Comparison of radiation-induced damage between livers from control and chimeric mice

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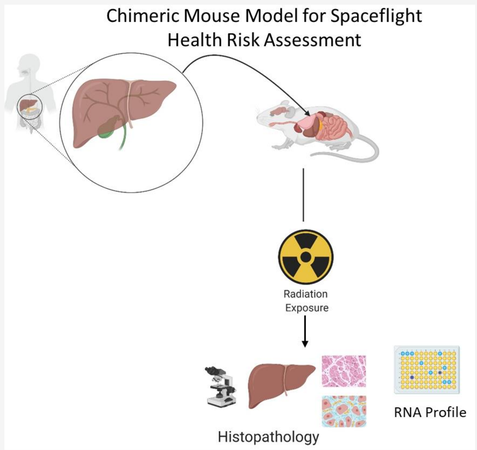
Abstract

Assessment of human health risks associated with space radiation exposure is based largely on the knowledge gained from studies in which animals, mostly rodents, are exposed to high-LET radiation on the ground. It has been recognized that translation of animal results to meaningful implications for human disease can be challenging, particularly for certain risk categories such as the high-LET radiation effects in the central nervous system (CNS). Considering limitations in utilizing non-human primates and clinical studies in humans, chimeric animals can potentially bridge the knowledge gap between rodents and humans. In a chimeric animal, a specific organ or a cell type is replaced with respective human cells that are functional. In this pilot study, we used PXB mice whose livers contain >90% human cells. These mice were exposed to gamma rays to investigate DNA damage and transcriptomics changes in the chimeric livers. Results obtained from PXB mice were compared to non-engrafted control animals from the same background strain that were exposed to identical conditions. Staining of the liver tissues with H&E indicated that the human liver tissue in chimeric mice responded differently than the mouse liver tissue to gamma radiation on the cellular level, as evidenced by differences in inflammation and cellular damage seen on histopathology. The gene expression data collected from the liver samples is also be presented, which potentially offers an explanation for the differential responses.

Chimeric Mice in Translational Research

- A chimeric mouse is a mouse carrying functioning human genes, cells, tissues, and/or organs.
- Assessment of human health risks associated with space radiation exposure is based largely on the knowledge learned from studies in which animals, mostly rodents, are exposed to high-LET radiation on the ground
- Translation of animal model results to meaningful implications for human disease can be challenging, particularly for certain risk categories such as the high-LET radiation effects in the central nervous system (CNS)
- Chimeric animals can potentially bridge the knowledge gap between rodents and humans

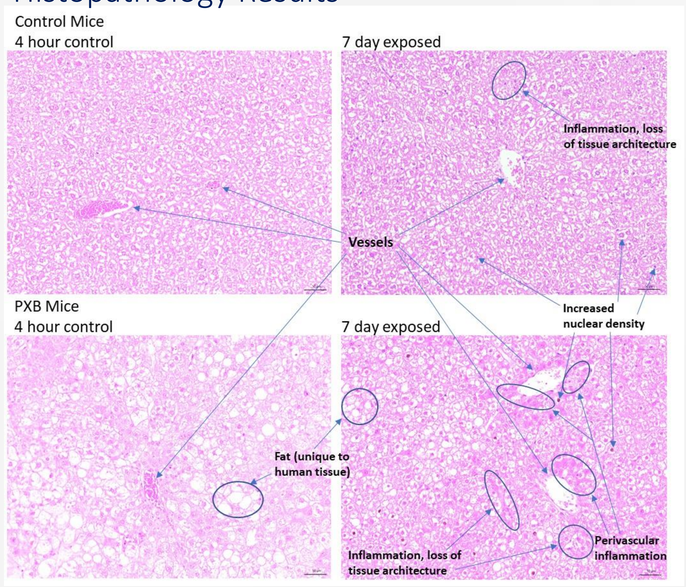


Study Plan

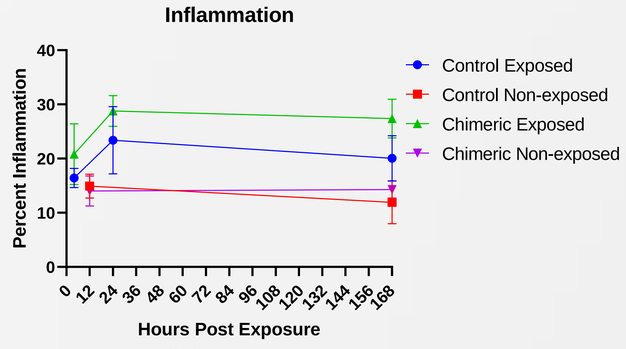
- Animals: PXB mice with chimeric livers and control (Fox Chase SCID) mice, 24 Male, 70 days old
- Timeline: 7 days environmental acclimation, 3 days restraint device acclimation, 1 day treatment (table below), tissue collection day 0-7 post-treatment
- Radiation: Gamma rays at a whole body dose of 2 Gy, with 1 Gy delivered from each side acutely, expose from side
- Analysis of DNA damage markers and transcriptomics will be performed on the humanized and mouse livers

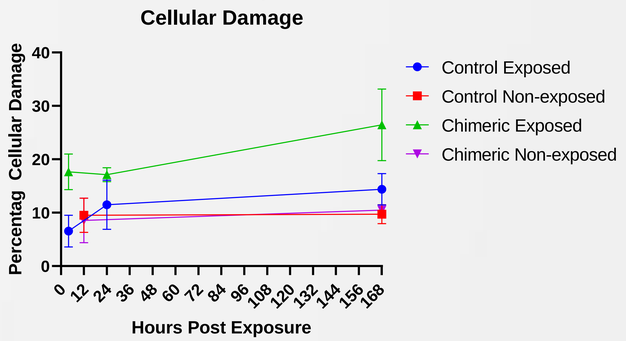
Group	Treatment
12 hr control 7 day control	Restraint only
4 hr exposed 24 hr exposed 7 day exposed	2 Gy Exposure

Histopathology Results



Increased nuclear density in irradiated animals 7 days after radiation, both groups. Increased inflammation, focused in perivascular areas in the PXB-mouse group 7 days after radiation.

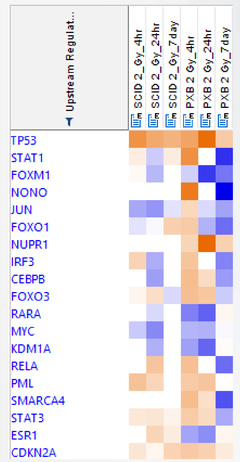




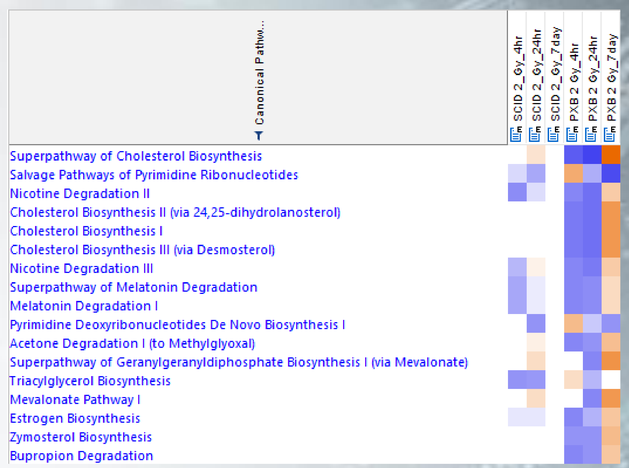
Both radiation-induced cellular damage and inflammation are higher in humanized livers in comparison to SCID controls. The damage appears to persist until Day 7 after irradiation.

Gene Expression Results

Upstream regulators



Metabolism related pathways



DNA damage response after irradiation appears to be similar between humanized and mouse livers. Differences in the responsive pathways were observed, particularly those involved in metabolic activities.

Preliminary Conclusions

- Chimeric mice are an opportunity to increase translatability from research animal data to implications in clinically-relevant human disease.
- The degree of radiation-induced damage after exposure to gamma radiation in chimeric mice is different than mouse liver tissue on the cellular level, as evidenced by differences in inflammation and cellular damage seen on histopathology.
- The DNA damage response mechanism shortly after irradiation appears to be similar between the mouse and humanized livers. However, some metabolism related pathways in humanized livers were more affected by radiation.
- Immunodeficiency in chimeric mice may limit the use of such models for investigations of long-term effects of radiation.

Future Directions

- Use of this model for high-LET particle exposure, investigating other health risks associated with spaceflight
- Potential flight experiments

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