Cross-Talk Between *VHL* Mutant Kidney Cells and the Tumor Microenvironment: The Role of IL-6 and Oncostatin M Signaling

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The development of renal cell carcinoma (RCC) has been linked to tissue inflammation. Using the *Hoxb7* promoter-specific knockout of mouse *VHL* allele (*Vhlh*) in limited compartments of kidney tubules, including collecting ducts, Henle's loops, and parts of distal and proximal tubules, we indeed observed severe inflammation and fibrosis associated with expected angiogenesis, hyperplastic and clear-cell phenotypes. Similar inflammation and fibrosis can also be observed in the adjacent normal tissue of ccRCC. However, how *VHL* mutant epithelial cells interact with and organize the inflammatory microenvironment is still unclear. Our laboratory has undertaken a systematic analysis of the stromal components in the microenvironment of *VHL* mutant cells. We have observed a dramatic increase in the number of infiltrated macrophages in the *Vhlh* KO kidney tissue and a distinct inflammatory signature (high phospho-JNK expression) in the vasculature of the KO kidney. Several analytical strategies were taken to unravel the mechanism and functional significance of the changes within the *VHL* mutant-containing microenvironment, including analyses of the cytokine repertoire secreted by the *VHL* mutant cells, the transcriptome profiling of the endothelial cells in the *Vhlh* mutant kidney, and the macrophage landscape of the ccRCC tissue at the single cell level. We found that *VHL* mutant tubule epithelial cells can stimulate macrophage infiltration and polarization, and activate vascular endothelial cells via the IL-6 and Oncostatin M signaling pathways, respectively. These two stromal components in turn influence each other in a feed-forward fashion, and stimulate the tumorigenicity of the *VHL* mutant epithelial cells. Inactivation of these two pathways can ameliorate the inflammatory and hyperplastic phenotypes of the *Vhlh* knockout in vivo. Finally, single cell analysis of the ccRCC patient samples identified tumor-specific immune cell populations that may represent a novel diagnostic and therapeutic markers. Taken together, the inflammatory microenvironment of the *VHL* mutant cells represents a viable alternative target for the treatment and early detection of ccRCC.