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Molecular profiling of renal cell carcinoma: building a bridge towards clinical impact

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Abstract

Purpose of review—The daunting task of identifying key molecular drivers of renal cell carcinoma (RCC) has begun to reveal significant insights into tumor biology. This review provides an update on recent discoveries in this field and their possible clinical implications.

Recent findings—Molecular profiles within the classic RCC histologic subtypes present distinctive insights into tumor biology and also allow for exploitation of the targeted treatment regimens for patients with metastatic disease. Prognostic signatures have demonstrated the ability to accurately predict many clinical outcomes.

Summary—The molecular and genomic profiling of RCC subtypes has identified a unique and diverse spectrum of alterations. Utilization of these characteristics to improve our prognostic and therapeutic outcomes in the clinical realm remains in its infancy but is rapidly advancing.

Keywords

mortality; mutation; prognosis; renal cell carcinoma; sequencing analysis; DNA

INTRODUCTION

The genomic characterization of renal cell carcinoma (RCC) has significantly evolved since clear cell renal cell carcinoma (ccRCC) was defined simply by alterations in the von Hippel-Lindau (*VHL*) tumor suppressor gene. Currently we have numerous tools and platforms to define RCC. These include the analysis of copy number alterations, DNA sequencing, and epigenetic changes, as well as transcriptomics (expression profiling) and proteomics. Many current research efforts not only focus on characterizing RCC with respect to these analytic and molecular variables but also seek to integrate these findings into clinical practice. Early in the study of the genetics of RCC, results were based on the investigation of familial and germline mutations found in hereditary cancer syndromes. More recently, the results of several large collaborative efforts have established the foundation of the molecular

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Conflicts of Interest

None

characterization of RCC and have paved the way for our current and future investigations [1–5].

Molecular Profiles of RCC

Historically, the subtypes of RCC have been identified by their histologic and morphologic features. Through the large-scale efforts of The Cancer Genome Atlas (TCGA) and other international collaborative groups, we have begun to elicit the molecular biology that underlies these classic subtypes. The results of these studies have demonstrated that the three major subtypes of RCC—ccRCC, papillary renal cell carcinoma (pRCC), and chromophobe renal cell carcinoma (chRCC)—are not only different histologically but are tremendously unique in their molecular profiles. A recent comprehensive analysis by Chen *et al.* of 894 RCC tumors from the TCGA initiative details unique molecular findings across the three major subtypes [6]. Through the integration of results from five different genomic platforms, they found nine distinct molecular subgroups of RCC (three within ccRCC, four in pRCC, one in chRCC, and one group with mixed features of RCC). Molecular profiles of the three most common histologic RCC subtypes are summarized in Table 1.

Clear Cell RCC

Using massively parallel sequencing technologies, researchers have found that ccRCC tumors can show considerable mutational heterogeneity. Even so, the *VHL* gene has continued to define this class of tumors [15–17], as it is inactivated in 50% to 90% of ccRCC tumors [1, 3, 18]. Chromosomal 3p loss is another ubiquitous finding in ccRCC [1, 3, 17]. Not surprisingly, several other recurrently mutated genes in ccRCC—including polybromo 1 (*PBRM1*), SET domain containing 2 (*SETD2*), and BRCA1 associated protein 1 (*BAP1*)—are also located on chromosome 3p [9, 10]. The stratification of patients with ccRCC on the basis of mutations in *BAP1* and *PBRM1* has been shown to correlate with clinical outcomes in localized disease [11, 19–23]. Currently, however, these biomarkers have not significantly improved the clinical stratification of patients beyond traditional clinical and pathologic variables [4, 9, 18–28].

We and several other authors have identified actionable targets or pathways that have significant clinical impact in ccRCC. For example, patients with metastatic disease and a mutation in mammalian target of rapamycin (*MTOR*) can show exceptional response to targeted agents such as everolimus [29–31]. This finding is not unique to ccRCC and has been described in several other solid malignancies [32, 33]. Unfortunately, mutations in the mTOR signaling pathway are seen in only a minority of patients with RCC. A recently published report on the RECORD-3 study [34], and another on correlations between molecular subclassifications of ccRCC and targeted therapy response [35] highlight several other possible mutations associated with treatment response in the metastatic setting, including *BAP1*, *PBRM1*, lysine (k)-specific demethylase 5C (*KDM5C*), tuberous sclerosis 1 (*TSC1*) and tuberous sclerosis 2 (*TSC2*) and phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (*PIK3CA*).

Several other genomic platforms, including RNA sequencing and gene expression microarray based methods, have been used to develop prognostic profiles or signatures in

ccRCC. Brannon *et al.*, using results from a gene expression microarray using 120 probes from 110 genes, identified two subgroups of ccRCC tumors, which they designated ccA (good risk) and ccB (poor risk) [36]. A distillation of this assay was used to develop a more clinically applicable test using 34 genes (ClearCode34) and was able to demonstrate independent prognostic value even when controlling for several relevant clinical and pathologic variables [37]. More recently, several other assays have been described in both the localized and metastatic setting [38, 39]. Specific single nucleotide polymorphisms have also been linked to adverse clinical outcomes [40, 41]. The ultimate clinical applicability of these various predictive molecular profiles and signatures has yet to be decided, as questions remain regarding their performance in prospective and randomized studies.

Papillary RCC

The group of cancers that comprise the pRCC subtype includes pRCC type 1, pRCC type 2, and unclassified RCC with papillary architecture. These cancers are histologically, molecularly, and clinically diverse. The recent publication of the TCGA pRCC study by the Cancer Genome Atlas Research Network highlighted this fact, and in their study they described several subgroups within both type 1 and type 2 tumors [5]. Alterations in several cancer-associated pathways were found across the spectrum of pRCC tumors, including alterations in the Hippo signaling pathway (mutations in the *NF2* [neurofibromin 2] gene), in the SWI/SNF complex (*PBRM1* and *SMARCB1* [SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily B member 1]) and in several chromatin modifier pathways (*SETD2*, *BAP1*, and *KDM6A* [lysine (k)-specific demethylase 6A]).

Several subgroups in pRCC type 2 were linked with particularly poor clinical outcomes. Tumors with the CpG island methylator phenotype (CIMP) had increased DNA methylation compared to loci that were unmethylated in matched normal tissue from the same patient. At the molecular and metabolic level many of these tumors have germline or somatic mutations in fumarate hydratase (*FH*). Patients with germline *FH* mutations can develop hereditary leiomyomatosis and renal cell cancer (HLRCC) syndrome [42]. The CIMP phenotype is not unique to pRCC and is linked with a poor clinical prognosis in a variety of human malignancies [43].

The TCGA study also noted poor outcomes for patients with alterations in cyclin-dependent kinase inhibitor 2A (*CDKN2A*). A more surprising result from the TCGA study was the finding that a large number of their adult cohort of patients with pRCC type 2 were identified as having mutations or fusions in their transcription factor binding to IGHM enhancer 3 (*TFE3*) or transcription factor EB (*TFEB*) genes.

For pRCC type 1 tumors, the TCGA study found a high percentage (81%) with a gain of chromosome 7, which carries the *MET* proto-oncogene. While germline mutations in *MET* occur in patients with hereditary papillary renal cell carcinoma, the high number of somatic alterations in *MET* for patients with spontaneous pRCC tumors presents a possible therapeutic target in select cases [44]. The *MET* gene encodes proteins such as hepatocyte growth factor receptor. Mutations or amplifications of this gene typically result in its over activation in pRCC tumors [45]. The exploitation of these findings has been the basis of

trials using targeted and multi-kinase inhibitors against specific genomic alterations in patients with metastatic disease [46–48].

Chromophobe RCC

The third most common histologic subtype of RCC is chRCC [49]. These tumors tend to be more clinically indolent but still possess the ability to metastasize in a small subset of patients [50–52]. Unique to this tumor subtype is the relatively reduced somatic mutational burden contrasting with a high frequency of heterozygous whole chromosomal loss (1, 2, 6, 10, 13, 17 and 21) [2, 53, 54]. In 2014 the TCGA group described this tumor subtype and reported that genes in the p53 or *PTEN* pathways were altered in about 53% of the 66 tumors they analyzed [2]. They found relatively high frequencies of somatic mutations in *TP53* (32% of samples) and *PTEN* (9%) [2]. These mutation frequencies are similar to those reported by Durinck *et al.* in a separate cohort of 49 patients with chRCC, with 21.3% for *TP53* and 6.4% for *PTEN* [12]. In a cohort of 37 patients with metastatic chRCC, enrichment for these mutations was seen with *TP53* mutations rising to 61% and *PTEN* to 27% [55].

Another interesting finding from the TCGA study was the possible significance of *TERT* promoter rearrangements (12%) in chRCC tumors [2]. These *TERT* promoter alterations, which many times lead to increased *TERT* expression, are being investigated in several other malignancies and may represent a unique or enhanced pathway for tumorigenesis [56–58]. Lastly, expression levels of mRNA from the TCGA studies substantiated the notion that chRCC tumors arise from the distal renal tubule cells, as opposed to ccRCC, which arises from proximal cells [1, 2, 17, 59].

Rare RCC Entities

The diverse spectrum of RCC is most evident in the arena of rare RCC subtypes and those with variant histologies. Many of these malignancies represent the most clinically aggressive subtypes known, but their rarity has been prohibitive to their study and investigation. Collecting duct carcinoma (CDC) and renal medullary carcinoma (RMC) together represent a category of highly aggressive tumors typically seen in younger patients and those with genetic predispositions [60, 61]. Several investigators have identified alterations in the tumor suppressor gene *SMARCB1* to be frequently associated with RMC tumors, with sensitivity ranging from 30% to 100% [60, 62, 63]. This finding has been suggested as a specific possible molecular difference between RMC and CDC, although the number of cases studied has been small [64]. Loss of *SMARCB1* in RMC tumors has also been associated with increased levels of *EZH2* (enhancer of zeste 2 polycomb repressive complex 2 subunit), which may represent a possible actionable target [65].

Sarcomatoid differentiation is a variant feature that can be seen in the context of several RCC subtypes, most frequently in ccRCC and chRCC [66–68]. When present, it usually portends a more aggressive clinical course [69, 70]. Two groups have recently published their findings on the molecular characterization of ccRCC with sarcomatoid features for a limited number of patients [66, 67]. Both studies reported an enrichment of *TP53* mutations (42.3% in Malouf *et al.*, 31.5% in Bi *et al.*) within tumor regions with sarcomatoid

differentiation. A third study reported no *TP53* mutations in seven cases of ccRCC with sarcomatoid differentiation that underwent whole genome sequencing [71]. Enrichment of other somatic mutations in these tumors was also identified but will need to be reproduced in larger cohort studies before their significance can be fully evaluated.

CONCLUSION

The pathogenesis of RCC is intimately involved with several regulators of the metabolic pathways within the cell. It is remarkable how little the molecular and genetic characteristics among the classic subtypes of RCC overlap. Through the use of molecular profiling, we have begun to understand the complicated interplay of genomic and metabolic changes found in RCC.

The enormous amount of data that have been generated from our exploitation of massively parallel sequencing and other genomic platforms has created a rich environment for future studies. We are coming closer to unlocking the key molecular drivers of tumorigenesis of RCC. Harnessing this information will improve treatments and outcomes for patients.

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Key Points

- Nine distinct molecular subtypes of RCC have been identified among the three classic RCC histologies (ccRCC, pRCC, and chRCC).
- Mutational profiling has revealed several potential actionable targets in RCC, including alterations in the *MTOR* and *c-MET* signaling pathways.
- Several gene expression assays and mutational signatures are currently being evaluated as clinically prognostic tools for patient stratification.

Table 1

Summarized table highlighting frequent genomic alterations and possible actionable targets across the three classic renal cell carcinoma subtypes.

	Recurrent somatic mutations	Chromosomal copy number changes	Actionable targets
Clear cell renal cell carcinoma (ccRCC) (1, 7–11)	<i>VHL, PBRM1, SETD2, BAP1, KDM5C, MTOR</i>	Loss 3p and 14q, Gain 5q	<i>MTOR, TSC1, TSC2</i>
Papillary renal cell carcinoma (pRCC) (5, 12–14)	<i>MET, SETD2, NF2, KDM6A, SMARCB1</i>		
Type 1	<i>MET</i>	Gain 7p and 17p	<i>MET</i>
Type 2	<i>FH, CDKN2A</i>		
Chromophobe renal cell carcinoma (chRCC) (2, 12)	<i>TP53, PTEN</i>	Loss of 1, 2, 6, 10, 13, 17 and 21	<i>PTEN</i>