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ABSTRACT

Primary Cilium: a Tumor Suppressor Organelle

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Renal cystic disorders are commonly associated with mutations in genes such as VHL, TSC2 and PKD1 that are commonly referred to as 'cystoproteins'. Loss of function of these cystoproteins promotes the development of renal cysts and often, renal cell carcinoma (RCC), as observedin the setting of VHL disease. Importantly, these cystoproteins localize to the primary cilium, an organelle, that in epithelial cells functions as an environmental sensor and participatesin spatial regulation of several signaling pathways, and cell polarity. Loss of primary ciliaresulting from cystoprotein deficiency is directly linked to cytsogenesis, although it is clear that additional events are required for the progression of the 'pre-cystic' lesions to cysts and renal cellcarcinoma. We are investigating how formation of cilia is regulated by VHL, and the oncogenic consequences of loss of this key signaling organelle in kidney epithelial cells. For example, the primary cilium is required for the maintenance of planar cell polarity (PCP), which refers to the polarization of cells perpendicular to their apical/basal axis. During development, loss of PCP leads to widening rather than elongation of renal tubules, resulting in the development of renal cysts. Given that the kidneys are exposed to a wide variety of renal insults and are constantly undergoing repair and regeneration, one of the key hypotheses we are testing is that preneoplastic cysts arise in the setting of VHL deficiency, and that these cysts arise as a reactive response to injury.