DELETIONS OF INK4, ARF, P53, OR PTEN COOPERATE WITH HZE PARTICLE-INDUCED DNA DOUBLE-STRAND BREAKS TO TRIGGER HIGH GRADE GLIOMAS IN MOUSE MODELS

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Glioblastomas (GBM) are terminal brain cancers characterized by cellular heterogeneity, invasiveness, and poor response to therapy. Extensive sequencing of patient tumor samples has identified concomitant alterations in the RTK-PI3K-AKT, ARF-MDM2-p53, and INK4-RB signaling pathways. Exposure to ionizing radiation (IR), even low dose exposure from CT scans, is a known risk factor for the development of GBM. During space missions astronauts are inevitably exposed to HZE particles, part of the galactic cosmic radiation (GCR). Thus, it is crucial to understand the risk of developing lethal brain cancer from HZE particle exposure, before any long term manned missions can be executed. Our goal is to examine how cooperation between IR-induced DNA damage and alterations in the above mentioned pathways leads to gliomagenesis. Transgenic mouse models with brain-specific deletions of Ink4a, Ink4b, Arf, p53, or Pten in relevant combinations were irradiated with high LET Fe ions or low LET X-rays. We identified two cohorts of mice that do not form spontaneous gliomas but develop high grade malignancies following irradiation. The first model carries heterozygous deletions of the p53 and Pten genes (p53⁺⁻;Pten⁺⁻). The second cohort is deficient in the Ink4a, Ink4b, and Arf genes (Ink4ab/Arf⁻⁻). Following intra-cranial irradiation with 600 MeV/nu Fe ions both models developed GBMs with a frequency of at least 25%. Four-fold higher dose of X-rays was necessary to achieve a comparable tumor frequency, suggesting a relative biological effectiveness (RBE) of 4 for transformation by Fe ions. Genomic analyses of IR-induced mouse tumors revealed additional alterations of GBM-relevant tumor suppressor pathways, very similar to those seen in humans. In the p53⁺⁻;Pten⁺⁻ model, loss of heterozygosity (LOH) of Pten, with concomitant activation of PI3K-Akt signaling was common. Simultaneously with tumor suppressor loss, up-regulation of the Pdgfr-α and Met receptor tyrosine kinases (RTK) signaling pathways was observed. Met amplification was also the predominant oncogenic alteration in the majority of IR-induced tumors in the Ink4ab/Arf⁻⁻ cohort. Met amplification in these tumors was critical for tumorigenesis and important for maintaining a GBM cancer stem cell phenotype. Preliminary studies with the latter model demonstrate gliomagenesis following exposure to silicon, carbon, and, to a lesser extent, protons. Our results are indicative of increased GBM risk following exposure to GCR elements and identify key genetic alterations that may be central to the development of IR-induced gliomas.