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Research Progress of Tumor Microenvironment Targeted Therapy for Clear Cell Renal Cell Carcinoma

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Abstract

Renal clear cell carcinoma (ccRCC) and the tumor microenvironment (TME) influence each other, leading to the tumor microenvironment that can guide the corresponding treatment. With the deepening of research, some treatment options have achieved good results, such as tyrosine kinase inhibitors, immune checkpoint inhibitors, and so on. As the link between TME and malignancy is constantly discovered, more targeted studies on different components of TME are increasing, and this targeted therapy is a new method for treating ccRCC, and also a current research hotspot. This review summarizes the characteristics of the ccRCC tumor microenvironment, the outcomes of different treatments, and some potential targets.

Keywords

clear cell renal cell carcinoma, tumor microenvironment, immune metabolism, the extracellular matrix, cancer-associated fibroblasts, exosomes, the immune system, combined treatment

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Introduction

Hundreds of thousands of deaths are associated with renal cell carcinoma (RCC).[1] Adult RCC can be classified into clear cell renal cell carcinoma (ccRCC, ~80% of cases), shape cell (pRCC, ~10-15% of cases), color thinning (chRCC, ~5% of cases), and other rare types.[2,3] For patients with advanced disease, mortality is as high as 82% within 5 years. RCC is not sensitive to conventional radiotherapy and chemotherapy, yet a large proportion of these patients develop drug resistance, making the treatment ineffective.[4] Rodolfo Passalacqua[5] et al found similar recurrence-free survival and overall survival using the IL-2 + IFN- α group compared with controls. M Kjaer[6] et al found no significant difference in postoperative radiotherapy and control productivity ($P > .05$). However, with the continuous research of targeted agents, increasing evidence indicates that targeted therapy of RCC has good therapeutic effects,[7] and currently, therapy targeting the tumor microenvironment (TME) in RCC has become a research hotspot.

TME consists of a variety of cells as well as the corresponding stroma, which influences tumor development.[8,9] The non-tumor cells of the TME release a series of factors, prompting the occurrence of the inflammatory response, the weakening of the immune response, the formation of blood vessels, and inhibiting the effects of therapeutic agents.[10] With the deepening of research, the different elements of targeting TME are multiple treatments. This article mainly reviews the research progress in therapy targeting the ccRCC microenvironment.

Targeting Angiogenesis

The Von Hippel-Lindau (VHL) gene is a tumor suppressor gene and is 1 of the important causes of tumor formation. The loss of VHL increases the hypoxia-inducible factor (HIF),

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which induces an increased expression of vascular endothelial growth factor (VEGF), and ultimately promoting the ccRCC formation. 95% of ccrcc had inactivation of VHL.[11] The VHL gene can produce dysfunctional VHL (pVHL) or no pVHL at all in ccRCC. The E3 ubiquitin ligase can degrade the hypoxia-inducible factor 1 α (HIF-1α) and HIF-2α, and the pVHL is involved in the formation of this enzyme.[12] In renal cells lacking pVHL, the synthesis of HIF increases, which changes cell metabolism; induces angiogenesis; promotes epithelial-mesenchymal transition; and finally can affect the tumor progression.[13]

Cells expressing predominantly HIF-1α are tumor-associated macrophages (TAM), whereas predominantly HIF-2α are tumor cells. Cowman et al[14] found that HIF-1 α expression affects ccRCC, the more advanced the higher the content, and a .10% increased expression associated with a 28% decreased likelihood of patient survival. Wu et al[15] found that the increased expression of HIF-1 α promoted the growth and metastasis of ccRCC. HIF1α and HIF2α play an important role in ccRCC carcinogenesis.[16] Yang et al[17] revealed the effect of long non-coding RNALINC01234 on ccRCC. Knockout of LINC01234 inhibited the HIF-2α pathway, which led to decreased HIF-2α expression, and causing the inhibition of ccRCC cell growth and metastasis. Therefore, the HIF pathway has a very important research significance.

When HIF exists stably, it can activate the angiogenesis-promoting gene, VEGF, promote angiogenesis and proliferation. Therefore, Therapeutic approaches targeting the pro-angiogenic tyrosine kinase receptor (VE GF R) have been approved by TKI.[18] In addition to stimulating endothelial cells to promote tumor vascular development, VEGF also has a tumor-promoting effect: for example, VEGF stimulates VEGFR2-Janus kinase 2 (JAK2)-signal transducer and activator of transcription 3 (STAT3) signal transduction and upregulated MYC and SRY box transcription factor 2 (SOX (2) to induce self-renewal in cancer cells.[19] With the advent of anti-angiogenesis therapy, targeting VEGF has become a favorable choice for cancer treatment, especially in ccRCC, Due to its anti-angiogenic characteristics. By alleviating the hypoxic state of TME, it promotes the drug delivery more effectively. VEGF mainly interacts with VEGFR1 and VEGFR2.[20] Anti-angiogenesis therapies targeting VEGF can be divided into 2 categories. The first category directly targets VEGF using monoclonal antibodies, soluble receptor ligand/ligand traps, or aptamers, such as bevacizumab. Tamma et al[21] found that decreased microvessel density in ccRCC tumor tissue in patients treated with bevacizumab, which directly affected the release of angiogenesis factors by tumor cells. The second category, defined by targeting VEGFR2 using monoclonal antibodies or small-molecule tyrosine kinase inhibitors (TKI), was demonstrated in phase III trials to improve patient progression-free survival (PFS).[22] Wei et al[23] found that TKIs can inhibit angiogenesis and showed anti-tumor activity. VEGFR2 Involved in the tumor angiogenesis, and TKIs can target VEGFR2 to resist angiogenesis, produce negative effects on the tumor and reduce patient mortality.[24] Cabozantinib as a drug for the treatment of advanced mRCC.[25] Median PFS was higher in the caborotinib group than in the everolimus group (7.4 vs3.8 months) and the objective remission rate (ORR) of the Cabozantinib group increased by 16% (21 vs. 5%, $P < .001$).

Although antiangiogenic therapy can provide significant short-term clinical benefits in terms of ORR and PFS, it often evolves into therapeutic resistance. TKI treatment can lead to compensatory increases of other angiogenic factors in the tumor environment, leading to TKI resistance.[26] Thus, lasting long-term remission or survival is rarely achieved. To improve patient survival, different combination treatments are under investigation.

Targeting the Extracellular Matrix

The tumor matrix is composed of cells and the extracellular matrix (ECM), which plays an important role in ccRCC.[27] The ECM is rich in proteins, mainly for fibrous proteins and glycosaminoglycans. Matrix metalloproteinases (MMPs) participate in the physiological and pathological. (Table 1)[28] When these proteins balance or degrade to cause abnormalities in the ECM, they produce the promoting effects on ccRCC, including the larger cell number, the suppressed effect of natural cell death and the increased blood vessels in the tumor tissue.[29]

In ccRCC, type I (Col 1) and type III (Col 3) collagen are expressed in most tumors. Fibronectin 1 (FN 1) expressed by ccRCC cells can promote tumor cell proliferation and invasion, while other components also have the effect of promoting tumor growth, including laminin (LNα1, β1-2, and γ1), type IV collagen (α1-2 chain) and endosin (nestin-1). Majo et al[38] found that the expression of Col1 (1A1 or 1A2) or FN1 is related to the decreased survival rate of patients with ccRCC; the expression levels of LNα1, LNγ, Col4A2 or nestin (nestin-10) are associated with an increased ccRCC survival rate; and LN β 1 expression is not conducive to patient survival. While Col4A3 expression favors patient survival and increases the expression of many potential targets for targeted therapy. Karabulut et al[39] found that the expression level of Col6A1 can reflect the response of patients with metastatic ccRCC to sorafenib treatment, identifying Col6A1 as a very valuable prognostic biomarker. Syndecans are a family of 4 transmembrane heparan sulfate proteoglycans (syndecan-1, -2, -3and-4) in mammals, and Syndecan-4 is mainly associated with cell aggregation, metastasis, and growth. Trastuzumab and panitumab can reduce the expression of Syndecan-4, thus inhibiting tumor development and development; and After zoledronate treatment, tumor growth and migration were inhibited, but Syndecan-4 expression was increased, Therefore, the role of Syndecan-4 needs further researchs.[40] Neumann et al[41] identified a key new lipid metabolic dependence in ccRCC, and indicated that inhibition of membrane phosphatidylinositol (PI) lipid remodeling driven by membrane

Table 1. Targeting the Different Components in the ECM.

Target	Machine-Processed	Result
Collagen	LOXL2 inhibition combined with gemcitabine	Useful for early-stage patients[30]
Fibronectin	Cisplatin combined with paclitaxel	Supbits cancer growth and blocks metastasis[31]
Elastin	Elastin-like polypeptides (ELP) -drug conjugates	Increase the therapeutic effect[32]
Laminin	Lupeol and paclitaxel	Inhibition of laminin generation[33]
Hyaluronic acid	Hyaluronic acid-octadecylamine (HA-ODA)/paclitaxel	Enhance the efficacy of paclitaxel[34]
Chondroitin sulfate	Chondroitin sulfate (CS) - calcium carbonate (CC)/ adriamycin	Enhance the efficacy of adriamycin[35]
Heparan sulfate	Integrin/heparan sulfate dual-targeting peptide assembly	Inhibits cancer cell migration and invasion[36]
MMP	Silibinin	Suphibiting expression of MMP-2 and MMP-9, thereby inhibiting angiogenesis and migration[37]

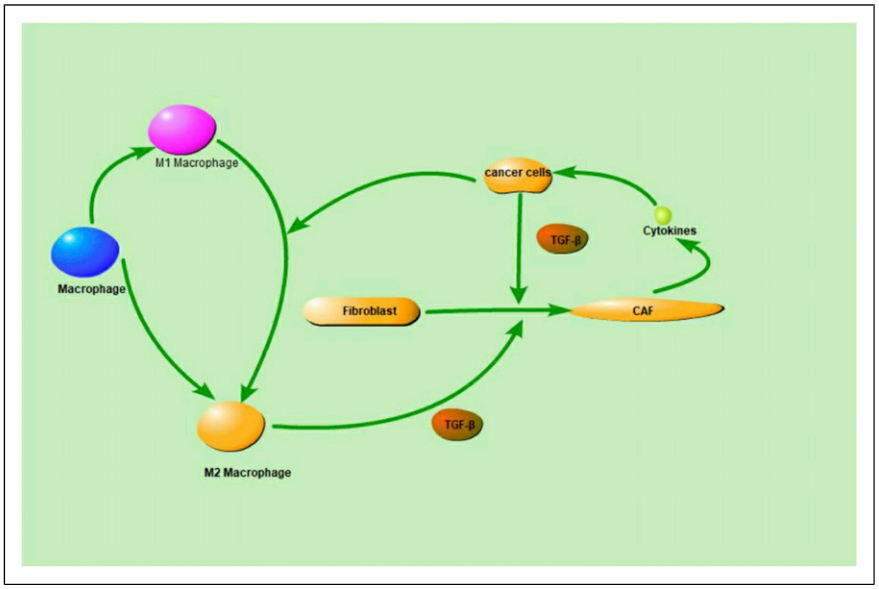

Figure 1. The signaling loop formed by the CAF. The signaling loop, formed by cancer cells, macrophages, and fibroblasts, promotes cancer development, in which TGF- β plays a central role, Macrophages can differentiate into M1 and M2; Cancer cells can induce M1 to become M2, andcancer cells and M2 secrete TGF-β, TGF-βinduced the Fibroblast to become CAF, However, CAF secreted Cytokines promoted tumor cells metastasis.

bound O-acyltransferase domain containing 7 (MBOAT7) might have therapeutic potential for patients with ccRCC. This follows that therapies targeting the ECM are feasible.

Although there are some links between several matrix macromolecules and the development of tumors, only with a deeper understanding of the mechanisms in this field can comprehensive and rational strategies be developed to promote targeted therapy of tumors.

Targeting Cancer-Associated Fibroblasts

CAF can be transformed from tissue fibroblasts, bone marrow-derived mesenchymal cells, epithelial cells, endothelial cells, stellate cells, pericytes, and adipocytes, etc.[42] TGF-β signaling plays a variety of biological roles in inflammatory diseases, and in the TME, it accelerates invasion, metastasis, angiogenesis, and immunosuppression (Figure 1).[43] Currently, To fully investigate tumors, the interconnections between cancer-associated fibroblasts and ECM, and to deeply explore the subtypes of different fibroblasts of ccRCC, so ccRCC fibroblasts were cultured using ccRCC-specific ECM components.[44] Fibroblasts in tumors are termed cancer-associated fibroblasts (CAFs). Only activated CAFs can produce ECM compounds. Targeting CAF may be an effective therapeutic approach for ccRCC.[45]

Normal fibroblasts (NF) transform into CAFs in the TME. CAFs then recruit monocytes and cause them to differentiate

into M2-like macrophages, which can play an immunosuppressive role through the programmed cell death 1 (PD-1) axis, This immunosuppressive effect leads to enhanced tumor metastasis capacity and also drives epithelial mesenchymal transition (EMT) in tumor tissue.[46] Chakiryan et al[47] found that the aggregation of tumor cells and CAF promotes tumor cell growth, resulting in reduced the overall patient survival time (OS) and resistance to targeted drugs. Fibroblast activating protein-α (FAP) is a general biomarker of CAFs.[48] Solano-Iturri et al[49] found that a positive correlation between the FAP expression level and the progression of ccRCC. Damien Ambrosetti et al[50] found that CAFs increased the migration and decreased the VEGFR-TKI-dependent cytotoxic effect of tumor cells. Thus, Targeting CAFs is also a therapeutic approach for ccRCC; however, more studies are needed to verify the effectiveness of targeting CAFs to treat ccRCC.

Although an increasing number of therapeutic strategies targeting CAF are constantly being developed, These treatments face 2 challenges: the absence of obvious markers and the relatively few randomized clinical trials.

Targeting Exosomes

Communication between cells is very important for cells to adapt to various intracellular and extracellular changes at different stages. As a unique form of intercellular communication, extracellular vesicles (EVs) produced by cancer cells can promote cell growth and survival, help to shape the TME, and increase cancer invasion and metastasis. EVs can be divided into 2 categories: microbubbles (MVS) and exosomes.[51,52]

Exosomes are nanoscale bilayer lipid vesicles with ranging in size from 30-100 nm, which can change the fate of recipient cells via autocrine and paracrine signaling.[53] Exosomes play important roles in cell homeostasis and intercellular communication, and have been extensively studied as biomarkers, pathogenic molecules, and therapeutic biological agents in many renal diseases and disorders.[54] Cancer stem cell (CSC) exosomes promote the EMT and metastasis of ccRCC, and CD103-positive exosomes can be used as biomarkers for metastatic ccRCC.[55] Haoyu et al found that the combination of exosome-stimulated $CD8^+$ T cells with granulocyte-macrophage colony-stimulating factor (GM-CSF) and interleukin 2 (IL-12) showed strong and specific cytotoxicity to RCC.[56] Hongyan et al[57] found that exosome circular RNA, cirC_400 068, may be a new oncogenic factor, and the cirC_400068/mir-210-5p/cytokine signaling inhibitor 1 (SOCS1) axis might be a candidate target for RCC treatment. Targeting exosomes has become a new target for tumor therapy.[58] The expression level of Mir-549a in TKI-resistant ccRCC is lower than that in sensitive cells, and mir-549a can be delivered to vascular endothelial cells through exosomes, inhibiting HIF1α and downstream VEGFR2 expression, thereby inhibiting vascular permeability and angiogenesis of renal cancer, which also provides a new direction for renal cancer treatment.[59] However, Targeting exosomes have not yet entered into clinical use and require extensive clinical trials for validation.

Studies have found that targeting exosomes may be a new approach to treating tumors by targeting up-regulating ways of exosome components that inhibit tumor growth while inhibiting tumor-promoting components.

Targeting the Immune System and Immune Metabolism

ccRCC is a highly invasive tumor with strong angiogenesis, which is not only related to HIF, but also related to tumor-infiltrating lymphocytes (TILs). ccRCC is usually infiltrated by a high level of TILs. The observation of RCC patients found that the immune system also has some influence on tumor formation.[60] Ghatali et al[61] found that TILs correlated with higher T cell, ImmuneScore, Tregs, CYT, Th1, Adaptive immune response, T helper cell and $CD8^+$ T cells. Overall, ccRCC is characterized by increased inflammation and angiogenesis, which further promote tumor metastasis and recurrence. Shiqiang et al[62] analyzed 530 tumor samples and found that the existence of Tregs, activated DCs (aDCs), $CD58^+$ NK cells, and Th2 cells was related to the poor prognosis of patients with ccRCC ($P < .05$). Th17 cells, neutrophils, mast cells, NK cells, γδ T cells, and central memory T cells were associated with good prognosis in ccRCC ($P < .05$). Wenzhong et al[63] studied the relationship between angiogenesis and the TME and found that B cells, Th1 cells, converted memory B cells, Th2 cells, CD8 naive T cells, naive B cells, $CD8^+$ T cells, CD8 central memory T cells, macrophages, CD4 effector memory T cells and M2 macrophages have been implicated in blood vessel formation. Immunocyte infiltration is a characteristic of ccRCC; however, the influence of lymphocytes on patient prognosis and the link between TIL and pathological features of the tumor are unclear. Whether perioperative immunotherapy can activate existing immune infiltration and reduce the recurrence of ccRCC is currently a hot research topic.

Tumorigenesis depends not only on the intrinsic characteristics of cancer cells, but also on their interaction with TME components. TAMs are immune cells in TME that can not only has anti-tumor effect in the early stage of tumor, but also participates in the whole formation of tumor. TAMs can be divided into 2 phenotypes: M1 and M2. Differentiation of the M1 phenotype into the M2 phenotype promotes occurrence and progression of cancer. Therefore, the mechanism and targeting of TAM phenotype transformation has become a new therapeutic approach.[64,65] Yutao et al[66] reported that there are 6 co-expressed genes (*F13A1*, *FUCA1*, *SDCBP*, *VSIG4*, *HLA-E*, and *TAP2*) in M2 macrophages that are most related to the M2 phenotype, and

may intervene M2 macrophages through these co-expressed genes and their related biological processes, in contrast to M1, M2 macrophages are less able to process tumor antigens. A positive regulatory loop was discovered in the targeted tumor-macrophage interaction ($SOX17^{low}$/YAP/TEAD1/CCL5/CCR5/STAT3, SOX17 is a new tumor suppressor in ccRCC), SOX17 expression was commonly downregulated and negatively correlated with TAM infiltration in ccRCC specimens, which provides a potential target for inhibiting targeted drug resistance and metastasis of advanced ccRCC.[67] Another study found that the macrophage-capping protein (CAPG) was a new prognostic marker for ccRCC. The CAPG expression was significantly elevated in ccRCC tissues, and the CAPG expression is closely correlated with the tumor progression; therefore, targeting the CAPG may also be an effective means.[68]

TAM targeting agents have quickly entered clinical practice, whether combined with traditional therapy or with other immunomodulators. Progress in the preclinical development of TAM-targeted drugs and new research progress in understanding the mechanism of TAMs, suggest that TAM-targeted therapy will become an important supplement to anti-tumor therapy; however, further research is still needed.

The progression of ccRCC is related to chronic inflammation, in which oncogenin M (OSM) signaling initiates inflammation and reconstruction of the TME through VHL-deficient renal tubular cells, this is very important for the occurrence and development of ccRCC.[69] Kuo et al found that lipid carrier protein 2 (LCN (2) can promote inflammatory responses in cells, leading to the enhanced chemotactic capacity of macrophages, which provides a potential treatment that interferes with the development of ccRCC.[70]

Immune checkpoint inhibitors (ICIs) act as an effective treatment modality. ICIs includes antibodies targeting the interaction between PD-1) and its ligand PD-L1, cytotoxic T lymphocyte associated protein 4 (CTLA-4), and its ligand B7-CTLA-4, to avoid the decline of cellular immune response in the tumor microenvironment.[71] Activated T cells are an important link in preventing tumor cell growth. PD-1 is mainly expressed on this cell and binds to PD-L1 to inhibit relevant signaling, while the immune effect of immune cells on tumors is affected by PD-L1.[72] CTLA-4 is a checkpoint receptor on cytotoxic lymphocytes, which can bind to B-7 expressed on antigen presenting cells (APC), and inhibit T cell proliferation, resulting in a decrease in anti-tumor activity.[73] ICI can enhance the cellular immunity of cancer cells by blocking the interconnection between PD-1/PD-L1, CTLA-4/B7-CTLA-4.

Navulumumab, an antibody acting on PD-1, was studied in the first-line treatment setting of phase CheckMate 374 IIIb/IV trials. In a cohort of 97 patients with ccRCC, the objective remission rate was under nivolumab treatment was 22.7%. Three patients had complete reactions and 19 patients had partial reactions.[74] Similarly, Avelumab found in a trial that the drug significantly prolonged the overall patient survival, with a 1-year OS rate of 71.3% and a median PFS of 3.7 months.[75]

Pembrolizumab is a PD-1 inhibitor that was studied recently in a single arm phase II clinical trial (KEYNOTE-427). Among the 110 patients, the median time from enrollment to data cut-off was 35.9 months, and the ORR was 36.4%, among which 4 of them (3.6%) showed complete remission and 36 of them (32.7%) showed partial remission. The disease control rate was 58.2%. The majority of patients (68.2%) had less target lesions, with 30.9% decreasing more than 60%. The proportions of the overall survival time reaching 12 months and 24 months were 88.2 and 70.8%, respectively.[76]

On April 16, 2018, FDA approved nivolumab (NIVO) and ipilimumab (IPI) combined immunotherapy (NIVO + IPI) for untreated RCC with moderate or low risk.[77] Among patients with moderate/low-risk disease, compared with sunitinib group, the probability of OS for 30 months in the NIVO + IPI group was 60%, and the mortality rate was 43%. In Sunitinib group, The likelihood of developing of OS at 30 months was 47%, and the mortality rate was 54%. The 30 month PFS rate in the NIVO + IPI group was 28%, while that in the sunitinib group was 12%.[78]

In summary, ICIs show notable efficacy to treat ccRCC; however, their side effects cannot be ignored, and further study is required to reduce these side effects. Finally, new immune checkpoint proteins, such as lymphocyte activating 3 (LAG-3) and T cell immunoglobulin mucin 3 (TIM-3), and new methods of cytokine therapy using IL-2 are also key research directions.

Cancer and immune cell metabolism is another important component of TME, able to modulate antitumor immunity and influence the response to immunotherapy, Genetic alterations cause metabolic changes, that cancer cells can also survive under hypoxic conditions. This phenomenon is called metabolic reprogramming, and ccRCC is also known as a "metabolic disease" because different metabolic pathways are affected by different genes.[79,80] It was found that many metabolic disorders are directly related to carcinogenesis (Table 2 Figure 2).[81] The findings of the study by Ren Liu et al, The positive feedback pathway formed by Glycerol-3-phosphate dehydrogenase 1 (GPD1) and HIF1α inhibited GPD2 expression and mitochondrial function, moreover, the overexpression of GPD1 inhibited the lipid metabolism of ccRCC, thus inhibiting the tumor activity.[82] Zhiyu Fang et al[83] found that succinate dehydrogenase subunit B (SDHB) is part of the mitochondrial respiratory chain, which can affect the metabolic changes of ccRCC and inhibit the growth of ccRCC by reducing the ability of glycolysis of cancer cells. Therefore, it is possible that the study of SDHB will also be a new target.[83] Giuseppe Lucarelli et al[84] found that stearoyl-CoA desaturase (SCD1) is related to the lipid metabolism, and that a small molecule SCD 1 inhibitor (A939572) blocks lipid metabolism, which suppresses ccRCC proliferation and

Table 2. Various Genes that Regulate the Metabolism.[30]

Gene	Metabolic Pathway	Relevance to ccRCC	Refs
PTEN	Inhibition of glycolysis through inactivation of Akt/mTOR	The PTEN/AKT/mTOR axis regulates ccRCC cell proliferation, invasion, metastasis, and drug resistance, patients with biallelic loss had poor overall survival (HR 3.1,95%CI 1.4-6.8, P < .05)	85-87
TSC1/2	The TSC 1/2 deficiency causes glycolysis and affects the ccRCC by activating the Akt/mTOR mutations	Mutation is a risk factor for ccRCC	88,89
AKT	Activation leads to the Warburg effect through activation of PI3K-Akt-mTORC1 the PI3K→AKT→GSK3β→AM signaling pathway correlated with increased angiogenesis	Akt inhibitors are being tested in clinical trials for ccRCC	90,91
VHL	Inhibition of the Warburg effect through deactivation of HIF	Loss-of-function mutation found in >90% of patients	92,93
p53	Downregulation of glycolysis by deactivation of GLUT1/3/4, upregulation of TIGAR and inhibition of HK2 and PGAM1 Upregulation of glutamine metabolism via increased transcription of SLC1A3	Mutation is rare in ccRCC	94,95
Myc	Upregulation of glycolysis increased through transcription of HK, LDHA, and PDK1 Upregulation of glutamine metabolism through GLS1/SLC1A5 activation Upregulation of lipid synthesis through activation of FAS and SCD1	Often mutated and overexpressed in ccRCC	95,96

PDK1, pyruvate dehydrogenase kinase 1; mTOR, mammalian target of rapamycin; ccRCC, clear cell renal cell carcinoma; PI3K, phosphatidylinositol-3 kinase; GSK3β, glycogen synthase kinase 3 beta; TSC1/2, tuberous sclerosis 1/2; SCD1, Stearoyl-CoA desaturase 1; HIF, hypoxia-inducible factor; GLUT, glucose transporter; TIGAR, p53-inducible glycolysis and apoptosis regulator; PGAM1, phosphoglycerate mutase 1; SLC1A3, glutamate/aspartate transporter; LDHA, lactate dehydrogenase A; FAS, fatty acid synthase; HK2, hexokinase 2.

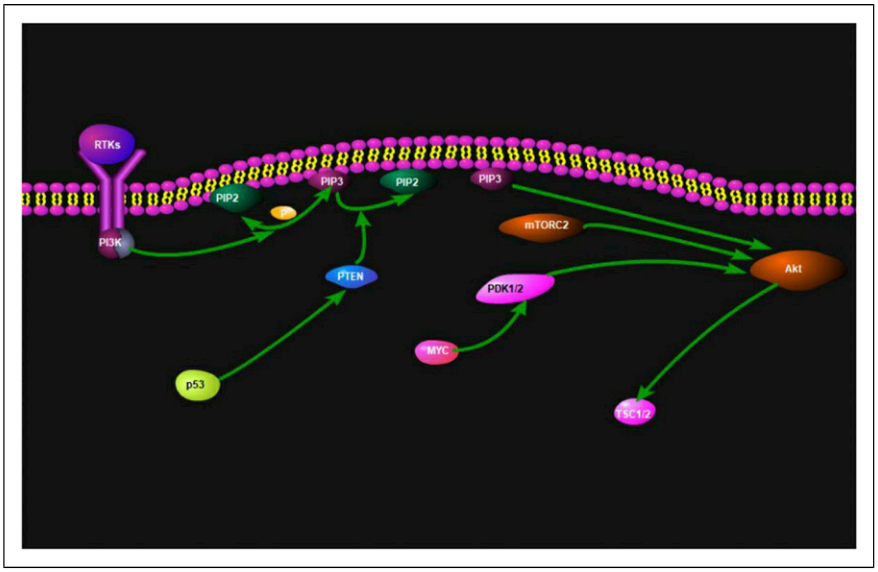

Figure 2. The classical PI3K/Akt pathway. PI3K promotes PIP3 generation; PTEN and p53 inhibit PIP3 generation and thus inactivate Akt/mTOR to inhibit glycolysis and inhibit cancer development; PIP3\mTORC2\MYC and PDK1/2 activate the Akt, While the lack of TSC 1/2, activation of Akt/mTOR leads to Warburg effect, promoting cancer development.

increases the sensitivity of cisplatin. ccRCC is not just a disease with abnormal cell cycle progression, but also involves the reprogramming of classical metabolic pathways, So some potential targets in the metabolic pathways need to be discovered.

The effects of immune cells in recognizing and delivering antigen are regulated by tumor cells and their own metabolic programming, ultimately leading to altered immunity. Therefore, affecting the metabolism of this class of cells and increasing the antigenicity of tumor cells facilitates treatment.

Table 3. Effect of the Partial Treatment.

	Results	*P*	Refs
Nivolumab + ipilimumab	Consiagreement was maintained between 0 and 6 IMDC risk factors, ORR (40-44%) OS(HR:0.50-.72) and PFS (HR: .44-.86)	<.05	105
Pazopanib	The median PFS in the favorable group was 27.1 months The remission rate in the favorable group was 43%	<.05	106
Cabozantinib + nivolumab	PFS for the favorable and moderate risk groups (HR: .62 and .54)	<.05	107
Lenvatinib + pembrolizumab	In the IMDC poor risk group (HR:0.30):71%ORR		108

Combined Treatment

Due to the increasing drug resistance, combination therapy has gradually become the mainstream of treatment.[97] MET is a proto-oncogene encoding c-Met, and the activation of c-Met promotes the development of tumor cells, which is an important mechanism for cancer development.[98] Angiopoietin/Tie-2 signaling promotes the blood vessels within the tumor tissue, and Tie-2 is specifically expressed in endothelial cells.[99] Angiopoietin/Tie2 and MET pathways promote tumor angiogenesis, metastasis, and macrophage infiltration. Elbannaet al.[100] reported that the combination of an Ang1/Ang2 inhibitor (trebananib) and a c-MET inhibitor (cabozantinib) could significantly reduce metastasis and prolong the survival time by changing the TME of ccRCC.

The exploration of ICIs combined with anti-VE GF therapy approaches compensates for the deficiencies in the field of ccRCC therapy. In the phase 3 KEYNOTE-426 trial, the experimental group treatment was palilizumab plus acicitinib and the control group sunitinib. Results showed a median FPS of 15.1 and 11.1 months ($P < .0001$). ORR of experimental group was 59.3% (95% CI:54.5-63.9), and ORR of control group was 35.7% (95% CI:31.1-40.4) ($P < .001$). After 1 year, the rate of surviving patients in the experimental group was higher than that in the control group (90%vs 78%, $P < .0001$). After 1 year, the combined group survival rate was higher than the control group (90 vs 78%, $P < .0001$).[101] Of course, there are some unsuccessful combination treatments with severe drug toxicity effects leading to discontinuation. Darren R. Feldman[102] et alfound that sunitinib combined with bevacizumab produced severe hypertension, hematologic disease, and vascular toxicity, eventually leading to treatment discontinuation in 48% of patients. Brian I Rini[103]et al found combining sunitinib with tramimumab to cause rapid onset renal failure. John D Hainsworth[104] et alfound that bevacizumab and everolimus caused an increase in proteinuria, pulmonary embolism and withdrawal in 14% of patients. Meanwhile, the efficacy of some therapeutic agents is listed according to the IMDC grade (Table 3). In the past decade, new treatment schemes for ccRCC have emerged, among which the combinations of VEGF and ICIs stand out. For more effectively prolonged survival of ccRCC patients, unknown combination therapy wait to be discovered.

Conclusion

There are many options for treating ccRCC, but targeted therapy may be optimal for inoperable treatment and having no effect for both chemotherapy and radiotherapy.[109] Here, Here, we outline the methods of targeting TME and elaborate different methods according to different elements of TME, collectively, the effect of showing different targeted therapies in patients with ccRCC. Therapeutic interventions, especially combination therapies, will be coordinated as precisely as possible.

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