

## Autocrine/paracrine cell death in Hashimoto's thyroiditis

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Hashimoto's thyroiditis (HT) is an autoimmune disorder of the thyroid gland. The destruction of thyrocytes associated with the disease exceeds the lifetime regenerative capacity of the gland about 5- to 10-fold (1). The mechanisms responsible for this destruction have been elusive until Giordano *et al.* (2) demonstrated recently that Fas (CD95/APO-1) and its ligand (FasL) may be involved in the pathogenesis of HT.

Fas is a cell surface receptor with structural similarities to a family of proteins that includes the two tumour necrosis factor (TNF) receptors (3). The ligand, FasL, is also a transmembrane protein and belongs to the TNF family (4). Activation of Fas triggers apoptosis of the Fas-bearing cells (for references see (5)). It can be induced as programmed cell death during development and tissue turnover or by cytotoxic T cells in the disease processes. In the normal thyroid gland, apoptosis is only occasionally observed, whereas pathological processes leading to hypothyroidism are associated with increased apoptosis (6). Giordano *et al.* (2) compared the expression of Fas in thyroid specimens from patients with active HT and non-toxic goiter (NTG). Immunohistochemical analysis showed that thyroid cells from patients with HT expressed large amounts of Fas on their surface compared with the control cells from patients with NTG that were Fas negative.

Interestingly, interleukin (IL)-1 $\beta$  was able to induce Fas expression in the NTG thyrocytes in a process requiring new RNA and protein synthesis. Other cytokines found in HT glands, such as TNF- $\alpha$ , interferon- $\gamma$ , IL-6 and IL-12, failed to promote Fas expression. Triggering of Fas expression in NTG thyrocytes by IL-1 $\beta$  also induced thyrocyte apoptosis dose-dependently in these cells that are normally non-apoptotic. In addition, Kawakami *et al.* (7) showed that Fas was expressed in approximately 40% of human thyroid cells incubated in the absence of thyrotrophin (TSH), and that IL-1 $\beta$  as well as interferon- $\gamma$  increased Fas expression whereas TSH attenuated it.

The Fas–FasL system serves an important role as one of the two effector mechanisms for cytotoxic T lymphocytes (5). T lymphocytes can both identify and lyse their targets, and Fas-expressing virus-infected cells can be eliminated by FasL on the cell membranes of activated T lymphocytes. Another important role for FasL on T lymphocytes is to delete activated T cells. Antigenic stimulation of mature B and T cells triggers both proliferation and Fas expression, which renders them increasingly susceptible to elimination by apoptosis.

Antigenic stimulation of T lymphocytes increases the expression of FasL and makes it possible to direct cytotoxicity against activated self. Two spontaneous mutations in mice, *lpr* (lymphoproliferation) and *gld* (generalised lymphoproliferative disease), were both associated with a combination of lymphadenopathy, splenomegaly and a large production of IgG and IgM antibodies as well as nephritis and arthritis (5). They were identified as loss of function mutations of Fas and FasL respectively, and a large deletion of the Fas gene has also been demonstrated in a patient with a syndrome of lymphoproliferation and autoimmunity (8).

The expression of the death signal of FasL is generally restricted to the T lymphocytes, but during diseases it has been shown in other cells as well. Hahne *et al.* (9) demonstrated FasL expression in malignant melanoma cells, and malignant cells may escape the immune system by using FasL to induce apoptosis in Fas-positive immune effector cells. Unexpectedly, Giordano *et al.* (2) showed that FasL is constitutively expressed in thyrocytes from both HT and NTG patients. They also demonstrated that the FasL on thyrocytes is functional, as cells from a Fas-sensitive subline of the human T cell lymphoma HuT78 were lysed by co-culturing them with normal thyroid cells. The cell lysis was blocked by incubating the cells in the presence of monoclonal antibodies against Fas. A Fas-insensitive variant of the HuT78 cell line with a defective Fas receptor was unaffected by the thyrocytes. Antibodies against Fas were also able to block the apoptosis associated with IL-1 $\beta$ -induced Fas expression in normal thyroid cells. These results strongly indicate that Fas and FasL interaction is essential for the apoptotic cell death induced by IL-1 $\beta$ , and that the level of IL-1 $\beta$  may represent a critical factor for the rate of thyroid cell destruction. Several cells in the thyroid gland, of which infiltrating monocytes and macrophages as well as activated endothelial cells are the most likely candidates, may release this cytokine and induce thyroid cell apoptosis in the absence of autoreactive T lymphocytes. Furthermore, the expression of FasL in infiltrating T lymphocytes in thyroid glands from patients with HT was minimal when compared with the expression in the thyrocytes.

The report by Giordano *et al.* (2) indicates that cell death associated with HT is caused by Fas–FasL interaction among thyrocytes and that it can be induced by IL-1 $\beta$  in the absence of other contributing cells. Implications of the activation of this signalling system may not be limited to the pathogenesis of HT. Recently,

acinar epithelial cells from salivary glands in patients with Sjögren's syndrome were shown to express both Fas and FasL mRNA, and the cells died of apoptosis (10). The same signalling system may be activated in other inflammatory conditions in the thyroid leading to hypothyroidism, or even contribute to cell death in autoimmune endocrinopathies such as Addison's disease and insulin-dependent diabetes mellitus.

## References

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