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The Role of Immune Checkpoint Inhibitors in Renal Cancer: Innovation, Resistance Mechanisms, and Next-generation Strategies

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Abstract: Renal cell carcinoma (RCC) is a prevalent and aggressive malignancy, often diagnosed at advanced stages with limited curative options. The development of immune checkpoint inhibitors (ICIs), especially those that target the PD-1/PD-L1 axis, has significantly transformed the therapeutic landscape of RCC, offering improved survival and disease control. However, a significant percentage of individuals either develop acquired resistance or have primary resistance, limiting the long-term efficacy of ICI-based therapies. This review explores the status of ICI treatment in RCC, summarizing key clinical milestones and response variability. Mechanisms contributing to resistance—such as defective antigen presentation, immunosuppressive tumor microenvironment, and T cell exhaustion —are examined in detail. To address these limitations, combination therapies involving VEGF inhibitors and dual checkpoint blockade (e.g., PD-1/CTLA-4) have demonstrated enhanced antitumor activity in clinical trials. Moreover, the potential of next-generation immune checkpoint targets, such as TIGIT, TIM-3, and LAG-3, to improve immune response is being intensively studied. In parallel, emerging technologies such as artificial intelligence-driven biomarker discovery, personalized neoantigen vaccines, and microbiome modulation are shaping the future of precision immunotherapy in RCC. These innovations aim to identify predictive markers, tailor therapies, and improve patient outcomes. By integrating mechanistic understanding with clinical and technological advancements, a more durable and personalized immunotherapy strategy may be achievable. This review provides a comprehensive overview of ongoing challenges, recent breakthroughs, and future directions for ICIs in RCC, highlighting the need for a multi-pronged approach to overcome resistance and optimize treatment efficacy.

Keywords: renal cell carcinoma, resistance mechanisms, immune checkpoint inhibitors, combination therapy, next-generation immunotherapy

1. Introduction

Renal cell carcinoma (RCC) is the most common type of kidney cancer, accounting for about 90% of all cases. The incidence of RCC has been increasing globally, and most of these patients are already diagnosed with advanced or metastatic stages when they are detected [1-3]. Although the surgical techniques and systemic treatments for RCC have been quite effective, due to its heterogeneity and resistance to conventional therapies, it remains a difficult disease to treat. Early-

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stage renal cell carcinoma can usually be successfully treated with surgical removal; However, advanced, and metastatic RCC requires treatment with a systemic approach, including targeted therapy and immunotherapy. In the past decade, immune checkpoint inhibitors (ICIs) have become the dominant pathway for RCC treatment. ICIs target inhibitory pathways in the immune system, activating T cells and generating an effective anti-tumor immune response [4]. Several studies have shown that PD-1 inhibitors and PD-L1 inhibitors have significant efficacy in kidney cancer [5]. Meanwhile, the approval of nivolumab, pembrolizumab and atezolizumab has extended survival for many patients. Despite the effectiveness of ICIs research, there are still many challenges. Despite the effectiveness of ICIs research, there are still many challenges. Different patients respond differently to ICIs, and some patients have no significant clinical response. People who are initially very effective at treating tumors with ICIs also develop resistance over time, which limits the long-term effectiveness of ICIs [5]. Tumor cells can also evade immune detection through a variety of mechanisms, such as downregulating antigen presentation, upregulating immunosuppressive cytokines, and inducing T cell exhaustion [6,7].

To address these limitations, researchers are investigating combined approaches that combine ICIs with other forms of treatment. The combination of vascular endothelial growth factor (VEGF) inhibitors with ICIs has emerged as a promising strategy because it targets both the immune escape pathway involved in RCC progression and the angiogenesis pathway [8]. In addition, dual checkpoint blocking has also been shown to be effective in RCC therapy, such as the combination of PD-1 and cytotoxic t lymphocyte-associated antigen 4 (CTLA-4) inhibitors, which has been shown to reactivate depleted T cells and improve outcomes in high-risk patients [9]. In addition to combination therapy, studying next-generation immune checkpoint targets may also serve to address limitations, T cell immunoreceptor with Ig and ITIM domains (TIGIT), lymphocyte-activation gene 3 (LAG-3), and T cell immunoglobulin and mucin domain-containing protein 3 (TIM-3) [10,11]. These molecules contribute to immunosuppression and tumor immune escape, which can be targets for immunotherapy intervention. In addition, technologies such as AI-driven biomarker analysis, personalized neoantigen vaccines, and gut microbiota offer promise for immunotherapy of RCC [12,13]. Artificial intelligence helps to predict the patient's response to ICI, and personalized neoantigen vaccines may enhance the immune response. In addition, the gut microbiota affects the efficacy of ICI. For instance, the treatment of RCC with probiotics and fecal microbiota transplantation (FMT) is currently under clinical study. In this review, the status of ICI treatment of RCC will be discussed, including its successes and limitations. The mechanisms underlying drug resistance, as well as the strategies being developed to overcome them, will also be examined. Finally, the potential of next-generation immune checkpoint targets and emerging technologies to shape the future of RCC immunotherapy will be explored.

2. Current Treatment of Immune Checkpoint Inhibitors in Renal Cell Carcinoma: Successes and Limitations

The immune checkpoint inhibitors have revolutionized the treatment system of metastatic renal cell carcinoma (mRCC) in recent years, which brings hope to patients with advanced disease. Among them, PD-1/PD-L1 inhibitors such as atezolizumab, pembrolizumab, and nivolumab have shown significant clinical success. One of the most successful is nivolumab, a PD-1 inhibitor, which gained approval following the CheckMate 025 trial [14]. This study displayed that the median overall survival (OS) for nivolumab was 25 months, whereas that of everolimus was 19.6 months., nivolumab prolongs survival, which is critical for patients receiving long-term treatment. In the KEYNOTE-426 trial, which evaluated pembrolizumab in combination with axitinib. This combination significantly outperformed sunitinib, the former first-line standard, in terms of progression-free survival (PFS), overall response rate (ORR), and OS [15]. Similar improvements

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were observed with atezolizumab in combination with bevacizumab. These ICI-based combinations induce a positive response in some patients. Some patients achieved long-term disease control and even functional remission, which is a remarkable achievement in the treatment of Renal cell carcinoma. Therefore, ICI combination therapy has become a key treatment method in the international RCC treatment guidelines.

Despite these advances, limitations remain. The response rate to ICI monotherapy is average, usually around 20-30%, meaning that most patients either do not respond or their condition worsens due to the resistance mechanism of the tumor [16]. Even though combination therapy is more effective, not all patients benefit. The absence of effective biomarkers to predict ICI response is a major challenge. Biomarkers including PD-L1 expression or tumor mutation load did not consistently predict RCC, in contrast to other malignancies like melanoma or non-small cell lung cancer. This can expose patients to ineffective and potentially toxic treatments. In addition, immune-related adverse events (irAEs) provide further difficulties. Immune-related complications such as colitis, pneumonia, hepatitis, and endocrine dysfunction, which may require immunosuppressive therapy or discontinuation of therapy, reducing efficacy. Real-world data show that not all patients will tolerate ICI-based combination treatment options. Factors such as age, comorbidities, and exercise status significantly affect treatment choice and outcome. Tailoring therapy based on patient-specific factors is crucial for optimizing efficacy and safety. PD-1/PD-L1 inhibitors have brought unprecedented advances in the treatment of metastatic RCC, providing longer survival for many patients, and combined strategies and personalized approaches may help overcome current limitations and expand the impact of ICIs in renal cell carcinoma.

3. Mechanisms of Resistance to Immune Checkpoint Inhibitors and Strategic Approaches

Primary and acquired resistance continue to be significant challenges in the treatment of renal cell carcinoma (RCC), with the extraordinary efficacy of immune checkpoint inhibitors (ICIs). Approximately 70-80% of patients either fail to respond to ICIs from the outset or develop resistance after an initial period of disease control. These resistance mechanisms stem from a complex interaction involving tumor-intrinsic factors, immune cell dysfunction, and the immunosuppressive tumor microenvironment (TME). One major resistance mechanism is impaired antigen presentation. The ability of cytotoxic T lymphocytes (CTLs) to recognize tumor antigens may be compromised by tumor cells' downregulation of major histocompatibility complex (MHC) class I molecules or alterations in components like beta-2 microglobulin (B2M) [6]. Consequently, T cells are unable to mount effective immune responses, allowing tumor cells to avoid being destroyed by the immune system. The TME of RCC is often highly immunosuppressive. Increased infiltration by regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs), together with elevated levels of cytokines like TGF-β and IL-10, inhibit the function of effector T cells. High VEGF levels promote angiogenesis while simultaneously excluding T cells from the tumor bed and supporting an immunosuppressive milieu. Another factor is T cell exhaustion, which is indicated by the upregulation of inhibitory receptors such as TIGIT, TIM-3, LAG-3, and PD-1. Exhausted T cells showed reduced cytokine secretion, proliferation, and cytotoxicity. In the context of chronic antigen exposure, such as in tumors, these exhausted states undermine the efficacy of ICI monotherapy [7].

To address these challenges, combination therapies are being used. Notably, combining ICIs with VEGF inhibitors (e.g., pembrolizumab plus lenvatinib) not only disrupts tumor angiogenesis, but also reprograms TME to support the invasion and activation of immune cells [8]. Major improvements in overall survival (OS) and progression-free survival (PFS) have been seen in clinical studies such as CLEAR. Dual immune checkpoint blocking can enhance T cell initiation and activation, such as a CTLA-4 inhibitor (ipilimumab) combined with PD-1 inhibitor (nivolumab).

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The CheckMate 214 trial showed that this combination led to higher rates of response and longer survival, especially in moderate-risk and low-risk patients [17]. Emerging strategies target tumor metabolism and epigenetic regulation. Hypoxia, acidosis, and nutrient depletion in TME impair T cell function. Drugs that target adenosine signaling, tryptophan catabolism (IDO inhibitors), or histone modifiers are being investigated to overcome these obstacles. Biomarker-driven approaches are also gaining popularity. Immune profiling, ctDNA analysis, and TCR sequencing can identify early resistance and adjust treatment strategies.

4. Next-generation Targets in Renal Cell Carcinoma: LAG-3, TIM-3, and TIGIT

Despite the revolutionary success of PD-1/PD-L1 blockade in renal cell carcinoma (RCC), a substantial proportion of patients exhibit primary resistance or eventually develop acquired resistance. This unmet clinical need has driven the exploration of next-generation immune checkpoints beyond PD-1, with TIGIT, TIM-3, LAG-3 and emerging as the most promising therapeutic targets. These molecules exhibit distinct yet complementary immunosuppressive mechanisms, offering opportunities for synergistic combination therapies to overcome resistance and improve clinical outcomes.

LAG-3, a type I transmembrane protein expressed on activated T cells, regulatory T cells (Tregs), and natural killer (NK) cells, exerts immunosuppressive effects by binding to MHC class II molecules [10]. This interaction not only inhibits T-cell receptor (TCR) signalling but also promotes Treg-mediated tolerance. In RCC, chronic antigen exposure within the tumor microenvironment (TME) leads to sustained LAG-3 upregulation, correlating with T-cell exhaustion and immune evasion. Dual blockade of PD-1 and LAG-3 has been shown in preclinical models to increase cytotoxic T-cell activity and tumor regression in a synergistic manner. The FDA approved relatlimab (anti-LAG-3) in combination with nivolumab for metastatic melanoma marked a paradigm shift in 2022. Early data suggest improved progression-free survival (PFS), particularly in patients with high baseline LAG-3 expression in tumor-infiltrating lymphocytes (TILs) [18].

TIM-3, a checkpoint receptor enriched in exhausted $CD8^+$ T cells and immunosuppressive Tregs, interacts with multiple ligands including Galectin-9, phosphatidylserine, and HMGB1. Its activation triggers apoptosis of effector T cells while amplifying Treg-mediated suppression. In RCC, TIM-3 overexpression is frequently observed in PD-1 therapy-refractory tumors, suggesting its role as a compensatory resistance mechanism [19]. Preclinical studies using anti-TIM-3 antibodies (e.g., sabatolimab) in RCC models have restored interferon-γ production in $CD8^+$ T cells and reshaped the myeloid compartment by reducing M2-like tumor-associated macrophages [20]. Notably, transcriptomic analyses of pre-treatment biopsies reveal that $TIM\text{-}3^+CD8^+$ T cells may serve as predictive biomarkers for patient stratification.

TIGIT is a checkpoint receptor that binds to CD155, competing with the co-stimulatory receptor CD226, thereby inhibiting T and NK cell activation. Co-expression of TIGIT and PD-1 is frequently observed in dysfunctional T cells within the RCC tumor microenvironment. Poor prognosis and immune escape have been related to TIGIT [11]. In preclinical models, simultaneous blockade of TIGIT and PD-1 work together to strengthen anti-tumor immunity and T cell functionality. Several clinical trials are now evaluating TIGIT inhibitors in combination with anti-PD-1 therapies in RCC, with early-phase results indicating tolerability and promising efficacy.

The co-expression patterns of LAG-3, TIM-3, and TIGIT with PD-1 in the RCC TME underscore the complexity of immune evasion. Spatial multi-omics technologies, such as multiplexed immunofluorescence and single-cell TCR sequencing, are being leveraged to map the geographical and functional interplay between these checkpoints. However, key challenges remain, including optimal sequencing of combination therapies, mitigation of overlapping toxicities (e.g., immune-related hepatitis), and identification of robust predictive biomarkers. Emerging strategies,

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such as bispecific antibodies targeting PD-1/TIM-3 or LAG-3/TIGIT, and engineered probiotics modulating checkpoint expression, represent innovative approaches to personalize RCC immunotherapy. Collectively, the targeting of next-generation checkpoints is redefining the therapeutic landscape for RCC. By dissecting their unique biological roles and leveraging advanced biomarker-driven strategies, these therapies hold immense potential to unlock durable responses in patients resistant to conventional immunotherapy.

5. Emerging Technologies in Immunotherapy of Renal Cell Carcinoma: Artificial Intelligence, Cancer Vaccines, and Microbiome Modulation

Immune checkpoint inhibitors (ICIs) become most important to the treatment of renal cell carcinoma (RCC), emerging technologies are offering new strategies to improve outcomes through personalization, biomarker discovery, and enhanced immune modulation. Notable innovations include artificial intelligence (AI), neoantigen-based cancer vaccines, and microbiome-targeted interventions. Artificial intelligence has become a powerful tool for analyzing complex biomedical data and supporting clinical decision making. Artificial intelligence can identify predictive patterns of response to or resistance to ICIs by integrating multiple omics datasets, such as genomic, transcriptomic, radiomic, and histopathological data [12]. Ai models have been used to detect immune gene signatures associated with tumor-infiltrating lymphocytes, tumor mutation burden, and checkpoint molecular expression. These predictive tools can stratify patients, distinguish those who benefit from ICI treatment from those who do not respond, and avoid unnecessary complications. In addition, AI-driven surveillance systems are being developed, which can detect immune-related adverse events (irAEs) early and reduce the impact of complications on treatment [12]. Another promising avenue is the development of personalized neoantigen cancer vaccines. Neoantigens are tumor-specific antigens produced by somatic mutations that are not present in normal tissues. The high tumor specificity and immunogenicity of neoantigens can provide a unique target for immunotherapy. And next generation sequencing and bioinformatics can be used to identify relevant neoantigens to create personalized vaccines. These antigens are then synthesized into peptides or mRNA-based vaccines to stimulate the target immune response. Neoantigen vaccines used in combination with ICIs have shown good safety and immune activity in early clinical trials.

Modulation of the gut microbiome has become an important research direction to improve the effect of immunotherapy. Gut microbes influence cancer treatment by regulating the systemic immune response. For example, certain flora such as Akkermansia muciniphila, Faecalibacterium prausnitzii, and Bifidobacterium longum are positively correlated with the efficacy of immune checkpoint inhibitors, while the imbalance of flora caused by antibiotics reduces the efficacy of drugs [13]. At present, clinical attempts are made to reconstruct the microbial environment for promoting and anti-tumor immunity by means of fecal bacteria transplantation and probiotic supplementation, while focusing on the immunomodulatory effects of microbial derived compounds such as short-chain fatty acids and tryptophan metabolites. Technological innovation also promotes the development of tumor immunotherapy spatial transcriptomics, single-cell sequencing, and CRISPR-based functional genomics technologies that can accurately analyze the tumor microenvironment, providing new targets for the development of a new generation of therapies. The application of wearable health monitoring devices and digital biomarkers can evaluate treatment effects and side effects in real-time and optimize treatment options. These breakthroughs are changing the landscape of kidney cancer immunotherapy, and through multidisciplinary collaboration and regulatory innovation, personalized treatment models are expected to become a reality, opening a new path for cancer precision medicine.

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6. Conclusion

Renal cell carcinoma (RCC) has witnessed a paradigm shift in its therapeutic management due to the emergence of immune checkpoint inhibitors (ICIs), especially agents targeting PD-1/PD-L1 pathways. These advancements have led to significant survival benefits for patients with advanced RCC. However, despite the initial enthusiasm, clinical outcomes remain heterogeneous, with many patients showing limited response or developing resistance over time. This highlights a fundamental challenge: the need for predictive biomarkers to identify responders and stratify patients more effectively. Recent research has made substantial progress in understanding the immunological landscape of RCC. Mechanistic studies have elucidated how tumors escape immune surveillance through downregulation of antigen presentation machinery, recruitment of immunosuppressive cells like Tregs and MDSCs, and induction of T cell exhaustion via alternative checkpoints such as LAG-3, TIM-3, and TIGIT. These findings have spurred the development of next-generation immunotherapies aimed at restoring anti-tumor immunity through combinatorial and sequential approaches.

Combination therapies, particularly ICIs with VEGF inhibitors and dual checkpoint blockade (e.g., PD-1 and CTLA-4), have demonstrated improved efficacy in clinical trials. Nonetheless, such regimens carry risks of increased immune-related toxicities, necessitating careful patient monitoring and dose optimization. Furthermore, non-clear cell RCC (nccRCC) remains understudied, and more inclusive clinical trials are essential to expand treatment options for this diverse subgroup. Emerging technologies offer promising avenues for addressing current limitations. Artificial intelligence enables the integration of multi-omics data to guide patient selection and therapeutic decisions. Personalized neoantigen vaccines and microbiome modulation are being explored to improve immunogenicity and overcome resistance. These approaches, while still in the early stages, have the potential to personalize treatment and extend the durability of response. In conclusion, while RCC immunotherapy has made remarkable strides, it continues to face scientific, clinical, and logistical challenges. Future research must focus on refining combination strategies, validating predictive biomarkers, and leveraging innovative technologies to develop personalized, durable, and effective immunotherapeutic regimens for RCC patients.

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