Letter to the Editor

Von Hippel-Lindau: implications in development and disease—response

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Provenance: This is an invited article commissioned by the Section Editor Dr. Xiao Li (Department of Urology, Jiangsu Cancer Hospital, Jiangsu Institute of Cancer Research, Nanjing Medical University Affiliated Cancer Hospital, Nanjing, China).

Response to: Park S, Kang SM, Park BJ. The novel and critical role of von Hippel-Lindau in nephron formation. Ann Transl Med 2019. doi: 10.21037/atm.2019.09.159.

Submitted Oct 30, 2019. Accepted for publication Nov 07, 2019.

doi: 10.21037/atm.2019.11.46

View this article at: http://dx.doi.org/10.21037/atm.2019.11.46

The authors would like to thank Park *et al*. for their insightful editorial commentary on our recently published article titled "*Von Hippel-Lindau Acts as a Metabolic Switch Controlling Nephron Progenitor Differentiation*" (1). The commentary provides an excellent overview of the VHL/HIF axis and its role in cellular oxygen sensing. The editorial authors correctly imply that our study revealed a novel role for VHL in kidney development such that nephron progenitors are required to undergo a metabolic switching event. This reprogramming from glycolysis to mitochondrial respiration was also found to be critical for adequate nephron formation (1).

Interestingly, the editorial relates our findings to the phenomenon known as the Warburg effect, a hallmark of cancer cell metabolism. The Warburg effect contributes to increased glucose uptake and enhanced lactate secretion seen in many types of cancer (2,3). This hallmark phenotype allows cells to generate energy quickly and undergo rapid proliferation (2,4). Additionally, increased lactate results in an acidic tumor microenvironment leading to reduced immune function, drug resistance, and poor prognosis. Therefore, understanding the metabolic demand of cancer and the role of the VHL/HIF axis is critical, particularly in VHL-associated renal cell carcinoma (RCC).

We agree with the editorial authors that investigation into VHL loss and the Warburg effect would greatly benefit the field and holds the potential to offer key insights into RCC treatment. In fact, studies such as Chan *et al*. (targeting GLUT1 in RCC) (5), Li *et al*. (targeting immunometabolism) (6), and Xie *et al*. (targeting LDHA) (7) have investigated metabolic control in RCC with varying success. However, many studies in VHL-deficient cancer metabolism focus on HIF induction and up regulation of glycolysis and fail to consider the role that VHL itself or HIF-alternative targets may play in the process as well. It is known that VHL interacts with more than 500 molecules, however only approximately 10–30% of those interactions have been significantly detailed (8). Therefore, it is probable that VHL loss, regardless of downstream mechanism, does play a prominent role in the metabolic reprogramming associated with RCC beyond the role of HIF stabilization.

Although HIF-alternative VHL targets have been identified, several therapeutic strategies have focused on HIF inhibition with varying success. Our original investigation focused more robustly on HIF-1α as it is highly and ubiquitously expressed developmentally. However, HIF-2α has been shown to have a more central role in promoting RCC over HIF-1α, therefore therapies most often target the HIF-2α subunit. Drugs such as the small molecule inhibitors PT2385 and PT2977—disruptors of HIFα/β dimerization—have recently undergone early phase clinical trial as single agents and in conjunction with immunotherapy for the treatment of VHL-associated RCC and VHL Disease. Both trials appear promising and are currently active under the clinical trial (ClinicalTrials.gov) identifiers NCT02293980 and NCT03401788, respectively.

Other mechanistic avenues of investigation have interrogated mutations in addition to VHL loss. As

previously discussed in our original manuscript, Wang *et al*. investigated the roles of *BAP1* and *VHL* in renal development and RCC progression using a *Six2Cre* conditional deletion (9). Moreover, they revealed that BAP1 and VHL synergistically cooperate to drive renal tumorigenesis (9). Although this group did not draw the same developmental conclusions from their study using the *Six2CreVHL*$^{-/-}$, we attribute the variability in the timing of reduced renal function and mortality to mouse background strain differences. This suggests that *VHL* loss alone may not be enough to result in disease, but may require the accruement of multiple mutations to become cancer-causing. Further, this theory may, in part, explain why individuals with VHL Disease and *VHL*-deficient RCC are often diagnosed later in life. Unfortunately, this study did not interrogate the metabolic implications of *VHL* loss in RCC, however due to our revelations using nephron progenitor-specific VHL deficient (*VHL*$^{NP-/-}$) mice, we would anticipate profound metabolic discrepancies linked to the Warburg effect.

Mouse models have also been generated with VHL deletion in the renal proximal tubules as well as in podocytes (10). These models appear to have relatively normal development with mild disease occasionally presenting later in life. None of the models described exhibited an RCC phenotype. Likewise, our renal vesicle-specific VHL knockout model (*VHL*$^{RV-/-}$) also did not exhibit an abnormal pre- or postnatal phenotype. This serves as further evidence for a multiple mutation hypothesis, however other renal-specific VHL Cre-driven conditional and inducible knockout models should be explored and phenotype should be established.

Of note, we did preliminary experimentation to determine whether metabolic alterations existed at postnatal day 21 (P21) in *VHL*$^{NP-/-}$ kidneys via immunofluorescent staining for GLUT1 and PCK1 (1). *VHL*$^{NP-/-}$ kidneys did not exhibit any abnormal patterns of expression for these proteins at this time (1). We believe this is because the proximal tubules that were capable of forming underwent early differentiation when oxygen availability was negligible. A more in-depth examination into the metabolism associated with *VHL*$^{NP-/-}$ kidneys would have proved challenging due to the mortality of the mouse model. To circumvent this, a VHL knockout inducible Cre line could have been used, but due to the developmental nature of our original manuscript, this was outside the scope of our investigation. However, the mortality of the *VHL*$^{NP-/-}$ mice does pose the question as to whether these mice would have had increased susceptibility to RCC later in life.

Future investigations into the significance of VHL and metabolic demand in kidney development and disease would greatly benefit the field and offer significant translational implications for the treatment of RCC. Preclinical studies should be aimed at generating conditional VHL-deficient mouse models in adult mice to mimic the clinical presentation and diagnosis of RCC later in life.

Acknowledgments

The authors would like to thank Dr. Xiao Li and Angelia Zhou for the opportunity to provide a discussion on the implications of our previous work.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Cargill KR, Sims-Lucas S. Von Hippel-Lindau: implications in development and disease—response. Ann Transl Med 2020;8(4):142. doi: 10.21037/atm.2019.11.46

