

Pancreatic Cancer

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Molecular Biology of Pancreatic Cancer - Are There Rational Novel Targets for Pancreatic Cancer Therapeutics? *Observations from the M. D. Anderson Cancer Center SPORE in Pancreatic Cancer*

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The recent failure of two large randomized phase III trials of the targeted monoclonal antibodies bevacizumab and cetuximab and the limited value of erlotinib have emphasized that translating our understanding of the molecular biology of pancreatic cancer into improved patient care will be challenging. For this disease it now appears that therapeutically targeting *individual* proteins involved in the growth of pancreatic cancer cells will only lead to minor incremental improvements in patient survival. What should be our collective response to this fact? The pancreatic cancer SPORE at the M. D. Anderson Cancer Center is attempting to exploit aspects of pancreatic cancer molecular biology in order to discover and evaluate new targets for therapeutic development. Three general approaches are being taken: (1) Understanding the molecular biology of transcription factors activated in pancreatic cancer and developing means to inhibit them. Thus far, we have analyzed NFκB and Specificity (Sp) proteins. NFκB has been targeted using the natural product curcumin with promising early activity documented in a pilot clinical trial. Sp proteins regulate many downstream proteins critical to cancer development and growth, including vascular endothelial growth factor. Non-steroidal anti-inflammatory agents such as celecoxib and tolfenamic acid promote proteasomal degradation of Sp1, Sp3, and Sp4 and could be assessed in future clinical trials. (2) Pancreatic cancer cells appear to be particularly susceptible to endoplasmic reticular (ER) stress and cellular proteotoxicity. ER stress can be induced in pancreatic cancer cells

using the FDA-approved agent bortezomib. The proteotoxicity of bortezomib against pancreatic cancer cells appears to be due to failure of bortezomib to stimulate the phosphorylation of PERK, leading to hypophosphorylation of eif2 α . Despite bortezomib's inhibition of protein degradation through inhibition of the proteasome, eif2 α allows protein translation to continue leading to cellular proteotoxicity. Combinations of bortezomib and protein-disrupting agents such as SAHA or specific HDAC inhibitors appear particularly effective in stimulating apoptosis in pancreatic cancer cell lines in vitro and in vivo. A clinical trial assessing this therapeutic approach is under way. (3) Finally, recent characterization of pancreatic cancer cell lines resistant to gemcitabine suggests that resistance to apoptosis was distinguished by markers of epithelial-to-mesenchymal transition (EMT). These cells also expressed cell surface markers consistent with pancreatic cancer stem cells as well as c-Met. Also noted was an inverse correlation between E-cadherin and one of its transcriptional repressors, Zeb-1. Silencing of Zeb-1 in the mesenchymal pancreatic cancer cell lines increased expression of E-cadherin and restored gemcitabine sensitivity. Additional preclinical studies targeting c-Met and Zeb-1 are under way and we are preparing to take these observations to the clinic. It is our belief that our efforts to develop new treatments for pancreatic cancer need to be closely integrated with the global efforts to understand the molecular biology of this disease and that, whenever possible, future strategies should be based on this evolving knowledge.