Fibroblastic FAK controls pancreatic cancer metastasis by enhancing extracellular matrix remodeling

AUTHORS
Emilie Decaup, Sonia Zaghdoudi, Rémi Samain, Stéphanie Cassant-Sourdry, Julia Rochotte, David Schlaepfer, Aurélie Perraud, Muriel Mathonnet, Yvan Martineau, Stéphane Pyronnet, Corinne Bousquet and Christine Jean

(1) Cancer Research Center of Toulouse (CRCT), team 6 “Protein synthesis & secretion in carcinogenesis”, Equipe labellisée LIGUE Contre Le Cancer, Labex TOUCAN, INSERM UMR 1037-University Toulouse III Paul Sabatier, 31037 Toulouse, France; (2) Department of Reproductive Medicine Moores Cancer Center, University of California, San Diego Cancer Center, La Jolla, CA 92093, USA; (3) Limoges University, EA 3842 Laboratory, Medicine and Pharmacy Faculties, Limoges, France.

Purpose:
Pancreatic ductal adenocarcinoma (PDAC) are composed for 80% of a fibrotic stroma. The most abundant stromal cells, the Cancer-Associated Fibroblasts (CAFs) promote tumor cell invasion by remodeling the extracellular matrix (ECM) and generating ECM tracks. One major protein involved in connective tissue remodeling is the protein tyrosine kinase Focal Adhesion Kinase (FAK). Pharmacologic FAK inhibitors are currently tested on PDAC patients for their inhibitory action on tumor cells but their activity on CAFs is unknown. The project is aimed to understand the potential role of FAK activity expressed by CAFs on PDAC progression.

Experimental Design:
FAK activity was comparatively quantified in fibroblasts from human healthy pancreatic and PDA tissues. Genetic or pharmacologic inhibition of FAK activity was achieved specifically in murine fibroblasts, or in primary cultures of CAFs (isolated from patient PDA resections), by using fibroblasts expressing a kinase inactive (kinase-dead) FAK, or a selective FAK kinase inhibitor, respectively.

Results:
In human pancreatic tissues, FAK over-activation, observed in CAFs compared to fibroblasts from healthy tissue, correlates with TNM stage 3, the first invasive step of PDAC. In vitro, fibroblastic FAK inactivation not only significantly decreases tumor cell migration/invasion, but also ECM protein and ECM maturation enzyme expression (LOXL2). Orthotopic syngeneic co-grafting of pancreatic tumor cells and fibroblasts show that specific fibroblastic FAK inhibition dramatically decreases fibrillar collagen expression and lung metastasis.

Conclusion:
Altogether, fibroblastic FAK activity positively regulates CAF-induced tumor metastasis, likely through the formation of collagen invasive tracks. Thus, targeting FAK activity in PDAC patients appears to be a promising strategy.