Institutionen för Onkologi-Patologi

Genetic and Epigenetic Mechanisms in Primary Hyperparathyroidism

AKADEMISK AVHANDLING

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ABSTRACT

Primary hyperparathyroidism (PHPT) is a common endocrine disorder characterized by abnormally excessive secretion of parathyroid hormone (PTH) and elevated serum calcium. PHPT patients can develop a wide range of complications affecting many body organs such as the skeleton, kidneys and heart. In the majority of patients, PHPT is due to a solitary adenoma and less frequently due to multiglandular disease. Very rarely PHPT is caused by a parathyroid carcinoma.

This thesis aimed at a better understanding of the genetic as well as epigenetic mechanisms involved in this disease in order to improve future patients management.

In study I we have investigated large parathyroid adenomas (≥ 4 grams) and detected frequent MEN1, but rare HRPT2/CDC73 mutations and low MIB1 proliferation index. The majority of the tumors had loss of parafibromin expression and positive APC expression. Furthermore, gain of chromosome 5 was the most unique and frequent copy number alteration detected in this group, while very rarely detected in unselected adenomas. We concluded that a subset of large parathyroid adenomas have distinct genetic profile and pronounced clinical features reflected by significantly higher serum calcium.

In study II we examined the role of constitutional APC mutations in parathyroid tumors from two patients with APC mutation-associated familial colorectal cancers. Pathological revision confirmed the benign nature of both tumors. None of them had somatic mutations or DNA copy number alterations of the APC gene and both tumors displayed strong APC and parafibromin expression with low MIB index. Although the APC 1A promoter was hypermethylated, promoter APC 1B was unmethylated and this was consistent with normal APC mRNA expression. Our results supported the benign nature of the parathyroid tumors and excluded a possible association between constitutional APC mutations and parathyroid tumorigenesis.

In study III we defined the molecular cytogenetic profile of CDC73/HRPT2-mutated parathyroid tumors. All the carcinomas displayed frequent DNA copy number losses on chromosome 1p and 13 while the adenomas did not display any significant alterations. All the carcinomas were diploid at the CDC73 gene locus, but three adenomas had loss at this locus. The CDC73 promoter was unmethylated in all the tumors. The carcinomas displayed more loss of heterozygosity (LOH) events than the adenomas, and two carcinomas had LOH at the CDC73 locus. These results suggest that CDC73-mutated parathyroid adenomas exhibit a partly unique cytogenetic profile in addition to that of carcinomas and unselected adenomas.

In study IV analyses of promoter methylation status in a panel of benign and malignant parathyroid tumors revealed frequent hypermethylation of APC 1A, β-catenin and RASSF1A promoters in the adenomas which correlated with reduced mRNA expression. Parathyroid carcinomas were hypermethylated for APC 1A and exclusively for SFRP1. No changes in global methylation could be detected and tumor groups with known MEN1 or CDC73 mutations did not display different methylation profile. We concluded that aberrant promoter methylation of APC 1A, β-catenin, RASSF1A and SFRP1 can play a role in parathyroid tumorigenesis and hypermethylation of SFRP1 can act as a potential epigenetic marker for parathyroid carcinomas.