7. Endocrine Disease and Apoptosis

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Endocrine cells are subjected to a physiological process of cell death, apoptosis, however, the longevity and the evidence of stem cells' presence in each endocrine organ have not yet been confirmed. The hormone-dependent endocrine tumors such as prostate cancer and breast cancer have been well analyzed. In particular, the fact that either withdrawal or addition of steroid hormone induces apoptosis in these cancer cells is well known. Here, I introduce the apoptotic pathway in endocrine diseases and the significance of apoptosis in various thyroid diseases, focusing on the molecular mechanism of radiation-induced apoptosis in human thyroid cells to understand the involvement of apoptosis in the development of thyroid diseases.

Endocrine cancer and apoptosis

Apoptosis is involved in the regulation of epithelial cell proliferation and differentiation, in such as hormone-dependent tissues like mammary and prostate glands, and apoptosis is readily induced by hormone depletion and by treatment with antiestrogens and antiandrogens (1, 2). The balance of cell life and death has been vigorously studied from the view point of Bax and Bcl-2 family gene expression in endocrine tumors (3–10). Bcl-2 family proteins regulate a distant step in an evolutionary conserved pathway of physiological death (11). Bax is a member of the Bcl-2 family, but acts as a proapoptotic protein whose expression is induced in a p53 dependent manner by radiation exposure, chemotherapeutic drugs and various genotoxic stresses (12, 13). In the breast and prostate, hormonal regulation of epithelial cell growth appears to be similar to relative expression levels of Bcl-2 and Bax. It is the ratio of Bcl-2 to Bax that determines sensitivity to apoptosis, rather than the absolute levels of either protein. The central role of p53 has been extensively studied but it is still difficult to conclude a true determinant of apoptosis through either p53 dependent or independent pathways (Fig. 1). The interaction between p53 and Fas is still obscure, however, dysregulation of apoptosis may contribute to the pathogenesis of these endocrine cancers.

Thyroid diseases and apoptosis

Thyroid diseases are of very high incidence and it is relatively easy to obtain human samples to analyze the apoptosis-

related gene expression. Recently the role of Fas and Fas ligand (L) has been extensively examined and the expression of Fas and Fas-L within the thyroid gland was demonstrated (14). Although it is hardly detected in normal thyroid glands, the immunohistochemical analysis revealed that both Fas and Fas-L exist in autoimmune thyroid disease tissues. Using biopsy materials from chronic thyroiditis, co-localization of Fas and Fas-L in the same thyroid epithelial cells suggest selective elimination of these cells during the process of disease worsening. Indeed various cytokines (IL-1 β , IFN- γ , TNF- α) induce Fas expression in cultured human thyroid cells, which can be inhibited by TSH (Fig. 2). TSH has an anti-apoptotic effect on thyroid cells, leading to thyroid cell proliferation (15–17). Similarly, co-localization of Fas and Fas-L is demonstrated in the same thyroid cancer cell, and corresponds to cancer cell apoptosis. The involvement of Fas and Fas-L in thyroid cell apoptosis is evident, and may play an important role in the elimination of not only normal thyroid cells but also cancer cells. The reason why thyroid cancer has a fairly good prognosis and slow in its clinical manifestation could be explained by the induction of Fas in thyroid cells. It is also demonstrated that an abundance of apoptotic cancer cells is observed in the sites of metastasis, especially those sites surrounding lymph nodes. The immunomodulation of thyroid cell survival as a result of immune cell activation receive consideration.

Next, I summarize our own data on radiation-induced cell cycle arrest and radioresistance of thyroid cells (18–19). p53 plays a central role in cell cycle arrest and the absence or general lack of p53 gene abnormality in well differentiated thyroid cancer supports the idea of good prognosis of thyroid cancer in general. However, once thyroid cancer becomes poorly-differentiated or undifferentiated histological types, a high incidence of p53 gene abnormality is detected. Therefore, the condition of p53 may be a prognostic marker of thyroid cancer. Experimentally we used cultured human thyroid cells obtained from Graves' thyroid glands and several established thyroid cancer cell lines which were papillary, follicular and anaplastic, all of whom express Fas/APO1, however, they were insensitive to radiation-exposure. Only a few cells are subjected to apoptosis after irradiation. FRO anaplastic cells which lacked p53 were stably transfected by a temperature-sensitive p53 (Val 138)

Figure 1. Role of p53 (cell cycle regulator and tumor suppressor gene) in thyroid cells.

Figure 2. Regulation of Fas antigen expression by TSH and cytokines in cultured human thyroid cells.

expression vector. Using the different type of thyroid cell culture condition, cell cycle arrest was confirmed after irradiation. As radiation could induce p53 and p21/Waf1/Cip1, but not Bcl-2, Bax, Fas/APO1 proteins, dysregulation between p53 and Bax was suggested (20–22). The molecular defect of Bax protein induction despite of Bax mRNA induction remains to be clarified. In contrast, p53 re-expression has been reported to inhibit proliferation and restore differentiation of human thyroid anaplastic carcinoma cells (23). Now it is clear that thyroid cells are subjected to p53-independent apoptosis and Bax may be a determinant of p53-dependent radiosensitivity by coordinating the activities of multiple effectors.

In summary, thyroid cells may become apoptotic spontaneously, however, much more so after being influenced by microenvironmental factors, such as TSH, various cytokines, growth factors and adhesion molecules. Based on their microenvironmental structure, apoptosis-resistance or escape from apoptosis could be characteristic features of thyroid cells, leading to a susceptibility to abnormal cell cycle regulation, and eventually tumor formation (Fig. 3). At a physiological and a pathological standpoint, a path to cell death should be considered in thyroid gland (24, 25). The significance of thyroid cell apoptosis is, therefore, should be investigated further and the clinical significance of apoptosis must be clarified to develop a new therapeutic approach to autoimmune thyroid disease and thyroid cancer.

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Figure 3. Characteristics of thyroid epithelial cells.

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