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Basic research in Kidney Cancer

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Introduction

Cancer of the kidney is expected to affect almost 100.000 patients in the United States and European Union in 2010[1;2]. Renal cell carcinomas (RCC) refer to cortically derived tumors of the renal parenchyma and encompass a heterogeneous group of cancers[3]. Advances in basic research aimed at defining pivotal molecular events in the development of these different entities has shown that renal cancers can be subdivided based on genetic profiles. Moreover, knowledge of underlying molecular characteristics identified the vascular endothelial growth factor (VEGF) and the mammalian target of rapamycin (mTOR) pathways as fundamental to the biology of clear cell RCC. This biologic insight provided a rationale for targeting these growth factor signaling pathways in RCC.

Basic science in RCC is a vast area therefore we will focus on four areas of research that were felt most relevant for renal cancer and are not discussed in-depth in other chapters: the molecular basis of renal cancer, targeted therapies, renal cancer and immunity, and genetic factors and RCC. Finally, it is important to note that great majority of basic research in RCC is focused on clear cell RCC given the high prevalence of this histological subtype. Additionally, while the vast majority of studies have been performed on material from primary lesions, future studies should consider examination of metastatic lesions as well.

The molecular basis of renal cancer

Historically, four main histological renal cancers were recognized in the Heidelberg classification: clear cell Renal Cell Cancer (ccRCC, 60–80%), papillary RCC (10–15%), chromophobe RCC (~5%) and renal oncocytoma (~5%)[3;4] Recently, translocation linked[5;6], mucinous tubular and spindle type RCC[7] and tubulocystic carcinoma[8] (all comprising <1% of cases) have been added to this list. It is now clear that these

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morphological subtypes represent highly dissimilar diseases in both genetics and clinical behavior, and thus may or may not be variants of a common cancer or common cell of origin.

The biology of the von Hippel-Lindau (*VHL*) gene product, pVHL, and its regulation of the hypoxia inducible factor (HIF) family of hypoxia-regulated transcription factors, is tightly linked to ccRCC biology. The discovery of the *VHL* gene, and its association with the *VHL* syndrome of central nervous system hemangioblastomas, pheochromocytoma/paraganglioma, and ccRCC, in 1993[9] quickly led to the discovery that *VHL* mutation is also tightly associated with sporadic ccRCC, detected in up to 90% of tumors[10–13]. The loss of *VHL* leads to the loss of regulation of HIF family members HIF1α, HIF2α[14–18], and HIF3α[19], which is further composed of several splice variants. Xenograft studies have demonstrated that restoration of pVHL expression or suppression of deregulated HIF2α impairs the growth of these tumors[20;21].

Papillary RCC, chromophobe RCC and renal oncocytoma are less dominated by mutations in a single gene. Mutations in c-met have been associated with familial papillary type 1 RCC, but only in a subset of sporadic papillary RCC, and is thus less dominant than *VHL* is for ccRCC[22]. A more rare, but also highly aggressive type of papillary type II renal cell carcinoma has been associated with mutations in the fumarate hydratase gene [23], although the relevance of this mutation in sporadic disease is unknown. Heterozygous knock-out of the gene implicated in the Birt-Higg-Dubé (BHD) syndrome in mice leads to the development of renal cysts and three different histological types of renal tumors, similar to human BHD which is closely associated with familial chromophobe RCC, but predisposes to other histologies as well [24].

In spite of the tight correlation of ccRCC with inactivation of *VHL*, the effect on HIF deregulation is not uniform: variant mutations in *VHL* may contribute to imbalances of HIF1α and HIF2α deregulation, leading to distinct effects on cell growth[25;26]. In a strategy to determine whether tumors could be defined based upon the most studied and understood pathway in RCC, gene expression profiles were linked with *VHL* mutation analysis and expression characteristics of the HIFs[27]. In this study, 160 ccRCCs were classified as *VHL* mutant or wild type and according to HIF protein expression. *VHL* mutant, HIF1 and HIF2 expressing tumors (H1H2) overexpressed the Akt/mTOR pathway, while *VHL* mutant tumors expressing solely HIF2 (H2 tumors) replicated more rapidly, marked by overexpression of Ki-67, which other groups have identified as a poor-risk marker[28]. ccRCC can thus be characterized as H1H2 or H2, with dramatically differing effects on tumor cell proliferation and C-myc regulation[27]. Recent evidence suggests that the H2 tumors may be derived from H1H2 tumors that lose HIF1α in a subset of tumors, suggesting a potentially selective pressure to lose the HIF1α gene during tumor progression[29]. These insights potentially narrow the key tumorigenic events within the *VHL*/HIF axis.

Besides *VHL* loss and HIF activation, major efforts have yet to identify a simple linear progression of genetic lesions accounting for the gains in aggressiveness in RCC[30–34]. Two recent ccRCC cytogenetic studies lend clues to understanding this progression. One

study performed both single nucleotide polymorphism (SNP) analysis and gene expression analysis on sporadic ccRCC and tumors from patients with *VHL* disease[30]. Importantly, this study demonstrated that tumors from sporadic and *VHL*-disease ccRCC tumors have overall similar profiles, but sporadic tumors are more heterogenous and contain a higher number of genetic events per tumor, but they cannot be distinguished using unsupervised analysis of gene expression data. In a prospective analysis of 282 ccRCC patients with up to 108 months of follow-up using traditional cytogenetic karyotyping techniques[32] chromosomal loss at 3p (the genomic home of the *VHL* gene) was significantly associated with improved disease-specific survival, while losses of 4p, 9p and 14q were significantly associated with reduced disease-specific survival, but the specific genes in these regions implicated in causing the poor prognosis remain to be characterized.

The first whole sequencing study in ccRCC confirmed that considerable genetic heterogeneity exists in ccRCC [29] emphasizing that even though the vast majority of ccRCC contain mutated *VHL* most likely every tumor has a unique gene signature. This study also substantiated findings in multiple mouse knock-out studies and a zebrafish study which demonstrated that *VHL* mutations/knock out alone is insufficient to produce ccRCC and that additional genetic events are required [35;36].

Although unable to cause sporadic ccRCC alone, the presence and type of *VHL* mutations in tumors have been consistently considered as possible biomarkers. Cowey, et al, recently reviewed its potential in prognosis and prediction[37]. Further research is still required to establish *VHL*'s efficacy as a biomarker, but given the frequency of its inactivation, more opportunities to understand the heterogeneity of this disease may lie in exploration of downstream factors. When *VHL* is inactivated and HIF expression constitutively stabilized, a host of other genes which make up various components of the hypoxia response are transcriptionally upregulated (reviewed in[38]). It remains to be determined which of these factors or pathways most significantly contributes to the formation or maintenance of ccRCC's malignant phenotype. One HIF target, the vascular endothelial growth factor (VEGF), has been found to be significantly upregulated in kidney tumors compared to its elevated expression in many other cancers. As a prognostic biomarker, VEGF has not been proven to be valuable, but may be predictive of response to VEGF targeted therapy, as described below.

In order to identify more effective biomarkers and further understand the underlying biology, several different groups performed gene expression analyses on ccRCC tumor samples. Table 1 gives an overview of these studies. One of the initial expression profiling studies examined 29 ccRCC tumors, identifying 51 genes that could classify tumors based on 5 year disease-specific survival[39]. This study verified the possibility that gene expression profiles could be used to predict outcome in ccRCC, but remains to be validated or defined by biological parameters that may account for this difference in disease activity. One study of 51 tumor samples identified vascular cell adhesion molecule-1, VCAM-1, as a prognostic biomarker [40], which has subsequently undergone retrospective validation [41;42]. Importantly, high expression of this molecule predicted for better overall survival in both clear cell and papillary tumors, suggesting that VCAM-1 expression may generally indicate

tumor cells with lower metastatic potential. The further implications for sensitivity to antiangiogenic therapy are not yet known.

Several gene signatures for RCC progression, for example three genes (caveolin 1, lysyl oxidase, and annexin A4) have been identified as associated with RCC aggression and/or survival[43] [44]. Similarly, survivin was shown to independently predict clear cell progression and risk of death [45][46]. Finally, the largest study, analyzing 177 clear cell tumors, identified 340 transcripts (including VCAM-1) significant in multivariate analysis with stage, grade and performance status[47][48].

While the above studies focused on clinical endpoints in their analyses, many started with an unsupervised analysis to get a general understanding of the data. The study that identified VCAM-1 as a prognostic biomarker saw the presence of potentially two subgroups within the stage IV tumors, with survival differences[40]. This suggests that molecular features beyond clinical staging could provide informative data in understanding even metastatic tumor behavior. The group of Zhao, et al. examined their 177 tumors using 3,674 genes also observed two larger groups of ccRCC, with significant survival differences as well as predicted biological pathway distinctions[47]. These studies helped to set the stage for further delineation of subgroups within ccRCC.

Two other studies stand out as being predominantly geared toward identifying the inherent subgroups and underlying biological differences of ccRCC. One group first looked at 16 ccRCC tumors and saw that there seemed to be two types of clear cell, one that more highly overexpressed metabolic genes and the other extracellular matrix/cell adhesion genes[49]. Most recently, a bioinformatic technique called unsupervised consensus clustering was used on 48 tumors to identify two subtypes of ccRCC, ccA and ccB, distinguished by fewer than 120 probes[50]. Validating these results in the Zhao, *et al.*, data set of 177 tumors, patients with ccA tumors have a marked survival advantage over those with ccB tumors. Additionally, this dataset validates the characteristics that ccA tumors display a profile of altered metabolism, whereas ccB tumors display characteristics of wound healing and epithelial to mesenchymal transition.

Finally, one study focused entirely on metastases[51], finding that late occurring metastases more highly expressed genes involved in angiogenesis, cell migration and adhesion. Additionally, genes related to cell division and cell cycle were overexpressed in samples from patients with multiple metastases, indicating that the presence of more metastases might be caused by an increased growth potential.

All of the potential biomarkers emerging from the gene expression studies require removal and processing of at least part of the tumor. Plasma serum proteins have traditionally been studied to find non-invasive diagnostic markers for the presence of ccRCC as compared to normal or benign renal tissue. Currently, there are no circulating tumor markers available for clinical use in management of RCC. Several molecules have been studied as candidates for diagnosis of RCC: In clear cell RCC the results with VEGF and VEGFR have been contradictory[52;53], and these markers might be more suitable as predictive than as diagnostic markers. Recent studies have shown elevated CAIX levels in ccRCC patients[54],

with a significant association between CAIX serum levels and occurrence of metastases[55]. Furthermore, in patients with localized disease an elevated CAIX level predicts the recurrence and is correlated with a shorter PFS. Again, there is not a complete concordance with tissue results. Other markers related to tumor biology like MMP-7, CD95, bFGF, hepcidin-25, Il-10 or IL-6 showed promising results as possible biomarkers for RCC[56–60], but these markers need to be validated in separate studies.

Because of the complexity of the tumor development and progression, identification of complex protein signatures is more promising. High throughput technologies like MALDI (Matrix-assisted laser desorption/ionization) or SELDI (Surface Enhanced Laser Desorption/Ionisation) allow the analysis of the whole proteome of many samples in a short time with high sensitivity. SELDI-TOF-MS (Time of Flight Mass Spectrometry) has especially been used to define prognosis related profiles. Unique protein signatures of tumor patients compared to normal controls with high sensitivity (70–87%) and specificity (89.9–92%) have been described[56–63]. One of the candidate proteins, SAA1, was identified by 3 groups[61;64;65]. In all published studies, elevated SAA1 concentration correlated with metastasis, poor prognosis and shorter survival[61;64–66], even though different cut-off values were used. Independent studies are needed to substantiate the value of SAA1.

Finally, an 831 tumor tissue microarray study analyzed 15 proteins that are associated with the pVHL and phosphatase and tensin homologue (PTEN) pathways[67]. Surprisingly, while pVHL and phospho-mTOR staining correlated inversely with tumor stage and grade, neither protein correlated with survival. Within the intermediate stage tumors (pT2 and pT3), tumors with p27 and CAIX expression associated with improved outcome. This study suggests that the dysregulation of several independent pathways are crucial for tumor progression, corroborating the sequencing study by Dalglish, et al.[29].

MicroRNA, 21–23 nucleotide segments of single-stranded non-coding RNA, have now been implicated in tumorigenesis of many cancers, even being identified as potential prognostic biomarkers in several of these (reviewed in [68]). The aberrant expression of these non-coding RNAs can provide a powerful method of epigenetic tumor regulation, as an individual microRNA can alter the expression of many target genes. In RCC, various studies have identified various individual or panels of microRNAs that are differentially expressed between normal renal tissue and tumor or between histological subtypes[69–76]. The identification of relevant targets of these tumor associated microRNAs are just becoming realized[74]. MicroRNAs can be easily extracted from formalin fixation, paraffin embedded tissue, and blood. The ability to easily use non-invasive measures to identify a stable target makes microRNAs a very attractive biomarker for diagnostic, prognostic, and predictive purposes.

A large number of potential biomarkers have emerged from all these gene expression studies. Encouragingly, trends are beginning to emerge between studies. The next important step will be bringing these potential biomarkers and biomarker profiles to the clinical arena.

Targeted therapies in RCC

The increased understanding of the fundamental disease biology of RCC has been translated into the development of therapies with inhibitory activity against the implicated pathways, particularly the VEGF and mTOR pathways. A number of tyrosine kinase inhibitors (TKI) have now been registered for treatment of metastatic RCC (mRCC) (sunitinib, sorafenib, pazopanib) and more TKI (e.g. axitinib, tivozanib) are being developed. The rapid and simultaneous emergence of several active compounds has far outpaced the ability to critically understand precise mechanisms of response and resistance[77].

Surprisingly, the TKI were clinically implemented with very few preceding pre-clinical studies. For example, the cross-reactivity of TKI with non-target (non-VEGF-receptor) TK[78] was established after clinical implementation and preclinical studies in various animal models demonstrated stabilization or regression of xenografted tumors (mostly in non-RCC models). The rationale to study this new category of drugs in RCC patients was based on theoretical considerations that these TKI attacked pathways essential in RCC biology and, therefore, might be appropriate new drugs for RCC therapy. Indeed, the effects of TKI in RCC patients are impressive, with objective response rates as high as 45% (reviewed by e.g., Rini et al. [79]), but treatment is often accompanied by many side effects requiring dose reduction or cessation of treatment.

TKI treatment of RCC patients leads to a massive destruction of the tumor vasculature with concomitant tumor necrosis. Whether RCC cells themselves are targeted remains uncertain[80]. At pharmacological relevant doses no effect on tumor cells was observed[80] and there is evidence that tumor co-option occurs, i.e., tumor growth along larger mature vessels, permitting tumors to escape TKI treatment. Additionally, resistance to existing VEGF blocking agents may include upregulation of HIF- and/or non-HIF-mediated angiogenic proteins or inadequate target inhibition. mTOR therapy resistance may involve a compensatory increase in upstream elements leading to HIF production[77].

Obviously, predictive biomarkers for response to TKI in mRCC patients are urgently needed, and some have been described. Serum from patients with clinical response or progression was screened by cytokine arrays to discover that TNF-alpha and MMP-9 levels remained low in responders[81]. Additionally, high levels of these proteins in the serum correlated with decreased overall survival. In another study, low serum levels of sVEGFR-3 and VEGF-C corresponded with longer progression free survival (PFS) and objective response rate in bevacizumab-refractory mRCC[82]. A third study suggested that large changes in serum VEGF, sVEGFR-2 and sVEGFR-3 levels corresponded with tumor response[83], and a fourth study found a correlation between fold-increase of serum VEGF and clinical benefit[84]. All of these potential predictive biomarkers require external validation in larger sample sizes, but suggest that serum may prove to contain cogent markers of survival and response.

RCC and the immune system

There is increasing evidence that TKI treatment leads to alterations of the immune status of RCC patients[85;86]. Sunitinib can reverse myeloid-derived suppressor cell induced immune suppression, but other studies indicate that Sunitinib can inhibit the proliferation of primary human T cells from normal healthy volunteers as well as from RCC patients[87]. Moreover, sunitinib treatment appears to reverse Th1 suppression and impairs NK function. Similarly, sorafenib treatment impairs NK activity and cytotoxicity at pharmacological levels[85]. Also, sorafenib treatment leads to a decrease of Treg in primary lesions and Treg levels decrease to normal levels after sorafenib treatment. Whether the immune component is important and might be used to our advantage in designing combination therapies is an uncharted field[86].

It is important to realize that RCC tumors develop in immune competent hosts and that these tumors have escaped from immune surveillance and immune editing leading to tumor cells that are resistant to immune-system mediated destruction[88]. Nevertheless, to date, immunotherapy is the only treatment that can consistently induce durable complete clinical responses in mRCC[89].

Several studies have demonstrated the ability of tumor infiltrating lymphocytes (TIL) to induce tumor response in mRCC with objective response rates between 0 and 25 %, with concomitant infusion of IL-2[90–95]. At UCLA, patients with largely advanced and metastatic disease received a combination of TIL/CD8+ and IL-2. Overall, 9.1 % of patients achieved CR while 25.5% had a PR showing the potential of TIL in mRCC[94]. Taken together these studies demonstrated the need of using highly selective and specific activation methods of effector cells in order to achieve a meaningful antitumor immune response. Unlike melanoma, where specific T-cell clones against well-defined tumor epitopes can be frequently generated, T-cell clones that specifically recognize kidney cancer tumor antigens are hard to generate. The proof of concept of isolating these clones and successfully treat patients with mRCC has however been well established. On the other hand, given the *in vitro* work needed to isolate TIL, this approach still needs to prove that it induces better clinical responses than HD-IL2 alone.

Side studies of clinical trials with dendritic cells loaded with cell lysates, peptides, or RNA or Treg depletion have demonstrated the induction of specific T cell responses, but no clear correlation between clinical benefit and the occurrence of a immune reaction was found[96;97]. There is evidence that various factor hamper an anti-tumor response: defective CD8 signaling, a Th2-bias, and elevated levels of gangliosides from T cells are associated with T cell dysfunction[98;99]. Basic research aimed at understanding the relation between RCC and immune cells have revealed an increasingly complex picture with many players. Cross-talk between RCC and dendritic cells (DC), Treg, CD4+, CD8+, NK-cells, γδT cells, NK-like T cells, and Myeloid Derived Suppressor Cells, have been described[100]. The plasticity of cells from the immune system is extraordinary and the tumor milieu plays a pivotal role and can greatly influence the outcome.

In recent studies, efforts were poised at gene-modified T-cells[101] and multimodality immune-based strategies[102]. Gene-modified T cells in melanoma has shown interesting results with two CR [103]. For RCC, infusion of gene-modified T cells with CAIX specificity lead to liver toxicity, probably due to destruction of bile epithelial cells that also express CAIX[101]. Although this demonstrated that the gene-modified did exert the desired specificity, the observed toxicity also highlights the potential problems of this approach: extraordinary tumor specificity appears to be of utmost importance. In the multi-modality immune-based strategy the CA9 and GMCSF genes were inserted in an adenovirus genome to infect DC which allowed the expression of the GMCSF/CA9 fusion protein[102]. Overexpression of the fusion protein in DC through adenoviral infection CA9 specific T cells could be generated with toxicity against RCC. Hence, this new strategy combines many immunotherapy approaches: 1) the immunostimulatory effects of cytokines; 2) the vaccine capabilities of DC and; 3) the specific antitumor activity generated by tumor antigen gene delivery in APC. Indeed, the CA9-GMCSF/DC based vaccine is an example of the new multimodality immune-based strategies that may enhance the well-established potentials of immunotherapy in RCC.

The effectiveness of tumor vaccines has been shown in many animal models. However, translation to the clinic has proven difficult, possibly because in these model systems naturally occurring tumors have not been studied, thereby avoiding tumor surveillance and tumor editing. Thus, the concept is tested in immune competent hosts that are vaccinated with peptides or tumor homogenates and challenged with viable tumor cells or, alternatively, vaccination strategies are tested in animals with established tumors. Initial tumor vaccines were based on total tumor cell lysates that were injected to the patients (autologous tumor cell vaccines). However, new strategies using genetically modified tumor cells, antigen presenting cells (APC) or tumor specific peptides have been developed to increase the specificity of the response. Two phase-III clinical trials that have used autologous cell lysate or peptides to prevent recurrence in high-risk RCC patients have been published[104;105]. Jocham et al. have reported a statistically significant increase in 5-year PFS (77.4 vs 67.8%, p=0.0204) for the vaccine group in high-risk non-metastatic RCC patients. More recently, Wood et al. published a similar study in high-risk non-metastatic patients using heat shock protein derived peptide vaccines and did not observe a statistical difference in PFS (p=0.51). However, secondary analysis did show an almost statistically significant PFS survival when only stage I and II patients where included (p=0.056). Therefore, vaccine approaches show great promise in preventing recurrence after nephrectomy but the subgroups of patients that would beneficiate from such therapy still need to be determined.

Genetic factors and RCC

Epidemiological studies have conclusively identified three risk factors for the development of RCC: hypertension, obesity and smoking[106–108]. Furthermore, there is evidence that genetic factors influence susceptibility to RCC; for instance, the life-time risk increases approximately two-fold for those with a first-degree relative with RCC[109]. Thus far, candidate gene studies have not yielded notable candidate genes. In a recent genome-wide association study (GWAS) of RCC three susceptibility loci on chromosomes 2p21 (*EPAS1*), 11q13.3 and 12q24.31 (*SCARB1*) were identified (Purdue et al, submitted). The findings

from the GWAS provided further evidence that *EPAS1* (HIF2α) is a key gene in RCC development, but additional studies are needed to identify the functionally relevant common variants associated with increased risk.

Up to now little attention has been paid to inter-ethnic variability or individual differences, whereas this is an important aspect in the current TKI era. Patients of afro-american descent have higher incidence rates and lower survival rates compared to all other races, also when diagnosed with localized disease. In contrast, Asian/Pacific Islander patients have lower incidence rates and higher survival rates than all the other ethnicities[110]. Furthermore, response to treatment and frequency of severe toxicity is related to ethnic origin, most likely due to different pharmacokinetics and not the genetic nature of the disease. Sunitinib, sorafenib and pazopanib have been associated with significant toxicity profiles which vary widely. Higher toxicities during cytotoxic chemotherapy have been reported in patients enrolled Japanese trials compared to patients in American or European trials[111]. Ethnic differences in hematological toxicity have been attributed to the varying activities of drug – metabolizing enzymes and transporters that are mainly associated with polymorphisms in the promoter and coding regions of these enzymes[111]. In a phase II study assessing the efficacy and safety of sunitinib in Japanese patients, the incidence of hematological adverse events was numerically higher than those previously reported in western trials, however the AUC values for sunitinib were similar in both groups[112].

In the only pharmacogenetic study published until now, 31 single nucleotide polymorphisms in 12 candidate genes, together with several non-genetic variants, were analyzed for a possible association with toxicity[113]. Encouragingly, particular haplotypes (most notably by polymorphisms in CYP1A1) could be correlated to sunitinib-related toxicity. Because race-related differences in the frequency distribution of four genetic polymorphisms in the CYP1A1 P450 enzyme genes have been identified between Japanese and Caucasian populations, this may partly explain the inter-ethnic differences observed[114].

Conclusions

In the last decade, great strides have been made in the understanding of molecular mechanisms underlying renal cell carcinoma patients. The state-of-the-art has clearly led this field to the enviable position of having a range of molecularly targeted therapies. Nevertheless, despite the clear improvement in the therapeutic options for mRCC patients, therapies targeting the tumor cells themselves are highly desirable. Better models, closer resembling the natural course of renal cancer are needed. It is foreseen that through integration of various high-throughput platforms personalized cancer treatment for renal cell carcinoma patients is possible. There are further improvements expected on the horizon: recent effort have made progress toward using formalin-fixed paraffin-embedded tissues for molecular analyses (including DNA and RNA recovery), which will permit studies on enormous archives of existing specimens [115] including metastatic lesions, a hitherto understudied area; mature profiles of protein and nucleic acid biomarkers will help us to define the spectrum of tumors that lie under the umbrella of ccRCC; and a future unmapped territory of genetic mutations to explore that may provide more tools and answers to the

questions we ask. There is great hope for the future of renal cell carcinoma treatment, and it will be exciting to see what new advances will be made in the decade to come.

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Table 1

Gene expression studies in RCC (reproduced with kind permission from Springer Science+Business Media: Curr Oncol Rep: Renal cell carcinoma: where will the state-of-the-art lead us? Volume 12 (2010) 193–201, Brannon AR, Rathmell WK, Table X[116]).

Study	Year	Samples	Analytical focus	Results
Clinically driven analyses				
Takahashi [39]	2001	29 clear cell 29 normal	5 year survival	51 probes associate with survival, 96% accuracy
Vasselli[40]	2003	51 clear cell 6 papillary 1 unknown	Survival	45 genes most associated with survival. VCAM-1 alone can stratify patients by survival.
Jones [117]	2005	22 clear cell 10 metastases 37 other 24 normal	Progression and metastases	31 genes that are continuously deregulated in disease progression. 155 genes that associate with metastases, 88.9% accuracy
Kosari [118]	2005	10 aggressive cc 9 non-aggressive cc 9 metastatic cc 12 normal	Tumor aggressiveness	35 genes distinguish between non-aggressive and aggressive tumors. Survivin expression associated with survival by multivariate analysis in 183 patients
Zhao [47]	2006	177 clear cell	Unsupervised	2 primary clusters composed of 5 subclusters with survival difference.
Yao [119]	2008	25 clear cell (14 metastatic) 2 metastases	Metastatic vs non- metastatic	3 genes (VCAM-1, EDNRB, RGS5) that by qRT-PCR associate with survival
Wuttig[51]	2009	20 metastatic clear cell	Disease-free interval Number of metastases	306 differentially expressed genes differentiate early (≤ 9 months) versus late (≥5 years) occurring metastases 163 probe sets differentiate patients with multiple (≥16) and “few” (≤8) metastases
Biology-driven analyses				
Vasselli [40]	2003	51 clear cell 6 papillary	Unsupervised	2 clusters of metastatic tumors with survival difference

Study	Year	Samples	Analytical focus	Results
		1 unknown		
Skubitz [49]	2006	16 clear cell 21 normal	Unsupervised	2 subtypes distinguishable by 546 genes, with possible pathway differences
Zhao [47]	2006	177 clear cell	Survival	259 genes associated with survival by univariate and multivariate analysis
Gordan [27]	2008	21 clear cell	Wild-type *VHL* vs H1H2 vs H2 tumors	3 groups have distinct biological pathways. H2 tumors overexpress c-Myc, leading to increased proliferation
Zhao [48]	2009	177 clear cell	Biology of survival gene set	Good prognosis tumors resemble normal renal cortex or glomerulus. Poor prognosis tumors associated with wound healing and loss of differentiation gene sets.
Brannon [50]	2010	48 clear cell 18 normal	Unsupervised consensus clustering	2 subtypes of clear cell (ccA and ccB) with pathway and survival differences, differentiable by <120 probes
Gene Expression and Cytogenetics/Sequencing Analyses				
Furge [31]	2004	60 clear cell 5 papillary 16 chromophobe	Histological classification by virtual cytogenetics	1018 gene classifier and cytogenetic classifier to distinguish between 3 subtypes, 99% and 81% accuracy, respectively.
Sultmann [34]	2005	65 clear cell 13 papillary 9 chromophobe 25 normal	Cytogenetics; Metastases and survival	136 genes significantly associated with cytogenetic abnormalities. 45 genes associated with survival. 85 genes associated with metastasis formation.
Beroukhim [30]	2009	49 sporadic cc 5 metastases 36 VHL tumors	VHL disease vs sporadic clear cell	VHL disease and sporadic clear cell tumors have similar gene expression and cytogenetic profiles, but sporadic cases have more frequent alterations.
Dalgliesh [29]	2010	96 clear cell	Genetics by sequencing	Mutations in histone modification and DNA damage repair genes may be important in RCC development or progression

cc, Clear Cell; H1H2, HIF-1 and HIF-2 overexpressing; H2, HIF-2 only overexpressing; VHL, von Hippel Lindau

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