GRANT SNAPSHOT

2005 Pancreatic Cancer Action Network – AACR Career Development Award

Grantee:	Mircea Ivan, MD, PhD
Institution:	Indiana University, Indianapolis
Project Title:	*Exploring Hypoxia Resistance in Pancreatic Tumors*
Award Period:	July 1, 2005 – June 30, 2007
Amount:	$100,000

Biographical Highlights

Dr. Ivan received his MD from Carol Davila University of Medicine and Pharmacy in Bucharest, Romania and his PhD in pathology from University of Wales College of Medicine in Cardiff, United Kingdom. He completed a postdoctoral fellowship at the Dana-Farber Cancer Institute and then served as a Scientist at AVEO Pharmaceuticals in Cambridge. In 2003, he joined the faculty of Tufts University School of Medicine and served as Director of the Proteomic Research Facility, Molecular Oncology Research Institute, where he remained until August 2008 when he relocated to Indiana University, where he currently is Assistant Professor of Hematology/ Oncology. His research interests include cancer biology and hypoxia, which is a deficiency in the amount of oxygen reaching body tissues.

Project Description

Tumors with widespread low oxygenation (hypoxia) have a poor prognosis, likely because of hypoxia effects on angiogenesis (blood vessel growth), metastasis (tumor spread), and therapy resistance. Pancreatic adenocarcinomas are considered to be among the most hypoxic of human cancers and this characteristic is thought to contribute to their resistance to conventional therapy. The response that pancreatic cancer cells have to low oxygen is very complex and involves the activation of over 100 genes. These genes are activated by a family of regulators known as hypoxia-inducible factors (HIFs). There is growing evidence that identifies HIFs as a potential target for therapy. This research project will focus on studying pancreatic cancer cells as they are exposed to extended periods of hypoxia (over a week), which mimics the situation that occurs in the human body. Both mouse and human pancreatic cancer cells will be studied in the laboratory, in order to learn more about how they survive in the environment of chronic hypoxia. By observing the cells' response to hypoxia, the aim is to identify which genes regulate the survival of the cancer cell in the extended low-oxygen environment. These genes may be responsible for the production of proteins that could ultimately become drug target candidates. New drugs and therapies would be tested in human clinical trials, with the goal of making improved treatments available to patients.

Results/Outcomes

The study identified miR-210 as a critical component of the hypoxic response, downstream of HIF, with likely roles in cell survival under prolonged hypoxic stress. This miR may enhance the ability of cancer cells to survive in the hypoxic microenvironment, and its increased expression

may worsen the course of pancreatic cancer. This was recently demonstrated for breast cancer and, if proven correct in the case of pancreatic cancer, may provide both a prognostic marker and therapeutic target.

Lessons Learned

While the analysis of classic hypoxia-inducible genes did not lead to the identification of hypoxia survival factors (at least in this research), the interrogation of specific microRNAs led to identification of potentially powerful players in the hypoxic response. As Dr. Ivan's states, "The development of a robust assay puts the researcher in a solid position to identify players with a biological impact, rather than simple responders to a stimulus/stress."

Next Steps

An investigation will be conducted of the role of miR-210 in pancreatic cancer, where it is frequently over-expressed. The impact on pancreatic tumorigenesis will be tested in a variety of cell lines overexpressing miR-210, initially using xenograft-based animal models. Additionally, In vivo expression of miR-210 in human pancreatic cancer samples will be studied by in situ hybridization using LNA technology.

Follow-Up Funding

Elsa Pardee Foundation Award and Indiana University Cancer Center start-up funds. Applications are currently in preparation for funding from NIH and the American Cancer Society.

Publications Related to Funded Project

Ivan M, Harris AL, Martelli F, Kulshreshtha R. Hypoxia response and microRNAs: no longer two separate worlds. *J Cell Mol Med,* 2008, June 23. Epub ahead of print.
PMID: 18624759 [PubMed - as supplied by publisher]

Borger DR, Gavrilescu LC, Bucur MC, Ivan M, Decaprio JA. AMP-activated protein kinase is essential for survival in chronic hypoxia. *Biochem Biophys Res Commun,* 2008;30:370(2):230-234. Epub 2008 Mar 24. PMID: 18359290 [PubMed - indexed for MEDLINE]

Kulshreshtha R, Davuluri RV, Calin GA, Ivan M. A microRNA component of the hypoxic response. *Cell Death Differ,* 2008;15(4):667-671. Epub 2008 Jan 25. Review.
PMID: 18219318 [PubMed - indexed for MEDLINE]

Fabbri M, Ivan M, Cimmino A, Negrini M, Calin GA. Regulatory mechanisms of microRNAs involvement in cancer. *Expert Opin Biol Ther,* 2007;7(7):1009-19. Review.
PMID: 17665990 [PubMed - indexed for MEDLINE]

Kulshreshtha R, Ferracin M, Negrini M, Calin GA, Davuluri RV, Ivan M. Regulation of microRNA expression: the hypoxic component. *Cell Cycle,* 2007;6(12):1426-31. Epub 2007 May 7. Review.
PMID: 17582223 [PubMed - indexed for MEDLINE]

Kulshreshtha R, Ferracin M, Wojcik SE, Garzon R, Alder H, Agosto-Perez FJ, Davuluri R, Liu CG, Croce CM, Negrini M, Calin GA, Ivan M. A microRNA signature of hypoxia. *Mol Cell Biol,* 2007;27(5):1859-1867. Epub 2006 Dec 28. PMID: 17194750 [PubMed - indexed for MEDLINE]