The antigenic link between thyroid autoimmunity and breast cancer

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ABSTRACT

The association between breast cancer and benign thyroid disorders, in particular thyroid autoimmunity, has been debated for decades. Autoantibodies to thyroid peroxidase, the hallmark of thyroid autoimmunity, have a higher prevalence among patients with breast cancer compared with the general population. Furthermore a correlation between their positivity and a better prognosis of breast cancer was found in several independent small-scale studies, even if such observation was not confirmed in a subsequent retrospective study conducted on the largest patient cohort to date.

The thyroid and mammary glands present several biological similarities, therefore the hypothesis of an immune response to shared thyroid/breast antigens could in part explain the association between thyroid autoimmunity and breast cancer. The sodium iodide symporter is expressed in both glands, however it seems unlikely to be the key common antigen, considering that autoantibodies targeting it are rare. Instead thyroid peroxidase, one of the major thyroid autoantigens, is also expressed in breast tissue and therefore represents the main antigenic link between thyroid autoimmunity and breast cancer. Furthermore lactoperoxidase, an enzyme of the same family that shares structural similarities with thyroid peroxidase, is expressed in neoplastic breast cells and is responsible for the cross-reactivity with some autoantibodies to thyroid peroxidase.

Novel strategies for the diagnosis and treatment of breast cancer might take advantage of the antigenic link between thyroid and breast tissues.

KEYWORDS

Breast Cancer; Thyroid autoimmunity; Thyroid peroxidase; Autoantigens; Autoantibodies

CONFLICTS OF INTERESTS

The authors declare that there are no conflicts of interest.

1 INTRODUCTION

Over decades many studies have described a higher prevalence of both autoimmune and non-autoimmune benign thyroid disorders in patients affected with breast cancer (BC) compared with healthy controls [1-12]. Similarly, patients with benign thyroid disorders were found to have a higher prevalence of BC [11-14], therefore the relationship between BC and benign thyroid disorders applies in both directions. However other studies did not support this association [15-20]; several reasons can explain the generation of contrasting data in the literature. First, both BC and thyroid disorders are two of the most common diseases among females and their prevalence increases with age, therefore it is difficult to distinguish a real correlation from a chance association. Secondly, the majority of existing studies are retrospective or cross-sectional and therefore more prone to biases compared with those that are prospective. Thirdly, BC is a highly heterogeneous disease, with only a minority of studies providing enough details about the histological and molecular subtypes of BC considered, as well as BC staging and other clinical parameters, such as the treatments received. Similarly, the classification of thyroid disorders and the selection of thyroid patients were not homogeneous among the different studies.

This review will focus in particular on the relationship between BC and benign thyroid disorders of autoimmune etiology and the possible mechanisms involved. Cancer and autoimmunity originate from a failure of the immune system, unable to defeat cancerous cells on one hand, and attacking self-cells on the other hand; therefore cancer and autoimmunity may be linked by a bi-directional immunological association [21]. The role of inflammation, especially if local, in cancer progression and prognosis has been known for long time, and cancer-related inflammation is considered the seventh hallmark of cancer [22]. In this review the key aspects of thyroid and breast glands will be first introduced separately, allowing to better understand the subsequent illustration of the association between thyroid autoimmunity (TA) and BC. Finally the mechanisms behind such correlation will be investigated analyzing the antigenic similarities of common biological components within thyroid and breast tissues.

2 OVERVIEW: MAIN BIOLOGICAL COMPONENTS OF THYROID AND BREAST GLANDS

2.1 THYROID GLAND

The thyroid is a large endocrine gland in the neck composed of closely packed follicles externally delimited by thyroid epithelial cells named thyrocytes, and containing proteinaceous colloid inside. As shown in **Figure 1**, the thyrocyte synthetizes thyroid hormones, thyroxine (T4) and triiodothyronine (T3), in the following passages [23]:

- The iodide ion (I^-) enters the cell through the sodium iodide symporter (NIS), a transmembrane glycoprotein on the basolateral cell membrane, and is transported through the apical membrane into the follicular lumen by a transporter named pendrin.
- Thyroid peroxidase (TPO), an (apical) transmembrane protein, catalyzes the iodination of tyrosine residues of thyroglobulin (Tg), the major component of lumen's colloid, to form thyroxine (T4) and triiodothyronine (T3).
- The lumen's colloid enters the thyrocytes by endocytosis; T3 and T4 are released by proteolysis within lysosomes, and secreted with a 1:10 ratio into the blood stream through transmembrane protein transporters [23,24]. Only the unbound free quote (<1%) is biologically active, therefore in clinical practice only the free-T4 (FT4) and free-T3 (FT3) are usually measured [23].

- The production of T3 and T4 is promoted by the thyroid-stimulating hormone (TSH) [25,26], a peptide produced by the anterior pituitary gland that binds its specific transmembrane G protein-coupled receptor (TSHR) located on the basolateral membrane of thyrocytes [27]. Thyroid hormones T3 and T4 exert a negative feedback on TSH secretion, and therefore counterbalancing its actions [28].

2.2 MAMMARY GLAND

The parenchyma of mammary glands consists of 15 to 20 lobes of glandular tissue organised into a system of draining ever-branching ducts that finally converges into a unique lactiferous duct opening on the nipple. At the other end each ducts system ends in a cluster of blind-ending terminal ductules (mammary lobule) embedded in a loose fibrous support tissue containing capillaries, adipose tissue and immune cells [29]. The mammary lobule is composed by alveolar cells, responsible for milk production and secretion during lactation [30].

Lactation is indeed the primary function of the mammary gland: the breast milk contains all the nutrients that an infant needs in the first 6 months of life and protects from infections [30,31]. The breast function is regulated by several agents including pregnancy-related hormones (oxytocin, prolactin, human placental lactogen), steroid hormones (oestrogens, progesterone, glucorticoids), various other hormones (growth hormone, insulin, T4, T3) and growth factors (including but not limited to fibroblast growth factor, epidermal growth factor, transforming growth factor beta family, insulin-like growth factors platelet-derived growth factor and colony stimulating factor-1) [30].

In particular, the receptors of thyroid hormones are expressed in both normal [32,33] and neoplastic [34,35] mammary epithelial cells. The thyroid hormones, especially T3, exert a permissive role in breast development and lactation since inducing its differentiation and lobular growth in an oestrogen-like manner [32,33,35-38]. Similarly, in rodent models of tumour transplant the tumour growth and metastases appeared to be stimulated by thyroid hormones, whereas treatment-induced hypothyroidism had opposite effects, determining a favorable outcome not only for breast cancer (BC), but also other cancer types [39].

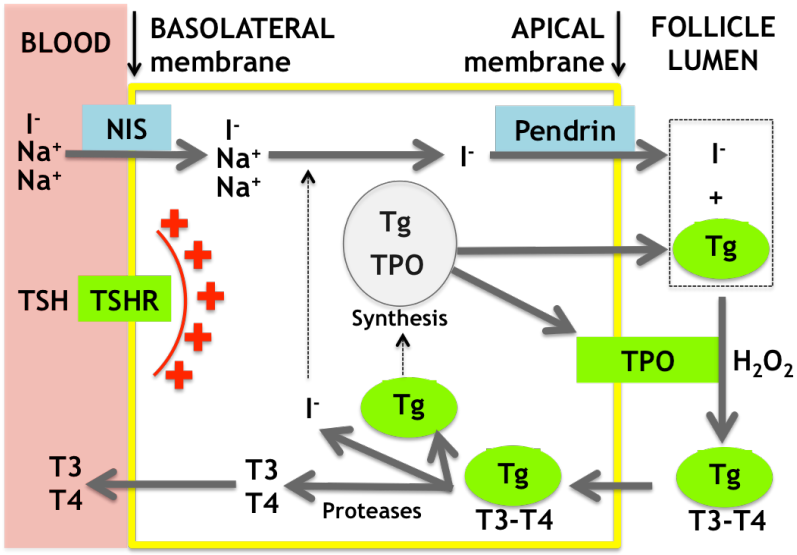
Iodine is an essential component not only for the synthesis of thyroid hormones, but also for the breast physiology; the iodide accumulation in breast tissue was first reported in 1957. During pregnancy and lactation iodine is incorporated into iodoproteins (e.g. iodocasein) and maternal milk is crucial to supply iodide to the newborn for the biosynthesis of thyroid hormones [40,41]. Iodine also has anti-oxidant properties, therefore iodine deficiency is associated with increased oxidative stress and cell damage [42-44]. In rodent models iodine deficiency caused evident dysplasia and atypia of mammary cells, reverted by iodine replacement [45]. Similarly, a reduced content of iodine was found in human BC tissue compared with breast benign tumours, e.g. fibroadenomas [43]. In fact patients affected with BC have an increased prevalence of goitre, one of the major signs of iodine deficiency [7,46].

3 THYROID AUTOIMMUNITY (TA)

3.1 Thyroid autoantigens and autoantibodies

The three major autoantigens of TA are well characterised, as well as their correspondent autoantibodies (**Figure 1**): 1) TPO and anti-TPO autoantibodies (TPOAb); 2) Tg and anti-Tg autoantibodies (TgAb); 3) TSHR and anti-TSHR autoantibodies (TRAb). The NIS and pendrin are considered minor antigens whose significance is debated (**Figure 1**) [47,48]. In this review we will mainly focus on TPO and NIS and their correspondent autoantibodies, considering their predominant role in breast physiology and BC.

Figure 1: Structure and function of the thyrocyte



Simplified representation of the thyrocyte and its function (synthesis of thyroid hormones).
H_2O_2= hydrogen peroxide; I^-= iodide; Na^+= sodium; NIS= sodium iodide symporter; Tg= thyroglobulin; TPO= thyroid peroxidase; TSH= thyroid-stimulating hormone; TSHR= TSH receptor; T3= triiodothyronine; T4= thyroxine. The thyroid autoantigens are highlighted in green (major) and azure (minor). The red plus signs indicate the stimulating function of TSH acting through TSHR, enhancing all phases of thyroid hormone synthesis.

3.1.1 TPO

The human TPO gene is about 150 kilo-base pairs (kbp) in size and consists of 17 exons and 16 introns [49]; the 3135-bp full-length mRNA encodes for a 2802-bp transcript (TPO1) that is translated into a transmembrane heme-containing enzyme consisting of 933 amino acids (AA) [50,51]. Human TPO is the largest member of the family of mammalian peroxidases, which utilizes hydrogen peroxide to oxidize a number of inorganic and organic substrates [52]. This family also includes lactoperoxidase (LPO), myeloperoxidase, eosinophil peroxidase and the vascular peroxidase [53,54]. TPO is the only membrane-bound enzyme, while the other peroxidases are intracellular or extracellular [53]; the AA sequences encoded by exons from 13 to 17 (AA 739 - 933), including the transmembrane region (AA 847 – 871), are exclusive to TPO [55,56].

As summarised in **Table 1**, several different isoforms of TPO mRNA lacking one or more exons as the result of alternative splicing of TPO gene have been described [51,57-62]. The TPO mRNA isoforms had been usually described studying only portions of the TPO gene due to its big dimensions. In 2014 for the first time the transcripts of the entire TPO gene region from exon 2 to 17 were amplified with the LongRange RT-PCR technique. The newly described isoforms mainly preserved exons from 2 to 7, while exons from 8 to 16, containing the catalytic site, the antigenic portion and the transmembrane region, were strongly subjected to deletion. The real number of different TPO mRNA isoforms resulting from different combinations between exons might be larger than those presented [61].

So far only the protein translated from the complete mRNA transcript TPO1 has been fully characterized and is commonly addressed as TPO protein. When analysed in denaturing western blot it appears as a 105-110 kilodaltons (kDa) doublet; it is still unclear whether this is due to variants of TPO protein [57,59] or different degrees of glycosylation [63,64]. Preliminary data suggest that also the smaller TPO mRNA isoforms might be translated into the correspondent proteins [61]. Further studies are needed to evaluate their function and immunogenic properties, and investigate the physiological consequences, and possible clinical applications, of TPO alternative splicing.

Table 1: Summary of known TPO mRNA isoforms

TPO mRNA Isoform	N° tot exons	Exon lacked	Exons studied	Full length mRNA (bp)
TPO 1	17	/	2-17	3135
TPO 2	16	10	9-17	2964
TPO 3	16	16	9-17	3005
TPO 4	16	14	9-17	3003
TPO 5	16	8	2-9	2616
TPO 6	12	10,12,13,14,16	9-17	2322
TPO 2/3	15	10,16	9-17	2834
TPO 2/4	15	10,14	9-17	2832
TPO breast	15	14, 16	13-17	2873
TPO M2000	15	8, 9	2-17	2357
TPO M1500	14	8-10	2-17	2186
TPO M1300	11	8, 10-14	2-17	1695
TPO M1000	10	8-14	2-17	1436
TPO M950	9	8-15	2-17	1336
TPO M850	8	8-16	2-17	1206
TPO M350	5	3-14	2-17	796

bp= number of base pairs. "TPO M…." refers to the isoforms described by Muller et al [60]: the number indicates the size (bp) described in the original manuscript.

3.1.2 TPOAb and TgAb

TPOAb and TgAb are the principal thyroid autoantibodies, both considered typical serum biomarkers of TA, especially TPOAb [65]. However they are also largely present in the general population, without being associated necessarily with the presence of thyroiditis, thyroidal damage or thyroid dysfunction; the reasons for which are still unclear [66,67]. The estimated prevalence among the general population of TPOAb and TgAb are respectively 13% (8.7% males, 17% females) and 11.5% (7.6% males, 15.2% females) [66], or 26.4% when considered together [68]. Their prevalence increases with age [66,68-71] and varies with ethnicity, being more prevalent among whites compared with blacks or Mexican Americans [66]. An increase of both TPOAb and TgAb prevalence has also been registered after iodization programs due to a sudden increase of iodine intake [72], possibly due to free radicals production and consequent thyroid damage [73] or major iodine-induced changes in Tg stereochemical configuration and consequent immunoreactivity [74,75].

TPOAb mainly recognize conformational epitopes in the immunodominant regions of TPO, formed by different parts of the AA chain often far between them in the protein primary structure, becoming juxtaposed as a consequence of the final folding of the protein in its tertiary structure [62]. Therefore, it is unusual for TPOAb to recognize linear antigens, consisting in epitopes formed by consecutive AA on the protein primary sequence. However some linear epitopes recognized by patients with TA have been identified using some recombinant TPO polypeptide fragments, and they form the "immunogenic site" of TPO protein: C2 (AA 590-622) and C21 (AA 710-722) [56,76].

3.1.3 NIS and NISAb

The human NIS gene encodes for a 643 AA membrane-bound glycoprotein, with a molecular weight of approximately 70-90 kDa depending on the glycosylation level, and composed of 13 putative transmembrane domains, 14 extracellular domains, an extracellular amino-terminus and an intracellular carboxyl-terminus [77,78]. The NIS protein is a carrier located at the baso-lateral portion of the thyroid follicular cell, where co-transports two sodium ions (Na^+) along with one iodide (I^-) [77].

In 1995 NIS was suggested as a potential additional thyroid autoantigen, in fact a few sera from patients with several types of autoimmunity were able to reduce the I^- uptake by selective inhibition of NIS carrier, and

this was likely due to the presence of autoantibodies to NIS (NISAb) with blocking function [79]. Subsequent studies reached very contrasting conclusions; some authors confirmed the presence of inhibiting NISAb in about 30% of sera from patients with Graves' disease [80,81], while others concluded that inhibiting NISAb are very rare or barely exist [82,83]. The presence of several non-specific I^- uptake inhibitors could have created experimental artifacts, providing a plausible explanation for such discordant results [79].

The presence of "neutral" NISAb (binding NIS but without affecting its biological function) has also been investigated, and found in 24% [81], 20.8% [84] and 14% [85] of sera from autoimmune hypothyroid patients. Neutral NISAb were also found in 4.8% [84], or none [81,85], of the healthy control subjects. A subsequent study did not find any neutral NISAb in neither patients with TA nor healthy controls; possibly this was due to the different technique used [86].

3.2 Autoimmune thyroid disorders

TA is the commonest autoimmune disease in humans and accounts for two main types of disease: autoimmune thyroiditis (AITD) and Graves' disease (GD) [87]. Early post-mortem studies confirmed histological evidence of chronic AITD in 27% of adult women and 7% of adult men with an increase in frequency in the past 50 years [88]. GD has an estimated incidence of 80/100'000/year in women and 8/100'000/year in Western countries [89].

All forms of TA are secondary to the breaking of tolerance to thyroid self-antigens, determining an autoimmune response that is mainly cell-mediated for AITD and antibody-mediated for GD [90]. In both conditions the thyroid gland presents some degrees of lymphocytic infiltration, usually more pronounced in AITD [91,92]. Thyrocytes have been found to express CD40 under stressful conditions, therefore potentially acting as antigen presenting cells and possibly activating the immune response [93].

3.2.1 Autoimmune thyroiditis

TgAb and TPOAb are the typical serum biomarkers of AITD, especially TPOAb [65] since present in 90% of AITD patients [94]. The term "thyroiditis" refers to a process of thyroid inflammation and damage, probably due to both cellular and humoral autoimmunity, in fact equal numbers of B cells and cytotoxic T cells usually infiltrate the gland [95]. The causative role of TPOAb in the autoimmune-mediated damage remains controversial [96-98]. Some authors consider the rise of TPOAb levels as a consequence of the thyroid damage mediated by cytotoxic T cells [94]; others propose a direct cytotoxic activity of TPOAb on thyrocytes [99], considering that TPOAb are complement-fixing [100]. The second mechanism is also supported by the evidence that TPOAb positive women are at increased risk of developing several pregnancy complications [101,102].

The obvious consequence of thyroid tissue inflammation and destruction is a reduced thyroid function (hypothyroidism), however the majority of patients with measurable thyroid autoantibodies have a normal thyroid function [95]. Sometimes hypothyroidism can be preceded by a transient phase of thyrotoxicosis due to the sudden release of pre-synthesized thyroid hormones stored within thyroid follicles [23].

3.2.2 Graves' disease

GD is a mainly humoral autoimmune disorder due to the presence of stimulating TRAb causing a persistent activation of the TSHR with consequent excessive production of thyroid hormones (hyperthyroidism); in the majority of cases a diffuse goitre is also present [103]. Up to 30-50% of GD cases present Graves' orbitopathy, a condition of inflammation of the orbital tissues that in severe cases leads to disfiguring and visual problems [104,105]. More rarely, GD patients can present with pretibial myxedema, an infiltrative dermopathy of the legs.

The pathogenesis of Graves' orbitopathy is complex and still unclear, likely involving immunological cross-reactivity between thyroid and orbital antigens in muscular, connective, and adipose tissues [106]. The extra ocular muscles were found to be infiltrated with T cells, mainly TSHR-reactive, and the expression of immunoreactive TSHR mRNA and protein has been found in orbital pre-adipocytes, fibroblasts and other cells [107]. The inflammation process results in glycosaminoglycans production by fibroblasts triggered by cytokines, and accumulation in the extracellular matrix, with consequent functional disruption and edema [23].

Interestingly, although TPOAb are not known to be involved in GD etiopathogenesis, TPOAb are often positive in GD patients, and subjects positive for TPOAb have an increased risk of developing GD [108]. This observation suggests the presence of a breakdown in immune tolerance to multiple thyroid self-antigens [47], possibly due to shared genes responsible for the genetic susceptibility to both AITD and GD [109].

3.3 Risk factors for TA

The precise mechanisms triggering TA are still unknown, however several risk factors have been identified, from genetic to environmental and likely acting in synergy [110,111]:

- **Genetic predisposition**. 1) Both HLA class I and II genes [112-114]. 2) Some immune signaling molecules including CD40, the cytotoxic T lymphocyte antigen-4 (CTLA-4), or the protein tyrosine phosphatase non-receptor type 22 (PTPN22) [115-118]. 3) Molecules related to regulatory lymphocytes' differentiation, survival and function, such as the forkhead box P3 (FOXP3) or CD25 [118-121]. 4) Single nucleotide polymorphisms (SNPs) of TSHR [117,118,122]. 5) Several genetic loci and SNPs identified with the genome wide association study (GWAS) [94,123-125].
- **Epigenetic mechanisms.** This category includes non-coding effects on gene expression and function that are mitotically stable, thus long lasting, such as DNA methylation, histone modifications and ribonucleic acid (RNA) interference by microRNA (miRNA), a group of small non-coding RNAs regulating gene expression at the post-transcriptional level [126]. This is a relatively recent research field that could explain the different penetrance of genetic susceptibility, and could also represent the mechanism of interaction between genetic predisposition and environmental factors [127]. The analysis of miRNA, alone or associated with proteomics, has also an interesting potential as biomarker of TA, especially GD [128].
- **Environmental factors.** *1) Infections* can induce autoimmunity by several mechanisms, including molecular mimicry and cross-reactive immune responses, tissue damaging and release of cryptic autoantigens [110], induction of local inflammation that triggers autoreactive lymphocytes and/or suppresses regulatory lymphocytes [129], or modifications of the microbiota, especially in the gut [130-133]. So far TA has been associated with several bacterial and viral infections [90,134,135] and alterations of the gut microbiota [136,137]. *2) Excessive iodine intake* is associated with an increased frequency of TA [138], possibly as a consequence of thyroid destruction and release of cryptic antigens [110] or iodine-induced conformational changes of Tg leading to its presentation by antigen presenting cells [75]. *3) Female gender* predisposes to TA likely acting via hormonal influences [110] possibly mediated by oestrogens [139] and leptin [90,140,141]. *4) The post-partum period* is characterized by a recovery from the physiological immunosuppression during pregnancy and is associated with a high incidence of autoimmune diseases, including TA [110,142]. The phenomenon of foetal microchimerism - the transfer of foetal cells to the mother - has also been proposed as possible additional mechanism [143-145]. *5) Irradiation*, both external and internal (i.e. by radioactive iodine) damages thyroid tissue and exposes autoantigens, therefore induces TA [110]. *6) Cigarette smoking* damages cells and induces a polyclonal activation of both B and T lymphocytes and cytokines production; for this reason it is linked to several autoimmune diseases including TA [110]. *7) Some immunosuppressive and*

immunomodulatory medications are associated with an increased incidence of TA, including highly active antiretroviral therapy in patients infected with human immunodeficiency virus (HIV), interferon-alpha, interleukin-2 and alemtuzumab [110,146-149]. *8) Stress* has been associated with predominantly humoral immune responses [110], and therefore GD [150]. *9) Similarly, some allergic conditions* showed a correlation with humoral autoimmunity such as GD and lupus erythematosus [151]. *10) Selenium* is a trace mineral with anti-oxidant and immunomodulatory properties; low selenium blood levels are associated with increased thyroid volume and thyroid hypoechogenicity, suggestive of lymphocytic infiltration [110].

4 BREAST CANCER (BC)

4.1 Classification and epidemiology of BC

BC is the commonest cancer and the leading cause of death among women; each year 1.4 million new cases of BC are diagnosed worldwide [152]. However the survival rates for BC have significantly improved in the last 40 years, rising from 40% to 78% (predicted) in patients diagnosed in 1971-72 and 2010-11, respectively (UK data) [153].

BC can be sub-classified into different clinical-pathological entities according to histological, biological and molecular criteria [154]. The most widely adopted histopathological classification of BC is from the World Health Organization (WHO) [155]. In the present review we have only included adenocarcinoma, i.e. malignant lesions derived from the epithelial cells of the mammary lactiferous ducts [156], traditionally classified into ductal and lobular, if originating from the mammary ducts or the terminal ductules, respectively [29]. More recently the definition "ductal" has been substituted with "carcinoma of no special type" [157] and accounts for 40-75% of total invasive BC cases, while the lobular is around 5-15% [155].

The molecular classification of BC has more recently become fundamental for optimal diagnostic, prognostic and therapeutic management. It depends on the assessment of oestrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor type 2 (HER2) and, in some centers, the proliferation index Ki67 [154]. These factors can be combined together to delineate five different BC categories, according to the 2011 St. Gallen International Expert Consensus: luminal A, luminal B HER2 negative, luminal B HER2 positive, HER2 positive and basal-like (triple negative) [158]. The oncological management of patients with these sub-types of BC is increasingly diverging.

4.2 Prognosis of BC

The presence of distant metastases, tumour size and lymph node metastatic involvement are the most important prognostic factors for BC [159] and represent the basis of the TNM staging classification for cancer [160]. The histological grading is also routinely adopted to assess BC prognosis and considers three biological parameters: 1) tubule and gland formation, 2) nuclear pleomorphism, 3) mitotic count [155,161].

The BC molecular phenotype is also crucial for both prognostic and therapeutic purposes. The main types of treatment for BC are surgery, local radiation therapy, systemic chemotherapy, hormonal therapy and targeted therapy [162]. Hormonal therapy consists of the oestrogen receptor modulator "tamoxifen", aromatase inhibitors and gonadotropin-releasing hormone (GnRH)-agonist (e.g. goserelin); it is successfully administered in BC with a positive expression of ER and/or PR [163]. Similarly, targeted therapy interrupts the HER2 pathway, therefore is administered only in BC cases expressing this molecule; the most used drugs are trastuzumab (Herceptin®), a monoclonal antibody targeting HER2, or lapatinib, a dual tyrosine kinase inhibitor which interrupts both HER2 and the epidermal growth factor (EGF) receptor pathways [155,164].

4.3 Risk factors for BC

BC risk factors can be classified as genetic, environmental and secondary to other medical conditions.

- **Genetic predisposition.** Around 5-10% of all BC are hereditary, with the best identified mutations affecting the two tumour suppressors genes BRCA1 and BRCA2 [165-167]; less known mutations in other genes have been also identified, including p53, PTEN, STK11, CHEK2, ATM, BRIP1 and PALB2 [168].
- **Environmental factors** were estimated to be involved in 26.8% of BC cases among the UK in 2010 [169]. They include: *1) Hormones*, oestrogens in particular [170], both endogenous (early menarche, late menopause) than exogenous (oral contraception, hormonal replacement therapy) [171]. The BC risk deriving from exogenous oestrogens is still highly debated since based on contrasting evidence [171-175]. Low parity, late pregnancy and abbreviated breastfeeding also represent risk factors for BC [176]. *2) Ionizing radiations* increase the risk of several tumours, including BC, in a dose dependent manner [177]. *3) Several chemicals* including pesticides are associated with an increased risk of BC [178,179]. *4) Iodine deficiency,* as previously introduced, is associated with increased oxidative stress and cell damage [42-44], and therefore an increased risk of BC. In fact Japanese women have one of the lowest prevalence of BC probably attributable to a diet rich in seafood/seaweeds and therefore of iodine [41]. *5)* Regarding *dietary components*, a Mediterranean diet rich in vegetables, fruit, fish and soy is associated with a decreased risk of BC [180]; alcohol is an other important risk factor for BC [181]. *6) Alterations of the microbiota* have been found in women with BC in comparison with healthy women [182].
- **Other medical conditions.** Obesity represents a risk factor for BC and other cancers, possibly due to certain adipokines supporting the tumor, the increased production of oestrogens from androgens (aromatase activity) and the frequent association with insulin resistance and increased levels of insulin and insulin-like growth factor (IGF) promoting cell growth [183]. Accordingly, moderate to vigorous physical activity seems to reduce the risk of BC by 25% compared with inactive women [184]. Type II diabetes mellitus is associated with an increased risk to develop many different types of cancer, including BC [185]. The precise mechanisms involved are unknown, however increased insulin levels and IGF signaling likely play a role [186-188], as well as the dysregulation of ovarian steroid hormones and chronic inflammation [189].

5 TA AND BC

Autoimmune processes affecting the thyroid gland very often cause also a reduction or increase of its function, hypothyroidism or hyperthyroidism respectively. Both the thyroid dysfunction and the autoimmune process have been described to impact on BC. Similarly, BC and its treatments can affect thyroid function and trigger thyroid disorders.

5.1 Impact of thyroid function on BC

During the last decades the impact of thyroid function on BC has been intensively debated, in consideration of several conflicting results being produced. At the end of the 19th century hypothyroidism was considered a poor prognostic factor for BC, therefore in 1896 the thyroid extract was proposed as a treatment for BC [190,191]. Other studies confirmed the association of hypothyroidism with an increased risk of developing BC [8,192,193], however others reported a reduced risk [194,195], while others did not support a correlation between the two conditions [2,16,17,46,196,197].

In contrast with the initial evidence, a subsequent investigation suggested thyroid supplementations as a possible risk factor for BC [198], but this finding was not confirmed by other studies [199,200]. However an

increased risk of BC and also other cancer types has been recurrently described among patients affected with hyperthyroidism, or having thyroid hormone levels higher than controls [39,201-203]. Furthermore, some studies identified high levels of thyroid hormones as a poor prognostic factor for BC. An American retrospective study based on 2226 women reported that hypothyroid BC patients were more likely to be diagnosed with a BC at an earlier stage, of smaller size and without pathologic lymph node involvement [194]. Similarly, in a Swedish prospective cohort study including 2185 women followed for more than 20 years, baseline T3 serum levels were associated with a more aggressive BC and increased risk of BC specific death; in particular the BC was larger in size, ER and PR negative and with a higher prevalence of positive lymph node metastases [204,205].

In support of these epidemiological findings, both the normal and neoplastic mammary epithelial cells express thyroid hormone receptors [34,35] and thyroid hormones show a tumor-promoting effect *in vitro* [32,33]. In particular they induce the differentiation and lobular growth of the mammary gland in an oestrogen-like manner [35-37]; in rodent models they stimulate tumor growth and the metastatic spread of cancerous cells, while an induced hypothyroidism results in favorable outcome for both BC and other cancer types [39]. In human hyperthyroidism a possible contribution of radioiodine treatment to the increased cancer risk has been investigated and excluded in a Finnish long-term study including 6148 patients [206].

5.2 Effects of treatments for BC on thyroid function

The impact of various BC treatments on thyroid function and autoimmunity has been debated for a long time with contrasting results being produced. In some cases the homolateral thyroid lobe can be included in the radiation field used for irradiation of internal mammary, supra- and infra-clavicular node chains, with consequent hypothyroidism [207,208]. An increased rate of hypothyroidism was also observed in patients treated with chemotherapy for BC [209,210], but not confirmed in an other study evaluating a longer follow up (5-year) [211]. A possible explanation is that chemotherapy causes a temporary reduction of thyroid function, not persisting long term. Furthermore, chemotherapy and radiotherapy could act synergistically on thyroid tissue. In fact chemotherapy sensitizes the thyroid gland to the effects of concomitant radiation therapy, and therefore their association is a major risk factor for thyroid damaging and hypothyroidism, as observed in patients treated for Hodgkin disease [212].

Regarding other treatments for BC, some authors reported that tamoxifen may have an anti-thyroid effect [213-215], while little if any studies explored the possible thyroidal effects of trastuzumab. Finally, the stress related to the surgical procedure itself has been suggested to have a possible immunomodulating effect that could therefore affect autoantibodies levels [216].

5.3 Combined prevalence of TA and BC

A higher frequency of serum anti-thyroid autoantibodies, especially TPOAb, has been repeatedly reported among patients with BC compared with healthy controls [2-10,217], not confirmed only in a few studies [15,20]. In particular the TPOAb prevalence has been described as 15-36% among BC patients compared with 8-19% among healthy controls [3,4,8]. Similarly, a higher prevalence of BC, up to three fold, has been described among patients with benign thyroid disorders, both autoimmune and non, compared with age-matched general population [11-14]. However the majority of these studies were cross-sectional and lacked a properly matched control population, therefore the BC prevalence might be overestimated due to a higher rate of medical visits and checks in the group of thyroid patients compared with the general population.

Contrasting conclusions about the association between TA and BC have been reached also by different meta-analysis. The 2002 study did not support such association [18]; the subsequent 2012 meta-analysis applied

a more specific and appropriate definition of TA and included additional studies, concluding in support of such association [11].

5.4 TA and prognosis of BC

When analyzing a large population of patients affected with benign thyroid disorders, the prevalence of BC was higher in those with negative thyroid autoantibodies compared with those positive, suggesting a possible protective role of thyroid autoantibodies against BC [12,14].

In fact several independent small-scale studies, with one exception [10], observed a more favorable outcome of BC in patients positive for serum TPOAb compared with those TPOAb negative, in particular a better long term (usually 5-year) disease-free and/or overall survival [5,10,218,219] and the absence of distant metastasis [220,221].

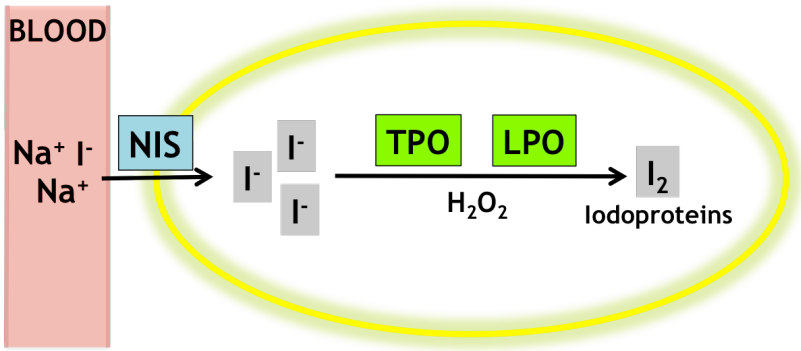
In 2017 the prognostic role of TPOAb and thyroid function was evaluated in a much larger cohort of nearly 2000 women affected with moderate-high risk early BC receiving systemic and local adjuvant treatments, and followed up to 96.7 months [222]. In this study neither the presence nor the titre of serum TPOAb had a substantial impact on long-term BC recurrence or mortality; similar findings were observed for the thyroid function. These results are seminal since obtained evaluating a large, homogeneous and precisely defined population in terms of BC subtype, stage and treatment; these criteria do not apply to the majority of previously evaluated small-scale cohorts of BC patients. However this study was also retrospective, lacked a clinical history for thyroid diseases and medications, and was based on plasma samples mainly collected during or after adjuvant therapy for BC, possibly interfering with the levels of thyroid autoantibodies and hormones [222].

Therefore in order to definitively end the debate about the impact of TA on BC prognosis, a large well designed and properly conducted prospective study is needed. Furthermore the different histological and molecular BC subtypes should be evaluated separately, since highly different in terms of etiopathogenesis, prognosis and treatment.

6 ANTIGENIC SIMILARITIES BETWEEN THYROID AND MAMMARY GLANDS

The increased prevalence of TPOAb among BC patients, and their debated role on BC prognosis, generated the hypothesis of a common immune response in TA and BC, triggered by one or more shared antigens. As summarized in **Figure 2**, the neoplastic mammary gland shares similar physiological components and activities with the thyroid gland [223].

Figure 2: Thyroid antigens and activities expressed by the tumoral breast cell



Schematic representation of a tumoral breast cell illustrating proteins and correspondent activities similar to those detected within the thyrocyte.
H_2O_2 = hydrogen peroxide; I^- = iodide anion; I_2 = molecular iodine; LPO = lactoperoxidase; Na^+ = sodium cation; NIS = sodium iodide transporter; TPO = thyroid peroxidase.

6.1 TPOAb cross-reactivity with LPO

The human LPO is a single chain monomeric protein of 712 residues highly expressed in breast tissue [53] and also present in other glands, i.e. lacrimary, salivary, tracheal and bronchial [224,225]. It is a member of the mammalian peroxidases family [52] and is 46% identical to human TPO (**Figure 3**) [225].

The LPO protein is very low or absent in the normal mammary gland, while its expression increases significantly in BC [226-229]. LPO could also be involved in BC pathogenesis, since it oxidizes oestrogens with consequent production of free radicals, which react with DNA and therefore can initiate or promote the tumoral process [230-232].

Some TPO epitopes are phylogenetically conserved through evolution and shared by different peroxidases, including LPO [233]; in fact around 40%-45% of human sera positive for TPOAb were shown to cross-react with LPO [234]. However the majority of TPOAb are directed towards the immunodominant region of TPO, and these seem not to cross-react with different peroxidases [235]. Therefore, different types of circulating TPOAb exist, some of them cross-reacting with the other peroxidases, including LPO, and some not. TPOAb cross-reactivity with LPO could explain why TPOAb are more prevalent among patients with BC [2-10].

Figure 3: Amino acidic sequence alignment and comparison of LPO and TPO

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HLPO    SLEVGCGAPAPVVRCD---PCSPYRTITGDCNNRRKPALGAANRALARWLPAEYEDGLSL 174
HTPO    ANMSGCLPYMLPPKCPNTCLANKYRPITGACNNRDHPRWGASNTALARWLPPVYEDGFSQ 187

HLPO    PFGWTPGKTRNGFPLPLAREVSNKIVGYLNEEGVLDQNRSLLFMQWGQIVDHDLDFAPDT 234
HTPO    PRGWNPGFLYNGFPLPPVREVTRHVIQVSNEVVTDDDRYSDLLMAWGQYIDHDIAFTPQS 247

HLPO    ELGSSEYSKAQCDEYCIQGDNCFPIMFPPNDPKAGTQGKCMPFFRAGFVCPTPP------ 288
HTPO    TSKAAFGGGADCQMTCENQNPCFPIQLP-EEARPAAGTACLPFYRSSAACGTGDQGALFG 306

HLPO    --YKSLAREQINALTSFLDASFVYSSEPSLASRLRNLSSPLGLMAVNQEVSDHGLPYLPY 346
HTPO    NLSTANPRQQMNGLTSFLDASTVYGSSPALERQLRNWTSAEGLLRVHARLRDSGRAYLPF 366

HLPO    DSKKP----SPCEFINTTARVPCFLAGDSRASEHILLATSHTLFLREHNRLARELKRLNP 402
HTPO    VPPRAPAACAPEPGIPGETRGPCFLAGDGRASEVPSLTALHTLWLREHNRLAAALKALNA 426

HLPO    QWDGEKLYQEARKILGAFVQIITFRDYLPILLG-DHMQKWIPPYQGYSESVDPRISNVF- 460
HTPO    HWSADAVYQEARKVVGALHQIITLRDYIPRILGPEAFQQYVGPYEGYDSTANPTVSNVFS 486

HLPO    TFAFRFGHLEVPSSMFRLDENYQPWGPEPELPLHTLFFNTWRMVKDGGIDPLVRGLLAKK 520
HTPO    TAAFRFGHATIHPLVRRLDASFQEHPDLPGLWLHQAFFSPWTLLRGGGLDPLIRGLLARP 546

HLPO    SKLMKQNKMMTGELRNKLFQPTHRIHGFDLAAINTQRCRDHGQPGYNSWRAFCDLSQPQT 580
HTPO    AKLQVQDQLMNEELTERLFVLSNSST-LDLASINLQRGRDHGLPGYNEWREFCGLPRLET 605

HLPO    LEELNTVLKSKMLAKKLLGLYGTPDNIDIWIGAIAEPLVERGRVGPLLACLLGKQFQQIR 640
HTPO    PADLSTAIASRSVADKILDLYKHPDNIDVWLGGLAENFLPRARTGPLFACLIGKQMKALR 665

HLPO    DGDRFWWENPGVFTNEQKDSLQKMSFSRLVCDNTRITKVPR-DPFWANSYPYDFVDCSAI 699
HTPO    DGDWFWWENSHVFTDAQRRELEKHSLSRVICDNTGLTRVPM-DAFQVGKFPEDFESCDSI 724

HLPO    DKLDLSPWASVKN 712
HTPO    TGMNLEAWRETFP ⟶933
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Adapted from [225]. HLPO = human lactoperoxidase; HTPO = human thyroid peroxidase. The identical sequences are highlighted in green. Cysteine (Cys) residues are highlighted in yellow. Numbers indicate the amino acids sequence.

6.2 TPO expression in BC

Considering that TPO gene is expressed not only in thyrocytes but also different cells, i.e. fibroblasts and fat cells within the orbital tissue [236], TPO gene expression in BC cells might represent an additional explanation for the selective rise of TPOAb among BC patients [2-10]. This hypothesis has been verified, since the expression of both TPO mRNA and protein has been confirmed in BC and breast peri-tumoral tissue, at a 10^4 fold reduced level than thyroid cells [61]. TPO was expressed also in adipose tissue from different depots (abdominal, subcutaneous, orbital and knee-derived) around 10^3 fold less than thyroid cells. Considering that fat

is abundant within the breast, experiments including BC cell lines and investigating the TPO protein expression by immunohistochemistry confirmed that in breast tissue the TPO was expressed by mammary cells and not only by surrounding adipocytes [61]. This level of TPO expression, even if lower than thyroid tissue, is enough to trigger an immune response. An independent research group confirmed the presence of TPO expression in both BC and adjacent breast peri-tumoral tissue, but observed a reduced expression of TPO in BC compared with the peri-tumoral tissue [62,229,237]. Even if the peri-tumoural breast tissue was considered "normal", it might express some neoplastic or pre-neoplastic features; to our knowledge to date non-pathological breast tissue (i.e. obtained from reductive mammoplasty) has not been investigated for TPO expression. Importantly, both the immunological and biochemical properties of TPO expressed by thyroid and breast tissues resulted similar [62,229,237]. However breast TPO had a slightly lower molecular weight (94 kDa) compared with thyroid TPO due to a reduced degree of glycosylation; similarly, the doublet band at western blot suggested the presence of different isoforms [229]. Importantly, the breast TPO was mainly located in the cytoplasmic compartment, while thyroid TPO is usually membrane-bound, and this likely explained the reduced enzymatic activity observed [229]. Despite these differences, the three-dimension structure of thyroid and breast TPO was similar, in fact conformation-dependent TPOAb and TPOAb from patients with TA were able to recognise both forms of TPO [229,237].

Considering that TPO is expressed also in peri-tumoral breast tissue but TPOAb levels increase in BC only, several mechanisms triggering TPO immunogenicity especially during tumoural processes can be hypothesized. Both TPO and LPO (the second expressed by lactating breast and BC only) are enzymatically active, and therefore can induce oxidative stress in breast tissue and participate to BC pathogenesis [229]. Adipocytes within BC, also expressing TPO, are dynamic cells that may also contribute to the tumoural progression [238]. The altered tissutal micro-environment present within BC may alter the expression and the antigenic properties of LPO and/or TPO and promote autoimmunity [239]. At the same time, the presence of chronic and dysregulated inflammation has been associated with increased BC risk [240].

Importantly, the expression of TPO mRNA isoforms seemed to differ according to the examined tissue; in particular, a TPO mRNA isoform missing exons 14 and 16 (**Table 1**, "TPO breast") was the most abundant in breast and adipose tissues, while very little if any was expressed in thyroid tissue [61]. Further experiments are needed to confirm whether this TPO isoform is fat and breast specific, and if it has different immunogenic properties possibly triggering or contributing to a rise of TPOAb levels in selective cases only.

6.3 NIS expression in BC

The expression of the transmembrane NIS glycoprotein was demonstrated by immunohistochemistry in both lactating and neoplastic human breast cells; on the contrary, it was absent in normal non-lactating specimens from reductive mammoplasties [241]. In particular NIS was expressed by 80% of human BC tissues and 23% of peri-tumoural breast tissues [241], therefore it could not serve as specific indicator of breast malignancy [241,242]. Furthermore, the expression of NIS protein or mRNA and the accumulation of iodide was found also in benign breast patologies, i.e. fibroadenoma [43,243]; interestingly, the NIS cDNA expression was even higher in fibroadenoma compared with BC [244].

Other studies subsequently confirmed the presence of NIS protein expression in 66-90% of BC tissues tested and were reviewed by Beyer et al.; it was noted that NIS protein was assessed by immunohistochemistry using only one NISAb, often polyclonal (therefore more prone to aspecific signal), and providing intracellular staining, instead of membranous as expected [245]. When using different NISAb, including monoclonal, the obtained data where much different from the previous results, and it was concluded that the number of BC

tissues positive for NIS protein had been likely overestimated so far due to aspecific staining [245]. Similar conclusions were reached in different studies, concluding that NIS was expressed by a minority of BC and usually at a low level [245,246]. This observation was supported by the fact that only 17-25% of BC apparently positive for NIS protein also demonstrated functional radionuclide uptake by scintigraphy [247,248]. However this could also be the consequence of a reduced NIS surface expression due to an impairment of cell surface trafficking in BC cells [245].

The nucleotide sequences of human NIS cDNA expressed in the thyroid and mammary glands were found to be identical [249]. Studies in rats showed a higher level of glycosylation in thyroid NIS protein compared with breast, with a molecular weight of respectively 100 kDa and 75 kDa [241]. The regulation of NIS expression in BC was found to positively correlate with the expression of oestrogen receptor [244].

6.4 NISAb and BC

A more than 3 fold lower molecular iodine (I_2) content was found in both BC tissue specimens and their correspondent PT tissue, compared with benign breast tumours (fibroadenoma). The authors described the presence of iodide (I^-) uptake inhibition activity in 19% of BC patients and 3% of healthy controls, but also in patients affected with fibroadenoma (16.3%) and Graves' disease (31.4%). The inhibiting activity was preserved after immunoglobulins purification, therefore they hypothesised the presence of NISAb inhibiting the function of NIS to explain the reduced I^- uptake [43]. Similar to what previously described for TA, subsequent studies did not confirm these results, excluding that the reduced content of iodine in BC was due to a reduction of the I^- uptake, and also suggesting non-specific I^- uptake inhibitors different from NISAb [250].

The presence of a different kind of serum NISAb, not interfering with NIS activity (neutral), was also investigated in BC patients, and compared with patients with TA or both TA and BC, and healthy controls. No NISAb were found in any of the sera tested, suggesting that also neutral NISAb are rare; therefore NIS is unlikely to be the main shared antigen responsible for the association between TA and BC [86].

7 CONCLUSIONS

An association between BC and TA, two of the commonest diseases among women, has been debated for decades, supported by many authors [2-11], with others not agreeing [15,18,20]. A positive impact of TA on BC prognosis was also observed in some [5,218-220], but not all [10] independent small scales studies, and excluded in the largest cohort to date [222]. Future well-designed prospective studies are therefore needed to definitively clarify this aspect and put an end to a debate lasting decades.

The association between TA and BC is also supported by the presence of several analogies between the thyroid and neoplastic breast tissues [223] that could trigger a shared immune response responsible for such association. NIS is expressed in both thyroid and malignant breast tissue [241], but at lower levels in the second [245,246]; even trace amounts of antigen could suffice to trigger lymphocyte activity. However NIS is unlikely to be the principal shared antigen between thyroid and breast tissue, since serum NISAb are rare in both TA and BC [79,82,83,86].

On the contrary, TPO is the antigen more suitable for this role: first, as for NIS it is expressed in both thyroid and, at lower levels, in breast tissues [61]. Secondly, TPOAb are the kind of thyroid autoantibodies more prevalent among BC patients. As additional mechanism, TPOAb can also cross-react with the LPO expressed in BC tissue, since having many structural analogies with TPO [225]. Furthermore, TPO gene is subjected to alternative splicing and expressed in different isoforms; some of them might be tissue specific and therefore be expressed in BC tissue but very low, or absent, in the thyroid gland [61]. Additional studies are needed to

confirm these preliminary observations, and explore the potential role of TPO isoforms for diagnostic, prognostic and treatment purposes in BC patients.

Such antigenic link between thyroid and breast tissues might represent a key opportunity for a translational strategy to develop novel diagnostic and therapeutic tools for BC.

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