Evaluating the effects of RAS and CK2 Inhibitors in ESR1 Mutated Breast Cancer

Camilo Suescum [1], Harikrishna Nakshatri[2]

[1]Indiana University School of Medicine, [2]Indiana University School of Medicine, Department of Surgery

Background and Hypothesis:

Estrogen Receptor alpha (ESR1) is rarely mutated in primary breast cancers but is frequently mutated in metastasis that can appear after many years of anti-estrogen therapy. Mutations to ESR1 can result in estrogen-independent activity of ESR1 causing anti-estrogen to become ineffective. Previous work on this project has led to the hypothesis that RAS pathway activation in metastatic cancer cells as a result of ESR1 mutation leads to elevated CK2 activity which ultimately results in metastatic progression. Therefore, we hypothesize that the use of RAS signaling inhibitors or CK2 inhibitors have efficacy in blocking or reducing the metastatic progression of metastatic breast cancers with hyperactive RAS pathways.

Experimental Design or Project Methods:

The estrogen receptor positive, anti-estrogen sensitive breast cancer cell line MCF-7 and the same cell line genomically modified to replace wild type ESR1 to breast cancer metastasis enriched Y537S or D538G ESR1 mutation were used in this study. Cells were treated with various concentrations of the RAS pathway inhibitor Salirasib or CK2 inhibitor Silmitasertib and cell proliferation rates were measured using bromodeoxyuridine incorporation ELISA.

Results:

Thus far, the use of RAS signaling inhibitors or CK2 inhibitors have not shown efficacy in decreasing the proliferation rates of modified ESR1 MCF-7 cells. While there is a general trend of growth inhibition by these inhibitors at a higher concentration, there is no significant difference between the ESR1 mutant expressing cells and their respective controls.

Conclusion and Potential Impact:

This study will establish the feasibility of using RAS signaling inhibitors or CK2 inhibitors in the treatment of metastatic estrogen receptor-positive breast cancer. Future studies testing the effects of these drugs either alone or in combination with the clinically used anti-estrogen Fulvestrant for not only primary tumor growth but also metastasis in clinically relevant in vivo models may ultimately lead to clinical translation. Finally, demonstrating efficacy in these types of drugs may fuel the further refinement of drugs targeting these pathways to treat metastatic breast cancer.