

Delayed effects of acute radiation exposure on the cardiovascular system using a murine model of the hematopoietic acute radiation syndrome

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Introduction. Exposure to high level radiation from accidents or belligerent activities results in acute and chronic organ damage. The hematopoietic system is the most sensitive organ to radiation damage (2-10 Gy) and results in the hematopoietic acute radiation syndrome (H-ARS). Survivors of H-ARS are plagued months to years later with delayed effects of acute radiation exposure (DEARE), characterized by chronic illnesses affecting multiple organ systems. Previous results using the murine H-ARS model showed numerous kidney and heart DEARE-related pathologies similar to humans, including tissue fibrosis and elevated blood urea nitrogen. The goal of this study was to utilize the murine H-ARS model to determine possible roles for abnormal iron metabolism, inflammation, oxidant stress, and senescence in the development of cardiac DEARE.

Methods. Mice (C57BL/6; 12 week-old) received total body irradiation (TBI: ~8.5-8.7 Gy, ¹³⁷Cs, LD₅₀ to LD₇₀) and hearts were harvested at various times post-TBI from H-ARS survivors. Paraffin tissue sections were stained with hematoxylin/eosin or Perls Prussian Blue, or reacted with a macrophage-specific antibody (F4/80). Total RNA was purified from fresh tissue and changes in mRNA expression were assessed by real-time PCR for the senescence marker p16 and NADPH oxidase subunits Nox2, Nox4, or p47phox.

Results/Significance. Compared to age-matched non-irradiated controls (NI), tissue iron deposits were increased in irradiated (IR) hearts at 4 months, and progressively declined with time post-TBI. Numbers of macrophages were greater in IR vs. NI sections at all time points and decreased with time post-TBI. Nox2 and Nox4 mRNA expression was increased at both 9 and 21 months post-TBI, but p47phox increased only at 21 months. Expression of p16 in IR heart was increased at 7, but not at 22 months post-TBI. Taken together, the results indicate abnormal iron metabolism, inflammation, oxidant stress, and early senescence may contribute to development of cardiac DEARE.