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Malignant gliomas can be converted to non-proliferating glial cells by treatment with a combination of small molecules.

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Gliomas, the most highly malignant central nervous system tumors, are associated with an extremely poor patient survival rate. Given that gliomas are derived from mutations in glial precursor cells, a considerable number of them strongly react with glial precursor cell-specific markers. Thus, we investigated whether malignant gliomas can be converted to glial cells through the regulation of endogenous gene expression implicated in glial precursor cells. In the present study, we used three small-molecule compounds, [cyclic adenosine monophosphate (cAMP) enhancer, a mammalian target of rapamycin (mTOR) inhibitor, and a bromodomain and extra-terminal motif (BET) inhibitor] for glial reprogramming. Small-molecule-induced gliomas (SMiGs) were not only transformed into exhibiting a glial-specific morphology, but also showed positive reactions with glial-specific markers such as glial fibrillary acidic protein (GFAP), 2',3'-cyclic nucleotide 3'-phosphohydrolase (CNP) and anti-oligodendrocyte (RIP). A microarray analysis indicated that SMiGs exhibited a marked increase in specific gene levels, whereas that of a malignant cancer-specific gene was greatly decreased. Moreover, proliferation of the cells was markedly suppressed after the conversion of malignant glioma cells into glial cells. Our findings confirmed that malignant gliomas can be reprogrammed to non-proliferating glial cells, using a combination of small molecules, and their proliferation can be regulated by their differentiation. We suggest that our small-molecule combination (with forskolin, rapamycin and I-BET151) may be the next generation of anticancer agents that act by reprogramming malignant gliomas to differentiate into glial cells.

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