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DICER Governs Characteristics of Glioma Stem Cells and the Resulting Tumors in Xenograft Mouse Models of GBM

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The RNAse III endonuclease DICER is a key regulator of microRNA (miRNA) biogenesis and is frequently down-regulated in a variety of malignancies. We characterized the role of Dicer in glioblastoma (GB), specifically demonstrating its effects on the ability of glioma stem-like cells to form tumors in a mouse model of GB. DICER silencing in glioma stem-like cells (GSCs) reduced their stem cell characteristics, while tumors arising from these cells were more aggressive, larger in volume, and displayed a higher proliferation index and lineage differentiation. The resulting tumors, however, were more sensitive to radiation treatment. Our results demonstrate that DICER affects the tumorigenic potential of GSCs, providing a platform for analysis of specific relevant miRNAs and development of potentially novel therapies against GB.

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Bone Marrow-Derived Mesenchymal Stem Cells-Mediated Radioresistance in Glioma

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Ionizing radiation (IR) is one of the conventional post-surgical treatments for Glioblastoma Multiforme (GBM). Mesenchymal stem cells (MSCs) constitute a subpopulation of bone marrow derived cells which are actively recruited to the site of radiation and/or tumour microenvironment (TME), both of which have important implications for neovascularization and tumor progression. The goal of this project is to investigate the functional contribution of MSCs in the TME. We postulate that Bone Marrow-MSCs promote radio-resistance in GBM via cell cycle arrest. We tested the effect of MSC on U87 glioblastoma cell line in response to IR. We found that MSC co-culture, MSC-conditioned media (MSCCM) and irradiated MSC-conditioned media (MSCIRCM) did not reduce IR-induced p53 (ser15) phosphorylation, signifying intact p53-dependent DNA damage pathway in all conditions. However, both MSCCM and MSCIRCM temporally increased phospho-Chk2, a kinase involved in ATM-dependent cascade and cell cycle arrest. This increase occurred at 24 hours and reverted to baseline levels by 48 hours. Interestingly, IR (15Gy) caused transiently heightened metabolic rate under MSC and MSC IRCM as opposed to IR-null treatment at 48 hours elevated cell proliferation. MSCCM, but not MSCIRCM, marginally reduced caspase 3/7-dependent apoptotic levels. The combination of IR and MSCCM as well as MSCIRCM first increased protein level of phospho-Chk2 at 24 hours; followed by increased metabolic rate at 48 hours; and lastly, boosted proliferation at 72 hours. This data combined proposes plausible machinery for BM-MSC mediated radio-resistance by initiating cell cycle arrest in tumour cells for DNA damage repair.

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Bone Marrow-Derived Mesenchymal Stem Cells Reverse Ionizing Radiation-Induced Active State of Endothelial Cells in Glioblastoma

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As the central component of heightened vascularization in glioblastoma (GBM), endothelial cells (EC) are arguably the most responsive stromal cells in the tumour microenvironment during conventional treatment using ionizing radiation (IR). Although the inherent tumor tropism and angiogenic property of mesenchymal stem cells (MSC) has been documented in many cancer types including GBM, little is known about the function of MSC that are recruited to the GBM tumor microenvironment. The purpose of this study was to elucidate the effect of MSC on irradiated EC. Here we studied the influence of IR, MSC or MSC condition media (CM) on human umbilical vein endothelial cells (HUVECs). IR was found to up-regulate mRNA levels of CXCL5, CXCL10, ICAM1, VCAM1, VEGF-c and tissue factor (TF) in a dose-dependent manner whereas MSC co-culture boosted the expression of ICAM1, VCAM1, VEGF-c, TF, and MCP3. An additive effect of IR and MSC-culture was most detected with respect to ICAM1, TF and CXCL5 under 2Gy. MSC co-culture decreased IR-induced phospho-p53 in HUVECs at 15Gy. In addition, IR decreased the level of phospho-Akt in HUVECs as well as cell proliferation. Notably, both effects were countered by MSC CM. Interestingly, up-regulation of the same set of IR-driven genes in GBM was positively correlated with poor survival in the TCGA GBM database, a correlation that was lost if using gene list that was obtained from IR and MSC combine. These findings suggest that MSC promotes angiogenesis in GBM by overturning the IR-induced active state of endothelial cells and rendering them radio-resistant.

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RXFP1 Promotes Temozolomide Chemoresistance by STAT3 Signaling Pathway Activation

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We identified the G protein coupled relaxin receptor RXFP1 in glioblastoma (GB) and discovered C1q-tumor necrosis factor related protein 8 (CTRP8) as a novel ligand of RXFP1 in this common and most aggressive form of brain tumor. The known RXFP1 ligand relaxin isoform 2 (RLN2) is not expressed in the