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TBK1 Serves as a Novel Therapeutic Target in Kidney Cancers with VHL Loss

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TECHNICAL ABSTRACT

Estimated new cases and deaths from renal (renal cell and renal pelvis) cancer in the U.S. in 2014 were 63,920 and 13,860, respectively. Kidney cancer incidence has been increasing steadily for the past several decades, although the reasons for this are unclear. Renal cancer is resistant to a variety of cancer therapies and is highly lethal. Therapies such as sunitinib and sorafenib provide only short-term benefits and are not curative. The VHL gene is the most important tumor suppressor in kidney cancer. HIF2 alpha stabilization, as a result of VHL loss, is sufficient and necessary for promoting kidney tumor growth. However, targeting HIF2 alpha alone yields variable response in kidney cancer. In addition, a significant portion of kidney cancer remains resistant to HIF2 alpha inhibitor treatment, highlighting the importance of identifying additional therapeutic vulnerabilities in VHL-deficient kidney cancer.

In this proposal, we identified TBK1 as a potential therapeutic target for VHL-deficient kidney cancer. TBK1 depletion or inhibition selectively diminished VHL-null kidney cancer cell proliferation, but did not affect cells restored with VHL expression.

We propose to address the following areas of emphasis in the DoD KCRP: (1) Develop targeted therapies in kidney cancer by using several complementary approaches targeting TBK including genetic knockout by CRISPR-Cas9 and a highly specific TBK1 inhibitor and (2) Examine the mechanism of therapeutic response in kidney cancer. We hypothesize that TBK1 can serve as a novel therapeutic target in kidney cancers that are frequently associated with VHL loss. Our objective in this proposal is to validate the role of TBK1 in kidney cancer with VHL loss, elucidate the molecular mechanism by which TBK1 is activated by VHL loss and explore the therapeutic potential of targeting TBK1 in kidney cancer. In specific aim 1, we will explore the mechanism by which VHL loss induces hyper-activation of TBK1 in kidney cancer. We will identify potential TBK1 prolyl hydroxylation site and determine whether TBK1 hydroxylation affects its activity. In addition, we will determine how VHL binding contributes to decreased TBK1 phosphorylation. In specific aim 2, we will elucidate the molecular mechanism by which TBK1 hyper-activation contributes to kidney tumorigenesis. We will identify novel TBK1 substrates and determine the role of TBK1 substrates in kidney cancer. In specific aim 3, we will explore the therapeutic potential of targeting TBK1 in orthotopic xenografts and patient derived xenografts (PDXs). We will examine the effect of TBK1 in kidney tumorigenesis in vivo by using CRISPR-KO. We will also examine the effect of a highly specific TBK1 inhibitor in kidney tumorigenesis by using orthotopic xenografts and PDXs. Successful completion of this proposal will help validate and explore the TBK1 targeting in kidney cancer.

TBK1 has largely been studied in innate immunity but its role in cancer remains enigmatic. This proposal identifies TBK1 as a novel synthetic lethality partner for kidney cancer with VHL loss. In addition, we propose a novel mechanism by which VHL loss may regulate TBK1 phosphorylation/activation in cancer. We argue that targeting TBK1 by using a newly developed specific inhibitor is therapeutically beneficial for kidney cancer. We are also using cutting-edge approaches, such as CRISPR-Cas9 knockin and knockout, mass spectrometry, and PDXes in this proposal.

Targeting VHL-deficient kidney cancer is still a daunting challenge and kidney cancer is largely resistant to classically cytotoxic chemotherapy. Identification and characterization of unique pathways that are lethal to VHL-deficient kidney cancer is critical for improving kidney cancer treatment. The proposed work can also have potentially significant impact on military beneficiaries because (1) cigarette smoking, which accounts for 30% of active-duty personnel, is a significant risk factor for renal cell carcinoma, and (2) occupational exposure to heavy metals, paints, organic solvents, and other combat-related chemicals significantly increases the risk of renal cell carcinoma. Therefore, the proposed research will directly address the immediate need for understanding and treating kidney cancer and prompt Service members' early return to active duties.

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