Snail drives the cell cycle and determines immune cell profile in pancreatic ductal adenocarcinoma

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Introduction
Current immunotherapies show only minimal benefits to pancreatic ductal adenocarcinoma (PDAC) patients, and one reason is that the complex interplay between the tumor cells and immune cells is still far from being fully understood. Our previous data show that Snail, a known epithelial-to-mesenchymal transition marker, accelerates PDAC progression and induces immune cell infiltration. Therefore, it can be used as a good example to study how genetic factors influence the immune cell profile and the roles of different immune cells in PDAC.

Objectives
This study aims at illustrating the of Snail on tumor cell intrinsic pathways and the immune landscape of PDAC and studying the functions of immune cells in PDAC development using genetically engineered mouse models and advanced novel imaging techniques.

Materials & methods
Our lab has previously generated a conditional Snail overexpressing mouse model and crossed it with the p48-Cre;LSL-KrasG12D PDAC model. Tumor development was monitored using FDG- and FLT-PET/MRI and tissue samples from tumor mice and timepoint mice were analyzed by histology, FACS and RNA-seq. To study the immune landscape in the tumor samples, we deconvoluted RNA-seq data based on available gene expression profile for mouse immune cells from the Immunological Genome Project (ImmGen). Prkdc-Scid and Il2rg-KO alleles from NSG mice and Rag2-KO allele were crossed respectively with the tumor models to deplete various immune cells and evaluate their functions on PDAC development.

Results
Snail-overexpressing mice developed PDAC significantly faster and had more infiltration of several immune cell types including B cells, macrophages, MDSC/neutrophils at an early age. PDAC samples from 14 genotypes showed distinct immune cell composition and clustered into 6 subtypes. In contrast, homogenous global gene expression profile is found in Snail-expressing PDACs, and these tumors fall into 2 clusters with the highest diversity of immune cells. Surprisingly, severe immunodeficiency significantly
delayed Snail-accelerated PDAC progression, while depletion of only mature B cells and T cells caused a marked reduction in survival time. The different cellular and molecular phenotypes resulted in distinct FDG- and FLT-PET signals indicating the potential to classify PDAC subtypes by PET imaging in vivo.

Conclusion
This study shows that PET imaging is capable of predicting PDAC subtypes and that Snail is a potent oncogene with a function of inducing immune cell infiltration in PDAC development. The immune subtype of PDAC is genotype-dependent, and Snail works as a strong driver in modeling the immune landscape. Depletion of B cells and T cells accelerates PDAC progression, in a marked contrast to that severe immunodeficiency leads to better prognosis, arguing for a prominent tumor-promoting role of other immune cells, e.g. macrophages.