

Bankhead-Coley Cancer Research Program

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*2006 Program
Bridge (1-year project)*

Project Title: Nicotinic Receptor Signaling Pathways in NSCLC

Project Summary: Tobacco smoke contains many cancer-causing agents, many of which are derivatives of nicotine. While nicotine has not been shown to initiate cancer, it can induce the growth of cancer cells and promote the formation of new blood vessels (a process called angiogenesis). We hypothesize that nicotine can promote the progression and spreading of cancers and such cancers respond less efficiently to chemotherapy. The first set of experiments proposed here will identify the signaling pathways by which nicotine induces the proliferation of non-small cell lung carcinoma cells. Specifically, the research team will study the role of signaling molecules like Src, Raf-1 kinase, retinoblastoma tumor suppressor gene, and E2F transcription factor in the process. Tissue culture cells will be used as well as animal models for these experiments. Common chemotherapeutic drugs used to treat lung cancer work by killing cancer cells. Such drugs include cisplatin, taxol, gemcitabine, etc. The team's previously published results show that nicotine can render resistance to cultured lung cancer cells from death induced by these drugs. This raises the possibility that individuals exposed to nicotine by smoking or by nicotine supplements may not respond effectively to chemotherapy. Indeed, there are epidemiological studies correlating smoking with poor chemotherapy response. The second set of experiments will assess the molecular mechanisms by which nicotine prevents the lung cancer cells from dying, with special emphasis on two molecules, XIAP and survivin in the process. Experiments will be carried out to assess how these proteins are regulated by nicotine, focusing on the signaling events and transcription factors involved in the process. Experiments will be done on cultured human lung cancer cells as well as mouse models of lung cancer. Solid tumors require blood supply to grow beyond a reasonable size, and tumors have the capacity of promoting the growth of new blood vessels to supply them with oxygen as well as nutrients. This process of new blood vessel formation, or angiogenesis, is a vital step for the growth and progression of tumors. It has been reported that nicotine can induce angiogenesis in cultured endothelial cells as well as in mouse models. The third set of experiments will attempt to understand how nicotine induces angiogenesis. Experiments will be carried out to understand the role of signaling molecules like Src and Raf-1 in the process; the research team will also assess the relative contribution of other molecules like Akt and cell cycle proteins in the process. Preliminary results show that the kinase Src is necessary for nicotine-induced angiogenesis, but Src is not needed for VEGF-induced angiogenesis. An attempt will be made to understand the special role of Src in this context. The team's belief is that these studies are directly relevant to lung cancer biology, and the experiments will lead to the identification of novel signaling pathways by which nicotine and other components of cigarette smoke might promote the growth and progression of cancers. Further, these experiments will also help elucidate whether exposure to nicotine alone, independent of other carcinogens present in tobacco smoke, affects lung cancer. It can be expected that these studies will result in the development of novel strategies to combat lung cancer.