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Title: Patient-derived Glioblastoma Stem Cell Secretome Modulates Blood-Brain Barrier Permeability via RAGE-Dependent Signaling Pathway

The blood-brain barrier (BBB) is a highly selective barrier that tightly regulates the passage of potentially harmful substances and cells to the brain to maintain brain homeostasis. It is composed of specialized endothelial cells (ECs) that line the capillaries within the brain, along with surrounding cells, such as pericytes and astrocytes.

In glioblastoma (GBM), the most prevalent primary malignant brain tumour in adults, the BBB is heterogeneously dysfunctional. Within the tumour microenvironment, glioblastoma stem cells (GSCs)-enriched regions are protected by intact BBB. So far, the impact of GSCs on BBB features has been poorly explored.

Here, we investigated the impact of the secretomes of patient-derived GSCs (PD GSCs) on human brain capillaries ECs in vitro. We found that PD GSCs secretomes could restrict BBB permeability leading to 2.5-fold increase of the transendothelial electrical resistance. Additionally, secretomes increase by 2-fold the levels of tight junction protein claudin-5 (CLDN5) and of the receptor of advanced glycation end-products (RAGE) levels, a multi-ligand pattern recognition receptor implicated in cancers and resistance to chemotherapy. RAGE overexpression in brain ECs resulted in increased expression and junctional organisation of tight junction proteins and reduced permeability. Finally, we show that RAGE modulates CLDN5 expression via activation of a pERK/ERK signaling pathway.

These findings highlight a functional pathway by which PD GSCs secretomes can restrict BBB permeability, which could have implications for therapeutic outcomes.