

2014 Research Award Update

Jonathan M. Hernandez, MD
Department of Surgery
Cell Biology Program
Memorial Sloan Kettering Cancer Center
New York, NY

Characterization of Dormancy and Outgrowth for Metastatic Pancreatic Cancer in the Liver

Resection for pancreatic adenocarcinoma is undertaken with curative intent for patients with localized disease, but the cancer uniformly recurs, most frequently in the liver. This occurs because certain subpopulation(s) of tumors cells within the primary pancreatic mass have acquired the ability to disseminate from the pancreas and seed the liver prior to resection. Following dissemination, metastatic pancreatic cancer cells must evolve to overcome the challenges posed by the foreign microenvironment. During this period of latency the tumor cells exist singly or in small clusters without significant increases in cell numbers. We believe significant progress can be made in the treatment of localized pancreatic cancer if the genetic programs governing metastatic dormancy and subsequent reactivation can be identified. As such, we have derived a pair of isogenic cell lines from the KPC mouse model that differ in their ability to colonize the liver following injection into the portal circulation. We evaluated the transcriptomes of our cell lines by RNA sequencing, and compared the results to the transcriptomes of a subset of patients in the pancreatic adenocarcinoma TCGA dataset (with or without early hepatic recurrence following resection) in order to frame our data in the context of clinical relevance. Intriguingly, we identified a 67-gene signature comprised of similarly differentially expressed genes between our derived cell lines the TCGA patients. Although this analysis has revealed numerous attractive potential targets, the assignment of causality as opposed to association is difficult. We have therefore sought to identify those genes responsible for governing colonization using forward genetic screens. We have constructed high complexity cDNA libraries in retroviral vectors from the metastatic cells, and have infected the dormant cells in order to identify genes responsible for metastatic outgrowth. We anticipate that the cDNAs we isolate will lead to new insights into the mechanisms required for dormant cells to reactivate. In a second screen, we have stably transfected dormant cells with the Cas9 endonuclease, and will screen a mouse gRNA library, which targets 19,150 mouse protein-coding genes. We anticipate that the gRNAs we isolate will target genes that are necessary to maintain dormancy. Our major goal in implementing these screening strategies is identify core components of signaling pathways that regulate colonization. We are currently validating and will subsequently prioritize the “hits” from our screens for follow up mechanistic work. Characterization of the core signaling pathways that govern disseminated pancreatic cancer cells should lead to the identification of novel targets for adjuvant therapy that will effectively interrupt the metastatic cascade prior to its completion, and prevent or delay the development of overt metastatic disease thereby prolonging survival.

Supported in part by the AHPB Foundation