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Pancreatic ductal adenocarcinoma (PDAC) is the most common form of pancreatic cancer and the third most deadly cancer overall. The PDAC tumor microenvironment (TME) contains a large proportion of stromal cells that influence tumor growth, matrix properties, and immune cell interactions. Cancer associated fibroblasts (CAF) are a heterogeneous cell type present in large numbers in PDAC and have historically been thought to contribute strongly to disease progression. However, preclinical studies in which CAF are ablated and clinical studies targeting the fibrosis produced by CAF have had surprising results in which tumor growth accelerated after the intervention. These studies demonstrate that we clearly do not understand how phenotypic heterogeneity of CAF populations influence tumor growth. Thus, we have used gene expression to develop a classifier that identifies CAF as either “tumor-promoting” and “tumor-restraining” subtypes based on their correlation to clinical outcomes in patients to identify their dichotomous roles. Stratifying patient by subtype results in a difference in overall survival of approximately 10 months ($p<0.001$). We then compared the behavior of these 2 CAF subtypes in vascular microphysiological systems to observe the functional effects they have on an in vitro model of the TME. In vasculogenesis assays, restraining CAFs (restCAFs) readily produced perfusable blood vessels using the self-assembly method with human umbilical vein endothelial cells. Tumor-promoting CAFs (proCAFs), on the other hand, did not result in patent lumens that permitted flow. However, this difference in vasculogenic capability was not due to a defect in angiogenesis, because proCAFs were able to stimulate robust sprouting of an endothelial monolayer. Instead, the primary difference appears to be strong contractility and matrix remodeling exhibited by restCAFs. In microfluidic devices containing CAF in fibrin hydrogels, we observed compaction of the gel that pulled it from the walls of the microfluidic device in 73% of the

restCAFs samples vs 7% of the proCAF samples ($p = 5.5E-7$). Furthermore, the fluorescent intensity of 647nm-labeled fibrin was significantly lower after 1 week of culture in restCAFs devices than proCAF devices ($p = 2.7E-22$). Ongoing studies will examine the mechanisms of tumor promotion or restraint, and our preliminary results suggest that secreted factors from proCAFs promote tumor invasion, while densely aligned matrix produced by restCAFs may inhibit tumor cell migration. Ultimately, we aim to improve treatment of patients with PDAC through manipulation of the stroma compartment of the TME in addition to targeting malignant cells.