**Pharmacological Targeting of SREBP-Dependent Lipid Metabolism to Treat Glioblastoma**

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Glioblastoma (GBM) is an incurable and deadly brain tumour, primarily owing to GBM stem cells (GSCs), which are the primary drivers of tumour propagation and therapeutic resistance. However, the pathways and processes in GSCs that are specifically sensitive to dysregulation have not been identified, which prevents the development of treatments that specifically target GSCs. Here, we show that GSCs are especially vulnerable to disruptions in lipid metabolism and that inhibiting SREBP1 signalling is a promising approach to treating GBM. To identify the metabolic pathways that are particularly active in GSCs, we screened previously published datasets of patient-derived GSCs. We found that *ABCA3* maintains lipid metabolic homeostasis in GSCs, and that knockdown of *ABCA3* induces phospholipid catabolism in GSCs but not non-GSCs. Upstream analysis revealed that such disturbance in lipid homeostasis decreases the activity of SREBP1, a transcription factor involved in lipid biosynthesis, limiting the viability and tumour-initiating capability of GSCs. By screening chemical compound libraries and optimizing the initial hits, we developed MFC0101-7043, a novel blood‒brain barrier-permeable small-molecule inhibitor that selectively blocks the interaction between SREBP1 and SCAP. In a mouse model, MFC0101-7043 suppressed the growth of intracranially grafted GBM and synergized with temozolomide, suggesting that MFC0101-7043 is a promising treatment for GBM.