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Perspective

Biomarkers in renal cell carcinoma: Towards a more selective immune checkpoint inhibition

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ABSTRACT

Immune checkpoint inhibitors such as programmed death protein 1/programmed death-ligand 1 and cytotoxic T-lymphocyte–associated protein 4 inhibitors are already playing a central role in the treatment of metastatic renal cell carcinoma. However, they seem to be only effective in a subset of patients, with a high risk of innate and adaptive tumor resistance. Consequently, biomarkers capable of predicting immune treatment efficacy in advanced renal cancer are needed both in the clinical and the experimental setting. We hereby present a brief summary of evidence on the most studied biomarkers in metastatic renal cell carcinoma with a focus on the possible future place of T cell immunoglobulin and mucin domain-3 (TIM-3).

Renal cell carcinoma (RCC)'s prognosis in the metastatic setting has historically been poor. For many years, cytokine therapies were the only available treatment of advanced RCC, with frequent poor results. Following the gradual understanding of the biology and genomic of RCC, immune checkpoint inhibitors have come afore. Immune checkpoint inhibitors (ICI) such as programmed death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) and cytotoxic T-lymphocyte–associated protein 4 (CTLA-4) inhibitors are already playing a central role in the treatment of metastatic RCC (mRCC) [1]. But even though targeted therapies improved the prognosis of patients with RCC, only 10% of patients with metastatic disease will survive 5 years [2]. This is mainly the consequence of innate and adaptive tumor resistance to checkpoint blockade [1]. To counter these mechanisms of resistance, researchers are gradually focusing on combination therapies, with positive results from numerous trials combining ICI plus ICI or ICI plus tyrosine kinase inhibitors. These combinations, however, don't come without a cost: they are expensive and expose to secondary side effects (grade 3 or 4 treatment-related adverse events in over 50% of the patients) [3]. Predictive biomarkers for ICI are therefore needed to optimize patient benefit and minimize risk of toxicities.

Tumor markers can have a prognostic and/or a predictive value: prognostic biomarkers discern patients more likely to have a particular outcome, while predictive biomarkers predict a favorable or unfavorable effect from a particular treatment (in our case, immunotherapy). Multiple prognostic markers are capable of predicting prognosis in advanced RCC. But despite intensive research in the field, biomarkers capable of predicting response to immune therapy are lacking (Table 1). PD-L1 and PBRM-1 loss of function, for example, have both shown controversial capability in predicting response to ICI in mRCC despite having a prognostic value [4, 5].

In an issue of your journal published earlier this year, Stenzel et al. [6] tackled this exact problem by characterizing the tumor microenvironment in clear cell RCC and studying its predictive value regarding ICI in this cancer population. They found out that significantly higher densities of intratumoral T-cells (CD3+), CTLs (CD8+), and PD-1-positive immune cells were observed in patients that responded to ICI compared with those with incomplete or no response. In this issue of *Translational oncology*, Kato et al. [7] explored the role of another biomarker that could predict RCC response to ICI: the T cell immunoglobulin and mucin domain-3 (TIM-3). This is an immune checkpoint that is frequently utilized by tumor cells to evade immune surveillance. In the tumor microenvironment of RCC, TIM-3 is a negative regulator of cytotoxic T cells and is detected in the majority of suppressive regulatory T cells (Treg). Despite numerous studies, the prognostic relevance of TIM-3 expression in RCC remains controversial with multiple contradictory results. In this small retrospective study of 25 cases, authors analyzed the tumor immunity of advanced RCC patients treated with anti-PD1 immunotherapy. Apart from being a good prognostic marker (TIM3-positive tumor showed significantly longer overall survival and progression-free survival than TIM3-negative tumors), TIM3 expression on tumor cells was strongly related to response to anti-PD-1 therapy on multi-immunofluorescence analysis. TIM3 overexpression can therefore be a potential predictor of efficacy of anti-PD-1 therapy, warranting more prospective evidence.

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Table 1
Summaries of evidence on the emerging biomarkers in metastatic renal cell carcinoma (mRCC). Prognostic and predictive value are presented as negative, positive, controversial (if data are conflicting) or no association (absence of negative or positive association).

Biomarker	Prognostic value in mRCC	Predictive response to PD1/PD-L1 inhibitors in mRCC	Additional comments
Mismatch repair deficiency (MMR-D) and/or microsatellite instability (MSI-H) [9]	Controversial	Positive	• MMR-D/MSI-H has a negative prognostic value in metastatic colorectal carcinoma. • MMR-D/MSI-H is FDA approved as a predictive biomarker for immunotherapy for metastatic cancers, irrespective of the cancer types.
Programmed Death-Ligand 1 (PD-L1) [4]	Negative	Controversial	• PD-L1(-) patients can still receive immunotherapy . • PD-L1 expression is linked to a worse response to TKI therapy.
Tumor Mutational Burden (TMB) [5]	Controversial	No association	TMB is an unreliable predictor of ICI response in mRCC and should not be used. It is however approved as a biomarker for response to pembrolizumab.
Loss of Polybromo-1 (PBRM-1) [10]	Negative in localized disease Positive in advanced disease	Controversial	To date, PBRM-1 cannot be used clinically. PBRM1 loss of function is linked to a better response to TKI therapy.
Neutrophile to Lymphocyte Ratio (NLR) [5,11]	Negative	Negative	Has the advantage of being easily available. An increase in NLR of 3 or more at 2 months following therapy start predicts for an increasing risk of death and impending treatment failure with a high PPV.

Abbreviations: TKI= Tyrosine Kinase inhibitors.

In the current era of immunotherapy, the implications of both studies are considerable. Clinically, availability of biomarkers that predict responders and non-responders to immunotherapy would minimize unnecessary exposure of patients to potentially immune-related toxicities and reduce the financial burden on health systems [7]. Secondly, these predictive markers could also be incorporated in the experimental setting. CPI-444, for example, is a novel immune checkpoint inhibitor that inhibits the action of the immunosuppressive metabolite adenosine by targeting the CD39-CD73-A2AR pathway [8]. CPI-444 proved encouraging results as a monotherapy with an objective response rate (ORR) of 14% in a phase I trial. The addition of atezolizumab, however, had small or no effect (ORR=13%). A subpopulation analysis using the above biomarkers could therefore potentially identify a selected population that could benefit from this combination therapy, laying the foundation to a more personalized and precise therapeutic research in experimental oncology.

In summary, biomarkers capable of predicting immune treatment efficacy in advanced RCC are urgently needed. Similarly to TIM-3, these prognostic factors could be helpful in both the experimental and clinical setting. Integrating biomarkers to the ongoing trials of combination therapies will give us more evidence about the future of personalized immunotherapy in kidney cancer.

Author contributions

Julien Sarkis: Conceptualization, Investigation, Resources, Data curation, Writing- original draft, Validation, Project Administration, Supervision

Joy Assaf: Writing- original draft, Writing- Review and Editing.

Marwan Alkassis: Methodology, Visualization, Resources

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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