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Involvement of multiple loci on chromosome 3 in renal cell cancer development

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SUMMARY

Genetic aberrations frequently occurring in a specific tumour type are thought to play an important role in the development of these tumours. Losses of specific chromosomal regions may point to regions containing tumour suppressor genes, whereas amplified regions may point to regions containing oncogenes. In renal cell tumours (RCT) loss of the short arm of chromosome 3 is detected frequently, which suggests the presence of (a) tumour suppressor gene(s) involved in the development of these specific tumours. This thesis describes an analysis of the role of different loci on chromosome 3 in the development of sporadic and hereditary RCT.

Chapter 1 presents a review of the literature with respect to the genetic characterisation of RCT. Loss of the short arm of chromosome 3 is clearly specific for the non-papillary/clear cell subtype of renal cell carcinoma (RCC). In the other RCT subtypes loss of chromosome 3 material is only rarely observed. Most likely, development of these tumours is caused by other genetic aberrations. The review focusses on the role of the different loci on 3p that have been suggested to be involved in RCC development.

Three cases of hereditary clear cell RCC have been published each with a constitutional translocation involving chromosome 3 and another chromosome. It has been suggested that the translocation might have inactivated a tumour suppressor gene on chromosome 3, thus causing a hereditary predisposition to cancer. One of the chromosome 3 breakpoints was mapped to the q-arm, the two other breakpoints to the p-arm. By FISH analysis we could clearly demonstrate that these two breakpoints were also different from each other (Chapter 2). Reports describing the analysis of several tumours in each of the three cases had revealed that the translocation chromosome which contained the p-arm and not the normal chromosome 3 homologue was always lost, in disagreement with the usual tumour suppressor model. Loss of heterozygosity analysis (LOH) in sporadic RCC indicated in addition that these breakpoint regions were not included in a smallest region of overlap (SRO) of heterozygous deletions (Chapters 1 and 5), implying that most likely these breakpoint regions do not harbor genes important in RCC development. However, a recently isolated gene (*FHIT*) crossing this breakpoint was reported to have abnormal-sized transcripts in a variety of primary tumours and cancer cell lines (although not including RCC), thus suggesting a kind of a general role of this gene in cancer development. Our analysis of RCC-derived cell lines and a great number of control tissues and cell lines showed that the presence of abnormal-sized transcripts is certainly not cancer-specific and thus should be explained by a mechanism independent of tumour development (Chapter 3). This excludes at least a major role of *FHIT* in RCC development.

A great number of polymorphic markers on 3p are available for LOH analysis. From the literature the order of these markers is, however, not always clear. For some markers contradicting data have been published. Chapter 4 presents the ordering of a number of polymorphic 3p21 probes by a combined genetic, FISH and deletion hybrid mapping

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approach. Most of these markers and an additional number together covering the whole p-arm of chromosome 3, have been used in an extensive LOH analysis of sporadic RCC (Chapter 5). This revealed that if 3p deletions were present, the 3p21 region was always included in combination with either the 3p25 region, or the 3p12-p14 region, or both. The 3p21 region thus seems to play a major role in the development of RCC. In four renal cell adenomas (RCA) from three unrelated patients with multifocal RCT allelic losses of only 3p25 or 3p12-p14 sequences were detected (Chapter 6). Together with the results of the LOH analysis of sporadic RCC, this might indicate that allelic losses of the 3p25 region or the 3p12-p14 region are associated with the more benign renal cell adenomas, whereas allelic loss of the 3p21 region is a prerequisite for malignant development of clear cell tumours.