Organoid Formation by Human Pancreatic Progenitors from Normal and Carcinoma Tissue

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In order to selectively study the subpopulation of pancreatic cells responsible for the survival and proliferation of pancreatic ductal adenocarcinoma tumors, we have used a collection of novel monoclonal antibodies - including DHIC5-4D9/HPd3 and DHIC2-4A10/HPd1 - which have been previously shown to label live duct cell subpopulations in normal human pancreas. In both normal and PDAC tissue from multiple donors, the capacity to initiate highly proliferative self-renewing “organoid” structures in a 3D culture assay (developed by the Clevers group for intestinal stem cell culture) was restricted to the DHIC5-4D9++ subpopulation of ductal epithelium when sorted and recovered by FACS. Although the overall live duct cell frequency is dramatically elevated in PDAC (15-96%) relative to normal tissue (1-4%), less than 1% of these are clonogenic cells. Transplantation of passage 6 organoids from multiple patient-derived donor lines to immune-deficient mice has revealed that PDAC-derived organoids can produce tumor masses, but that normal organoid lines do not survive in this environment. Comparisons of post-transplant outcomes with clinical parameters and parent tumor morphology are in progress.

The identification of functional heterogeneity of duct subpopulations in PDAC may allow selective targeting of the key cells in these tumors. The ability to grow both normal and tumor-derived pancreatic organoid cultures will also permit parallel screens of anti-neoplastic agents to identify molecules that selectively inhibit self-renewal in PDAC while sparing normal pancreatic progenitors.