Thyroid autoimmune disorders and cancer

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Abstract

In the last decades, many studies conducted *in vitro*, and *in vivo*, have shown that thyroid autoimmunity and thyroid cancer (TC) (mainly papillary TC) can be concomitant, even if the exact mechanisms at the basis of this association are still not clear. Growing incidence of TC coincides with increased registration of autoimmune thyroid disorders (AITD) suggesting an association between those pathologies. Elevated TSH levels and thyroid autoimmunity were defined as independent risk factors for TC.

However a lot of evidence suggests that autoimmunity and inflammation, *per se,* are risk factors for TC. The link between inflammation and TC involves multiple components of the immune system, extracellular matrix, stroma, and adipose tissue, with pro-tumoral activity of inflammation being opposed to anti-inflammatory effects, favoring protection against cancer progression. Within the tumor microenvironment, inflammatory cells, belonging both to innate (macrophages) and adaptive (lymphocytes) immune responses, are interconnected with fibroblasts, endothelial cells, adipocytes, and extracellular matrix through cytokines, chemokines and adipocytokines. Under the influence of transcriptional regulators (such as Nuclear Factor-kappa B, mitogen-activated protein kinases, or Phosphoinositide-3 kinase/protein kinase-B), oncogenes connected to the different subtypes of TC promote their farthermost proliferative effect on the tumor microenvironment.

Future studies will be necessary to understand the connections between thyroid autoimmunity and cancer, also in order to design a tailored therapy for TC patients with AITD.

Keywords: autoimmune thyroid disorders, thyroid cancer, immunity, Graves' disease, Hashimoto's thyroiditis.

1. Introduction

Immunity and cancer have a functional relationship. T-cells, antigen presenting cells (APCs), B-cells, antibodies, cytokines, chemokines, etc. have a determinant role both in immune response and cancer, but the underlying pathogenic meaning is still unclear [1].

The immune system differentiates self from non-self, and reacts against extraneous insults, but once the immune-tolerance is broken, cancer and/or autoimmune diseases can arise [2]. The immunonogical surveillance is able to limit the tumorigenesis, but some malignancies evade it. When tumors occur, APCs and natural killer (NK) gain tolerance to these new cells, and T lymphocytes, that belong to cellular mediated-response, go through apoptosis, releasing inhibitory cytokines that lessen the interaction with APCs [2]. Among APCs, dendritic cells (DCs) are important regulators of the adaptive immune-response, and as such are very important, both in thyroid autoimmunity, and for cancer immunity mediated by T lymphocytes [3,4].

Autoimmune phenomena and cancer development are often concurrent. Sera of oncologic patients have autoantibodies specific for cancer antigen (e.g. against oncosoppressor, or oncogene enzymatic products), or specific for other antigens not tumor-derived (e.g. nuclear-autoantibodies, and thyroid autoantibodies) [1].

Cancer onset can be associated to the extended and serious immune stimulus linked to the autoimmune disease, and paraneoplastic autoimmune diseases characterized by rheumatic manifestations can occur before, contemporaneously or after the onset of tumors [5]. Paraneoplastic rheumatic syndrome has been described in patients affected by breast cancer, blood malignancies, melanoma, colon cancer, and thyroid cancer (TC) [1].

Chronic immune processes appear to be linked to tumorigenesis, in fact, in

Hashimoto's thyroiditis (HT) the gland microenvironment is charactized by the presence of infiltrating lymphocytes and other immune competent cells, and **by** soluble mediators, including chemokines, cytokines, and growth factors, that are essential components of cellular transformation and tumor progression [4,6]. This supports the possible involvement of inflammatory molecular mechanisms in the development of tumors; even if the immune system is involved also in the later stages of tumor development [4].

We aim to review the literature about thyroid autoimmune disorders and thyroid cancer, in order to understand their underlying association.

2. General aspects

2.1 Thyroid cancer

Among endocrine tumors, TC has the highest incidence, representing the eighth most commonly diagnosed cancer worldwide [7], and in the last 20 years there has been more and more of its diagnosis [8-10].

Different risk factors are associated with differentiated thyroid cancer (DTC), including the exposure to ionizing radiations in childhood or adolescence, that can cause in particular papillary thyroid cancer (PTC) [11], and secondary radiations, or nuclear explosions or nuclear accidents [12]. Even the exposure to low doses of radiations may cause the onset of thyroid nodules and cancer [13].

Another risk factor is iodine deficiency, associated with a higher frequency of follicular thyroid cancer (FTC), while in iodine deficient areas an elevated frequency of PTC has been reported, after the introduction of iodine prophylaxis [14]. Hashimoto's thyroiditis is associated with PTC and thyroid lymphoma [15,16].

Surgery (lobectomy or total thyroidectomy) is the elective treatment for both PTCs and FTCs, whereas less favourable histological PTCs and FTCs subtypes require also subsequent radioactive iodine (131I) remnant ablation [12].

Basal thyroglobulin (Tg), and Tg after recombinant thyroid-stimulating hormone (TSH) determination, and neck ultrasound are the key elements for the subsequent evaluation of DTC patients, previously been submitted to surgery [12,17,18], however the presence of circulating anti-thyroglobulin antibodies (AbTg) might reduce the value of Tg determination.

Papillary thyroid cancer (about 85% of TCs), FTC (about 10% of TCs), and medullary thyroid carcinoma (MTC) (<5% of TCs) represent almost the entirety of TC cases [19,20]. Anaplastic thyroid cancer (ATC) is rarer (<2% of TCs) but **it** is one of the most lethal human cancers, and it causes around 15-40% of death for TC [21-25].

Well-differentiated TCs (PTC, FTC) generally have a favorable prognosis, while MTC, or ATC, have much worse survival rates [26].

Papillary thyroid cancer incidence is increasing and it will be the 4th most frequent malignancy by 2030 in United States [27]. Approximately one fifth of PTC patients show lymphatic involvement, with an increased patient morbidity and mortality [28].

A link between inflammation and cancerogenesis is well known, since the year 1863 when Virchow showed leukocytes in cancer tissues and suggested an association with the development of cancer [29,30].

In fact, it is well established that chronic inflammatory stimulus among certain tissues, can lead to precancerous lesions, through an oncogene signaling pathway that is induced by the inflammation-related genes expression [31]. Chronic thyroiditis is founded in 20-50% of PTC samples [32] and it is linked itself to a higher risk of PTC

[33,34]. A notable perilesional lymphocytic infiltrate (LI) or foci of lymphocytic thyroiditis are more frequently detected in PTC [29], than in benign thyroid lesions [35], even with no signs of HT. It has been hypothesized that this perilesional LI can play an active role in the tumorigenesis of PTC [36].

Furthermore inflammation, and the presence of high cytokine and chemokine levels, seem to predispose to RET/PTC rearrangements, which **are** a key mutation in the carcinogenesis of thyroid cells [29].

2.2 Autoimmune thyroid disorders (AITD)

Autoimmune thyroid disorders are characterized by a pathological activation of the immune system against the thyroid tissue [37] and they represent the most widespread T lymphocytes mediated organ specific autoimmune diseases [38,39].

The two extreme of these disorders are: Graves' disease (GD) and HT, with the common pathologic feature being LI of the gland parenchyma. Hypothyroidism and thyrotoxicosis represent the clinical hallmarks of HT and GD, respectively [37].

The crude prevalence of AITD is approximately 5% [40], and that of anti-thyroid antibodies (ATA) without clinical disease could be higher [41].

It has been shown [42,43] that: women have a higher risk (approximately 4–10/1, female/male) than men to develop HT; HT-related hypothyroidism is more frequent at old age; an important geographic heterogeneity exists in the incidence of HT; prevalence of HT, such as ATA**,** differs with race and rises with age, with the peak at 45–55 years; and iodine-sufficient populations have a greater prevalence and incidence of HT than those in iodine-deficient areas.

Many systemic autoimmune disorders, such as systemic lupus erythematosus (SLE), Sjögren's syndrome (SS), systemic sclerosis (SSc), or rheumatoid arthritis (RA), are

associated with the development of AITD in the same patients [44-46]. An exception is given by pemphigus. In fact, in a recent cross-sectional study, pemphigus was associated with HT only in male patients, and no association was shown with TC [47]. We also reported that [48] SSc patients affected by PTC, showed all some grade of thyroid autoimmunity features on the hystological examination of the gland, compared to only 40% of those without TC. This observation supports the hypothesis that autoimmunity to thyroid may play a causative role in the development of PTC. The TSH values were also higher in SSc patients than in control subjects, leading to a further increase of risk of malignancy of pre-existing thyroid nodules [48]. Furthermore the exposure to certain medications has been hypothesized to be a risk factor fo the thyroid carcinogenesis among SSc patients [49], but there is no evidence of this and our PTC patients were not associated with any specific therapy. Whether the BRAF-MEK-ERK pathway activation has a shared function in PTC, such as in SSc, remains to be clarified too: BRAF V600E mutation was observed among 1 of 3 studied patients, in accordance with the prevalence showed in not SSc PTC patients [50,51].

As for other autoimmune disorders, also AITD seem to be influenced and induced by the synergy of both genetic such as environmental factors [37].

The epidemiological proofs of a genetic susceptibility to AITD come from the high sibling risk ratio (approximately 17) for AITD, the familial clustering of the AITD disorders in siblings of affected patients (20–30%; with 50% ATA) [52]. Among monozygotic twins a concordance of 0.3-0.6 or AITD has been found, compared to 0.00-0.1 among dizygotic ones; GD heritability is about 79%, and that of the presence of ATA 70% [53].

AITD occurrence is associated with environmental factors (as smoking, radiation,

stress, iodine, drugs, and infection) in about 20% of cases, where the external insult probably causes a cellular/tissue damage able to switch on the innate immune system with subsequent progression to an AITD if a genetic susceptibility exists [54,55].

For example, GD and Graves' ophthalmopathy (GO) can arise in patients treated with radioactive iodine for toxic goiter [56]; furthermore, children survived to the Chernobyl nuclear accident showed a higher incidence of ATA [57].

GD and GO have been linked also to cigarette smoking [58].

The prevalence of AITD is higher in regions of iodine suffiency. Iodine supplementation of earlier iodine deficient people can lead to both temporary autoimmune subclinical hyper- and hypothyroidism [59]. Interestingly also PTC has been associated with a normal or high iodine intake, while FTC is associated with a low iodine intake [60].

The thyroid contains high levels of selenium as it expresses specific selenoproteins. Low levels of selenium are sufficient for deiodinases, even if the selenium status impacts on AITD development. The role of selenium supplementation for the treatment, or prevention, of AITD has been overstressed [61,62].

Among drugs, lithium seems to increase the chance of developing ATA, hypothyroidism and, partially, GD [63]. Stress also appears to trigger GD [64].

Moreover, the role of viruses in AITD has been evaluated, even if with no clear results [65]. However, interestingly a recent meta-analysis showed an association between hepatitis C virus chronic infection and PTC [66,67].

2.3 Chemokines in AITD and TC (Figure 1)

Cytokines and/or chemokines are determinant in the etiopathogenesis of autoimmune thyroiditis, or GD. In the thyroid gland, interferon (IFN)-γ and tumor necrosis factor (TNF)-α are synthesized by activated T helper 1 (Th1) lymphocytes, and stimulate in thyrocytes the secretion of CXCL10 (the prototype of the IFN-γ-inducible Th1-chemokines), starting and supporting the autoimmune process via an amplification feedback loop [37].

CXCL10 is released upon IFN-γ-stimulation, and it interacts with the chemokine (C-X-C motif) receptor 3 (CXCR3), activating specific downstream cellular pathways [68].

CXCL10 and its receptor, CXCR3, are involved in the etiopathogenesis of various autoimmune diseases, organ specific [as GD and GO, and type 1 diabetes], or systemic [as SS, SLE, sarcoidosis, mixed cryoglobulinemia (MC), psoriasis or SSc] [69-73].

The release of CXCL10 by (CD)4+, CD8+, and NK depends on IFN-γ. Stimulated by IFN-γ, in combination with TNF-α, CXCL10 is produced by thyroid cells [37]. Therefore high CXCL10 serum levels are a potential sign of Th1-immune type activation [37].

Patients with autoimmune thyroiditis, with a hypoechoic echostructure, and those with hypothyroidism, have elevated serum CXCL10, which may represent a sign of a stronger immunological response that leads to the parenchyma damage and its functional impairment [37].

Moreover, detectable CXCL10 serum levels are found in both new diagnosed and relapsed GD patients, suggesting its pathogenetic role in the development of GD and GO. Stimulated by IFN-γ, CXCL10 is released from thyroid GD cells, GO fibroblasts, or preadipocytes [74,75].

CXCL10 decreases after thyroidectomy and radioiodine in GD patients, suggesting that it is synthesized directly in the thyroid, while in GO patients the elevated CXCL10 levels reflect the activity of orbital inflammation [76].

As stated above, inflammation is determinant in the tumor microenvironment and chemokines play an important role in the setting of peritumoral inflammation [77]. These mediators and their receptors are reported in tumors and often their expression and signaling are deregulated [78], promoting tumor growth, invasion and metastasis [79]. For this reason, it has been hypothesized that the cytokines released by the malignant cells and/or by the leucocytic infiltrate are decisive for the cancer natural history [79]. The chemokines inducible by IFN-γ (CXCL-9, -10 and -11) and their main receptor, CXCR3, are also determinant for the initial development of autoimmune thyroiditis [37].

The CXCR3-ligand pathway is implicated in thyroid autoimmunity and CXCR3 **is** overexpressed in cancer, indicating its carcinogenetic activity together with the inflammatory microenviroment. CXCR3 ligands (CXCL4, CXCL9, CXCL10 and CXCL11) provoke opposite reactions in part owing to the presence of 2 splice variants, CXCR3A (that promotes cell proliferation) and CXCR3B (that induces apoptosis) [79].

In thyroidal tissues, serum CXCL10 is associated with Th1 cell infiltration that has been shown in autoimmune thyroiditis and it is tightly related to TC [80]. Th1 lymphocytes recruited to a tumor site are responsible for the increased production of IFN-γ and TNF-α that induces the CXCL10 release from different cells, maintaining and increasing the cytokine release in the tumor microenvironment [80]. The CXCR3 pathway has a key role for cancer development: it has antiangiogenetic and proimmunogenetic activity toward cancer cells [81]. The upregulation of CXCR3 has

been shown in various human cancer types and it is associated with lymph node metastasis and poor prognosis [82].

The paper by Urra [79] reported that non-metastatic PTC tissue displayed high concentrations of CXCR3A and CXCL10 mRNA compared to non-neoplastic thyroid tissues, as it has been observed also in the PTC cell line, TPC-1. IFN-γ, in normal and tumor thyroid cells, highly activated the CXCL10-CXCR3A pathway, supporting the hypothesis that persistent inflammation may represent a significant step in the tumor progression [79].

3. Association between AITD and TC (Table 1)

Controversial results from the literature about the association among AITD and TC are broad, while data regarding the possible link between AITD and MTC or thyroidal C-cells hyperplasia are anecdotal [83].

An association between AITD and PTC has been shown [84].

In PTC the usual classification discerns microcarcinomas (PTMC; with a diameter ≤ 1 cm), from macrocarcinomas (> 1 cm) [85,86].

PTMC are often diagnosed as incidentalomas among samples derived from thyroidectomy perfomed due to non neoplastic disease, and for this reason they are also called "occult" carcinoma [87,88].

The incidence of PTC has increased worldwide [89], and most of this increasing trend is associated to PTMC, accounting to a maximum of 43% of PTC cases with a new diagnosis [90].

The increasing prevalence of HT, such as that of PTC/PTMC, led to verify whether HT can cause TC [26,91,92].

The presence of lymphocytic cell infiltration, lymphoid follicles, oxyphilic cells, and

reactive germinal centers was reported in PTC histological samples ranging from 10% to 58% of cases [93].

In a paper evaluating 2 466 patients after thyroidectomy for benign thyroid disease, the overall prevalence of PTMC was 16.3%, significantly higher in patients with histological findings of HT, than in those without [89].

In other papers the reported rate of PTMC was higher (39%) [94].

In a case-control study conducted retrospectively in 927 PTMC patients, *vs*, 927 (sex-, age-matched) control subjects, the rate of positive anti-thyroperoxidase antibodies (AbTPO) or AbTg was 18.4% or 23.4%, in comparison to the reciprocal rates of 12.7%, or 12.0% in control subjects (P<0.01, for both comparisons) [91]. Patients positive for either antibody had a two-times augmented risk of PTMC, especially in those aged 18-30 years [91].

To evaluate the influence of chronic lymphocytic thyroiditis (CLT) on PTC, 505 PTC cases were collected and the presence of HT was reported in 33.3% of them [95], similarly to what shown in 919 PTC cases from Turkey (34.5%) [93], and in 1 250 PTMC cases from China (29.1%) [96], but it was superior to that described in 11 155 PTC cases in Denmark (18.9%) [26].

The prevalence of PTC, TSH levels and ATA has been evaluated in 13 738 patients (9 824 untreated and 3 914 in treatment with L-thyroxine) [97]. PTC frequency was significantly more elevated in nodules associated with HT than in nodular goiter and it was also combined with higher circulating TSH. TSH levels were reduced by the treatment with L-thyroxine, as the occurrence of clinically detectable PTC [97].

These data agreed with those of another study showing that 34% of PTC patients had high AbTPO levels in association with LI [98].

According to other studies both elevated TSH levels and thyroid autoimmunity are

independent risk factors for malignancy [99].

Hypothyroidism is the most frequent clinical presentation of AITD, and thyroid cells keep on growing under TSH stimulation. The tight relationship between serum TSH and TC risk has been shown, and it was even demonstrated for TSH levels within the reference range [100].

This topic has been evaluated also by a review, about the association between AITD and TC, focused on cytological samples [101]. The review reported that genetic and/or environmental factors, conditions related to thyroid autoimmunity (inflammatory molecules, serum ATA, etc.), such as high TSH levels, are independent risk factors of PTC. This agrees with the hypothesis that overt HT could be linked to thyroid malignancy, instead of nonspecific serologic reactivity. In this way, thyroid autoimmunity could directly promote tumor growth, or via the increase of TSH levels resulting from an initial autoimmune thyroid failure [101].

However also discordant results have been reported. In fact, a paper showed that the prevalence of AITD was not increased in patients with PTC [102].

The increased prevalence of PTC among AITD patients has also important clinical impact as approximately 10–30% of these patients are affected by aggressive forms of TCs, and need second and third levels therapy [103,104].

Another study reported a higher prevalence of cervical lymph node metastases, but a lower prevalence of distant metastases, in AbTg positive PTC patients, vs, AbTg negative [105,106].

In terms of prognosis, the complicated interplay between immunity and tumors needs to be further investigated. The presence of lymphocytes could represent a sign of the immune response of the host, or only a coincident element [1]. A restricted number of studies showed a poorer prognosis of PTC associated with lymphocytic thyroiditis,

while the most reported that lymphocytic thyroiditis has a better outcome, or does not interfere with PTC clinical prognosis [107].

A study evaluated the role of lymphocytic thyroiditis in a cohort of PTC patients, in relation to BRAF V600E mutation status [108]. The Authors showed that lymphocytic thyroiditis was associated with a lower prevalence of central compartment nodal metastases and extra-thyroidal extension, independently from the presence of BRAF mutations. However, patients with TC coexisting with lymphocytic thyroiditis showed a higher prevalence of bilateral, or multifocal disease [108], while another paper reported that children, or adolescents, with CLT more commonly had familial PTC [109]. Concerning this, more aggressive TC subtypes (poorly differentiated and ATC) show a decreased lymphocyte infiltration [32].

Patients with non-thyroid autoimmune diseases, as SLE [110], SSc [48,111], and hepatitis C virus-associated MC syndrome [112], have also shown an elevated prevalence of HT and PTC, indicating that persistent immunological stimuli favor the development of AITD and PTC. The over-activation of the Th1 lymphocytes was reported in CLT and PTC patients [37]. Lymphocytes secrete IFN-γ, that leads to the secretion of chemokines inducible by IFN-γ (CXCL-9, -10, -11) by thyroid cells, in this way perpetuating the autoimmune process [37].

3.1 Genetic susceptibility and genome-wide association studies (GWAS)

Autoimmune thyroiditis and TC show a high heritability [113].

Thyroid function is finely regulated, even if the inter-individual variability is high, suggesting that there is a personal homeostasis of the thyroid function [113]. Approximately 40-60% of variability in thyroid function is determined by genetic factors [113].

TCs have an elevated degree of heritability, as genetic factors represent >50% of TC causes [113]. MTC is linked to somatic, or germline, mutations, while the prevalence of familial PTC accounted for 2-11% of DTC cases [114].

For these reasons, genetics has a significant impact on thyroid phenotypes.

In the last decades, GWAS have been performed to investigate the genes implicated in several diseases [115], as AITD, thyroid function, and TC, identifying susceptibility genes for thyroid-related phenotypes [113].

Different genes are associated with the presence of ATA, or AITD [116,117] (**Table 2**; 118-126).

GWAS and Immunochip reported other AITD genes (**Table 2**; 118-126).

Other AITD genes have been assessed by GWAS, whose function is not known in AITD [116]. Considering these last genes, 7/11 are implicated in the function of T cell, indicating its importance in the pathogenesis of AITD [37].

The first GWAS of TC was reported in 2009 [127]. Differentiated thyroid cancer was associated with the most frequent variants on 14q13.3 (NK2 homeobox 1) and 9q22.33 (FOXE1), and a link between disrupted in renal carcinoma 3 (DIRC3), FOXE1, MBIP/NK2 homeobox 1, and Neuregulin 1 (NRG1) was reported [127-130]. Other markers associated with DTC, as "small nuclear RNA activating complex polypeptide 4", "binner mitochondrial membrane peptidase subunit 2", "asic leucine zipper ATF-like transcription factor", "DEAH-box helicase 35", "WD Repeat Domain 11 antisense RNA 1", "5-hydroxytryptamine receptor 1B", FOXA2, "UDP-N-acetyl-alpha-D-galactosamine:polypeptide N-acetylgalactosaminyltransferase-like 4", and "retinoic acid receptor responder 1" were reported only by some papers [129-132].

Five new loci [near "telomerase RNA component", pecanex-like 2 (PCNXL2), near

"oligosaccharide-binding folds containing 1", "SMAD family member 3", and between "neuronal regeneration related protein" and "erythrocyte membrane protein band 4.1 like 4A"] were reported by a meta-analysis of GWAS in 3 001 DTC patients, and 287 550 control subjects, from 5 European studies [133].

The strongest association was reported with 9q22.33 (FOXE1) in Caucasian people [127]. Moreover, FOXE1 is a key gene for radiation-induced TC [134,135]. Variants of FOXE1 were linked to PTC size, tumor stage, extrathyroidal extension, and lymphocytic infiltration, that are correlated to its clinical aggressiveness [136].

Another GWAS study, conducted on 1 085 DTC patients and 8 884 controls, showed 15 variants of 11 loci linked to DTC; with the strongest signals in the NRG1 gene [137], that encodes NRG1, acting on the erb-b2 receptor TK (ERBB) family of TK receptors. NRG1 isoforms expression level was related with genotypes [138].

NRG1 dysregulation is associated also with the "mitogen-activated protein kinase" and Phosphoinositide-3 kinase/protein kinase-B (PI3K/Akt) pathway via ERBB [139]. NRG1 was associated with different pathways involved in cellular growth or cancer, indicating that its expression in thyroid tissues could increase the DTC risk through ERBB signaling.

Besides the earlier loci (PCNXL2, NKX2-1, DIRC3, and FOXE1) reported in European people, another paper identified new susceptibility loci associated with DTC [septin 11, "vav guanine nucleotide exchange factor 3", Insulin Receptor, solute carrier family 24 member A6 (SLC24A6), "Methionine Sulfoxide Reductase B3", and "fragile histidine triad"] [113]. In particular, one SLC24A6 variant seemed to be a risk factor for FTC [113].

Signals on Insulin Receptor, "vav guanine nucleotide exchange factor 3", "fragile histidine triad", "Methionine Sulfoxide Reductase B3", SLC24A6, and septin 11 were

shown in the Korean patients, indicating heterogeneity in GWAS of DTC, between studies [113].

GWAS studies conducted in Korean, or European, patients showed common genetic loci (PCNXL2, NKX2-1, NRG1, DIRC3, and FOXE1), whereas some of them were identified exclusively in either the European, or Korean, patients [140]. Moreover, the risky SNPs allele frequency varies by race, and the genotypes with higher risk of DTC differ across ethnicities (i.e., the risky allele variants on FOXE1 were found in 0.08 to 0.13 among Asians and in 0.14 to 0.34 among Europeans). These data confirm ethnic differences in allele frequencies, but show little genetic impact of variants on FOXE1 in DTC development among people from East Asia [140]. Furthermore, frequent variants on FOXE1 were linked to a rised risk of DTC (odds ratio of 1.80 in European people, and of 1.35 in East Asians) [140].

3.2 Genetic alterations (Table 3)

RET/PTC rearrangements [RET/PTC1; RET/PTC3] are present in 3–60% of PTC patients [141], and cause the constitutional activation of the tyrosine kinase (TK) domains, with subsequent upregulations of genes implicated in proliferation and immortalization pathways.

Moreover, RET/PTC are described in almost the totality of AITD patients [142], and many cases of RET/PTC-induced PTCs have been diagnosed among people with AITD and precedent exposition to the radioactivity from Chernobyl nuclear accident [143]. Lastly, engineered transgenic mice expressing RET/PTC develop chronic thyroiditis and PTCs [144].

There are two hypotheses to explain how PTC and autoimmune thyroiditis can be linked by RET/PTC mutation [1]. The first one relies on the idea that certain TC

oncogenes are also able to induce an inflammatory protumorigenic microenvironment [1]. It has been noted that, when RET/PTC1 is expressed in normal human thyroid cells, it stimulates the expression of various genes taking part in inflammation and tumor invasion [as cytokines (CSF-1, IL-1B, G-CSF, and GM-CSF), chemokines (CXCL12, CCL2, CXCL8, and CCL20), chemokine receptors (CXCR4), enzymes degrading matrix (urokinase-type plasminogen activator, its receptor, and metalloproteases), and adhesion molecule L-selectin] [145]. Other papers reported that RET/PTC3 thyroid cells express at high level pro-inflammatory cytokines and proteins implicated in the immune response [146]. These data suggest that RET/PTC oncoproteins could take part in the initial phase of immune response and could stimulate the chronic inflammatory infiltrates with a chronic status of inflammatory thyroiditis (that was shown in about 20–50% of PTC patients) [146].

Furthermore, it has been shown that RET/PTC, BRAF and RAS proteins (included in RET-PTC/RAS/BRAF/ERK pathway, and mutated in FTC and PTC), can up-regulate chemokines, that contribute to neoplastic proliferation, survival, and migration [147,148].

The second hypothesis suggests that inflammation, linked to free radical and cytokine production, and cell proliferation, could favor the RET/PTC rearrangement [1]. It is also important to remind that Nikiforova et al. [149] reported RET/PTC rearrangements exclusively in PTC without concomitant signs of thyroiditis, and Rhoden et al. [150] detected low levels of RET/PTC in a very small portion of follicular cells within HT parenchyma.

Considering other genetic alterations, the p63 protein was shown to be frequently expressed in PTC and HT [151], indicating that it could be a pathobiological connection between these 2 disorders [152].

The phosphoinositide-3 kinase/protein kinase-B pathway is determinant in the balance between TC cell survival, the inflammatory response, and apoptosis of cancer cells, promoting leukocyte migration, and/or activating chemokine receptors [33]. Larson et al. [33] reported an elevated expression of p-Akt, Akt1, and Akt2 in the gland parts affected by thyroiditis and TC in comparison to normal ones, indicating that PI3K/Akt could take part in these two diseases.

BRAF V600E was knocked-in, in BRAF V600E/TPO-Cre mice, to develop hypothyroidism and invasive PTC [153]. When these BRAF V600E/TPO-Cre mice are crossed with mice knocked out for TSH receptor, the results are mice [BRAF V600E/TPO-Cre/Gnas-E1(fl/fl)] with PTC showing an attenuated phenotype, in particular with a small size and less invasiveness, which resemble the indolent PTMC, reported in humans [153]. The suppression of TSH in BRAF V600E/TPO-Cre mice does not revert the phenotype of cancer [153].

The highest prevalence of BRAF mutations are found in 50% of PTMC patients with the sclerosing variant, or the tall cell variant [154,155], and they are associated with large tumor size, multifocality, extrathyroidal extension, advanced stage, or lymph nodal metastases [154,156]. As reported by Jung et al., the stable occurrence of BRAF mutations in association with the stable proportion of microcarcinomas within BRAF-positive classic variant PTCs **suggest** that the increasing incidence of TC does not derive only from better diagnostic power of incidental, not aggressive tumors because BRAF V600E occurs in aggressive histopathologic features of PTCs, progressing tumors [157]. BRAF mutations are more frequent among PTC than in PTMC [158]. Moreover, in PTC patients and autoimmune thyroiditis the prevalence of BRAF mutations is lower [159], and concomitant lymphocytic infiltration of HT seems to be associated with less aggressive PTC forms, independently from the BRAF status

[160]. Moreover, a meta-analysis evaluating the clinical features of PTMC regarding BRAF V600E demonstrated that BRAF V600E was not associated with concomitant HT [161].

3.3 The role of Nuclear Factor-kappa B (NF-kB)

Nuclear Factor-kappa B is a transcription factor, taking part in the immune responses, and in the modulation of the transcription of various genes implicated in proliferation, cell survival, and/or differentiation [162]. NF-kB has 5 subunits in mammals, able to bind the promoters of target genes (as heterodimers., or homodimers). The p50/p65 heterodimer is the most common.

In thyroid cells, NF-kB was shown in a human TC cell line [163] and in a non-transformed thyroid cell line from rat [164], more than 20 years ago. From then on, the engagement of NF-kB in thyroid-specific gene regulation, thyroid autoimmunity, and TC, has been shown by various studies [165-167].

NF-kB is determinant in innate and adaptive immune responses [162], and its activation is induced by cytokines receptors, pattern recognition receptors, and lymphocyte receptors, and for this reason it plays a crucial role in the pathogenesis of auoimmune disorders [167].

Thyrocytes have functional pattern recognition receptors, as RIG-like receptors and toll-like receptors, that are susceptible to different molecular patterns (damage-associated or pathogen-associated) inducing the secretion of chemokines and cytokines [168]. It has been speculated that different insults to thyroid cells via the production of molecular patterns (damage-associated or pathogen-associated) can induce innate immune response, making thyroid cells behave as APCs, able to enroll lymphocytes which begin the immune response [168,169].

Different NF-kB heterodimers bind to the MHC class I gene in a hormonally-regulated manner, and for this reason the role of NF-kB in AITD has been suggested [162].

NF-kB is implicated in cancer development, too. Altered activation of NF-kB has been linked to lymphoid malignancies [170], and tumors of epithelial origin, as TC [165,171]. NF-kB induces the secretion of chemokines, growth factors, cytokines, and other molecules involved in the tumor microenvironment, and increasing the expression of anti-apoptotic genes (as BCL2), and mitogenic genes (as c-MYC and cyclin D1) [171].

For these reasons, cancer cells with high NF-kB level expression are less susceptible to proapoptotic stimuli, as it has been described for TGF-b apoptotic effects within TC cells [172]. Increased NF-kB expression within cancer cells is secondary to common inflammatory stimuli, but also to infectious and physical or chemical insults, and to oncogenes activation [77], such as RET in TC [173].

3.4 Microchimerism

'Microchimerism' is a phenomenon that generally occurs during pregnancy, and it is characterized by the coexistence of fetal and maternal cell lines in the same organism [1]. Fetal cells pass through the placenta and establish cell lineage within the mother. During pregnancy, AITD often ameliorate while worsen after childbirth [174], for this reason many studies have been conducted to evaluate the function of fetal cell microchimerism in AITD, as it has been described in HT [175] and GD [176] patients, while a link between microchimerism and thyroid autoimmunity has not been reported by other papers [177].

Fetal cell microchimerism was found in 47.5% of women affected by PTC during the

earlier phase of a male pregnancy, with microchimerism interesting more tumoral tissues than the normal ones [178]. In tumor and normal tissues fetal cell microchimerism expressed Tg, while only those in tumor tissues stained with CD45 (a marker of hemopoietic cells). Positively stained for Tg and CD45 cells for the MHCII (a marker of APCs) were evaluated to assess their function. Male cells positive for both Tg and CD45 did not express MHCII antigens. Tg+/MHCII– male cells seem to induce tissue recovery whereas CD45+/MHCII– are NK cells with cytotoxic surveillance activity against maternal malignant cells, indicating a defensive function of microchimerism in TC [178].

3.5 Iodine, AITD and TC

The role of iodine in AITD is determinant, while it is still not completely clear in TC. Iodine intake appears to worsen HT [179] and elevated levels of ATA are present after adequate restoration [180].

Iodine seems to increase Tg immunogenicity modifying and displaying new cryptic and pathogenic peptide residues, which become apparent to the immune cells [181].

Iodine intake could explained the increased PTC incidence among those countries where new iodine supplementation programs have been adopted [182], whereas other papers show higher TC incidence linked to nodular goiter, which derived from diet iodine shortage [183].

According to animal studies, iodine deficiency supports thyroid carcinogenesis [184], while iodine excess weakly promotes it [185].

Studies conducted in humans reported that PTC/FTC ratio increases [186] and ATC ratio decreases [187] with salt iodization.

4. Future Perpectives

There is a huge evidence that chronic smouldering inflammation plays a protumorigenic role in TC [188].

As recently reported, cancer-related inflammation could be an important target for innovative diagnostic and therapeutic strategies in TC [6,189].

The molecular patterns of cytokines and chemokines are key orchestrators and could explain the involvement of the immune system in tumor progression. In fact, anticancer immunotherapy, in particular the immune checkpoint inhibitors, promotes lymphocyte activation, to destroy cancer cells and counteracts immune-suppressive signals derived from tumor cells [190]. In this way, they also activate immune memory, leading to a sustained anti-tumor response [190].

Another promising strategy has been described combining BRAF inhibitor and checkpoint inhibitor immunotherapy, as shown in a study conducted in an immunocompetent mouse model of orthotopic ATC [191].

Further information on the inflammatory microenvironment may help to explain tumor aggressiveness and identify potential novel targets of therapy.

5. Conclusion

Immunity and cancer have a functional interplay. Autoimmune phenomena and cancer development are often concurrent.

AITD have the highest incidence and prevalence, which are even increasing worldwide, among both thyroid disorders and autoimmune disease overall. Their precise origin is still unknown, but studies of epidemiology suggest that the autoimmune attack to the thyroid may be triggered by environmental factors in genetic susceptible people. Associations exist in the same patient among AITD and other organ specific, or systemic autoimmune disorders, as SS, RA, SLE and SSc, because common susceptibility, and environmental triggers.

TC is the most frequent endocrine tumor, representing the eighth most common cancer diagnosed worldwide, and its incidence has been increasing worldwide during the last decades. A link between inflammation and cancer is well-known.

In the last decades, many studies conducted *in vitro* and *in vivo* have shown that thyroid autoimmunity and TC (mainly PTC) can be concomitant, even if further research is needed to understand the exact mechanisms of the co-occurrence of thyroid autoimmune and neoplastic pathology, which remain still not clear. Growing incidence of TC coincides with increased registration of AITD suggesting an association between those pathologies.

According to other studies, elevated TSH levels and thyroid autoimmunity were defined as independent risk factors for malignancy. A tight relationship between serum TSH and TC risk has been shown, and it was even demonstrated for TSH levels within the reference range. However other studies have shown that autoimmunity and inflammation, *per se*, are risk factors for TC.

Microchimerism and iodine also appear to be implicated in the pathogenesis of both

AITD and TC.

The link between inflammation and TC involves multiple components of the immune system, extracellular matrix, stroma, and adipose tissue, with pro-tumoral activity of inflammation being opposed to anti-inflammatory effects, favoring protection against cancer progression.

Within the tumor microenvironment, inflammatory cells, belonging both to innate (macrophages) and adaptive (lymphocytes) immune responses, are interconnected with fibroblasts, endothelial cells, adipocytes, and extracellular matrix through cytokines, chemokines and adipocytokines. Under the influence of transcriptional regulators, such as NF-kB, PI3K-AKT and mitogen-activated protein kinases, oncogenes connected to the different subtypes of TC promote their farthermost proliferative effect on the tumor microenvironment.

Future studies will be necessary to understand the interplay between thyroid autoimmunity and cancer, also in order to design a targeted immunotherapy for TC patients with AITD.

Conflict of Interest statement

The authors declare that there are no conflicts of interest.

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Figure legend

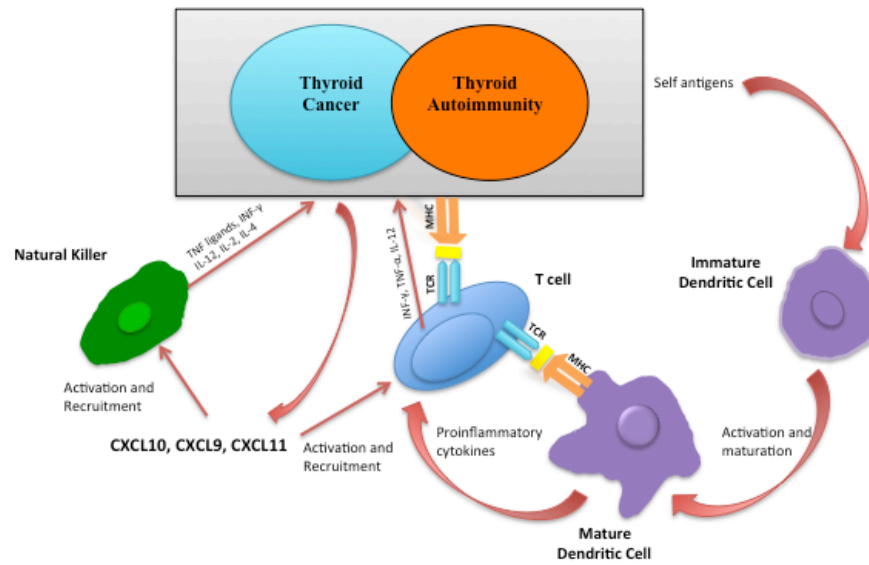**Figure 1.** Thyroid autoimmune disorders and cancer, and the role of cytokines.

Figure 1