Proteomic Analyses of Extracellular Matrix in Pancreatic Cancer

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Abstract: Pancreatic ductal adenocarcinoma (PDAC) is characterized by accumulation of an extensive extracellular matrix (ECM) that has been implicated in the resistance to therapeutic drugs. Our goal will be to apply recently developed methods for comprehensive proteomic analysis of ECM by mass spectrometry to characterize changes occurring as PDAC progresses, metastasizes and responds (or does not respond) to therapy. We have developed these methods in our ongoing research into various mouse models of cancer (melanoma, mammary carcinoma, insulinoma) and human colon carcinomas and their metastases. The data from those studies demonstrate that we can readily detect reproducible changes in ECM during tumor progression and can distinguish tumors that will and will not metastasize using these ECM biomarkers. The changes detected include many proteins that we have subsequently shown play causal roles in promoting metastasis and therefore offer novel targets for therapeutic intervention. We will apply these methods both to human PDAC patient samples and to mouse models of PDAC developed by us - the former with the aim of establishing signatures of various stages of PDAC and converting them into immunohistochemical (IHC) assays for introduction into routine pathology lab procedures; the latter to allow investigation of the functional consequences of the alterations that we detect by using both *in vitro* culture methods and *in vivo* transplantation experiments. The studies proposed will characterize PDAC ECM in detail and provide new leads for diagnosis, prognosis and, in the longer term, new imaging methods and novel therapies for this challenging disease.