11. THE MOLECULAR PATHWAYS INDUCED BY RADIATION AND LEADING TO THYROID CARCINOGENESIS

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INTRODUCTION

The association between ionizing radiation and thyroid cancer is well established. It was first proposed in 1950 in children who received X-ray therapy in infancy for an enlarged thymus (1). During the following decades, numerous reports have documented an increased incidence of thyroid neoplasms in children after external radiation for different benign conditions of the head, neck and thorax (2). Since the early 1960s, when the use of radiotherapy for benign conditions was abandoned, the incidence of radiation-associated thyroid malignancy in children gradually decreased (3). Currently, radiation therapy for malignancy continues to be a source of radiation-associated thyroid cancer (4). An increased risk of thyroid cancer has also been linked to environmental irradiation. This was documented in survivors of atomic bomb explosions in Japan in 1945(5), and in residents of the Marshall Islands exposed to fallout after detonation of a thermonuclear device on the Bikini atoll in 1954 (6). In the U.S., exposure to radioiodines from atmospheric nuclear tests in Nevada in the 1950s has been suggested to lead to an excess of thyroid neoplasms (7, 8). In April 1986, an accident at the Chernobyl Nuclear Power Station in the former USSR produced the most serious environmental disasters ever recorded and led to a dramatic increase in the frequency of childhood thyroid cancer in contaminated areas of Belarus, Ukraine, and western Russia (9, 10). This tragic disaster has created one of the most striking paradigms of radiation-induced thyroid tumors and allowed significant progress in the understanding of the molecular pathways induced by radiation. In this chapter, I

review the genetic events and molecular mechanisms underlying radiation carcinogenesis in the thyroid gland.

RET/PTC REARRANGEMENTS

Over the last decade, rearrangements of the RET proto-oncogene have been identified as the most common genetic event in thyroid tumors associated with radiation exposure.

The RET proto-oncogene is located on chromosome 10q11.2 and encodes a cell membrane receptor tyrosine kinase (11, 12). The receptor consists of three functional domains: an extracellular domain containing a ligand-binding site, a transmembrane domain, and an intracellular domain that includes a region with protein tyrosine kinase activity. The ligands for RET receptor are neurotrophic factors of the glial cell-line derived neurotrophic factor (GDNF) family, including GDNF, neurtulin, artemin, and persephin (13). Binding of a ligand causes the receptors to dimerize, leading to autophosphorylation of the protein on tyrosine residues and initiation of intracellular signaling cascade. Wild-type RET is expressed in neuronal and neural-crest derived tissues including thyroid parafollicular C-cells, but not in thyroid follicular cells. In thyroid follicular cells, RET can be activated by fusion to different constitutively expressed genes. The product of this rearrangement is a chimeric oncogene named RET/PTC (PTC for papillary thyroid carcinoma).

Structure of RET/PTC oncogenes

Since the original report on RET activation by rearrangement in papillary thyroid carcinomas (14), three major types of the rearrangement have been identified: RET/PTC1, RET/PTC2, and RET/PTC3 (Figure 1). All of them are formed by

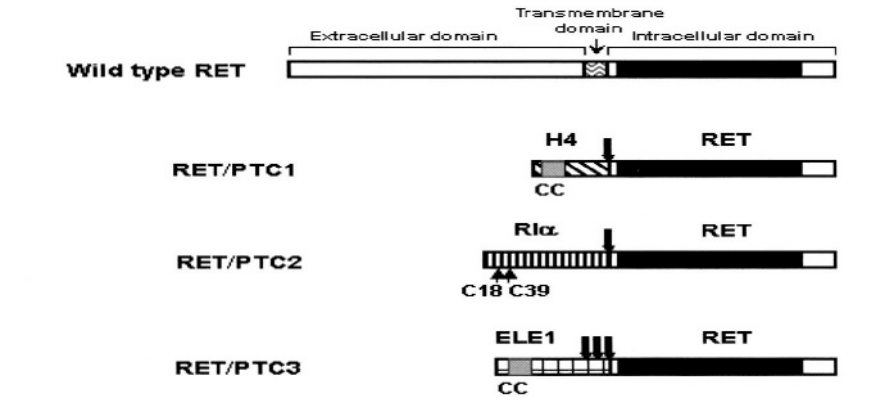

Figure 1. Schematic representation of the wild type RET gene and three major types of RET/PTC rearrangement. The 3′ portion of RET participating in the fusion encodes the tyrosine kinase domain (black box) but lacks the transmembrane and extracellular domains. The genes fused with RET encode dimerization domains, either coiled-coil domain (CC) or cysteine residues forming disulfide bonds during dimerization (C18, C39), allowing ligand-independent dimerization and activation of the truncated RET receptor. Block arrows indicate breakpoints.