Genetic causes of medullary thyroid carcinoma and Hirschsprung's disease

Abstract

Medullary thyroid carcinoma (MTC) and Hirschsprung's disease (HSCR) are classified as simple neurocristopathies, i.e. diseases linked to neural crest-derived cells. MTC is derived from parafollicular cells of the thyroid and HSCR is characterized by absence of enteric ganglia in the gastrointestinal tract. The *RET* proto-oncogene is only expressed in neural crest-derived cells, including parafollicular cells and enteric neurons. The *RET* encodes a transmembrane tyrosinekinase receptor that plays an important role during proliferation, differentiation and cell survival, and activates many signaling pathways. If the strictly regulated activation fails, e.g. due to mutations in the specific gene locations, the *RET* becomes a highly effective oncogene. Activating germline mutations in the *RET* proto-oncogene lead to hereditary forms of MTC, whereas sporadic forms of MTC are caused by somatic mutations in the tumor tissue. On the contrary, inactivating mutations induce migration failure of ganglion cell precursors during the development of enteric nervous system and result in the development of HSCR. In rare cases, the coexistence of both diseases is caused by mutations with a dual gain-of-function and loss-of-function character. Linkage studies confirm the influence of the *RET* proto-oncogene in the pathogenesis of diseases even in patients without a detected causing mutation. Therefore, the attention has also been turned on polymorphisms such as modifying factors which may affect protein expression and contribute to the disease formation and modulation. The thesis is focused on different roles of the *RET* proto-oncogene in the pathogenesis of MTC and HSCR. In addition to detection of the major genetic causes in MTC and HSCR patients, the risk of MTC in HSCR patients was defined. Polymorphisms in selected regions were studied and the risk in association with specific variants was evaluated. Genetic alterations - mutations and polymorphisms, were correlated with phenotype manifestation using extensive clinical and pathological data of patients providing information on the form, aggressiveness and development of the disease. Genotype-phenotype correlations enabled to deduce the disease prognosis and the risk for family members. Thanks to molecular genetic testing in families with MTC and HSCR, the prevention and treatment of hereditary MTC have been improved and resulted in the disease prediction in preclinical stage and prevention by early intervention with prophylactic thyroidectomy.