Title

ATIM-02. SUCCESSFUL CANCER-SELECTIVE GENE DELIVERY FOLLOWING INTRAVENOUS TOCA 511 DELIVERY IN PATIENTS WITH RECURRENT HIGH GRADE GLIOMA (HGG)

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miRs involved in this process, we identified miRs that were consistently up-regulated in HUVEC 6 hours after 20 Gy exposure to ionizing irradiation or hydrogen peroxide treatment. miR-103 emerged as the top candidate. Importantly, irradiation of a brain tumor xenograft resulted in rapid upregulation of miR-103 in the tumor vasculature but not in the tumor cells. Transfection of endothelial cells (EC) with miR-103 mimics increased accumulation of DNA strand breaks and apoptosis in ECs. Moreover, inhibition of radiation induced miR-103 expression suppressed EC apoptosis in vitro and in vivo, suggesting that induction miR-103 expression is a key mediator of the cytotoxic effects of radiation on EC. Using substractive expression and RISC-trap assay, we identified and confirmed that the radiation sensitizing effects of miR-103 on EC is mediated through 1) suppression of key DNA repair genes (TREX1 and FANCF) as well as 2) increased release of anti-angiogenic cytokines, including IP10. Local and systemic delivery of miR-103 in vivousing a patient derived, orthotopic glioblastoma xenograft model caused DNA damage accumulation in ECs, increased anti-angiogenic cytokine release form ECs, and suppressed glioblastoma growth. CONCLUSION: Our findings reveal miR-103 play critical roles in modulation endothelial DNA repair through regulation of EC DNA repair capacity and cytokine release. Disruption of the crosstalk between vasculature and tumor cells that can be exploited as a glioblastoma therapeutic strategy.

ANGI-10. GENETIC DOWN REGULATION OF CXCR4 IN GLIOMA CELLS REDUCES INVASION, REDUCES TUMOR PROGRESSION, AND INCREASES SENSITIVITY TO RADIATION

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Glioblastoma multiforme (GBM) is a lethal brain tumor. Radiation therapy has been an essential part of treatment for glioma patients. Despite high radiation therapy along with anticancer drugs, GBMs invariably recur. Glioma Stem Cells (GSCs) resistant to chemo and radiation therapies are mainly responsible for GBM recurrence. Therefore, increase sensitivity of GBM cells to radiation and/chemo therapies could be of therapeutic value. We have recently described that GBM derived glioma stem cells grow along blood vessels (Baker et al, 2014). In this study we observed that different primary human glioma stem cell lines, HF2303, MSP-12, IN859 and IN2045, and a mouse glioma Gl26-cit cell line, showed significant directional migration towards human and mouse brain-derived endothelial (MBVE) cells. To uncover the mechanism of GBM cell migration, we tested the role of various chemokines and inhibitors utilizing in vitromigration assays. Notably, migration of Gl26-cit and HF2303 towards MBVE was significantly inhibited by AMD3100 (CXCR4 inhibitor). We further confirmed these findings by knocking down of CXCR4 in GL26-cit cells using shRNA. The migration of CXCR4 knock-down in GL26-cit-shCXCR4 cells towards MBVE was significantly reduced compared to control shRNA treated Gl26-cit cells (Gl26-cit-NT). We next established an orthotopic brain tumor in mice using GL26-cit-shCXCR4 and Gl26-cit-NT cells. Mice implanted with down regulated CXCR4 GL26-cit-shCXCR4 cells exhibited prolonged survival compared to Gl26-cit-NT mice. Brain section analysis showed that GL26-cit-shCXCR4 cells are less invasive. Lastly, we tested the effect of radiation on mice implanted with GL26-cit-shCXCR4 or Gl26-cit-NTcells. Mice implanted with GL26-cit-shCXCR4 cells showed further improvement in survival compared to Gl26-cit-NT tumor-bearing mice upon radiation. In summary, CXCR4-CXCL12 signaling is critical for the perivascular invasion of GBM cells and targeting this axis makes tumors less invasive and more sensitive to radiation therapy. Targeting CXCR4-CXCL12 signaling could be a potential therapeutic strategy for treatment of GBM.

ANGI-11. BONE MARROW-DERIVED MESENCHYMAL STEM CELLS-MEDIATED RADIORESISTANCE IN GLIOBLASTOMA ANGIOGENESIS

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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 tumor microenvironment (TME) during conventional treatment using ionizing radiation (IR) and have important implication in cancer progression as well as therapy-resistance. Although the inherent tumor tropism and angiogenic property of mesenchymal stem cells (MSC) has been documented in GBM, little is known about the function of MSC that are recruited to the GBM Tumor microenvironment. To elucidate the effect of MSC on irradiated EC, we studied the influence of IR, MSC or MSC condition media (CM) on human umbilical vein endothelial cells (HUVECs). IR decreased HUVEC cell proliferation at 24 and 48 hours whilst MSCCM increased cell proliferation at 48 hours. MSCCM doubled the viable number of non-irradiated HUVECs at 48 hours. IR caused phosphorylation of p53 in HUVECs regardless of MSC presence. While 2Gy of radiation was able to transiently increase p-ATM level at 4 hours post IR, MSCCM prolonged this process up to 8 hours. IR preferentially increased p-Akt levels (but not p-ERK1/2) at 8 hours post IR while MSCCM advanced this event to 4 hours and amplified it by two folds when given 15Gy. IR was found to up-regulate mRNA levels of CXCL5, CXCL10, ICAM1, VCAM1 and tissue factor in a dose-dependent manner whereas MSC co-culture boosted the expression of above angiogenic factors. 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 strong correlation that was absent if using gene list that was obtained from IR and MSC combine treatment in HUVEC. These findings suggest that MSC promotes angiogenesis in GBM by facilitating the IR-induced active state as well as the effectiveness of DNA damage repair in endothelial cells.

ADULT CLINICAL TRIALS (IMMUNOLOGICAL)

ATIM-02. SUCCESSFUL CANCER-SELECTIVE GENE DELIVERY FOLLOWING INTRAVENOUS TOCA 511 DELIVERY IN PATIENTS WITH RECURRENT HIGH GRADE GLIOMA (HGG)

Timothy Cloughesy[1], Tobias Walbert[2], Daniela Bota[3], Michael Vogelbaum[4], Linda Liau[5], Derek Ostertag[6], Douglas Jolly[6], Harry Gruber[6], Liqiang Yang[6], Jolene Shorr[6] and Steven Kalkanis[7]; [1]University of California, Los Angeles, Los Angeles, CA, USA, [2]Henry Ford Health System, Detroit, MI, USA, [3]UC Irvine Medical Center, Orange, CA, USA, [4]Cleveland Clinic Burkhardt Brain Tumor and Neuro-Oncology Center, Cleveland, OH, USA, [5]UCLA Neurosurgery, Los Angeles, CA, USA, [6]Tocagen Inc., San Diego, CA, USA, [7]Henry Ford Hospital, Detroit, MI, USA

Recurrent HGG remains resistant to therapy with survival ranging from 7.2–9.2 months. An ongoing clinical study (NCT01985256) using a retroviral replicating vector (RRV), Toca 511, in combination with oral Toca FC (extended-release 5-fluorocytosine [5-FC]) is evaluating the highest tolerated doses and viral pharmacokinetics in patients with recurrent HGG. Toca 511 (vocimagene amiretrorepvec) encodes a yeast-derived, codon-optimized, heat-stabilized cytosine deaminase (CD) that converts 5-FC to the anti-cancer drug 5-FU in infected tumors. Toca 511 was intravenously administered over 1, 3, or 5 days with subsequent tumor resection and injection of Toca 511 into resection cavity walls. Six weeks later Toca FC was administered for 7 days every 6 weeks. Resected tumor was evaluated for presence of virus and transgene. Tumor samples have demonstrated presence of viral DNA signal in a dose dependent manner with 14/17 (82%) detectable overall of which 7/9 (78%) were in subjects treated with 3-day delivery and 100% (3/3) with 5-day delivery. Quantifiable viral DNA was found in 8/17 (47%) overall of which 5/9 (56%) was in the 3-day and 2/3 (67%) in the 5-day IV cohorts. Expression of the transgene was detectable by IHC. Five weeks after Toca 511 injection, viral RNA could not be detected in blood above the lower quantification limit. Median overall survival for efficacy evaluable population is 13.6 months (95% CI 7.2, NR). Based on 11 subjects evaluated by independent radiology review, 1 was reported to have a radiologic CR (with an unrelated stroke) and 2 to have stable disease. Safety data to date shows good tolerability with low grade pyrexia (n=2, 18.2%) and related SAEs of cerebral cyst and vasogenic edema. This study demonstrates successful gene transduction following IV delivery of Toca 511 and shows encouraging survival data. Updated safety and efficacy data will be presented.

ATIM-03. ACT IV: AN INTERNATIONAL, DOUBLE-BLIND, PHASE 3 TRIAL OF RINDOPEPIMUT IN NEWLY DIAGNOSED, EGFRvIII-EXPRESSING GLIOBLASTOMA

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