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Smad4 inhibits cell migration via suppression of KPNA4 and MMP26 in human pancreatic cancer cells

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Introduction : Smad4 was known as a tumour-suppressor gene that frequently mutates in pancreatic cancer. Previous studies indicated that Smad4 is the central component of the bone morphogenetic protein (BMP) signaling pathway, forming a complex with p-smad1/5/9 and regulating the target genes in the nucleus. It is attractive to explore the potential genes regulated by the complex and uncover the molecular mechanism of Smad4 in pancreatic cancer cells.

Methods : The enrichment of BMP signaling pathways in three GEO databases was analyzed by GSEA software. Immunohistochemistry was used to detect the expression of Smad4 in pancreatic cancer and adjacent tissues. ChIP-sequence analysis explored the target genes regulated by Smad4/p-smad1/5/9 complex. The cell migration and invasion ability were assessed by Transwell assays. The nude mouse lung metastasis model was used to detect the invasive ability of pancreatic cancer cell lines in vivo.

Results : The BMP signaling pathway is hyperactivated in pancreatic cancer, and its key molecule Smad4 is highly expressed in 80 pancreatic tissue specimen and is related with prognosis. Ectopic expressed Smad4 in Smad4-deficient BxPC-3 significantly inhibited cell migration and invasion. Downregulated Smad4 in Mia-PaCa-2 dramatically promoted cell migration and invasion, and we demonstrated that p-Smad1/5/9-Smad4 complex can regulate the expression of KPNA4 and MMP26, and hence regulate the migration and invasion ability of pancreatic cancer cells.

Conclusions : The present findings indicate that Smad4 may suppress the expresion of KPNA4 and MMP26 mediated by p-smad1/5/9 and inhibit the tumor characteristics of pancreatic cancer cells.

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