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Targeting IGF1R Signaling in MTAP-Deficient Kidney Cancer

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TECHNICAL ABSTRACT

Background: Patients with metastatic kidney cancer (or renal cell carcinoma, RCC) have a strikingly poor prognosis as well as a near-universal ultimate resistance to all current therapies. Although immune checkpoint inhibitors have shown considerable potential in the treatment of RCC, many issues remain to be resolved, especially identification of patients who are unlikely to show early benefit from this therapy. RCC has emerged as a metabolic disease characterized by dysregulated expression of metabolic enzymes and altered levels of metabolites as a signature of metabolic reprogramming. To improve survival of patients with RCC, there is an urgent need to reveal the mechanisms by which metabolic enzymes and aberrant pathways regulate oncogenic signaling and to discover potential biomarker metabolites useful for predicting response to therapy. Through an integrated two-step analysis of RCC metabolic pathways, we have identified dysregulated expression of methylthioadenosine phosphorylase (MTAP) in aggressive RCC. MTAP plays a critical role in polyamine metabolism where it cleaves methylthioadenosine (MTA) to generate precursor substrates for the methionine and adenine salvage pathways. Accumulation of cellular MTA has been observed in MTAP-deleted cancer cells. Interestingly, MTA is not only a metabolite associated with the polyamine pathway but also serves as an inhibitor of protein arginine methyltransferase. Recent studies have demonstrated a cross-talk between protein post-translational modifications, such as methylation, and phosphorylation, which serves as an important regulatory mechanism in receptor tyrosine kinase (RTK) signaling. Our preliminary data demonstrated that knockout of MTAP expression in RCC cell lines increases cell invasion and migration. In addition, a decrease of protein-methylation level concomitant with an increase in tyrosine phosphorylation was observed in MTAP-knockout cells. Surprisingly, we noticed an elevation of the immune checkpoint protein PD-L1 after MTAP knockout. Using a phospho-kinase antibody array screen, we identified the type 1 insulin-like growth factor-1 receptor (IGF1R) as the top one RTK regulated by MTAP expression.

Areas of Emphasis: The scientific premise for this application is evidence-based and target-driven mechanistic research. The proposed study addresses the following research topics under kidney cancer including (1) targeted therapies; (2) immunotherapies; and (3) metabolism.

Hypothesis/Objective: Based on the above observations, we hypothesize that MTAP loss and/or downregulation promotes PD-L1 expression and subsequent RCC progression through IGF1R signaling. Direct inhibition of IGF1R may reduce the aggressive nature of MTAP-deficient RCC and downregulate their PD-L1 expression. The overall objective of this application is to determine whether MTAP deficiency serves as a novel RCC therapeutic target, and our study will provide mechanistic rationales for the combination of IGF1R inhibitors with immunotherapy in advanced RCC patients.

Specific Aims: To test our hypothesis, two specific aims are proposed.

Aim 1: To elucidate the molecular basis of MTAP in the regulation of IGF1R signaling and PD-L1 expression.

Aim 2: To determine the bifunctional roles of MTAP in reducing both RCC malignancy and immunosuppression.

Study Design: MTAP-knockout and -overexpression RCC cell lines will be used to identify the arginine methylation sites of IGF1R where arginine methylation affects autophosphorylation on tyrosine residues. The major protein arginine methyltransferase (PRMT) responsible for IGF1R methylation will also be determined. In addition, the effect of MTAP-mediated IGF1R methylation on signaling networks will be confirmed. We will assess the MTAP-mediated signaling networks with IGR1R as a central hub using antibody arrays. Next, whether PD-L1 is posttranscriptionally regulated by IGF1R signaling pathways will be confirmed in the context of MTAP loss (Aim 1). To determine the functionality of MTAP, MTAP-manipulated cells will be subjected to in vitro and in vivo bio-functional assays. Furthermore, we will confirm the effect of IGF1R inhibition on cell proliferation, invasion, migration in both MTAP wild-type and knockout cells using a selective inhibitor of IGF-1R, linsitinib. Lastly, we will evaluate the therapeutic efficacy of the combination of linsitinib and anti-PD-L1 or PD-1 using several immunocompetent mouse models (Aim 2).

Innovation: We will define the novel functions of MTAP and MTA in mediating protein methylation-phosphorylation crosstalk, signal transduction pathways, and posttranscriptional regulation of immune checkpoint proteins. We will also identify the mechanisms by which arginine methylation regulates cell signaling via interplay with tyrosine-phosphorylation. In addition, our study will link metabolism and signal pathways to the regulation of PD-L1 expression and immunosuppression.

Impact: These studies will contribute to a better understanding of how metabolic enzymes participate in the regulation of post-translational modifications and cancer progression as well as immunosuppression, allowing for the development of novel targeted therapies and potential therapeutic strategies to enhance cancer immune therapy efficacy for RCC.

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