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INSIGHTS INTO THE TRANSCRIPTOMIC PROFILING OF ADRENOCORTICAL TUMORS

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ABSTRACT

An adrenocortical tumour (ACT) can be detected in up to 5% of the population older than 50 years of age. The frequency increases with age. More ACTs are being detected in parallel with the increased use of high-resolution imaging. When there is clinical or biochemical evidence of excess hormonal secretion from an ACT, a careful and systematic clinical evaluation is compulsory. An abnormally elevated secretion of a particular steroid such as aldosterone, cortisol or dehydroepiandrosterone is frequently associated with a benign phenotype, adrenocortical adenoma (ACA). Adrenocortical carcinoma (ACC) is a rare tumour with a relatively poor prognosis; 5-year overall survival is about 30-35%. Approximately half of ACCs are hyperfunctioning, and therefore ACC diagnosis is more often based on its imaging phenotype or by histological characteristics (Weiss Score) rather than the hormonal profile. Suspicion of malignancy or proven hormone production with clinical significance in ACTs should lead to prompt surgical resection. The overall aim of this thesis was to explore by means of transcriptomic profiling the differences between ACT regarding the malignant and hyperfunctioning phenotypes.

Paper I shows the main divergences between ACC and benign ACT at the transcriptomic level. Several genes were up regulated in ACC, including genes related to the IGF family. Transcriptional profiling through the use of cDNA arrays allows discrimination between ACC and ACA.

Paper II emphasizes the use of mRNA transcriptomics for distinguishing the hyperfunctioning phenotypes and prognosis in ACA and ACC respectively. Some specific mRNAs are closely related to certain functional phenotypes, for example aldosterone-producing adenoma (APA) with *OSBP* and *VEGFB*. Additionally, two subgroups of ACC with different survival times were distinguished based on their transcriptomic mRNA profiles.

Paper III demonstrates that the transcriptomic profile based on microRNA (miRNA) expression is also useful for discriminating ACA from ACC. Moreover, certain miRNAs were significantly associated with survival time among ACC patients. The functional role of some stochastic miRNAs determined in ACC was additionally investigated. Transcriptomic profiling of miRNAs is not limited exclusively to classification but also for predicting clinical outcome in ACC.

Paper IV also explores miRNA-based transcriptomics for classifying the most common ACA phenotypes: cortisol-producing adenoma (CPA), APA and non-hyperfunctioning adenoma (NHFA). CPA and APA clustered separately from each other, when NHFA were excluded. Moreover, NHFA were spread out in these two clusters. Certain miRNAs were specific mainly among hyperfunctioning ACA. Specific miRNAs associated with different tumour phenotypes.

Keywords: Adrenocortical tumours, adrenocortical adenoma, adrenocortical carcinoma, RNA expression, microRNA, non-hyperfunctioning, cortisol-producing adenoma, aldosterone-producing adenoma, tumour phenotype.

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