From Surfaceome Discovery to Therapeutic Opportunities: Proteomic Targets in Patient-Derived Glioblastoma Stem-Like Cells

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Glioblastoma (GBM) is the most common and aggressive primary brain tumor in adults, with limited treatment options and systematically fatal outcomes, highlighting the urgent need to find new therapeutic approaches. Cell surface proteins (CSP) represent attractive therapeutic targets because of their accessibility and their involvement in key physio-pathological processes.

To identify novel target CSP candidates in GBM, untargeted cell surface proteomic analysis was performed on patient-derived glioblastoma stem-like cell (GSC) cultures. Proteomic data were integrated with RNA-seq and publicly available databases to prioritize therapeutically relevant targets. This workflow identified five CSPs of interest: PTK7, PTPRZ1, OSMR, CSPG4, and IGDCC4. To further investigate these candidates, a targeted UHPLC-multiple reaction monitoring (MRM) assay was developed and optimized to assess their expression and relative abundance across different GSC models and cell passage levels, providing insights into their intra- and inter-cell cultures variability. These results were then further supported by qPCR analysis across cell passage and target localization confirmation by flow cytometry and western blot analyses.

Overall, these observations support PTK7, PTPRZ1, OSMR, CSPG4, and IGDCC4 as promising therapeutic targets in GBM. Furthermore, this study illustrates the strength of combining multi-omics and translational approaches as well as the interest of clinically relevant three-dimensional patient-derived GSC models in drug target discovery.

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