Development of a new, immunocompetent brain metastatic model of HER2-positive breast cancer

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ABSTRACT

Brain metastasis is a frequent and devastating complication in over 50% of patients with HER2-positive breast cancer. The lack of effective and durable therapeutic options for brain metastasis continues to be a harbinger of accelerated morbidity and mortality in HER2$^+$ breast cancer patients. Therefore, a better understanding of the underlying mechanisms that drive brain metastasis is critically important for successfully targeting brain metastasis. Since genetically engineered mouse models (GEMMs) of HER2-positive breast cancer do not metastasize to the brain, tractable immunocompetent models for studying brain metastatic progression are currently lacking. Here, we report the generation of a fully immunocompetent, experimental model of brain metastasis of HER2-positive breast cancer. To develop this model, we injected the murine HER2/neu-expressing mammary tumor cell line via intracardiac injection in syngeneic FVB/N mice and panned brain metastatic derivatives in mice via the process of in vivo selection. By repeating this process five times, we selected for highly brain-tropic derivatives denoted as neu-BrM5 that generate brain metastasis in 100% of mice upon intracardiac injection. Using this new, immunocompetent model of brain metastasis, we show that there is increased infiltration of macrophages, neutrophils and CD4$^+$ T cells in the mice with brain metastasis compared to healthy control mice. We envision that this immunocompetent brain metastatic model will be a unique resource to investigate the role of innate and adaptive immune interactions between the cancer cells and infiltrating immune cells in brain metastatic progression.

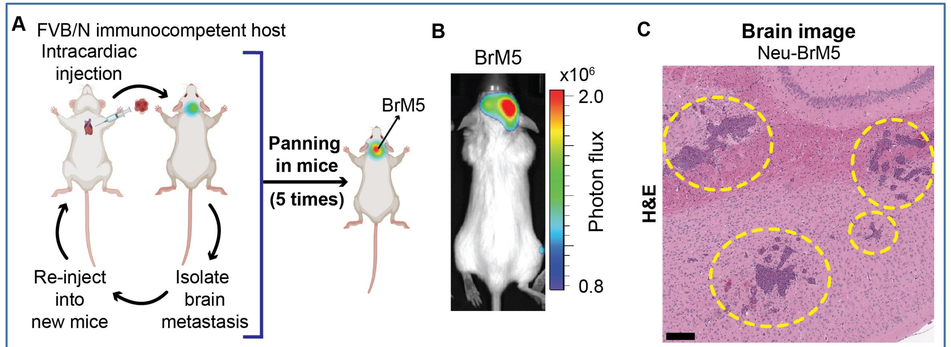

Fig 1. Generation of the immunocompetent brain metastatic model of HER2-positive breast cancer

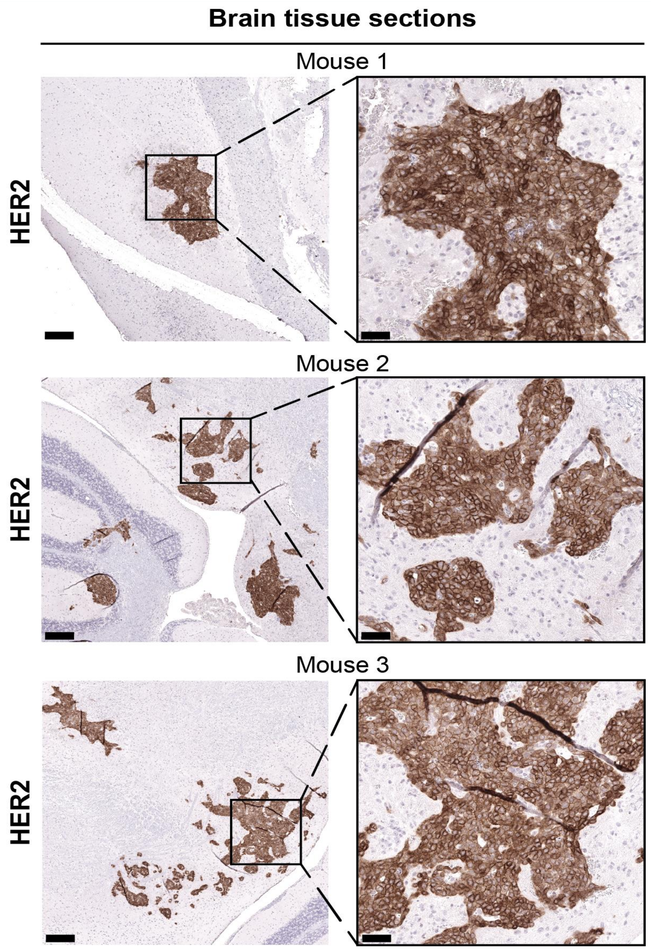

Fig 2. Representative images of neu (mouse HER2) IHC on brain sections from mice injected with neu-BrM5 tumor cells

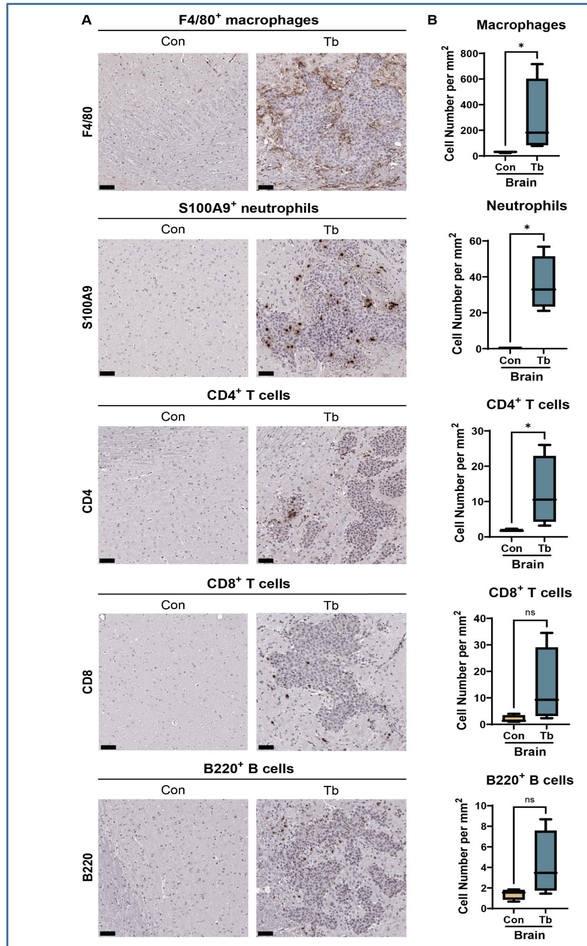

Fig 3. Increased immune cell infiltration in the brains of tumor-bearing mice compared to control mice

CONCLUSION

We generated a novel immunocompetent murine model for HER2-positive brain metastasis, characterized by high penetrance, brain-tropism and robust recapitulation of human disease biology. The neu-BrM5 cells demonstrated consistent brain metastasis formation in all tested animals, as confirmed through bioluminescence imaging and histological analysis. HER2 expression was well-maintained in metastatic sites. Furthermore, we observed significant immune cell infiltration in brain metastases, including F4/80$^+$ macrophages, S100A9$^+$ neutrophils, and CD4$^+$ T cells. CD8$^+$ T cells and B220$^+$ B cells also exhibited a trend of increased presence. The model can provide valuable insights into immune interactions in the brain TME and accelerate new immune-based therapies against brain metastasis.