CALIFORNIA STATE SCIENCE FAIR
2015 PROJECT SUMMARY

Name(s)

Vincent Lok

Project Number

35808

Project Title

DNA Damage Induced by a Novel Drug Cocktail Regulates Chemokine Production in Leukemia through Cytosolic DNA Sensing

Abstract

Objectives/Goals

This project seeks to elucidate a second possible mechanism of tumor death by treatment with a novel chemotherapy cocktail (3-AP, DI-82, and VE-822). This drug combination induces DNA permanent damage in tumor cells by targeting cells' nucleotide metabolism pathway (3-AP inhibits ribonucleotide reductase, DI-82 inhibits deoxycytidine kinase) and DNA repair pathway (VE-822 inhibits ATR). In addition to tumor death by apoptosis, this DNA damage can lead to cytosolic DNA leakage and sensing, prompting the secretion of immunostimulatory proteins, causing the infiltration of immune cells into the tumor node and inducing the tumor to undergo an immune-mediated cell death. This project seeks to establish a correlation between this cocktail treatment and chemokine production, suggesting a potential heightened immune response.

Methods/Materials

A cell culture was used as an in vitro model to directly measure chemokine production after treatment. A xenograft of these tumor cells into mice with subsequent treatment accounted for a functioning immune system on the regulation of the chemokines. For the cell culture, precursor B-ALL (Acute Lymphoblastic Leukemia p 185) were grown in media with a drug concentration of 500 nM 3-AP, 100 nM VE-822 for 4 days.

For the xenograft, 200,000 pre B-ALL cells were injected into mice via tail vein. Mice in the cancer group were orally given 50 mg/kg DI-82 daily, 40 mg/kg VE-822 daily, and 7.5 mg/kg 3-AP twice a day. Chemokine levels in blood samples and cell culture supernatent were analyzed using the Multi-Analyte ELISArray (Qiagen) according to the protocol provided with the kit.

Results

12 chemokine levels were examined. In vitro the chemokine levels of RANTES, MIP-1a, MIP-1B, SDF-1, MIG, Eotaxin, and KC increased. The in vivo model showed an increase in MCP-1 and IP-10, and a reduction in MIG, MDC, KC, and 6CKine.

Conclusions/Discussion

There is a direct correlation between chemokine production (RANTES, MIP-1a, MIP-1B, SDF-1, MIG, EOTAXIN, KC) and drug treatment, suggesting a secondary mechanism to this drug cocktail: an immune-mediated tumor death mechanism.

Summary Statement

This project investigates the possible immunostimulatory effect of this novel drug combination on chemokine production in treated ALL cells and treated mice xenografted with ALL cells.

Help Received

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