

Bankhead-Coley Cancer Research Program

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Bridge (1-year project)*

Project Title: Bile-Induced Growth in Barrett's Esophagus

Project Summary: Esophageal cancer remains one of the most deadly human cancers with only a 15 percent cancer cure rate. In the U.S., almost 14,500 new cases of esophageal cancer and 13,700 deaths due to cancer of the esophagus are expected in 2006, making it the sixth leading cause of cancer deaths. Unfortunately, the incidence of esophageal cancer appears to be rising. Since 1974 the incidence of esophageal cancer has increased sixfold, a rate faster than that of all other gastrointestinal cancers. Moreover, there has been a change in the type of esophageal cancer, with less squamous cell carcinoma, and more adenocarcinoma, currently being diagnosed. Barrett's esophagus (BE) is a cancerous condition caused by chronic heartburn (gastroesophageal reflux disease or GERD), and the vast majority of esophageal adenocarcinomas are thought to arise from BE. The increase in the frequency of adenocarcinoma is perplexing since it has occurred during a time when our ability to treat acid reflux has significantly improved with the introduction of H₂-blockers and proton pump inhibitors, drugs that decrease stomach acid secretion. Intriguingly, clinical studies show that patients with BE have significantly higher levels of bile salts along with acid in the refluxed material than patients without BE. Agents that make cells at risk for becoming cancer proliferate are called promoters because they promote the development of cancer. Prior research has shown that both bile salts and acid exposure make Barrett's cells proliferate and activate molecules called mitogen activated protein kinases (MAPK) in other cancer cell types, suggesting that reflux of bile salts may act as a cancer promoter in BE and esophageal cancer. The research team will carry out a systematic evaluation of the signaling pathways that mediate the effects of bile salt-induced esophageal mucosal proliferation. This bridge grant examines the mechanisms by which bile salts act as cancer promoters in BE and esophageal cancer. The way that bile salts act on cells to activate the Ras molecule and make cells proliferate will be examined. (Ras is a key molecule in cell growth, a commonly mutated molecule in many forms of cancer, and an important activator of MAPK, which are known to be activated by bile salts.) The team will accomplish this by utilizing specific recombinant DNA inhibitors of Ras and MAPK and examining their effects on bile salt-stimulated cell growth. The team will also look at the ability of these inhibitors to block bile salt-induced protection from apoptosis, a normal process that the body uses to kill abnormal cells before they become cancer. Finally, the team will examine the role of special areas of the cell membrane known as lipid rafts in bile salt-stimulated cell growth. These lipid rafts are parts of the cell that are rich in cholesterol and are important in cell growth signaling. Because one of the normal functions of bile salts is to help dissolve cholesterol, the team has hypothesized that this may be how bile salts make cells proliferate. One of the best ways to cure cancer is to prevent it from occurring. If bile salts do activate cell growth in BE and act as cancer promoters, then preventing bile reflux may help prevent esophageal cancer. Considerable uncertainty currently exists regarding the appropriate treatment of Barrett's esophagus with the current options consisting of either antacid medications or surgery to prevent

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reflux. If bile salts alone can activate cell growth in Barrett's metaplasia, it may be necessary to modify our current management strategy for BE. In this case, replacement of the current strategy with either surgical elimination of reflux or complete pharmacological suppression of reflux would be justified. Furthermore, a detailed understanding of the molecular mechanisms leading to cancer promotion in Barrett's esophagus may lead to the identification of new targets at which to direct cancer prevention or treatment drugs in Barrett's esophagus and esophageal adenocarcinoma.