

The Molecular Biology of Pancreatic Cancer

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In the prevailing progression model of pancreatic carcinogenesis, pancreatic adenocarcinomas are hypothesized to arise from precursor lesions termed pancreatic intraepithelial neoplasia (PanIN). Increasing degree of dysplasia (and therefore grade) exhibited by these lesions correlates with increasing prevalence of intralesion genetic derangements. The most prevalent of these derangements in pancreatic adenocarcinoma include activating KRAS mutations (present in 95% of cases), CDKN2A mutation, deletion, or promoter hypermethylation (present in 80% to 95% of cases), TP53 mutations (present in > 50% of cases), and SMAD4/DPC4 loss (present in > 50% of cases). A temporal sequence in which these abnormalities arise has been proposed, with KRAS mutation being among the earliest events during pancreatic carcinogenesis.

Other well-described features of pancreatic adenocarcinoma include chromosomal abnormalities (eg, losses of 17p, 9p, and 18q), activation of mitotic and pro-survival signaling cascades (eg, MAPK, PI3K/Akt, and NF- κ B signaling), and activation of developmental signaling pathways (eg, Notch and Hedgehog signaling). High-throughput genomics and proteomics platforms are increasingly exploited to identify gene products that are overexpressed in pancreatic adenocarcinoma tissues and in body fluids (eg, serum and pancreatic exocrine secretions) from patients with pancreatic adenocarcinoma relative to their normal counterparts.

For example, the adhesion molecule carcinoembryonic antigen-related cell adhesion molecule 6 (CEACAM6) recently has been shown to be overexpressed in greater than 90% of pancreatic adenocarcinomas. Further, tumoral CEACAM6 expression is negatively correlated with patient survival following surgical resection for pancreatic

adenocarcinoma. In vitro and in vivo studies have demonstrated that CEACAM6 promotes pancreatic adenocarcinoma cellular invasiveness, metastatic potential, and survival under anchorage-independent conditions. Finally, targeted therapy directed against CEACAM6 promotes chemosensitivity to gemcitabine and prolongs survival in a preclinical model of pancreatic adenocarcinoma.

In conclusion, knowledge of the molecular biology of pancreatic adenocarcinoma is undergoing rapid growth. The challenge is to translate this knowledge to develop new biomarkers and therapeutic targets that will have impact on the clinical care of patients with this deadly cancer.