Apoptosis in Thyroid Cancer

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Introduction

Thyroid cancer can be divided into four types: papillary thyroid carcinoma (PTC) and follicular thyroid carcinoma (FTC), both of which may be classified as differentiated thyroid carcinoma (DTC); anaplastic thyroid carcinoma (ATC), also called undifferentiated thyroid carcinoma (UTC); and medullary thyroid carcinoma (MTC). Estimates will vary, but PTC accounts for about 78 % of thyroid cancer cases, FTC 13 %, MTC 4 %, and ATC 2 % [1]. The etiology of thyroid cancer is not yet fully known. However, it is believed that its development is a multifactor and multistep process. There are several issues that are thought to predispose to thyroid cancer, including radiation, nutrition, sex hormones, environment, and genetics. It appears that all of these factors are related to apoptosis. Radiation is probably one of the most well-studied predisposing factors. The source of radiation is usually traceable, such as from the therapeutic or diagnostic use of radiation and from environmental disasters. The effects are dose dependent and show strong age dependence, with exposure in childhood and adolescence showing almost an order of magnitude higher in the incidence of cancer [2]. Both iodine deficiency and excess iodine can contribute to the development of thyroid cancer [3–5]. Intake of cruciferous vegetables may reduce the risk of thyroid cancer [5]. One of the specific features of thyroid carcinoma is its predilection for women of reproductive age relative to men, suggesting a role of sex hormones in the formation of thyroid cancer. The incidence of thyroid carcinoma is three times more frequent in females than in males [6, 7]. An elevated risk has been documented in women who use estrogens for gynecological reasons, but not in postmenopausal women on low-dose estrogens [8]. Although a responsible gene is not identified for thyroid cancer, its occurrence has been reported in several familial syndromes [9]. Women under 35 years of age with familial adenomatous polyposis, a disease associated with altered apoptosis, have been estimated to have 160-fold higher risk of thyroid cancer than the general population [10].

Apoptosis or programmed cell death is an active process in which a cell dies for the benefit of the whole organism, and this mode of cell death is critical in the development and maintenance of multicellular organisms. Specific morphological features characterize apoptosis. The process starts with chromatin aggregation along the inner walls of the nuclear envelope and is followed by cytoplasmic shrinkage, formation of membrane blebs, extensive DNA degradation, and nuclear pyknosis. Finally, the cell condenses into membrane-bound fragments that are eliminated by surrounding macrophages without an inflammatory reaction. Most of the abovementioned factors are involved in cell proliferation and growth, and they can be directly or indirectly associated with apoptosis.

Although radiation has been reported related to the induction of apoptosis in thyrocytes [11], its carcinogenesis may be more related to its ability to damage DNA and cause mutation in tumor-suppressive genes including p53 [12]. It is reported that high concentrations of iodine increase the rate of Fas-induced apoptosis in thyrocytes, but low concentrations of iodine are able to inhibit apoptosis [13]. Iodine may reduce the sensitivity of papillary thyroid carcinoma cells to apoptotic stimulation via increasing the activity of heme oxygenase (HO) and p21 [14]. A recent study showed that iodine induced the apoptotic pathway in thyroid cancer cells through its involvement in the activation of MAPKs-related p21, Bcl-xL, and mutant p53 regulation [15]. The growth stimulatory effect of estradiol (E2 or 17β-estradiol) has been intensively studied in various estrogen receptor-expressing cells including breast cancer, prostate cancer, and thyroid

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cancer [16–18]. Experimentally, circulating estrogens may activate the estrogen receptor alpha (ERα) on thyroid tissue which increases the incidence of thyroid disease in mice, predisposing them to the development of thyroid cancer, with a higher incidence in female mice [19]. High levels of estrogens may also facilitate the development of thyroid cancers with metastatic phenotypes [20]. Interestingly, the activation of ERα by the ERα agonist PPT promotes, whereas activation of ERβ by the ERβ agonist DPN inhibits, thyroid tumor cell proliferation [21, 22]. The proliferative role of ERα was further supported by a siRNA experiment in which the knockdown of ERα by its siRNA significantly attenuated the PPT-mediated proliferation and growth. The activation of ERα by PPT increased the level of Bcl-2, whereas the activation of ERβ by DPN exerted an opposite effect on its expression in thyroid cancer cells [21], suggesting the involvement of Bcl-2 in ER-mediated regulation of thyrocyte proliferation. These findings appear to support the concepts that the level of ERα is more pronounced in malignant thyroid tissues than in nontumor tissues [23] and that E2/ERα contributes to the increased susceptibility of thyroid tissue to become malignant [19].

Apoptosis and Cancer

The deregulation of apoptosis has been implicated in various clinical disorders, including cancer. Two fundamental lesions are believed to be the underlying pathogenesis of cancer. The first are mutations that give rise to excessive proliferation, and the second is a disruption of apoptotic signaling that allows mutated cells to continue to proliferate and to live beyond their normal lifespan, perpetuating cycles of mutation and oncogenesis. This cycle of mutational activity results in the accumulation of active oncogenes and defective tumor suppressor genes within cells, which makes apoptosis unable to restrict cellular proliferation, and the balance between proliferation and apoptosis is shifted in favor of the former [24].

Apoptosis plays an essential role in the elimination of mutated or transformed cells from the body. During the development of cancer, cancer cells and their precursors must develop highly efficient, and usually multiple, mechanisms to avoid apoptosis. In fact, aborting apoptosis is regarded as one of the hallmarks of cancer cells [25]. A frequent, apparently paradoxical finding in tumors and their precursor lesions is an increased rate of apoptosis, while at the same time, there is an increased resistance to apoptosis as well. The increased apoptosis reflects the enormous pressure on these abnormal cells to undergo programmed cell death, while the increased resistance represents defense mechanisms developed by the mutated cell in an effort to survive. Without the development of apoptotic resistance early during tumorigenesis, the preneoplastic cells would not survive long enough to become invasive cancers. Because apoptosis involves a complex network of interacting checks and balances utilizing several hundreds of genes, cancer cells must develop resistance to apoptosis at multiple levels. To date, two major apoptotic pathways, death receptor-mediated apoptosis and mitochondria-mediated apoptosis, have been described [25, 26] (Fig. 6.1). The death receptor-mediated apoptotic pathway can be achieved by one of several death receptors when bound by the appropriate ligands, including TNF, FasL, and TRAIL. Currently, the most clearly understood aspect of the receptor pathway is the interaction between the Fas receptor and its ligand, FasL, and the activation of the TNF-R1 by TNF. The interaction between the death receptor and its ligand results in receptor aggregation and recruitment of the adaptor molecule Fas-associated death domain (FADD) and caspase-8. Upon recruitment, caspase-8 becomes activated and initiates apoptosis by direct cleavage of downstream effector caspases. UV irradiation, growth factor deprivation, and increased reactive oxygen species cause apoptosis through the mitochondria-mediated apoptotic pathway, which is initiated by the release of apoptogenic factors such as cytochrome c. Cytochrome c forms a multiprotein complex with the adaptor molecule Apaf-1 and procaspase-9. Procaspase-9 is activated upon recruitment to this complex and in turn activates the effector caspases. The receptor and the mitochondria pathways can be interconnected at different levels [27, 28]. Following death receptor stimulation, activation of caspase-8 may result in cleavage of Bid, a BH3 domain-containing protein of the Bcl-2 family, to a truncated form of Bid (tBid). tBid may stimulate cytochrome c release and subsequently initiate a mitochondrial amplification loop.

Apoptosis in Thyroid Carcinogenesis

Solid evidence has indicated that apoptosis plays a significant role in the development of thyroid cancer. An early study on PTC showed that the apoptotic index calculated by the result of TUNEL was directly related to the p53 protein but inversely correlated with the anti-apoptotic molecule, Bcl-2 [29]. It appears that resistance to apoptosis and the ability to proliferate are different among various types of thyroid cancer cells. But they increase with tumor aggressiveness, from PTC to poorly differentiated and undifferentiated thyroid cancers. Among various apoptotic molecules, the Fas/FasL system has been extensively investigated in thyroid cancer. Fas-mediated apoptosis is considered as a key mechanism of T cell-mediated cytotoxicity against neoplastic cells. Thyroid cancer cells express a significant level of Fas, and, upon anti-Fas antibody stimulation in vitro in the presence of interferon gamma and cycloheximide, the cancer cells can undergo apoptosis, suggesting that the Fas on the thyroid cancer cells

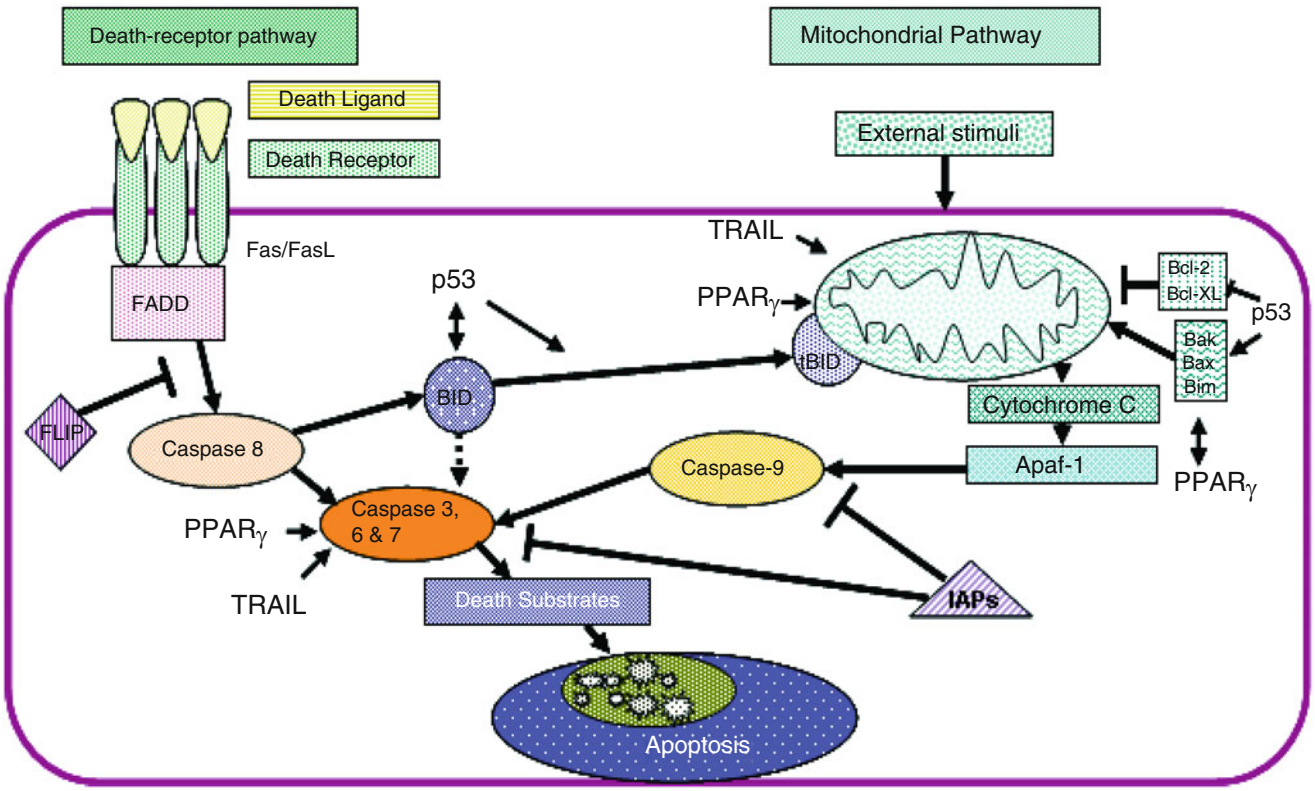

Fig. 6.1 Death receptor-mediated and mitochondria-mediated pathways and the involvement of p53, TRAIL, and PPARγ in the induction of apoptosis in thyroid cancer cells

is functional when there are certain cytokines and protein inhibitors available [30]. Though Fas is functional in thyroid cancer cells, it may not be able to induce apoptosis, and resistance to Fas is found in thyroid cancer cells [31–33]. The mechanism responsible for the resistance is not yet known, but it may be related to decreased numbers of Fas receptors available on the cell surface or to a change in the thyroid cytokine microenvironment. Fas expression has been documented to be lower in thyroid nodules [34]. Studies have indicated the existence of regulators that block apoptosis in thyroid cancer cells, thus pro-inflammatory cytokines may induce apoptosis in noncancer thyroid cells but not in thyroid cancer cells [32, 35]. The levels of Fas and FasL in different thyroid cancer cells may substantially differ, and the expression of Fas has been found to be negatively associated with the advanced stage of thyroid cancer [36]. Furthermore, Fas level is significantly higher in well-differentiated PTC and FTC than in poorly differentiated or undifferentiated PTC and FTC. These observations are consistent with the finding that there is an increasing resistance to apoptosis when thyroid cancer becomes more aggressive [29].

As mentioned before, cancer cells usually develop resistance to apoptosis at multiple levels. One true example is thyroid cancer cells. Thyroid cancer cells cannot only escape apoptosis by either reducing Fas expression on their cell membrane or/and displaying blockers that inhibit the Fas/FasL system [31–33] but can also utilize the Fas/FasL system to downregulate the ability of immune surveillance to kill tumor cells by inducing apoptosis of infiltrating lymphocytes and other immune effector cells [32, 37]. Therefore, FasL expression may correlate with more aggressive types of thyroid cancer [32]. Thyroid cancer cells are not killed by their own FasL because of their inherent resistance to Fas-mediated apoptosis [31–33, 35]. Such FasL-mediated suppression of immune surveillance is called "Fas counterattack" or the "tumor immune privilege" [38, 39].

In addition to the involvement of Fas/FasL death receptor-mediated apoptosis in the development of thyroid cancer, mitochondria-mediated apoptosis, represented by the alternation of Bcl-2 family members, may also play a role in promotion of thyroid cancer cell growth. High levels of Bcl-2 and Bcl-xL, both of which are anti-apoptotic, are found in malignant epithelial cells from PTC, FTC, and ATC [40–42]. Further, the level of pro-apoptotic Bax is reduced in thyroid cancer [42, 43]. The aberrant expression of Bcl-2, Bcl-xL, and Bax is thought to result from a change in the cytokine microenvironment of the thyroid, especially IL-4 and IL-10 [40, 43]. Obviously, the changes in Bcl-2 family members

disturb the balance between pro-apoptotic Bax and anti-apoptotic Bcl-2 and Bcl-xL and thus reduce the sensitivity of thyroid cancer cells to apoptotic stimuli. This assumption is in line with the observation that the expression of Bcl-2 is inversely correlated with the apoptotic index in thyroid cancer cells and chemotherapy-induced apoptosis [29, 44].

The function of Bcl-2 and its other family members is closely associated with p53. For example, p53 is able to upregulate pro-apoptotic Bax in a variety of cell types [45, 46]. Unfortunately, evidence directly linking between p53 and Bcl-2 family members in thyroid cancer is lacking. However, apoptosis in poorly differentiated thyroid cancer cells is associated with a high protein level of p53 but a low protein level of Bcl-2 [47]. By overexpression of p53, the proliferation of poorly differentiated thyroid cancer cells is reduced and the cells exhibit malignant behavior [48]. These findings suggest that thyroid cancer cells with a lower level of p53 or lacking p53 are more likely to grow fast and less sensitive to apoptosis. It is believed that mutations of tumor suppressor genes such as p53 are important events in thyroid tumor progression once the early stages of oncogene-driven cell transformation have been established [49]. Some p53 mutants can gain anti-apoptotic functions. For example, mutant p53 (G199V) in anaplastic thyroid cancer cells gains anti-apoptotic function through signal transducer and activator of transcription 3 (STAT3) and thus promotes the growth of tumor cells [50]. Excitingly, the reactivation of p53 mutants can enable thyroid cancer cells to arrest the growth by promoting apoptosis [51]. Peroxisome proliferator-activated receptor gamma (PPARγ) is another important molecule that is involved in apoptosis and tumor development of thyroid cancer. PPARγ is frequently downregulated in thyroid cancer [52, 53]. The mechanism responsible for the PPARγ downregulation is not fully known. However, thyroid hormone receptor beta (TRβ) mutant is able to function as dominant negative inhibitor of PPARγ and thus suppresses the function of PPARγ [53]. In follicular thyroid carcinomas, the downregulation of PPARγ may be caused by a chromosomal translocation that fuses the thyroid-specific transcription factor paired box gene 8 (PAX8) with PPARγ, forming a PAX8-PPARγ fusion protein, PPFP [53–55]. This PPFP can dominantly inhibit expression of the PPARγ-responsive promoter, resulting in enhancement of follicular thyroid cell growth and loss of differentiation that ultimately leads to carcinogenesis [53, 54]. In a transgenic mouse model of thyroidal PPFP expression, it is found that the mice develop thyroid hyperplasia but not carcinoma, suggesting that additional events are required to cause follicular thyroid cancer [55, 56]. Nevertheless, the activation of PPARγ by its ligands has been shown to induce apoptosis, inhibit the growth of thyroid cancer cells, and facilitate the radioiodine treatment of thyroid cancer [57–59]. Therefore, PPARγ activation may counteract the uncontrolled proliferation and thyroid malignant cell growth through induction of apoptosis or promotion of cellular terminal differentiation. It is concluded that the alteration of PPARγ may serve not only as a feature of thyroid cancer development but also as a promising target for cancer therapy.

Though Fas/FasL, Bcl-2 family members, p53, and PPARγ are major players that regulate apoptosis in thyroid cancer cells (Fig. 6.1), a number of new molecules have recently been described to contribute to thyroid cancer development and/or treatment by regulating apoptosis. BAG (Bcl-2-associated athanogene) is found to specifically express in thyroid carcinomas and not in normal thyroid tissue or goiter [60]. The downregulation of BAG3 can significantly sensitize human neoplastic thyroid cells to apoptosis induced by NF-related apoptosis-inducing ligand (TRAIL). TRAIL-induced apoptosis in thyroid cancer cells is also regulated by another novel molecule, DJ-1 [61]. DJ is a cancer-associated protein, which protects cells from multiple toxic stresses. Importantly, DJ-1 is specifically expressed in thyroid carcinomas and not in the normal thyroid tissue. siRNA downregulation of DJ-1 can significantly sensitize thyroid carcinoma cells to TRAIL-induced apoptosis, whereas the forced exogenous expression of DJ-1 significantly suppresses cell death induced by TRAIL [61]. In the study by Siraj et al. [62], TMS1, a tumor suppressor gene that encodes for caspase recruitment domain-containing regulatory protein, is downregulated in a subset of thyroid cancer samples by hypermethylation. Its demethylation can also sensitize thyroid cancer cells to TRAIL-induced apoptosis. A very recent study demonstrates that Ret oncoprotein regulates CD95 (Fas, APO-1)-mediated apoptosis by increasing Fap-1, a potential inhibitor of CD95 (Fas, APO-1) in MTC cells [63]. Therefore, the functional interplay of the Ret mutant with the receptor-mediated apoptosis pathway may provide a mechanism contributing to MTC malignant phenotype and a rational basis for novel therapeutic strategies combining Ret inhibitors and CD95 agonists.

Potential Apoptotic Intervention for Thyroid Cancer

Therapies designed to stimulate apoptosis in target cells play an increasing role in the prevention and treatment of human cancer, including thyroid cancer. For several decades, the classical view of an anticancer drug mechanism has relied on the specific interaction of a drug with its target, and such an interaction can lead to tumor cell death via its direct and injurious effect on the proliferating tumor cells. However, emerging data based on an increasing understanding of the cell cycle control and apoptosis process indicate that, rather than being intrinsically toxic, many anticancer drugs merely stimulate tumor cells to self-destruction via apoptosis. Studies have

demonstrated that most, if not all, of currently available anticancer drugs including those that target DNA replication, DNA integrity, mitochondria, and cytokines induce apoptosis in thyroid cancer cells. For example, paclitaxel and manumycin are now known to induce apoptosis in ATC via stimulating p21 expression [64]. UCN-01, a selective protein kinase inhibitor, can significantly induce apoptosis of various types of thyroid cancer cells, probably via inhibiting the expression of Bcl-2, as the overexpression of Bcl-2 can block the UNC-01-activated cell death pathway [65]. Some extracts from traditional Chinese herb medicines have also shown a strong antiproliferative effect via provoking apoptosis in MTC [66].

With the tremendous amount of knowledge gained about apoptosis in thyroid cancer, some promising targets/therapies for certain types of thyroid cancer cells have emerged. Among these targets are aforementioned p53, PPARγ, and TRAIL [51, 57–62]. The major advantage of TRAIL-mediated apoptosis against thyroid cancer is its selective killing of tumor cells without affecting normal thyroid cells [65, 67], thus reducing the possible side effects. Some emerging agents such as histone deacetylase inhibitors [68], Cl-IB-MECA that is adenosine receptor A3 agonist [69], and R-roscovitine that is a novel cyclin-dependent kinase inhibitor [70] have recently shown to either enhance or optimize the TRAIL-induced apoptosis in thyroid cancer cells. In addition to these well-documented targets, the glutathione-dependent redox system may play an important role in the sensitivity to proteasome inhibition-induced apoptosis in thyroid cancer cells [71]. Inhibition of nuclear factor-kappaB is shown to enhance apoptosis of thyroid cancer cells by reducing the levels of MMP-9 and MMP-13 [72]. Resveratrol, a phytoalexin found in grapes and other food products, and rosuvastatin, a statin drug, have been demonstrated to induce apoptosis in thyroid cancer cells by increasing caspase-3 activity [73, 74]. Epigallocatechin-3-gallate (EGCG), a major catechin in green tea, can induce apoptosis of human anaplastic thyroid carcinoma cells through suppression of EGFR/ERK pathway and cyclin B1/CDK1 complex [75].

Conclusion

Apoptosis in thyroid cancer is a multifactor and multistep process, and this process is controlled by a number of different molecules including but not limited to Fas/FasL, Bcl-2 family members, p53, PPARγ, and TRAIL. There is no clear evidence which one is more important than the others in the development of thyroid cancer. It appears that all of them can independently induce or enhance apoptosis in thyroid cancer cells. It is important to understand how they interact with each other since such interactions may greatly optimize the therapeutic targets and enhance apoptosis induced in thyroid cancer cells.

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