CALIFORNIA STATE SCIENCE FAIR
2010 PROJECT SUMMARY

Name(s)
Angela Zhang

Project Number
S0423

Project Title
Identification of a Novel Pathway and Its Therapeutic Targets of Tobacco Promotion of Lung Cancer

Abstract

Objectives/Goals
Lung cancer is the main cause of cancer death in the world, causing ~1.2 million to die annually. 90% of lung cancers are related to tobacco smoking; Furthermore, nicotine contained in tobacco causes the metastatic spread of malignant tumor cells; however, despite the tremendous advancements in our knowledge about lung cancer, the molecular mechanism of nicotine promotion of lung cancer and metastasis remains unclear. The objectives of this experiment are to identify the molecular pathway that nicotine undergoes in lung cancer cells and to find a method of inhibiting the effects of nicotine. The hypothesis is that nicotine in tobacco stimulates pathological lung tumor progression and metastasis through a moesin-RhoA mediated novel signal pathway. Targeting components in the novel signal pathway will allow for novel therapeutic approaches to the treatment of lung cancers.

Methods/Materials
To study nicotine-induced cell invasion in lung cancer cell line H345, a transwell cell migration model was applied. The phosphorylation state of moesin was examined through western blotting and immunocytochemistry using fluorescence microscopy. Silencing of moesin with siRNA was subjected to transwell migration and proliferation assays. Furthermore, Rho-A kinase ROCK inhibitor Y27632 was applied to the H345 cells and subjected to cell invasion assay.

Results
It was found that nicotine induced the inactivation of moesin, a membrane-cytoskeleton linker protein, through dephosphorylation of the protein. This inactivation is mediated by nAChR, since silenced nAChR blocks nicotine-invoked dephosphorylation of moesin. Silencing of moesin caused a spontaneous lung cancer cell invasion which was not able to be further potentiated by nicotine. This indicates that moesin is the primary tumor suppressor that negatively regulates nicotine effects. Furthermore,ROCK and thioredoxin were further identified to be downstream of Moesin in the nicotine signaling pathway. Inhibition of ROCK by Y27632 or silencing of thioredoxin by siRNA aborogated nicotine-induced cell migration.

Conclusions/Discussion
These results strongly indicate that moesin is a direct modulator of nicotine-induced lung cancer cell invasion. Furthermore, the therapeutic modulation of moesin and its signaling pathway might be proved beneficial in the treatment of tobacco related cancers.

Summary Statement
This project discovered a novel signal pathway and therapeutics targets of nicotine promotion of lung cancer progression and metastasis

Help Received
Used lab equipment at Stanford University under the supervision of Dr. Cheng; Participated in the Molecular Imaging Program at Stanford University(MIPS)