Title

Reverse immunosuppression and metastasis formation in pancreatic cancer through pharmacological targeting of cancer associated fibroblasts

AUTHORS

(1) Rémi Samain*; (2) Stéphanie Cassant-Sourd*; (3) Christine Jean*; (4) Julia Rochotte*; (5) David Müller*; (6) Herbert Schmid#; (7) Yvan Martineau*; (8) Stéphane Pyronnet*; (7) Corinne Bousquet*
*CRCT, INSERM U1037, Toulouse, France - #NOVARTIS, Basel, Switzerland

Purpose:

Pancreatic ductal adenocarcinoma (PDAC) presents an exuberant stroma. Stromal activated Pancreatic Stellate Cells (PSC) secrete soluble and extracellular matrix (ECM) proteins that promote cancer cell aggressiveness and immunosuppression. We discovered a pharmacological approach to inhibit PSC's deleterious effects on tumor cells by targeting protein synthesis through activation of the somatostatin receptor sst1 with the analog SOM230 (Pasireotide). The association of SOM230 and chemotherapy (gemcitabine) demonstrated anti-tumor and anti-metastatic effects in an immunocompromised mouse model.

Experimental Design:

Longitudinal monitoring of tumor volumes by ultrasound, as well as histopathology and flow cytometry analyses, are performed on pancreatic tumors isolated from transgenic KPC mice (Pdx-1-Cre; LSL-KrasG12D/+; LSL-Trp53R172H/+), or from a model of orthotopic syngeneic grafting of pancreatic cancer cells with PSC (primary cultures).

Results:

The sst1 receptor is expressed in PSC in pancreatic tumors, and de novo in isolated PSCs during their activation, simultaneously with the activation of protein synthesis. Therapeutic benefit of the gemcitabine+SOM230 combination, as compared to gemcitabine, is observed, with reduced primary tumor growth demonstrating drastic decreased ECM deposit, and inhibition of metastasis formation. PSC promote the recruitment into the tumor of immunosuppressive cells (MDSC and M2 macrophages), that is inhibited upon SOM230 treatment.

Conclusion:

Inhibition of protein synthesis in PSC with SOM230 represents a promising strategy for the treatment of PDAC, by indirect targeting both of cancer cells and of immunosuppressive cells.