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Dissecting brain metastasis response to immunotherapy in new immunocompetent mouse models

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As the therapeutic responses of extracranial tumors continue to improve, brain metastasis (BrM) is increasingly a leading cause of cancer patient mortality. Recent trials of immune checkpoint blockade (ICB) achieved similar response rates to extracranial disease for melanoma patients with asymptomatic BrM. However, the benefit for symptomatic disease is not clear and the mechanisms of resistance remain unknown. The challenge of sample collection from BrM patients limits the identification of key molecular drivers and predictive biomarkers, highlighting the importance of preclinical models. Here we characterize a set of brain metastatic models, developed by intracardiac injection of UV-induced mouse melanoma cell lines, which exhibit diverse histopathology and metastatic potential. Notably, M4-BR1 and M4-BR3 responded differently to ICB mono- and combination therapies at the brain but similarly when implanted subcutaneously in mice. M4-BR1 was highly sensitive to ICB whereas M4-BR3 was resistant at the brain but surprisingly responded at other organs (e.g., liver and bone), mimicking the diversity observed in patients**.** Single-cell RNA sequencing and high-parametric spectral flow cytometry of untreated M4-BR1 and M4-BR3 metastases revealed marked differences between the models. More than 50% of microglia from M4-BR1 bearing brains presented a distinct phenotype that was associated with increased infiltration of dendritic cells, natural-killer, and a high diversity of T cell subsets, including CD8+, effector T cells. In contrast, M4-BR3 metastases were enriched in neutrophils that are involved in ICB resistance of extracranial melanomas. Mutational and transcriptomic profiling of the brain metastatic melanoma cells uncovered pathways recently identified in human data sets. Our unique mouse cell lines provide a powerful tool for the mechanistic study of BrM progression and immunotherapy response, addressing a critical deficiency in the field.