ABSTRACTS

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biological parameters to evaluate differential effects of ^{56}Fe and g-irradiation in C57BL/6J mice on two radiosensitive tissues - hematopoetic and gastrointestinal (GI). Methods: 6 to 8 weeks old wild type female C57BL/6J mice were irradiated with 3 to 8 Gy of iron ion (^{56}Fe; 1 GeV/nucleon) and 5 to 15 Gy of g radiation. All the mice except the three and a half day time point mice were monitored for survival and weight for 30 days. For partial body ^{56}Fe exposures hind limbs were shielded using tungsten bricks. For experiments at three and half day post-irradiation, mice were exposed to 7.25, 10, and 15 Gy of g radiation or 5 to 8 Gy of ^{56}Fe radiation. Results: With an average RBE of 1.25 for 30-day survival ^{56}Fe was not markedly more toxic than c rays. Gamma radiation showed typical GI (15 Gy) and hematopoetic toxicity (7.25 & 10 Gy). With ^{56}Fe irradiation, all the lethality occurred earlier than 10 d, suggestive of GI toxicity. However, mice irradiated with hind limbs shielding, 100% survival was observed for 30 days even after 8 Gy of ^{56}Fe. GI toxicity in ^{56}Fe-irradiated mice was further excluded by bacterial colony count in blood culture. The number of surviving crypts at doses that caused lethality before 10 d post-radiation were significantly less in g irradiated samples. More TUNEL positive crypt cells were observed in small and large intestine of c-compared to iron-exposed mice. In contrast, ^{56}Fe irradiated bone marrow showed higher TUNEL positive and lower number of progenitor cells per HPF. Body weight in mice irradiated with c-rays, ^{56}Fe TBI and ^{56}Fe PBI showed marked differences. While there were dose dependent decreases in WBC counts after c and ^{56}Fe radiation, significantly greater decreases were seen for the later at equitoxic or equal doses. Conclusions: We conclude from our results that ^{56}Fe, although with an RBE of 1.25 was not much more lethal than g-rays, showed greater hematopoetic toxicity than g-rays at equitoxic doses and suggests that ^{56}Fe-induced accelerated hematopoetic toxicity is due to preferentially greater ablation of myeloid progenitor cells in the bone marrow.

(PS4.61) Fat accumulation by ionizing radiation and its amelioration by anti-obestic drug. Sung-Kee Jo[1], Changhyun Roh[1], Hae-Ran Park[1], Namhee Choi[1], Uhee Jung[1], Sung-Tae Yee[2], Sung-Ho Kim[3], [1]Advanced Radiation Technology Institute (ARTI), Korea Atomic Energy Research Institute (KAERI), Jeonbuk, Republic of Korea, [2]Sunchon National Univerisity, Sunchon, Republic of Korea, [3]Chonnam National University, Gwangju, Republic of Korea

Ionizing radiation has become a health concern emanating from natural sources like space travel and artificial sources like medical therapies. Although the risk of degenerative diseases by radiation has been reported, the detailed mechanisms are poorly understood. By revealing the underlying mechanisms, ionizing radiation can be used as a method to construct disease model systems. The regulation of adipocytes can be considered as a way to balance both glucose uptake and energy expenditure in order to derive the amount of fat stored. Thus, increases in glucose uptake or decreases in energy expenditure results in elevated fat deposition. In this study, we showed that c-irradiation could trigger the biological response resulting in the fat accumulation of white adipose tissue in mice and that this can be a useful model for evaluation of anti-obestic drugs. To induce the fat accumulation by c-irradiation, 2-months-old female C57BL/6 mice were irradiated at 5Gy and further raised for 6 months. Then, the mice were i.p. injected daily with orlistat (25 mg/kg) or vehicle for 3 weeks and analyzed for the adipose tissue weight and serum TG levels. The abdominal adipose tissue of the c-irradiated mice weighed an average of 3.9g per 100g body weight, 1.7 fold higher than what was seen in the normal mice (2.3g per 100g body weight), indicating that c-irradiation induced the fat accumulation in the adipose tissue. However, the administration of orlistat, a well-known anti-obestic drug, signifi-cantly reduced the adipose tissue weight to 1.7 g per 100g body weight in irradiated mice. Also, in these orlistat-treated mice, a significant reduction of serum triglyceride level by 14% was observed. The findings of this study that the fat accumulation is induced by radiation exposure and it can be ameliorated by an anti-obestic drug suggest that c-irradiated mice can be applied as a useful model for the development of novel therapeutic approaches for obesity. [This study was supported by the Nuclear R&D Program of MEST (Grant No. 2007-00091)]

(PS4.62) Irradiation decreases SGLT1 mediated glucose absorption. Liangjie Yin, Kunzhong Zhang, Jacob Karimpil, Jeevan Gurijala, Pooja Vijaygopal, Mei Zhang, Paul Okunieff, Lurong Zhang, Vidyasagar Sadasivan, UF Shands Cancer Center, Gainesville, FL

Radiation affects rapidly dividing cells of the gastrointestinal (GI) tract causing epithelial dysfunction that leads to electrolyte and nutrient malabsorption. Treatment of dehydration and nutritional deprivation associated with secretagogue-induced diarrhea are derived from the resilience of the sodium dependent glucose transport system (SGLT1), which is the primary mechanism for glucose absorption across the brush-border membrane of enter-ocytes. There is little known information about the glucose transport following radiation induced secretory diarrhea. Our aim was to investigate the SGLT-1 function and consequently, its affect on glucose absorption following irradiation. These studies were done on small intestinal mucosa of Swiss mice on day 6 after exposure to 0, 1, 3, 5 or 7 Gy. Briefly, glucose-stimulated short circuit current (I_{sc}) measured in Ussing chamber was used to study SGLT1 transport function. Survival studies were carried out in 9 Gy TBI and 15.6 sub-TBI mice. The results showed that 1) glucose-stimulated I_{sc} decreased with increasing IR doses; 2) K_m values for glucose were (mM) 0.38 ± 0.04, 0.49 ± 0.06, 1.76 ± 0.16, 1.91 ± 0.3, 2.32 ± 0.4 in 0, 1, 3, 5 and 7 Gy respectively; 3) V_{max} values for glucose were 387.4 ± 16.2, 306.6 ± 16.4, 273.2 ± 14.9, 212.9 ± 9.14, 188.1 ± 9.12 in 0, 1, 3, 5 and 7 Gy respectively; 4) Changes in K_m and V_{max} measured with time since IR showed that their values returned to normal levels approximately 14 days after IR; 5) Survival studies showed that withholding glucose from supportive care for first 10 day showed increased survival; and 6) Western blot analysis for SGLT-1 brush border membrane showed increased protein levels with increasing IR dose. Conclusion: Increase in K_m with increasing IR dose suggestion decreased affinity for glucose. Decrease in V_{max} could suggest increasing loss of villus epithelial cells with increasing IR dose, which is supported by histopathology sections. Increased protein levels with IR in Western blot analysis suggest that the SGLT1 transporters are non-functional and further studies are essential to validate this observation. These studies suggest that inclusion of glucose in food may lead to osmotic diarrhea resulting from malabsorption of glucose and electrolytes, which further complicates IR-induced toxicity.

(PS4.63) Effects of ionizing radiation on stromal-epithelial communication in esophageal carcinogenesis. Zarana S. Patel[1], Katharine D. Grugan[2], Anil K. Rustgi[2], Francis A. Cucinotta[3], Janice L. Huff[1], [1]NASA Johnson Space Center / USRA, Houston, TX, [2]Division of Gastroenterology, University of Pennsylvania, Philadelphia, PA, [3]NASA Johnson Space Center, Houston, TX

Esophageal cancer is the 6th leading cause of cancer mortality worldwide and is associated with a variety of risk factors including tobacco use, heavy alcohol consumption, obesity, and dietary factors. In addition, a link between esophageal cancer and radiation exposure is revealed by its high excess relative risk among the tumor types observed in survivors of the atomic bomb detonations in Japan. To better understand the role of radiation exposure in the development and progression of esophageal cancer, we are using hTERT-immortalized human esophageal epithelial cells and genetic variants grown in co-culture with esophageal stromal fibroblasts (Okawa et al. Genes & Development 2007). Because the stromal compartment plays an essential role in the maintenance and modulation of epithelial cell growth and differentiation and is implicated in cancer development, we examined how irradiation of stromal fibroblasts affected epithelial cell behavior. After exposure to conditioned media from irradiated fibroblasts, we quantified epithelial cell migration and invasion, both behaviors associated with cancer promotion and progression. These assays were conducted in modified Boyden chambers. Our results using low LET gamma radiation showed a dose-dependent increase in migration of epithelial cells when exposed to conditioned media from irradiated vs. non-irradiated fibroblasts. We also observed enhanced invasion through a basement membrane matrix in similarly treated cells. Antibody-capture arrays and ELISAs were used to identify increased secretion of hepatocyte growth factor