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Potential New Therapeutic Approaches for Renal Cell Carcinoma

David C. Yang, MS and Ching-Hsien Chen, PhD

Summary: Renal cell carcinoma (RCC) is increasing in incidence and one third of newly diagnosed cases already are metastatic. The metastatic spread of solid tumors renders RCC incurable by surgical resection and consequently more difficult to treat. New molecular-targeted therapies have played a pivotal role in RCC treatment. Unfortunately, tumors frequently develop resistance to these targeted therapies by activating bypass pathways in which alternative signaling or biochemical pathways are activated in response to targeted inhibition of a signaling pathway, allowing cancer cells to continue to survive. Although the advent of immunotherapy with checkpoint inhibitors has led to significant changes in the treatment landscape for advanced RCC, many issues remain to be resolved. For these reasons, there is an urgent need to develop novel therapies and new treatment paradigms for patients with RCC. Much research has been performed thus far in identifying novel targets and treatment strategies in RCC and many of these currently are under investigation and/or in clinical trials. In this article, we discuss therapeutic options in the management of RCC with a focus on the new therapeutic approaches currently investigated in research and for use in the clinic. We divide these potential novel therapies into five groups: nonbiologics, small-molecule drugs, biologics, immunomodulatory therapies, and peptide drugs. We also present some therapeutics and treatment paradigms.

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Renal cell carcinoma (RCC) is a frequently lethal urological disease and is currently the ninth most common cancer in men and the 14th most common in women worldwide. The disease accounts for roughly 403,000 new cases (2.2% of all diagnoses) and roughly 175,000 deaths (1.8% of all cancer-related deaths) yearly.[1] In the United States, RCC accounts for roughly 74,000 (4.2%) new cases and 15,000 (2.4%) deaths yearly.[2] RCC primarily afflicts patients in the fifth or sixth decades of life,[3] and primarily affects men at roughly a 2:1 ratio.[4] Approximately 65% of patients with RCC who present to the clinic have localized tumors that typically are treated and potentially cured via total or partial nephrectomy. The remaining 35% of patients present with metastatic RCC, which often is incurable by surgical removal, necessitating the use of systemic treatments. RCC has a wide range of subtypes, with the most common being clear cell carcinoma, which accounts for approximately 75% of all RCCs. Other subtypes such as papillary (10%), chromophobe (5%), and other less common subtypes account for the remainder of cases.[5]

Risk factors for RCC include multiple genetic and nongenetic factors. Nongenetic factors, such as obesity, hypertension, smoking, chronic use of pain medications, and exposure to certain chemicals (eg, trichloroethylene), have been implicated in the pathogenesis of RCC.[6] Genetic risk factors include BRCA1-associated protein-1, folliculin, fumarate hydratase, hepatocyte growth factor receptor, phosphatase and tensin homolog, succinate dehydrogenase complex iron sulfur subunit B, succinate dehydrogenase complex subunit C, succinate dehydrogenase complex subunit D, tuberous sclerosis 1 complex subunit 1, tuberous sclerosis 1 complex subunit 2, and von Hippel-Lindau tumor-suppressor (VHL) genes.[4] Of these factors, the most well-defined, researched, and frequently observed is *VHL*. This tumor-suppressor gene encodes the VHL protein, which is an E3-ubiquitin ligase that plays a role in promoting the degradation of hypoxia-inducible factor 1α (HIF-1α) under normal conditions.[7]

In RCC, the *VHL* gene often is silenced or lost, resulting in unrestricted activation of HIF-1α target genes, which leads to the up-regulation of an array of proangiogenic genes including vascular endothelial growth factor (VEGF), dysregulation of cellular metabolism, and apoptosis, which drive the highly vascularized pathology observed.[7,8] The phosphatidyl-inositol-3-kinase–protein kinase B (AKT)-mammalian target of rapamycin (mTOR) pathway is thought to be a driver of RCC, with frequent mutations in this pathway observed in tumors.[9] Much of

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the recent advances in the field have reflected a better understanding of the molecular basis of RCC; many first- and second-line treatments concentrating on various targets such as VEGF and mTOR have been approved and in clinical use within the past decade, with many more therapies currently undergoing clinical trials.[10]

CURRENT MANAGEMENT OF RCC

When patients with RCC present to the clinic, the RCC most often is treated via surgical resection if the tumor is localized. This is accomplished through partial or total (radical) nephrectomies in which the tumor tissue is removed surgically. This may result in a complete cure, but 20% to 40% of RCC cases still return with resurgent tumors after the initial removal.[11] Surgical removal also may be complicated or rendered impossible by the proximity to the vasculature, the ureter, and other areas that are intractable to surgical removal. In addition, total removal or removal of a large portion of the kidney mass may give rise to complications such as chronic kidney disease and loss of kidney function. For patients who present with advanced disease in which the tumor already has spread, systemic treatments may be the only option.[12,13] Historically, systemic treatments have consisted of interferon (IFN) and interleukin (IL)2, which provided some durable responses in a small percentage of patients (7%-8%) but had significant drawbacks in toxicity and provided only a meager median survival of 12 months. These limitations, along with an increasing breadth of knowledge on the molecular basis and biology of renal tumors, have led to rapid advances in the field in the past decade and more.[4]

With the introduction of sorafenib in 2005, the treatment landscape for patients with RCC was revolutionized. Since then, many more therapies have been investigated and approved for clinical use. Today, there are 11 Food and Drug Administration–approved therapies for first-line and second-line treatments targeting a wide array of targets including VEGF (bevacizumab, lenvatinib, cabozantinib, pazopanib, axitinib, sorafenib, and sunitinib), mTOR (everolimus and temsirolimus), immunomodulatory targets such as programmed cell death protein 1 (PD-1; nivolumab and pembrolizumab) and programmed death-ligand 1 (PD-L1; avelumab and atezolizumab), and other signaling molecules (lenvatinib, cabozantinib, pazopanib, axitinib, sorafenib, and sunitinib).[13-15] Currently, there is an effort to uncover the factors underlying treatment response to tailor therapies to individual patients. Work currently is underway and we likely will see the fruits of this labor in the coming years.

THERAPEUTIC CHALLENGES IN RCC

Treatment of advanced RCC often is complicated by a plethora of factors. Of note, there may be significant intertumor and intratumor heterogeneity,[9] potentially explaining why patients may have a good initial response to frontline therapies but also may have relapsing tumors that are resistant. It has been shown that within the tumor, there is a wide array of clones present with different mutations, suggesting clonal evolution giving rise to heterogeneous tumors that are difficult to target. In addition, patient responses to therapies are not equal, some patients may benefit greatly from a certain type of therapy whereas another patient may have a minimal response. The tumor itself also may adapt to therapies and become resistant to therapeutics through modulation of alternative biochemical or signaling pathways, recruitment of supporting cells, sequestration or removal of drugs, and also increasing invasion through promoting mesenchymal transition.[16] Figure 1 summarizes multiple strategies that exist to target RCC tumors through different cell types. In addition to an overview of the current practices (Fig. 2) and challenges with these therapies, this article presents potential novel therapeutic approaches and future directions in the management of this disease (Fig. 3).

NEW TREATMENT OPTIONS AND STRATEGIES FOR RCC

Nonbiologics

RCC tumors typically are thought to be radiation-resistant tumors, typically used in a palliative setting to address distant metastases such as in the brain and bone. However, as suggested by De Felice and Tombolini[17] in their review of radiation therapy in RCC, radiation therapy still may be a promising technique in the nonpalliative setting. Of particular note, the use of stereotactic techniques in stereotactic body radiation therapy, which allows for precise control over the treatment area, has provided a way for targeted dosages of radiation to ablate primary tumors and metastases with minimal damage to surrounding tissue. In addition, the use of hypofractionated radiation, that is, a higher dose of radiation (>3 Gy/fraction), has been shown to be effective. In lower conventional dosages, tumor cell death is mediated through the classic p53 pathway. This presents a problem because most RCC tumors have VHL deficiency, leading to up-regulation of proangiogenic factors such as VEGF and fibroblast-derived growth factor, which promotes cell survival. In higher doses of radiation (>8 Gy/fraction), the sphingomyelin pathway is activated in cells, leading to ceramide-mediated cell death and collapse of the vasculature. This method also has shown low toxicity and good control of local tumors and may be a promising strategy to target primary tumors or manage metastases in patients.[18]

The use of stereotactic body radiation therapy is a current area of investigation with multiple trials being

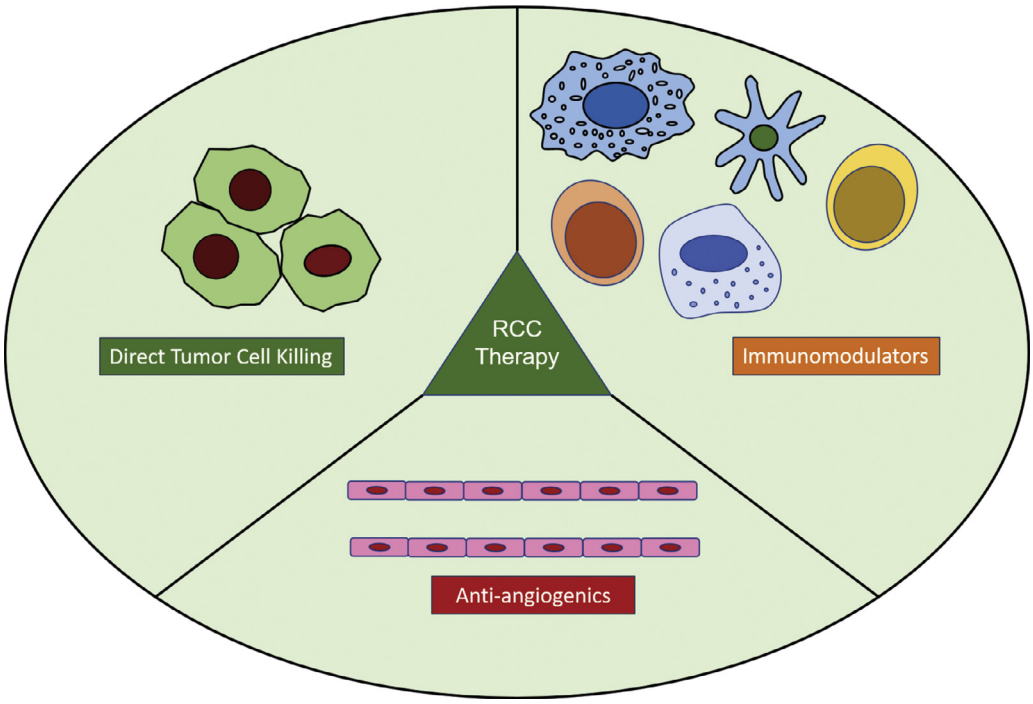

Figure 1. Approaches to target RCC. Multiple approaches exist to target RCC tumors through different cell types.

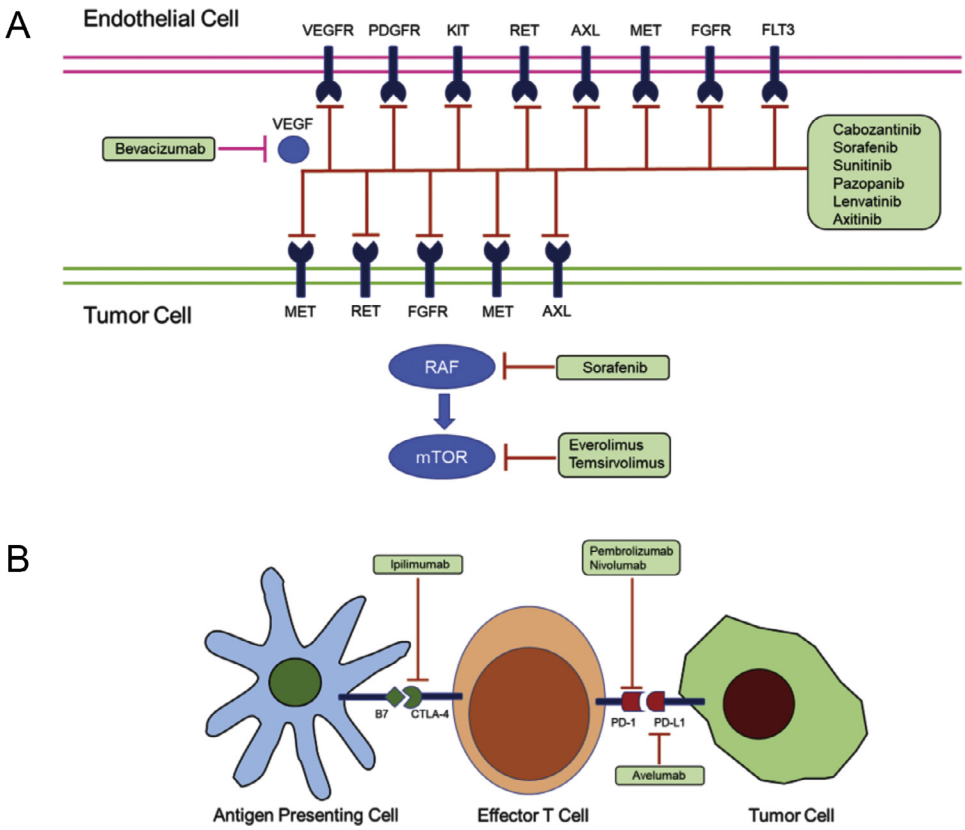

Figure 2. Current targeted therapies for RCC. In the clinic, multiple targeted therapeutics are used to target (A) angiogenesis, tumor cell growth, and (B) the immune response. Abbreviations: AXL, AXL receptor tyrosine kinase; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; FGFR, fibroblast growth factor receptor; FLT3, fms like tyrosine kinase 3; KIT, mast/stem cell growth factor receptor; MET, hepatocyte growth factor receptor; PDGFR, platelet-derived growth factor receptor; RAF, rapidly accelerated fibrosarcoma kinase; RET, rearranged during trasnfection proto-oncogene; VEGFR, vascular endothelial growth factor receptor.

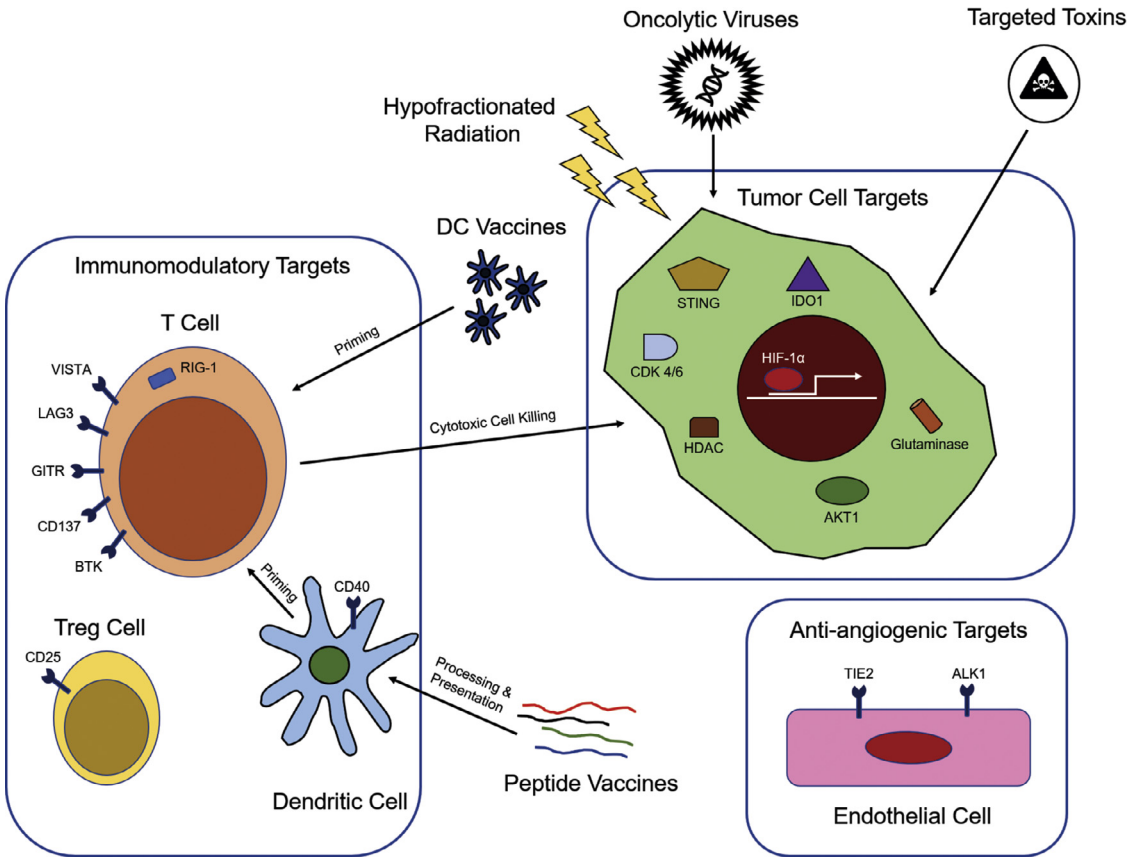

Figure 3. Novel targets for therapies in RCC. A range of factors in the immune cells, the tumor cells themselves, as well as the endothelial cells present as promising targets for therapeutic targeting. Abbreviations: AKT1, RAC-alpha serine/threonine-protein kinase; ALK-1, activin receptor-like kinase 1; BTK, bruton tyrosine kinase; GITR, glucocorticoid-induced TNFR-related protein; TIE2, angiopoietin-1 receptor; VISTA, V-domain Ig suppressor of T-cell activation.

run in the United States (NCT03065179, NCT02542202, NCT01896271, NCT03575611, NCT02141919, NCT01890590, NCT02781506, and NCT02782715) as a single therapy or in combination with other therapies (Table 1). Of interest, Cyberknife, a robotic radiation system developed by Accuray (Sunnyvale, CA), currently is undergoing clinical trials to assess its efficacy in a wide array of malignancies. This system provides the capability to accurately deliver targeted doses of radiation through the use of a robotic guidance system with a complementary image guidance system. The system has been tested and has shown local control of the tumor and low toxicity,[19] suggesting that this method may be a viable option for patients who may be precluded from surgical resection or systemic treatment.

Surgical reduction of renal tumors offers a potentially curative route for RCC. Surgical removal of renal tumor masses is standard procedure, and recent advances in minimally invasive procedures and nephron-sparing surgery and partial nephrectomies have shown a considerably favorable disease-free survival rate greater than 97.5%. These types of surgeries also do much to preserve renal function while achieving similar tumor control compared with radical nephrectomy. Other surgical practices such as cytoreductive nephrectomy and metastasectomy have shown good outcomes for patients and may be complementary with targeted therapies.[20,21] In addition, debulking of the tumor before surgery has shown some promise with rendering previously unresectable tumors to being amenable to nephron-sparing surgery and partial nephrectomy. Currently, the utilization of immunotherapies in the preoperative setting is an active area of investigation with multiple clinical trials underway, and it remains to be seen whether or not these therapies could improve surgical treatment in RCC.[22]

Small Molecules

Immune Response

Targeted therapies with small-molecule drugs remain a mainstay of therapy for advanced RCC and relapsed RCC. Before 1998, much of cancer therapy relied on chemotherapy, which had a wide array of adverse effects owing to the untargeted nature of chemotherapeutic drugs. With the advent of imatinib in 1998, small-molecule inhibitors have transformed the treatment landscape

Table 1. Novel Therapeutics for RCC

Drug/Treatment	Drug Type	Target	Mechanism	Active Clinical Trials
Hypofractionated radiation/SBRT	Radiation	Tumor cells	Ceramide-mediated cell death, collapse of vasculature	NCT03065179, NCT02542202, NCT01896271, NCT03575611, NCT02141919, NCT01890590, NCT02781506, NCT02782715
MK-1454	Small molecule	STING agonist	Activation of cross-presentation by APCs	NCT03010176
MK-46212	Small molecule	*RIG-1* agonist	Stimulation of IFN response, activation of immune cells	NCT03739138
Dalantercept	Small molecule	ALK-1 inhibitor	Blocking ALK-1–mediated angiogenesis	NCT01727336
Ibrutinib	Small molecule	BTK, ITK inhibitor	Shift of Th1 and Th2 balance, promoting antitumor response	NCT02599324, NCT02899078
Abemaciclib	Small molecule	CDK4/6 inhibitor	Disruption of CDK4/6 and G1 to S cell-cycle transition	NCT03905889
Vorinostat	Small molecule	HDAC inhibitor	Reduction of proliferation and activation of apoptosis	NCT02619253
Abexinostat	Small molecule	HDAC inhibitor	Reduction of proliferation and activation of apoptosis	NCT03592472
CT053PTSA	Small molecule	VEGFR2, c-MET, AXL, FLT3, and Mer inhibitor	Inhibition of angiogenesis and tumor progression	NCT03876925
CB-839	Small molecule	Glutaminase inhibitor	Reducing cell proliferation and survival	NCT03163667, NCT03428217, NCT02771626, NCT03875313, NCT02071862
Epacadostat	Small molecule	IDO1 inhibitor	Promotes effector T-cell activity by down-regulating immunosuppressive environment	NCT03260894, NCT02178722, NCT03277352
AS1411	DNA aptamer	DNA synthesis	Binds to nucleolin and prevents DNA synthesis	N/A
RX-0201	Antisense oligonucelotide	AKT1 antisense	Targets AKT1 mRNA, preventing translation	NCT02089334 (terminated)
AGS-16C3F	Targeted toxin	Tumor cells	Internalized by tumor cells and exerts cytotoxicity	NCT02639182
Pexastimogene devacirepvec	Oncolytic vaccinia virus	Tumor cells	Replicates in and lyses tumor cells, promotes immune response through expressing GM-CSF and β-galactosidase	NCT03294083, NCT02977156
Anti-VISTA	Immunomodulatory	T cells	Blockade improves T-cell activity	N/A
Anti-TIM-3	Immunomodulatory	T cells	Inhibition increases T-cell proliferation and cytokine production	NCT02817633, NCT03708328, NCT02608268
Anti–*LAG-3*	Immunomodulatory	T cells	Inhibition results in immune activation	NCT03538028, NCT03849469, NCT02460224
CD40/CD154 agonist	Immunomodulatory	APCs	Binding leads to B-cell and T-cell activation	NCT03502330, NCT03538028
GITR agonist	Immunomodulatory	T cells	Activation of T cells	NCT02697591, NCT03277352, NCT03126110
CD137 agonist	Immunomodulatory	T cells	Promotes T-cell proliferation and activation	NCT03809624, NCT02315066
CD25	Immunomodulatory	Treg cells	Depletion of immunosuppressive Treg cells	N/A
AGS-003	DC therapy	DCs	Primes immune response to tumor	N/A
HIF-1α278-287	Peptide vaccine	APCs, T cells	Priming immune system against HIF-1α	N/A
Neovax	Peptide vaccine	APCs, T cells	Priming immune system against personalized tumor antigens	NCT02950766
CAR-T cells	Adoptive cell transfer	T cells	Engineered T cells targeting tumor cells	NCT02830724, NCT03399448
AMG-386	Peptide	Endothelial cells	Prevents Ang1/2 binding to TIE2, preventing angiogenesis	NCT01664182, NCT03239145
HBS1	Peptide	Tumor cells	Prevents transcription of HIF-1α target genes via binding to p300 and CBP	N/A

Multiple investigational drugs currently are being evaluated for clinical use in multiple clinical trials. The mechanism of action and active clinical trials to the best of our knowledge are listed.
Abbreviations: AKT1, RAC-alpha serine/threonine-protein kinase; ALK-1, activin receptor-like kinase 1; AXL, AXL receptor tyrosine kinase; BTK, bruton tyrosine kinase; CBP, cAMP response element-binding protein-binding protein; CAR-T, chimeric-antigen receptor T; c-MET, hepatocyte growth factor receptor; FLT3, fms like tyrosine kinase 3; GITR, glucocorticoid-induced tumor necrosis factor–receptor family-related protein; GM-CSF, granulocyte macrophage colony-stimulating factor; ITK, interleukin-2-inducible T-cell kinase; Mer, Proto-oncogene tyrosine-protein kinase MER; mRNA, messenger RNA; SBRT, stereotactic body radiation therapy; Th1, T helper type 1; Th2, T helper type 2; TIE2, angiopoietin-1 receptor; Treg, T regulatory; VEGFR2, vascular endothelial growth factor receptor 2; VISTA, V-domain Ig suppressor of T-cell activation.

in cancer therapy. Showing an impressive 95% complete response rate in chronic myeloid leukemia, this landmark study propelled the world into the era of targeted therapy.[23] Since 2005, much of the current standard therapies for RCC and metastatic RCC have included small-molecule inhibitors of various receptors and other signaling molecules at play in the disease. The majority of the focus has been placed on the VEGF-receptor and mTOR pathways, but targeting of other pathways with a wide array of different small-molecule inhibitors is an active area of investigation. Herein, we provide an overview of several small molecules on the horizon of the therapy landscape in RCC.

The stimulator of interferon genes (STING) pathway is part of the innate immune system responsible for sensing DNA from pathogens and mounting an immune response. Upon activation, the pathway induces the production of type 1 IFNs, which in turn activates cross-presentation of tumor antigens by antigen-presenting cells (APCs) and promotes a proinflammatory tumor environment. The antigen presentation induced tumor infiltration of CD4+ and CD8+ T cells and activated these cell types to kill tumor cells.[24,25] Given this activity, the STING agonist MK-1454 was developed to activate this pathway through binding to STING. There is currently one phase I clinical trial underway set to complete in 2021 (NCT03010176).

Likewise, the *RIG-1* agonist MK-46212 exerts its effects through a similar mechanism. Binding to *RIG-1*, the agonist stimulates IFN response, in turn activating immune cells such as CD8+ T cells and natural killer (NK) cells to destroy the tumor cells.[25] There is currently one active trial underway for this therapeutic agent for solid tumors (NCT03739138).

Activin receptor-like kinase 1 (ALK-1) plays a well-studied role in angiogenesis.[26] Given the role of this kinase in modulating angiogenesis, inhibition of the receptor tyrosine kinase has been considered as a therapeutic strategy in RCC owing to the vascular nature of the disease. Dalantercept, an ALK-1 inhibitor, had shown promise in a phase I clinical trial with 13 patients achieving stable disease and 1 patient with a partial response.[27] Furthermore, the combination of dalantercept with multikinase inhibitor sunitinib had promising antitumor effects in vivo.[28] However, in a phase II clinical trial (NCT01727336), dalantercept in combination with multikinase inhibitor axitinib showed no improvement in treatment outcome despite being well tolerated. It remains to be seen whether dalantercept could be combined with immunotherapy drugs such as pembrolizumab or nivolumab given dalantercept's proinflammatory effects through modulation of IFNs.

Ibrutinib is a bruton's tyrosine kinase inhibitor that also has activity on IL2-inducible T-cell kinase. Signaling through these receptors modulates B-cell and T-cell activation. Down-regulation of these signaling pathways has been suggested to shift the T helper type 1/T helper type 2 T-cell ratio and to enhance antitumor immune responses.[29,30] For this reason, ibrutinib has been considered for use in RCC and a study has found some antitumor effects in two patients treated when used in combination with nivolumab.[31] Currently, there are two active clinical trials examining the use of ibrutinib in RCC (NCT02599324 and NCT02899078).

Cell Nucleus and Signaling

Cyclin-dependent kinases (CDKs) are important regulators of the cell cycle through mediating progression through phases in the cell cycle. Of note, CDK4 and CDK6 play a role in phosphorylation of the retinoblastoma protein, transitioning the cell from the G1 phase to the S phase, allowing cells to proliferate. The retinoblastoma protein has been shown to be expressed in 95% of RCCs and may be a viable target to stop tumor proliferation. Abemaciclib is a potent CDK4/6 inhibitor that prevents the phosphorylation of the retinoblastoma protein by disrupting the activity of CDK4/6.[32] It has shown efficacy in a xenograft mouse model of RCC with a significant reduction in tumor volume and in vitro cell models of RCC with treatment promoting cell apoptosis. Based on the promising preclinical results, abemaciclib currently is being evaluated for clinical use in combination with sunitinib (NCT03905889).

Histone deacetylases (HDACs) have been shown to be overexpressed in RCC tissues and it has been observed that overall acetylation of proteins is lower in RCC.[33] Inhibition of HDAC activity can result in activation of apoptosis and reduction of proliferation. These findings indicate that HDACs may be a potential target. There are a few examples of HDAC inhibitors being investigated for use in RCC with vorinostat and abexinostat. In clinical trials, vorinostat with bevacizumab showed clinical benefit with 6 patients having a complete or partial response.[34] Abexinostat, which functions similarly through inhibition of HDACs, has been shown to provide durable responses in patients, with six patients in the trial experiencing a partial response lasting more than 2 years. In addition, 70% of the patients in the trial who had prior disease progression on pazopanib showed a reduction in tumor size during the trial.[35] Vorinostat currently is being evaluated in combination with pembrolizumab in advanced RCC and urothelial cancers. The phase III abexinostat trial in RCC still currently is underway and is expected to finish in 2022 (NCT03592472).

CT053PTSA is an inhibitor of VEGF-receptor 2, hepatocyte growth factor receptor, AXL receptor tyrosine kinase, fms like tyrosine kinase 3, and proto-oncogene tyrosine-protein kinase MER. These signaling molecules have been implicated to play roles in tumor pathogenesis and angiogenesis. A study by Xi et al[36] found CT053PTSA to be effective in inhibiting angiogenesis and this inhibitor has shown good activity in a wide range of tumor xenograft models. Currently, it is in

a phase I trial in China and is expected to wrap up in 2020 (NCT03876925).

Metabolic Pathways

Glutaminase is a metabolic enzyme that regulates glutamine metabolism in the cell. In RCC, glutamine utilization is increased in RCC and tumor cells become addicted to glutamine.[37,38] Exploiting this dependency, glutaminase inhibitors could prove capable of shutting down cellular proliferation and survival. CB-839 is a glutaminase inhibitor that has been used in combination with cabozantinib and has shown some promising results in clinical trials, with a partial response or stable disease achieved in most patients enrolled.[39] There are five clinical trials currently in progress evaluating its efficacy in combination with various tyrosine kinase inhibitors or immunotherapy agents (NCT03163667, NCT03428217, NCT02771626, NCT03875313, and NCT02071862).

Indoleamine 2,3-dioxygenase 1 (IDO1) is an intracellular enzyme that catalyzes the conversion of tryptophan to kynurenine. IDO1-mediated depletion of tryptophan and production of other metabolites has been linked to an immunosuppressive tumor environment in which effector T-cell activity is reduced and immunosuppressive cell activity is increased. A study by Trott et al[40] indicated that the failure of IFNα therapy likely was owing to the immunosuppressive environment generated by increased levels of IDO1. Epacadostat is an inhibitor of IDO1 that promotes effector T-cell activity and down-regulates immunosuppressive cell types via inhibiting the degradation of tryptophan by IDO1. Prior studies have shown that epacadostat is well tolerated in patients and had promising clinical activity. There currently are three clinical trials (NCT03260894, NCT02178722, and NCT03277352) in progress evaluating the efficacy of epacadostat in RCC and a wide array of other neoplastic malignancies. Notably, in the trial using epacadostat in combination with pembrolizumab, the study achieved objective response in 19% of the patients enrolled.[41] Given the role of IDO1 in modulating the immune response in the tumor environment and the results observed in this trial, we may see more strategies combining immunotherapy with modulators of the tumor immune environment.

Biologics

Despite the successes of targeted therapies with small-molecule inhibitors, several challenges remain in the treatment of RCC with targeted inhibitors. One of the most pressing issues is the development of resistance to targeted therapeutics after an initial response. Kinase inhibition exerts a strong selective pressure for development of resistance to the inhibitor treatment and many acquired resistance mechanisms can involve activation of alternative pathways and mutations on the kinases targeted by therapeutics. In addition, targeting angiogenesis may promote increased tumor invasiveness because cells may undergo epithelial-mesenchymal transition to escape the hypoxic environment of the tumor resulting from decreased vascularization.[42,43] In lieu of targeting the protein of interest, targeting the DNA and RNA may provide a promising alternative route. Various microRNAs, long noncoding RNAs (lncRNAs), various other noncoding RNAs, and DNA synthesis are dysregulated in RCC.[44,45] For example, the lncRNA metastasis Associated Lung Adenocarcinoma Transcript 1 is associated with proliferation and migration in RCC and targeting this lncRNA with short hairpin RNA reduced these activities.[46] A more comprehensive exploration of microRNAs and lncRNA in cancer can be found in recent cancer studies.[44,45,47] A wide range of options exist to target these biomolecules. These include the use of antisense oligonucleotides, which are modified DNA that bind to targeted RNA; ribozymes, which are enzymes that cleave RNA; small interfering RNA, which are small RNAs that can target complementary RNAs; and RNA sponges, which sequester RNAs, preventing them from exerting their effects.[44] In addition, nucleotide therapeutics also may have the potential to target protein through shape-specific recognition.[48] A few of these therapeutics are being evaluated for use in RCC.

AS1411 is a DNA aptamer that targets the nucleolin protein, which is overexpressed in RCC. Binding of this aptamer to nucleolin on the cell surface leads to the internalization of this complex and inhibits DNA synthesis in the cells. In clinical testing, AS1411 showed limited efficacy but had a few significant and durable responses in select patients (one patient experienced an 84% decrease in tumor dimensions).[48] These findings suggest that further studies are warranted to determine the patient population that would benefit from this therapy. Up-regulated phosphatidyl-inositol-3-kinase/AKT activity frequently occurs in a wide range of cancers. RX-0201 is an AKT-1 antisense oligonucleotide that targets AKT-1 messenger RNA, preventing the translation of the messenger RNA transcript. In clinical trials, it has shown promising results with tumor burden reduction and stable disease observed in some patients.[49,50] RX-0201 was being evaluated in combination with mTOR inhibitor everolimus (NCT02089334); however, the study was terminated for unclear reasons.

Given that there are a plethora of RNAs at play in RCC, with many having roles in modulating aspects of tumor cell proliferation, invasion, and progression, we may see more and more of these technologies transition from preclinical studies into clinical practice, and perhaps eventual clinical use.[51-55]

Immunotoxins

Another potential avenue of treatment is the use of drugs conjugated to antibodies or ligands to selectively target cells with toxins.[56,57] Much work already has been

performed in this area, with many peptides and antibody fragments being developed that can home to cancer cells and are conjugated to a wide range of cytotoxic agents.[56] One example of an antibody drug conjugate is AGS-16C3F, which is currently in phase II clinical trial (NCT02639182). AGS-16C3F comprises an antibody targeting ectonucleotide pyrophosphatase/phosphodiesterase 3, which is overexpressed in RCC cells. Conjugated to monomethyl auristatin F, AGS-16C3F has been shown to be internalized by tumor cells and exert cytotoxic effects. During the phase I trial for the drug, a portion of the patients experienced partial response or stable disease beyond 100 weeks and 37 weeks, respectively, indicating that the therapy may benefit a subset of patients.[58]

Targeted therapy with oncolytic viruses is also a promising direction. Pexastimogene devacirepvec is a modified vaccinia virus that is able to selectively target tumor cells via a thymidine kinase gene inactivation. This inactivation renders the virus dependent on the heightened thymidine kinase activity in tumor cells, which can support viral replication. Furthermore, the engineered virus expresses granulocyte macrophage colony-stimulating factor and β-galactosidase transgenes, which promote an immune response to the tumor.[59] In a phase II trial, pexastimogene devacirepvec showed disease control in 76% of the patients enrolled in the study and also a complete response in one patient.[60] Currently, this virus is being evaluated in combination with other therapeutics in two trials for solid tumors and RCC (NCT03294083 and NCT02977156).

Immunomodulatory

Modulation of the immune response is a critical part of a complex system, controlling the immune response to tumors and infections while protecting normal tissue from damage. A wide range of cell types are at play in this complex weave of interactions: T cells, B cells, NK cells, macrophages, the subtypes of each cell, the tumor stroma, and the tumor cells themselves are some of the cell types at play in modulating the immune environment within the tumor. Much focus has been placed on the effector T cell in recent years with the focus of many current drugs targeting cytotoxic T-cell inhibitory molecules such as cytotoxic T-lymphocyte−associated protein 4, PD-1, and PD-L1. The intensive studies of these molecules have resulted in many therapeutics in use in the clinic today for RCC including pembrolizumab, nivolumab, atezolizumab, and avelumab. Although these targets have provided clinical benefit to many patients, some patients do not respond to these therapies, underscoring the need to investigate other targets. Herein, we provide some of the targets that may hold promise for use in a therapeutic setting.

There is a vast array of other inhibitory or stimulatory molecules at play in modulating the immune response that currently are being investigated. T-cell immunoglobulin-3 (TIM-3) is a negative regulator of T cells and is expressed on NK and macrophage cells and is found on exhausted T cells in the tumor. Furthermore, it can promote the expansion of immunosuppressive myeloid-derived suppressor cells.[61] Targeting of TIM-3 has been shown to increase T-cell proliferation and increase cytokine production, leading to a more robust immune response. Currently, there are three clinical trials evaluating TIM-3 targeting in RCC (NCT02817633, NCT03708328, and NCT02608268).

V-domain Ig suppressor of T-cell activation is a stimulator of antigen-presenting cells and a negative regulator of T-cell activity.[62] Blockade of this signal molecule has been shown to improve T-cell activity in tumor[63] and may prove beneficial in combination with PD-1/PD-L1 therapies.[64] To the best of our knowledge, there are currently no V-domain Ig suppressor of T-cell activation −targeted therapies being evaluated for RCC.

LAG-3 is an inhibitory signaling molecule expressed on T cells and NK cells after binding to major histocompatibility complex II and plays a role in protecting normal cells and tissue from damage by these immune cells.[65] In tumors, *LAG-3* frequently is overexpressed on the tumor-infiltrating lymphocytes that become exhausted, leading to tumor progression. Blockade of this pathway has been considered for use in various cancers. Currently, there are three clinical trials evaluating the use of *LAG-3* targeting in RCC (NCT03538028, NCT03849469, and NCT02460224).

CD40 is a cell surface protein that is expressed on the surface of APCs and B cells and it binds to its ligand CD154, which resides on T cells. Binding of these two molecules results in the co-activation of B cells and T cells with increased cytokine secretion and increased T-cell activity, respectively.[66] It is currently under investigation in two clinical trials for use in RCC (NCT03502330 and NCT03538028).

Glucocorticoid-induced tumor necrosis factor−receptor family-related protein, a cell surface protein found on both T cells and NK cells, is increased markedly after T-cell activation. Thus, agonism of these proteins has been considered a therapeutic strategy.[64] There are three active trials in the United States investigating the use of glucocorticoid-induced tumor necrosis factor−receptor family-related protein agonists in RCC (NCT02697591, NCT03277352, and NCT03126110).

CD137 is another cell surface protein expressed by T cells, NK cells, and APC cells. This protein functions in promoting cell proliferation and activation.[67] Ligation of CD137 also promotes antibody-dependent cell killing by CD8+ T cells and NK cells. Given this array of effects, it is suitable for complementing with antibody drugs and potentially vaccine therapy in RCC because it is able to mediate an antibody-dependent response. Currently, there are two trials underway

on the use of CD137 agonists in therapy in RCC (NCT03809624 and NCT02315066).

CD25 is a cell surface protein that is expressed mainly on T regulatory cells and depletion of these cells by blockading CD25 has been considered a potential strategy. Arce Vargas et al[68] further developed this concept by also inactivating inhibitory crystallizable fragment (Fc) γ receptor IIb, which is up-regulated at the tumor and prevents effective depletion of the T regulatory cells. They showed that the blockade of the Fc γ receptor IIb and CD25 was effective in increasing the ratio of effector T cells as well as reducing tumor size in an animal model.

Antigen presentation by APCs has an important role in mounting an effective immune response to cancer. Dendritic cells (DCs) play a vital role in this aspect through efficient presentation of tumor antigens to CD4+ and CD8+ T cells.[69] Based on these activities, the use of DCs in cancer therapy has been considered.[70] AGS-003 is used in DC therapy, in which DCs are electroporated with tumor RNA and CD40L RNA. The antigens are presented by the DCs and prime the immune system to mount a response to the tumor. In a phase II study of AGS-003 with sunitinib, 62% of RCC patients showed clinical benefit, with many surviving for 4.5 years or more.[69] Other studies have been performed with similar strategies and also have shown some clinical promise.[71]

Along similar lines, cancer vaccines have the same intent as DC therapies in mounting an effective immune response to tumors via priming the immune system. HIF-1α278-287 peptide, a HIF-1α derivative, was shown to be able to induce tumor-reactive T cells that had increased efficacy against RCC cells in the peripheral blood monocytes derived from RCC patients.[72] Such strategies in selecting overexpressed proteins in RCC can hold promise as a new direction in targeting RCC.

An interesting approach currently is being spearheaded by the Dana Farber Institute based on the work of Catherine Wu.[73] In this approach, sequencing data are collected from patients and validated. The validated targets then are put into a prediction model to determine which ones are able to bind to HLA and synthesized as peptides and mixed with carboxymethylcellulose, polyinosinic-polycytidylic acid, and poly-L-lysine double-stranded RNA, an immune adjuvant. The study showed remarkable results in patients enrolled in the study with 67% of the patients enrolled having no recurrence 25 months after vaccination, and 33% of the cases had recurrent disease and subsequent treatment with anti−PD-1 therapy, achieving complete response.[73] This study holds exciting potential in combination of personalized medicine and in combination with current immunotherapeutic agents in the effective treatment of tumors. Sequencing data from patients can be collected to generate personalized vaccines that can be used in complement with existing immunotherapeutics such as anti−PD-1 and anti−PD-L1 therapies to produce positive outcomes for patients. Based on these promising studies, a phase I study is currently underway (NCT02950766) and is expected to be completed by 2022.

Yet another approach is the utilization of engineered T cells. Chimeric-antigen receptor T cells have been explored as a possible treatment route. T cells are edited to include an antigen recognition domain linked to signaling domains that are required for T-cell activity. These cells then are put into the patient to target the antigen in question.[74] This currently is being explored in RCC (NCT02830724) despite lackluster results in a prior study.[75] Patient-derived T cells also are being evaluated for use in the clinic. There is an ongoing trial (NCT03399448) that is exploring the use of T cells edited with clustered regularly interspaced short palindromic repeats gene editing to remove the endogenous T-cell receptor and PD-1 in T cells with the addition of a New York esophageal squamous cell carcinoma 1, an antigen present on many cancer cells. This combination of a tumor-specific antigen complemented with the removal of immune checkpoints would allow for increased activity against tumor cells in a tumor-suppressive environment.

Peptide Drugs

Peptides as therapeutic drugs have gained traction in recent years. Occupying the space between small-molecule drugs and large antibody drugs, peptides offer a promising combination of good target selectivity, tolerability, and efficacy. Although peptide drugs may possess some weakness such as chemical and physical instability, as well as potential immunogenicity, the field is expanding and much has been performed to negate these weaknesses. Alteration of the amino acids and size of the peptides could reduce the potential for immunogenicity and increase the stability of such drugs.[76] In RCC, there have been a few promising developments in the past few years.

AMG-386 is a peptide drug with a peptide domain capable of binding angiopoietin 1 (Ang1) and angiopoietin 2 (Ang2) linked to a Fc region of an antibody. This drug inhibits the binding of Ang1 and Ang2 to the angiopoietin 1 receptor. Ang1 and Ang2 binding to angiopoietin 1 receptor are part of the angiogenic process and play a role in maintaining tumor vasculature.[77-79] AMG-386 has shown antitumor activity in treating solid tumors with one trial observing a partial response in one patient and four cases of stable disease for more than 16 weeks.[80] The peptide drug also had only low-grade toxicities and was well tolerated in this study. Currently, there are two active clinical trials (NCT01664182 and NCT03239145) investigating the drug as monotherapy and also as a combination with small-molecule inhibitors or anti−PD-1 immunotherapy.

HBS1 is a protein mimetic of the C-terminal activation domain of the HIF-1α protein developed by Kushal et al[81] to target the activation of HIF-1α target genes. The peptide exerts its efficacy through blocking the interaction of HIF-1α with the transcriptional co-activators p300 and cAMP response element-binding protein-binding protein by selectively binding to these transcription factors. They show that this targeting was able to down-regulate various HIF-1α target genes and showed antitumor activity in a mouse xenograft model. Furthermore, they assessed the toxicity to normal cells and found minimal toxicities in the range tested from 1 to 100 μmol/L. Although to the best of our knowledge the peptide has not yet entered into clinical development, the results shown are promising and the peptide, or similarly designed peptide drugs, may enter into clinical testing in the coming years.

CONCLUSIONS

Over the past decade or so, much development has occurred in the field of RCC, which has transformed the field. Although more than a decade ago few tools existed outside of surgical resection and systemic therapies with IL2 and IFN, today there is a wide range of targeted therapies and advanced techniques that are being used to improve patient outcomes and prolong survival. Ranging from new small-molecule inhibitors to RNA-targeting strategies, novel immunomodulatory targeting strategies and the priming/editing of the immune system, there is much to anticipate in the coming years in the treatment of RCC. In addition to these novel strategies, a large number of combination strategies combining these new novel therapies with other novel therapies or with existing therapies could provide an even greater benefit in the treatment of RCC.

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