A potential combination therapy for brain metastases of breast cancer

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A Ludwig Cancer Research study has identified and preclinically validated combination treatments for the brain metastases of breast cancer, a common and typically lethal manifestation of the malignancy. The combination therapy, reported in the current issue of *Nature Cancer*, targets tumor-associated macrophages and microglia (TAMs), immune cells found within brain metastases that cancer cells can manipulate to support their growth and survival.

Led by Ludwig Lausanne’s Johanna Joyce and Florian Klemm, along with Lisa Sevenich of Georg-Speyer-Haus Institute for Tumor Biology and Experimental Therapy, in Frankfurt, the study also describes how a TAM-targeted therapy—which inhibits a signaling protein named CSF1R—is initially effective yet ultimately fosters an adaptive resistance mechanism in the immune cells. That mechanism, which engages an alternative signaling pathway in TAMs centered on a secreted protein factor named CSF2 and a protein that helps transmit its signals, STAT5, revives tumor growth by promoting the expression of genes involved in inflammation and wound repair. The researchers show that blocking this signaling pathway in concert with CSF1R inhibition significantly extends survival in mouse models of breast-to-brain metastases.

"There is an urgent, unmet need for effective treatments for brain metastases," said Joyce, Member of the Ludwig Institute for Cancer Research, Lausanne. "Current therapies can ease some of the side effects of these tumors, but they do not appreciably extend the lives of patients. Our study identifies a rationally-devised combination therapy that engages an anti-cancer immune response and simultaneously undermines a resistance mechanism that, we have now shown, can develop in response to the initial therapy, CSF1R inhibition."

The Joyce lab has previously explored the targeting of TAMs associated with primary brain tumors—specifically, gliomas—using inhibitors of CSF1R, whose activity is essential to the cells. These studies have shown that CSF1R inhibition significantly prolongs survival in preclinical mouse models of these tumors. Notably, Joyce’s team found that the treatment did not result in the death of TAMs in these mouse models, but rather in their "re-education" into agents of anti-tumor immunity. The same CSF1R inhibitor (BLZ945) that the Joyce lab used in their preclinical studies is currently being evaluated in an early-phase clinical study in patients with a range of solid tumors, including glioblastomas.

Joyce, Klemm, Sevenich and colleagues wanted to examine whether the CSF1R inhibitor would have a similar effect on TAMs in breast cancer-brain metastases, and to get key insights from preclinical studies as to how the treatment might play out over the long term in patients.

They report in the *Nature Cancer* publication that treatment with the CSF1R inhibitor, BLZ945, initially reduced the establishment of breast cancer-brain...
metastases, stalled their growth for several weeks and induced some regressions of established brain tumors in mouse models. However, CSF1R inhibition resulted in the killing of all but a subset of TAMs, not their reeducation into an effective anti-tumor immune corps, as happened in gliomas. Over the long term, the treatment also triggered adaptive changes in TAMs that drive inflammation and resulted in damage to neural tissue around the brain metastases.

Subsequent analysis revealed that TAMs had compensated for the blockade of CSF1R signaling by engaging an alternative signaling axis switched on by the related CSF2 receptor (CSF2R) and mediated by STAT5 within the cells. The researchers found that combining BLZ945 with an inhibitor of STAT5 signaling (or an anti-CSF2 antibody) durably stalled the growth of breast cancer-brain metastases in the mouse model. STAT5 inhibition also stopped the inflammation and reversed the nerve damage associated with CSF1R inhibition in these metastatic tumors. It additionally reprogrammed the TAMs into an anti-tumor state.

"Our results reveal the potential risk of unleashing pro-inflammatory responses in brain metastases following CSF1R inhibition and suggest a compelling strategy to overcome this adaptive resistance mechanism," said Joyce. "These findings have important translational implications for efforts to modify the immune microenvironment of brain tumors for therapy, showing how important it is to have a detailed understanding of the unique landscape of each tumor type in devising these rational combination treatment strategies."
