INSIGHTS INTO THE REGULATION OF BRAIN METASTASIS BY NATURAL KILLER CELLS

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Background Brain metastasis represents a common and rapidly fatal progression of many distinct types of primary cancer. Current treatment options for brain metastasis are limited to chemotherapy and radiation therapy since no existing immunotherapies have demonstrated efficacy for this condition. Natural killer (NK) cell therapies have significant potential to address this unmet clinical need. NK cells have a well-defined anti-metastatic function in peripheral organs, infiltrate the brain under conditions of inflammation, and are under active investigation as both drug targets and adoptive cell therapies.

Methods Using both immunocompetent C57BL/6J and immunocompromised Rag1-/- mouse models, we are working to more fully characterize the regulation and response to brain metastasis by NK cells. Ultrasound-guided intracardiac injection of labeled tumor cell lines has allowed us to recapitulate key aspects of the metastatic cascade including intravasation and extravasation, while antibody-mediated NK cell depletion has provided us with additional insight into the importance of NK cells in anti-metastatic neuro-immunity. Flow cytometry, immunofluorescence microscopy, bioluminescence imaging (BLI), and single-cell RNA sequencing (scRNA-seq) facilitate the examination of immune cell infiltrates and micro/macrometastasis in the brains and peripheral organs of tumor-challenged mice.

Results NK cells robustly infiltrate the brains of wildtype mice with metastatic brain tumors. In immunocompetent C57BL/6J mice, systemic NK cell depletion leads to more severe metastasis in the peripheral tissues but not in the brain. In Rag1-/- mice lacking B and T cells, NK cell depletion leads to more severe metastasis in both peripheral tissues and in the brain. Current follow-up studies are examining the interactions between NK cells and regulatory populations of T and B cells (Tregs, Bregs) using in vitro co-culture assays and in vivo tumor challenge cohort studies.

Conclusions NK cells play a critical role in regulating metastasis in peripheral organs of both humans and wildtype mice. However, NK cell anti-metastatic immunity in the brain remains an understudied problem and appears to be tightly regulated. Our data demonstrates that NK cell anti-metastatic immunity in the brain may depend on the presence or absence of other immune cell populations. Further study of this problem will identify potential drug targets or modulatable pathways which may increase the anti-metastatic efficacy of NK cells in the brain.

Ethics Approval All experiments performed in this study have been approved by the Institutional Animal Care and Use Committee (IACUC) at the University of California, Irvine

http://dx.doi.org/10.1136/jitc-2023-SITC2023.0420