

2022 WUOF/SIU International Consultation on Urological Diseases: Genetics and Tumor Microenvironment of Renal Cell Carcinoma

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Abstract

Renal cell carcinoma is a diverse group of diseases that can be distinguished by distinct histopathologic and genomic features. In this comprehensive review, we highlight recent advancements in our understanding of the genetic and microenvironmental hallmarks of kidney cancer. We begin with clear cell renal cell carcinoma (ccRCC), the most common subtype of this disease. We review the chromosomal and genetic alterations that drive initiation and progression of ccRCC, which has recently been shown to follow multiple highly conserved evolutionary trajectories that in turn impact disease progression and prognosis. We also review the diverse genetic events that define the many recently recognized rare subtypes within non-clear cell RCC. Finally, we discuss our evolving understanding of the ccRCC microenvironment, which has been revolutionized by recent bulk and single-cell transcriptomic analyses, suggesting potential biomarkers for guiding systemic therapy in the management of advanced ccRCC.

Introduction

Understanding the genomic landscape of clear cell renal cell carcinoma (ccRCC), which accounts for approximately 75% of all renal cell carcinomas, has been critical to the development of targeted systemic therapies to treat this classically chemo- and radiotherapy-resistant disease. However, malignant cells exist in a dynamic and heterogeneous ecosystem of immune cells, stromal cells, cytokines, and extracellular proteins that together constitute the tumor microenvironment (TME)[1], which modulates tumor development and response to systemic therapies in RCC[2]. Better understanding of the TME of ccRCC has helped understand the heterogeneity of response to systemic therapies within ccRCC patients, particularly in the age of immuno-oncologic agent-based therapies. Furthermore, while ccRCC constitutes the majority of RCC tumors, the remaining 25% are represented by an ever-expanding group of tumor subtypes, each with unique histologies and genetic features. This review begins with a summary of recent molecular analyses of clear and non-clear cell RCC subtypes, followed by a discussion of the current understanding of

Key Words

Renal cell carcinoma, clear cell carcinoma, non-clear cell renal cell carcinoma, genetics, tumor microenvironment

Competing Interests

None declared.

Article Information

Received on August 30, 2022
Accepted on October 3, 2022
This article has been peer reviewed.

Soc Int Urol J. 2022;3(6):386–396

DOI: 10.48083/BLPV3411

Abbreviations

ccRCC	clear cell renal cell carcinoma
FH	fumarate hydratase
RCC	renal cell carcinoma
SCNAs	somatic copy number alterations
SWI/SNF	switching defective/sucrose non-fermenting
TAMs	tumor-associated macrophages
TME	tumor microenvironment

the TME of ccRCC and its role in driving the response to systemic therapies in advanced ccRCC.

Genetics of Clear Cell RCC

The first step toward malignant transformation in ccRCC is the loss of the short arm of chromosome 3 (3p loss), which harbors 4 tumor suppressor genes that constitute the most common sites of mutation in RCC: *VHL* on 3p.25, and *PBRM1*, *BAP1*, and *SETD2* on 3p.21[3,4]. Of these genes, *VHL* is the most commonly altered in both hereditary and sporadic RCC, through point mutations and methylation in 70%–80% and 5%–10% of patients, respectively[3,5]. Inactivation of the VHL protein results in loss of regulation and thus constitutive activation of its ubiquitin ligase target, the protein HIF. Resulting de-regulation of HIF targets, including vascular endothelial growth factor (VEGF), promotes tumor cell proliferation, neoangiogenesis, and metastases[6,7]. *PBRM1* is the second most commonly mutated gene (40% of cases)[3,4], and encodes BAF180[6,8], a component of the switching defective/sucrose non-fermenting (SWI/SNF) family of chromatin-remodeling complexes, which determine DNA accessibility to transcription factors and polymerases[8–10]. Similarly, *BAP1*, mutated in 10%–15% of ccRCC patients[11], encodes a nuclear deubiquitinase protein that interacts with host cell factor-1 (HCF-1), which is involved in chromatin remodeling[12,13]. Interestingly, *BAP1* and *PBRM1* mutations are generally mutually exclusive[3,5,14]. Lastly, while the mechanism by which *SETD2*, mutated in 10%–15% of ccRCC, affects tumorigenesis remains unclear, it is suspected to involve DNA double-strand break repair, DNA methylation, and RNA splicing[4,15] (Table 1).

The mechanism of 3p loss that results in loss of heterogeneity (LOH) for the above genes frequently involves chromothripsis, a process in which some chromosomes undergo multiple breaks simultaneously, followed by random joining of chromosomal fragments, resulting in hundreds of genomic rearrangements[16]. This initial 3p loss constitutes the “first hit” event and occurs somatically years before the presentation of ccRCC.

A “second hit” resulting in biallelic inactivation of *VHL* then promotes malignant transformation through upregulation of the hypoxia response in the presence of normoxia. This is usually followed by mutations involving the neighboring *PBRM1*, *SETD2*, and *BAP1* genes, and less frequently, alterations of *TP53*, *mTOR*, *TSC1*, *TSC2*, *PIK3CA*, *PTEN*, *KDM5C* and *SMARCA4*[17].

Although the repertoire of mutations and somatic copy number alterations (SCNAs) that drive ccRCC is relatively narrow, molecular diversity is achieved through clonal evolution, i.e., selection of cell subpopulations characterized by different driver mutations, resulting in intratumor heterogeneity (ITH)[6]. Consequently, molecular profiling of tumor samples collected from a single spatial location may capture clonal events propagated in all the cancer cells of a given tumor, but can easily miss events in subclones, and under- or over-estimate the frequency of altered genes, an issue that is amplified by the particularly high levels of ITH in ccRCC[18,19]. Therefore, multi-region sampling is critical to capturing the clonal evolution of ccRCC, as demonstrated by the TRACERx Renal program[19]. In the interim analysis TRACERx, molecular profiling of > 1200 primary tumor regions from 100 patients demonstrated clear evidence for highly conserved evolutionary mutational patterns in ccRCC within different clones[20]. Broadly, 2 modes of evolution were observed: linear, in which only a single clonal population is evident, with consequently low ITH; and branched, which involves multiple subclonal populations with high ITH. These populations then evolve either through a linear Darwinian-like process of sequentially selected mutational events, or punctuated evolution, which is noted by short bursts of many genomic alterations occurring in a relatively brief period early in the tumor’s evolution, most likely due to SCNAs and structural chromosomal alterations[21].

ccRCC tumors in the TRACERx cohort that were characterized by linear evolution harbored only 3p loss and *VHL* mutation/methylation with low ITH, and were thus termed “VHL mono drivers”[20]. These tumors were enriched for small renal masses (SRMs, < 4 cm in maximal dimension), with limited progression and metastatic risk given the limited fitness advantage provided by isolated *VHL* mutation[22]. In contrast, ccRCC tumors characterized by branched evolution harbored high levels of ITH and parallel evolution[20], i.e., repeat selection of distinct driver mutations in the same gene or pathway, with a highly conserved order of genomic events across clones. Intriguingly, these tumors were larger and more likely to produce metastases than their *VHL* mono driver counterparts, but with an intermediate metastatic efficiency resulting in solitary metastasis or oligometastases[20]. However, other studies suggest that *VHL* mutations alone are not

TABLE 1.

Summary of most common genetic alterations of reviewed RCC subtypes

RCC subtype	Most common and/or characteristic genetic alterations	Most common chromosomal alterations	Notes
Clear cell RCC	<i>VHL</i> (75%-90%) <i>PBRM1</i> (40%) <i>BAP1</i> (10%-15%) <i>SETD2</i> (10%-15%) <i>KDM5C</i> (6%-7%)	Loss of the short arm of chromosome 3 (3p), likely through chemotherapies	<i>VHL</i> is altered through point mutations and methylation in 70%–80% and 5%–10% of patients <i>BAP1</i> and <i>PBRM1</i> mutations are generally mutually exclusive
Papillary RCC, type 1	<i>MET</i> (10%-15%) in non-hereditary cases	Frequent gains of chromosomes 7 (almost universal) and 17 as well as less frequent gains of chromosomes 2, 3, 12, 16, and 20	
Papillary RCC, type 2	No specific pattern of mutations or SCNAs		See section 2
Chromophobe RCC	<i>TP53</i> (~30%) and <i>PTEN</i> (~8%)	Most frequently associated with combined loss of chromosomes 1, 2, 6, 10, 13, and 17. Less frequent additional individual losses can occur for chromosomes 3, 5, 8, 9, 11, 18, and 21q	ChRCC tumors have a generally lower mutational burden than ccRCC or type 1 pRCC tumors
Renal medullary carcinoma	<i>SMARCB1</i>	Gain of chromosome 8q	
FH-deficient RCC	<i>FH</i>	Loss of chromosome 1q	<i>FH</i> gene germline mutations are seen with HLRCC, but <i>FH</i> gene can also be somatically mutated
SDH-deficient RCC	SDH enzyme subunit genes, including <i>SDHB</i> , <i>SDHC</i> , or <i>SDHD</i>	Deletion of chromosome 1p	
Translocation RCC	Somatic translocations of <i>TFE3</i> , followed by <i>TFEB</i> and <i>MITF</i>	Gain of chromosome 17q and chromosome 9p loss	

sufficient for ccRCC development[23,24]. In contrast, ccRCC tumors characterized by punctuated evolution had low ITH and were dominated by a single clone but exhibited additional molecular alterations in the dominant clone that distinguished them from the similarly monoclonal *VHL* mono drivers. This tumor evolution group included a *VHL*-wildtype subtype, a *VHL*-followed by *BAP1* mutation (*BAP1*-driven) subtype, and tumors with multiple clonal driver mutations (*PBRM1*, *BAP1*, *STED2* or *PTEN*). These tumors grew rapidly to a large size and were linked to widespread and rapid metastases[20]. Within this group, *BAP1*-deficient tumors were associated with higher grade and aggressiveness than *PBRM1*-deficient tumors[11,24,25], while

PBRM1 loss was associated with metastasis tropism to the pancreas[26], and these tumors are characteristically indolent. However, *PBRM1*-deficient tumors can become more aggressive with further evolution and mutations in the mTOR pathway[24] or *SETD2*[27], with which *PBRM1* cooperates[25].

Genetics of Non-Clear Cell Carcinoma

Papillary renal cell carcinoma

Papillary renal cell carcinoma has been classically subdivided into 2 subtypes on the basis of histology and genetic features[28]. Genetically, type 1 pRCC is associated with frequent gains of chromosomes 7 and 17, as well as less frequent gains of chromosomes 2, 3, 12, 16,

and 20[29–32]. The most frequent somatic mutational events in type 1 pRCC are activating mutations of the *MET* oncogene on chromosome 7, present in 10%–15% of type 1 pRCC cases[33]. Notably, germline activating mutations of the *MET* oncogene are the pathogenic cause of hereditary papillary renal cell carcinoma (HPRC) syndrome, in which patients present with bilateral, multifocal type 1 pRCCs[31,34] (Table 1).

In contrast, type 2 pRCC tumors are not associated with a specific pattern of copy number alterations, and are now seen to represent a heterogeneous group of what are now distinct RCC subtypes, including translocation RCC, FH-deficient RCC, and SDH-deficient RCC. In light of the above heterogeneity and the absence of characteristic genomic features for this group, pRCC type 2 tumors may also be interpreted as aggressive, unclassified RCC that exhibit papillary features but require specific genomic subclassification for clinical outcome prediction[35]. Similarly, while type I pRCC is considered the “classical” morphologic entity, certain neoplasms that exhibit its features may also be considered variants or potential new RCC entities[36], with distinct molecular features, such as papillary renal neoplasm with reversed polarity (PRNRP)[37] and biphasic hyalinizing psammomatous RCC (BHP RCC)[38], which have distinct driver mutations (KRAS and NF2, respectively).

Chromophobe renal cell carcinoma (chRCC)

Like ccRCC and pRCC type 1 tumors, most chRCC are characterized by a distinct pattern of chromosomal alterations, defined by combined loss of chromosomes 1, 2, 6, 10, 13, and 17, seen in approximately 80% of chRCC. Less frequent additional individual losses can occur for chromosomes 3, 5, 8, 9, 11, 18, and 21q in 12%–58% of cases[39,40]. The histology of chRCC can include a rarer eosinophilic variant in which the classic pattern of chromosomal losses is less common. ChRCC have a lower mutation burden than ccRCC or pRCC-1; only *TP53* and *PTEN* are frequently mutated in ~30% and ~8% of cases, respectively[33,41]. Loss of *CDKN2A*, by either loss of 9p21 or hypermethylation, is the next most common alteration, affecting 19.8%[33] (Table 1). Increased *TERT* expression has been observed in approximately 17% of ChRCC, resulting from either mutations or genomic rearrangements in the *TERT* gene promoter, the latter including intra-chromosomal rearrangements and translocations with chromosome 13.11[42].

Medullary Renal Carcinoma

Renal medullary carcinoma (RMC) is a rare and aggressive subtype of kidney cancer that accounts for less than 1% of all RCC and has a propensity for early metastases, resulting in a median overall survival of little more than a year[43–45]. RMC predominantly afflicts individuals with sickle cell trait, creating a

preponderance of patients with African or Mediterranean descent, and the young, with a median age from 19 to 22 years[43–49]. The characteristic genetic and immunohistochemical feature of RMC is the near universal loss of expression of the SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily B member 1 (SMARCB1) protein, also known as integrase interactor 1 (INI1), BRG1-associated factor 47 (BAF47), or sucrose non-fermenting 5 (SNF5). The SMARCB1 protein is encoded by the *SMARCB1* gene on chromosome 22q11.23, and in most tumors both copies of this gene are lost through a combination of mutation and chromosomal deletion (Table 1)[50]. SMARCB1 is a core subunit of the SWI/SNF chromatin remodeling complex; its loss results in transcriptional dysregulation of many pathways[9,51].

FH-deficient and SDH-deficient renal cell carcinoma

Hereditary leiomyomatosis and renal cell carcinoma (HLRCC) is a familial cancer syndrome characterized by the development of cutaneous and uterine leiomyomas and a highly aggressive form of kidney cancer [52–55]. HLRCC is associated with germline mutation of the Krebs cycle enzyme gene *fumarate hydratase* (*FH*); because the associated tumors demonstrate loss of FH enzyme activity, they are referred to as FH-deficient RCC[56–58]. *FH* can also be mutated somatically. Similarly, germline mutations of several subunits of the Krebs cycle succinate dehydrogenase enzyme, including *SDHB*, *SDHC*, or *SDHD*, have been associated with increased risk for paraganglioma (PGL), pheochromocytoma, gastrointestinal stromal tumor (GIST), and RCC[59–61].

The complete loss of either FH or SDH enzyme activity impairs the normal function of the Krebs cycle, resulting in accumulation of intracellular fumarate and succinate, respectively[62,63]. This accumulation promotes a pseudo-hypoxic state that upregulates several enzymes, particularly enzymes involved in chromatin hypermethylation[32,64–67]. Furthermore, FH and SDH loss results in aberrant succination of KEAP1 protein, which promotes constitutive upregulation of the NRF2-antioxidant response element (ARE) pathway and inactivation of the core factors responsible for replication and proofreading of mitochondrial DNA (mtDNA), resulting in both a significant decrease in mtDNA content and increased mtDNA mutation[68,69].

While SDH and FH-deficient tumors share similar genetic characteristics, a recent germline analysis comparing these tumors noted that while most of these tumors harbored germline alterations in their respective genes, SDH-deficient RCCs had a lower mutation burden and SCNA burden than FH-deficient RCCs[70]. In addition to patients with germline mutation, a small

number of sporadic tumors have also been shown to have complete somatic loss of FH, resulting in a non-hereditary form of FH-deficient RCC[32].

Translocation renal cell carcinoma involving *TFE3*, *TFEB*, or *MITF* gene fusions

Translocation renal cell carcinomas (T-RCCs) are driven by somatic chromosomal translocations that fuse members of the MiT transcription factor family genes, *TFE3*, *TFEB*, or *MITF*, with various partner genes that result in fusion proteins[31,71,72] that affect many pathways, such as organelle biogenesis, cell proliferation, and cellular fate commitment, all of which may promote tumorigenesis[72–74]. T-RCCs represent one of the most common forms of RCC in children and young adults, making up 20%–50% of pediatric RCC patients and 15% of RCC patients under the age of 45[72,75]. T-RCC in adults can present with a variety of histologies, including both papillary or clear cell[32,72]. To date, fusions involving *TFE3* are the most common, followed by *TFEB*[31,33,71,72,76].

Tumor Microenvironment of RCC

While initial profiling studies of the TME of RCC tumors grouped its tumor phenotypes into either immune-infiltrated or excluded phenotypes[77,78], more recent studies have found infiltrating T cell populations to exist in a continuum from activated antitumor to dysfunctional “exhausted” T cells[79,80]. Similarly, while the function of tumor-associated macrophages (TAMs) has classically been divided into either the pro-inflammatory/antitumor M1 or the anti-inflammatory/pro-tumor M2 phenotypes (polarizations)[81–85], recent evidence shows that TAM populations are highly plastic, existing in more of a phenotypic spectrum between the M1 and M2 phenotypes in vivo[81,83,84,86].

More recent studies have shifted to transcriptomic analyses that utilize microarray and next generation sequencing (RNA-seq) technologies along with computational techniques to deconvolute the TME to its cellular components and explore their role in tumor response to systemic therapies through an array of gene expression signatures representative of novel cell phenotypes and processes[77,87–89]. Such studies noted a generally negative correlation between enrichment of T-helper subtype 2 (Th2) cells and T-reg cells and survival in ccRCC[77], explaining previously reported negative association between T cell infiltration and clinical outcomes in ccRCC[83,84,90,91]. Similarly, worse overall survival and lower likelihood of response to TKI agents were associated with higher levels of M2-type macrophage infiltration in the TME[92]. This understanding of the TME led to investigations of prognostic and theranostic transcriptomic gene signatures that may predict survival and response to systemic therapy

in advanced RCC. These include angiogenesis-associated signatures to predict response to tyrosine kinase inhibitors[89,92,93] or immune signatures to predict response to immune checkpoint blockage (ICB)-based combinations[89,93,94]; and transcriptomic classifiers such as the 4 molecular subtypes (ccRCC 1-4) described by Beuselinck et al. for metastatic ccRCC (m-ccRCC)[95], which were shown to predict both survival outcomes as well as therapeutic response to TKI (sunitinib or pazopanib) monotherapy, which were attributed to inherent differences in their underlying TME[95–97]. Prospective patient selection for ICB-based or TKI-monotherapy based on these subtypes was recently evaluated in the phase II BIONIKK trial, which demonstrated the feasibility of biomarker-driven tailored systemic therapy in m-ccRCC[98], potentially maximizing therapeutic benefit while reducing unnecessary toxicity from systemic therapy regimens in m-ccRCC.

Understanding of the TME was further revolutionized by single-cell based analyses such as single-cell RNA sequencing (scRNA-seq) and single-cell mass cytometry (scMC), which allow for massively parallel, high-dimensional analyses of specific cell populations in the TME, enabling prediction of potential interactions between various cell populations based on their expressed surface molecules, promoting a much more granular understanding of the dynamics of the TME of RCC than what was offered by bulk RNA-sequencing approaches, which are bound to oversimplify tumor cell populations and their dynamic interactions[81,83,84,86,99]. In this regard, Chevrier et al.[86] used scMC to profile adaptive and innate (T cell and TAM) populations in the TME of 73 patients with untreated advanced RCC and 5 healthy matched kidney samples. Using computational phenotype clustering, they identified 22 T cell and macrophage phenotypes[86], noting a “terminally exhausted” PD1+ cluster and a corresponding “progenitor exhausted” cluster of potentially ICB-responsive T cells. They also noted 17 different TAM clusters, arguing that the M1/M2 polarization phenotypes are an oversimplification of this plastic and dynamically changing cell population. Finally, they noted immunosuppressed T cell compartments to be associated with high levels of regulatory CD4 cells and a pro-tumor TAM population[86].

Following this study, Braun et al.[83] performed scRNA-seq and T cell receptor (TCR) sequencing of ccRCC tissue from 13 patients with tumors of a range of clinical stages to explore changes in the immune TME with advancing disease. They again noted significant diversity within the TAM and T cell populations, and found T cells to exhibit an overall trend of progressive dysfunction and exhaustion with advancement in disease stage, which was associated with a concurrent shift from M1 to M2-like signatures in the TAM population and increasing T cell and TAM interactions, again

confirming that TAMs play a key role in the progression of T cells toward exhaustion in ccRCC[83].

To examine the influence of ICB on the RCC TME, Krishna et al.[81] used scRNA-seq to compare the TME of multi-regional tumor samples from 4 ICB-treated to 2 ICB-naïve advanced ccRCC patients. They noted significant intratumoral and inter-patient heterogeneity, along with differences in the overall TME between ICB-treated versus naïve patients. Focusing on tumor specimens from an ICB-treated patient that exhibited complete response, they noted enrichment of CD8A+ tissue-resident populations and low TAM infiltration in all tumor regions. In contrast, specimens from ICB-resistant patients exhibited high TAM infiltration but low T cell enrichment (i.e., T cell exclusion)[81]. Similarly, Bi et al. compared tumors from 5 ICB-exposed to 3 ICB-naïve patients with advanced ccRCC, and noted that while ICB-exposed tumors were enriched in CD8+ T cells that expressed costimulatory molecules associated with the “progenitor exhausted” phenotype described by Chevrier et al.[86], they also paradoxically expressed inhibitory molecules associated with terminally exhausted T cells, suggesting that these ICB-responsive cells were potentially undergoing a shift toward

terminal exhaustion as well. Similarly, antitumor TAM populations in ICB-exposed patients were noted to paradoxically express molecules that correlate with a pro-inflammatory, antitumor phenotype, but again with upregulation of immune checkpoint and anti-inflammatory signaling genes. The authors proposed that these seemingly paradoxical changes in both T cell and TAM populations within the tumors of ICB-exposed patients may explain the initial response and eventual transition to resistance to ICB agents noted in ccRCC[84]. All 3 scRNA-seq studies also identified and externally validated novel gene signatures that may allow for the detection of specific T cell and TAM populations[81,83,84].

Summary

The genetic determinants of RCC have become more clearly defined, which has led to increased understanding of its evolution and metastatic development, particularly in ccRCC. While increasing data support the role of the TME in determining therapeutic response, the molecular links to immune response are only beginning to be characterized. Future studies of both human tissue and murine models will facilitate further progress in the quest to understand and better manage this disease.

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