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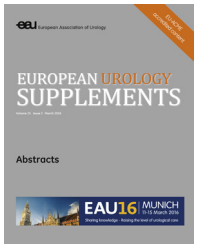

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Clinical Trials for Specific Renal Cancer Subtypes—The Time Will Come!

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Abstract

Renal cell cancer is a heterogeneous group of cancers with different histological phenotypes. Recent 2016 WHO classification acknowledges the genetic background of most renal cancer subtypes, whereas treatment for metastasized renal cell carcinoma (RCC) considers only clear cell and non–clear cell RCCs. Clear cell RCCs are characterized by the presence of at least three tumor suppressor genes on chromosome 3p. Owing to inactivation of von Hippel–Lindau (VHL), clear cell renal cancer produces the hypoxia-inducible factor–responsive vascular endothelial growth factor (VEGF). Other specific gene alterations have been identified in non–clear cell renal cancers, for example, *PTEN*, *p53*, and *FLCN* in chromophobe carcinomas; *TFE3*, *TFEB*, and *MITF* in translocation carcinomas; or *MET* and *FH* in variants of papillary RCC. Current treatments target VEGF or VEGF receptor using tyrosine kinase inhibitors, monoclonal antibodies, and mTOR inhibitors. Renal cancer immunotherapy using immune checkpoint inhibitors is currently tested in early clinical phases. We review current clinical trials on the basis of the molecular background of specific renal cancer subtypes.

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1. Introduction

In the last years, specific renal tumor subtypes have been characterized on the basis of characteristic molecular alterations [1]. Not only is the histological classification of prognostic significance, but renal cancer subtypes also show different response to novel systemic therapies [2]. This different treatment response is potentially the consequence of the involvement of various tumor suppressor genes or oncogenes [3], but in contrast to lung cancer, colorectal cancer, or melanoma, molecular alterations are not predictive for treatment response [4]. At least 12 different genes associated with the development of kidney cancer have been identified: the *VHL*, *MET*, *FLCN*, *TFE3*, *TFEB*, *MITF*, *FH*, *SDHB*, *SDHD*, and *PTEN* genes [5–8]. Many of these genes have first been described in hereditary renal cancer syndromes, for example, von Hippel–Lindau (VHL), hereditary papillary renal carcinoma (HPRC), Birt–Hogg–Dubé (BHD), hereditary leiomyomatosis renal cell carcinoma (HLRCC), succinate dehydrogenase renal cell carcinoma (SDH RCC) syndromes, and Cowden's disease [9].

For many years, *VHL* gene has been regarded as the most important driver gene in clear cell renal cell cancer (ccRCC), the most frequent renal cancer subtype [9]. Apart from *VHL*,

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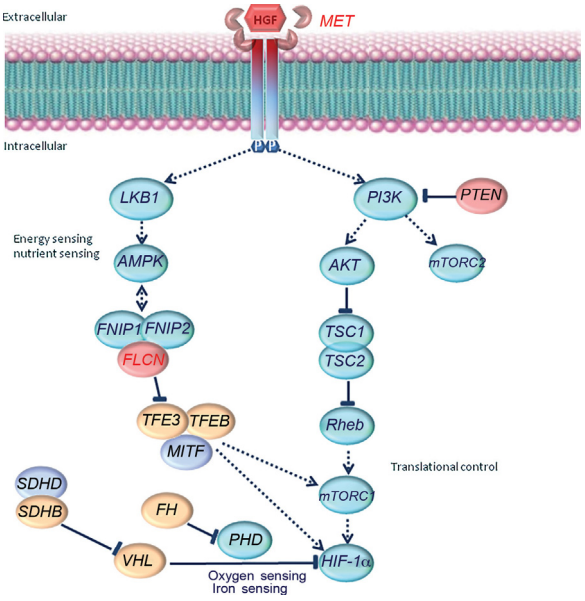

Fig. 1 – Genes involved in the development of different histological subtypes of renal tumors. HGF = hepatocyte growth factor. Adapted from the work of Linehan and Ricketts [13].

chromatin modifiers *PBRM1* and SETD2 were also identified as relevant ccRCC genes [8,10–12]. The tumor-suppressing function of pVHL is associated with its function to target the hypoxia-inducible factor (HIF)-alpha transcription factors. HIF transcription factors regulate glucose transport, glycolysis, and angiogenesis [9,13].

Most clinical trials include only ccRCC or categorize renal cancer in ccRCC and non-ccRCC (nccRCC). The group of nccRCCs is a heterogeneous group of many RCC subtypes with different molecular alterations, for example, papillary, chromophobe, translocation, collecting duct, and other RCCs. Analysis of key metabolic pathways in RCC subtypes may influence the response to novel treatment modalities [13] (Fig. 1). This review summarizes the impact of the current histological classification on design of clinical trials.

2. Targeting HIF2α or HIF2α-responsive gene products in ccRCC

Clear cell RCCs are characterized by a very vascular tumor stroma, and the tumor cells have a high lipid content (Fig. 2A). Some sporadic ccRCCs form cysts and cyst formation is regarded as a precursor of at least some sporadic ccRCCs, but most ccRCCs are developed via a cyst-independent pathway [14–16]. Both tumor progression pathways are a consequence of biallelic VHL inactivation due to chromosome 3p deletion, somatic mutations, and/or hypermethylation [17–19]. The frequency of *VHL* mutations in sporadic ccRCC is approximately 50%. This prevalence is probably higher, because a number of novel tumor entities with clear tumor cell cytoplasm but without VHL mutations have been described in the last years. Such tumor entities include translocation RCC, clear cell papillary RCC, and acquired cystic kidney disease–associated RCC [4] (see below). Recently, a number of genes have been described as recurrently mutated in ccRCC including *PBRM1*, *BAP1*, *SETD2*, and *JARID1C* [8,10]. *PBRM1*, *BAP1*, and *SETD2* are also localized on chromosome 3p and are frequently codeleted with *VHL* in tumors with chromosomal losses on 3p [11,12]. There is evidence that BAP1 mutations are associated with aggressive disease and that BAP1 and PBRM1 mutations are mutually exclusive [20,21].

The *VHL* gene encodes pVHL, which is a multifunctional protein [22]. When the *VHL* gene is mutated, the VHL complex cannot degrade the HIF in normoxia with the consequences that HIF is accumulating and downstream genes are stably upregulated. The *VHL* mutations compromise the ability of pVHL to suppress HIF, but in a different level [23]. HIF1α, HIF2α, and HIF3α are HIFα family members. There is evidence that HIF2α is a renal oncoprotein, whereas HIF1α acts as a renal tumor suppressor (for review see the study by Shen and Kaelin [9]). HIF1α and HIF2α are transcription factors regulating the activity of a number of downstream genes important in regulating tumor cell behavior, proliferation, metastasis, angiogenesis, microtubule formation, and others. Such downstream targets include vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), EGF, and the glucose transporter GLUT1. The upregulation of VEGF explains the high vessel density of ccRCC and the responsiveness to VEGF inhibitors.

Medical treatment for metastasized ccRCC has been developed in numerous clinical trials. The VEGF-neutralizing antibody bevacizumab is approved for the treatment of renal cell carcinoma (RCC) [24]. The tyrosine kinase inhibitors (TKIs) sunitinib [25] and sorafenib [26] target VEGF and PDGF receptors on tumor cells. Pazopanib, another TKI, targets the VEGF receptors VEGFR1, VEGFR2, and VEGFR3 [27]. Other drugs are known to indirectly downregulate HIFα. Such components include mTOR [28] inhibitors, HSP90 inhibitors, and HDAC inhibitors [29]. Everolimus and temsirolimus as mTOR inhibitors have been approved for ccRCC treatment [30].

Cytokine therapy with interferon (IFN)-α or interleukin-2 was effective only for a small group of patients [31–35] with significant toxicity [36]. Recently, the following treatment approaches have been recommended [37] (Table 1). The anti-VEGF antibody bevacizumab combined with IFN-α showed prolonged progression-free survival (PFS), but no benefit in overall survival (OS) probably due to effective second-line treatment. This led to the registration of this drug combination as first-line treatment for metastatic RCC (mRCC) [24,38]. The currently used TKIs for mRCC target VEGF receptors 1, 2, and 3 and many other receptor tyrosine kinases, for example, platelet-derived growth factor receptor (PDGFR), FLT-3, and c-KIT (multikinase inhibitors). Owing to this multitarget activity, their clinical efficacy and toxicity profiles vary. Sunitinib was compared with IFN-α [25,39] and showed a significant PFS advantage, which lead to its registration as first-line treatment.

Pazopanib [27] was compared with sunitinib in the COMPARZ trial proving noninferiority in the first-line

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