

Renal Cell Carcinoma

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Contributor: Yoon Soo Hah

Renal cell carcinoma (RCC) is a malignant tumor associated with various tumor microenvironments (TMEs).

biomarkers

clinical trials

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1. Introduction

Renal cell carcinoma (RCC) is the most common type of kidney malignancy, constituting 2–3% of all cancers. This nephron-arising neoplasm consists of heterogenous subgroups according to histologic and molecular subtypes. Clear cell RCC (ccRCC) is an aggressive subtype, constituting 70–80% of all RCCs [1]. Von Hippel-Lindau (VHL) is a crucial component for maintaining the oxygen homeostasis of the cellular environment [2]. The loss of the VHL tumor suppressor drives the hypoxic pathway by hypoxia-inducible factors (HIF) transcription factors. It activates several hypoxia-driven genes, such as vascular endothelial growth factor (VEGF), and subsequently induces angiogenesis and cell growth [3][4]. This VHL mutation course is the main pathway of ccRCC. Modifications of various genes similarly manifest as other types of RCC. Papillary RCC is the second most common subtype of RCC, and is classified into two subtypes: type I, which is mainly associated with MET alterations, and type II, which is associated with the NRF2-antioxidant response component [5]. Chromophobe RCC is associated with mutations of TP53 and PTEN, while translocation RCC is associated with fusions of TFE3 or TFEB genes [6][7].

Decades ago, there were few options for systemic therapy in advanced RCC. Cytokine therapy, represented by interleukin-2 (IL-2) and interferon alfa (IFN- α), showed some benefits in a few advanced patients with RCC, but only proved efficacy in a limited proportion of patients [8]. Moreover, cytokine therapy is associated with a high level of toxicity, which limited its general use. With advances in genomic research by the Cancer Genome Atlas (TCGA), targeted molecular therapeutics, specifically tyrosine kinase inhibitors (TKIs) targeting the VEGF receptor pathway, have now replaced cytokine therapy and are widely used as first- or second-line therapy. The development of the TCGA also led to a better understanding of the mammalian target of the rapamycin (mTOR) pathway that is known to induce cell growth and division in ccRCC [3][9]. Subsequent development and use of mTOR inhibitors have shown similar oncological outcomes to TKIs [10][11][12].

Immunity against malignancy varies depending on several components that make up the tumor microenvironment (TME), and therefore clinical symptoms and the course of treatment differ accordingly. RCC is classified as an immunogenic tumor based on its response to immunotherapy, the incidence of spontaneous regression, and a high

level of tumor T cell infiltration [13]. Recent advances in immune checkpoint inhibitor (ICI) therapy up-regulating immune responses by blocking the programmed cell death protein 1 (PD-1) receptor, ligand of PD-1 (PD-L1) or cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), and T cells have overtaken cytokine-based regimens and are now key players in the field of immunotherapy [14][15]. Unlike IFN- α and IL-2, for which only a limited range of patients are eligible due to toxicity, ICIs are characterized by superior safety profiles and oncological efficacy. Recently, updated guidelines recommend combining VEGF targeted agents with ICIs depending on patient performance and comorbidity.

Risk stratification systems are essential for selecting the optimal treatment for a specific patient. Unfortunately, there are no predictive biomarkers for RCC, which limits effective strategies for management. Current international guidelines for risk stratification rely on clinical variables to guide prognosis and treatment selection. The Memorial Sloan Kettering Cancer Center (MSKCC) criteria incorporate five prognosticators: low performance status, high level of serum dehydrogenase, high level of serum calcium, low concentration of hemoglobin, and interval less than one year from diagnosis to treatment [16]. The International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) utilizes similar prognosticators to those of MSKCC but includes high levels of neutrophil and platelet counts instead of serum lactate dehydrogenase level [17][18]. Patients without any corresponding prognostic factors are classified into a low-risk group, patients with one or two prognosticators into an intermediate-risk group, and three or more into a poor-risk group.

2. Tumor Microenvironment in Renal Cell Carcinoma

Chromosome 3p loss is the first genetic event characterizing sporadic ccRCC, followed by VHL mutation [19]. VHL negatively regulates HIF 1/2 α , which reduce oxygen demand in the cellular environment by increasing glycolytic flux and reducing oxidative phosphorylation. This pathway induces oxygen supply by hyper-vascularization. Based on metabolic pathway analysis by RNA sequencing, ccRCC is known to possess high levels of metabolites during glycolysis and to reduce levels of metabolites associated with oxidative phosphorylation [20]. Hyper-vascularity and the immune system are not independent, and treatment targeting the VEGF receptor promotes the immune pathway by modifying the aberrant blood supply [21].

TME are complicated, containing transformed cells and immune infiltrates. Tumor-infiltrating cells promote or inhibit cancer activity according to the type of cancer. The immune system is activated by cancer development and drives T cell anti-tumor response by suppressing tumor cells directly, modulating various anti-tumor responses, facilitating the emerging memorial system, and preparing specificity for tumor-derived proteins [8]. T cell activation, according to immunotherapy response, is a core component in the prognosis of ccRCC. CD8 T cells play a crucial role in combating malignant tumors and are associated with favorable clinical outcomes and response to immunotherapy [22][23][24][25][26]. Presentation of major histocompatibility class I (MHC-I) molecules on cancer cells helps T cell receptors recognize antigens. This pathway activates CD8 T cells, which subsequently activates antigen-specific immune response, and directly removes antigen-bearing cells [27]. The antigen-presenting machinery (APM) promoted by activated CD8 T cells is a component that interlinks antigens and MHC-I. Upregulation of APM genes refers to the increased production of antigen-presentation and the number of T cells. CcRCC is characterized by

the highest T cell infiltration and immune infiltration when compared to other malignancies. The immunogenicity of ccRCC is related to MHC-I and APM gene expression, which may potentially serve as indicators of response to PD-1 inhibitors. The promotion of APM expression is a unique feature of ccRCC [28]. In contrast, Th2 and regulatory T cells are negatively associated with prognosis. An abundant environment with Th2 and regulatory T cells suppresses the immune response and is associated with the tumor mutation load [28].

Macrophages are phagocytic innate immune cells that regulate responses to tissue damage. Macrophages are promoted based on consecutive signals from the damaged microenvironment and mount proinflammatory responses to pathogens [29]. Macrophages are abundantly observed in growing cancer cells and mediate lymphocyte trapping according to interactions with CD8 T cells in tumor stroma. Cytokines and chemokines expressed by tumor-associated macrophages (TAMs) suppress immunity against malignancy and lead to tumor progression [30]. In an in vivo study, the efficiency of T cells increased when TAMs were depleted by pexidartinib, a small molecule tyrosine kinase inhibitor that acts against colony-stimulating factor 1. The depletion of TAMs not only increased the number of tumor-infiltrating CD8 T cells but also improved their migration and ability to reach cancer cells [31][32][33].

Tertiary lymphoid structures (TLS) are a lymphoid environment usually associated with reactions to infection or inflammation [34]. TLS neogenesis is induced by chronic bacterial or viral infection or by chronic inflammatory diseases such as multiple sclerosis, Sjögren's syndrome, or allograft rejection [35][36][37][38][39]. TME is similar to TLS and includes several components associated with the immune system and T cell activation. Mature dendritic cells (DCs), which are associated with activated CD8 T cells within the TLS, are associated with favorable survival outcomes in ccRCC. On the other hand, DCs outside of TLS are associated with poor survival outcomes in response to dysfunctional CD8 T cells [40][41].

The wide variety of clinical features and outcomes of immunotherapy in patients with ccRCC are due to the heterogeneity of TME. A study that utilized mass cytometry confirmed the subsets of T cells and TAMs, the critical components of TME [42]. In a study comparing 73 patients with ccRCC and five healthy controls, 20 T cell phenotypes and 17 TAMs phenotypes were identified. With ongoing research on the mechanisms of treatment failure, TME heterogeneity is being perceived as a key factor.

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