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Host Immune Signatures as Therapy Response Biomarkers in Metastatic Renal Cell Carcinoma

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TECHNICAL ABSTRACT

Background: Recent years have seen a paradigm shift in the treatment of metastatic renal-cell carcinoma (mRCC) from cytokines, to therapies targeting the vascular endothelial growth factor (VEGF-targeted agents, VEGF-TT) and, more recently, to immune checkpoint blockers (ICB). Several clinical trials on ICB have demonstrated improved survival and induced long-term responses in mRCC patients, although only a fraction of mRCC patients respond. Since VEGF-TT has significant immune-modulating effects, potentially synergizing the efficacy of ICB, trials of VEGF-TT/ICB combination therapy in the first line for mRCC were initiated. The development of response biomarkers becomes critical to guide effective therapy selection, limit adverse effects, and maximize clinical benefits.

T and B cell receptors (TCR/BCR) are key players in tumor antigen recognition. Studies have shown that VEGF-TT can promote a more active anti-cancer immune environment by enhancing dendritic cell function and decreasing inhibitory T cell populations. Additional studies showed significant increases in the size and diversity of the TCR-beta repertoire after treatment with a CTLA-4 inhibitor in cancer patients. We have recently reported the association of better ICB response with loss-of-function mutations of PBRM1 in the PBAF SWI/SNF chromatin remodeling complex in mRCC, although additional biomarkers likely exist. To facilitate the immune response biomarker discovery, we developed novel computational approaches including TRUST for extracting tumor infiltrating TCR/BCR repertoire, TIMER for inferring immune cell composition, and TIDE for predicting immunotherapy response from tumor bulk RNA-seq profiles. We propose to use these computational approaches to perform a comprehensive analysis of the dynamics of immune factors in tumor microenvironment and in blood of mRCC patients receiving VEGF-TT, ICB or their combinations.

Objective/Hypothesis: (1) RNA-seq profiles from pre-treatment tumors are informative of tumor immune microenvironment and ICB/ ICB+VEGF-TT response;

(2) the increase of tumor-infiltrating TCR/BCR repertoires in blood during early treatment reflects tumor response to VEGF-TT, ICB and ICB+VEGF-TT. We propose to perform the study using our resource of RCC biobank and clinical data at Dana-Farber.

Aim 1: Identify immune response factors by characterizing the tumor immune microenvironment from pre-treatment mRCC tumor RNA-seq data, using our computational algorithms, TIMER, TRUST, and TIDE.

Aim 2: Evaluate whether observing an expansion of tumor-infiltrating immune repertoire in post treatment blood is associated with patient later response to VEGF-TT, ICB, and ICB+VEGF-TT. Deep TCR/BCR-seq from pre- and on-treatment blood samples of mRCC patients will be performed.

Aim 3: Validate results using other mRCC cohorts with VEGF-TT, ICB, and ICB+VEGF-TT treatment.

Areas of Emphasis: The proposal defines signatures of the host immune system in the course of kidney cancer and development of treatment resistance. The study will address the FY18 KCRP Areas of Emphasis on Biomarker Development, Mechanism of Response and Resistance, Immunotherapy and Targeted Therapies.

Innovation: We have already developed several novel computational approaches to study the diversity of immune repertoires. This proposal focuses on the host immune system responding to therapies, by investigating the dynamics and complexity of immune factors in the peripheral blood and tumor microenvironment. The theme and approach are innovative, leading to novel discoveries. Biomarkers for VEGF-TT and ICB are urgently needed, as well as for emerging combinational strategies.

Impact: This project will lead to an understanding of the extent of changes of host immune factors during the treatment course in kidney cancer, how such changes potentially help to improve therapeutic strategies. In addition to the discovery of predictive biomarkers of responses, the information generated by this study will inform rational drug choices and combinations and reveal the optimal timing and sequencing for mRCC.

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