GRANT SNAPSHOT

2006 Michael Landon – Pancreatic Cancer Action Network – AACR Career Development Award

Grantee:	Brian C. Lewis, PhD
Institution:	University of Massachusetts Medical School, Worcester
Project Title:	*Pancreatic Cancer Induction by Activated Notch Signaling*
Award Period:	July 1, 2006 – June 30, 2008
Amount:	$100,000

Biographical Highlights

Brian Lewis received his PhD in Human Genetics and Molecular Biology from Johns Hopkins University and completed postdoctoral training at the National Institutes of Health and Memorial Sloan-Kettering Cancer Center. Dr. Lewis joined the Program in Gene Function and Expression at the University of Massachusetts Medical School as an Assistant Professor in 2003. His lab focuses on identifying correlations between specific genetic changes, tumor behavior, and cell signaling pathways.

Project Description

This study examines how specific genetic alterations commonly found in pancreatic cancer contribute to tumor initiation and progression. Activation of the notch signaling pathway has recently been described in a large subset of pancreatic ductal adenocarcinoma (PDAC) samples and is seen in early precursor lesions. However, the role of this signaling pathway in the pathogenesis of PDAC is unknown. The aim of this study is to identify the consequences of activated notch signaling on cells that line the surface of the pancreatic duct (i.e., epithelial cells), using cell culture and orthotropic transplantation systems (i.e., grafting of tissue in a natural position). Epithelial cells are the presumptive target cells in PDAC. Plans are to determine whether active notch signaling induces the proliferation and survival of duct epithelial cells and whether these effects are influenced by the presence of cooperating tumor suppressor gene mutations. This project is expected to shed light on the role of notch signaling in pancreatic tumorigenesis and identify whether the notch signaling pathway is a good therapeutic target in pancreatic cancer.

Results/Outcomes

The data suggest that activated notch signaling does not contribute to pancreatic tumorigenesis through the stimulation of either cell proliferation or survival, inconsistent with the stated hypothesis. However, these results are consistent with the known role of activated notch signaling during pancreatic development during embryogenesis. In this context, notch signaling acts to

inhibit differentiation and to maintain cells in a progenitor-like state. Thus, it is hypothesized that notch signaling may contribute to pancreatic tumorigenesis by maintaining cells in a progenitor-like state, and cooperates with additional oncogenic events, such as activation of Kras or stimulation of sonic hedgehog (Shh) signaling, that act as proliferation and survival cues. Tests were conducted to determine whether activated notch signaling can cooperate with Shh in the development of pancreatic tumors. Preliminary results suggest that this is the case, and efforts are underway to repeat and extend these findings.

Lessons Learned

Perseverance is important. In contrast to published findings of the consequences of notch activation in other tumor types, the results of this study refuted the initial hypothesis that notch signaling would enhance the proliferation and survival of pancreatic epithelial cells. However, subsequent data suggest that although notch signaling may not contribute to pancreatic tumor development through these mechanisms, it likely contributes in other ways. Dr. Lewis continues to persevere in his attempts to clearly delineate these mechanisms.

Next Steps

Current plans are to repeat the tumor development studies to determine whether activation of notch signaling does in fact stimulate pancreatic tumor development. Experiments will be performed to identify whether notch signaling cooperates with other common changes found in pancreatic cancer cells such as mutations in Kras and stimulation of the hedgehog signaling pathway.