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Novel Signaling Pathway in Barrett's Esophagus and Development of Gene Therapy for Pancreatic Cancer

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Barrett's esophagus is an inflammatory process associated with severe gastroesophageal reflux disease and bile acids — the strongest known risk factor for the development of esophageal adenocarcinoma. In this study, we attempt to identify the influence of bile acid on Barrett's adenocarcinoma and examine whether gastroesophageal reflux with bile acid could dysregulate the TSC1/mTOR signaling pathway, which may be a molecular switch for Barrett's cancer pathogenesis. TSC1, a well-known tumor suppressor responsible for the development of tuberous sclerosis complex (TSC), negatively regulates the mammalian target of rapamycin (mTOR) pathway. Our current preliminary results indicate that the TSC1/mTOR pathway may be involved in the development of Barrett's esophageal carcinoma as evident from increasing phosphorylation of S6 kinase in Barrett's esophagus cancer cell lines.

In an attempt to develop an efficacious systemic gene therapy for pancreatic cancer, we engineered a robust and pancreatic cancer-specific promoter, CTP (CCKAR/TSTA/WPRE). It is based on the cholecystokinin type A receptor promoter, the two-step transcriptional activation system, and the post-transcriptional regulatory element. The CTP transcriptionally targets transgene expression effectively to pancreatic tumors in vivo. Targeted expression of enhanced proapoptotic gene Bik mutant BikDD, driven by CTP after systemic liposome-mediated delivery, exhibited significant antitumor effects on pancreatic cancers with minimal or no toxic effects, and prolonged survival in multiple xenograft and syngeneic orthotopic mouse models.