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Review article

Strategies to overcome therapeutic resistance in renal cell carcinoma

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Abstract

Background: Renal cell cancer (RCC) is a prevalent and lethal disease. At time of diagnosis, most patients present with localized disease. For these patients, the standard of care includes nephrectomy with close monitoring thereafter. While many patients will be cured, 5-year recurrence rates range from 30% to 60%. Furthermore, nearly one-third of patients present with metastatic disease at time of diagnosis. Metastatic disease is rarely curable and typically lethal. Cytotoxic chemotherapy and radiation alone are incapable of controlling the disease. Extensive effort was expended in the development of cytokine therapies but response rates remain low. Newer agents targeting angiogenesis and mTOR signaling emerged in the 2000s and revolutionized patient care. While these agents improve progression free survival, the development of resistance is nearly universal. A new era of immunotherapy is now emerging, led by the checkpoint inhibitors. However, therapeutic resistance remains a complex issue that is likely to persist.

Methods and Purpose: In this review, we systematically evaluate preclinical research and clinical trials that address resistance to the primary RCC therapies, including anti-angiogenesis agents, mTOR inhibitors, and immunotherapies. As clear cell RCC is the most common adult kidney cancer and has been the focus of most studies, it will be the focus of this review.

Keywords: Renal cell carcinoma; Resistance; Angiogenesis; Immunotherapy; mTOR

1. Resistance to antiangiogenesis therapies in renal cell carcinoma

1.1. Background

Hanahan and Weinberg [1] outlined over 15 years ago the principles necessary for the uncontrolled proliferation of cells causing tumor formation. Included in their original 6 hallmarks of cancer was angiogenesis, or the formation of new blood vessels. Although initially small tumor populations may live by simple diffusion of nutrients, data show that tumor formation and growth eventually requires neovascularization [2]. Targeting angiogenesis was hypothesized to be especially important in clear cell renal cell carcinoma (RCC), a highly vascular tumor, in part due to its molecular hallmark of *VHL* inactivation. *VHL,* or the von Hippel-Lindau gene, encodes the substrate recognition component of an E3 ubiquitin ligase complex [3]. When considering both gene mutation and promoter hypermethylation, VHL function is lost in as many as 90% of clear cell RCC tumors, leading to the accumulation of the transcription factor hypoxia inducible factor (HIF) [4]. HIF triggers an intense hypoxic and proangiogenic response [3]. Targeting this proangiogenic response heralded a new era in the therapy of these cancers, dominated by the use of potent single-agent antiangiogenics. Although clearly efficacious for many patients in inducing response and in establishing disease control for a period averaging several months, as many as 10% of patients demonstrate intrinsic resistance with lack of response to first-line antiangiogenics [5]. These patients have a poor prognosis even with subsequent lines of therapy [6]. For patients who demonstrate an initial

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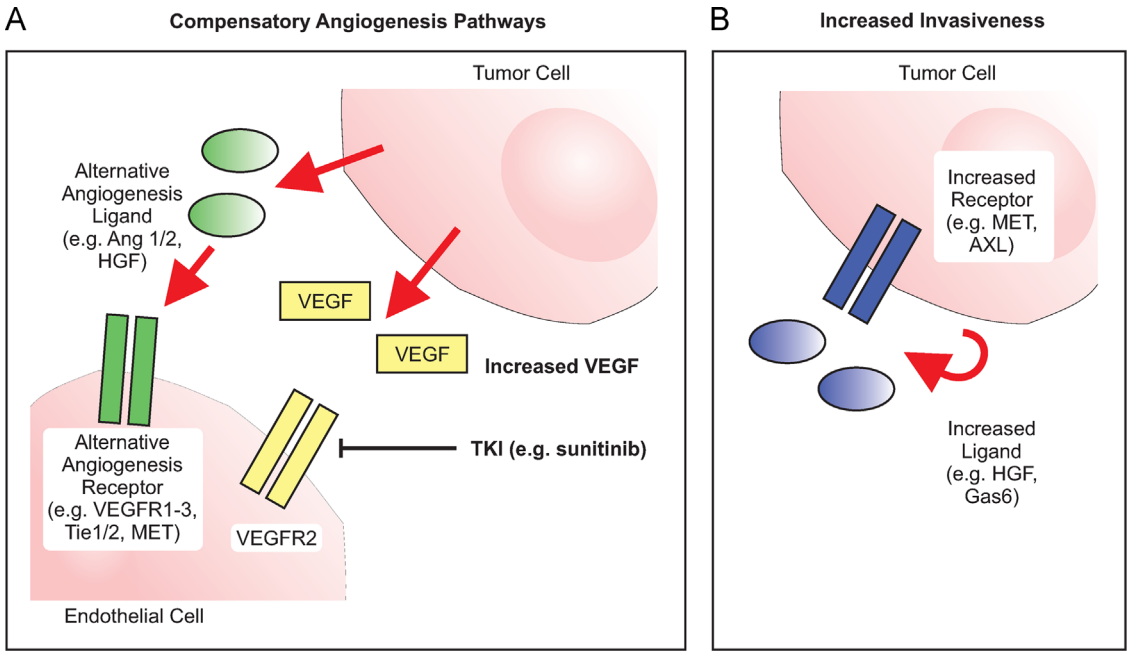

Fig. 1. Mechanisms of antiangiogenesis resistance. Tumors are capable of continued survival, growth, and proliferation in the setting of persistent VEGFR2 inhibition by several mechanisms including (A) activating alternative, compensatory pathways that can continue to support tumor neovascularization and (B) reprogramming tumor cells so that they become more invasive, invade deeper into normal tissue, and thus survive using the normal, physiologic vasculature. Ang = angiopoietin, HGF = hepatocyte growth factor; TKI = tyrosine kinase inhibitor; VEGF = vascular epithelial growth factor, VEGFR = vascular epithelial growth factor receptor. (Color version of figure is available online.)

response to sunitinib and other similar antiangiogenic therapies, the response is often not durable. Potential mechanisms of acquired resistance include activation of alternative or compensatory angiogenic pathways and increased tumor invasiveness (Fig. 1) [7]. In this review, we focus on acquired or adaptive resistance mechanisms and new therapies designed to address acquired resistance (Table).

1.2. Adaptive resistance via compensatory angiogenesis pathways

The adaptive resistance that emerges in RCC during antiangiogenesis therapy is distinct among targeted therapies. Most receptor-targeted therapies develop emergent resistance through an acquired point mutation, such as that occurs frequently in targeting endothelial growth factor

Table
Clinical strategies for acquired resistance in renal cell carcinoma.

Mechanism of resistance	Therapeutic target	Design/results	Reference
Compensatory angiogenesis pathways	VEGFR1–3	Axitinib with superior PFS relative to sorafenib in sunitinib-resistant disease	Rini et al. [10]
	VEGFR/FGFR+mTOR	Lenvatinib + everolimus improved PFS relative to everolimus alone	Motzer et al. [12]
	ALK-1 + VEGFR	Dalantercept + axitinib in heavily pretreated patients with RCC	NCT01727336
	VEGF	VEGFR TKI–refractory patients had stable disease on aflibercept	Pili et al. [16]
Increased tumor invasion	MET/AXL	Cabozantinib improves PFS and ORR compared to everolimus	Choueiri et al. [19]
Persistent AKT activation	AKT	AKT allosteric inhibitor MK2206 not superior to everolimus	Jonasch et al. [39]
Compensatory mTORC2 signaling	mTORC1 and mTORC2	Apitolisib more toxic, no improvement in PFS compared with everolimus	Powles et al. [40]
Immune suppression	PD-1	Nivolumab improved survival for patients with VEGFR TKI–refractory clear cell RCC compared with everolimus	Motzer et al. [53]
	PD-1 + VEGF	Pembrolizumab + aflipercept in patients with VEGFR TKI–refractory RCC	NCT02298959
	PD-1 + CTLA-4	Pembrolizumab + interferon α-2b or ipilimumab in refractory clear cell RCC	NCT02089685

ALK-1 = activin receptor–like kinase; CTLA-4 = cytotoxic T-lymphocyte–associated protein 4.