CALIFORNIA STATE SCIENCE FAIR
2012 PROJECT SUMMARY

Name(s)
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Project Number
S0510

Project Title
PI3-Kinase and STAT3 in Cancer

Abstract

Objectives/Goals
Two important causes of oncogenic transformation, the phosphoinositide 3-kinase (PI3K) pathway and the STAT3 transcription factor, have until recently been thought to be separate. New studies have suggested a link between PI3K and STAT3, mediated by the protein kinase BMX, part of the TEC kinase family of non-receptor tyrosine kinases. This link between two important signaling proteins may be exploited for cancer therapy.

Methods/Materials
This study first examined ten human cancer cell lines for differential phosphorylation of STAT3 after TEC inhibition. Phosphorylation of STAT3 and other important downstream targets of PI3K was analyzed by Western blot. This study also tested the effects of drug combination treatment on H1047R-transformed 10T1/2 cells through a cell viability assay.

Results
In the cell lines experiment, TEC kinase inhibition by LFM-A13 reduces STAT3 phosphorylation in some cell lines, a result consistent with the hypothesis that BMX bridges the PI3K-STAT3 link. However, cell lines with mutations in KRAS and EGFR show unchanged or even enhanced STAT3 phosphorylation with TEC kinase inhibition, suggesting that these cells bypass PI3K and directly phosphorylate STAT3 through mutated receptor tyrosine kinases. In the drug combinations experiment, the combination of Rapamycin and LFM-A13 showed a synergistic interaction, most likely through inhibition of parallel pathways that converge on a similar oncogenic phenotype.

Conclusions/Discussion
There is evidence for TEC kinase mediation of the PI3K-STAT3 link in human cell lines. This, however, is not universal and is more complicated than suggested by previous experimentation. TEC inhibitors in cancer therapy may be best suited in drug combinations. Further study will determine the full practical application of TEC kinase inhibition in treating PI3K-induced oncogenesis and other cancers.

Summary Statement
The project examined the cell signaling link between PI3-kinase and STAT3 in a variety of cell lines and as a potential target for cancer therapy.

Help Received
Jonathan Hart, PhD. provided instruction in the scientific background and laboratory techniques required for this project. He assisted with experimental design and was available for questions. The project was conducted at the lab of Peter K. Vogt, PhD. at the Scripps Research Institute.