Irradiation of primary human gliomas triggers dynamic and aggressive survival responses involving microvesicle signaling.

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Abstract
Malignant gliomas are heterogeneous populations of dynamically interacting cells. Genomic and transcriptional changes define this cellular hierarchy and allow certain tumor cells to co-opt metabolic machinery and adopt gene expression profiles that promote cellular reprogramming. Resultant expansion of privileged subpopulations can then rapidly adapt to microenvironmental stress that ultimately influence tumor response to therapeutic intervention. In this study, primary gliomas were subjected to acute or chronic irradiation and analyzed for changes in survival parameters, oxidative stress, gene expression, and cell invasion before and after treatment with secreted microvesicles isolated from irradiated and nonirradiated glioma cells. We found that primary gliomas exposed to ionizing radiation undergo metabolic changes that increase oxidative stress, alter gene expression, and affect the contents of and response to cellular secreted microvesicles. Radiation-induced changes were exacerbated under chronic as compared to acute irradiation paradigms and promoted cellular reprogramming through enhanced expression of key transcription factors and regulators involved in differentiation and pluripotency (SOX2, POU3F2, SALL2, OLIG2, NANOG, POU5F1v1, MSI1). Irradiation also affected changes in paracrine signaling mediated by cellular secreted microvesicles that significantly altered target cell phenotype. Primary gliomas treated with microvesicles exhibited increased radioresistance and treatment with microvesicles from chronically irradiated gliomas promoted invasion via induction of increased matrix metalloproteinase II activity. Together, our data describe a complex radiation response of primary glioma cells involving metabolic and transcriptional changes that alter radiation sensitivity and induce invasive behavior. These important changes can contribute to tumor growth and recurrence, and confound interventions designed to forestall disease progression. Environ. Mol. Mutagen., 2015. © 2015 Wiley Periodicals, Inc.

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