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MICROGLIA RECRUIT AND ACTIVATE NATURAL KILLER CELLS TO CONTROL TUMOR PROGRESSION IN BREAST CANCER BRAIN METASTASIS

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Background Metastatic brain tumors are incurable, rapidly fatal, and five times more common than primary glial or meningeal tumors of the central nervous system (CNS). Up to 30% of metastatic breast cancer patients will develop brain metastasis as a complication of their disease. This represents a significant clinical problem for the 1 in 8 women who will receive a diagnosis of invasive breast cancer during her lifetime. Natural Killer (NK) cells are cytotoxic lymphocytes with strong *in vivo* anti-tumor activity, a native ability to cross the BBB, and a demonstrated role in regulation of metastasis in peripheral organs. NK cells perform critical roles in antitumor immunosurveillance via the expression of germline-encoded activation and inhibition receptors on the cell membrane. These receptors recognize ligands on both normal and transformed cells, and ultimately determine whether an NK cell will be stimulated to kill a neoplastic cell or inhibited from killing a healthy cell. Notably, NK cells are under investigation in clinical trials as both drug targets and adoptive cell therapies.

Methods We have performed single-cell RNA sequencing (scRNA-seq) in conjunction with a fluorescent cytokine screen to determine the cytokine secretion profile of microglia under tumor-bearing conditions. We have also carried out NK cell-depletion experiments using intraperitoneal injections of i.p. injections of anti-Asialo GM1 IgG to determine the functional significance of NK cells in the response to breast cancer brain metastasis.

Results Our scRNA-seq data and cytokine screen suggest that NK cell activation and recruitment to the brain in BCBM depends on the secretory action of microglia. Furthermore, we observe a complete lack of NK cell infiltration in microglia-knockout mice harboring breast cancer brain metastasis. We confirm with selective antibody-mediated NK cell depletion that NK cells are critical for preventing the outgrowth of disseminated tumor cells in the brain. However, we also observe NK cell dysfunction within the microenvironment of brain metastasis—a clear obstacle to the development of NK cell-based therapies for intracranial metastatic lesions.

Conclusions Microglia appear to play a necessary role in the recruitment of NK cells to the brain under metastatic conditions. An improved understanding of the native functional status of NK cells in the context of brain metastasis, including their interactions with microglia, will inform the development of neuroprotective anti-metastatic therapies aimed at modulating and potentiating the anti-tumor action of both native and adoptive NK cells.

Ethics Approval All experiments were approved by IACUC at the University of California, Irvine

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