Evaluating the Effects of Targeted Drug Therapies for 8q24.3 Amplified Breast Cancer

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Background/Objective: Cancer studies have helped us understand recurrent chromosome abnormalities leading to tumor progression. One such recurrent genomic aberration found in breast cancer is chromosome 8q24.3 (Chr. 8q24.3) amplification. We identified Tonsoku Like, DNA Repair Protein (TONSL) located within this amplicon as an immortalizing oncogene, with TONSL-overexpressing cells exhibiting distinctively upregulated homologous recombination (HR). Further experiments have shown that cancer cells with TONSL amplification are sensitive to the FACT inhibitor CBL0137, which is in early phase of clinical development. Based on known functions of TONSL in promoting dsDNA repair, we hypothesized that drug combinations targeting multiple pathways of DNA repair would synergize to kill chromosome 8q24.3 amplified breast cancer cell lines.

Methods: Chr.8q24.3-amplified breast adenocarcinoma cell line TMD436 was utilized in this study. Cells were treated with various drugs targeting DNA repair pathways such as ATR inhibitor (VE-822), PARP inhibitor (Talazoparib), and PI3K inhibitor (BYL719). Cell proliferation rates were measured using bromodeoxyuridine incorporation ELISA.

Results: Thus far, the use of PI3Ki and PARPi combination has had an additive effect - the combined effect of the two drugs is equal to the sum of the effect of each agent given alone. The effect of ATRi and PARPi combination was antagonistic.

Conclusion/Potential Impact: This study establishes the potential feasibility of using DNA repair signaling inhibitors in the treatment of TONSL-overexpressing breast cancer. Future studies extending the range of drug concentrations and newer combinations may ultimately lead to translation of these drugs to in vivo models and clinical trials. By targeting multiple DNA repair pathways, similar approaches may sensitize patients to lower doses of chemotherapeutics, thus decreasing unwanted side effects. Moreover, negative data concerning the ATRi/PARPi combination helps to further refine which drugs may be used to treat Chr. 8q24.3 amplified tumors and to understand signaling pathways active in TONSL-overexpressing breast cancer.

NIH NHLBI-T35 Award

Savannah Phipps (she/her) is a third-year medical student, who is currently undecided about her future specialty, though she is drawn towards the idea of caring for patients of all ages and backgrounds.

"Connecting with my patients on a personal level and being their partner and advocate in healthcare is one of the most important parts of medicine for me, no matter what specialty I decide to pursue. My biggest takeaway from this research experience has been a newfound appreciation for the detail and rigor that goes into basic science research. Without the dedicated individuals who devote their lives to scientific research, we would not be able to provide our patients with the quality of care they deserve."

A Cancer Cell's Toolbox for Conquering Other Organs: Discovering and Combating the Secretome of a Metastasis Capable Cancer Cell

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Background and Hypothesis: Previous studies have recognized that abnormal signaling by RAS oncogenes is predominantly observed in metastatic breast cancer. A hypothesis was developed: the cancer cells with abnormal RAS genes release protein factors into the blood stream which can reorganize the signaling of non-breast tissue in a way that mimics breast tissue therefore making this organ prone to metastasis. These RAS-dependent factors can be targeted therapeutically to decrease metastasis.

Experimental Design: Three cell lines were plated for the experiment: KTB-hTERT immortalized cell line as the control line, KTB-hTERT transformed derivatives TKTB RAS + SV40, which forms metastatic adenocarcinomas in NSG mice, and TKTB PIK3CA + SV40, which forms non-metastatic adenocarcinoma in NSG mice. Three Western Blots were conducted with protein readings for phospho-PAK4, PAK4, phospho-PIK3CD, and PIK3CD. These experiments were done to begin to test the hypothesis that phospho-proteome unique to RAS transformed cells regulate secretome with an effect on distant organs. These cell lines were examined for sensitivity to PIK3CD inhibitor Idelalisib and MEK1/MEK2 inhibitor Trametinib, which mediates signals downstream of RAS that regulate PIK3CD, using BrdU-incorporation ELISA proliferation assay.

Results: Through the western blot analysis, it was consistently shown that there is a significant increase in the production of phospho-PIK3CD and PIK3CD in RAS over PIK3CA which shows that PIK3CD could be a protein that leads to metastasis of RAS transformed cells. Idelalisib did not display activity in any cell lines. Trametinib showed decreased growth of all cell lines and RAS transformed cells were less sensitive to the drugs suggesting hyperactivation of this pathway in RAS-transformed cells

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Conclusion and Impact: This study brings breast cancer research closer to pinpointing which proteins, in this case PIK3CD, can be targeted to decrease metastasis. The development of a drug that is specific to PIK3CD should be pursued to discover a treatment that decreases breast cancer metastasis.

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Sarah Spivak is a third-year medical student, who is currently interested in neurosurgery. She wants to advocate for patients experiencing difficult diagnoses, and is intrigued by how much has yet to be discovered about the human brain.

"Research is a lot of trial and error, but when you get that one promising result after so many fails it feels like you are on top of the world. I love knowing that the work we are doing could lead to a future treatment that could impact so many people. It is extremely rewarding."