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Effect of EphA2 silencing on inhibiting the progression of non-metastatic renal cell carcinoma in an orthotopic mouse model of renal cell carcinoma

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Introduction & Objectives: To determine whether EphA2 inhibition can reduce the progression of renal cell carcinoma (RCC) in an orthotopic murine RCC (RenCa) mouse model.

Materials & Methods: EphA2 knockdown RenCa cells expressing luciferase (Luc) prepared using RNA interference (shRNA) method. We divided a total of 16 BLAB/c mice into two orthotopic RCC group: 1) a group implanted control RenCa-Luc cell (n=8), 2) a group implanted EphA2 knockdown RenCa-Luc cell (n=8). Each RenCa cell line were injected under the right renal capsule for implantation. Tumor progression was assessed by in vivo bioluminescence (BLI) on day 4, 7, 14 and 18. At day 18, the kidneys were harvested, and apoptosis in the tumor was evaluated by TUNEL assay. Tumor growth was also compared with ex vivo BLI and wet weight of orthotopic kidney. Changes in FAK/RhoA signaling caused by EphA2 knockdown were also determined by western blot and reverse transcription polymerase chain reaction.

Results: BLI signal in both groups increased from day 7, but no metastasis was observed for 18 days. At day 18, TUNEL assay showed that apoptosis in the tumor of the EphA2 knockdown group was significantly higher (p=0.021). The tumor wet weight was significantly decreased in the EphA2 knockdown group compared to the control group (1569.9 ± 595.5 mg vs. 636.5 ± 288.9 mg, p = 0.009). Also, EphA2 knockdown significantly reduced membrane-bound RhoA and FAK phosphorylation in orthotopic RCC kidneys (p=0.049, p=0.042, respectively).

Conclusions: EphA2 knockdown had a significant effect in inhibiting tumor growth of the orthotopic RCC mouse model by inducing tumor apoptosis and suppressing the FAK/RhoA signaling. Therefore, the EphA2/FAK/RhoA signaling pathway may play an important role as a potential target for adjuvant treatment to suppress the progression of RCC.