Profiling of Small Intestine Neuroendocrine Tumors

Akademisk avhandling

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av

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Avhandlingen baseras på följande arbeten:

I. Arvidsson Y, **Andersson E**, Bergström A, Andersson M K, Altiparmak G, Illerskog A, Lamazhapova D, Ahlman H, Nilsson O. Amyloid precursor-like protein 1 is differentially upregulated in neuroendocrine tumours of the gastrointestinal tract. *Endocrine-Related Cancer* 2008; 15: 569-581.

II. **Andersson E**, Swärd C, Stenman G, Ahlman H, Nilsson O. High-resolution genome profiling reveals gain of chromosome 14 as a predictor of poor outcome in ileal carcinoids. *Endocrine-Related Cancer* 2009; 16: 953-966.

III. **Andersson E**, Kristiansson E, Arvidsson Y, Swärd C, Hofving T, Wängberg B, Nilsson O. Expression profiling of small intestine neuroendocrine tumors identifies subclasses of clinical relevance, therapeutic targets and biomarkers for prognosis. *Manuscript.*

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ABSTRACT

Small intestine neuroendocrine tumors (SI-NETs) are malignant neoplasms usually presenting with disseminated disease and symptoms of hormone overproduction. Radical surgery is curative but can only be performed for localized disease. For most patients the disease follows a progressive and fatal course. New treatment strategies for cure and palliation are therefore needed. To explore the mechanisms of SI-NET formation and to define candidate therapeutic targets and biomarkers of prognosis, we examined the gene expression profiles and somatic copy number alterations (SCNAs) in SI-NETs by array-based techniques.

Tumors from forty-three patients with SI-NETs were investigated by high-resolution array-CGH. The number of SCNAs per tumor was low, indicating that SI-NETs are genetically relatively stable tumors. The most frequent SCNA was loss of chromosome 18 (74%), occurring in both primary tumors and metastases. In some tumors loss of chromosome 18 was the only SCNA, indicating an early event in tumor formation. Two separate groups of tumors with distinct patterns of SCNAs were observed: a major group of tumors with loss of chromosome 18 and a minor group of tumors with gain of whole chromosomes (chr. 4, 5, 14 and 20). Survival analysis showed that gain of chromosome 14, a characteristic event in the minor group, was a strong predictor of poor survival. Gene expression profiles of SI-NETs were analyzed in two different studies. In the first study we examined the expression profile of five SI-NETs and found amyloid precursor like protein 1 (APLP1), a member of the APP-family (APP, APLP1 and APLP2), to be differentially upregulated in SI-NETs. Higher expression of APLP1 in metastases compared to primary tumors indicated a role of APLP1 in tumor progression. Localization of the APP-family proteins in SI-NET cells (GOT1) by confocal laser microscopy showed partial co-localization with synaptophysin, Rab5 and FE65, suggesting a role in tumor cell adhesion and gene regulation. In the second study tumor tissue from thirty-three patients was subjected to expression profiling. We identified three different groups of SI-NETs by unsupervised hierarchical clustering with significant differences in patient survival. Genes related to patient survival included genes involved in cell cycle progression, apoptosis and DNA damage response. Genes involved in tumor invasion and immunity also correlated to patient survival. Cell cycle related genes were differentially expressed in tumors with gain of chromosome 14. Forkhead box M1 (*FOXM1*), a master regulator of cell cycle progression, was identified as an upstream regulator in these tumors by pathway analyzes. Analysis of upregulated genes in SI-NETs identified a number of candidate drug targets including SSTR2, receptor tyrosine kinases, transcriptional regulators and molecular chaperones. *In vitro* experiments on GOT1 cells demonstrated effective inhibition of tumor growth by multi-tyrosine kinase inhibitors as well as by inhibitors of AKT, HDAC and HSP90.

In conclusion, these studies have established the expression and SCNA profiles of SI-NETs. These data demonstrate a molecular heterogeneity among SI-NETs, and identifies a correlation between deregulation of cell cycle genes and patient survival. Furthermore, profiling of SI-NETs provides novel candidate therapeutic targets related to tumor subgroups and a platform for patient stratification in clinical trials.