

LAY REPORT

Brain metastasis is a common complication in patients with advanced breast cancer; however, brain-metastatic breast cancers do not respond well to current treatments, and fewer than 20% of patients with symptomatic brain metastases survive for longer than 1 year. Consequently, there is an urgent need to identify therapeutically targetable factors that promote breast cancer brain metastasis and develop drugs to inhibit them. In our previously work, we have found that when metastatic breast cancer cells colonize the brain, they increase the secretion of a factor named CCL2. CCL2 attracts immune cells called tumor-associated CCR2⁺ myeloid cells into the brain. Mice with breast tumors in which CCL2 gene was reduced (i.e., CCL2-knockdown) lived longer and had fewer CCR2⁺ myeloid cells in the brain than did mice with high CCL2 breast tumors because CCL2-knockdown tumor cells in the brain metastatic lesions grew more slowly and even died. Following these findings, we further investigated “Impeding Breast Cancer Brain Metastasis by Blocking CCR2⁺ Myeloid Cell Infiltration” with the support of the 2019 METAVivor award.

The primary goal of this project is to develop effective therapeutic options for breast cancer patients with brain metastasis by blocking CCR2⁺ myeloid cell brain infiltration and investigate the roles of the CCL2-CCR2 signaling axis in immune dysregulation of brain metastasis. In the last two years, we have successfully finished our proposed two Specific Aims with unexpected findings. We found that overexpression of CCL2 promotes brain metastasis in a patient derived xenograft (PDX) model, indicating the crucial role of CCL2 in enabling brain metastasis outgrowth. We also found that CCL2-blocking antibody can delay brain metastasis outgrowth, which might be developed as a new therapeutic for breast cancer patients with brain metastasis since CCL2-blocking antibodies are clinically applicable (have been tested in clinical trials for treating other cancers). Unexpectedly, although CCR2 antagonist PF-04136309 can pass blood-brain-barrier and partially inhibited CCR2⁺ myeloid cell infiltration into the brain metastasis lesions, CCR2 antagonist PF-04136309 single treatment and in combination with anti-PD1 antibody didn't significantly impede breast cancer brain metastasis outgrowth, neither did depleting the CCR2 gene. Our data showed different effects of CCL2-blocking versus CCR2-targeting therapies in breast cancer brain metastasis, and the reasons could be 1) CCL2 secretion by tumor cells might recruit CCR2 negative (-) immune cells having CCR1 or CCR4 receptor expression, and these CCR2- immune cells might induce immunosuppressive brain microenvironment. 2) CCR2⁺ immune cells are heterogeneous and can also include dendritic cells, natural killer cells and T cells, which can elicit anti-metastatic functions and might counter the effect of blocking immunosuppressive CCR2⁺ myeloid cells.

In summary, our proposed studies yielded new insights into the role of cytokine CCL2 and CCR2 myeloid cells in breast cancer brain metastasis, and we found targeting CCL2 or in combination with immune checkpoint inhibitors might be more efficient for treating breast cancer patients with brain metastasis, but CCR2 antagonist does not benefit breast cancer patients.