Heterozygous deletions of p53 and PTEN cooperate with DNA damage induced by Fe ions to trigger high grade gliomas in mouse models

P.K. Todorova[1], C.V. Camacho[1], C.R. Gil del Alcazar[1], R.M. Bachoo[2], and S. Burma[1]

Departments of [1]Radiation Oncology, and [2]Neurology, University of Texas Southwestern Medical Center, Dallas, Texas, USA

Glioblastoma multiforme (GBM) are therapy-resistant, highly lethal brain tumors, arising from astrocytes, oligodendrocytes, or neural stem cells. Extensive mapping of the GBM genome by The Cancer Genome Atlas Network (TCGA) has identified alterations in three core signaling pathways: RTK-PI3K-Akt, ARF-MDM2-p53, and Ink4a-RB. The only known risk factor for the development of these tumors is exposure to ionizing radiation (IR). We are examining how IR-induced DNA damage, especially HZE-induced damage, might cooperate with mutations in these signaling pathways to trigger gliomagenesis. Towards this end, we are using two cohorts of transgenic mice with brain-specific deletions of Ink4a, Ink4b, Arf, p53, or PTEN in combinations representing progressive stages of gliomagenesis. The first cohort is deficient in the Ink4a, Ink4b, and Arf genes. In these animals, IR-induced DNA damage results in a high-incidence (up to 25%) of malignant gliomas that closely mimic human GBMs (see accompanying abstract by Camacho et al). The second cohort harbors deletions in p53 and PTEN in incremental combinations. In this cohort, we find that loss of one allele of p53 and one allele of PTEN ($p53^{+/-}$;$PTEN^{+/-}$), in combination with Fe ion-induced DNA double-strand breaks, is sufficient to induce high grade glial tumors. Mock-irradiated animals do not form tumors spontaneously, while Fe-irradiated mice develop gliomas with a frequency of at least 25% and an average latency of 7 months. In contrast, tumor frequency is lower (10%) even with higher doses of X-rays indicating a higher transforming potential for Fe ions (studies are still ongoing). Comparative analyses reveal considerable similarity between HZE-induced tumors and those arising spontaneously in mice deficient in both copies of p53 ($p53^{-/-}$;$PTEN^{+/-}$). Both groups develop highly heterogeneous tumors, expressing astrocytic, neuronal, and stem cell lineage markers. Interestingly, immunohistochemical and quantitative PCR data indicate loss of heterozygosity of PTEN in both sets of tumors. Ongoing genomic analyses of IR-induced and spontaneous tumors may reveal mutational patterns that are unique to HZE-triggered GBMs. In sum, mice with single deletions of p53 and PTEN represent a sensitive model system to evaluate the tumorigenic potential of HZE particles.

.