A TRANSLATIONAL APPROACH TO CATALOG PANCREATIC CANCER HETEROGENEITY USING SPATIAL GENOMICS IN LARGE PATIENT COHORTS FOR TARGET VALIDATION AND RATIONAL COMBINATION SELECTION

Omar Jabado*, Li Fan, Patricia Coutinho de Souza, Angela Harris, Arturo Chaparro, Mohammed Qutachi, Han Si, Jan-Herman Dannenberg, Kate Sasser, Suzanna Couto, Mark Fereishteh, Gennab, Princeton, NJ, USA

Background Pancreatic ductal adenocarcinoma (PDAC) is an aggressive cancer with short overall survival; the standard of care (SoC) is chemotherapy. Immunotherapies in development aim to remodel the stroma by depleting immunosuppressive cell types or using T-cell redirection to kill tumor cells. To date, none of these methods have improved overall survival beyond SoC. Next generation immunotherapies that employ histopathology and molecular subtyping⁴ for target and patient selection may succeed. Here we leverage a spatial transcriptomics platform (Nanostring Digital Spatial Profiling, DSP) to reveal molecular signaling in tumoral and stromal cells in 57 PDAC patients using tumor microarrays (TMAs). This approach is rapid and clinically relevant as molecular and histology data can be easily bridged.

Methods TMAs generated from surgical resection tissue were commercially sourced. DSP was performed using the CTA RNA panel (1,800 target genes) using PanCK fluorescence for chromogenic staining; (D) heatmap of selected genes differentially expressed in tumor and stroma (n=57 patients).

Results Differential gene expression and correlation to IHC confirmed the DSP platform successfully profiled tumor and stromal compartments (figure 1). Immune cell signatures⁵ and pathway analysis revealed a heterogenous stromal environment. Using a fibroblast gene signature derived from single-cell RNAseq⁶ we found fibroblast density was positively correlated to PDGFR signaling and MHC-II expression but negatively correlated to B, CD4+ T and neutrophil cell levels (figure 2a). This finding supports the idea that atypical antigen presentation in cancer associated fibroblasts (CAFs) may be exploitable for immunotherapies.⁷ We constructed a co-expression network from in-situ stromal gene expression and used it to identify receptors coordinately expressed with the immunosuppressive macrophage marker CSF1R as a bispecific antibody partner (figure 2b).⁸ Classical macrophage markers were identified but also receptors with lesser-known functions in macrophages (TIM3/HAVCR2, FPR3, MS4A6A, LILRB4). Surveying target pairs in this method allows rapid, patient-specific confirmation in serial TMA sections with singleplex IHC or RNAscope.

Conclusions In this study we were able to recapitulate known PDAC biology using very small samples of primary tumors. The combination of TMAs and DSP enables a rapid validation of targets and hypothesis generation for bispecific parings. Further analysis of untreated (n=14) and post-adjuvant chemotherapy (n=26) patients using RNA DSP, IHC and bulk RNAseq is underway. Results from this cohort will enable an integrated histopathology and molecular approach to developing next-generation immunotherapies.

REFERENCE


Ethics Approval Specimens were harvested from unused tissue after a surgical tumor resection procedure. A discrete legal consent form from both hospital and individuals was obtained by the commercial tissue vendor BioMax US for all samples analyzed in this abstract. All human tissues are collected under HIPPA approved protocols.

Consent Written informed consent was obtained from the patient for publication of this abstract and any accompanying images. A copy of the written consent is available for review by the Editor of this journal.

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