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Review

Metastasis in renal cell carcinoma: Biology and implications for therapy

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Abstract Although multiple advances have been made in systemic therapy for renal cell carcinoma (RCC), metastatic RCC remains incurable. In the current review, we focus on the underlying biology of RCC and plausible mechanisms of metastasis. We further outline evolving strategies to combat metastasis through adjuvant therapy. Finally, we discuss clinical patterns of metastasis in RCC and how distinct systemic therapy approaches may be considered based on the anatomic location of metastasis.

1. Introduction

Approximately one-third of patients with renal cell carcinoma (RCC) present with metastatic disease, and amongst those patients with localized disease, a substantial proportion will recur [1]. For patients with metastatic renal cell carcinoma (mRCC), the landscape of therapy has evolved dramatically over the past decade. Prior to 2005, immunotherapy represented the mainstay of therapy with agents such as interleukin-2 (IL-2) and interferon-α (IFN-α) [2,3]. Estimates of overall survival (OS) in that era coalesced around 1 year. Since 2005, multiple targeted therapies have been approved, primarily directed at vascular endothelial growth factor (VEGF) or its cognate receptor (VEGF receptor, or VEGFR), or the mammalian target of rapamycin (mTOR) [4]. In this generation of therapies, inhibitors of VEGF include axitinib, bevacizumab, pazopanib, sorafenib and sunitinib, while inhibitors of mTOR include

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everolimus and temsirolimus [5—10]. These agents have collectively improved median survival estimates to approximately 2.5—3 years [11]. Over the past year, 3 additional FDA approvals have been granted for mRCC for a VEGFR/MET/AXL inhibitor (cabozantinib), a programmed death-1 (PD-1) inhibitor (nivolumab) and a multikinase inhibitor (lenvatinib, approved with everolimus) [12—14]. It remains to be seen how these agents will alter OS estimates for mRCC, although it will surely move the bar in a positive direction.

Despite these critical advances, the reality is that the vast majority of patients with mRCC have incurable disease [15]. A goal of treatment is to maximize the yield of existing systemic therapies through personalized approaches. In the current review, we explore how clinical and biological properties of metastases may potentially alter paradigms for systemic therapy.

2. Biology of RCC

2.1. Differing biology by histology

It is critical to acknowledge that mRCC is comprised of multiple distinct histologies, each with unique biologic underpinnings. The most common histology is clear cell, comprising 75%—80% of cases. Approximately 70% of patients with clear cell RCC bear alterations in the Von-Hippel Lindau (*VHL*) gene [16]. Wild type VHL protein functions as an ubiquitin ligase, participating in degradation of hypoxia inducible factor (HIF). In patients bearing *VHL* alteration, the resulting high levels of HIF result in upregulation of VEGF. VEGF activates VEGFR, triggering the phosphoinositol-3-kinase (PI3K)-Akt signaling cascade. Downstream, mTOR is activated and leads to transcription of a variety of tumor-promoting factors, resulting in increased cellular migration and angiogenesis. Although VEGFR has typically been implicated as the key driver of tumor progression in RCC, there is emerging evidence that other transmembrane receptors may potentially drive metastasis, including MET and AXL [17].

Non-clear cell RCC histologies comprise roughly 20%—25% of patients overall. The most prevalent of these is papillary RCC, which represents 10%—15% of patients. Papillary RCC is frequently subdivided into type I and type II disease. Type I disease is characterized by alterations in the MET proto-oncogene, while type II is characterized by a variety of alterations. Recent data from The Cancer Genome Atlas (TCGA) investigators highlighted alterations in *SETD2*, *CKDN2A* and *TFE3* fusions as frequent events in type II papillary RCC [18]. Chromophobe type disease comprises approximately 5% of all RCC cases. TCGA data pertaining to chromophobe RCC suggest frequent changes in the *TERT* promoter region, and mitochondrial DNA analyses suggest changes in mitochondrial function [19]. Beyond papillary and chromophobe RCC, other histologies of RCC represent $<1\%$ of all cases. Despite their rarity, there are efforts to characterize the genomic changes occurring in these entities. For instance, our group has identified frequent alterations in *NF2* in patients with collecting duct RCC, an exquisitely rare diagnosis with a dismal prognosis [20].

Admixed with any histological subset of RCC may be sarcomatoid elements. Sarcomatoid RCC is thought to coexist with other histologies in about 25% of cases [21]. Sarcomatoid disease tends to be particularly aggressive, although (as discussed subsequently) the current treatment paradigm is not distinct from clear cell disease. Our group has identified frequent alterations in the aurora kinase pathway, and *NF2* alterations have also been detected in this disease [22,23].

2.2. Tumor heterogeneity

Although histology is frequently used to offer prognostic data to patients, it is critical to acknowledge that the biology of tumors may differ across sites of metastasis. One of the first detailed studies to identify this intratumoral heterogeneity was from Gerlinger and colleagues [24]. In an effort that included just 4 patients with mRCC, separate sites of metastasis were evaluated. Alterations in the mTOR pathway were variable across sites of metastasis, as were alterations in *SETD2*, *PTEN* and *KDM5C*. Subsequent sections will highlight potential therapeutic strategies for these alterations. With the evolution of novel immunotherapeutic strategies, there has also been substantial interest in characterizing PD-L1 expression in metastatic sites. A recent study from the Dana Farber Cancer Institute compared tissues derived from 53 primary RCC specimens and 73 corresponding metastases [25]. PD-L1 expression appeared to be consistent, although PD-L1 expression was noted to be heterogeneous within lesions.

2.2.1. Biological mediators of metastasis

Little is agreed upon regarding the biological mechanisms that drive RCC metastasis. On a macromolecular level, Grange et al. [26] have proposed that tumor-derived microvesicles (which essentially break off from the primary site) may disperse tumors through hematogenous routes. These microvesicles appear to bear CD105-positive cells, which carry a cancer stem cell phenotype, and microRNAs which stimulate angiogenesis. The immune milieu may also play a critical role in the evolution of metastases. In preclinical models, neutrophilic infiltration in the lungs (accompanied by secretion of neutrophil chemokines) was accompanied by suppression of pulmonary metastases of RCC [27]. In contrast, loss of neutrophil chemokines in the lung was accompanied by an increase in pulmonary metastases. Other immune cells with negative effects on antitumor immunity (e.g., myeloid derived suppressor cells, or MDSCs) have been shown to have a pro-angiogenic effect and cause propagation of RCC in preclinical models [28].

Beyond these macromolecular events, several molecular mediators of RCC metastasis have been identified. In the setting of clear cell RCC bearing *VHL* alteration, it has been proposed that CUB-domain-containing protein (CDCP1) may drive metastasis [29]. CDCP1 is regulated through HIF dependent pathways and drives activation of protein kinase C-δ (PKCδ), which in turn increases cellular migration. Expression of MUC1, a membrane-bound glycoprotein, is also HIF-dependent, and knockdown of MUC1 has been shown to markedly decrease cellular invasion and migration in *in vitro* RCC models [30]. Various chemokine receptors, including CXCR4, also appear to be upregulated in the