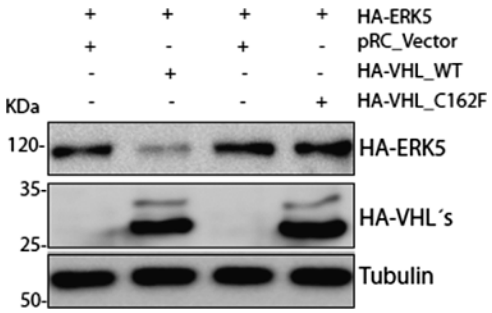

Figure W1. Effects of VHL mutant C162F onto HA-ERK5. Cos7 cells were transfected with HA-ERK5 WT alone or in the presence of prc/CMV HA-pVHL WT or C162F mutant and processed as in Figure 1*B*. TCLs (50 μg) were blotted against the indicated antibodies.

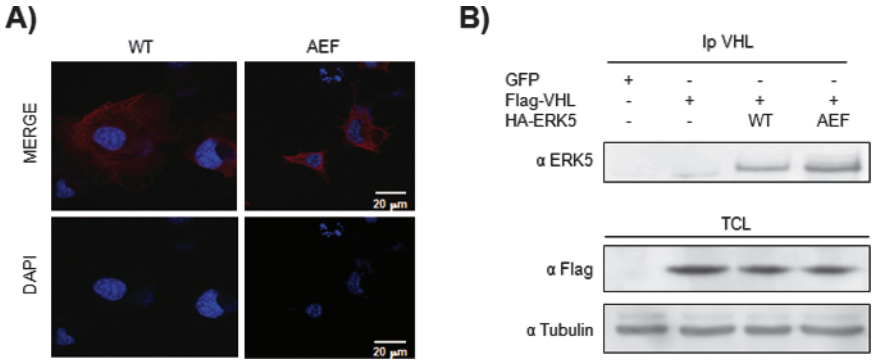

Figure W2. Subcellular distribution and binding to pVHL of HA-ERK5-AEF. (A) Cos7 cells were transfected with HA-ERK5-WT or HA-ERK5-AEF and processed as in Figure 2*D*. (B) 293T cells were transfected (5 μg of HA-ERK5-WT or HA-ERK5-AEF plus 5 μg of Flag-VHL) and processed as in Figure 2*B*. TCLs were blotted against Flag or tubulin.

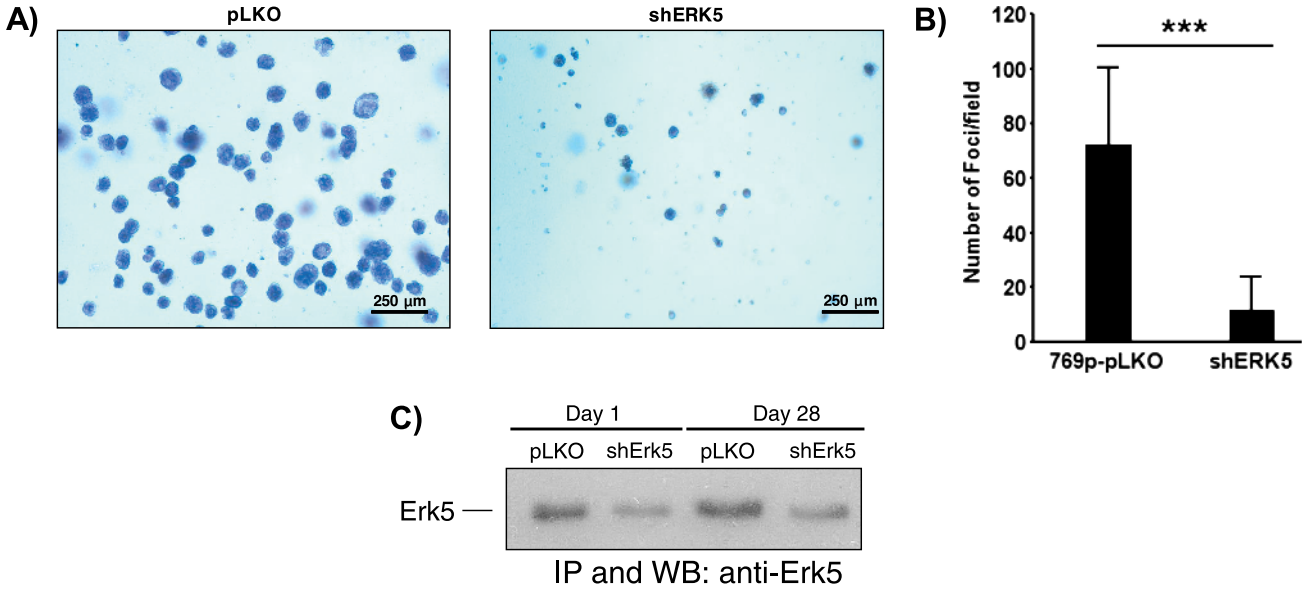

Figure W3. (A) Representative fields of 769-P pLKO and shERK5 cells at 28 days. Soft agar assay was performed according to Guerrero et al. [1]. (B) Histogram representing the mean ± SD of 12 different fields. Statistical comparison of differences from the means was performed by the Student's *t* test; ***$P = .004$. (C) Western blot analysis of ERK5 in parallel cultures of cells at the indicated time points of the soft agar assay.

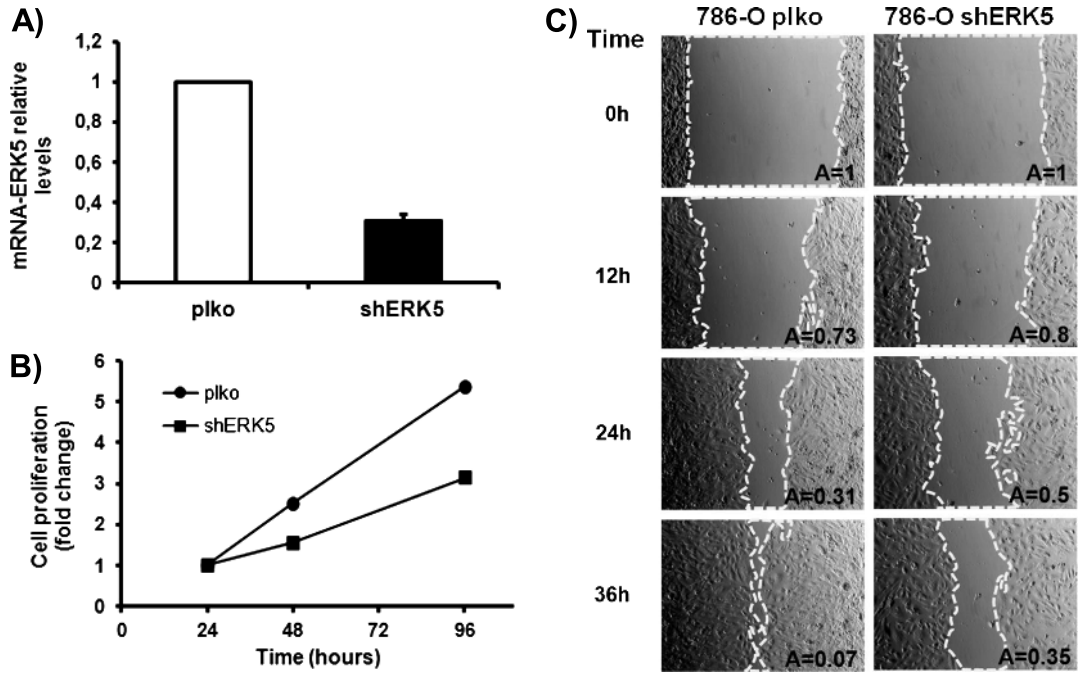

Figure W4. (A) 786-O cells were infected with control vector (pLKO) or carrying shRNA against ERK5 (shERK5). Selected pools were evaluated by qRT-PCR. (B) Proliferation assays in 786-O cells. Values of OD at 570 nm at 24 hours were referred as 1. Image shows a representative experiment performed in triplicate cultures of three. (C) Wound healing assays was performed in 786-O cells. Images show a representative experiment of two independent experiments performed in duplicated cultures.

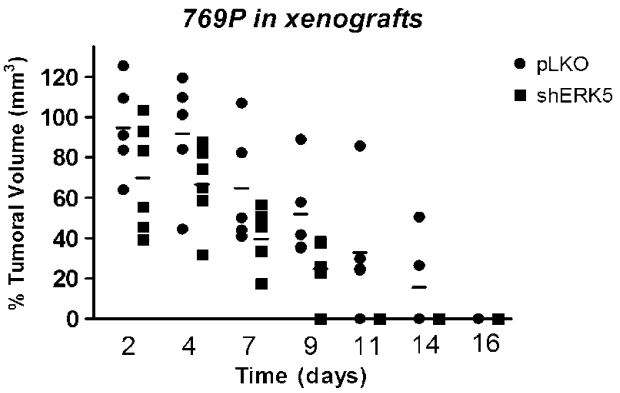

Figure W5. Xenograft model using 769-P cells. pLKO ($n = 5$) or shERK5 769-P ($n = 6$) cells were injected subcutaneously (6×10^6 cells) in nude mice (BALB/c), and volumes were evaluated every 2 days until apparent tumor mass regresses. Mice were kept alive until day 45 with no observable tumors.

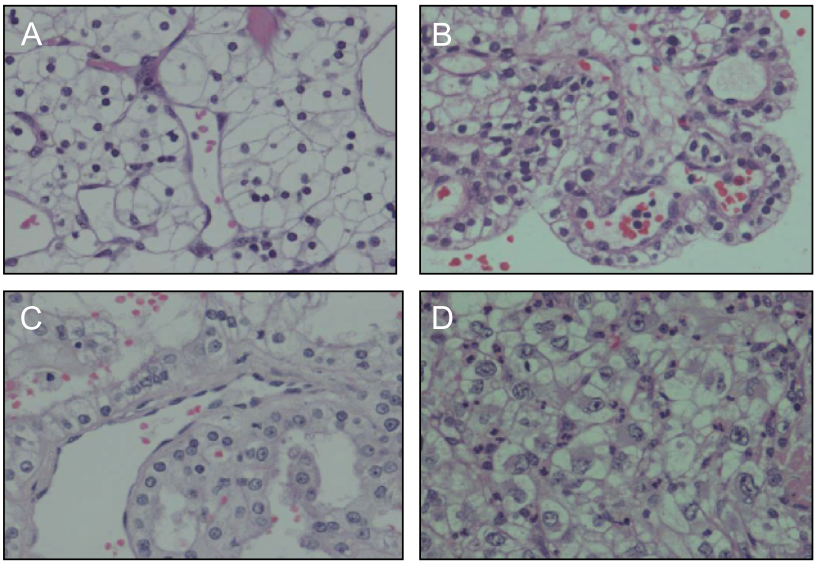

Figure W6. Histologic features of diagnosed cases of CCRCC. Four representative images (40×) of different Fuhrman grades observed. (A) Grade I (case 12/09). (B) Grade II (case 08/09). (C) Grade III (case 02/09). (D) Grade IV (case 06/09).

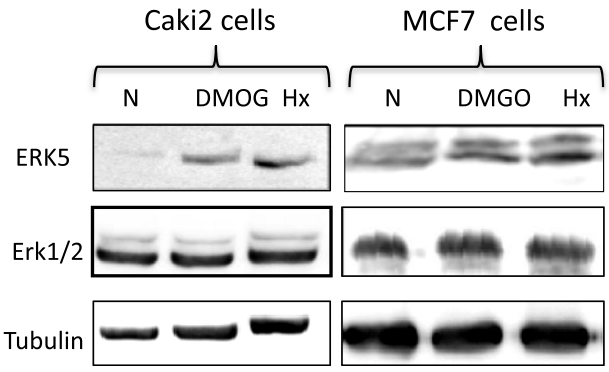

Figure W7. Effect of hypoxia onto ERK5 in Caki-2 and MCF7 cells. For hypoxia treatments, cells were grown at 37°C in sealed chambers and flushed with 1% O_2, 5% CO_2, 94% N_2 gas mixture for 9 hours. As a positive control, cells were treated with DMOG (1.5 mM) for 9 hours.