# Targeting GLUT3 as an anti-metastasis regimen in Triple-Negative Breast Cancer

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Glucose is a preferred nutrient for most cells, including cancer cells. The tumor microenvironment is both hypoxic and hypoglycemic. Glucose levels in tumors are ten times lower than in normal tissues due to poor vascularization and high glucose consumption by cancer cells, which adapt to hypoglycemic condition.

Obesity, often accompanied by hyperglycemia, hyperinsulinemia, and hypertriglyceridemia, is linked to increased breast cancer metastasis. High extracellular glucose levels have been shown to promote cancer cell motility, though the mechanisms remain unclear. Given cancer cells' reliance on aerobic glycolysis (the Warburg effect), we hypothesized that hyperglycemia in obesity promotes cancer metastasis by modulating glucose metabolism and related cell mechanics pathways.

Using Triple-Negative Breast Cancer (TNBC) cells, we reported that elevated extracellular glucose levels increase glycolysis and activates the RhoA GTPase signaling pathway. These metabolic and mechanical alterations resulted in greater cell stiffness and contractility, which were correlated with increased cell invasion. Our unpublished data, which I will present, validate these findings in obese-TNBC mouse models and further elucidate the glycolysis-mediated activation of the RhoA-ROCK axis. Our results show increased lung metastasis of breast cancer cells under hyperglycemic conditions in vivo. By inhibiting glucose uptake using GLUT3-selective inhibitor, we discovered that the glycolysis-AMPK axis regulates RhoA-ROCK activity. GLUT3 inhibition activated AMPK, reduced F-actin levels via the AMPK-VASP axis, and decreased non-muscle myosin activity through the AMPK-RhoA axis. These changes in cell mechanics correlated with reduced cell motility.

Our study suggests that targeting glucose metabolism and cell mechanics could be a novel approach to inhibit cancer metastasis, particularly in obese patients.

Keywords: Breast cancer metastasis, Glucose, Cell mechanics