REGULATORY T CELLS AS KEY MODULATORS OF BREAST CANCER BRAIN METASTASIS

1Isam Adam*, 1Aaron J Longworth, 2Devon A Lawson. 1University of California, Irvine, Irvine, CA, USA; 2University of California, Irvine School of Medicine, Irvine, CA, USA

Background Breast cancer brain metastasis (BCBM) is a disease with a dismal prognosis. Current therapeutics fail to control BCBM development, partially due to the presence of the blood-brain barrier and the distinct immune environment within the brain. Thus, there is a critical need to understand the function of infiltrating immune cells within BCBMs. A key population implicated in the pathogenesis of tumors are regulatory T cells (Tregs). Tregs directly inhibit effector cells and promote a suppressive tumor microenvironment by modulating the function of other players in the immune response, such as antigen presenting cells. However, the specific mechanisms by which Tregs exert these modifying functions in the brain remain unknown.

Methods To elucidate the role of Tregs in the development of BCBM, we intracranially injected E0771 cells into C57BL/6J mice and monitored tumor development and immune cell infiltration for 14 days. Using the Foxp3-DTR mouse model, we selectively depleted Tregs and assessed the effects of Treg depletion on tumor burden, immune cell infiltration, and resident microglia phenotype.

Results We found that Tregs prominently infiltrated BCBM tumors seven days after tumor introduction. Furthermore, the systemic depletion of Tregs using Foxp3-DTR mice led to a near-complete loss of tumor burden, showing that Tregs are key regulators of tumor progression in the brain. This can likely be attributed to the observation of a massive accumulation of CD8+ and CD4+ T cells in the absence of Tregs. Additionally, we demonstrated that microglia, a unique population of brain-resident macrophages, displayed a more prominent antigen-presentation phenotype in Treg-depleted mice bearing BCBM tumors.

Conclusions With this data, our current working hypothesis is that BCBM-infiltrating Tregs suppress the infiltration and activation of CD8+ and CD4+ T cells by inhibiting the antigen presentation capacities of microglia. The mechanisms by which Tregs are influencing microglial function, however, are still unclear and warrant further investigation. Therapeutic targeting of Treg-mediated modulation of microglia could be a promising novel therapeutic for the treatment of brain metastases.

Acknowledgements Timothy McMullen, Paige Halas, Sharmila Mallick (Lawson Lab)
  Pascal Naef, Dennis Ma, Kai Kessenbrock (Kessenbrock Lab)
  Shannon Geels, Francesco Marangoni (Marangoni Lab)
  Pauline Nguyen, Vanessa Scarfone (UCI SCRC Cytometry Core)
  UCI Sue & Bill Gross Stem Cell Research Center
  Chao Family Comprehensive Cancer Center
  National Cancer Institute
  UCI Medical Scientist Training Program

REFERENCES