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Kidney Cancer

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Abstract

Over 65,000 Americans are diagnosed with kidney cancer each year and nearly 13,000 die of this disease. Kidney cancer is not a single disease, it is made up of a number of different types of cancer, each with a different histology, a different clinical course, responding differently to therapy and caused by a different gene. Study of the thirteen genes that are known to cause kidney cancer has led to the understanding that kidney cancer is a metabolic disease. Recent discoveries of chromatin remodeling/histone modifying genes, such as PBRM1 and SETD2, has opened up new areas of intense interest in the study of the fundamental genetic basis of kidney cancer. New approaches to immunotherapy with agents such as the CTLA4 inhibitor, ipilumumab, have opened up promising new directions for clinical trials. A number of new agents targeting of VEGF receptor signaling and the mTOR pathways as well as novel approaches targeting HIF2 will hopefully provide the foundation for the development of effective forms of therapy for this disease.

Keywords

Kidney; Cancer; Methbolic; Disease

Kidney Cancer I

Kidney cancer is not a single disease; it is made up of a number of different cancers, each with a different histology, a different clinical course and caused by a different gene. Understanding the genetic basis of cancer of the kidney provides the opportunity for the development of effective forms of therapy for this disease.(1) Dramatic progress has been made in targeting the VHL pathway in clear cell kidney cancer. To date there are six approved drugs that are in use for patients with advanced kidney cancer. Although these targeted agents provide clinical benefit for thousands of patients with advanced kidney cancer, most patients develop resistance and eventually progress on targeted agents.

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Kidney Cancer is a Metabolic Disease

Marston Linehan provided an overview on the genetic basis of kidney cancer and noted that there are currently at least twelve well studied genes known to cause kidney cancer: *VHL*, *MET*, *FLCN*, *fumarate hydratase*, *succinate dehydrogenase B*, *succinate dehydrogenase D*, *TFE3*, *TFEB*, *MITF*, *TSC1*, *TSC2* and *PTEN*. Each of these genes is involved in the cell's ability to sense oxygen, iron, nutrients or energy; thus, it can be concluded that kidney cancer is fundamentally a metabolic disease.(2) Targeting the metabolic pathways in kidney cancer provides a novel approach for the development of effective forms of therapy for this disease. In order to highlight the potential for targeting the metabolic basis of kidney cancer, Linehan discussed two types of kidney cancer, which are characterized by mutation of Kreb's cycle enzymes, Hereditary Leiomyomatosis and Renal Cancer and Succinate Dehydrogenase Kidney Cancer.

Fumarate Hydratase Kidney Cancer

Hereditary Leiomyomatosis and Renal Cell Carcinoma (HLRCC) is a hereditary cancer syndrome in which affected individuals are at risk for the development of cutaneous and uterine leiomyomas and kidney cancer. HLRCC is characterized by germline mutation of the Krebs cycle enzyme, fumarate hydratase. HLRCC patients are at risk for the development of a very aggressive form of early onset, bilateral and/or multifocal type 2 papillary kidney cancer. HLRCC-associated kidney cancer can spread when the tumor is very small (less than 2 cm) and these patients should not be managed with active surveillance; surgical resection is recommended as soon as a solid tumor is detected. HLRCC patients should have imaging annually and genetic testing and abdominal imaging is recommended at age eight for at risk individuals.

Fumarate hydratase is a tumor suppressor gene; both copies (the germline allele and the somatic allele) are inactivated in HLRCC-associated kidney tumors. When fumarate hydratase (the Krebs cycle enzyme that takes fumarate to malate) is deficient, fumarate accumulates. The excess fumarate inhibits prolyl hydroxylase, which results in an inability of the VHL complex to target and degrade hypoxia inducible factor. HIF accumulates, producing an increase in VEGF transcription (which provides greater vasculature to the tumor) and an increase in GLUT 1 transcription (which increased the transport of glucose into the cell). (3) Loss of fumarate hydratase additionally dramatically impairs mitochondrial function and ATP production. Fumarate hydratase-deficient kidney cancer undergoes a metabolic shift to aerobic glycolysis; the electron transport chain is impaired and the tumors take up very little or no oxygen; i.e., normal oxidative mitochondrial function is disabled. These cancers shift to aerobic glycolysis; glucose transport and glycolysis increase and the cells become dependent on glycolysis for ATP generation. Activation of AMPK, the cell's main energy sensor, is decreased and mTOR and fatty acid synthesis are increased.(4) In addition, FH-deficient kidney cancer has been shown to be characterized by a reductive, glutamine-dependent pathway in which many of the normal Krebs cycle reactions are reversed to generate increased lipid pools critical to rapid cell division.(5) These findings provide the opportunity for the development of novel approaches

for targeting the metabolic basis of tumors characterized by aerobic glycolysis, such as agents directed at AMPK (such as metformin), fatty acid synthesis or glutamine metabolism.

Succinate Dehydrogenase Kidney Cancer

Succinate dehydrogenase kidney cancer (SDH-RCC) is another inherited form of kidney cancer characterized by germline mutation of a Krebs cycle enzyme. Patients affected with SDH-RCC are at risk for the development of pheochromocytomas, paragangliomas and kidney cancer.(6) Patients affected with SDH-RCC have germline mutation of succinate dehydrogenase B or succinate dehydrogenase D, and like FH-deficient kidney cancer, these tumors are characterized by aerobic glycolysis. SDH-RCC can also present with early onset and kidney lesions are at risk to spread when the tumors are small (less than 3 cm).

Targeting the Metabolic Basis of Kidney Cancer

Advanced HLRCC kidney tumors grow fast and are resistant to currently available chemotherapeutic and targeted therapies. Ramaprasad Srinivasan reported on a pilot trial utilizing an approach targeting the metabolic pathway in patients with advanced HLRCC-associated kidney cancer with bevacizumab and erlotinib. HLRCC tumors are very PET-avid, as the tumors have a very high rate of glucose transport compared with other tumors. It is possible that these tumors, which are exquisitely sensitive to glucose, (7) are also very sensitive to agents which target the tumor vasculature (such as bevacizumab). In a preliminary analysis of the results from this pilot trial, there were a number of patients who underwent objective partial responses and on patient who had a complete response to therapy. A formal trial is currently underway to evaluate the effect of bevacizumab and erlotinib in patients with advanced HLRCC-associated kidney cancer.

JNK Pathway Overexpression in Kidney Cancer

Kevin White reported on an elegant series of studies in which a novel JNK pathway factor was found to be overexpressed in clear cell kidney cancer. White and colleagues constructed a large-scale functional network model in *Drosophila* to evaluate transcription factors involved in the process of embryonic segmentation. In this model they studied an ubiquitin E3 ligase complex factor, SPOP, which mediates degradation of the Jun kinase phosphatase Puckered, which induces tumor necrosis factor-dependent apoptosis. To determine whether or not SPOP is associated with human tumors, White and colleagues screened SPOP protein expression on tissue arrays from 20 tumors from 18 different organs. They found that 85% of renal cell carcinomas expressed SPOP, while normal kidney tissue was negative. When they evaluated a tissue array containing more than 300 RCC samples, they found 77% were positive for SPOP expression. When tumor samples were classified by histologic type, 99% of clear cell RCC and 86% of chromophobe RCC samples were positive for SPOP and only a very small percentage of papillary RCC tumors were positive. When SPOP staining was screened in confirmed metastases from RCC 97% were found to be positive, indicating that SPOP staining may be useful for identifying clear cell RCC metastases.(8) This study identifies SPOP as a new marker for clear cell kidney cancer and could provide the foundation for novel approaches to therapy for this malignancy.

State of the Art: Novel Kidney Cancer Genes: PBRM1/Histone Modifiers

In the Kidney Cancer State of the Art presentation, Andrew Futreal, from the Cancer Genome Project of the Wellcome Trust Sanger Institute, reported on their remarkable results of systematic sequencing of renal cell carcinoma. In their first report in 2010, Dalgliesh, et al. reported on the sequencing of the coding regions of 3,544 genes in 101 clear cell RCCs which identified inactivation of two genes encoding enzymes involved in histone modification, *SETD2*, a histone H3 lysine 36 methyltransferase, and *JARIDIC*, a histone H3 lysine 4 demethylase, as well as *UTX*, a histone H3 lysine 27 methylase. Mutations in *NF2* were also identified in non-VHL mutated RCC.(9) In their second report, Futreal's group revealed truncating mutations of the SWI/SNF chromatin remodeling complex gene, PRBM1, in 41% (92/227) of cases. Inhibition of PBRM1 expression by small interfering RNA (siRNA) knockdown in clear cell RCC lines resulted in increased proliferation in 4/5 RCC lines and increased both cell migration, validating PBRM1 as a second major clear cell kidney cancer gene. Many of the cancers had mutations of VHL, PRBM1 as well as SETD2, indicating that these three genes, which are all located on chromosome 3p in an area commonly deleted in clear cell kidney cancer, may have complementary function.(10) The finding that the SWI/SNF complex is important in a number of cellular responses to hypoxia, including hypoxia-induced cell cycle arrest (11), may provide some early insights in the role of chromatin remodeling genes in the genesis of clear cell kidney cancer.

Kidney Cancer II

Numerous advances have been made in the management of renal cell carcinomas. In the area of managing localized disease, most priorities have focused on reducing morbidity and mortality in the setting of surgical procedures that have been proven to provide adequate oncologic control. Particularly in the case of managing localized renal cancers, the development of safe and effective strategies for partial nephrectomy emerged simultaneously as a widely used practice concurrently with the only randomized study to be undertaken to compare partial with radical nephrectomy. Such an opportunity to randomize patients according to surgical plan was fraught with complicating factors, and it is unlikely that such a study could ever be seriously considered in this era. Although the randomized study is underpowered, and suffers from several sources of bias, Dr. Van Poppel presents thoughtfully what is the only randomized data addressing this important question, which fails to show a survival and recurrence benefit to the partial nephrectomy arm (12;13). It is important to note that only a handful of patients of the over 500 randomized in the study have succumbed to metastatic disease, indicating the local control with either approach is generally excellent.

Turning to the management of metastatic disease, substantial advances have been made in tailoring immunotherapy, developing highly specific VEGF receptor targeted therapy, and identifying innovative new targets for therapeutic development. In a review of immunotherapy strategies, Dr. David McDermott examined tumor and host specific challenges that can be met by newer immune therapy approaches. Specifically, inhibition of co-stimulation presents a highly tractable strategy to train the host immune response to break tolerance, and attack tumor cells. The CTLA4 inhibitor, ipilumumab, recently approved for

treatment of melanoma is now undergoing study in renal cell carcinoma (14), and significant attention to another costimulation signal, PD-1/PD-1L interaction has resulted in numerous pharmaceutical companies prioritizing PD-1 inhibitory therapeutics for development for renal cell carcinoma (15). Phase 1 data has been promising in 16 of 18 patients treated in the RCC group, with some complete and durable responses, and this target is now being investigated in phase II studies.

The targeting of VEGF receptor signaling has become the mainstay of treatment in renal cell carcinoma, but modulation of this pathway continues to evolve, and was reviewed by Dr. Robert Motzer, the worldwide leader in the development of these therapeutic options. Two new drugs with very high potency to the VEGF receptor 2 are on the horizon, axitinib and tivozanib (16;17). These drugs do complicate the already full field of VEGF receptor inhibitors, which already includes the approved drugs sunitinib, sorafenib, and pazopanib, but also provide new highly potent on target opportunities with fewer off target side effects. Of the two, axitinib is the further along, and will soon be evaluated for FDA approval on the basis of second line randomized evidence demonstrating the superiority of axitinib to produce response and duration of progression free survival after sunitinib failure, as compared to sorafenib (18). In contrast, the data for tivozanib is largely limited to data from a randomized discontinuation trial, although patients treated with tivozanib demonstrated a greater than 15 month progression free survival, longer than has been observed with any of the prior tyrosine kinase inhibitors (19). The phase III results with this agent are highly anticipated. Finally, new VEGF receptor tyrosine kinase inhibitors, which simultaneously targets fibroblast growth factor receptor (FGFR) are also in development, demonstrating early indications of activity, and presenting an interesting new paradigm to watch.

Numerous other novel therapeutic targets are undergoing development predicated on the biology advancements which continue to emerge for renal cell carcinoma. Dr. Michael Atkins provided an overview of the most interesting of these agents. In understanding the mechanisms of resistance to VEGF receptor inhibitors, IL-8 has emerged as a factor that can predict for response, and neutralization of this secreted factor restores sensitivity to sunitinib in resistant xenograft tumors (20). Other strategies to target tumor angiogenesis have led to therapeutics targeting the angiopoietins, secreted pro-angiogenic factors, which like VEGF, are targets of HIF transcriptional activity. Specific inhibitors (ie AMG386) remain under investigation (21), and results will be forthcoming. Certainly, efforts to reduce HIF-2α have dominated the landscape since recent discoveries of this transcription factor as the dominant factor in promoting clear cell renal cell carcinoma (22). Pharmacologic alternatives to siRNA-type strategies include inhibition of additional members of the mammalian target of rapamycin (mTOR) family. mTOR complex 1 has been targeted with short, but significant survival benefits in renal cell carcinoma. However, mTOR complex 2, is the more relevant of the mTOR complexes to the sustained translation of HIF-2α. Dual inhibitor of both mTOR complexes are potent in vitro to reduce HIF-2α levels (23), and are undergoing clinical investigations, as are highly specific small molecules targeting iron responsive factors which regulate HIF-2α gene transcription (24). Finally, the targeting of signaling molecules common to many histologic subtypes of renal cell carcinoma remains interesting to consider, and cMet presents the most immediate and tractable target in this category, in which it is expressed in mutant form in some forms of papillary renal cancer, and inhibition

of Met signaling has been shown to be preferentially disabling in VHL deficient cells (25). Numerous inhibitors of cMet are in development, and have shown promise even in highly refractory cases.

Overall, the prospects for improving the lot of patients with renal carcinomas are plentiful and promising. Continued emphasis on good clinical trial design is needed to accelerate the development of management strategies that reduce morbidity and improve survival from renal cell carcinoma.

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