Epidemiology, Aetiology, and Pathogenesis of Renal Cell Carcinoma

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Abstract

Significant advances in molecular medicine have made renal cell carcinoma (RCC) the prototype solid organ malignancy for targeted medical cancer treatment. These new options have made it possible to prolong the life of patients with metastatic disease. However, we are far from thoroughly understanding the molecular processes of RCC development let alone from being able to cure advanced renal cancer. RCC is the most common renal neoplasia and it remains a very aggressive and often fatal disease.

There are several known histologic subtypes of this heterogeneous tumor entity with associated distinct molecular alterations and different clinical outcomes [1–4]. The clear cell renal cell carcinoma (ccRCC) is the most common and apparently most aggressive RCC subtype with the highest rates of local invasion, metastasis and mortality. It constitutes 70–80% of all renal cancers [1,5]. It is estimated that more than 30% of patients with RCC have metastatic disease at the time of diagnosis and 30% of organ-confined RCCs will develop metastatic disease after local treatment [6]. Thus, RCC remains a very major challenge.

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1. Introduction

Significant advances in molecular medicine have made renal cell carcinoma (RCC) the prototype solid organ malignancy for targeted medical cancer treatment. These new options have made it possible to prolong the life of patients with metastatic disease. However, we are far from thoroughly understanding the molecular processes of RCC development, let alone being able to cure advanced renal cancer. RCC is the most common renal neoplasia, and it remains a very aggressive and often fatal disease.

There are several known histologic subtypes of this heterogeneous tumour entity with associated distinct molecular alterations and different clinical outcomes [1–4]. Clear cell renal cell carcinoma (ccRCC) is the most common and apparently the most aggressive RCC subtype with the highest rates of local invasion, metastasis, and mortality. It constitutes 70–80% of all renal cancers [1,5]. It is estimated that >30% of patients with RCC have metastatic disease at the time of diagnosis, and 30% of patients with organ-confined RCCs develop metastatic disease after local treatment [6]. Thus, RCC remains a very major challenge.

2. Frequency

RCC overall accounts for 2% of all adult malignancies [7]. Worldwide, based on probably incomplete figures, about 270 000 new cases are diagnosed per year, and about 116 000 patients die per year [8]. In the United States alone, 58 000 new RCC cases were diagnosed in 2010, and approximately 13 000 patients died of RCC in the same year [7,9]. This corresponds to 65 000 new RCC cases per year in the European Union with >25 000 RCC deaths every year [10].
Thus at least 20–40% of patients diagnosed with RCC die of the disease.

Overall, there are some geographic, racial, and gender differences in the incidence of RCC. RCC occurs more than twice as often in men as in women. In Europe, the highest incidence is seen in the eastern parts of Europe; Portugal and Spain report the lowest incidence (Fig. 1). The reasons for this distribution are unclear. The overall incidence rate for Europe is estimated at 14.5 per 100,000 for men and 6.9 per 100,000 for women [10].

There are some indications that a recent increase in incidence together with a stage shift to more organ-confined stages can be observed [11,12]. An apparent stage shift is mainly attributed to a more widespread use of imaging for early detection.

3. Mortality

The mortality from RCC has continually decreased over the last decades. A recent analysis showed a decline in mortality rates (death from RCC per unit of the population) from 4.8 per 100,000 in the period 1990–1994 to 4.1 per 100,000 in 2000–2004 in men [10]. This decline in RCC mortality is also attributed to earlier and the often incidental diagnosis of small RCCs by imaging.

The mortality rates vary, however, among different European countries (Fig. 1). There is no clear explanation for this other than perhaps differences in the use of imaging techniques. As a consequence of the decrease in mortality rates, the 5-yr survival after RCC treatment has increased [13–15].

4. Aetiology

It is poorly understood why people develop RCC. Only a few aetiologic factors have been clinically identified as risk factors for RCC. In contrast, the understanding of some important molecular and genetic factors of RCC development has increased considerably.

4.1. Demographic factors

Age, sex, and race are important factors in RCC development. The incidence of RCC correlates with age, and the highest incidence is found in the sixth and seventh decades. About 80% of all RCC patients are between 40 and 69 yr of age [16]. Due to the increasing life expectancy in many countries and increased early diagnosis, the peak age of RCC diagnosis might shift still further into the seventh and eighth decades of life.
RCC is less common in Asia than in Europe or North America. Asian populations in the United States also show a lower risk of developing RCC [6]. Although the reported incidence rate of RCC in Africa is also relatively low, African Americans in the United States have a higher incidence of RCC compared with the US white population [6,16,17]. This may well be multifactorial, and it is presumably related to the lower rates of imaging use and early RCC diagnosis in African countries.

4.2. Toxic substances

Cigarette smoking has been shown to be a significant risk factor for the development of RCC. A meta-analysis described a significantly higher risk for ever smoking compared with never smoking [18]. The risk for renal cancer increased by 54% in men and 22% in women who ever were smokers. A clear correlation between high doses of tobacco smoke and a higher risk was shown [18]. Due to the limited data available, the influence of smoking cessation for a potential risk reduction as well as the potential risk of passive smoking remain unclear [18,19].

Several studies in the 1990s examined occupational toxicities. An international case-control study demonstrated an increased risk for RCC in people in industries working with cadmium (relative risk [RR]: 2.0), coke ovens (RR: 1.7), steel (RR: 1.6), and gasoline/petroleum (RR: 1.6) [20,21]. In contrast, other studies failed to show an increased risk for diesel and gasoline exposure or for European asphalt workers [22,22].

Trichloroethylene (TCE) exposure leads to carcinogenesis in animal models. Although some studies found an increased RCC risk in populations with high TCE exposure [10,23], other studies did not confirm this finding. The exposure to perchloroethylene does not seem to be associated with an increased risk [24].

Regarding pesticides, a significantly increased risk for RCC development was reported in a recent case-control study. Supporting this, a higher risk for RCC was reported in Asian agricultural workers [25].

4.3. Obesity and nutritional factors

Several case-control and cohort studies have demonstrated an increased risk for RCC in association with excess body weight. An estimated increased risk of 1.24 in men and 1.34 in women per 5 kg/m² increase in body mass index was reported in a meta-analysis of prospective studies [26].

Regarding nutritional factors, there is no reported association between protein and fat consumption and the risk of RCC [27]. Vitamins or other supplements did not show any influence on the incidence either [10]. Only one case-control study in 2009 reported a possible role of a genetic polymorphism of the vitamin D receptor gene for the risk of RCC [28]. Whether this really relates to nutritional factors is not clear.

Several large studies have examined dietary habits [10]. Only one study reported an inverse association between fruit and vegetable consumption and the incidence of RCC [29]; two other studies failed to show such a correlation [30,31]. There are only insignificant data for fish and meat consumption in relation to RCC risk. Coffee consumption as well as total fluid intake is not associated with an increased risk. However, several studies demonstrated a significant association between moderate alcohol consumption and an increased risk of RCC.

5. Genetic changes in renal cancer

Because several hereditary RCC syndromes are known (Table 1), genetic and epigenetic changes in the carcinogenesis of renal cancer are strongly suspected [32].

5.1. The hypoxia inducible factors pathway in clear cell renal cell carcinoma and the von Hippel-Lindau syndrome

The genetic association of RCC associated with the von Hippel-Lindau (VHL) gene with chromosomal loss in 3p25–26 was found in 1993 [33]. Mutations of the VHL gene were also found in 60–80% of sporadic RCC [34]. The hereditary VHL syndrome leads to hemangioblastomas of

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Gene (chromosome)</th>
<th>Tumour type</th>
<th>Extrarenal manifestation</th>
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<tbody>
<tr>
<td>Von Hippel-Lindau</td>
<td>VHL (3p25)</td>
<td>Multiple, bilateral ccRCC, renal cysts</td>
<td>Hemangioblastoma of retina and central nervous system, phaeochromocytoma, neuroendocrine tumours, pancreatic, renal, epididymal, and parametrical cysts</td>
</tr>
<tr>
<td>Hereditary papillary RCC and RCC</td>
<td>c-MET (7p31)</td>
<td>Multiple, bilateral papillary RCC type 1</td>
<td>Papillary RCC type 2</td>
</tr>
<tr>
<td>Hereditary leiomyomatosis</td>
<td>Fumarate</td>
<td>Multiple, bilateral papillary RCC type 1</td>
<td>Papillary RCC type 2</td>
</tr>
<tr>
<td>Birt-Hogg-Dubé</td>
<td>Hydratase (1q42)</td>
<td>Papillary RCC type 2</td>
<td>Papillary RCC type 2</td>
</tr>
<tr>
<td>Tuberous sclerosis</td>
<td>TSC1 (9q34)</td>
<td>Multiple, bilateral angiomylipomas, lymphangioleiomyomatosis, rare ccRCC</td>
<td>Papillary RCC type 2</td>
</tr>
<tr>
<td>Constitutional translocation</td>
<td>TSC2 (16p13)</td>
<td>Multiple, bilateral ccRCC</td>
<td>Papillary RCC type 2</td>
</tr>
<tr>
<td>(familial ccRCC)</td>
<td>3p translocation</td>
<td>Multiple, bilateral ccRCC</td>
<td>Papillary RCC type 2</td>
</tr>
</tbody>
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ccRCC = clear cell renal cell carcinoma.
the central nervous system; retinal angiomas; benign tumours of the inner ear, pancreas, and epididymis; and pheochromocytomas [35].

The VHL protein is a tumour suppressor, which is one component of the E3 ubiquitin-ligase complex [36,37]. Under normal functional conditions (without mutations) and a normoxic cell situation, the VHL complex targets the hypoxia inducible factor (HIF) transcription factors [37]. HIF1α in particular regulates important downstream targets such as vascular endothelial growth factor (VEGF), platelet-derived growth factor, and glucose transporter 1 [37]. As a result of VHL gene mutations, HIF accumulates and leads to a massive stimulation of growth factors (Fig. 2). Interestingly, HIF1α synthesis is inhibited by the multikinase inhibitor sunitinib [36].

5.2. The mesenchymal-epithelial transition pathway and hereditary papillary renal cell carcinoma

The proto-oncogene mesenchymal-epithelial transition (MET) encodes a tyrosine kinase membrane receptor [36]. The ligand is the hepatocyte growth factor (HGF). The MET gene is located at chromosome 7q31. Gain-of-function mutations result in a consecutive activation of the receptor [38,39]. The activation of the signalling cascade results in multiple tumourigenic processes (eg, angiogenesis). The hereditary papillary RCC syndrome is characterised by bilateral multifocal papillary type 1 tumours. Interestingly, up to 75% of sporadic papillary RCCs show trisomy 7 [40]. Multikinase inhibitors and anti-HGF antibodies are potentially valuable for the future treatment of papillary RCC [36].

5.3. The fumarate hydratase gene and the hereditary leiomyomatosis renal cell carcinoma

Mutations in the fumarate hydratase gene (FH), located at chromosome 1q42, are found in patients with hereditary leiomyomatosis RCC [37]. FH is a tumour suppressor gene encoding an important enzyme of the carbohydrate metabolism of the cell (tricarboxylic acid cycle). Due to derangement of the mitochondrial conversion of fumarate to malate, fumarate is overaccumulated, and hypoxia leads to upregulation of HIF [36,41]. A minority of patients with FH mutations develop papillary type 2 RCC or collecting duct tumours that are very aggressive [42]. Other typical problems of hereditary leiomyomatosis are cutaneous leiomyomas and, in women, early multiple leiomyomas of the uterus [10].

5.4. The folliculin gene and the Birt-Hogg-Dubé syndrome

Birt-Hogg-Dubé (BHD) syndrome is characterised by loss-of-function mutations in the folliculin gene (FLCN) at chromosome 17p11.2. Renal tumours of BHD show variable histology like chromophobe RCC, ccRCC, oncocytoma, and oncocytic-chromophobe hybrid [37,43].

The function of the protein folliculin is not completely known [36]. Inactivation of the FLCN gene leads to polycystic kidney degeneration and renal tumours in mouse models. A tumour suppressor function has been discussed [44,45]. An interaction of FLCN with the mammalian target of rapamycin complex 1 (mTORC1) may play an important role in nutrient and energy sensing of cells [44,45]. Loss of FLCN function was shown to be associated with mTORC1
activity during renal tumourigenesis [45–47]. This fact promises a potential therapeutic role for mTOR inhibitors in RCC with FLCN gene mutations [36].

5.5. The phosphatidylinositol-3-kinase/Akt pathway

The phosphatidylinositol-3-kinase/Akt messenger system is important for the regulation of different cellular processes of survival and cell cycle regulation. One important target again is mTOR [36,48]. The Akt–mTOR interaction is mediated by the tuberous sclerosis heterodimer protein complex, which suppresses mTOR activity [36]. Changes in the phosphatidylinositol-3-kinase/Akt pathway are known to be involved in the oncogenesis of many carcinomas [47].

5.6. The mammalian target of rapamycin pathway

mTOR is a multifunctional serine-threonine kinase that plays a central role in the regulation of cell growth, proliferation, apoptosis, and metabolism of the cell. Consequently, mTOR is also involved in renal carcinogenesis by the modulation of expression and stability of oncogenic proteins such as HIF, VEGF, cyclin D, and c-MYC [49,50]. mTOR forms multimolecular complexes with raptor (regulatory-associated protein of mTOR) to form mTORC1 and with rictor (rapamycin-insensitive companion of mTOR) to form another multimolecular complex named mTORC2. The activation of mTOR results from the phosphatidylinositol 3-kinase (PI3K) pathway by growth factors receptors such as epidermal growth factor receptor (EGFR) or insulin-like growth factor receptor (IGFR). The activated mTORC1 complex phosphorylates its downstream effectors, for example, eukaryotic translation initiation factor 4E-binding protein (4E-BP1) and S6 kinase 1 (S6K1). This mTOR activation downstream leads to an increased translation of messenger RNA and protein biosynthesis, increasing metabolism and energy balance as well as decreasing autophagy (Fig. 3) [51,52].

5.7. Other genetic aberrations

Constitutional chromosome 3 translocations are also found in patients with familial RCC. Potential tumour suppressor genes of this area are FHIT, LSAMP, NORE1, and FBXW7 [53].

The tuberous sclerosis complex (TSC) is associated with inactivating mutations of TSC1 at 9q34 (hamartin) or of TSC2 at 16p13.3 (tuberin). TSC1 and TSC2 inhibit mTOR, and therefore these patients show an increased risk for RCCs [53,54].

Other frequently mutated genes in RCC are RAS, BRAF, p53, pRB (retinoblastoma), cyclin-dependent kinase inhibitor 2A (CDKN2A), PTEN, and ERBB2 [53,55]. Further frequent alterations are found at chromosomes 5q, 7, 1p, 4, 9, 13q, and 14q [53,56].

5.8. Epigenetic alterations in renal cell carcinoma

5.8.1. DNA hypermethylation

DNA hypermethylation around the promoter regions silences tumour suppressor genes and therefore plays an important role in carcinogenesis and tumour progression. The number of candidate genes silenced by DNA hypermethylation in RCC is rising [53]. Data suggest that the average number of methylated genes is higher in VHL
wild-type tumours than in VHL-mutated tumours. The Ras association domain family member 1 (RASSF1), twist homolog 1 (TWIST1), cadherin 13 (CDH13), matrix metalloproteinase 2 (MMP2), and tumour suppressor candidate 3 (TUSC3) are frequently methylated in sporadic RCC with wild-type VHL. Proapoptotic genes are also often hypermethylated (eg, APAF1 and DAPK1) [53,57]. Wnt antagonists (SFRP1/2/5, WIF1, and DKK3) frequently show hypermethylation [58,59]. Other candidate genes are UCHL-1, TGFBR3, GATA3, TIMP3, FHIT, BIK, TU3A, and XAF1 [53].

5.8.2. Histone modifications

The role of histone modifications in RCC remains unclear. The levels of H3K4 methylation seem to be associated with the prognosis of RCCs as well as the role of H3K27 as previously reported [60,61]. Further mutations in the histone methyltransferase and demethylase encoding genes were described in RCC [53,55].

6. Individualised molecular approach

The molecular characterisation of individual RCC may potentially be useful for the better individual assessment of prognosis, and the identification of biomarkers and targets of specific treatments may eventually help improve treatment. Despite advances in targeted therapies that allow a prolongation of overall survival in patients with metastatic disease, improvements in individualised diagnosis and prognosis would be desirable [62–64].

Nevertheless, considerable progress has been made in the understanding and characterisation of metastatic disease progression, especially in ccRCC, by microarray expression profiling analyses [65–67]. However, currently there are no biomarkers for established daily clinical use in a diagnostic, prognostic, and/or predictive individualised setting for RCC. In spite of everything, there are still a lot of variations between the extensive published data and a lack of consistency due to the technologies and experimental set-ups associated with differences of the applied biostatistic analytic algorithms. The challenge of analysing the molecular nature of RCC by gene expression profiling consists of the meaningful analysis of the mass of data obtained. At present, the problem seems no longer related to obtaining gene expression profiles but to the interpretation of the results [68]. The creation of a useful and robust workflow for standardising the statistical interpretation provides an opportunity to reduce this problem. A systematic approach such as warranted by the recently described gene set enrichment analysis (GSEA) is clearly needed to analyze raw data from microarray analyses in an effective way with consideration to the complexity of tumour biology [69,70]. GSEA provides numerous sets of genes with similar function and affiliation to certain cellular subunits or molecular pathways by integrating information from manually accumulated databases with large-scale expression data. However, several genes have been repeatedly reported as deregulated in RCC but still with considerable variation and a lack of consistency between published data.

<table>
<thead>
<tr>
<th>Table 2 – Potential future marker profile for renal cell carcinomas</th>
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<tr>
<td>Hypoxia inducible</td>
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<tr>
<td>CA IX</td>
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<td>CA XII</td>
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<tr>
<td>CXCR4</td>
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<td>VEGF</td>
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<td>IGF-1</td>
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<tr>
<td>Proliferation</td>
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<td>Ki-67</td>
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<td>Anilin</td>
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<td>GST</td>
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PTEN = phosphatase and tensin homologue; VEGF = vascular endothelial growth factor; IGFL = insulin-like growth factor; GST = glutathione-S-transferase.

* Modified according to references Jones et al. [65], Marusichle et al. [68], Lam et al. [71], and Eichelberg [72].

7. Conclusions

Due to the complex processes of tumour development, progression, and metastatic behaviour of RCC, it is not feasible to get only a few established single biomarkers for clinical application. Prospectively, there will rather be a whole panel of genes generated with respect to the different cellular functions and to the special indication in a predictive, diagnostic, or therapeutic manner (Table 2) [71,72].

Conflicts of interest

The authors have nothing to disclose.

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References


