GRANT SNAPSHOT

2007 Skip Viragh – Pancreatic Cancer Action Network – AACR Career Development Award

Grantee:	Huamin Wang, MD, PhD
Institution:	MD Anderson Cancer Center, Houston
Project Title:	*Functional Study of Hematopoietic Progenitor Kinase-1 in Pancreatic Cancer*
Award Period:	July 1, 2007 – June 30, 2009
Amount:	$100,000

Biographical Highlights

Dr. Wang received his MD from Tongji Medical University in Wuhan, China and PhD in Biomedical Sciences from University of Texas. He then completed a residency program and fellowship at the University of Texas. Dr. Wang is board certified in combined anatomical pathology and clinical pathology. His daily clinical services involve reviewing histology slides of many different types of cancer specimens from gastrointestinal tract, liver and pancreas. He was fascinated by the fact most of the pancreatic ductal cancers are moderately or well differentiated and yet they behave as one of the most lethal diseases among all human malignancies. Recognizing the need to look beyond the histology (i.e., microscopic structure) of the disease and to better understand its biology led Dr. Wang to pursue laboratory research on the molecular mechanisms of pancreatic cancer.

Project Description

Hematopoietic progenitor kinase-1 (HPK1) is a mammalian Ste20-like serine/threonine kinase and functions as a MAP4K in the MAP kinase signaling module. HPK1 regulates NFkB activities and activates the c-Jun N-terminal kinase (JNK) pathway. While a number of studies have identified the role of HPK1 in stress responses, its impact on the transformation, proliferation and invasion of human malignancies has not been fully examined. Preliminary data demonstrate a strong association between the loss of HPK1 expression and the progression from benign pancreatic ducts to pancreatic intraepithelial neoplasia (PanIN), to invasive pancreatic carcinoma in human tissue samples. Furthermore, over-expression of HPK1 in Panc-1 pancreatic cancer cells increased gemcitabine or gamma-radiation induced apoptosis (i.e., cell death). The funded study carefully examines the role of HPK1 in tumor invasion and metastasis as well as the underlying molecular mechanisms by which HPK1 regulates apoptosis, invasion, and/or metastasis in pancreatic cancer. Results are expected to help identify new biomarkers and therapeutic targets.

Results/Outcomes

Findings show that HPK1, one of the major kinases involved in apoptosis and proliferation, is expressed in normal pancreatic ducts but is lost in more than 95% of human pancreatic cancer samples. The loss of HPK1 protein is strongly associated with the progression from low-grade pancreatic intraepithelial neoplasia (PanIN) to invasive pancreatic cancer. The study also showed that the loss of HPK1 in pancreatic cancer was due to proteasome-mediated degradation. More importantly, restoring wild-type HPK1 protein expression in pancreatic cancer cells causes cell-cycle arrest and growth inhibition. Thus, the data showed, for the first time, that HPK1 may function as a novel tumor suppressor and its loss plays a critical role in the development of pancreatic cancer. The data also provide support that proteasome inhibitor may inhibit pancreatic cancer growth by up-regulating HPK1 protein.

Lessons Learned

Conventional treatment approaches, such as chemoradiation, have little impact on the course of pancreatic cancer. There is an urgent need for better understanding of the molecular mechanisms and the development of targeted therapy toward aberrant molecular pathways in pancreatic cancer. Continuous support for the career development of young scientists in pancreatic cancer research is critical.

Next Steps

The findings from this study showed that HPK1 may function as a novel tumor suppressor and its loss plays a critical role in the development of pancreatic cancer. Dr. Wang is examining the downstream signaling molecules involved in HPK1 pathways. These studies are expected to not only provide novel insights into the molecular mechanisms involved in the development of pancreatic cancer, but also identify novel molecular targets for pancreatic cancer therapy.

Follow-Up Funding

Lockton Grant Matching Program for Pancreatic Cancer Research, MD Anderson Cancer Center (1/08-12/08; Amount $25,000).

Publications Related to Funded Project

Liang JJ, Wang H, Rashid A, Tan T-H, Hwang RF, Hamilton SR, Abbruzzese JL, Evans DB. Expression of MAP4K4 is associated with worse prognosis in patients with stage II pancreatic ductal adenocarcinoma. *Clinical Cancer Research*, 2008.

Wang H, Song X, Logsdon C, Zhou G, Evans DB, Abbruzzese JL, Hamilton SR, Tan T-H. Proteasome mediated degradation and the functions of hematopoietic progenitor kinase-1 in pancreatic cancer. *Cancer Research* (in revision).