Title: Mechanisms of Anoikis Resistance in Breast Cancer Cell Lines

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Objectives: In the present study, we aim to characterize the association of Nck1 and eIF2-α; in the process of anoikis resistance, a hallmark of metastatic breast cancer is resistance to a form cell death induced by anchorage-dependent cells detaching from the extracellular matrix.

Background: Breast cancer is the second most common cause of death due to cancer among women and leads to approximately 8,000 to 10,000 deaths per year in the United States. Mortality in breast cancer arises mainly from metastasis, and a hallmark of metastatic tumor cells is the ability to escape from anoikis and invade other organs. Lapatinib is a chemotherapeutic agent recently approved for the treatment of metastatic breast cancer, but outcomes are still not optimal. In this regard, our laboratory recently explored the combination of lapatinib with the chemotherapeutic, OSU-03012, in vitro. This combination therapy killed breast cancer cells in a synergistic fashion with the greatest effect observed on triple negative breast cancer cell line.

Mechanistic studies demonstrated that phosphorylation of eIF2-α; on serine-51 was a required step in the synergistic killing induced by the lapatinib/OSU-03012 combination. Further studies demonstrated that the downregulation of Nck1 is upstream of the phosphorylation of eIF2-α; in cell death induced by these drugs.

Methods: The Nck1/eIF2 complex was evaluated by a combination of molecular approaches to modulate Nck1 and eIF2-α; expression/phosphorylation in breast cancer cells. Cells were then assayed for apoptosis, anoikis resistance, motility and invasiveness in vitro after modulating Nck1 expression and eIF2-α; phosphorylation.

Results: Anoikis resistant breast cancer cell lines demonstrated suppression of ER stress pathways characterized by dysregulated Nck1 expression and eIF2-α; phosphorylation. Our data suggest that the Nck regulated phosphorylation of eIF2-α; impacts breast cancer metastasis.

Conclusion: In conclusion, these studies suggest that disruption of Nck1/eIF2 complex reduces aggressiveness of breast cancer cells in pre-clinical models.