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Papillary renal cell carcinoma: A review of the current therapeutic landscape

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Abstract

Renal cell carcinoma (RCC) is the most common cancer of the kidney and accounts for 2–3% of all adult malignancies. Clear cell carcinoma represents the most common histologic subtype, while papillary Renal Cell Carcinoma (pRCC) accounts for 10–20% of all renal cell cancers. While the inactivation of VHL gene can be found in the majority of clear cell carcinomas, different molecular mechanisms are involved into pRCC biology. Mutations in the MET oncogene are an essential step into the pathogenesis of hereditary pRCC forms, but they can be found only in a small rate of sporadic cases. Several agents, including anti-VEGF drugs and mTOR inhibitors, are possible options in the

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treatment of advanced and metastatic pRCC, following the demonstration of efficacy obtained in clinical trials including all RCC histologic subtypes. However, data specifically obtained in the subgroup of patients affected by pRCC are limited and not conclusive. Several ongoing trials are evaluating the efficacy of targeted therapy in papillary form. However, more rationale approaches based on molecular studies would help improving the outcome of these patients. Among others, MET inhibitors and targeted immunotherapy are promising new strategies for hereditary and sporadic disease. This review summarizes current knowledge on pRCC tumorigenesis and discusses recent and ongoing clinical trials with new therapeutic agents.

Keywords: Papillary renal cell carcinoma; MET mutations; MET inhibitors; Targeted immunotherapy

1. Introduction

Renal cell carcinoma (RCC) is the most common cancer of the kidney and accounts for 2–3% of all adult malignancies [1]. RCC types can be differentiated on the basis of histological and genetic features. The most common histological subtype is clear cell carcinoma (70–80%), while papillary (10–20%) and cromophobe (5%) types represent the remaining 20–30% of cases. Usually, papillary renal cell carcinoma (pRCC) occurs in sporadic forms, while it is estimated that only 4% of renal cancers are familial [2]. From a clinical point of view, presentation of patients with pRCC is similar to other renal histologies. Clinical symptoms such as hematuria, flank pain and a palpable abdominal mass are usually associated with advanced stage presentation, but this classic triad is now rare (6–10%) and correlates with aggressive histology. A few patients present at diagnosis with symptoms caused by metastatic disease, such as pain related to bone metastases or persistent cough due to lung metastases. Early diagnosis is quite unusual, and the majority of cases are diagnosed in locally advanced stage or metastatic disease. Surgery remains the cornerstone treatment for localized disease, although recurrence occurs in approximately 40% of the surgically resected patients. In advanced stages, cytotoxic chemotherapy and immunotherapy have been widely used in the past, although with limited efficacy [3].

Several studies on hereditary cancers have shown the role of specific genetic mechanisms in cancer pathogenesis. Molecular therapies targeting these abnormalities have been developed with a clinically meaningful improvement of the efficacy outcomes. However, as for the different histologic subtypes of RCC, the more convincing data have been generated for the clear cell type whereas treatment of non-clear cell RCC is still based on less solid data and a lower level of evidence.

2. Clear cell carcinoma

The biology of clear cell RCC (ccRCC) has been well studied, in both hereditary and sporadic forms, and the greatest amount of evidence about the activity and efficacy of molecularly targeted agents in patients with RCC has been produced in this common histologic subtype. Germline mutations in the *VHL* tumor suppressor gene (TSG) are responsible of the autosomal dominantly inherited disorder von Hippel–Lindau disease (VHL). VHL mutations predispose to the development of a variety of tumors (most commonly retinal and central nervous system haemangioblastomas, clear cell RCC and phaeochromocytomas) [4].

Sporadic ccRCCs have shown biallelic inactivation of *VHL* gene in 60–70% of cases, through somatic mutations, loss of heterozigosity and promoter hypermethylation [5].

The product of *VHL* gene is a component of an E3 ubiquitine ligase complex, involved in the ubiquitination of HIFs (hypoxia-inducible factors) [6]. In the normal tissue environment, the VHL gene targets HIFs for degradation through O_2-dependant post-transcriptional hydroxylation of two proline residues [7]. In hypoxic conditions, HIFs accumulate due to the lack of suppression from *VHL* gene product. HIF1-α dimerize with HIF1-β and then these hetero-dimers translocate to the nucleus. Hence, the complex binds to DNA, promoting the transcription of hypoxia response factors (including VEGF, EPO, EGFR, GluT-1 among others), involved in angiogenesis and survival in anaerobic setting [8].

Pharmacological strategies to inhibit the Vascular Endothelial Growth Factor (VEGF) pathway include antibodies directed against VEGF (bevacizumab) or VEGF receptor (VEGFR, ramucirumab), soluble VEGFR/VEGFR hybrids, soluble analogues of the VEGFR (VEGF-Trap) and tyrosine kinase inhibitors (such as pazopanib, sunitinib, sorafenib, axitinib). Many of these drugs are currently used in the treatment of patients with advanced RCC, following the demonstration of efficacy in randomized trials.

Furthermore, interesting clinical activity in patients with RCC was observed with inhibitors of mTOR, a central component of the nutrient-sensing PI3 kinase pathway. Subsequent work identified that mTOR also regulates the expression of hypoxia inducible factor (HIF), which is regulated by VHL outside of the setting of inactivating mutations or deletions. mTOR is one of the proteins forming mTOR complex 1 (mTORC1) and complex 2 (mTORC2). mTORC1 promotes protein translation through the phosphorylation of S6K1 (S6 kinase 1) and 4E-BP1 (4E-binding protein 1) [9]. The inhibition of mTORC1 by rapamycin analogues (everolimus and temsirolimus) blocks activity of several growth factors, including EGFR and VEGFR.