US Department of Energy
Low Dose Radiation Research Program
Award number DE-SC0012092
“Links between persistent DNA damage, genome instability, and aging.”
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The purpose of this award was to allow completion of portions of Aim 3 of a previous award, DE-SC0002343, also entitled “Links between persistent DNA damage, genome instability, and aging.” Aim 3 was as follows:

> *Aim 3. To determine whether simulated space radiation produces the same or different effects as low doses of low LET radiation. We will use similar quantitative endpoints as in Aim 1 (DNA damage, genomic instability) and Aim 2 (molecular and cellular markers of aging) but substitute exposure to high-energy protons, high Z energetic particles, or mixed radiation fields for exposure to low LET gamma rays. We will determine whether the response spectrum is the same or different as for low doses of low LET radiation. Where linear responses are observed, we will calculate relative biological effectiveness of different radiation types*

The work used the Japanese medaka fish (Oryzias latipes), as a vertebrate model organism that can be maintained in large numbers at low cost for lifetime studies. Like other small laboratory fish, Japanese medaka share many anatomical and histological characteristics with other vertebrates, and a variety of genetic and genomic resources are available.

To determine whether simulated space radiation produces the same of different effects as low doses of low LET radiation, medaka embryos were irradiated at doses ranging from 0.1 Gy to 27 Gy of γ-rays and 0.1 to 9 Gy of high-LET charged particle radiation (1000 MeV/nucleon ^{56}Fe ions).

Results showed that, except for the highest dose group for each radiation type, all of the groups, including non-irradiated controls, showed very similar mortality curves. Median survival was in the range of 17-18 months.

To examine the effect of irradiation on potential biomarkers, the population was sampled at intervals from 8 to 28 months post-irradiation and liver tissue was subjected to histological and molecular analysis. Analysis showed that charged particle radiation and aging contributed synergistically to accumulation of lipid peroxidation products, which are a marker of chronic oxidative stress. This was mirrored by a decline in PPARGC1A mRNA, which encodes a transcriptional co-activator required for expression of oxidative stress defense genes and for mitochondrial maintenance. Consistent with chronic oxidative stress, mitochondria had an elongated and enlarged ultrastructure. Depending on the endpoint, effects of γ-rays in the same dose range were either lesser or not detected. Together, results indicate that a single exposure to high-LET, but not low-LET radiation, early in life, leads to increased oxidative stress throughout the normal lifespan of the individual.

<u>Other work.</u>

Project personnel contributed to analysis of a radiosensitive phenotype associated with deficiency in NONO, a multifunctional RNA and DNA binding protein. This work has been submitted to *DNA Repair* and is currently being revised to address reviewer comments.

Publications.

1. Zheng, X, Zhang, X, Ding, L, Lee, JR, Weinberger, PM, and **Dynan, WS**, Synergistic effect of high charge and energy particle radiation and chronological age on biomarkers of oxidative stress and tissue degeneration: a ground-based study using the vertebrate laboratory model organism *Oryzias latipes.* PloS One. 2014 Nov 6; 9:e111362. PMCID: 4222877.

   Note that the original version of this article acknowledged only award number DE-SC0002343. An additional acknowledgment of DE-SC00012092 has been posted as a comment.

2. Li, S, Shu, FJ, Li Z, Jaafar, L, Zhao, S, and **Dynan, WS**. NONO ($p54^{nrb}$), a multifunctional nuclear protein, protects male germ cells against radiation-induced cell death *in vivo. Submitted to DNA Repair.*