Delayed effects of acute radiation exposure (DEARE) in a murine model of the hematopoietic acute radiation syndrome: Multiple-organ injury consequent to total body irradiation

Ariel Quickery1, Joseph L. Unthank1,2, Steven J. Miller1,2, Christie M. Orschell3

Departments of 1Surgery, 2Cellular and Integrative Physiology, 3Medicine
Indiana University School of Medicine, Indiana University-Purdue University Indianapolis

ABSTRACT

Determine the extent to which DEARE-related heart and kidney pathology and dysfunction occur in a mouse model of H-ARS survivors.

OBJECTIVE

Animals and tissue collection. All procedures were approved by the Indiana University School of Medicine (IUCUC). Mice (male and female C57Bl/6J) received total body irradiation (TBI) of 5-8.75 Gy. L50(90)/10 to LD50(90) with 120 Cs at 12 weeks-of-age. After 30 days, irradiated survivors were paired with age-matched non-irradiated controls, and kidney and heart were harvested at 9 and 21 months (n=4-5 per group). Serum was collected at 4, 9, and 21 mo post-TBI and from non-irradiated control mice.

RESULTS

1. Acute, high dose radiation exposure, such as that resulting from terrorist use of radiation or radiation accident, results in acute and chronic organ injury requiring multiple approaches for treatment.
2. Exposures of 2-10 Gy in mice result in the hematopoietic acute radiation syndrome (H-ARS), which if untreated results in death within weeks.
3. Survivors of H-ARS are plagued months to years later in life by delayed effects of acute DEARE.
4. DEARE results in multiple chronic illnesses affecting multiple organ systems characterized by systemic oxidative stress, inflammation, and tissue fibrosis, which affects tissue structure and function.
5. DEARE-related fibrosis and collagen deposition have been shown in heart and kidney at organ-specific doses ≥15Gy, but this pathology has not been shown to occur following lower doses used in the H-ARS total body irradiation mouse model.
6. This study utilized the H-ARS mouse model to determine the extent to which, if any, DEARE-related pathology occurs at the lower radiation doses used for this model.

RESULTS

Renal Interstitial Fibrosis Increased with Time After Total Body Irradiation (TBI)

Figure 1. Interstitial fibrosis in the mouse kidney was detectable, but limited, at 9 months post-TBI (left). At 21 months post-TBI (right) renal fibrosis had become extensive. Thus, a clear progression of pathology is evident between time points in the irradiated mouse kidney.

Renal Function Decreased with Time Post-TBI

Figure 4. Blood urea nitrogen (BUN) was determined as an indicator of kidney function. BUN was significantly elevated in irradiated (IR) mice at 9 and 21 months compared to controls, indicating a decrease in function with time. BUN was unaltered with aging in non-irradiated (NI) mice.

Gloromerular Sclerosis Developed with DEARE

Figure 3. Normal glomeruli showing no disorganized cellular material with several nuclei (white arrow) and capillaries (black arrow). Sclerosed glomeruli (21 mo post-TBI) with lack of cellular material replaced with collagen (arrow) and significantly decreased nuclei and capillaries.

SUMMARY/CONCLUSIONS

1. Significant DEARE-related renal pathology occurred in H-ARS survivor mice from 9 to 21 months post-TBI (Figs. 1 - 3 and Table 1).
2. Decreased renal function, as assessed by BUN, also was associated with DEARE in H-ARS survivor mice (Fig. 4).
3. Significant cardiovascular DEARE characterized by fibrosis and collagen deposition occurred in hearts of H-ARS survivors 21 months post-TBI (Figs. 5 & 6).
4. Cardiac oxygen stress, indicated by elevated Nox2 expression, was apparent at 9 and 21 months post-TBI in H-ARS survivor mice (Fig. 7).
5. Taken together, the results indicate that renal and cardiac DEARE occur at lower radiation doses than previously thought. Thus, the H-ARS mouse model is suitable for study of mechanisms related to DEARE-related pathology, especially in kidney.

Future Work

1. Evaluate changes in organ pathology and function at additional time points.
2. Determine age-related effects on DEARE development.
3. Evaluate radiologic mitigators of H-ARS on DEARE organ pathology and dysfunction.