Underexpression of Tumor Suppressor LKB1 in Clear Cell Renal Cell Carcinoma is Common and Confers Growth Advantage in vitro and in vivo

Introduction and Objective: Accumulating evidence suggests that deregulation of energy-sensing pathways, a common feature of several hamartoma syndromes, closely associates with renal cell carcinoma (RCC) development. The metabolic regulation that coordinates the energy demands of a cancer cell with its energy-consuming malignant phenotype is largely controlled by AMPK via regulation of mTOR. Here we demonstrate that, reminiscent of Peutz-Jeghers hamartoma syndrome, most sporadic cases of clear cell RCC (ccRCC) underexpress liver kinase B1 (LKB1), the master regulator of AMPK.
Results: At the transcript level, 10 out of 10 ccRCC patients had reduced expression of LKB1 in their tumor tissue as compared to the normal surrounding renal parenchyma. At the protein level, image analysis of a tissue microarray of 201 ccRCC and 26 normal renal tissues stained for LKB1 revealed a significant reduction in LKB1 expression in the tumor tissues. *In vitro*, lentiviral particle-mediated knockdown of LKB1 in human RCC cells (shLKB1) resulted in reduced AMPK signaling, increased cellular proliferation, invasion, migration and VEGF secretion compared to cells stably expressing control vector (shControl). *In vivo*, the take rate and growth of shLKB1 RCC xenografts in nude mice was significantly higher than shControl xenografts.
Conclusions: Collectively, these results indicate for the first time that LKB1 acts as a tumor suppressor in ccRCC and that loss of LKB1 expression is a common event in the disease.