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INVITED EDITORIAL

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The genetic make-up of renal cell tumors

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Abstract Recent developments in (molecular) genetics have led to a better understanding of renal tumor biology. The current knowledge of the genetics of benign as well as malignant renal tumors is discussed briefly. This knowledge may, in the near future, be used to more accurately diagnose these tumors and also to optimalize individually based therapy.

Keywords Kidney · Neoplasms · Genetics · Pathology

At the end of the 19th century, Grawitz published the first classification of renal tumors. This classification was based on the erroneous assumption that renal tumors are derived from an ectopic adrenal rest. This assumption was subsequently adopted by others which led to the confusing term hypernephroma. Even nowadays, a tumor that should be classified as a renal cell carcinoma (RCC) is still often termed a 'Grawitz' tumor.

Histologically, the kidney is a very complex organ composed of a large number of cell types. It is therefore not surprising that many different tumors, either benign or malignant, may develop in it. During the last decades, several authors have tried to classify renal tumors based on, for example, origin within the kidney, radiological appearance or cellular characteristics. Recent developments in genetics and molecular biology have led to an increasing knowledge of the origin and biology of these tumors. In 1997, the Union Internationale Contre le Cancer (UICC) and the American Joint Committee on Cancer (AJCC) adopted a new histopathological classification which was, among others, based on genetic characteristics [15] (Table 1). The following discussion will follow this classification, but will focus mainly on malignant tumors. Table 1 also shows the most characteristic genetic findings (if known). For most renal tumor types, familial (either hereditary or not) and sporadic forms exist. Most of the knowledge of the molecular genetics of RCC was originally derived from studies on familial forms. In subsequent studies, it was often found that these mechanisms may also play a role in the sporadic forms of the disease.

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Renal tumor genetics

Hereditary conventional (clear cell) RCC

The genetics, both at the chromosomal and molecular levels, has been studied most extensively in conventional RCC as this is the most frequently occurring renal tumor.

Von Hippel-Lindau (VHL) disease is a rare familial tumor syndrome (incidence 1 in 36,000) in which patients develop multiple tumors at an early age in several organs (kidney, cerebellum, spine, retina, epididymis). The kidney tumors in these patients are uniformly of the conventional type and are typically bilateral and multifocal. The disease is caused by a germ-line mutation in the VHL gene, a tumor-suppressor gene located on chromosome 3p25 [4, 5, 13]. Recently, other genetic defects have been found in the tumors of VHL patients and even differences between several tumors within one patient could be identified [7]. These findings may point to downstream VHL effects but may also reflect the genetic instability of malignant tumors, which acquire increasing genetic defects during tumor progression.

A number of families with hereditary conventional RCC, but without the VHL mutation, have been described. These families carried a germ line chromosomal translocation [t(3;2), t(3;6), t(3;8)] with the breakpoint on a region of chromosome 3p (3p 13-p 14.2) apart from the VHL locus.

Table 1 UICC and AJCC classification of renal tumors and 'typical' genetic findings. $^{(*)}+$ C4 indicates chromosomal gain, – indicates chromosomal loss

UICC and AJCC classification of renal tumors	'Typical' genetic findings
Benign neoplasms	
1. Oncocytoma	Several patterns
2. Papillary adenoma	7+(*), U+, Y–$^{(*)}$
3. Metanephric adenoma	Not known
Malignant neoplasms	
1. Conventional (clear cell) carcinoma	VHL inactivation, 3p LOH
2. Papillary renal carcinoma	c-met mutation or gain, 7+, U+, Y–
3. Chromophobe renal carcinoma	Near haploid, 17p 11.2(?)
4. Collecting duct carcinoma	Not known
5. Renal cell carcinoma unclassified	

Sporadic conventional RCC

Many studies have shown that a loss of heterozygosity (LOH) at the VHL locus frequently occurs in sporadic conventional RCC [17]. The remaining allele may either be mutated or inactivated, for example by hypermethylation of the promotor region, resulting in loss of the suppressor function of the gene. VHL inactivation by either mechanism occurs frequently (in about 50%–75% of the tumors) and there is strong evidence that it is an early event in the development of conventional RCC. The exact function of the VHL gene still remains to be defined, but one of the established effects of the loss of VHL function is an increased expression of transforming growth factor α (TGFα), which may cause the unbalanced proliferation that is characteristic for malignancy. Indeed, increased TGFα expression has been found in up to 60% of conventional RCC.

Other studies have shown that besides the VHL locus, other regions on chromosome 3p (3p12–14, 3p21.2-p21.3 and 3p25–p26 containing the VHL locus) may play an important role in tumor formation [2]. The fragile histidine triad (FHIT) gene is located on chromosome 3p14.2 and contains the 3p breakpoint of one of the families with non-VHL hereditary conventional RCC. However, conflicting results have been published on the putative role of FHIT in sporadic conventional RCC. In the near future, it is likely that one or more tumor suppressor genes will be identified in these regions.

As mentioned above, during progression, malignant tumors tend to acquire more and more genetic abnormalities. Many authors have found that allelic loss of many chromosomes or parts of chromosomes is associated with advanced conventional RCC, among which 8p, 9p, 11p, 13q, 14q and 17p have been recognised. At the gene level, this correlated with the expression or loss of expression of several proto-oncogenes and tumor suppressor genes (c-jun, bcl-2, c-myc, p53, vascular endothelial growth factor and many others).

Hereditary papillary RCC

As in VHL, patients with hereditary papillary RCC have bilateral multifocal renal tumors. However, LOH at the VHL locus has not been found in these tumors. At the chromosomal level, trisomy of chromosomes 7 and 17 and the loss of the Y chromosome were found and appear to be early steps. Subsequent studies identified a proto-oncogene at 7q31 (cmet) which is mutated in patients with hereditary papillary RCC [3]. The c-met gene codes for the cellular receptor of the hepatocyte growth factor (HGF). HGF is a mitogen in many tissues and the mutant HGF receptors in patients with hereditary papillary RCC are constitutively active, giving rise to a continuous mitogenic signal. Experimental studies have shown that in vitro transfection of mutant c-met transformed non-tumor cells to tumor cells which were subsequently tumorigenic in nude mice [9, 10, 18]. This indicates that c-met expression is an early step in tumorigenesis. Families with familial papillary RCC, but without c-met mutations, have been identified. No clear genetic defect has as yet been identified in these families.

Sporadic papillary RCC

Although c-met mutations have been found in sporadic papillary RCC, this appears to be an infrequent finding [8]. In these tumors, a two- to threefold gain of chromosome 7 or the 7q31 region is often found. If this indeed leads to increased HGF-receptor expression, it may explain the similarities between the hereditary and sporadic forms of this tumor. LOH at the VHL locus has not been found in sporadic papillary RCC, but loss of 1p, 6q, 9p, Y and Xp has been demonstrated. As in the hereditary form, gains of chromosomes 7 and 17 have also been found. Because papillary RCC and papillary adenoma show many histological similarities, and also often show the same chromosome alterations, it has been suggested that papillary adenoma represents an early form of papillary RCC.

In a subset of papillary RCC (eosinophilic papillary RCC), a somatic translocation between chromosomes 1 and X (t(X; 1)(p1 1.2;q2 1)) has been found [16]. The breakpoint Xp11.2 contains, among others, a transcription factor TFE3. The translocation leads to the formation of two fusion genes (designated TFE3PRCC and PRCCTFE3) and the loss of TFE3 expression [1, 12, 14]. This suggests that TFE3 is a tumor suppressor gene.

Familial chromophobe RCC

Recently the Birt-Hogg-Dubé syndrome has been described [11]. This is an autosomal, inherited disease characterized by the development of multiple, different, benign skin tumors and possibly also of lung cysts and spontaneous pneumothorax. These patients also develop multifocal, bilateral renal tumors, mostly of the

chromophobe type, although conventional RCC, oncocytomas and mixed tumors have also been found. The disease has very recently been mapped to 17p11.2 and future studies will probably identify the gene responsible [11].

Sporadic chromophobe RCC

Chromophobe RCC is characterized by a near haploid genome with frequent losses of chromosomes 1, 2, 6, 10, 13, 17 and 21 [8]. LOH in 3p has also been found in about 25% of the tumors, but VHL inactivation appears to be rare. Because many chromosomal abnormalities have been found, it is difficult to find 'the' gene which is responsible for this particular tumor type, although mapping the Birt-Hogg-Dubé syndrome to 17pl 1.2 may prove a big step forward in the near future.

Collecting duct RCC

At present, there is too little literature to identify a genetic pattern that is specific for collecting duct RCC. Loss of chromosomes 18, 21 and Y and gain of chromosomes 7, 12, 17 and 20 have been reported. LOH has been found at 1q, 6p, 8p, 13q and 21q. Conflicting results have been published on 3p LOH.

Benign tumors

Knowledge of the (molecular) genetics of most benign renal tumors is limited compared to their malignant counterparts. The main reason is probably that less patient tissue is available because benign tumors are usually not operated on. Genetic knowledge is only available on oncocytomas and papillary adenomas. The latter has already been mentioned under papillary RCC.

Oncocytoma

A familial form of oncocytoma exists, characterized by the occurrence of multiple, small, bilateral oncocytomas. There is no literature on the genetics of this tumor. In sporadic oncocytomas, three distinct patterns can be recognized: (1) loss of chromosome 1 or Y, (2) translocations with the breakpoint in 11q13 and (3) heterogenous abnormalities such as the gain and/or loss of several chromosomes, gain of chromosomes 1, 7, 12 or 14 and LOH at 3p, 10q, 17p and 17q [17]. VHL mutations have been described in sporadic oncocytomas, but not in familial tumors.

Clinical implications

A better understanding of the genetic and molecular events which take place during tumorigenesis and tumor progression may have important clinical implications in the future:

1. It may help to establish the exact diagnosis in cases were this cannot be accomplished by routine histology.
2. In families with familial or hereditary RCC it may be used to establish a diagnosis at an earlier age which may lead to better treatment strategies.
3. It may yield prognostic information that may guide optimal therapy, although only few studies have been performed on this subject so far.
4. Specific genetic disturbances (like an oncogene mutation or tumorsuppressor gene inactivation) might be the target for gene-therapy. It should be noted, however, that it is not one genetic defect which causes a malignancy. It is possible that correction of a VHL mutation in a conventional RCC patient will not be curative because all kinds of 'down-stream' effects function in an autonomous way, independently of VHL function.

In conclusion, knowledge of the (molecular) genetics of renal tumors is expanding rapidly and may lead to important changes for the clinical care of patients with these tumors in the near future [6].

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