ABSTRACT CITATION ID: NOAE064.088

DMG-35. OVERCOMING THE BLOOD-BRAIN BARRIER CHALLENGE IN DIFFUSE MIDLINE GLIOMA
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Diffuse midline gliomas (DMGs) are aggressive paediatric brainstem tumours with no known cure. The development of effective treatments is greatly impeded by the failure of most anti-tumour agents to penetrate the blood-brain barrier (BBB). Our research, along with that of others, has revealed that the BBB remains intact in DMG. We employed DMG orthotopic models to explore potential region-specific variations in response to the therapeutic agent temsirolimus as well as confocal microscopy and single-cell RNA sequencing (scRNAseq) to elucidate the impact of DMGs on brain endothelial morphology and pathways governing BBB integrity. We first assessed the effectiveness of the mTOR inhibitor temsirolimus when administered in cortex-injected DMG models compared to brainstem-injected DMG. We found significantly increased survival rates, elevated temsirolimus levels, and reduced tumour cell proliferation in the cortex versus the brainstem. Confocal imaging analysis indicated no structural differences between DMG and Matrigel-injected animals. However, scRNAseq unveiled distinct transcriptomic changes: brainstem-injected DMG exhibited downregulation of genes related to inflammatory and apoptotic pathways, whereas cortex-injected DMG showed downregulation of interferon pathways. To overcome the tightened barrier in the brainstem, we explored three MCL1 inhibitors and SNGR-TNFα (targeting CD13) as potential blood-brain barrier modulators. These inhibitors significantly reduced transendothelial electrical resistance, increased tracer dye leakage in an in vitro DMG BBB model, and decreased the protein expression of claudin-5. Moreover, in vivo, we found that administration of a single dose of either SNGR-TNFα or the MCL1 inhibitor S63845 improved penetration of Texas-Red (3KDa) in DMG-engrafted animals, indicating the effective opening of the BBB. In summary, our study revealed that DMG directly affects BBB pathways in endothelial cells, tightening the barrier and reducing treatment efficacy. MCL1 inhibitors and SNGR-TNFα show promise in modulating the BBB and have the potential to enhance therapeutic activity.