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Review

Resistance to sunitinib in renal cell carcinoma: From molecular mechanisms to predictive markers and future perspectives

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ABSTRACT

The introduction of agents that inhibit tumor angiogenesis by targeting vascular endothelial growth factor (VEGF) signaling has made a significant impact on the survival of patients with metastasized renal cell carcinoma (RCC). Sunitinib, a tyrosine kinase inhibitor of the VEGF receptor, has become the mainstay of treatment for these patients. Although treatment with sunitinib substantially improved patient outcome, the initial success is overshadowed by the occurrence of resistance. The mechanisms of resistance are poorly understood. Insight into the molecular mechanisms of resistance will help to better understand the biology of RCC and can ultimately aid the development of more effective therapies for patients with this infaust disease. In this review we comprehensively discuss molecular mechanisms of resistance to sunitinib and the involved biological processes, summarize potential biomarkers that predict response and resistance to treatment with sunitinib, and elaborate on future perspectives in the treatment of metastasized RCC.

Contents

Abbreviations: (cc)RCC, (clear cell) renal cell carcinoma; FDA, Food and Drug Administration; IFN-α, interferon alpha; VHL, Von Hippel–Lindau; HIF, hypoxia inducible factor; IL, interleukin; VEGF, vascular endothelial growth factor; VEGFR, VEGF receptor; PDGF, platelet-derived growth factor; PDGFR, PDGF receptor; TKI, tyrosine kinase inhibitor; HRE, hypoxia-responsive element; TGF-α, transforming growth factor alpha; EPO, erythropoietin; MMP, matrix metalloproteinase; EGF, epidermal growth factor; EGFR, EGF receptor; HGF, hepatocyte growth factor; HGFR/cMET, HGF receptor; SDF1, stromal-derived factor 1; CXCR4, CXC chemokine receptor 4; HAP, hypoxia-activated prodrug; FGF, fibroblast growth factor; bFGF, basic fibroblast growth factor; FGFR, FGF receptor; MAPK, mitogen-activated protein kinase; PI3K, phosphoinositide 3-kinase; NF-kB, nuclear factor kappa-light-chain-enhancer of activated B cells; PlGF, placental growth factor; Ang, angiopoietin; Tie, tunica intima endothelial kinase; DLL4, delta-like ligand 4; BMDC, bone marrow-derived cell; TAM, tumor-associated macrophage; TAF, tumor-associated fibroblast; EPC, endothelial progenitor cell; Bv8, bombina variagata peptide 8; G-CSF, granulocyte-colony stimulating factor; STAT3, signal transducer and activator of transcription 3; ALK, anaplastic lymphoma kinase; EMT, epithelial-to-mesenchymal transition; SK1, sphingosine kinase-1; S1P, sphingosine 1 phosphate; ERK, extracellular signal-regulated kinase; GSK-3β, glycogen synthase kinase 3 beta; SNP, single nucleotide polymorphism; miRNA, microRNA; mTOR, mammalian target of rapamycin; ZEB, zinc finger E-box-binding homeobox; mCEC, mature circulating endothelial cell; CEP, circulating endothelial progenitor cell; TNF-α, tumor necrosis factor alpha; NGAL, neutrophil gelatinase-associated lipocalin; NEFH, neurofilament heavy polypeptide; LAD1, ladinin 1; CST6, cystatin E/M; OS, overall survival; PFS, progression-free survival; RR, relative risk; HR, hazard ratio; OR, odds ratio; 95% CI, 95% confidence interval

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1. Introduction

Renal cell carcinoma (RCC), which arises from the renal parenchyma, is the most common kidney cancer subtype, accounting for approximately 90% of all cases [1,2]. Of the patients diagnosed with RCC, 20–30% present with metastasized disease, and another ~30% of the patients treated for localized disease develop metastases during follow-up [3]. RCC is not a single entity, but comprises a heterogeneous group of malignancies, of which clear cell RCC (ccRCC) is the most common (75–80%) and the best studied to date. ccRCCs are highly vascularized tumors that are characterized by frequent inactivation (50–75%) of the Von Hippel–Lindau (*VHL*) gene [2,4,5]. The product of the *VHL* gene, pVHL, plays an important role in down-regulating the expression of the hypoxia inducible factor 1 (HIF1) transcription factor, which leads to decreased angiogenesis (Fig. 1). Inactivation of pVHL, e.g. by mutation, deletion or promoter CpG island methylation of the *VHL* gene, leads to accumulation of HIF1 and increased transcription of HIF1 target genes e.g. vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF). The frequent inactivation of *VHL* provided the rationale for the development of antiangiogenic drugs to treat ccRCC such as sunitinib, pazopanib, sorafenib, and axitinib [4]. Sunitinib is an oral multiple tyrosine kinases inhibitor (TKI), that inhibits the family of vascular endothelial growth factor receptors (VEGFR-1, VEGFR-2 and VEGFR-3), the platelet-derived growth factor

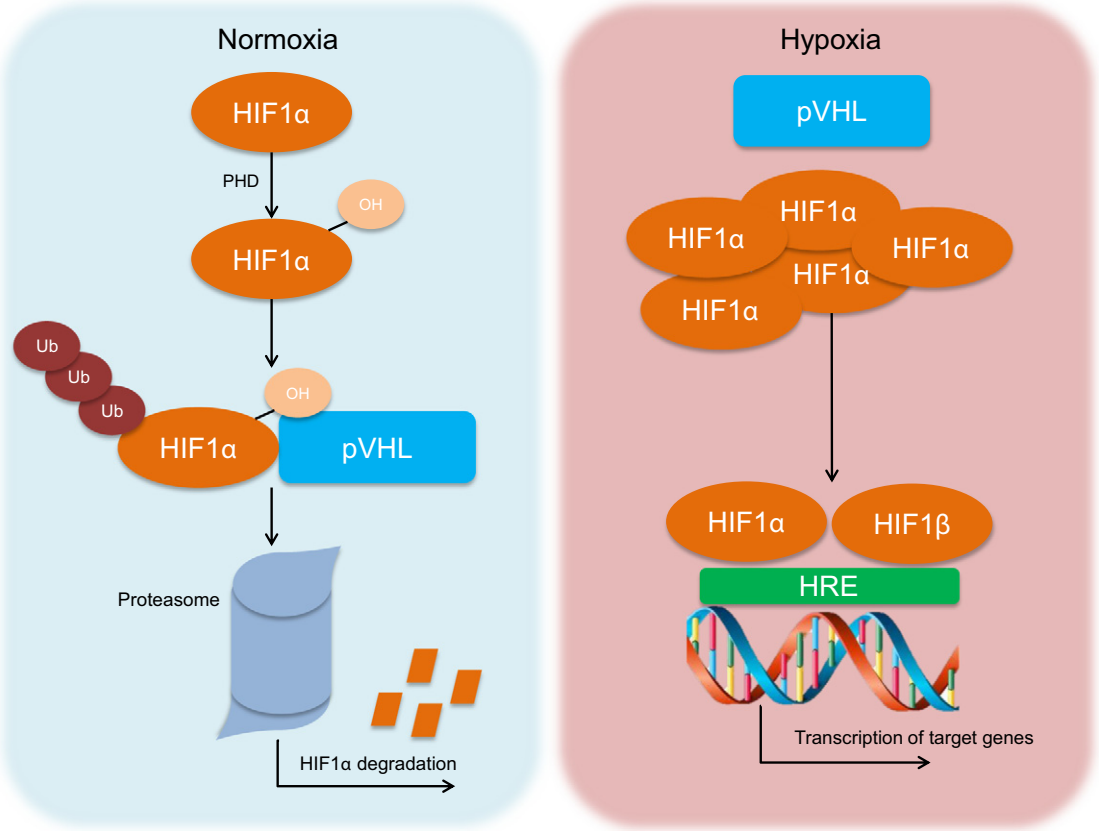

Fig. 1. VHL-signaling in the presence and absence of oxygen. Under normoxic conditions (left-hand side), the VHL protein (pVHL) binds HIF1α which makes it a target for proteasomal degradation. Under hypoxic conditions (right-hand side), or inactivation of pVHL (as in RCC), pVHL cannot bind HIF1α, which leads to the accumulation of HIF1α and binding of HIF1α to HIF1β. The so formed heterodimer translocates to the nucleus and activates the transcription of target genes such as *VEGF* and *PDGF*. Abbreviations: pVHL, VHL protein; HIF1α, hypoxia inducible factor 1α; HIF1β, hypoxia inducible factor 1β; HRE, hypoxia responsive element; PHD, prolyl hydroxylase domain; Ub, ubiquitin; OH, hydroxide.