1724P Secreted kinase FAM20C promotes stromal remodeling via inflammatory cancer-associated fibroblast activation in pancreatic cancer microenvironment

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Background: Cancer associated fibroblasts (CAFs) play a key role in the tumor microenvironment by promoting ideal circumstances for cancer cell proliferation, angiogenesis, metastasis, and chemo-resistance. Pancreatic ductal adenocarcinoma (PDAC) growth is fueled by autocrine and paracrine interaction between tumors and cancer-associated fibroblasts and macrophages in the tumor microenvironment. We recently discovered that a family of proteins with sequence similarity to 20-member C (FAM20C), a novel secreted kinase that phosphorylates secretory proteins or an ectodomain of membrane proteins containing an S-x-E motif, promotes cancer progression and metastasis through tumor associated macrophages (TAMs), implying a novel role for stromal remodeling in tumors. The purpose of this study was to demonstrate FAM20C's potential for metastasis in the tumor microenvironment by validating CAF development using pancreatic stellate cells (PSC) and mesenchymal stem cells (MSC), which are primary sources of CAF.

Methods: The conditioned medium of FAM20C-overexpressed cells, which reflected the pancreatic cancer milieu, was used to confirm the effect on differentiation of MSCs or PSCs into iCAF, as well as the microenvironment remodeling effect in pancreatic cancer orthotopic mouse model.

Results: Under the conditioned medium of FAM20C-overexpressing CFPAC-1 cells, the mRNA expression of α-smooth muscle actin (α-SMA), a hallmark of myofibroblastic CAFs (myCAFs) was reduced in both MSCs and PSCs. In contrast, iCAF marker expression was dramatically elevated, including fibroblast activation protein (FAP), IL-6, and IL-1. Moreover, FAM20C secretion promoted collagen accumulation and migration. Furthermore, tumor growth was accelerated in an orthotopic model using FAM20C-overexpressing pancreatic cancer cells derived from patients. Collagen was also considerably deposited in the stroma as compared to the control cell-injected orthotopic model.

Conclusions: FAM20C might be a critical regulator of PDAC progression by remodeling microenvironment including TAM, CAF and extracellular matrix in pancreatic cancer.

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1725P Metastasis-resident bacteria in advanced hormone receptor-positive breast cancer are related to primary tumor microbiota and show distinct composition

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Background: Tumor-resident bacteria are an emerging component of the tumor microenvironment. Recent studies have shown their presence over multiple cancer types. Lately, mechanistic evidence in a murine breast cancer model indicates that these bacteria promote the metastatic process. However, the presence and conformation of the microbiome of human metastatic tumors have not been determined. Here, we characterized tumor-resident bacteria in a cohort of metastatic hormone receptor-positive breast cancer (MHRBC) patients with matched primary tumors.

Methods: We performed bacterial 16S rDNA sequencing targeting hypervariable regions V2-4 and V6-9 on FFPE tissues from 40 patients with MHRBC and their matched primary tumors. Sequence data were processed using high resolution sample inference with DADA2. Controls included normal breast tissue, paraffin from all blocks and a simulated bacterial community, comprising known intra and extracellular bacteria. Taxonomy was assigned using the SILVA database v138. Feature selection was used to determine amplicon sequences in primary tumors related to their metastasis. A machine learning classifier was generated to predict the metastatic site from selected amplicons.

Results: α-diversity was similar among sample types, while β-diversity showed segregation between metastatic and primary tumors. *Alphaproteobacteria*, *Gammaproteobacteria* and *Bacilli* had increased relative abundance across metastatic and primary tumors. Differential abundance of *Proteobacteria* and *Firmicutes* species was identified in metastatic tumors. A machine learning classifier using the 5 top ranked amplicons in primary tumors was capable of 100% precision and high recall for prediction of bone and liver metastatic site, but not lung metastases.

Conclusions: We identified and categorized the tumor-resident bacteria of MHRBC. To our knowledge, this is the first study looking at the composition of metastatic breast cancer microbiome. While insights have been gained on primary tumor microbiota, the role of metastasis-resident bacteria including local immunity and treatment resistance warrants further study.

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1726P Investigating adipocytes-tumor cells interaction and its effect on disease progression in lobular breast cancer with spatial transcriptomics

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Background: Invasive lobular breast carcinoma (ILC) represents 5 to 15% of all invasive breast cancers (BCs). Adipose tissue has shown a role in BC development. Here, we aim to investigate adipocytes-tumor cells interaction and its prognostic value in ILC with spatial transcriptomics (ST).

Methods: We performed ST (10X Genomics) on frozen tumor samples from 43 primary hormone receptor-positive, HER2-negative ILC patients. The quantification of the contacts between cell types and the selection of ST spots on the tumor-adipocytes contact region were performed via H&E slides annotation. A gene expression signature of 27 genes was derived by performing differential gene expression analysis between patients with vs without relapse on the selected spots. TCGA and METABRIC were used to check the correlation of our signature with *PIK3CA* mutational status and immune/proliferation related signatures, and to perform survival analysis (Cox proportional hazard models). Signature association with drug sensitivity in cell lines was assessed using PharmacoGx R package.

Results: Adipocytes-tumor contacts were enriched in samples from patients who relapsed ($n = 9$, $p = 0.035$). This region was enriched in heme-metabolism and IFN α-γ pathways (padj < 0.25). The signature was more expressed in samples with *PIK3CA* mutations ($p < 0.001$ in TCGA and METABRIC), and associated with worse prognosis in ILC at uni- and multivariate (correcting for clinical variables) analyses for disease-specific survival and distant metastasis-free survival in METABRIC ($p < 0.05$). The same trend was observed when correcting for proliferation and immune signatures, and in invasive ductal breast carcinoma (IDC). No strong correlations (> 0.2 rho) between our signature and immune/proliferation related signatures were observed. Higher levels of the signature were associated to sensitivity to chemotherapeutic (including Epirubicin and Cisplatinum, $p < 0.05$) and PI3K pathway-targeting agents ($p < 0.1$) in luminal BC cell lines.

Conclusions: Tumor-adipocytes interaction has a role in defining prognosis in ILC. Our signature has the potential to guide treatment strategies in luminal BC. Further validation is required.

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