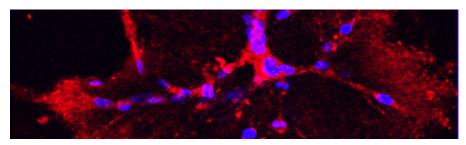
research>>

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Pancreatic Ductal Adenocarcinoma (PDA) is a fearsome diagnosis; it accounts for 95% of all exocrine pancreatic cancers and carries with it a 3% five-year survival rate. Clinical diagnosis is often late allowing rapid growth and metastasis. Clearly, preventing PDA's invasion and dissemination would provide an immediate therapeutic tool. Numerous pathologic observations correlate PDA with a desmoplastic tumor microenvironment (TME) consisting of an altered extracellular matrix (ECM) architecture, increased fibrosis, and cellular proliferation. Additionally, 90% of PDA tumors carry a constituently activated K-Ras G12V mutation. However, the relationship between the 3-D TME and its Growth Factors, their synergistic activation of the K-Ras GTPase, their ability to transform 'normal' epithelia into tumorigenic, and their direct effects on matrix metalloproteinase (MMP) gene expression & invasion are not well understood.

As no relevant human pancreatic models exist *in vitro* to understand this phenomenon, we first developed a novel, 3-D, human pancreatic model composed of (1.) a 'normal' to 'transformed' pancreatic epithelial cell (PEC) progression series, (2.) ECM Matrigel Compositions, (3.) and defined culture media. Organization of the cellular model was analyzed via confocal microscopy for polarization and morphology. We then will analyzed the effect of growth factors and serum on synergizing K-Ras activation, transformation characteristics, and MMP production within PECs via western blot analysis, fluorescent staining, qRT-PCR, and cDNA microarrays. Our data suggests that distinct alterations in the Ras-MEK-ERK pathway due to growth factors and a 3-D ECM surrounding PECs leads to synergistic upregulation of the K-Ras mutation which differentially modulates invasion via MMPs and TIMPs. These metalloproteinases have yet to be implicated as clinically-relevant in PDA. We surmise that our studies can be translated into prognostic biomarkers or pharmacological targets able to significantly assist in the early diagnosis of PDA and a reduction in its metastasis.