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Genetics of papillary renal cell tumours and related neoplasms

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Papillary RCT has been described as a genetic entity displaying trisomies of chromosomes 3q, 7, 8q, 12q, 16q, 17, and 20 and loss of the Y chromosome by my supervisor. He has also called the attention to the correlation of precursor lesions of embryonal origin and development of papillary RCTs.

During my work on papillary and related RCTs, I have applied microsatellite, BAC- and oligo-array technology to detect highly specific genomic changes. Comparing the basic genetic alterations of trisomies of chromosome 7 and 17 and morphological variation of papillary RCTs I have confirmed the original description that papillary RCT is a genetically well-defined entity. It was suggested earlier by my supervisor that papillary RCAs are characterised by trisomy 7 and 17, and that papillary RCCs acquire additional trisomies of 3q, 8q, 12q, 16q, and 20. My study, by comparing the genetic alterations, morphological variations and clinical outcome of the disease, revealed a strong correlation between duplication of chromosome 1q (and expression of KIF14) and fatal outcome of the disease. Trisomy of chromosome 1q and monosomy of -6q, -9p, -14q are progression associated markers irrespectively of the cytomorphological variation of tumours.

I have detected smaller DNA alterations in papillary RCTs at several autosomes including chromosome 17q12 and also at the homologous Xq21.3-Yp11.2 block. The transcription factor HNF1B from chromosome 17q12 region may be one of the candidate genes, the overexpression of which is instrumental in the disturbance of normal tubular differentiation and hence in the persistence of nephrogenic rest-like lesions and development of papillary RCAs. The PCDH11 gene from the Xq21.3-Yp11.2 block is a good candidate for papillary

RCTs, but the lack of appropriate antibody makes it impossible to confirm its role in the development of normal embryonal kidney and papillary RCTs.

The results of global gene expression analysis using the Affymetrix platform were disappointing. Although we found a differential expression profile for distinct genetic types of RCTs, such as conventional, papillary and chromophobe RCCs and renal oncocytomas, and also for papillary RCTs with and without fatal progression, only few of the genes were confirmed by real time RT-PCR analysis and practically none of them expressed exclusively in the target group of tumours when analysed by immunohistochemistry.

I have confirmed the specific genetic changes in MTSCC and excluded the occurrence of small genomic changes by high resolution oligo-array analysis. Moreover, I have excluded the genomic alterations in MAs by using the same platform. The differences in genetic alterations of the three types of tumours, papillary RCTs, MTSCC, and MA with overlapping histological pattern may be helpful in the differential diagnosis.

Applying immunohistochemistry (KRT7, KRT8, KRT18, KRT19, WT1, and HNF1B) to analyse the precursor lesions of Wilms' tumours, papillary RCTs and MTSCCs separated two distinct types of precursors with distinct immunoprofile: one for Wilms' tumour (positive for WT1, negative for KRT7 and HNF1B) and another for papillary RCTs, and MTSCCs (negative for WT1 and positive for KRT7 and HNF1B). These findings modified our original hypothesis that Wilms' tumour, papillary RCT, and MTSCC develop from the same type of precursor lesions, which persist after cessation of the development of normal kidney.