Review article

Immune response determines the outcome in renal cell carcinoma

La respuesta inmune determina el desenlace en el carcinoma de células renales

Raquel González Garza,[1] Adrián Gutiérrez González,[1] Mario César Salinas Carmona,[1] Nallely López López,[1] Raquel Garza Guajardo,[1] Manuel Mejía Torres.[1*]

Abstract

Renal cell carcinoma (RCC) is a significant health burden that is associated with morbidity and mortality. Factors exacerbating the challenges of this condition include late diagnosis, intrinsic resistance to chemotherapy, and the cellular heterogeneity of tumors. In addition, the role of immunity in this condition was suggested by the successful use of immunotherapy in advanced RCC, which requires an understanding of the underlying immunopathological mechanisms involved in the progression of the disease. Moreover, the functional status of infiltrated immune cells and histological tumor subtypes could be used as predictive tools for selecting individualized treatments. This review summarizes the available information on the role of immunity in clinical outcomes and response to treatment in patients diagnosed with RCC.

Keywords:
renal cell carcinoma, immunotherapy, immune checkpoint inhibitors, tumor microenvironment, immunopathology

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***Corresponding author:**
Manuel Mejía Torres.
Address: Av. Dr. José Eleuterio González S/N, Mitras Centro, 64460 Monterrey, N.L. México.
Email: mmejia.me0126@uanl.edu.mx

[1.] Universidad Autónoma de Nuevo León.

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Resumen

El carcinoma de células renales representa una carga sanitaria significativa, asociada a morbilidad y mortalidad. Entre los factores que agravan los desafíos de esta condición se incluyen el diagnóstico tardío, la resistencia intrínseca a la quimioterapia y la heterogeneidad celular de los tumores. Además, el papel de la inmunidad en esta afección fue sugerido por el uso exitoso de la inmunoterapia en el RCC avanzado, lo que requiere comprender los mecanismos inmunopatológicos subyacentes implicados en la progresión de la enfermedad. Asimismo, el estado funcional de las células inmunes infiltradas y los subtipos histológicos tumorales podrían utilizarse como herramientas predictivas para la selección de tratamientos individualizados. Esta revisión resume la información disponible sobre el papel de la inmunidad en los resultados clínicos y la respuesta al tratamiento en pacientes con diagnóstico de RCC.

Palabras clave: Carcinoma de células renales, inmunoterapia, inhibidores de puntos de control, microambiente tumoral, inmunopatología

Introduction

Renal cell carcinoma (RCC) is a heterogeneous group of malignant neoplasms originating in the nephron epithelium, comprising approximately 2-3 % of all oncological pathologies. Globally, the annual incidence of RCC is estimated to be 270,000 new cases, with 58,000 cases diagnosed in the United States alone.[1] GLOBOCAN 2022 reported 35,990 new cases of RCC in Latin America and the Caribbean, resulting in 15,831 deaths. RCC is characterized by its aggressive nature, with a 5-year overall mortality rate of 75 % for local cancer and 12 % for metastatic disease. Over the past two decades, the incidence of RCC has increased by approximately 2 %.[2]

RCC can be histologically classified into three main subtypes: clear cell RCC (ccRCC, 80 % of cases), papillary (10-15 %), and chromophobe (4-5 %). Other less frequent subtypes, such as TFE-3-rearranged, TFEB-altered, and ELOC-mutated RCC, comprise less than 1 %.[3] The histological classification has prognostic value as it describes pathogenic indicators of tumor aggressiveness, including nuclear grade, sarcomatoid characteristics, microvascular invasion, and presence of tumor necrosis.[4]

RCC cases are sporadic and incidentally detected tumors that typically affect patients during the sixth and seventh decades of life. Men are two to three times more susceptible to RCC than women.[5] Lifestyle habits and comorbidities, such as smoking, obesity, and arterial hypertension, are recognized as predisposing factors. Due to the asymptomatic nature of many renal masses, up to 50 % of patients are diagnosed with metastatic disease, which leads to poorer prognosis and a decrease in 5-year overall survival (OS) from 50-69 % to 10 %.[3]

The advanced stage and histological grade at diagnosis determine the treatment. In this group of patients, first-line treatment options are often inadequate to achieve complete pathological responses. Cytotoxic therapies for RCC include surgery (partial or complete nephrectomy), chemotherapy, and radiotherapy. Proximal tubule tumors exhibit higher levels of P-glycoprotein, resulting in resistance to most chemotherapies, which alone is generally insufficient to cure metastatic disease.[6]

Considering these challenges, current therapies have garnered attention, particularly because of their success in the treatment of other solid tumors. Immunotherapy using monoclonal antibodies has emerged as a promising therapeutic approach, and advanced RCC has highlighted the complexity of the immune system in cancer progression. Although the relationship between cancer and the immune system is well established, the precise mechanisms underlying these interactions remain unclear. Lymphocytes recognize tumor-specific antigens (TSAs), initiating a cytotoxic response against tumor cells.[7] Immunotherapy with monoclonal antibodies has demonstrated the ability to restore lymphocyte function, leading to cytotoxicity in tumor cells. However, the factors contributing to the differential patient responses to therapy remain elusive.[8]

Immunopathology in renal cell carcinoma

In RCC, the tumor microenvironment (TME) includes various cell types in addition to highly proliferating tumor cells, such as stromal cells and immune cells.[9]

TME influences tumor progression and treatment resistance. Tumor-infiltrating leukocytes are key mediators of tumor progression and immune regulation, and include various cell types, as described in Table 1. For most solid tumors, lymphocyte infiltration is a sign of a good prognosis and response to immunotherapy, but the opposite is true for patients with RCC. The immune landscape in RCC often reflects dysfunction or exhaustion, resulting in resistance to immunotherapy and the progression of metastatic disease.[10]

Table 1. Tumor elements regulating cancer progression

Element	Description	Function	Clinical implication	Reference
Immune Infiltrates	TME-infiltrating leukocytes, including T cells, B cells, natural killer, and dendritic cells	Antitumor immunity	Associated with overall prognosis and response to immunotherapy.	Chen et al., (2020).[9]
TAMs	Tumor-supportive macrophages	Mostly pro-tumor immunity	Increased TAM infiltration is associated with poor prognosis.	Chen et al., (2020).[9]

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MDSCs	Immature myeloid cells with immunosuppressive functions	Inhibition of immune responses	Increased MDSC infiltration is associated with poor prognosis and resistance to immunotherapy.	Chen et al., (2020).[9]
TAFs	Tumor-supportive stromal cells	Promotes tumor growth and metastasis	TAFs are associated with poor prognosis and resistance to immunotherapy.	Sarkar et al., (2023).[11]
Hypoxia	Insufficient oxygen supply in TME favoring Warburg effect in cancer cells	Promotes tumor progression, angiogenesis, and immune suppression	The presence of hypoxia is associated with therapy resistance and poor prognosis.	Fujita et al., (2022).[10]
ECM remodeling	Changes in the composition and structure of TME	ECM interactions support tumor growth and invasion	ECM remodeling promotes tumor progression.	Fujita et al., (2022).[10]
Angiogenesis	Neovascularization in tumor tissue	Supply of nutrients and oxygen. Promotes metastasis	Enhanced angiogenesis associated with tumor growth and poor prognosis.	Fujita et al., (2022).[10]
Cytokines	IL-10 favor an immunosuppressive microenvironment	Evasion of immune surveillance, suppression of antitumor immunity	Immunosuppressive cytokines contribute to immune evasion and therapy resistance.	Mirlekar et al., (2022).[12]
Altered metabolism	Energy production through anaerobic metabolism leads to tissue acidification	Enhanced energy production supports tumor growth	Acidic microenvironment promotes tumor cell selection and treatment resistance.	Zhang et al., (2025).[13]

Currently, the immune response in cancer is the subject of intense research, especially after the successful use of immunotherapy. It is now accepted that antitumor immunity determines the success or failure of cytotoxic treatment. Nonetheless, there is a lack of information regarding the host immune response in RCC.

In clinical settings, some researchers consider the inclusion of immunity in clinical staging, suggesting that it should be integrated into the current TNM clinical classification.[14] Acknowledging the immune landscape of tumors may enhance staging accuracy and identify potential therapeutic targets, thereby improving patient outcomes.

Treatment for renal cell carcinoma

The current treatments for RCC include surgery, radiotherapy, cytotoxic chemotherapy, targeted therapy, and immunotherapy. In RCC, the survival rate depends on disease stage. The 5-year survival rates are 93 %, 72 %, 40 %, and 12 % for stages I to IV, respectively.[3] However, there are additional factors that influence the overall prognosis, such as nuclear grade, histological type, and presence of tumor necrosis.[5] Fortunately, the widespread use of abdominal imaging has contributed to increased early stage diagnosis, and incidentally detected tumors are typically associated with a better prognosis. Currently, approximately 60–70 % of all RCC patients are initially diagnosed with incidentalomas.[15]

In localized disease, surgery is curative, and surgical approaches range from partial to radical nephrectomy, including the removal of the perinephric tissues beyond Gerotas's fascia. For selected cases, the minimally invasive approach minimizes the loss in renal function, reducing morbidity and shortening the length of hospital stay.[16]

Approximately 30 % of patients with locally diagnosed RCC develop advanced or metastatic disease. These individuals typically have a median survival of 6–10 months and 2-year survival rate of 20 %. The poor prognosis of these cases is attributed to the limited efficacy of treatments and the use of combined treatments is recommended.[17]

Abscopal effect in radiotherapy

Radiotherapy (RT) is used as adjuvant or palliative treatment for RCC. From an immunological perspective, the term "abscopal effect" was coined to describe the phenomenon in which ionizing radiation exerts effects at sites distant from the irradiated tissue. Initially observed in normal tissues, the concept has since evolved to describe regression of metastatic lesions that were not directly irradiated, suggesting that localized RT can trigger a systemic antitumor response, where we now know that the immune system was involved.[18]

Targeted therapy

Targeted therapies include: a) tyrosine kinase inhibitors (TKIs), a class of orally administered small molecules that disrupt signaling pathways driven by tyrosine kinases, and b) Vascular-Endothelial Growth Factor receptor inhibitors (VEGFi). In general, TKIs have a lower toxicity than chemotherapy.[19] TKIs approved for RCC treatment include sunitinib, pazopanib, axitinib, cabozantinib, and lenvatinib. Sunitinib is a first-line treatment for metastatic clear cell RCC (ccRCC).[20] These drugs have demonstrated efficacy in halting disease progression and improving the survival of patients with RCC.

Tivozanib, a selective inhibitor of vascular endothelial growth factor receptors (VEGFRs) 1, 2, and 3, was approved by the US Food and Drug Administration (FDA) in March 2021 for the treatment of relapsed RCC. Clinical trials have shown that tivozanib effectively prolongs progression-free survival in RCC patients and exhibits a favorable safety profile compared to other TKIs.[21]

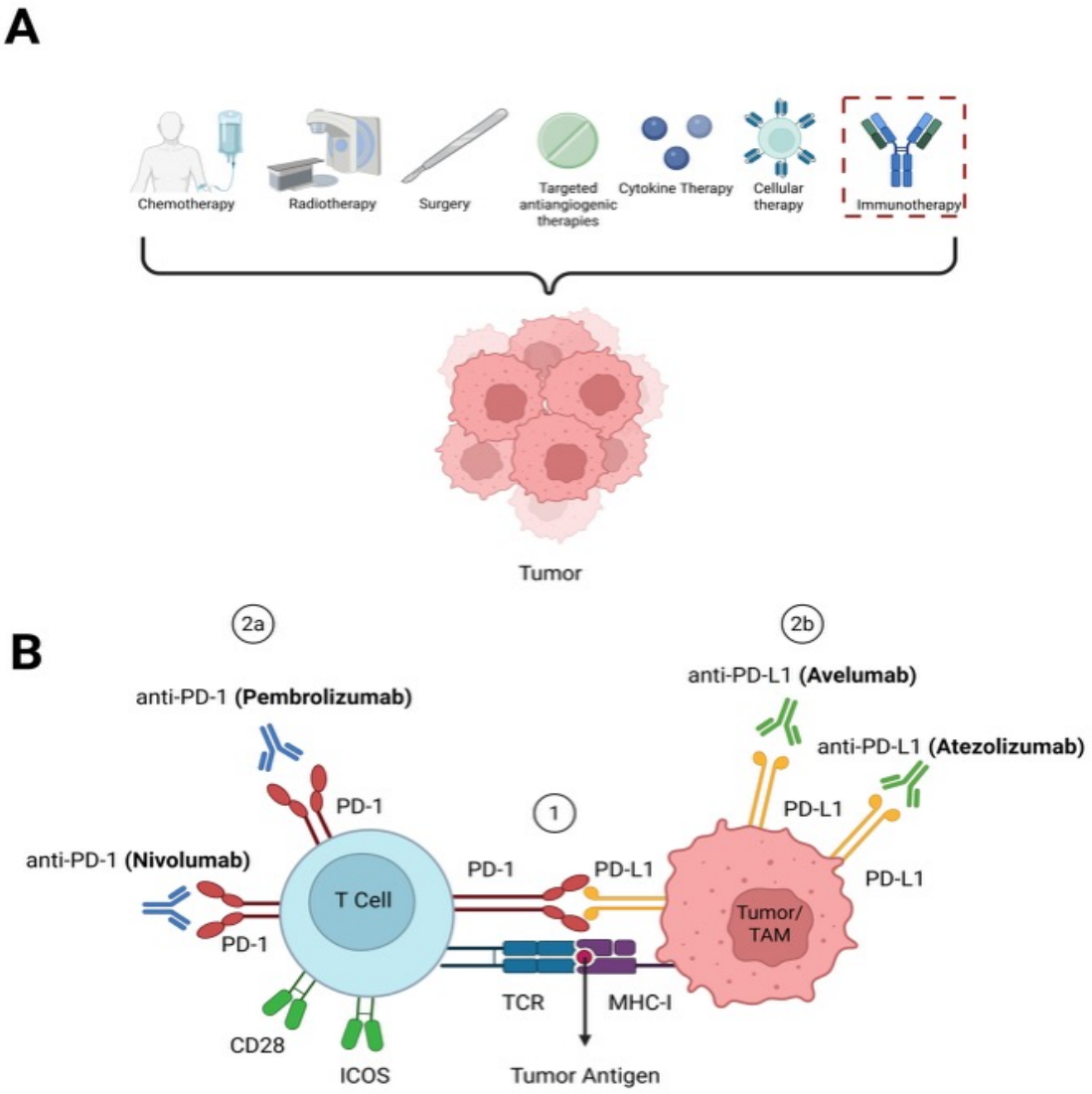
Despite the clinical benefits offered by TKIs, they are associated with various adverse effects, such as fatigue, nausea, diarrhea, hypertension, and skin rash. In some cases, these side effects can be severe and require dose adjustments or discontinuation. Furthermore, TKIs are not curative and disease progression may occur despite treatment. Therefore, ongoing research has focused on the development of new therapeutic approaches.

Immunotherapy with monoclonal antibodies

Monoclonal antibodies targeting the Cytotoxic T Lymphocyte Antigen 4 (CTLA-4), the Programmed Cell Death protein-1 (PD-1) or its ligand, programmed death-ligand-1 (PD-L1), have emerged as a successful therapeutic approach for the treatment of advanced RCC.[22] PD-1 and CTLA-4 are membrane receptors on T cells that negatively regulate activation

to prevent overactivation and tissue damage. However, several tumors activate ligands for these receptors, blocking the antitumor effector functions of T lymphocytes and driving cancer progression. The use of antibodies targeting PD-1, CTLA-4, or PD-L1 disrupts this interaction and restores T-cell function, thereby enhancing antitumor immunity (Figure 1).[23]

Figure 1. Immune-directed mechanisms in the treatment of renal cell carcinoma



(A) Available treatments for RCC include cytotoxic chemotherapy, radiotherapy, surgery, targeted anti-angiogenic therapies, cytokine therapy, cellular therapy, and immunotherapy (highlighted in red). (B) Cellular mechanisms of immune checkpoint inhibitors in cancer treatment. The interaction between PD-1 and PD-L1 inhibits the immune response of T lymphocytes.(1) The blocking of either PD-1 (2a) or PD-L1 (2b) receptors unblock the antitumor effector lymphocytes.

Among immunotherapy, collectively known as immune checkpoint inhibitors or ICIs, the PD-1 inhibitor Nivolumab was the first antibody approved for advanced RCC in 2015, exhibiting a 25 % overall survival rate compared to everolimus.[24] Currently, there are five antibodies approved for treating advanced RCC: the PD-1 inhibitors Pembrolizumab and Nivolumab; the CTLA-4 inhibitor Ipilimumab; and the PD-L1 inhibitors Atezolizumab and Avelumab. Currently, the combined use of Ipilimumab + Nivolumab is approved as first-line therapy for metastatic RCC.[25]

Despite the overall successful use of ICIs, response rates remain limited for some patients with RCC. Monotherapies often induce compensatory immune resistance through the upregulation of other immune regulators. Emerging checkpoints such as Lymphocyte Activation Gene-3 (LAG-3), T Cell Immunoglobulin and Mucin Domain Containing 3 (TIM-3), and T Cell Immunoreceptor with Ig and ITIM Domains (TIGIT) have shown promise and are currently under clinical investigation. Co-expression of these ICIs has been observed in RCC and preclinical models, suggesting their potential for combination therapies.[26] Table 2 shows pivotal studies addressing the use of approved immunotherapy in treating patients with RCC.

Table 2. Pivotal clinical trials for RCC immunotherapy

Study	Participants	Treatment	Results	Reference
KEYNOTE-426	861	Pembrolizumab + Axitinib *vs* Sunitinib	Combination therapy improved PFS compared to sunitinib, with a 47 % reduction in the risk of death and a 31 % reduction in disease progression.	Rini et al., (2019).[27]
Javelin Renal 101	886	Avelumab + Axitinib *vs* Sunitinib	Avelumab + axitinib showed improved OR (55.2 %) and OS (11.6 months) compared to sunitinib (OR 25.5 %, OS 10.7 months).	Motzer et al. (2019).[28]
IMmotion 151	915	Atezolizumab + Bevacizumab *vs* Sunitinib	Atezolizumab + bevacizumab improved PFS (11.2 months) compared to sunitinib (7.7 months).	Rini et al., (2019).[29]
CheckMate 9ER	651	Nivolumab + Cabozantinib *vs* Sunitinib	Nivolumab + cabozantinib showed superior PFS (8.3 months) and 12 month OS (85.7 %) compared to sunitinib.	Choueiri et al.,(2021).[30]
CLEAR	1069	Lenvatinib + Pembrolizumab *vs* Lenvatinib + Everolimus	Lenvatinib + pembrolizumab demonstrated significantly longer PFS (23.9 months) compared to lenvatinib + everolimus.	Motzer et al., (2021) .[31]
KEYNOTE-426	693	Pembrolizumab + Axitinib *vs* Sunitinib	Pembrolizumab + axitinib in RCC is associated with an increased risk of liver enzyme elevation compared to sunitinib.	Plimack et al., (2023) .[32]
CONTACT-03	692	Atezolizumab + Cabozantinib *vs* Cabozantinib	The addition of atezolizumab to cabozantinib did not improve clinical outcomes and led to increased toxicity.	Pal et al., (2023).[33]
PIVOT-09	623	BEMPEG + Nivolumab *vs* Sunitinib or Cabozantinib	First-line BEMPEG + Nivolumab failed to show efficacy benefit in RCC patients.	Tannir et al., (2024) .[34]

OR, objective response; OS, overall survival; PFS, progression-free survival; PD-L1, Programmed-Death Ligand 1; RCC, renal cell carcinoma; BEMPEG, Bempegaldesleukin.

Immune cellular therapy

Among experimental therapies, cell therapy has been successfully translated into clinical practice in recent years. In particular, chimeric antigen receptor T-cell (CAR-T) therapy shows promise in treating solid tumors, including RCC.[35]

In CAR-T therapy, autologous lymphocytes are genetically transferred with a T cell receptor specific for a particular tumor antigen. However, the probability of developing serious adverse effects had limited its widespread use for the moment.[36] CAR-T cells targeting carbonic anhydrase-IX (CAIX) have been tested for RCC, but the results have been inconclusive.[37]

Despite progress in CAR-T cell therapy, identifying suitable antigens on the surface of cells in solid tumors remains challenging. Solid tumors impede CAR-T cell penetration, promoting TSAs escape mechanisms, treatment-related toxicity, and immunosuppressive cytokine production. Although CAR-T cell therapy has shown promise in the treatment of hematologic diseases, its efficacy in solid tumors remains a subject of active research.[38]

Complementary to cytotoxic lymphocytes, NK cells play a pivotal role in antitumor immunity through their ability to recognize and destroy malignant cells but with an antigen-independent mechanism. The use of unmodified NK cells is limited because of RCC's immune evasion mechanisms of RCC, and the use of chimeric antigen receptor NK-cell (CAR-NK) has not been formally achieved.[39]

Dendritic cells (DCs) can induce antigen-specific cytotoxic lymphocytes (CTL- and DC-based vaccines have emerged as a promising strategy for cancer immunotherapy. In principle, DCs can be primed to present TSAs to endogenous lymphocytes, offering a more targeted and safer approach than CAR-T and CAR-NK therapies. However, these therapies have not been validated in clinical trials.[40]

Other therapies

The phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT)/mammalian target of rapamycin (mTOR) signaling pathway regulates cell growth, survival, and angiogenesis in RCC. Therapeutic targeting of RCC involves VEGF, RTK (receptor tyrosine kinase) and mTOR inhibitors. Temsirolimus and everolimus, both mTOR inhibitors, have been approved for the treatment of advanced RCC. Clinical trials have shown that temsirolimus significantly improves survival in patients with metastatic RCC compared with IFN-α alone.[41]

However, resistance to mTOR inhibitors is limited. While temsirolimus showed benefits in some trials, other studies have suggested that axitinib (an RTK inhibitor) may offer better outcomes in ccRCC. Everolimus and temsirolimus blocked mTOR downstream effectors (S6K1 and 4EBP1), leading to cell cycle arrest in the G1 phase and reduced proliferation. A novel dual PI3K-mTOR inhibitor, GNE-477, has shown promising preclinical results by suppressing RCC growth in vitro and in vivo, indicating its potential as a novel therapeutic option.[42]

Future perspectives

Combined therapies seek to enhance treatment efficacy, reduce the risk of resistance, and mitigate the side effects associated with standard

monodoses. According to the European Society for Medical Oncology, the first-line treatment for ccRCC involves the use of anti-PD-1 in combination with either VEGFR or CTLA-4 inhibitors. For second- and third-line treatments in ccRCC, prospective datasets exist for axitinib, pazopanib, and sunitinib; however, these datasets include mixed patient populations and limited sample sizes.[43] Notably, there is a lack of robust prospective data that specifically focuses on combination therapies involving first-line PD-1 inhibitors.

Beyond monoclonal antibodies and cell therapy, several emerging therapeutic approaches are being explored for RCC, including the use of the Hypoxia-Inducible Factor-2α (HIF-2α) inhibitor belzutifan, a drug targeting the HIF pathway, which is implicated in RCC tumorigenesis.[44] Finally, messenger RNA (mRNA) therapy has emerged as a potential treatment for cancer because of its potential to stimulate the expression of selective antigens on DCs, in turn stimulating a directed endogenous immune response. However, mRNA therapy is still in the early stages of development and has not yet been approved for RCC treatment. In this context, it is important to note that currently there is an ongoing Phase-I trial (KEYNOTE-942) over an mRNA-based personalized cancer vaccine, mRNA-4157, for patients with metastatic solid tumors, including RCC.[45]

Conclusion

Renal cell carcinoma presents a complex tumor microenvironment whichere infiltrated immune cells become dysfunctional. Most treatments are directed toward either the depletion of tumor cells or enhancement of antitumor immunity. Among the latter, there are many novel approaches to successfully target the advanced stages of RCC. In the future, immune cell strategies will be crucial for the treatment of advanced stages of most solid tumors, as is the case for RCC.

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Conflict of interest

The authors declare no conflict of interest.

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