

LONG-TERM EFFECTS OF A SINGLE EXPOSURE OF THE VERTEBRATE EMBRYO TO HIGH CHARGE AND ENERGY (HZE) PARTICLE RADIATION

Xuan Zheng^{1,2}, Farlyn Hudson¹, Lahcen Jaafar¹, and William S. Dynan¹

¹Georgia Health Sciences University, Augusta, GA, ²Zhongnan Hospital of Wuhan University, Wuhan, China

High charge and energy (HZE) particle radiation has a unique effect on tissue due to its ability to deliver concentrated energy along relatively few radiation tracks. Long-term effects of exposure to the HZE particle radiation on normal tissues remain incompletely understood. Here we investigate these effects using a vertebrate model organism, the Japanese medaka (*Oryzias latipes*). Embryos (stage 28) were exposed to 1 GeV/nucleon ⁵⁶Fe ion radiation at the NASA Space Radiation Laboratory in Brookhaven, NY. Genome target size in medaka is 4-5 smaller than in humans or mice, and accordingly, exposures were performed over a 0 to 9 Gy dose range (n≈250 per dose group). A separate gamma ray irradiation arm was performed using a ¹³⁷Cs source, with exposures over a 0 to 27 Gy dose range. Mortality was observed daily following irradiation. Histologic and molecular analysis was performed on exposed cohorts at 250 days post-exposure. Among the HZE particle radiation-exposed groups, acute mortality was seen only in the highest dose group (9 Gy). Studies of the potential effects of lower-dose exposures on lifespan remain in progress. Biomarkers of the oxidative stress response, superoxide dismutase 2 (SOD2) and catalase (CAT) mRNAs, were significantly elevated in liver in 3 Gy and 9 Gy groups (p<0.01). A biomarker of mitochondrial function, PGC1- α mRNA, was down regulated in most exposed groups (p<0.01). Histologic analysis of liver for the 9 Gy group showed premature appearance of aging-associated changes, including steatosis, spongiosis hepatitis and ballooning degeneration. In the gamma ray arm, acute mortality was again seen only in the highest dose group (27 Gy). Despite the comparable mortality, we have thus far not observed molecular and histopathological changes to the same extent as in the HZE particle radiation-exposed individuals. At 250 d post exposure, there was no significant change in CAT, SOD2, or PGC1- α mRNA levels. Preliminary analysis of liver histology also suggested that the changes were less extensive than in the HZE particle-exposed group. Similar analyses are planned at intervals for the duration of the anticipated lifespan of the fish (a further 15 months). Results here provide support for the hypothesis that exposure to a single dose of HZE particle radiation early in life initiates long lasting molecular and histopathological alterations in normal tissues.

This work was supported by the Emory-GHSU NSCOR and by the US Department of Energy Low Dose Radiation Research Program.