

**Stony Brook University
The Graduate School**

Doctoral Defense Announcement

Abstract

MMP-7 modulates the transition of normal pancreatic acinar cells to metaplastic ducts associated with the neoplastic epithelium of pancreatic ductal adenocarcinoma

By

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Pancreatic ductal adenocarcinoma (PDA) is the most common among pancreatic tumors and one of the most fatal human cancers, killing approximately 30,000 people each year in the United States. PDA is thought to arise from premalignant lesions known as pancreatic intraepithelial neoplasia (PanIN). A preneoplastic lesion that is always associated with PDA as well as patients at risk for PDAC, such as those with chronic pancreatitis (CP), is known as the metaplastic duct lesion (MDL). MDLs arise from a process known as acinar-to-ductal metaplasia (ADM), in which healthy acinar cells are progressively replaced by duct-like MDLs. The association with full blown PDAC and patients at elevated risk for PDA has led to the hypothesis that MDLs act as PanIN precursors.

Matrix metalloproteinase-7 (MMP-7), a member of a family of MMPs, is expressed by tumor cells in adenocarcinomas of many tissues including 98% of PDA samples at all stages of tumor progression, including 100% of MDLs. Although MMP-7 has been shown to contribute to both the formation and invasion of a number of adenocarcinomas, the frequency of MMP-7 expression in pancreatic tumors exceeds expression of MMP-7 in other tumors. Consistent with the role of MMP-7 in the earliest stages of pancreatic tumorigenesis, all MDLs in tumor samples of patients with PDA express MMP-7 and MMP-7 is required for MDL formation in a mouse CP model. Taken together these data suggest that in pancreatic cancer MMP-7 has a function that precedes, but is not limited to the onset of tumor formation. Therefore, we have directed our focus to MMP-7 and its involvement in early tumor progression and ADM. It is the purpose of this dissertation to define how MMP-7 regulates ADM associated with CP and PDA and contributes to the overall progression of PDA.

Date: May 11, 2007

Time: 1:00 pm

Place: (BST, 5th fl. Room 140)

Program: Physiology and Biophysics (HBY)

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