Single cell resolution analysis of the human pancreatic ductal progenitor cell niche

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PURPOSE
To analyze the human ductal progenitor cell niche at single cell resolution

METHODS
FACS-sorting of ALK3bright+ cells from human pancreatic samples, corresponding to the pancreatic ductal tree. Principal Component Analysis and Clustering. Validation. Sorting and transplantation into immunodeficient mice.

SUMMARY OF RESULTS
We have described multipotent progenitor-like cells within the major pancreatic ducts (MPDs) of the human pancreas. They express PDX1, its surrogate surface marker P2RY1, and the BMP receptor 1A (BMPR1A)/Activin-like Kinase 3 (ALK3), but not carbonic anhydrase II (CAII). Here we report the single cell RNA sequencing (scRNAseq) of ALK3bright+ -sorted ductal cells, a fraction that harbors BMP-responsive progenitor-like cells.
CONCLUSIONS

Our analysis unveiled the existence of multiple sub-populations along two major axes, one that encompasses a gradient of ductal cell differentiation stages and another featuring cells with transitional phenotypes towards acinar tissue. A third potential ducto-endocrine axis is revealed upon integration of the ALK3\textsuperscript{bright+} dataset with a single-cell whole-pancreas transcriptome. When transplanted into immunodeficient mice, P2RY1\textsuperscript{+}/ALK3\textsuperscript{bright+} populations (enriched in PDX1\textsuperscript{+}/ALK3\textsuperscript{+}/CAII\textsuperscript{−} cells) differentiate into all pancreatic lineages, including functional $\beta$-cells. This process is accelerated when hosts are treated systemically with an ALK3 agonist. We found PDX1\textsuperscript{+}/ALK3\textsuperscript{+}/CAII\textsuperscript{−} progenitor-like cells in the MPDs of type 1/2 diabetes donors, regardless of the duration of the disease. Our findings open the door to the pharmacological activation of progenitor cells \textit{in situ}. 