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Developing precision therapies for glioblastoma by targeting glioblastoma stem cells

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The dismal prognosis of glioblastoma is, at least in part, attributable to the difficulty in eradicating glioblastoma stem cells (GSCs). However, whether this difficulty is caused by the differential responses of GSCs to drugs remains to be determined. To address this, we isolated and characterized ten GSC lines from established cell lines, xenografts, or patient specimens. Six lines formed spheres in a regular culture condition, whereas the remaining four lines grew as monolayer. These adherent lines formed spheres only in plates coated with poly-2-hydroxyethyl methacrylate. The self-renewal capabilities of GSCs varied, with the cell density needed for sphere formation ranging from 4 to 23.8 cells/well. Moreover, a single non-adherent GSC either remained quiescent or divided into two cells in four-seven days. The stem cell identity of GSCs was further verified bythe expression ofnestin or glial fibrillary acidic protein. Of the two GSC lines that were injected in immunodeficient mice, only one line formed a tumor in two months. The protein levels of NOTCH1 and platelet derived growth factor receptor alpha positively correlated with the responsiveness of GSCs to γ-secretase inhibitor IX orimatinib, two compounds that inhibit these two proteins, respectively. Furthermore, a combination of temozolomide and a connexin 43 inhibitor robustly inhibited the growth of GSCs. Collectively, our results demonstrate that patient-derived GSCs exhibit different growth rates in culture, possess differential capabilities to form a tumor, and have varied responses to targeted therapies. Our findings underscore the importance of patient-derived GSCs in glioblastoma research and therapeutic development for precision medicine.

Biography:

Dr. Sheng obtained his PhD at the State University of New York Downstate Medical Center in 2005. He conducted his postdoc research focusing on delineating cancer cell survival pathways in leukemia and glioblastoma in Dr. Michael Green's laboratory at the University of Massachusetts Medical School. He is currently an assistant professor at the Virginia Tech Carilion Research Institute. His research team has recently identified several new survival pathways in glioblastoma and they are investigating how to translate their findings into precision therapies for glioblastoma.