The Brain Microenvironment Preferentially Enhances the Radioresistance of CD133 Glioblastoma Stem-like Cells.

Jamal M, Rath BH, Tsang PS, Camphausen K, Tofilon PJ.

Radiation Oncology Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA.

Abstract

Brain tumor xenografts initiated from glioblastoma (GBM) CD133(+) tumor stem-like cells (TSCs) are composed of TSC and non-TSC subpopulations, simulating the phenotypic heterogeneity of GBMs in situ. Given that the discrepancies between the radiosensitivity of GBM cells in vitro and the treatment response of patients suggest a role for the microenvironment in GBM radioresistance, we compared the response of TSCs and non-TSCs irradiated under in vitro and orthotopic conditions. As a measure of radioresponse determined at the individual cell level, γH2AX and 53BP1 foci were quantified in CD133(+) cells and their differentiated (CD133(-)) progeny. Under in vitro conditions, no difference was detected between CD133(+) and CD133(-) cells in foci induction or dispersal after irradiation. However, irradiation of orthotopic xenografts initiated from TSCs resulted in the induction of fewer γH2AX and 53BP1 foci in CD133(+) cells compared to their CD133(-) counterparts within the same tumor. Xenograft irradiation resulted in a tumor growth delay of approximately 7 days with a corresponding increase in the percentage of CD133(+) cells at 7 days after radiation, which persisted to the onset of neurologic symptoms. These results suggest that, although the radioresponse of TSCs and non-TSCs does not differ under in vitro growth conditions, CD133(+) cells are relatively radioresistant under intracerebral growth conditions. Whereas these findings are consistent with the suspected role for TSCs as a determinant of GBM radioresistance, these data also illustrate the dependence of the cellular radioresistance on the brain microenvironment.