CALIFORNIA STATE SCIENCE FAIR
2014 PROJECT SUMMARY

Name(s)

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Project Number

S1732

Project Title

Novel Prediction of Anticancer Drug Chemosensitivity in Cancer Cell Lines: Evidence of Moderation by microRNA Expression

Abstract

Objectives/Goals

MicroRNAs are known to regulate gene expressions through mRNA degradation and translation inhibition, and expression levels of certain genes that code for drug-metabolizing enzymes, drug transporters, or drug targets can modulate chemosensitivity or response to anticancer drugs. The objectives of this study are (1) to investigate miRNA expression as a prognostic biomarker of drug chemosensitivity; (2) to understand the mechanism by which miRNA and gene expressions influence chemosensitivity, and (3) to develop an improved prediction model of drug chemosensitivity, specifically for HSP90 inhibitors applied to human cancer cell lines.

Methods/Materials

A novel moderation model integrating the interaction between miRNA and gene expressions was developed to examine if miRNA expression affects the strength of the relationship between gene expression and chemosensitivity. Comprehensive datasets on miRNA expressions, gene expressions, and drug chemosensitivities were obtained from National Cancer Institute's NCI-60 cell lines including nine different cancer types. A workflow including steps of selecting genes, miRNAs, and compounds, correlating gene expression with chemosensitivity, and performing multivariate analysis was utilized to specifically test the proposed model.

Results

The drug chemosensitivity model identified 12 significantly-moderating miRNAs: miR-15b*, miR-16-2*, miR-9, miR-126*, miR-129*, miR-138, miR-519e*, miR-624*, miR-26b, miR-30e*, miR-32, and miR-196a, as well as two genes ERCC2 and SF3B1 which affect chemosensitivities of Tanespimycin and Alvespimycin--both HSP90 inhibitors. A bootstrap resampling of 2,500 times validates the significance of all 12 identified miRNAs.

Conclusions/Discussion

This study is the first analysis of NCI-60 datasets to examine the moderation, as opposed to the direct, effect of miRNA on drug chemosensitivity. The results confirm that miRNA and gene expressions interact to produce an effect on drug response. The lack of correlation between miRNA and gene expression themselves suggests that miRNA transmits its effect through translation inhibition rather than mRNA degradation. The moderation models consistently achieve higher adjusted R^2 than the baseline gene and miRNA models. The results have the potential of using miRNAs not only as prognostic biomarkers for cancer treatment outcome but also as interventional agents to modulate desired chemosensitivity.

Summary Statement

This project developed a novel "moderation" model of drug chemosensitivity and investigated if microRNA expression moderates the relationship between gene expression and drug chemosensitivity, especially for HSP90 inhibitors on cell lines.

Help Received

My teacher supervised the project and my parents helped me on the background research.