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Endogenous Retrovirus Expression, Chromatin Abnormalities, and Response to Immune Checkpoint Blockade in Clear Cell Renal Cell Cancer

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TECHNICAL ABSTRACT

Background: Immune checkpoint blockade (ICB) leads to durable objective responses in a subset of patients with CCRCC, and there is a pressing need to develop high value biomarkers of response and resistance. A high mutation burden, from exposure to exogenous carcinogens, or intrinsic defects in DNA repair and replication, predicts response to ICB in some cancer types, presumably through the presence of somatic neo-antigens. Further, expression of certain exogenous viruses in tumors, such as Epstein-Barr virus (EBV) in gastric cancer and NK/T-cell lymphoma and Merkel-cell polyomavirus (MCPyV) in Merkel-cell cancer, is also associated with response to ICB, presumably through viral antigens. However, clear-cell renal cell carcinoma (ccRCC) has clinically significant response rates to ICB, despite low mutation burden and absence of known exogenous viral infection. One interesting aspect of ccRCC is the strong link to mutations in chromatin modifying genes PBRM1, SETD2, KDM5C, and BAP1. A recent study reported an association between PBRM1 loss and response to non-first-line PD-1/PD-L1 blockade in ccRCC. Intriguingly, ccRCC with PBRM1 loss have lower levels of CD8+ T-cell marker interferon gamma and immune checkpoint genes compared to ccRCC with intact PBRM1 in multiple cohorts, so the mechanism underlying the above association is currently a subject of uncertainty. We propose an alternative mechanism of immune activation that may be relevant in low mutation burden cancers such as ccRCC: re-expression of repetitive RNA elements including endogenous retroviruses (ERV).

KCRP Area of Interest: in basic/translational science, chromatin and gene regulation and microenvironment and immunology; in treatments/survivorship, immunotherapy.

Hypothesis: Our hypothesis is that abnormalities in chromatin regulation leading to inappropriate expression of normally silenced endogenous retroviruses may lead to local immune activation and be a predictor of response to immune checkpoint therapy in ccRCC. If successful, this project will lead to new insight into a novel mechanism of immunogenicity and lead to development of a tractable biomarker of response to immune checkpoint therapy that may be independent of mutation burden.

Specific Aims:

*Determine relationship between histone methylation, mutations in chromatin remodeling genes and expression of ERVs in renal cell cancer

*Determine relationship between ERV expression and the immune microenvironment in ccRCC

*Investigate relationship between expression of specific ERVs and response to immune checkpoint blockade in ccRCC

Study Design: We propose to investigate the relationship between ERV expression with underlying chromatin abnormalities, and associated immune activation through use of cell line models of renal cell cancer, and analysis of human renal cell cancer specimens. Cutting-edge analysis of the genomic and epigenetic landscape of ccRCC will be employed to determine epigenetic and genetic determinants of ERV expression in ERV. Cell line models will be employed to determine if perturbation of DNA methylation and/or histone methylation and acetylation can impact ERV expression and immunogenicity. Further analysis of clinical specimens of ccRCC in patients treated with immune checkpoint therapy will be used to validate ERV expression as a marker of response and to explore potential mechanisms of acquired resistance.

Innovation: This proposal is testing the highly innovative hypothesis that expression of ERVs due to underlying chromatin abnormalities will drive immunogenicity in low-mutation burden ccRCC and may function as a biomarker of response to immune checkpoint therapy.

Impact: This proposal may lead to development of a novel biomarker of response to immune checkpoint therapy that is independent of mutation burden and may have broad application in many cancers. Moreover, this project may also lead to the development of rational combinational epigenetic strategies to improve response rates to immune checkpoint therapy in ccRCC and ultimately improve survival in this disease.

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