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Notch signaling contributes to the maintenance of both normal neural stem cells and patient-derived glioma stem cells

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Background: Cancer stem cells (CSCs) play an important role in the development and recurrence of malignant tumors including glioma. Notch signaling, an evolutionarily conserved pathway mediating direct cell-cell interaction, has been shown to regulate neural stem cells (NSCs) and glioma stem cells (GSCs) in normal neurogenesis and pathological carcinogenesis, respectively. However, how Notch signaling regulates the proliferation and differentiation of GSCs has not been well elucidated.

Methods: We isolated and cultivate human GSCs from glioma patient specimens. Then on parallel comparison with NSCs, we inhibited Notch signaling using g-secretase inhibitors (GSI) and assessed the potential functions of Notch signaling in human GSCs.

Results: Similar to the GSI-treated NSCs, the number of the primary and secondary tumor spheres from GSI-treated GSCs decreased significantly, suggesting that the proliferation and self-renewal ability of GSI-treated GSCs were attenuated. GSI-treated GSCs showed increased differentiation into mature neural cell types in differentiation medium, similar to GSI-treated NSCs. Next, we found that GSI-treated tumor spheres were composed of more intermediate progenitors instead of CSCs, compared with the controls. Interestingly, although inhibition of Notch signaling decreased the ratio of proliferating NSCs in long term culture, we found that the ratio of G2+M phase-GSCs were almost undisturbed on GSI treatment within 72 h.

Conclusions: These data indicate that like NSCs, Notch signaling maintains the patient-derived GSCs by promoting their self-renewal and inhibiting their differentiation, and support that Notch signal inhibitor GSI might be a prosperous candidate of the treatment targeting CSCs for gliomas, however, with GSI-resistance at the early stage of GSCs cell cycle.