

Targeting metabolic symbiosis in the brain-metastatic breast cancer tumor microenvironment

In 2020, approximately 170,000 women were projected to be living with metastatic breast cancer in the United States. Although metastatic breast cancer can often be managed as a chronic disease using systemic therapies, the onset of brain metastases (BMs) is considered an end-stage event, with median survival after diagnosis measured in months. As increasing numbers of breast cancer patients survive the typical latency for BMs of 2-3 years, the incidence is increasing. Moreover, with current therapy options for BMs typically restricted to surgery or radiation, both the disease itself and its treatment can have severe impacts on patient quality of life. Thus, there is a pressing need to develop new therapeutic approaches for patients with brain-metastatic breast cancer.

Tumor growth depends on cancer cells acquiring nutrients from their environment and processing them through metabolic pathways that support cellular proliferation. Metastatic breast cancer cells that cross the blood-brain barrier encounter a unique and challenging nutrient environment, where many important metabolic fuels are maintained at much lower levels than in other tissues. In ongoing research, I have found that brain-metastatic breast cancer cells upregulate a highly efficient metabolic pathway for harnessing energy from available nutrients. Importantly, this pathway can be targeted with drugs that are already approved for other indications, and I have discovered that brain-metastatic breast cancer cells are extremely sensitive to this approach.

Recent studies have shown that metastatic breast cancer cells interact closely with other cell types in the brain, and even form synapses that activate signaling pathways to promote tumor growth. In preliminary experiments, I have found that normal brain cells can also provide metabolic support to metastatic breast cancer cells, fueling their growth in the restricted nutrient environment of the brain. Here, I propose to develop therapeutic approaches that effectively starve breast cancer BMs by cutting off these fuel supplies. By simultaneously targeting critical metabolic pathways in the cancer cells and blocking their ability to acquire key nutrients from their environment, I aim to achieve a synergistic effect against BMs while minimizing adverse side effects. The overall goal of this proposal is to develop new treatment options for breast cancer patients with BMs, focusing on promising preclinical compounds that are known to cross the blood-brain barrier, and on drugs that are already approved for other indications.