Protein Kinase C Epsilon and Environmental Carcinogenesis

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Abstract

In this pilot application, we propose to elucidate the involvement of PKCe, an oncogenic kinase, in lung carcinogenesis elicited by tobacco smoke. Our previous studies identified PKCe, which is aberrantly up-regulated in lung cancer, as a major player in the maintenance of the tumorigenic phenotype of KRAS mutated lung cancer cell lines and their metastatic dissemination. In a recently published study, we reported that PKCe KO mice were resistant to benzo[a]pyrene (B[a]P)-induced lung tumorigenesis. Moreover, a PKCe-deficient, conditionally activatable allele of oncogenic Kras is less efficient in forming lung tumors, strongly indicating the requirement of PKCe for the initiation of chemically- and oncogene-induced carcinogenesis. The main hypothesis we wish to test is that PKCe plays a role in early transformation events caused by tobacco smoke, a major source of lung carcinogens, and elucidate the mechanisms involved. In Aim 1, we aim to identify PKCe effector genes and pathways driving tobacco smoke-induced responses in lung epithelial cells. Transcriptome and phosphorylation profiles will be derived from HBEC-kt lung epithelial cells subjected to PKCe KO and overexpression and exposed to tobacco smoke using a Vitrocell system. We will pay particular attention to gene expression programs and phosphoproteome landscapes associated with PKCe-related functions, including those related to oxidative response, DNA damage, cell cycle inflammation, immune evasion, EMT and invasiveness. In Aim 2, we will determine the involvement of PKCe in phenotypes induced by carcinogen treatment in lung epithelial cells, particularly oxidative stress, changes in proliferative status, transformation, and the acquisition of invasive/EMT traits. We will also examine whether tobacco carcinogens lead to PKCe up-regulation in lung epithelial cells, a characteristic trait of human KRAS mutant lung cancer cells and tumors. We expect our studies to identify fundamental mechanistic events contributing to PKCe-mediated carcinogenesis and dissect its role in lung cancer initiating events.