Title: MerTK Drives Proliferation and Metastatic Potential in Triple-Negative Breast Cancer

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Scientific Abstract:

Triple-negative breast cancer (TNBC) is characterized by the absence of the estrogen receptor, progesterone receptor, and receptor tyrosine kinase HER2 expression. Due to the limited number of FDA-approved targeted therapies for TNBC, there is an ongoing need to understand the molecular underpinnings of TNBC for the development of novel combinatorial treatment strategies. This study evaluated the role of the MerTK receptor tyrosine kinase on proliferation and invasion/metastatic potential in TNBC. Immunohistochemical analysis demonstrated MerTK expression in 58% of patientderived TNBC xenografts. The stable overexpression of MerTK in human TNBC cell lines induced an increase in proliferation rates, robust in vivo tumor growth, heightened migration/invasion potential, and enhanced lung metastases. NanoString nCounter analysis of MerTK-overexpressing SUM102 cells (SUM102-MerTK) revealed upregulation of several signaling pathways, which ultimately drive cell cycle progression, reduce apoptosis, and enhance cell survival. Proteomic profiling indicated increased endoglin (ENG) production in SUM102-MerTK clones, suggesting that MerTK creates a conducive environment for increased proliferative and metastatic activity via elevated ENG expression. To determine ENG's role in increasing proliferation and/or metastatic potential, we knocked out ENG in a SUM102-MerTK clone with CRISPR technology. Although this ENG knockout clone exhibited similar in vivo growth to the parental SUM102-MerTK clone, lung metastasis numbers were significantly decreased ~4-fold, indicating that MerTK enhances invasion and metastasis through ENG. Our data suggest that MerTK regulates a unique proliferative signature in TNBC, promoting robust tumor growth and increased metastatic potential through ENG upregulation. Targeting MerTK and ENG simultaneously may provide a novel therapeutic approach for TNBC patients.

Written Lay Abstract:

One kind of breast cancer is triple-negative breast cancer (TNBC). In TNBC, the cancer cells lack three hormone receptors – they do not have estrogen receptors, progesterone receptors, or the receptor for HER2, which helps breast cells grow and stay healthy. There are not many therapies to specifically treat TNBC.

The researchers in this study looked at how TNBC cancer works so we can better treat it. They studied how the protein MerTK works in TNBC and may be a target for future cancer therapy. MerTK is a protein found on the surface of cells that helps remove old, damaged, or unhealthy cells.

For this study, the researchers used breast cancer cells that were grown from patients' cancer cells. The scientists studied these cells *in vitro* (outside of a body), and *in vivo* (inside the body, in mice in this study) to see how MerTK worked in cancer cells both inside and outside of the body.

The researchers found that most human TNBC cells had increased MerTK, and this increased the spread, growth, and size of cancer in mice. Increased MerTK also increased cell-to-cell communications that were not good for the cell or body, such as for higher levels of cell growth and less removal of unhealthy cells. The researchers also found that MerTK may be increasing spread and growth of cancer by increasing the amount of another protein called ENG.

This research tells us that, in triple-negative breast cancer, MerTK increases the growth and spread of cancer by increasing ENG. Next steps for this work are to target MerTK and ENG in new therapies for breast cancer.

Visual Lay Abstract:

Carbone Cancer Center
UNIVERSITY OF WISCONSIN
SCHOOL OF MEDICINE AND PUBLIC HEALTH

Finding New Treatments for Breast Cancer

Triple-Negative Breast Cancer (TNBC)

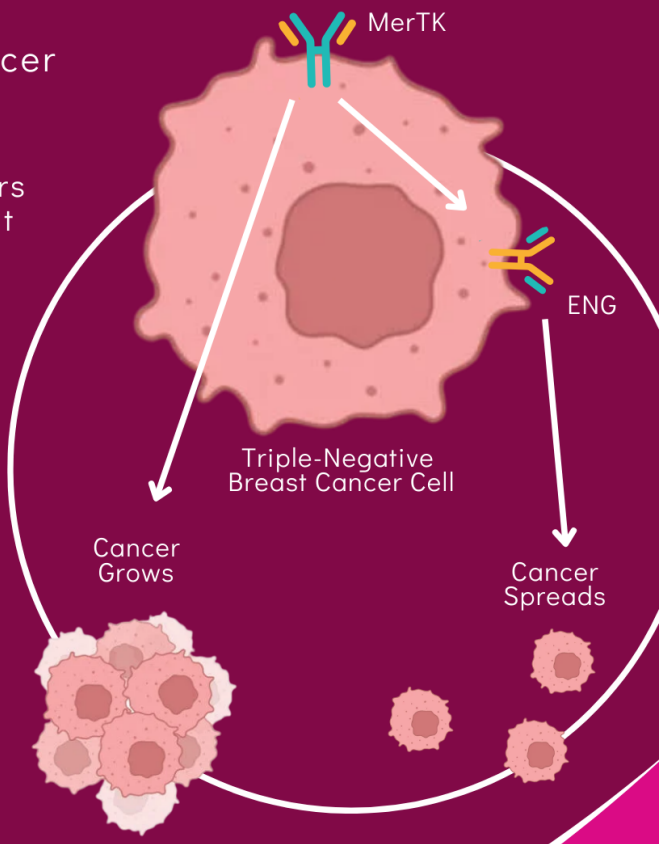
- Breast cancer cells that lack 3 different hormone receptors
- Not many therapies can treat this type of cancer

MerTK

- Protein on surface of cells
- Helps remove old, damaged, or unhealthy cells

Finding New Treatments

- Scientists studied cancer cells and mice to see how MerTK impacts TNBC
- Found that TNBC cells have more MerTK
- Mice with more MerTK have more cancer tumors
- MerTK may be increasing cancer by affecting another protein called ENG
- Future research could target MerTK or ENG to treat TNBC



Research Article

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