

Oceans of Opportunity

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analyzed using Significant Analysis of Microarray and Ingenuity Pathway Analysis. Whole brains were analyzed for changes in myelin and astrogliosis. Intravital microscopy also used to quantify blood brain-barrier (BBB) permeability and leukocyte activity. Functional changes at 65 days post implant resulted in a significant increase in astrogliosis and BBB permeability ($p,0.05$) in the RT+tumor implant compared to sham but no change in leukocyte activity was measured. However, structural changes in myelination were observed. The heatmap of the groups shows a clear visual difference between sham implant, RT+sham implant, and RT+C6-tumor. A total of 84 genes had a false discovery rate of $\leq 3.5\%$ and no significant exon splicing was detected. The top functional networks for the RT+sham implant group was hematological system development and function/tissue morphology/cellular development and for the RT+C6-tumor group cell morphology/cellular development-inflammatory response. To find the effect of the tumor we compared RT+sham implant to RT+C6-tumor implant. The highest canonical pathway effected by the presence of the tumor was the acute phase response signaling ($p=0.003$), an inflammatory response. The influence of the tumor also affected the networks associated with cell morphology/cancer/cell cycle. In conclusion, tumor presence during radiation significantly influenced function and genomic response following treatment. We have developed a clinically relevant rat brain tumor model that incorporates the effect of tumor on RT side effects.

(PS4.27) Barrier function of mouse small intestinal mucosa alters with irradiation dose. Kunzhong Zhang, Liangjie Yang, Mei Zhang, Pooja Vijaygopal, Pooja Vijaygopal, Jeevan Gurijala, Ayala Dvir, Paul Okunieff, Lurong Zhang, Vidyasagar Sadasivan, UF Shands Cancer Center, Gainesville, FL

Gastrointestinal (GI) mucosa performs the function of electrolyte and nutrient absorption and performing the barrier function. Loss of intestinal lining mucosa with irradiation (IR) leads to barrier defect, giving intestinal commensal bacteria and peptides easy access to systemic compartment leading to endotoxemia. We therefore hypothesize that IR dose dependent damages to the intestinal mucosa will have alterations at functional, systemic and structural levels. Functional loss of epithelial barrier were determined in Ussing chamber studies based the principle that mucosa will maintain the electrochemical potential gradient irrespective of the ionic strength of the bathing solution. Plasma endotoxin levels were measured using tachypleus amebocyte lysate kit. Changes in tight junction protein were determined in Western blot studies. These studies were done on small intestinal mucosa of BALB/c mouse on 3 or 6 days after exposure to 0, 3, or 7 Gy. Relative permeability of Cl^- and Na^+ (P_{Cl}/P_{Na}) were determined using the modified GHK equation. The results showed that 1) Non-IR mice showed a membrane selectivity ratio of 0.52 with Na^+ ions more permeable than Cl^- ; 2) 3 Gy IR mice showed selectivity ratio of 0.32, suggesting increased selectivity; 3) 7 Gy IR mice showed decreased selectivity, with a ratio of 0.78; 4) Plasma endotoxin levels measured in 0, 3 or 7 Gy showed significant increase only at 7 Gy when compared to 0 Gy; 5) Conductance measured in Ussing chamber studies showed a significant decrease 3 Gy (13.2 \pm 0.9 vs 8.3 \pm 0.6 mS) and a significant increase at 7 Gy (13.2 \pm 0.9 vs 23.7 \pm 1.4 mS) when compared to non-IR mice. 6) the western blot analysis for tight junction proteins showed that the claudin-1, JAM-A were increased in 3 or 5 Gy mice while their protein levels showed significant decrease at 7 Gy. Conclusion: low dose IR shows increased selectivity and better preservation of paracellular structures. However, higher doses of IR were associated with both structural and functional loss of tight junction that was associated with increased plasma endotoxin level. Increased selectivity of paracellular spaces and tighter epithelium at low dose irradiation may be a protective mechanism resulting from increased proliferation of epithelial cells. Further studies are however essential to better understand these mechanisms.

(PS4.28) Overcoming cell adhesion mediated radiation resistance by altering A6B1 integrin function. Thomas C. Sroka,

Ryan Cameron, Raymond B. Nagle, Anne E. Cross, University of Arizona, Tucson, AZ

Previous work has documented the presence of cell adhesion mediated radiation resistance (CAM-RR) dependent upon integrin function. Prostatic Intraepithelial neoplasia (PIN) is resistant to the killing effects of ionizing radiation (IR) as compared to invasive cancer. We show that during human prostate cancer progression, a profound alteration of cell adhesion occurs during the transition of PIN to human invasive prostate cancer. PIN lesions retain focal expression of laminin 332 and its receptor (A6B4 integrin), whereas invasive prostate cancer has lost expression of A6B4 and the ligand, laminin 332. Invasive cancer switches to express A3B1 and A6B1, receptors for laminin 511. We investigated here whether an IR survival response (as measured by AKT activation) was modified by altering A6 integrin function or supplying laminin 332. Our results indicate that prostate cancer cells that reside on exogenously supplied laminin 332 or laminin 511 at the time of irradiation have an amplified phospho-AKT response as compared to cells residing on a tissue culture surface. Interestingly, IR given prior to adhesion of PC3N cells onto laminin 332 or 511 will suppress the ECM induced Akt signal. The suppression was time and dose dependent upon IR. These data suggest that IR delivered to prostate cancer cells prior to their engagement with a laminin 332 or 511 containing ECM (such as that found on vessels, nerves and within bone) will result in a suppression of a pro-survival and migration event. These data implicate the use of IR as an invasion or metastasis prevention strategy in addition to its traditional use as a lethal anti-cancer modality.

(PS4.29) Delayed wound healing after whole body irradiation can be reversed by bone marrow transplantation. Benny J. Chen, Divino Deoliveira, Kayla Corbin, Yiqun Jiao, Joel Ross, Nelson Chao, Duke University Medical Center, Durham, NC

Local and systemic radiation can cause skin lesion directly and delay the healing of surgical wound. In this study, we investigated specifically how whole body radiation affected the healing of surgical wound using a modified ear skin punch model. Surgical wounds were induced by a 2 mm surgical punch in the ear pinnae of MRL/MpJ mice. Pictures of the wounds were taken and the sizes of the ear punch wounds were quantified by using Photoshop software. Local radiation was delivered by X-ray using a special constructed jig. Using this model, we demonstrated that 10 Gy of local radiation significantly delayed the healing of ear punch wounds (2862.2% vs. 6662% at day 7 and 7665.6% vs. 9662.3% at day 28; $P,0.05$). Addition of sublethal whole body irradiation (7 Gy) further delayed the healing of ear punch wounds (1666.6% at day 7 and 4468.1% at day 28; $P,0.05$ compared with local irradiation alone). The delay in wound healing could be at least partly reversed by bone marrow transplantation (5566.7 vs. 4468.1 at day 28 and 9763.3 vs. 8768.2%, $P,0.05$). These data were further confirmed by histological analyses. Our data demonstrated that whole body irradiation has dramatic effect on the speed of wound healing and bone marrow transplantation could reverse this negative effect.

(PS4.30) Energy metabolism and radiosensitivity of two HNSCC tumor cell lines. Christian G. Fabian, Wolfgang Mueller-Klieser, Ulrike G. A. Sattler, Institute of Physiology and Pathophysiology, University Medical Center of the Johannes Gutenberg University Mainz, Mainz, Germany

Unlike normal tissue, most tumors show an increased glycolytic flux and an enhanced accumulation of lactate even in the presence of oxygen. This phenomenon, termed "aerobic glycolysis" or "Warburg effect", is mainly caused by an upregulation and/or transactivation of glycolysis-related enzymes and transporters. Previous studies showed that lactate accumulation in tumors is associated with a high incidence of distant metastases, local recurrence and poor survival of patients. Furthermore, lactate concentrations were positively correlated with radioresistance in human tumor xenografts. In the present experimental study, two HNSCC (head and neck squamous cell carcinoma) cell lines (UT

