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# Enhanced expression of proapoptotic and autophagic proteins involved in the cell death of glioblastoma induced by synthetic glycans

## Laboratory investigation

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*Object*. Glioblastoma is the most aggressive malignant brain tumor, and overall patient survival has not been prolonged even by conventional therapies. Previously, the authors found that chemically synthesized glycans could be anticancer agents against growth of a series of cancer cells. In this study, the authors examined the effects of glycans on the growth of glioblastoma cells both in vitro and in vivo.

*Methods*. The authors investigated not only the occurrence of changes in the cell signaling molecules and expression levels of various proteins related to cell death, but also a mouse model involving the injection of glioblastoma cells following the administration of synthetic glycans.

*Results*. Synthetic glycans inhibited the growth of glioblastoma cells, induced the apoptosis of the cells with cleaved poly (adenosine diphosphate-ribose) polymerase (PARP) expression and DNA fragmentation, and also caused autophagy, as shown by the detection of autophagosome proteins and monodansylcadaverine staining. Furthermore, tumor growth in the in vivo mouse model was significantly inhibited. A dramatic induction of programmed cell death was found in glioblastoma cells after treatment with synthetic glycans.

*Conclusions*. These results suggest that synthetic glycans could be a promising novel anticancer agent for performing chemotherapy against glioblastoma.
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**Key Words** • **synthetic glycan** • **glioblastoma** • **apoptosis** • **autophagy** • **oncology**

Glioblastoma is the most aggressive and lethal malignancy of the CNS, and patients with glioblastoma have an average life expectancy of 1 year after the standard treatment of surgery followed by radiation therapy.[26,45] Recently, clinical studies have shown that chemotherapy in addition to radiation therapy could increase patient survival up to 2 years.[45] The continuing problems caused by glioblastoma and the failure of conventional therapy for this advanced invasive brain tumor indicate that novel strategies and anticancer drugs are critically needed to improve the prognosis.

Glioblastoma cells are naturally resistant to cell death,[16,26] which has been considered to be attributable to the activation of phosphatidylinositol 3-kinase (PI3K) by growth factors and the subsequent hyperactivation of its downstream targets, the serine/threonine kinases protein kinase B (Akt) and mammalian target of rapamycin (mTOR). These targets are known to release a variety of

*Abbreviations used in this paper:* Akt = protein kinase B; AMPA = α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; CPI = cell proliferation inhibition; HP-β-CD = hydroxypropyl-β-cyclodextrin; GalβChol = D-galactose β cholestanol; GChol = GlcNAcβChol; GGChol = GlcNAcβ1,3 GalβChol; GlcNAcβ1,3 = *N*-acetyl-D-glucosamine β1,3; GluR1 = glutamate receptor 1; GluR4 = glutamate receptor 4; HO342 = Hoechst 33342; MDC = monodansylcadaverine; mTOR = mammalian target of rapamycin; PARP = poly (adenosine diphosphate-ribose) polymerase; PI3K = phosphatidylinositol 3-kinase; Z-VAD-FMK = benzyloxycarbonyl-Val-Ala-Asp(OMe)-fluoromethylketone.

This article contains some figures that are displayed in color online but in black-and-white in the print edition.