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Discovering Biomarkers within the Genomic Landscape of Renal Cell Carcinoma

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Abstract

Recent advances in molecular sequencing technology have led to the discovery of numerous biomarkers in renal cell carcinoma (RCC). These biomarkers have the potential to predict clinical outcomes and aid in clinical management decisions. The following commentary is a review of the preliminary data on some of the most promising genetic biomarker candidates.

Keywords: Biomarker; Renal cell carcinoma; Genomics

Introduction

Kidney cancer is a growing epidemic in the United States and the incidence is rising, leading to 65,000 new cases and over 13,000 deaths per year [1]. The most common histologic subtype of RCC is clear cell RCC, which accounts for over half of all renal cortical tumors [2]. Clear cell tumors are characterized by aggressive behavior and comprise 90% of all cases of metastatic RCCs.

Almost thirty years ago, the underlying mechanism of clear cell RCC tumorigenesis was discovered to be the biallelic loss of *VHL*, which is located on chromosome 3p25 [3]. This double loss is typically the consequence of 3p loss and subsequent *VHL* mutation or promoter hypermethylation. The gene product of *VHL* ubiquitinates hypoxia-inducible transcription factors (HIF's), targeting them for proteasome mediated degradation. When *VHL* transcription is absent, HIF's are stabilized, leading to upregulation of proangiogenic genes, including vascular endothelial growth factor (VEGF). Therapeutic drugs targeting dysregulated VEGF pathways are currently the standard of care of systemic therapy for advanced RCC.

Multiplatform sequencing studies have recently identified additional driver genes in ccRCC [3-6]. These genes (*PBRM1, SETD2, BAP1,* and *KDM5C)* function as tumor suppressors through epigenetic regulation. They remodel chromatin via histone modification. The modification of histones via methylation can have effects of enabling or repressing gene transcription. Functional loss of chromatin remodeling genes can lead to widespread epigenetic dysregulation. This is thought to be a key feature driving carcinogenesis, particularly in renal tumors. Interestingly, these chromatin remodeling genes are among the top frequently mutated genes in RCC after *VHL* (*PBRM1* ~33%, *SETD2* 12%, *BAP1* ~10%, *KDM5C* ~7%).

There appears to be a strong association between the mutational status of these chromatin remodeling genes and tumor behavior. This suggests that these genes may be valuable prognostic biomarkers in RCC. Detection of their mutational status in an individual's tumor may aid in clinical decision making. Additionally, mutational aberrations in genes involved in cellular growth and proliferation such as the *mTOR/TSC1* pathway may have value in predicting which patients will respond to certain systemic therapies.

Conclusion

Tumor biomarkers may provide valuable data during many clinical scenarios. Below are examples of such scenarios.

Can genomic biomarkers identify tumors with advanced pathologic stage prior to resection?

Mutations in *PBRM1, SETD2, BAP1*, and *KDM5C* are associated with tumors of advanced stage (odds ratio range 2.34 to 6.40, 2.5, 2.62 to 4.57, 7.6, respectively). Additionally, mutations in *BAP1* are associated with higher grade tumors (odds ratio range 2.43 to 8.17) [7,8]. Biopsies of renal masses can be sequenced and provide valuable data to aid in clinical management, such as the decision to resect vs. observe a renal mass.

Can genomic biomarkers identify patients that will relapse after resection of primary tumor?

Multiple studies have demonstrated a higher likelihood of dying from disease if patients have a tumor harboring mutations in *BAP1* (hazard ratio range 2.21 to 7.71) and/or *SETD2* (hazard ratio 1.68) [8,9]. The exact mechanism underlying the higher mortality risk is unknown, but it is likely a downstream consequence of epigenetic dysregulation. Patients with *BAP1* and/or *SETD2* mutations in their primary tumor may be counseled that they are of higher risk of death from disease after nephrectomy, and as such, they may benefit from more frequent surveillance imaging and from adjuvant therapy after nephrectomy.

Can genomic biomarkers predict clinical response to systemic targeted therapy in metastatic disease?

Voss et al. identified patients with metastatic RCC who achieved durable clinical remissions after receipt of salvage therapy with an mTOR inhibitor [10]. The tumors of these exceptional responders revealed aberrations in genes within the *mTOR/TSC1* pathway. This study provides a biologic basis for exceptional responders to mTOR therapy. By identifying functional somatic mutations in an individual's renal tumor, systemic therapy can be tailored specifically for that individual by treating with agents that directly target specific molecular pathways that are altered.

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With recent advances in sequencing technology, we are entering a renaissance of molecular biomarker discovery. Some genomic biomarkers are already showing value by aiding in clinical management decisions including: should a renal mass be resected or observed?, should a patient have adjuvant therapy after nephrectomy?, and which systemic therapy should be used in an individual with metastatic disease?. A significant obstacle in biomarker development is the presence of regional mutational heterogeneity within renal tumors which may lead to biomarker under detection if only a single tumor site is sequenced [11,12]. Before molecular biomarker based decision making becomes standard of care, prospective large scale validation studies that sample multiple tumor regions must be conducted.

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