BP OP 4-7

Pancreatic stellate cells promote epithelial-mesenchymal transition of cancer cells by Notch-3 promoter demethylation

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Introduction : Pancreatic stellate cell(PSC) promoted epithelial-mesenchymal transition(EMT). However, the potential mechanism had not been fully elucidated. The aim of this study was to explore the effect of Notch-3 on EMT of PANC-1 cells induced by PSC.

Methods : We explore the effect of PSC on PANC-1 cell EMT . The potential signal pathway involved in EMT is determined by adding different inhibitors. The role of Notch-3 in EMT process is verified through Notch-3 siRNA transfection. Bisulphite sequencing PCR and chromatin immunoprecipitation are performed to explore the methylation status of Notch-3 promoter. To confirm the relationship between EMT, Notch-3 status and patient survival, Kaplan-Meier analysis is performed.

Results : After co-culture with PSC, the ability of migration is significantly enhanced, and the PSC can also induce EMT phenomenon of PANC-1. Meanwhile, the Notch-3 expression is also promoted. The effect blocked by Notch signal pathway inhibitor(L1790) and Notch-3 siRNA revealed the critical role of Notch-3 in EMT process. The methylation status of three CpG islands located in promoter region of Notch-3 has been uninfluenced after co-culture with PSC. However, immunoprecipitation reveals a significant increase in hmC for Notch-3 promoter. Our study also demonstrate that Notch-3 level is positively correlated with Vimentin and negatively with E-cadherin expression in pancreatic cancer patients. Overexpression of Notch-3 also predicts the poor prognosis of pancreatic cancer.

Conclusions : PSC induces Notch-3 expression by demethylation and promote EMT phenotype of PANC-1 cell. EMT and Notch-3 are the poor prognostic factors in pancreatic cancer patients. Notch-3 might be a potential target for treatment of pancreatic cancer.

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