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ABSTRACT

Endothelial Fenestrations in Tumor Microvasculature associated with VHL Gene Alteration

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Introduction: VEGF-targeted therapy shows anti-tumor effects for mRCCs. However, neither precise mechanisms nor potent target of this therapy had been largely unknown. Experimental studies using VEGF neutralization in mice model revealed that VEGF-dependent capillaries were characterized by the existence of fenestrations in endothelium on electron microscopy study.Objectives and

Methods: We examined the microcapillaries of human ccRCC specimens for the existence of fenestrations and analyzed possible mechanisms of developing of microvasculature with distinctive phenotype by using the mouse xenograft model.

Results: Abundant endothelial fenestrations were found in the majority of sporadic CC-RCCs with VHL mutation. This finding was also recapitulated in mice xenograft models in that tumor microvasculature from VHL-/- pRC3 cells harbored more abundant endothelial fenestrations compared to those from VHL restored WT8 or even WT8/HIF2a P531A cells. Accordingly, treatment with Bevacizumab resulted in a significant repression of tumor size in pRC3 tumors with the reduction of MVD and the number of endothelial fenestrations but not that of WT8 or WT8/HIF2aP531A cells.

Conclusions: Our results suggest that sporadic RCCs with VHL mutation harbor VEGF-dependent tumor vessels with abundant fenestration on their endothelium. Unexpectedly, HIF independent pathways of pVHL mainly regulate the development of tumor vasculatures with distinctive structure. Importantly, our preliminal results from shRNA mediate JunB knockdown in 786-O cells highly suggestthat JunB, at least in part regulate the ECM remodeling including the endothelial fenestrations. Collectively, aPKC/JunB pathway would be a potent therapeutic target for VHL-/- RCC cells.