

CELL SIGNALING AND CANCER THERAPY & CELL METABOLISM AND CYTOPATHOLOGY

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PAI-1 activates pancreatic stellate cells to increase the stiffness of tumor and determines early relapse of pancreatic cancer

Pancreatic stellate cells (PSCs) can be activated to induce intra-tumor fibrosis and influence patient survival; however, the molecular basis for the regulation of PSC activation remain unclear. The organotypic coculture system was used to study the interaction between pancreatic cancer cells and PSCs. Cytokine arrays, qPCR, and Western blotting were performed to identify the potential factors in PSC activation and elucidate the underlying pathway. From clinical pathology, we found that activated PSCs was correlated with increased stiffness of pancreatic tumors, shorter disease-free survival and overall survival of after resection. Organotypic coculture with cancer cells activated PSCs, which in turn increased the invasiveness of PANC-1 and MiaCapa-2 cells and the stiffness of coculture gels. Cytokine array revealed elevated plasminogen activator inhibitor 1 (PAI-1) secretion after co-culture. Treatment with PAI-1 activated PSCs to secrete fibronectin and collagen type 1 and consequently increased gel stiffness. Knockdown of PAI-1 in tumor cells or knockdown of PAI-1 receptor LRP-1 prevented PSC activation after coculture. KRAS mutation in pancreatic cancer cells was associated with increased PAI-1 expression. Pharmacological inhibition of KRAS downstream signaling molecule ERK decreased PAI-1 expression. In addition, in PSCs, PAI-1 triggered ERK phosphorylation and its downstream target c-JUN expression. Inhibition of ERK activation or c-JUN expression blocked PAI-1-induced PSC activation and expression of fibronectin and collagen type 1. In conclusion, KRAS-mutant pancreatic cancer cells can activate PSCs through PAI-1/LRP-1 signaling to increase fibrosis and cause an early relapse.

Biography

Yan-Shen Shan has completed his MD in 1993 and PhD in 2004 from National Cheng Kung University. He is now the distinguished professor and the director of Institute of Clinical Medicine, College of Medicine, NCKU. He majors in surgical oncology, molecular oncology, surgical nutrition, and regenerative medicine. He is an expert HPB and GI cancer. He has published more than 120 papers in reputed journals.

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