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Studying BAP1 in Regulating Glucose Dependency in Renal Cancer: Mechanisms and Preclinical Translation

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Institution Receiving Award: M.D. ANDERSON CANCER CENTER, UNIVERSITY OF TEXAS
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TECHNICAL ABSTRACT

Background: Specific genetic alterations in cancer cells may reprogram their metabolism networks and render such cancer cells highly dependent on particular nutrients for survival. Mechanistic understanding of nutrient dependency in cancer cells has important therapeutic implications for cancer treatment. BAP1 is a nuclear deubiquitinating (DUB) enzyme that reduces histone 2A ubiquitination (H2Aub) on chromatin and regulates gene transcription. BAP1 is often mutated and deleted in clear cell RCC (ccRCC), and patients with BAP1-mutant ccRCC have particularly poor clinical outcomes. At present no effective therapy has been identified for RCC with BAP1 mutation or deficiency. SLC7A11 is an amino acid transporter that imports cystine and exports glutamate. Our preliminary data showed that (i) SLC7A11 is an important BAP1 target in human RCC; (ii) BAP1 represses SLC7A11 expression by decreasing H2Aub occupancy on the SLC7A11 promoter, and (iii) SLC7A11 overexpression or BAP1 deficiency promotes glucose dependency, likely through SLC7A11-mediated glutamate export, and sensitizes renal cancer cells to glucose transporter (GLUT) inhibition. We propose that targeting glucose dependency in BAP1-deficient renal tumors may be an effective approach to treat RCC patients with BAP1 mutation or deficiency.

Areas of Emphasis: Our proposed study will address the following FY18 KCRP Areas of Emphasis: (i) targeted therapies, (ii) metabolism, (iii) chromatin and gene regulation, and (iv) biomarker development.

Objectives/Hypothesis: The objective of this application is to determine the roles and mechanisms of BAP1 in regulating glucose dependency in renal cancer cells and to therapeutically target glucose dependency in BAP1-mutant RCC. The central hypotheses of our proposal are that (i) BAP1-deficient/-mutant renal cancer cells exhibit aberrant expression of SLC7A11 and are highly dependent on glucose for survival, partly owing to SLC7A11-mediated glutamate export, and (ii) BAP1-mutant renal tumors are sensitive to GLUT inhibition.

Specific Aims and Study Design:

Specific Aim 1: To determine the role and mechanisms of BAP1 in regulating glucose dependency in renal cancer cells. In this aim, we will correlate (i) glucose dependency (sensitivity to glucose starvation-induced cell death), (ii) sensitivity to the GLUT inhibitors KL-11743 and BAY-876, and (iii) SLC7A11 expression with BAP1 status in a panel of BAP1-proficient and -deficient renal cancer cell lines. We will then conduct genetic and metabolic studies, including (i) BAP1 CRISPR KO or SLC7A11 restoration in BAP1- proficient cells, (ii) BAP1 restoration or SLC7A11 knockdown in BAP1-deficient cells, and (iii) manipulation of glutamate-alpha-ketoglutarate metabolism pathway, and determine whether BAP1 deficiency enhances glucose dependency and sensitizes renal cancer cells to GLUT inhibition through SLC7A11-mediated glutamate export.

Specific Aim 2: To determine if GLUT inhibition is an effective treatment for BAP1-deficient/-mutant renal tumors. In this aim, we will collaborate with Dr. Eric Jonasch, a renal cancer clinician-scientist at MD Anderson Cancer Center, and test the hypothesis that BAP1-deficient/-mutant renal tumors with aberrant SLC7A11 expression are sensitive to GLUT inhibitors in preclinical mouse models, including (i) xenograft models from established renal cancer cells with BAP1 deletion or restoration and (ii) patient-derived xenograft (PDX) models derived from patients with BAP1-wild-type or -mutant renal cancer.

Innovation: This application proposes the novel concept that, owing to the unique function of SLC7A11 in importing cystine and exporting glutamate, cancer cells with high expression of SLC7A11, such as BAP1-mutant renal cancer cells, are more resistant to ferroptotic cell death, leading to increased tumor development. However, these cancer cells are also more dependent on glucose for survival, a metabolic vulnerability that can be therapeutically targeted. The application may also identify BAP1 mutation as a novel predictive biomarker for RCCs with high SLC7A11 expression and uncover an innovative therapeutic approach in which drugs that block glucose metabolism (e.g., GLUT inhibitors) can be used to treat patients with BAP1-mutant RCC. Finally, our studies will use innovative approaches, such as the catalytically dead Cas9 approach, to target BAP1 to specific gene loci, and generate several unique reagents/resources, including renal cancer PDX models.

Impact: (i) Fundamental impact: Our proposed study will provide important mechanistic insight into nutrient dependency in renal cancer. (ii) Clinical impact: Our studies may identify GLUT inhibitors as effective therapies to treat renal cancer patients with BAP1 mutation or deficiency.

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