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"Notch Dependency in Triple Negative Breast Cancer Mitochondrial Metabolism"

Introduction: Triple Negative Breast Cancer (TNBC) makes up 15 – 20% of breast cancers. It has the worst prognosis amongst the breast cancer carcinomas. TNBC lacks expression of human epidermal growth factor receptor 2 (HER2) and the endocrine receptors for estrogen and progesterone. Because it is negative for all three therapeutic targets, TNBC is difficult to treat. Chemotherapy is the standard for treatment of TNBC, however, about 80% of TNBC patients do not completely respond to chemotherapy. Resistance to therapy and the recurrence of breast cancer is thought to be caused by breast cancer stem cells. Notch signaling (canonical) is an identified contributor to breast cancer and cancer stem cell maintenance. Recent studies also highlight the importance of non-canonical Notch signaling. Previously, we reported that Notch signaling regulates mitochondrial metabolism in TNBC and is present on the mitochondrial membrane. *However, the role of non-canonical Notch signaling in TNBC metabolism is unknown.*

Objectives: This study aims to determine the role of non-canonical Notch signaling in TNBC mitochondrial metabolism.

Methods: We analyzed the metabolic profile of MDA-MB-231 human TNBC cells and mammospheres using Seahorse Analyzer. Mammospheres were generated using Mammocult medium (STEMCELL Technologies) as per manufacturer protocol. The oxygen consumption rate (OCR) and extracellular acidification rate (ECAR) were assessed for Notch1 over-expressed cells (N1IC) and mammospheres versus the vectors (controls). Afterward, sulindac sulfide, (10μM) a non-steroidal anti-inflammatory drug was used as a Notch inhibitor.

Results: N1IC 231 cells and mammospheres had a greater basal and reserve capacity (difference between the basal and maximal OCR) than the vector cells respectively. Both OCR and ECAR were significantly elevated for the N1ICs. A greater reserve capacity suggests that N1IC 231 cells and mammospheres are more metabolically active than the vectors. Even after administering sulindac sulfide to inhibit Notch, the N1ICs still had a significantly elevated OCR and ECAR.

Conclusion: The results suggest that the mitochondrial metabolic activity is Notch dependent. In the future, we will run proteomics on the samples to determine the associated mitochondrial proteins that are also influenced by non-canonical Notch signaling. This will help point us towards the direction of possible therapeutic targets for TNBC treatment.