23. RET ACTIVATION IN MEDULLARY CARCINOMAS

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INTRODUCTION

RET gene encodes a receptor tyrosine kinase acting as the subunit of a multimolecular complex that binds four distinct ligands and activates a signaling network crucial for neural and kidney development.

Different alterations of *RET* are associated to five diseases. *RET* is the susceptibility gene for the inherited cancer syndrome multiple endocrine neoplasia type 2 (MEN2), which includes MEN2A, MEN2B and familial medullary thyroid carcinoma (FMTC), as well as a major susceptibility gene for the syndrome characterized by the congenital absence of enteric ganglia, the Hirschsprung's disease (HSCR). Finally, somatic tumor-specific rearrangements of RET gene, which originate constitutively activated fused proteins, have been found in a consistent fraction of papillary thyroid carcinomas.

This review focuses on *RET* alterations in medullary thyroid carcinoma, a rare malignancy of thyroid gland present either in sporadic or MEN2-associated hereditary forms.

RET

RET gene and RET proteins

The human *RET* gene is located on chromosome 10q11.2 (Ishizaka, Y. et al., 1989) and comprises 21 exons. Homologues of *RET* have been identified in higher and lower vertebrates, as well as in *Drosophila melanogaster* (Hahn, M. et al., 2001).

Table 1. *RET* related pathologies

Disease	Genetic alteration	Pathogenic mechanism
PTCs	Chromosomal rearrangements	Constitutive TK activity
MEN2A	Germline point mutations in the Cys-rich domain	Constitutive disulfide linked dimerization
MEN2B	Germline point mutations in RET TK domain	Altered substrate specificity Constitutive TK activity
FMTC	Germline point mutations:	
	– in the Cys-rich domain	Constitutive dimerization
	– in RET TK domain	Constitutive TK activity? Altered substrate specificity?
HSCR	Germline mutations (deletions, insertions, frame shift, nonsense or missense):	
	– in RET extracellular domain	Impairment of RET cell surface expression
	– in RET TK domain	Partial loss of RET TK activity
	– in RET C-terminus	Impairment of binding of docking proteins

RET gene was identified in 1985 as a novel oncogene, following transfection of NIH3T3 cells with DNA from a human T-cell lymphoma (Takahashi, M. et al., 1985). The transforming gene resulted from a recombination event between two unlinked DNA sequences, which occurred during the transfection process; hence the name *RET,* for '*re*arranged during *tr*ansfection'. The resulting chimaeric gene encoded a fusion protein comprising an amino-terminal region that displayed a putative zinc finger motif fused to a tyrosine kinase domain. Subsequently, the name *RET* has been retained to designate the gene coding for the tyrosine kinase protein of the fused oncogene. Rearrangements of *RET* with different genes are found frequently in papillary thyroid carcinomas (RET/PTCs) (Grieco, M. et al., 1990; Santoro, M. et al., 1992). On the other hand gain-of-function mutations of *RET* cause sporadic thyroid and adrenal cancers (Lindor, N. M. et al., 1994; Beldjord, C. et al., 1995; Komminoth, P. et al., 1996) as well as cancer syndromes, such as multiple endocrine neoplasia types 2A and 2B (MEN2A and MEN2B) and familial medullary thyroid carcinoma (FMTC) (reviewed in Mulligan, L. M. et al., 1995a; Goodfellow, P. J. et al., 1995; Pasini, B. et al., 1996). Interestingly, loss-of-function mutations of the same RET gene cause Hirschsprung's disease (HSCR) or colonic aganglionosis (reviewed in Amiel, J. et al., 2001) (Table 1).

RET encodes a transmembrane tyrosine kinase displaying a structure similar to that of other receptor tyrosine kinases (RTKs), comprising extracellular, transmembrane and cytoplasmic domains.

The large extracellular portion, preceded by a typical cleavable signal sequence of 28 aminoacids, has no similarity with other RTKs and contains a conserved cysteine-rich region close to the cellular membrane and a more distal region with homology to the cadherin family of cell adhesion molecules (Takahashi, M. et al., 1988; Schneider, R., 1992; Iwamoto, T. et al., 1993; Takahashi, M. et al., 1989). Cadherins are Ca^{2+}-dependent cell—cell adhesion proteins and their adhesive properties depend on a domain of about 110 amino acids tandemly repeated in the extracellular region. RET