# 9.ABNORMALITIES OF NUCLEAR RECEPTORS IN THYROID CANCER

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## INTRODUCTION

Nuclear receptors comprise a large family of ligand-inducible transcription factors that are critically important for growth, differentiation, development, and maintenance of metabolic homeostasis. They regulate the expression of target genes by binding to the specific DNA sequences at the promoters to mediate the biological effects. Many nuclear receptors have multiple isoforms with over-lapping functions or isoform-specific functions (1, 2). The expression of these receptor isoforms is regulated in a tissue- and development-dependent manner. A host of coregulatory proteins that influence the ligand selectivity and DNA binding capacity further modulates the transcriptional activities (3, 4).

Abnormal expression and/or aberrant functions of sex steroid nuclear receptors are known to be involved in the development and progression of such endocrine cancers as breast, ovarian, endometrium, and prostate, but less is known about the role of nuclear receptors in the carcinogenesis of the thyroid. Progress in this area has recently been made as a result of the discoveries of the fusion gene of PAX8 with the peroxisome proliferator-activated receptor $\gamma$ (PPAR$\gamma$; PAX8-PPAR$\gamma$) in follicular thyroid carcinoma and of the spontaneous development of follicular thyroid carcinoma in the homozygous knock-in mutant mice harboring a mutated thyroid hormone $\beta$ receptor (TR$\beta$). This review will first examine the latest findings on the possible roles of several sex steroid nuclear receptors in thyroid carcinogenesis. It will then discuss the molecular actions of the mutant TR$\beta$ in carcinogenesis, particularly in relation to a unique knock-in mouse model of thyroid cancer.

## ABNORMAL EXPRESSION OF ESTROGEN AND PROGESTERONE RECEPTORS IN THYROID CANCER

Thyroid carcinoma is more common in women than in men (5). For 2003, the estimate of new cases of thyroid cancer has a female predominance with a 2.9:1 ratio (6). This predominance suggests that estrogens may play a critical role in the development of thyroid carcinoma. In the past two decades, efforts have been made to demonstrate the presence of estrogen receptors (ERs) in thyroid tumors and to correlate tumor malignancy with ER expression. Using a dextran-coated charcoal method and analysis by the method of Scatchard, Miki et al. did not detect ER in the cytosol of normal thyroids, but they found a significantly higher ER in the neoplastic and hyperplastic thyroid tissues (7). Using different biochemical methods, Mizukami et al. (8) and Yane et al. (9) also showed a higher expression of ER in neoplastic thyroid lesions than in normal thyroids or in adjacent normal tissues. Lewy-Trenda examined 72 thyroid glands for the expression of ER by using immunochemical assays with anti-ER antibodies. Positive staining occurred in the nuclei of differentiated thyroid cancer cells (24%), but not in non-neoplastic cells. A small number of oxyphillic (4%) and follicular adenomas (6%) also stained positive for ERs (10).

Consistent with these findings, several studies showed that estrogens stimulate the proliferation of thyroid carcinoma cells (11–13), whereas the antiestrogen, tamoxifen, inhibits the proliferation of a tumor cell line derived from medullary thyroid carcinoma (11). These studies clearly showed that cell proliferation induced by estrogens is mediated by ERs, but little is known about the specific molecular pathways. One study suggested that activation of the mitogen-activated protein kinase by phosphorylation might be one of the key steps in the estrogen-mediated cell proliferation of thyroid cancer cells (13).

The relevance of the increased expression of ERs in thyroid tumorigenesis is not obvious, particularly given that there is no clear correlation in the extent of expression of ER to age, sex, presenting clinical or pathological features, or, in cases of carcinoma, to subsequent metastatic potential (10, 14, 15). Furthermore, the failure of several studies to detect a greater expression of ERs in thyroid tumors than in normal tissues casts further doubt on the significance of expression of ERs in thyroid tumor development and progression (16–19). It is unclear whether the discrepancy among studies is due to the sensitivity of the detection or the intrinsic variability in the expression of ERs in tumor samples. Plainly, more studies are needed to understand whether estrogens and ERs are the major factors that contribute to thyroid cancers predominance in females.

Fewer studies have investigated the roles of progesterone receptors (PRs) in thyroid carcinogenesis. Because of the interest in understanding thyroid cancer's predominance in females, the expression of PRs in thyroid tumors has been evaluated by means of ligand binding assays, enzyme immunoassays, and/or immunohistochemistry. In a few limited studies, the presence of PR and ER was assessed concurrently in the same samples. In 135 thyroid lesions that included papillary, follicular, medullary, and Hurthle cell carcinomas, van Hoeven detected the presence of PR in 51% of the cases, with the highest abundance in papillary carcinomas, particularly in male patients and women older than 50 years (15). In that same study, ER was found in 46% of the