Review

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Hashimoto's thyroiditis and papillary thyroid cancer: are they immunologically linked?

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Hashimoto's thyroiditis (HT) is the most common autoimmune disease in humans frequently leading to hypothyroidism. HT is characterized by a cellular immune response with lymphatic infiltration of the thyroid gland by T and B cells, as well as by a humoral immune response leading to specific antibody production. The synchronous appearance of HT and papillary thyroid cancer (PTC) indicates an immunological link between the two entities. Three different pathomechanisms may be postulated, including preexisting autoimmunity leading to malignancy due to inflammation, immunity towards preexisiting tumor cells leading to specific autoimmunity, and immune tolerance leading to malignancy despite (auto)immunity. In this article we review data describing these potential mechanisms that might lead to the synchronous appearance of HT and PTC.

Hashimoto's thyroiditis and papillary thyroid cancer: two immunological opposites?

The thyroid gland is affected by autoimmune attacks more than any other organ, with Hashimoto's thyroiditis (HT, see Glossary) being the most common thyroidal autoimmune disease [1]. The annual incidence of HT worldwide is estimated to be 0.3–1.5 cases per 1000 persons [1,2]. The key factor in the pathogenesis of HT is the breakdown of immune tolerance towards the thyroid gland. Following an initial stimulus, such as environmental factors including iodine intake, among others (reviewed in [3]), formerly thyroid-tolerant immune cells become activated and lose their thyroid tolerance. As a consequence, leukocytes infiltrate the tissue thus promoting the development of an autoimmune response [4]. In fact, HT is defined as a destructive tissue-specific autoimmune disease with detectable anti-thyroglobulin (Tg) and anti-thyroid peroxidase (TPO) antibodies. As a result, HT frequently leads to hypothyroidism, which is characterized by a deficit of thyroid hormones [triiodothyronine (T3) and thyroxine (T4)] and elevated thyroid-stimulating hormone (TSH) levels. The elevated TSH might potentially increase the risk of thyroid cancer owing to TSH-induced proliferation of thyroid cells [5]. In fact, a relation between papillary thyroid cancer (PTC) and serum TSH levels has been shown. Treatment with L-thyroxine reduces TSH levels and decreases the occurrence of clinically detectable PTC [5].

Glossary

Antigen-presenting cell (APC): displays antigens (peptide fragments) complexed with MHC molecules on their surfaces for T cell activation.
Autoimmune thyroiditis (AIT): an autoimmune thyroid disease. It is usually used as a synonym for Hashimoto's thyroiditis. Graves' disease, another autoimmune thyroid disease leading to hyperthyroidism, is occasionally also classified as AIT.
B7 homolog 1 (B7H1): also known as CD274, programmed cell death-1 (PD-1) ligand. Binding to its receptor (PD-1, CD279), results in apoptosis of target cells (e.g., immune cells).
Cytotoxic T lymphocyte (CTL): usually expresses CD8 and recognizes peptides displayed by MHC molecules. Following, altered cells (infected host cells, cancer cells) are killed by CTLs.
Dendritic cell (DC): an antigen-presenting cell that induces adaptive immune responses by activating naïve T lymphocytes.
Fas ligand (FasL): a member of the TNF family that upon binding to its receptor, triggers apoptosis. It plays a role in the regulation of the immune system and the progression of cancer.
Hashimoto's thyroiditis (HT): one type of autoimmune thyroiditis. HT is characterized by thyroidal lymphatic infiltration leading to tissue destruction and frequently hypothyroidism.
High mobility group box 1 (HMGB1): a key chromatin protein. In the nucleus, HMGB1 interacts with histones, nucleosomes, and transcription factors. In necrotic cells it is released passively and behaves as a trigger of inflammation.
Histocompatibility antigen, class I, G (HLA-G): a non-classical HLA class I molecule that exerts an overall negative immune function by inhibiting the activity of NK cells, CTLs, and APCs.
Immunosubversion and immunoediting: immunosubversion is a mechanism by which the tumor is not recognized as being immunologically conspicuous; immunoediting is initiated by immunosurveillance, a mechanism by which resistant tumor cells are selected potentially due to T cell tolerance.
Major histocompatibility complex (MHC) molecule: a membrane protein that displays peptides for recognition by T lymphocytes. MHC class I molecules are recognized by $CD8^+$ T cells and MHC class II molecules by $CD4^+$ T cells.
Papillary thyroid carcinoma (PTC): a common (75–85% of all thyroid cancer cases) well-differentiated thyroid cancer. It originates from epithelial cells and is mainly characterized by slow growth and lymphatic spread with rarely occurring distant metastasis.
Papillary thyroid microcarcinomas (PTMC): a subset of PTC that is less than 10 mm in diameter.
Regulatory T cell (T_{reg}): a subpopulation of T cells that modulate the immune system. T_{regs} maintain tolerance to self-antigens and can help abolish autoimmune disease.
T helper 1 (Th1): a type of T cell that plays an important role in the adaptive immune system. Th1 cells release cytokines that activate other immune cells.
Thyroglobulin (Tg): the most-abundant protein of the thyroid gland. Tg is composed of two polypeptide chains that give rise to triiodothyronine (T3) and thyroxine (T4).
Thyroid peroxidase (TPO): the major enzyme involved in thyroid hormone synthesis. It assists the chemical reaction that adds iodine to Tg for the production of T4 or T3.
Thyroid-stimulating hormone (TSH): a hormone secreted by the pituitary gland. TSH stimulates the thyroid gland to produce T4 and T3.

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In fact, the thyroid gland is affected by one of the most common endocrine tumors such as differentiated thyroid cancer, with PTC being the most common. Differentiated thyroid cancer comprises 90% of all cases of thyroid carcinoma, is generally indolent, and shows an excellent prognosis (10 year survival of more than 90%) unless it is metastasized and is not treatable with radioactive iodine therapy or surgery [6]. The incidence of differentiated thyroid cancer has been increasing over the past 30 years from 3.6/100000 persons in 1973 to 12.2/100000 persons in 2010 [7]. The reason for this increase is likely multifactorial and not entirely understood. One explanation is the increase of coincidentally identified microcarcinomas owing to more sensitive diagnostic procedures.

An association between HT and PTC has been a topic of discussion for a considerable time because contradictory data have been obtained [8–12]. PTC commonly develops in patients with autoimmune thyroiditis [5,13,14], raising the question of how thyroid malignancies develop despite immune responses. Or, does autoimmune thyroiditis develop because of an antitumor immune response? In this article we review the current research advances in our understanding of cellular and humoral immune mechanisms of HT, with a particular emphasis on the immunological correlation between autoimmune diseases and thyroid cancer.

Hashimoto's thyroiditis

Target antigens

The idea of specific thyroid molecules that are recognized by autoimmune cells has been known for decades. In 1995, Sugihara and colleagues described thyroid epithelial cell reactive CD8 T cells in autoimmune thyroiditis (AIT) patients, and delivered a proof of MHC-I restricted T cell activation [15]. Regarding the specificity of these cells, TPO and Tg have been described to represent the key autoantigens.

TPO is the major enzyme involved in thyroid hormone synthesis. Together with dual oxidase-1 (DUOX-1), caveolin-1, and other proteins, it forms the thyroxisome, a multiprotein complex that is required for thyroid hormone synthesis on the apical surface of the thyrocyte [16]. Anti-TPO antibodies are high-affinity IgG-class antibodies with two immunodominant regions that are recognized by sera from about 74% of HT patients [17]. Immunity to TPO in humans does not appear to develop in response to TPO released from damaged cells: thyrocytes seem to present TPO epitopes, acting thereby as antigen-presenting cells for the induction of anti-TPO antibodies as well as TPO-specific autoimmune T cells [18].

Tg is the most abundant protein of the thyroid gland giving rise to the thyroid hormones T3 and T4. Tg is stored in the thyroid follicules, leaks into the circulation, and is exposed to the immune system. Existence of anti-Tg antibodies is one of the clinical features for HT diagnosis that is met in approximately 90% of HT patients. Anti-Tg antibodies are believed to reflect a more initial type of immune response because HT patients with different thyroid functional status exhibit a different Tg epitope recognition pattern [19].

Both TPO and Tg also seem to represent target antigens for autoreactive T cells because T cells recognizing these molecules have been found in sera and thyroid infiltrates of HT patients [20]. Recent evidence indicates a balanced TPO- and Tg-specific cellular immune response in HT [20]. The cells were also able to lyse TPO- and Tg-epitope-presenting target cells [20]. Furthermore, in thyroiditis mouse models, TPO and Tg represented the targets for the immune reaction towards the thyroid, including direct cellular toxicity by $CD8^+$ T cells and a humoral immune response by production of specific antibodies [21,22].

Cellular immune response

The etiology of HT is yet unknown. Certainly, intrathyroidal accumulation of leukocytes and the secretion of cytokines and chemokines that commonly belong to the T helper 1 (Th1) immune response are consistently observed [23,24] (Figure 1). This process is believed to start with the infiltration of antigen-presenting cells (APC), for example dendritic cells (DCs). Already in 1988 Kabel *et al.* described a higher number of DCs in the thyroid of HT patients versus healthy thyroid tissue [25]. In addition, these DCs were often seen in contact with intrathyroidal lymphocytes, probably leading to their stimulation.

Th17 cells, a proinflammatory cell type that is characterized by the secretion of interleukin 17 (IL-17), seem to participate in the context of cell mediated cytotoxicity in murine and human HT because a higher frequency of IL-17-positive T cells was found in HT [26].

In addition, regulatory T (T_{reg}) cells that are important for the peripheral homeostatic immune suppression might play a role in the pathology of HT. In fact, in autoimmune thyroiditis mouse models, thyroiditis was induced after overcoming the immunoregulatory effect of T_{reg} cells [27]. In humans, HT patients and healthy controls show an equal frequency of T_{reg} cells but, interestingly, HT-derived T_{reg} cells seem to be partly dysfunctional: they were less capable of inhibiting the proliferation of effector T cells compared to controls, possibly explaining their contribution to autoimmunity [28].

A further imbalance in the amount of chemokines and cytokines favoring the proinflammatory fraction [e.g., interferon-γ (IFN-γ) in first line, IFN-α, tumor necrosis factor-alpha (TNF-α)] was found in thyroid tissue samples and the peripheral blood of HT patients, with some leading to thyroid tissue damage, thus directly accelerating the ongoing inflammatory condition [24,29–34]. In line, lower amounts of the anti-inflammatory tumor growth factor-β1 (TGF-β1) are described to contribute to disease progression as a result of decreased immunosuppressive effect [35].

Remarkably, thyrocytes themselves (HT-derived or stimulated), as a source of cytokine and chemokines [36,37], are directly involved in the immunological process as both target and immune influencing cells (Figure 1).

Humoral immune response

Humoral immunity in HT mainly consists of antibodies recognizing TPO and Tg as specific antigens, as mentioned above (Figure 1). An age-depended increase of these antibodies has already been demonstrated in the

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