BP OP 3-6

BMPR2 promotes pancreatic cancer proliferation via the GRB2-mediated PI3K-Akt-mTOR pathway

Huahu GUO, Yazhou WANG, Zhengkui ZHANG, Mingzhe LI, Qi WANG, Kai ZHANG, Xiaodong TIAN, Yinmo YANG*

General surgery, Peking university first hospital, China

Introduction : Tumor microenvironment favors aberrant expression of tumor cells characterized by dysregulated release of cytokines, chemokines, and growth factors that the tumor exploits for survival and invasion. The crosstalk of bone morphogenetic proteins and its receptors between tumor and its surrounding stromal cells have been reported in breast cancer, but effects of the interaction in pancreatic cancer remain unclear.

Methods : The enrichment of BMP pathway gene set was anlaysis by GSEA software in three database of GEO. BMPR2 were reduced in PDAC cells via specific shRNA-mediated knockdown. Quantitative proteomic analysis was performed to explore the mechanism of BMPR2 regulation. The cell growth rate was assessed by CCK-8, FACS and colony formation assays. ChIP-sequence was performed to identify and characterize smad complexes target genes.

Results : Here we demonstrate that BMP pathway was hyperactived in pancreatic cancer.BMPR2 was overexpressed in human pancreatic cancer specimens and associated with the prognosis of pancreatic cancer patient. Down-regulated BMPR2 markedly inhibits the growth of pancreatic cancer cell lines Mia-PaCa-2 and PANC-1 in vitro and vivo. Mechanistically, disrupt the expression of BMPR2 suppresses the expression of GRB2 in a smad-independent manner, and then inactivates GRB2-associated signaling pathways, PI3K-Akt-mTOR pathway. In addition, LDN193189, a BMP pathway inhibitor, can also impair the expression of BMPR2 and inhibit the functions of pancreatic cancer cells by GRB2-mediated PI3K-Akt-mTOR pathway.

Conclusions : Thus, our results suggest that BMPR2 is an important mediator of pancreatic cancer cells and its surrounding microenvironment and offer insight into therapeutic applications for better survival of patients with this deadly disease.

Corresponding Author. : **Yinmo YANG** (yangyinmosci@163.com)