CALIFORNIA SCIENCE & ENGINEERING FAIR
2018 PROJECT SUMMARY

Name(s)
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Project Number
38136

Project Title
Targeting eIF4A3 by RNA Interference: A New Strategy for Breast Cancer Therapy

Abstract

Objectives/Goals
The major challenge in triple negative breast cancer (TNBC) therapy is to identify therapeutic targets to improve the efficacy and safety. Genomic instability generates abundant low quality mRNA which is removed by exon junction complex (EJC) to avoid detrimental consequences and promote cancer survival. Eukaryotic initiation factor eIF4A3 is the key mRNA helicase in EJC to control mRNA quality crucial for cancer survival, and could be an effective target for breast cancer therapy. The project objectives are to determine that (1) eIF4A3 is overexpressed in TNBC and correlated with poor patient survival, and (2) inhibiting eIF4A3/EJC activity exhibits outstanding anticancer activity in TNBC.

Methods/Materials
Bioinformatics analysis was performed to determine eIF4A3 levels in breast cancers, followed by western blot, to compare with the levels in normal tissues. Kaplan-Meier analysis was conducted to assess the correlation of eIF4A3 expression and patient survival. RNA interference reagents (shRNA) were used to knock down eIF4A3 expression in TNBC cell lines, followed by cell proliferation assay to determine the impact on cell growth and survival. Colony formation assay was performed to test the effect of inhibiting eIF4A3 activity by dominant negative eIF4A3 on TNBC tumorigenic capacity.

Results
eIF4A3 is significantly overexpressed in breast cancers (>6000 patients), comparing to normal tissues. Overexpression of eIF4A3 is significantly correlated with TNBC patient survival ($p = 0.013$). Knocking down of eIF4A3 expression by RNA interference inhibited TNBC cell growth (100%) and caused cell death. Repressing eIF4A3 activity by dominant negative eIF4A3 inhibited active growth phenotype of TNBC cancer colonies and led to a large reduction (~80%) of TNBC colony formation, indicating a remarkable inhibition of tumorigenic capacity.

Conclusions/Discussion
It was predicted that targeting eIF4A3 will be an effective therapy for breast cancers, especially TNBC. This study shows that eIF4A3 is overexpressed in breast cancers, and is strongly correlated with poor patient survival in TNBC. Inhibiting eIF4A3 activity (by RNA interference or dominant negative mutant) caused cancer cell death and largely reduced TNBC cancer colony formation. My data suggest that targeting eIF4A3 exhibited a strong anticancer activity and could be developed to an effective therapy in TNBC, the current unmet medical need.

Summary Statement
My project discovered that targeting eIF4A3 activity by RNA interference is an efficient and safe strategy for breast cancer therapy

Help Received
The idea and work of this project were completely original. I designed and conducted the study independently in Dr. Jun Ling's laboratory at Geisinger Commonwealth School of Medicine. The primary help I received from Dr. Jun Ling consisted of his supervision and lab facility/supply maintenance.