Fibroblastic FAK activity modifies PDAC microenvironment

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Purpose:
Pancreatic Ductal Adenocarcinoma (PDAC) represents more than 90% of the cases of the pancreatic cancer. The incidence is in constant progression for these last 30 years. The survival rate is around 6% at 5 years due to a very late diagnosis of the disease. 80% of PDAC are composed of a fibrotic stroma. Cancer-Associated Fibroblasts (CAFs), the most abundant stromal cells are known to promote tumorigenesis and metastasis. We recently identified that the activity of Focal adhesion kinase (FAK), a cytoplasmic tyrosine kinase, within CAFs promote tumor cell invasion by remodeling the extracellular matrix (ECM) and generating ECM tracks. We hypothesize that such ECM modification could influence immune cells recruitment to the tumor.

Experimental Design:
For this research project we performed in vitro experiments using primary CAFs isolated form PDAC human tumor, treated or not with FAK inhibitor. Regarding in vivo experiments, a mouse model where PDAC tumor cells are orthotopically co-grafted with fibroblasts expressing FAK-WT or FAK-KD (Kinase dead) was developed.

Results:
Preliminary data obtained on orthotopically co-grafted mouse model show that FAK inactivation tends to increase anti-tumoral cells number whereas pro-tumoral macrophage M2 cell number decreases. The loss of fibroblastic FAK activity not only leads to a decrease of ECM protein deposition but also influences immune cell localization within primary tumor. Finally, FAK inhibition on primary human CAFs modifies soluble factor secretions leading to a decrease of M0 macrophages polarization into M2.

Conclusion:
In conclusion, preliminary data supports that FAK activity within CAFs may impact pro-tumoral immune cell recruitment within the tumor. Thus, targeting FAK activity in PDAC patients appears to be a promising strategy.