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The Role of Apoptosis in Thyroid Autoimmunity

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There is increasing evidence showing that apoptosis plays a role in the development of the autoimmune thyroid diseases—Hashimoto's (lymphocytic) thyroiditis (HT) and Graves' disease (GD). The immune pathogenesis of HT and GD is not yet fully understood, but evidence points toward several steps. A defect in $CD4^+CD25^+$ T regulatory cells breaks the immunological tolerance of the host and induces an abnormal production of cytokines, which facilitates the initiation of apoptosis. Though apoptosis appears to play a role in the pathogenesis of both HT and GD, the mechanisms that mediate these processes appear different. The induction of apoptosis in HT results in the destruction of thyrocytes, while apoptosis in the GD leads to damage of thyroid-infiltrating lymphocytes. The differences in the apoptotic mechanisms produce two very different forms of thyroid autoimmune responses, eventually developing into HT and GD, respectively.

Introduction

Autoimmune thyroid disease (AITD) is the most common organ-specific autoimmune disorder. The etiology of AITD is still unclear, but the susceptibility to it is determined by a combination of genetic and environmental factors. The pathogenesis of AITD is known to be associated with autoimmune processes against various constituents of thyroid tissues, including cell membranes, receptors, and enzymes. AITD affects 1–2% of the population, with a 5- to 10-fold increase among women. AITD encompasses two entities: autoimmune thyroiditis and autoimmune hyperthyroidism. The former is represented by Hashimoto's (lymphocytic) thyroiditis (HT) and the latter by Graves' disease (GD).

No unique immune response to thyroid autoantigens has been identified that is absolutely correlated with the expression of clinical AITD (1). The triggering event for AITD is not known, but the pathogenesis of AITD appears to be multifactorial. Genetic background and environmental and endogenous factors are thought to play important roles in determining the activation threshold of immune cells or the efficacy of the immunoregulatory pathways. However, the procedures responsible for this process are just being clarified.

Apoptosis—or programmed cell death—is an evolutionarily preserved mechanism of the self-elimination of damaged cells. It is important throughout the life of an organism, playing a role in every process from development to aging. The apoptotic cascade can be triggered either through a death receptor–mediated pathway or through mitochondrial-mediated changes. During the past few years, increasing evidence has suggested that receptor-mediated apoptosis plays a key role in the process of AITD development, the common feature of which is the survival of specific, unchecked self-reactive lymphocytes against the thyroid (2–4). While several of our prior reviews have focused on the regulation of apoptosis in the thyroid, we are focusing this discussion on the role of apoptosis in immune pathogenesis of these diseases. The homeostasis of the self-reactive lymphocytes is decided by the balance between antiapoptotic and proapoptotic molecules. The loss of this balance may lead to the self-immune system's attack on the thyroid, during which organ-specific lymphocytes can convey death signals to thyroid follicular cells. This initiates damage to the thyroid, leading to hypothyroidism in HT or to hyperthyroidism in GD. In this review, we will discuss the role of apoptosis in the pathogenesis of HT and GD.

Hashimoto's Thyroiditis

HT is characterized by inflammatory cell infiltration of the thyroid parenchyma, causing a dense accumulation of lymphocytes, plasma cells, and macrophages with germinal center formation and thyroid enlargement (5). The central feature of HT is the presence of autoantibodies to thyroglobulin and to thyroid peroxidase. The etiology of HT is not known, but it is believed to involve an interplay among genetic, environmental, and endogenous factors. The relative contribution of each is not clearly defined and may vary from patient to patient.

There are several steps hypothesized to play a role in the immune pathogenesis of HT. Initially, the immune system in an individual susceptible to HT is altered by changes in

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environmental factors and/or endogenous elements. Such alterations in the immune system appear to result in defects in the Cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), $CD4^+CD25^+$ T regulatory cells (Treg cells) (6–8), which normally represent an important mechanism for the maintenance of self-tolerance. Supporting this concept, studies have shown that removal of $CD4^+CD25^+$ Treg cells from mice that do not develop autoimmunity can result in autoimmune thyroiditis (6). Furthermore, adoptive transfer of Treg cells is able to prevent experimental autoimmune thyroiditis (7–9). The reason that there are fewer and/or dysfunctional Treg cells in autoimmune pathogenesis remains unclear. However, in several autoimmune disease models, a mutation of the forkhead box protein P3 (Foxp3) gene, which is a characteristic and functional marker of Treg cells, has been observed (10). A specific genetic defect may also be responsible for causing an autoimmune response by inducing autoreactive T cells to break self-tolerance. This type of genetic defect has also been reported to be associated with a decreased number of Treg cells (11). Nevertheless, even in normal hosts, the depletion of Treg cells can result in defects in the immune surveillance system, leading to an "unchecked" status with a decrease or defect in the inhibitory functions of $CD4^+$ and $CD8^+$ T cells (6,12,13). In such a situation, the host loses immunological tolerance and eventually develops autoimmune diseases (14,15).

Despite intensive efforts during the past several years, the molecular mechanisms by which Treg cells exert their immunosuppressive function still remain undiscovered. A change in the thyroid microenvironment is believed to follow the defect in Treg cells. One of the important functions of Treg cells is to inhibit T helper 1 (Th1)-driven autoimmune and inflammatory responses (16,17). The defect in Treg cells thus removes its inhibition on the function of Th1 cells, resulting in the overproduction of Th1 cytokines, including interleukin 1 beta (IL-1β), interferon gamma (IFNγ), and tumor necrosis-related alpha (TNFα). The Th1 cytokine production pattern occurs not only in intrathyroidal but also in peripheral $CD4^+$ and $CD8^+$ T lymphocytes in HT patients (18). These cytokines are able to trigger a number of events, including apoptosis in thyroid cells (19,20).

Increasing evidence has emerged to support the theory that the destruction of thyroid follicles occurs by the apoptotic mechanisms (19,21). Thyroid cells are known to express apoptotic ligands and receptors, such as TNF, Fas, and Tumor necrosis-related apoptosis-inducing ligand (TRAIL) (1). Under normal physiologic conditions, the apoptotic molecules remain inactivated or will lack a trigger. Therefore, the thyrocytes are normally safeguarded against apoptosis through the physiological inhibition of their apoptotic pathways. Though Fas is known to express constitutively on the thyrocytes, it does not normally cause apoptosis—even in the presence of excess Fas-inducing ligands. However, the expression of FasL on thyroid-infiltrating lymphocytes is usually increased, which leads to apoptosis of these invading lymphocytes (22). In order to maintain this finely tuned Fas-FasL pathway, apoptotic signaling would be inhibited in thyrocytes but activated in infiltrating lymphocytes. The molecules that are responsible for apoptosis regulation in thyrocytes remain unknown. However, the inhibition can be reversed by the administration of cycloheximide, an inhibitor of protein translation, suggesting it involves a labile protein (although there may be more than one inhibitor or labile protein involved) (23). Quite interestingly, the activation of the Fas-FasL pathway normally inhibited in thyrocytes is induced by certain combinations of proinflammatory cytokines, such as IL-1β, IFNγ, and TNFα, but not by any one single cytokine (1,20,21,24). The apoptosis activation has been associated with an increase of caspases 7, 8, and 10, as well as the concentration of Bid and Bak. A decrease of p44/42 mitogen-activated protein kinase activity is concomitantly observed (19,20,24). Therefore, it appears that the apoptotic pathway initiated by the Fas-FasL interaction may be further amplified by the proapoptotic molecule Bid, leading to the release of Bak from the mitochondria and the activation of caspases. These observations suggest that apoptosis of thyrocytes in HT is both a cell death receptor–dependent and a mitochondrion-dependent event. Unfortunately, apoptotic cell clearance does not appear to produce an anti-inflammatory situation in autoimmune diseases; instead, the impaired apoptotic cells and secondary necrotic cells induce a proinflammatory state (25), which may provide sufficient levels of self-antigens to intensify a dysregulated autoimmune response. Therefore, the apoptosis of thyrocytes in HT may be both the result of defective immunological tolerance and a positive feedback loop to exacerbate thyroid inflammation.

While defects in the $CD4^+CD25^+$ Treg result in the activation of Th1 cells and the overproduction of Th1 cytokines, they may also promote an autoimmune response by the downregulation of a number of molecules that are known to have immunosuppressive effects. These molecules include CD25, IL-2, CTLA-4, IL-10, glucocorticoid-induced tumor necrosis factor receptor (GITR), lymphocyte activation gene-3 (LAG-3), Foxp3, and transforming growth factor-beta (TGFβ). Although none of these molecules can fit into a single model of immune regulation, it is possible that the reduction of several of these molecules may enhance the activity of B cells, which produce autoantibodies, the diagnostic feature of HT (26,27).

It is not known how the thyroid microenvironment leads to the defect in $CD4^+CD25^+$ Treg cells in the thyroid. The Treg cells appear to be abundant in inflamed thyroid tissues. However, they are apparently dysfunctional in most cases and are unable to downmodulate the autoimmune response (28). The expression of Fas in $CD4^+CD25^+$ Treg cells is greater in patients with severe HT than in those with mild HT (29). This phenomenon is consistent with the observation that the proportion of apoptotic cells among $CD4^+CD25^+$ Treg cells is higher than that among $CD4^+CD25^-$ Treg cells in the thyroid of a patient with AITD. In addition to the high expression of Fas in $CD4^+CD25^+$ Treg cells in the thyroid, these cells also strongly express other proapoptotic genes, such as TRAIL and TNFα, and weakly express antiapoptotic genes, such as Bcl-2. This appears to make the Treg cells uniquely susceptible to Fas-mediated apoptosis (30,31). Therefore, it has been proposed that the defect or reduction of $CD4^+CD25^+$ Treg cells results from the increased apoptosis of $CD4^+CD25^+$ Treg cells in an inflamed thyroid gland (12). In addition, our recent data also suggest that TRAIL, a death receptor ligand, can enhance $CD4^+CD25^+$ Treg cell proliferation *in vitro* (32). This may involve inhibition of the development of experimental autoimmune thyroiditis by TRAIL. Further study is underway to address it.

Graves' Disease

GD accounts for most cases of hyperthyroidism. The identification in the serum of patients with GD of an abnormal thyroid stimulator protein, originally named long-acting thyroid stimulator (LATS), that was subsequently identified as an autoantibody against thyroid follicular cell thyrotropin (TSH) receptors first identified this disorder as an autoimmune disease (5). Similar to HT, GD is characterized by lymphocytic infiltration of the thyroid gland although much less severe in nature and not associated with disruption of the normal thyroid architecture. It is believed that T cells and B cells accumulate in the thyroid gland as a result of various factors, such as viral/bacterial infection, stress, sex hormones, and genetic abnormality. Cytokines and other cellular molecules released during these interactions can upregulate the expression of major histocompatibility complex (MHC) class I and class II molecules on the surface of the thyroid cells (33). These cells may then become adequate antigen-presenting cells and present a display of TSH receptor peptides. Alternatively, infection might produce mimic molecules or alter host cell components such that they could be attacked by the immune system (34,35).

An immune response is initiated in GD when T-cell receptors recognize foreign peptides or self-peptide fragments bound to human leukocyte antigen (HLA) molecules encoded by MHC genes (33,35). Class II antigens are usually expressed only on antigen-presenting cells, such as B cells and macrophages, and not on epithelial cells, such as thyrocytes. Several HLA molecules encoded by class II gene region are known to be associated with GD. Abnormal or aberrant expression of these antigens on thyrocytes and lymphocytes may play a key role in the development of GD (33,35).

Analysis of the phenotypic profile of intrathyroidal T lymphocytes in GD reveals a $CD4^+$ T-cell predominance, but with some of these T cells expressing CD8 (28). $CD4^+$ T cells may be capable of helping local B cells to produce antibodies. Recent studies have indicated that some of the $CD4^+$ T cells in the thyroids of GD patients are $CD4^+CD25^+$ Treg cells (29,36). The role of the $CD4^+CD25^+$ Treg cells in GD is not quite clear. However, there is evidence that shows that the inhibition of Treg cells may induce Th2-like cells (37). The cytokines generated by Th2 cells are IL-4, IL-5, and IL-10, the levels of which are increased in GD (38,39). Similarly to HT, the number of Treg cells in GD may also be decreased—probably via the Fas-mediated apoptotic pathway (36). Therefore, it would appear that the reduction of Treg cells could favor Th2 cytokine production in GD.

Th2 cytokine predominance promotes humoral immunity instead of cellular immunity, enhancing autoantibody production by the B lymphocytes. Interestingly, increased concentrations of Immunoglobulin G (IgG) due to the activity of Th2 cells or Th2 cytokines may downregulate the expression of Fas but upregulate the antiapoptotic molecules, such as Bcl-2, Bcl-xL, and cFLIP in thyrocytes (2,39–42). This could lead to the protection of thyrocytes from apoptosis (2,40–43). In addition, soluble Fas may also play a role in the inhibition of the Fas-FasL system in patients with GD because the serum concentration of sFas is increased in patients with GD (44,45). The overexpression of antiapoptosis molecules such as Bcl-2 may render the thyrocytes of GD resistant to Fas-FasL–mediated cell death (46). However, this resistance is not likely to be present in thyroid-infiltrating lymphocytes, where the expression of proapoptotic Bax and Bak proteins is apparent (47). Therefore, the infiltrating lymphocytes in GD thyroids are susceptible to apoptosis, but the thyrocytes may escape apoptosis via the overexpression of antiapoptotic molecules (45,46).

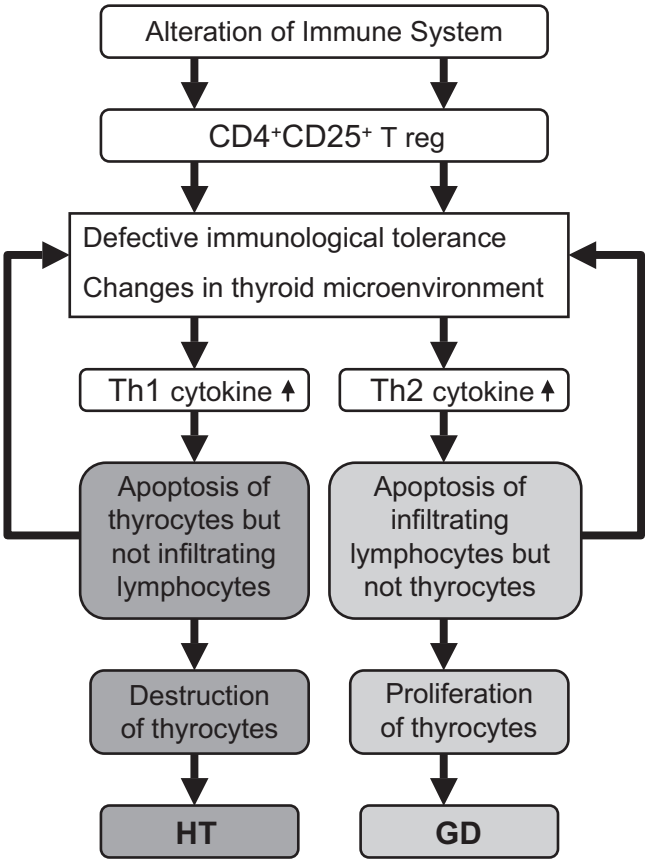

FIG. 1. Pathogenesis of Hashimoto's (lymphocytic) thyroiditis (HT) and Graves' disease (GD).

Therefore, it appears likely that the thyroid microenvironment in GD is regulated in a manner that is almost completely opposite to that of HT (Fig. 1). In GD, the immune response promotes thyrocyte survival and hypertrophy and may lead to lymphocyte apoptosis.

Conclusion

Strong evidence has supported the theory that apoptosis plays an important role in the development of AITD (Fig. 1). HT and GD are two major forms of AITD. Apoptosis of thyrocytes is initiated by Th1 cytokines in HT, which overcome the built-in apoptosis inhibitory mechanisms of the thyrocytes. In GD, the production of Th2 cytokines dominates in the thyroid, and thyrocytes are protected from apoptosis via overexpression of antiapoptotic molecules such as Bcl-2. The infiltrating lymphocytes appear unable to invoke these protective mechanisms and thus undergo apoptosis. A defect in $CD4^+CD25^+$ Treg cells is associated with both HT and GD and is believed to play a critical role in determining the

production of Th1 and Th2 cytokines. It remains unknown why the defect in $CD4^+CD25^+$ Treg cells favors Th1 cytokine production in HT, whereas it prefers Th2 cytokine production in GD. This warrants future investigation.

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