Lay Abstract

Spread of tumor throughout the body is the cause for the majority of death from cancer. Although earlier diagnosis and improved treatments of breast cancer during the last two decades have led to significant decline of its mortality, the rate of breast cancer metastasis occurrence has increased significantly in recent years. The overall survival in breast to brain metastatic (BBM) patients is very short ranging from 2 to 25 months. Considering the high incidence of brain metastases and the limitation of available therapies, developing preventive strategies and early detection methods can improve the survival rate in the patients.

Several key zones of restriction have evolved for protection in the brain: the blood-brain barrier (BBB) and the blood-cerebrospinal fluid barrier (BCSFB) The current prevailing view which has dominated research focus is metastatic cancer cells enter the brain by crossing the BBB. However, other than the popular BBB, the central nervous system has another crucial barrier which cells can utilize to cross over and enter: blood-CSF barrier (BCSFB), which up to now has received very little focus.

Choroid Plexus (CP) are small lining cells along the border of the brain's ventricles which are the gateway and supervisor of the relationship between the brain and the rest of the body through the BCSFB. CP cells produce cerebral spinal fluid (CSF), which bathes the brain parenchyma and provides nourishment (analogous to water through rice fields). The CP cells have various functions: 1) fluid-filled brain ventricles/canals are a critical source of communication between brain cells, 2) eliminates waste products from brain tissues. Unlike the tightly connected BBB, the BCSFB is "leaky" -- thus it makes for a less formidable, more permeable barrier for tumor cells and certain chemotherapies to cross.

Many breast cancer patients treated with chemotherapy complain of impaired memory and several basic cognitive dysfunctions before brain metastases diagnosis. Several studies have confirmed the detrimental effects of chemotherapy on cognitive performance, known as "chemo brain" or "chemo fog". Recent evidence show chemotherapy promotes breast cancer metastasis. Brain metastases are associated with progressive neurological deficits and neurodegeneration. Tau is known as a critical protein associated with neurodegeneration like Alzheimer's Disease.

Here, we show tau expression is highly elevated in primary breast cancer cells treated with chemo and in breast to brain metastases (BBMs). Besides, chemotherapy increases BCSFB permeability. Thus, it is critical to determine whether chemotherapy facilitates crossing of the tumor cells and metastasis to the brain by affecting the permeability of the two main brain barriers: blood-cerebral spinal fluid barrier and blood-brain barrier. We hypothesize that chemotherapy induces tau expression in primary breast cancer cells leading to BCSFB permeability and breast to brain metastasis. To test our hypothesis, we will investigate the effect of different chemotherapeutic agents on tau expression in primary breast cancer lines. Using different complementary approaches, we will define how chemotherapy affects the permeability of BCSFB and how that facilitates breast cancer metastasis to the brain. Next, we will determine tau is solely the cause of neurodegeneration in breast to brain metastatic patients. Given the significance of tau as a biomarker in neurodegenerative diseases and the possibility of neurodegeneration being mediated by BBM-derived tau in brain metastases, our research can open a new path towards using tau as a novel biomarker for early detection and prevention of further brain metastases.