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The Updated Tumor Immune Microenvironment (TIME) Landscape of Clear Cell Renal Cell Carcinoma (ccRCC)

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ABSTRACT

The development of efficacious immunotherapies to cure clear cell renal cell carcinoma (ccRCC) requires a greater understanding of the tumor immune microenvironment (TIME). The profound immunosuppressive tumor microenvironment poses unique challenges for applying immunotherapy techniques that have had great success in hematological malignancies to solid tumors. Recent studies of the ccRCC TIME have characterized the tumor-infiltrating lymphocytes (TILs) and revealed mechanisms of immune evasion and potential targets for immunotherapies using mass cytometry and single cell RNA sequencing (scRNA-seq). These results characterizing the TIME landscape will be helpful in developing immunotherapies for ccRCC, which will benefit patients across the globe.

Keywords: Tumor Immune Microenvironment (TIME); Clear Cell Renal Cell Carcinoma (ccRCC); Single Cell RNA Sequencing (scRNAseq); Immunotherapy

Abbreviations: TIME: Tumor Immune Microenvironment; ccRCC: Clear Cell Renal Cell Carcinoma; TILs: Tumor-Infiltrating Lymphocytes; ICIs: Immune Checkpoint Inhibitors

Introduction

Studying the ccRCC tumor immune microenvironment (TIME) is necessary to understand disease progression and response to immunotherapies [1]. Recent studies characterized the composition and phenotypic states of immune cells, including CD8+ T cells, CD4+ T cells, M2-like tumor associated macrophages (TAMs) and tertiary lymphoid structures (TLS). In addition, crosstalk between different immune cell populations was also identified.

Cellular Composition of the ccRCC TIME

CD8+ T cells

Across solid tumors, infiltration by CD8+ T cells is associated with an improved prognosis, but paradoxically in ccRCC, such infiltration has been associated with a worse prognosis [2]. Somehow the CD8+ cytolytic T cells hijacked by the tumor cells were not functional within the ccRCC TIME. Terminally exhausted CD8+ T cells were observed, expressing PDCD1/PD-1, the transcriptional regulator of exhaustion TOX, and high levels of HAVCR2/TIM-3 and other inhibitory checkpoints [3-5]. In addition, with advancing ccRCC disease state, there is an observed increase of exhausted CD8+ T cells [3]. In 2021, Su, et al. applied digital cytometry to investigate the TIME of 526 tumors found a higher proportion of CD8+ T cells relative to CD4+ within the TME with tumor progression [6].

CD4+ T cells

CD4+ regulatory T cells are typically immunosuppressive and have been associated with worsened prognosis among various cancer types [2]. The overall enrichment of CD4+ T cells was observed in normal tissue and early-stage ccRCC, however, some subpopulations were well represented in more advanced stages [3]. Single-cell profiling of the ccRCC TIME was carried out by mapping 25,688 immune single-cells from matched tumor and peripheral blood samples from treatment-naive ccRCC patients. A lower CD4+ T cell count was found in healthy kidney samples compared to peripheral blood, with CD4+ T cells counts decreasing even more in ccRCC samples, indicating that the development of ccRCC is associated with decreased concentrations of CD4+ T cells [7].

TAMs

In 2017, Chevrier, et al. analyzed samples from 73 ccRCC patients with varying tumor grades and 5 healthy controls using mass cytometry to study the role of immune cells in the TME in disease progression. They observed a correlation between CD38+, CD204+, and CD206- TAMs and immunosuppression in the ccRCC TME [8]. In many cancer types, the M2 phenotype, which is associated with the production of proangiogenic and immunosuppressive factors, predominates and is associated with worsened cancer prognosis [3,8].

TLS

TLS are the structures resembling secondary lymphoid organs and are found to be present in solid tumors [9]. TLS contains high endothelial venules (HEVs), dendritic cell-lysosomal associated membrane protein (DC-LAMP)+ dendritic cells (DCs), CD20+ B cells and CD3+ T cells with essential markers CD4, CD8, CD31, CD23, CD163, and FOXP3, but may or may not include an active germinal center (GC), proliferating B cells or T follicular helper (TFH) cells [10]. A spatial transcriptomic analysis from ccRCC patients revealed an association of TLS+ tumors with presence of B cell lineages, higher IGHG1 and IGHA1 expressing plasma cells and apoptotic cells mediating antitumor response [11]. The intra-tumoral TLS have a positive prognosis correlation with ccRCC and thus possess a positive therapeutic outcome in immunotherapy [12].

Crosstalk within ccRCC TIME

Single cell RNA sequencing (scRNA-seq) has provided important insights into the transcriptional states of tumor-infiltrating lymphocytes (TILs) in ccRCC. Studying the composition of TILs may improve our understanding of the immune system's role in facilitating ccRCC progression and immunotherapy resistance. With advancing ccRCC disease state, there is an observed increase of exhausted CD8+ T cells and M2-like macrophages, and the crosstalk between exhausted CD8+ T and M2 forms an immune dysfunction circuit which supports T cell dysfunction and M2-like polarization, leading to a worse prognosis [3]. In this bidirectional circuit, M2-like TAMs express ligands for multiple T cell inhibitory receptors (PD-1, CTLA-4, TIGIT, TIM-3) and terminally exhausted CD8+ T cells produce factors that encourage M2-like polarization (CSF1 and MIF) [3]. Whereby M2-like TAMs express ligands for multiple T cell inhibitory receptors (PD-1, CTLA-4, TIGIT, TIM-3, among others), and terminally exhausted CD8+ T cells produce factors that encourage M2-like polarization (CSF1 and MIF) [3].

Discussion

A better understanding of the landscape of ccRCC TIME can speed the development of immunotherapy from the bench side to the bedside. Despite these immune cells playing significant roles in predicting tumor severity, it is important to note that other cell types have been found to be associated with disease progression or response to immunotherapy. For example, Su et al. described patients with primary ccRCC who responded to treatment had a higher percentage of mast cells within the TME compared to patients who did not respond [6]. Studies have demonstrated that immune checkpoint inhibitors (ICIs) reshape TIME, shifting macrophages toward pro-inflammatory states in response to an interferon-rich microenvironment but also upregulating immunosuppressive markers [13]. In addition, it has demonstrated the association of TLS at tumor site with improved prognosis and response to ICIs in ccRCC patients [11,12].

Conclusion

Here, we highlight the key immune components in the ccRCC TIME and the crosstalk within and discuss the impact of TIME in immunotherapy response, providing novel insights to guide immunotherapy development.

Author Contributions

G.K. and Y.W. drafted the manuscript. All authors edited and approved the manuscript.

Conflict of Interest

W.A.M has patents in the PD-1/ PDL1 field.

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