5. MOLECULAR EPIDEMIOLOGY OF THYROID CANCER

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INTRODUCTION

Molecular biology studies have greatly enhanced our knowledge of thyroid tumorigenesis, although their impact in clinical practice is still negligible.

Most benign and malignant thyroid tumors have a monoclonal origin, suggesting that genetic events are responsible for their occurrence (34). These may involve the activation of oncogenes or the inactivation of tumor-suppressor genes. Several genetic abnormalities (point mutations or gene rearrangements) have been evidenced in human thyroid tumors (review in 14,40,53). Several *in vitro* and *in vivo* animal models, including transgenic mice that reproduce the human situations, are also available.

ONCOGENES AND THYROID TUMORS

Tyrosine kinase receptors

Growth factors act on the target cell through interaction with specific membrane receptors, some of which belong to the family of tyrosine kinase receptors. The genes encoding these receptors are frequently involved in the pathogenesis of human cancers, including thyroid cancer. Whenever uncontrolled activation of a tyrosine kinase receptor gene occurs, either through overexpression or activating mutations, increased responsiveness to growth factors or ligand-independent gene activation ensues, both of which then activate the signaling pathways downstream. Three tyrosine kinase receptor

genes are known to be associated with the pathogenesis of papillary thyroid cancer: the *met* gene through overexpression and the *ret* and *trk* genes through gene rearrangements.

Ret */PTC oncogene*

MOLECULAR BASIS OF *Ret*/PTC REARRANGEMENTS. The *ret* proto-oncogene is a 21-exon gene located on chromosome 10q11-2 that encodes a membrane tyrosine kinase receptor. The ret receptor together with the glial cell line-derived neurotropic factor (GDNF) receptor (GFRα-1), an extracellular protein tethered to the cell membrane, form a receptor for GDNF. The ret receptor may also combine with other members of the GFRα receptor family, thereby forming receptors for other peptides (artemin, neurturin, persephin). The ret protein is composed of an extra-cellular domain, with a distal cadherin-like domain and a juxta-membrane cystein-rich domain, a transmembrane domain and an intra-cellular domain with tyrosine-kinase activity. The gene is expressed in a variety of neuronal cell lineages including thyroid C cells and adrenal medulla but is not expressed in normal thyroid follicular cells.

Under normal conditions, the ret ligands induce receptor dimerization and tyrosine trans-phosphorylation of the receptor kinase domain, thus activating the pathways downstream. When the gene is mutated, ligand interaction is no longer needed for receptor activation and the downstream pathways are continuously activated: ret/PTC kinase activity promotes interaction with shc, an intermediate in the RAS-RAF-MEK-MAP kinase pathway. Inappropriate activation of this pathway induces abnormal proliferation and differentiation in many human cancers and also induces genomic instability.

Ret activation was first evidenced by transfection experiments and was initially found exclusively in papillary thyroid carcinoma (PTC). The resulting oncogene was thus called *ret*/PTC (16,18,40). All activated forms of the *ret* proto-oncogene are due to chromosomal rearrangements in which the 3′ or tyrosine kinase domain of the *ret* gene is fused with the 5′ domain of a foreign gene. The foreign gene is constitutively expressed, resulting in permanent expression of the rearranged *ret* gene. These rearranged genes have coiled-coil domains that activate the ret protein through permanent dimerization. They also lack the intracellular juxta-membrane domain that normally exerts a negative regulatory effect on ret tyrosine kinase activity. Finally, the chimeric protein lacks the extracellular and transmembrane domains and is located in the cytosol. Three major forms of the *ret* rearrangements have been identified in epithelial thyroid tumors:

Ret/PTC$_1$, is formed through an intra-chromosomal rearrangement fusing the *ret* tyrosine kinase domain to a gene designated H4, whose function is still unknown.

Ret/PTC$_2$, is formed through an inter-chromosomal rearrangement fusing the *ret* tyrosine kinase domain to a gene located on chromosome 17 that encodes the RIα regulatory subunit of cAMP-dependent protein kinase A.

Ret/PTC$_3$, is formed through an intra-chromosomal rearrangement fusing the *ret* tyrosine kinase domain to a gene designated ELE1, whose function is still unknown.

In the three major *ret* rearrangements (*ret*/PTC$_{1;2;3}$), the breakpoints of the *ret* gene are located in the same intronic region, between exons 11 and 12. Several other