcinoma (PTC), which will be described later on this review [20]. As for the pathogenesis of HT, it is known that genetic and environmental factors predispose the expression of the disease [20-24].

Among the exogenous factors that increase the incidence of HT, we highlight: (i) iodine supplementation in geographical areas where there is shortage of this element, (ii) the continued use of amiodarone hydrochloride and lithium, (iii) interferon and interleukin-2 therapies [25-29], (iv) incidence of some viral types such as T-lymphotropic virus type 1 (HTLV-1), and (v) *Yersinia enterocolica* (family Enterobacteriaceae) [21].

Patients with Turner Syndrome, Alzheimer's disease on family history and with Down Syndrome are more likely to have HT disease, as its occurrence is linked to environmental and endogenous factors due to a genetic predisposition [21].

Some genes that influence genetic predisposition to HT are related to the families of: (i) human leukocyte antigen DR (HLA-DR), (ii) thyroid stimulating hormone receptor (TSHR), (iii) thyroglobulin (Tg) producing genes, and (iv) protein tyrosine phosphatases non-receptor type 22 (PTPN22) [23,24]. In addition to those, dysfunction of the genes families (i) CD40-related to a decreased CD40 expression on B cells - APCs, and thyrocytes [23,24], (ii) RET/PTC, proto-oncogene, (iii) RAS and BRAF, proto-oncogene [30], (iv) hOGG1 - a major

repair gene for free radical-induced oxidative DNA damages [31], and also (viii) FOXP3, a transcription factor involved in the development and function of regulatory T cells [32].

One of the most important altered gene groups in HT is the regulatory gene family immunity antigen 4, associated with the cytotoxic T lymphocyte (CTL-4), which regulates the expression of these proteins in T cells, while competing with CD28 for B7-1 and B7-2 receptors, causing the reduction of the secondary signal transmission of the T cell inactivation pathway, and subsequent apoptosis [21,33-35].

The mechanism behind this disrupted self-immune response seems to be quite complex, the general immunological mechanism is better described by the infiltration of thyroid gland by B and T lymphocytes, which are directly involved in cell apoptosis events. The secreted cytokines result in extensive lymphocytic infiltration, triggering the destruction of thyroid cells [24,36].

The T lymphocyte helper Th1 produces IL-2, IFN γ , and TNF α and β causing a cascade of reactions that initiate cytotoxic and inflammatory activities. Moreover, the cytokines IL-4, IL-5, IL-6, IL-10, and IL-13 produced by T lymphocyte helper Th2 activates the process of antibody production and increases the amount of eosinophils and mast cells [21].

Regarding the role of IFN γ in the autoimmune process of HT, this effector acts as an amplification enhancer of CXCL10 Th1 modulated (the prototype of the IFN γ -inducible Th1 chemokines) [37,38]. This chemokine is, therefore, secreted by the thyrocytes that display a chronic infiltration of TNF- α [37], becoming a marker of a Th1 orientated immune response [39]. In this scenario, "...CXCL10 could be a marker of a stronger and more aggressive inflammatory response in the thyroid, subsequently leading to thyroid destruction and hypothyroidism..." [38].

Although, Hashimoto's Thyroiditis (HT) have been described for decades as a Th1 autoimmune disease, there were some phenotypic results that could not be explained solely by the Th1/Th2 hypothesis [40]. A new group of T cells (Teff), T helper 17 cells (Th17), have been described as an important immune effector on the development of TH [40,41], as well as in other autoimmune diseases such as multiple sclerosis/experimental autoimmune encephalitis, uveitis, rheumatoid arthritis, Sjogren's Syndrome, myasthenia gravis, and psoriasis [16,40,41].

The signaling activation of Th17 induces the production of interleukin 17 (IL-17), interleukin 21 (IL-21) and interleukin 22 (IL-22). For Th17 differentiation regime, other important effectors are necessary to keep the signaling activate: TGF- β , interleukin 6 (IL-6), interleukin 23 (IL-23) and interleukin 1 (IL-1) [42]. This pathway was also corroborated by the work of Figueroa-Vega et al. [43] that investigated patients with HT. Their research described an increased number of Th17 cells, increased levels of IL-17 mRNA and a stronger immunohistochemical expression of IL-17 and IL-22 in thyroid tissues in HT patients [43].

Another evidence supporting HT as a Th17 phenotype autoimmune disorder instead of a Th1 phenotype was described by Horie et al.[44]. Using non-obese diabetic-H2h4 mice, they showed a decreased severity of thyroiditis in IL-17 knockouts.

Recently, Zhu et al. [41] described a new subset of follicular helper T (Tfh) cells and interleukin 21 (IL-21), which regulate the development of antigen-specific B-cell immunity, present in human autoimmune

thyroid diseases (AITD) (as Graves' disease (GD) and HT). Thus, this work gives support to the idea that Tfh cells might play an important role in the pathogenesis of AITDs through activation of antigen-specific helper T, and again not only through Th1 activation.

The large quantity of pro-inflammatory substances secreted by those cells, and the imbalance between anti and pro-apoptotic molecules, result in thyroid cells destruction. This leads to a reduction in thyroid hormones synthesis, which make the cells defective in thyroid iodine organification. Therefore, T cells, in addition to having cytotoxic activity to thyroid epithelial cells, also stimulate B cells to produce anti-thyroid antibodies (anti-TPO, anti-TG and antireceptor antibody TSH) [24,32,36,45].

Thyroid Cancers and Papillary Thyroid Carcinoma (PTC)

Thyroid cancer is the most common endocrine neoplasia [46], and represents 1.1% of all malignant tumors diagnosed worldwide, affecting more the female gender [9,47]. According to the SEER database (Surveillance Epidemiology and End Results; National Cancer Institute, <http://www.seer.cancer.gov>, accessed on 30th August 2015) in the United States of America (USA), approximately 13.5 per 100,000 individuals per year present this condition. In recent years, there has been a significant growth in global rates, which positions this affection as the fastest growing in incidence rates among all types of cancer (an increase of 5% per year between 2002 and 2012) [46].

These types of cancer are heterogeneous, with distinct histological, anatomical and clinical characteristics. They can be divided into four categories: (i) the medullary carcinoma (which is derived from parafollicular cells), (ii) anaplastic or undifferentiated carcinoma, (iii) follicular thyroid carcinoma (FTC), (iv) and papillary thyroid carcinoma (PTC). The FTC and PTC are well-differentiated carcinomas, which are originated in the follicular cells [48,49]. The FTC has a variant called Hurthle Cell Carcinoma [50,51]. Although, papillary carcinoma is the most common type, it has the best prognosis. In the other hand, the follicular carcinoma is rare and has the worst prognosis [50,52].

The PTC has distinct morphological characteristics [53,54], presenting oval and elongated contour core forms, stacking of the nucleus, inclusions and cracks, and the tendency to form metastases, which are taken to the lymph nodes. The main forms of histopathological variants are: (i) classical, (ii) the follicle, (iii) tall cells, and (iv) diffuse sclerosing [54,55]. Each one of them has different phenotypes, and also differentiated morbidity and mortality rates [54,56].

Among de molecular characteristics of PTC, there are those related to changes in chromosomal rearrangements such as RTK, RET and TRKA, and those related to mutational changes like BRAS, RAS, PI3K, PTEN, IDH1 and p53 [57-63].

One of the most important alterations present in the PTC occurs in the encoding gene of the RET protein (discussed in details later on), which is also associated with molecular modifications in thyroid tissue of Hashimoto's Thyroiditis (HT) patients [64-66].

Thyroid Cancers and Chronic Inflammation

In most neoplasias, the relationship between chronic inflammation and cancer development seems to be well established: gastric infection

by *Helicobacter pylori*, which causes chronic gastritis, increases the risk of gastric cancer by 75% [67-70]; Crohn's disease and ulcerative colitis are associated with colorectal cancer [67,69-72]; both the viral Hepatitis B and C and alcoholic liver cirrhosis are described as progression factors of hepatocellular carcinoma [69,70,73]; chronic reflux esophagitis can result in Barrett's carcinoma [70,71]; cervical infection by Human Papillomavirus (HPV) results in cervical cancer [70]; prostatitis is associated with prostate cancer [67-69].

Nevertheless, the association between chronic inflammation caused by HT and PTC has been described as controversial [74,75]. Since Dailey et al. first described the possible correlation between inflammation and thyroid cancers in 1955, the majority of the events involving these two conditions have not been clearly elucidated [65,74,76].

Molecular Events of Hashimoto's Thyroiditis (HT) and Papillary Thyroid Carcinoma (PTC)

Although controversial, the increasing incidence of Hashimoto's Thyroiditis (HT) and Papillary Thyroid Carcinoma (PTC) suggests that there is a close relationship between these conditions [77]. Studies reveal associations between the presence of anti-thyroid antibodies and the progression of malignancies [30,65,78].

Frequently, chronic inflammation predisposes the organism to cell proliferation reactions, cytokines secretion and other phenomena that influence rearrangements and mutations in follicular cells [52,79,80]. In their microenvironment, cancer cells secrete cytokines and chemokines, enabling positive feedback regarding the regulation of neoplasia immunomodulation. In a positive feedback, these elements of the immune system recruit leukocytes to tumor site, thus producing reactive oxygen species (ROS) and reactive nitrogen species (RNE) in an attempt to eliminate the pathogens [59,80,81].

However, because they are very reactive metabolites, they induce the production of mutagenic agents causing damage to the DNA [59,80]. When the damaged cells neighbor DNA mutations or gene rearrangements, there is an increase in the likelihood of oncogenes activation, as well as loss of tumor suppressor functions, such as the p53 gene [66,82].

One of the most important events in the PTC carcinogenesis is the deregulation of the Mitogen-activated Protein Kinase (MAPK) signaling pathway with rearrangements of RET/PTC, TRKA and mutation points in RAS and BRAF, where these nucleotide base changes contribute significantly to the PTC genotypes [30,79,83]. In PTC, these gene mutations can occur in 70% of the cases [30,65].

Borrello et al. [84] showed that the oncogene RET/PTC1 expressed in human thyrocytes induces a myriad of molecular events such as i) inflammatory genes modulation, M-CSF, GM-CSF, G-CSF (stimulating factors and colonization of macrophages) [84]; ii) production of chemokines and cytokines such as CCL20, CXCL8 [84-86], which are related to E-cadherin expression, consequently increasing the metastatic events [87], and CXCR4 (chemokine receptor type 4) upregulating the MAPK1/MAPK3 activation, IL-1B mediating an inflammatory response involved with cell proliferation events, differentiation and apoptosis [88]; iii) enzymes that degrade the matrix and adhesion molecules: MMP14 (related to collagen degradation), MMP7 (matrilysins production, fibronectin degradation and pro-collagenase activation), MMP9 (gelatinase production), MMP10 (stromelysins production, fibronectin degradation and activation of

the pro-collagenase) and L-selectin (leukocyte adhesion molecules); and iv) other proinflammatory transcription related elements such as UPAR (monocyte activation) [86,89].

In thyroid cells that are positive to RET/PTC rearrangements, chemokines and cytokines released by tumor stroma collaborate to cell survival by selecting clones with gene mutations and apoptosis resistance, which are induced by these oncogenes [30,88].

The RET/PTC3-RAS-BRAF axis triggered upregulation of CXC chemokines and their receptors, which in turn stimulate the mitogenic and invasive capacity of thyroid cancer cells [89-92]. In this signaling mechanism, the tumor microenvironment modulates an autocrine/paracrine pathway, overexpressing several chemokines that positively feedback the mitogenic and invasive phenotypes in cancer [59,93].

In a very elegant work, Melillo et al. [89] described the activation of RET/PTC3-RAS-BRAF axis and its relevance on chemokines modulation on sustained proliferation and motility of thyroid tumor cells. Using genomic, transcriptomic and proteomic assays on thyroid cell cultures (PC Cl 3 (PC) and follicular cell line - derived from 18-month-old Fischer rats on Matrigel® -, they demonstrated that RET/PTC3-RAS-BRAF axis acts synergistically to alter thyroid cells (in vitro and in vivo) into an invasive phenotype. Moreover, CXCL1 and CXCL10 were key effectors on this malignant transformation [89]. According to Guarino et al. [30], the immune system cells play an ambiguous role in thyroid cancer, since the resultant phenotype depends on specific cells population, as the effect can be pro-tumorigenic or anti-tumorigenic [30]. Particularly, the presence of innate immunity cells, as observed in pathological phenotypes in HT, increase tumor progression and is associated with a poor prognosis [30,65].

Other researches on molecular alterations caused by thyroid neoplasms suggest that RAS and BRAF proteins, all components of RET-PTC/RAS/BRAF/ERK pathway can interfere with chemokines regulation, which also contribute to proliferation, migration and survival of neoplastic cells [89].

Although, the histopathology and the mechanistic events on the majority of thyroid disorders have been, in some level, characterized, new important data with a strong application on clinics still being adding on those events. Recently, Nikiforov et al. [94] reclassified, through a retrospective study, the follicular variant of PTC (FVPTC), regarding its subsets: infiltrative (or nonencapsulated) and encapsulated. Their findings generate relevant information on clinical conduct to noninvasive follicular thyroid neoplasms with papillary-like (NIFTP) thyroid cancers, indicating that 45,000 patients worldwide would be affect with this new reclassification, "... reducing the psychological burden, medical overtreatment and expense, and other clinical consequences associated with a cancer diagnosis..." [94].

Conclusion

As Wirtschafter et al. [57] and other authors [59,80,84,86] described, there are strong evidences that Hashimoto's Thyroiditis (HT) is a prior condition for papillary thyroid carcinoma (PTC); this conclusion comes from the literature, which points out that there is an increase incidence of cancer in patient with HT. Inflammation can predispose the cell and metabolism rearrangement through well-orchestrated molecular events, causing the development of cancer phenotype, progressed by the chronic inflammatory momentum. Therefore, a chronic inflammatory environment, derived from

Hashimoto's Thyroiditis, in addition to metabolic disorder caused by neoplastic events, produce synergistic effects of negative prognosis on the progression of both diseases (HT and PTC). The milieu of these events results in the rearrangement of RET/PTC gene in follicular cells, as the primer alterations.

Declaration of interest

The authors declare that there are no conflicts of interest.

Acknowledgements

Sincere thanks to Pedro Luiz Simpson and to Juliana Alves Thom for providing helpful comments on an earlier draft. Thanks to Arthur H. PonteS for very important language revision. Thanks also to Flavio Luis Leite Sousa and to Ciro Yoshio Joko FOR their support.

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