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Contact Monitor:	Zawaski, Janice	Contact Phone:	
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Key Personnel Changes/Previous PI:	PI notes additional collaborators who are assisting with the project: Lahouaria Hadri, Kenneth Walsh, and Venkata Naga SrikanthGarikpati (Ed., 5/26/23).		
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	<p>Ed. note 2/10/2020: Continuation of "Space Relevant Radiation-Induced Cardiovascular Disease Risk Thresholds: Effect of Sex on the Outcome," grant 80NSSC18K0921 with the same Principal Investigator Dr. David Goukassian, due to PI move to Icahn School of Medicine at Mount Sinai from Temple University.</p> <p>During the future Moon, near Earth asteroids, and Mars missions, astronauts will be exposed to higher total doses of space irradiation (IR) (~0.4-0.5 Gy) from galactic cosmic rays (GCR). Most of what we know about harmful effects of IR on cardiovascular (CV) system is from epidemiological studies of long-term survivors of cancer radiotherapy (RT). A recent study of 2,168 women who underwent RT for breast cancer has shown that the rates of major coronary events increased linearly with the mean dose to the heart by 7.4% per Gy, with no apparent lower or upper threshold. In this study, it was determined that average of the mean doses to the whole heart was 4.9 Gy with the range of 0.03 - 27.72 Gy. Furthermore, metabolomics studies, in patients undergoing hematopoietic stem cell (HSC) transplantation as part of cancer treatment (1.25 Gy total-body irradiated), identified seven urine-based biomarkers with distinct differences between pre- and post-exposure samples. The levels of these markers were found to be sex-dependent suggesting that separate biomarker signatures may exist for males and females.</p> <p>Hypotheses: Our central hypothesis is that low-dose proton and HZE (high energy) particle IR-induced biological responses are long-lasting, IR type- and dose-dependent and may augment excess relative risk (ERR) estimates for the development of cardiovascular diseases (CVDs) during and after long-duration space missions. In addition, we hypothesize that sex differences could further modify radio-biologically effective (RBE) IR thresholds for CV risk estimates. Gene expression and epigenetic modifications in protein and microRNA (miRNA) in exosomes from the blood (e.g., plasma/serum) may be altered before the onset of the cardiac symptoms, which could be used as potential biomarkers to predict the CVD risks. We will test our hypotheses with the following specific aims:</p> <p>Task Description:</p> <p>AIM 1. Determine the longitudinal effect of IR type, dose, and sex on cardiovascular physiology in wild type mice and ApoE null mice after full-body 5-ion simplified mixed field and gamma radiation.</p> <p>AIM 2. Determine space-type IR mediated modulations in exosomal cargo in the blood, and determine whether these changes are associated with alterations in the heart function, structure, and vasculature before the manifestation of clinical symptoms.</p> <p>AIM 3. Utilize known and newly identified biomarkers in the blood to develop human-relevant point-of-care tests (POCT) for predicting and monitoring possible CV alterations before and during space flights.</p> <p>We anticipate that the results of our proposed work may be beneficial for human space exploration and could (1) Determine single whole body mixed field dose-response, radio-biologically effective IR thresholds in the heart and cardiac vasculature, and whether sex differences could modify radio-biologically effective IR thresholds for CV risk estimates; 2) Determine whether space radiation leads to modifications in the circulating exosomal cargo contents and whether IR-induced exosomal cargo modulations are reflective of subclinical changes in the cells and organs of origin; 3) Ascertain if modulations of exosomal cargo may be representative of chronic oxidative stress and inflammation and could serve as early biomarkers of IR-induced CVD initiation and progression; 4) Integrate physiological CV endpoint data sets with gene expression and epigenetic data to identify biomarkers in bio-fluids that could be used for prediction of asymptomatic CVD in the setting of space IR, which will include known early and intermediate biomarkers of cardiac damage, inflammation, and oxidative stress, as well as currently unknown novel radiation-associated cardiac biomarkers.</p>
<p>Rationale for HRP Directed Research:</p>	<p>We anticipate that the results of our work could be beneficial for human space exploration as well as for the Earth-based applications on several levels -- (1) determine whether low dose space-type and terrestrial IR may present an increased risk for CVD development during and after prolonged space missions, as well as after conventional and particle cancer radiotherapy; (2) determine the underlying molecular signaling of CV alterations; (3) identify biomarkers in the blood that could be used for prediction of asymptomatic CV disease, which will include known early and intermediate biomarkers of cardiac damage, as well as currently unknown novel cardiac biomarkers; (4) the identification of sub-clinical CV disease biomarkers that could be used for monitoring the effectiveness of mitigating factors for prevention and treatment of IR-induced CVDs in space and in Earth-bound civilian population, in general.</p>
<p>Research Impact/Earth Benefits:</p>	<p>Our new findings for the reporting period are organized below by four sub-titles containing corresponding background, methodology, main findings, and the summary.</p> <p>Sub-project 1:</p> <p>Title: "Radiation-Induced Clonal Hematopoiesis as an Independent Risk Factor for Carcinogenesis and Heart Disease"</p> <p>Background. Acquiring and accumulating somatic mutations is a hallmark of aging and can be accelerated by space irradiation (IR). While most mutations leading to advantageous phenotypes leading to clonal events in normal tissues. In HSCs, the expansion of mutated cells is termed clonal hematopoiesis (CH). In the absence of concomitant malignancy, the presence of mutations in these known CH "driver" genes, with a variant allele fraction (VAF) of at least 2%, is termed CH of indeterminate potential (CHIP). While mutations in leukemogenic "driver" genes represent an early step in the progression toward hematologic malignancy, unexpectedly, CHIP also predisposed patients to an increased risk of cardiovascular disease (CVD), including a 2-4-fold increased risk of coronary artery disease, early-onset myocardial infarction, and thrombotic stroke when adjusted for other covariates (age, sex, type 2 diabetes, etc.). Our group analyzed the somatic mutational profile in 14 astronauts (binned age ~42) and identified 34 nonsynonymous mutations of relatively low VAF in CHIP-driver genes in leukocytes, predominantly in TP53 and DNMT3A, which is consistent with the development of an early stage of CHIP. While these clones were small, there is a possibility for additional clonal instability with longer duration missions, which may be facilitated by aging and many other extrinsic factors in space. Thus, longitudinal lifetime murine studies assessing the effects of space-type IR on CH, cancer, and CVD would provide a mechanistic framework to investigate the direct connection between CH, cancer, and CVD pathophysiology.</p> <p>Hypothesis. We hypothesize that exposure to space-type IR will increase the lifetime accumulation of somatic mutations within known CHIP "driver" gene candidates. Further, we hypothesize that the aberrant clonal events resulting from these mutations will be associated with accelerated carcinogenesis, particularly evident in the later stages of life. In</p>

addition, these processes may be IR exposure type-dependent, i.e., acute or chronic/intermittent.

Methodology. We exposed 3-month-old male age-matched C57BL/6J wild type (WT) mice to 137Cs- γ -IR at 100 cGy and simGCRsim-IR at 50 cGy 500 MeV/nucleon. During this study mice were observed for gross tumor development in all internal organs, cardiac function was assessed by echocardiography (ECHO) and blood was collected at 14, 28 days and 12, 16, 22 months post-IR. Genomic DNA was isolated from white blood cells (WBC) and processed for whole exome sequencing (WES). The sequencing was performed on the Illumina NovaSeq-6000 platform, using 150bp paired ends sequencing with an average of ~24 million raw reads/sample and with a depth of 50x. Sequencing reads were aligned to mm10 reference mouse genome with BWA mem aligner. Somatic variant calling was performed with the GATK Mutect2 pipeline. Mutation data was further analyzed with the maftools R package. The left ventricles of mice, from the same experiments, were bisected at 16- and 22-months post-IR and total RNA was isolated and sequenced with Illumina NGS. RNA-seq reads were spliced-aligned to the mm10 mouse reference genome using the STAR aligner. Raw read counts were converted to log2 CPM values with the DESeq2 R package. Normalized gene expression data were then analyzed using a machine learning-based Self-Organizing Map (SOM) algorithm implemented in the oposSOM R package.

Main findings for longitudinal mouse lifetime cardiovascular studies in male and female C57bl/6j mice.

In male C57BL/6J mice we found acute “in-flight” cardiac function changes - 1) global LV systolic function (LVEF) is impaired in all IR groups and doses at 14 and 28 days; 2) at 14 days, reduced LV systolic function is paired with structural alterations (reduced LV size, mass, and stroke volume) in 50 cGy simGCRsim-IR mice.

In male C57BL/6J mice we found longitudinal/degenerative cardiac changes - 1) at 365 days global LV systolic function remains reduced in all IR groups and doses; 2) at 440 days there is no significant difference in LV structure and function in all IR groups; 3) at 660 days there is no significant alteration in LV function or structure in γ -IR mice compared to no-IR ND-fed mice; 4) in 50 cGy simGCRsim-IR mice decrease in diastolic wall strain (DWS), smaller overall LV size, and LV mass, suggests that these mice may exhibit diastolic dysfunction.

In female mice LV function was evaluated at 28, 180, 365, 440, and 550 days post-IR following the same cohort of mice for each treatment condition longitudinally. There was no significant alteration in global LV systolic function across any treatment groups at 28, 180, 365, 440, and 550 days post-IR in female mice.

Main findings in longitudinal mouse lifetime carcinogenesis studies in male and female C57bl/6j mice.

- The incidence of macroscopic tumors is 4.5-times higher in male WT compared to female WT mice after the same doses of γ - and simGCRsim-IR or Western diet (WD) suggesting underlying genotypic variance may attenuate pathways involved in tumorigenesis. - The incidence of IR-induced internal organ tumors was higher in 100 cGy gamma-versus 50 cGy simGCRsim-IR, suggesting higher carcinogenic potential of gamma-IR at these doses. - The liver is the most affected organ by tumor growth, followed by the spleen then the lung. - Pathologic evaluation of macroscopic tumors revealed the highest number of malignant tumors during the lifetime of WT mice was detected in the WD-fed group, but not in either of the IR groups. - The incidence of malignant tumors of internal organs (liver, spleen, lungs) was 3-times higher in male (N=21) vs female (N=7) mice (i.e., macroscopic tumors). - All microscopic tumors in both male and female mice at all time points and treatment conditions were diagnosed exclusively as lymphomas.

Findings in whole exome sequencing of WBC in male mice.

In animals with pathologically confirmed liver tumors, nonsynonymous mutations in somatic genes were the most prevalent, followed by stop-gain, nonframeshift, and one frameshift mutations. The mutation count and type were similar for both types of IR for hepatocellular carcinoma, their mutations in mice with histiocytic sarcoma were exclusively in simGCGsim IR mice, whereas mutations in mice with hemangiosarcoma were exclusively in γ -IR mice. The majority of somatic variations observed were nonsynonymous SNVs regardless of age and exposure type. Transition and transversion mutations were more frequent in γ -IR group. Mutations in 6 genes (Cdh11, Muc4, Vmn2r116, Sp110, Zfp987, Gm2022) had the highest frequency in all studied groups. Cdh11 is overexpressed in 15% of breast cancers and seems essential to tumor progression in some other cancer types. Muc-4 plays a role in cancer progression by repressing apoptosis and increasing tumor cell proliferation via downregulation of Cdkn1b. Also stabilizes Her2 signaling.

In summary, our results provide compelling scientific evidence that gamma and/or space IR exposure induces “long-lasting” effects in the hearts of male but not female C57BL/6J mice. Moreover, murine lifetime carcinogenesis studies in various internal organs showed a 4.5-fold higher number of malignant tumors in male but not female mice after exposure to exactly the same doses of gamma and simGCRsim IR. Further, whole exome sequencing of leukocytes collected from male C57BL/6J mice showed that mutations-affected genes are mainly implicated in cancer and liver and kidney cancer were the top disease types across all groups. In animals with pathologically confirmed liver tumors, nonsynonymous mutations in somatic genes were the most prevalent, followed by stop-gain, nonframeshift, and one frameshift mutations. The mutation count and type were similar for both types of IR for hepatocellular carcinoma, but mutations in mice with histiocytic sarcoma were exclusively in simGCGsim IR mice, whereas mutations in mice with hemangiosarcoma were exclusively in γ -IR mice. There was a small number of known CHIP gene mutations observed. This data could provide a well-controlled genotype/phenotype system in which IR-induced changes in clonal hematopoiesis (i.e., CHIP) and expression of these genes in the heart and other organs can be assessed for their contributions to the development of clinical phenotypes over the lifetime.

Sub-project 2:

Title: “Evaluation of Mosaic Loss of Y Chromosome and Y-Linked Gene Mutations after Exposure to Gamma and Simgcrsim Radiation during Lifespan of Male C57bl6/J Mice”

Background. The Y chromosome carries a mere 154 genes - less than one-tenth of the X chromosome. The vast majority of these 154 genes are not even characterized. Until this year, the Y chromosome has been the last human chromosome to be fully sequenced. Nevertheless, researchers have found the Y chromosome is missing from at least some white blood cells (WBC) in about 40% of 70-year-olds and 57% of 93-year-olds. In some older men, more than 80% of the cells can be short of the Y chromosome. Further, random microdeletions in the azoospermia factor (AZF) a, b, and c regions were detected in >90%, and tandem duplication and copy number polymorphism (CNP) of an additional 11 different Y-linked genes were detected in about 80% of males exposed to natural background radiation in Kerala, India. Interestingly, large structural clonal mosaicism of the X chromosome was analyzed in 38,303 women from cancer

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genome-wide association studies (20,878 cases and 17,425 controls) and detected 124 mosaic X events 42 Mb in 97 (0.25%) women. However, a small X chromosome mosaicism frequency increased with age (0.11% in 50-year-olds; 0.45% in 75-year-olds). These findings may suggest that the Y chromosome undergoes mosaic events ~90 times more frequently than the X chromosome in females. This could have substantial implications in the higher prevalence of men dying on average about 5 years earlier than women in the United States due to aging-related ailments such as cancer and cardiovascular disease.

Hypothesis. We hypothesize that gamma (?-IR) or simplified Galactic Cosmic Ray simulated radiation (simGCRsim-IR) of mice at a younger age may increase the rate of mutations in Y chromosome-linked genes and lead to mosaic loss of Y (mLOY) chromosome during their lifetime.

Methodology. We exposed 3-month-old male C57Bl/6J wild-type (WT) mice to a single dose of 100 cGy, 0.662 MeV of ¹³⁷Cs gamma-IR (?-IR) and 50 cGy, 500 MeV/n simGCRsim-IR. All control (no-IR), ?- and simGCRsim-IR were housed at 12/12h light cycle, and food and water were provided ad libitum for 22 months post-IR at which time mice were approaching the end of their lifespan. During this study, mice were observed for gross tumor development, all internal organs and blood as well as assessment of cardiac function by transthoracic echocardiography (ECHO) was performed at 14, 28 days and 12, 16, 22 months post-IR. Genomic DNA was isolated from white blood cells (WBC) and processed for whole exome sequencing (WES) on the Illumina NovaSeq-6000 platform, achieving an average coverage of 92% at a depth of 50x in the target region. Sequencing reads were aligned to the mm10 reference mouse genome using the BWA mem aligner and deduplicated PicardTools. Somatic variant calling was performed with the GATK Mutect2 pipeline. The detection of copy number changes was performed using the Control-FREEC tool.

Main Findings. Distribution of somatic mutation types in all study groups revealed that exonic mutations in the Y chromosome were detected only in irradiated groups, 11% in simGCRsim and 16.6% in Gamma. Distribution of the copy number variations (CNVs) across the genome in studied animals reveals that natural aging in non-IR samples leads to gain of CNVs on the Y chromosome, whereas IR samples showed a loss of CNVs in the Y chromosome. Exploration CNVs data revealed that IR led to a decline in copy numbers for the following 12 Y-linked genes: Usp9y, Uty, Ddx3y, Kdm5d, Eif2s3y, Tspy-ps, Uba1y, Zfy1, Gm16501, Gm6026, Zfy2, and Sry. The average copy numbers for the non-IR 12 and 22-month groups were 3 and 12.1, respectively. For the simGCRsim-IR groups at 12 and 16 months, the averages were 2.33 and 1.58, and for the 12, 16, and 22 months for gamma-IR groups, the averages were 1.83, 3.45, and 1.16. simGCRsim and gamma-IR induced CNV that were found in Y-linked genes in our studies are known to regulate male sex-related processes, such as spermatogenesis, initiation of male sex determination, spermatogonial stem cells via Wnt6/ β -catenin pathway. A set of the affected genes have been linked to various cancer such as colorectal cancer (Kdm5d, a histone demethylase), gonadoblastoma, testicular and prostate cancer (Tspy-ps) as well as in the pathophysiology of pulmonary hypertension (Uty) through negative regulation of proinflammatory cytokine levels. The most frequent type of mutation is IGR, however, exonic mutations are observed only in IR groups: 0.5 Mix (Gm21677) and gamma (Zfy2).

It must be noted that CNVs affect more nucleotides in the human genome than SNPs and can arise via several mechanisms including non-allelic homologous recombination (HR), and non-homologous end joining (NHEJ), both, are DNA repair mechanisms known to remove IR-induced damage, and retroelement insertions. As the fidelity of the HR and NHEJ are low and tend to introduce various mistakes into DNA sequence, CNVs can also lead to many negative consequences and have been implicated in intellectual disability, epilepsy, cancer, and other degenerative disease processes.

In summary, our findings suggest that both terrestrial and space-type IR led to a decline in copy number of protein-coding genes as early as 12 months after a single exposure which continues to decline towards the end of mice's lifespan. We strongly believe that well-designed and in-depth studies of the effects of IR are warranted to extend mLOY studies from discovery to mechanistic studies. An improved understanding of IR-mediated mLOY will allow advance determination of individual susceptibility and provide an early opportunity for the development of personalized mitigation of a wide spectrum of human diseases including cancer, neuro-, and cardiovascular diseases.

Sub-project 3:

Title: "Female and Male Hearts Respond Differently to Same Doses of Gamma and Simgersim Radiation – Sex Matters"

Background. Space radiation (IR) from Solar Particle Events (SPE) and Galactic Cosmic Rays (GCR), also known as high charge and energy (HZE) IR, is a primary risk associated with deep-space missions. There are limited animal and human studies on the risk of cardiovascular disease (CVD) development due to space-IR. During future exploration-type space missions, astronauts could be exposed to doses of space-type radiation (IR) (~0.4–0.5 Gy) from galactic cosmic rays (GCR). The cardiac effects induced by space-type IR, specifically simplified GCR simulated (simGCRsim)-IR, are not well-known. Sex-specific differences in response to gamma and simGCRsim IR are yet to be discovered.

Hypothesis. We hypothesize that there may be sex-specific differences in long-term gamma and simGCRsim-associated alterations in differential gene expression in the heart tissue. We also hypothesized that gamma and simGCRsim IR-induced biological responses are chronic, IR type-dependent, and may increase the relative risk for developing CVD.

Methodology. To test our hypotheses, we exposed 3-month-old male and female age-matched C57Bl/6J wild-type (WT) mice to ¹³⁷Cs-?-IR at 100 cGy, 0.662 MeV, and simGCRsim-IR at 50 cGy 500 MeV/n. We assessed cardiac function by transthoracic echocardiography (ECHO) at 28 days, and 12, 16, 22/18.5 (male/female)-months post-IR. To evaluate sex-associated differences in the regulation of the transcriptional landscape, total RNA isolated from male and female LV hearts was sequenced with Illumina NGS. Sequenced reads were splice-aligned to the mm10 mouse reference genome using the STAR aligner. Raw read counts were normalized with the DESeq2 R package and converted to log2 CPM values. Differential expression analysis and downstream bioinformatics analysis were performed using oposSOM R package.

Main findings. Longitudinal Mouse Lifetime Echocardiography. Compared to no-IR controls, in male WT mice, ECHO data revealed that a single full-body ?- and simGCRsim-IR, lead to a 25-30% decrease ($p < 0.01$) in Fractional Shortening % (FS%) and Ejection Fraction % (EF%) of the heart 28 days post-IR. Interestingly, the EF% and FS% were not affected in female mice, indicating no change in systolic function 28 days after exactly the same exposure doses of ?- or simGCRsim-IR. The EF% and FS% decrease in male mice were associated with a 10-15% decrease ($p < 0.05$) in LV posterior wall thickness (PWth) in systole and an increase in end-systolic volume (ESV), indicating that decreases in

FS% and EF% are starting to affect cardiac morphology and function in male mice. No change in these parameters was observed in female mice at 28 days. These early time point findings suggest that at these doses female mice do not reveal any CV functional and structural changes, whereas male mice show significant decreases in global systolic function that are also associated with structural changes. There were no additional degenerative IR-induced changes relative to normal aging at 12 and 16 months post-IR. Interestingly, at 22 months, 50 cGy simGCRsim-IR male mice exhibited preserved LV systolic function but altered LV size and mass, which were associated with elevated levels of cardiac fibrosis, inflammation, and hypertrophy markers Tgfβ1, Mcp1, Mmp9, and βMhc in LV tissue (qPCR), suggesting that space-type IR may induce the cardiac remodeling processes that are commonly associated with diastolic dysfunction. Again, no alteration in LV systolic function or LV size and mass was detected in female mice at 18.5 months (the last time point examined for females).

Main findings. RNAseq Analyses of Male and Female LV Tissue. RNA-seq analyses of male and female LV tissue at 16 and 22/18.5 (male/female) months revealed genes that were upregulated in response to IR in mice of both sexes. Enrichment analysis of the upregulated genes in LV from both male and female mice showed an overlap with pathways such as sarcolemma, cardiac muscle contraction, and regulation of heart rate. Interestingly, LV tissue isolated from male mice exhibited down-regulation of hemoglobin alpha and beta chain genes in response to both simGCRsim- and gamma-IR, while no change in the expression of these genes was observed in LVs from female mice. In male LVs, the top enriched pathways were chloride transmembrane transport and cytokine activity. In addition, a set of ribosomal genes was upregulated only in simGCRsim-IR LVs of male mice, while females showed only age-related changes for the same set of ribosomal genes.

Differential gene expression in males - 1) changes in LV transcriptome at 16 months observed only for simGCRsim; 2) gamma radiation results only in downregulation of a small number of genes at 22 months. Differential gene expression in females - 1) simGCRsim and gamma irradiation resulted in a comparable number differentially expressed genes (DEGs) in LV at 16 months; 2) changes in LV transcriptome at 18.5 months observed only for simGCRsim. Therefore, simGCRsim causes a substantially higher number of differentially expressed genes than gamma radiation at all time points.

More than 95% of DEGs are sex specific. There were only 6 overlapping DEGs between male and female groups at all times and IR types examined. Specific overlapping DEGs are: Tspan4: tetraspanin 4 regulation of cell development, regulates activation, growth, and motility. Or5m3b: olfactory receptor family 5 subfamily M member 3B sensory perception of smell. Arntl: aryl hydrocarbon receptor nuclear translocator-like involved in abnormal circadian regulation of heart rate, decreased heart rate, decreased heart weight. Spon2: Spondin 2 cell adhesion protein essential in the innate immune responses, macrophage phagocytosis. Tef: thyrotroph embryonic factor circadian clock associated gene, has a role in the smooth muscle cell and blood pressure regulation. Mid1p1: Midline 1 interacting protein 1 involved in liver lipogenesis, HCC metastasis via MMP9.

We also observed shared DEGs within sex comparison groups. There are 7 shared DEGs between 18.5 female gamma and simGCRsim radiated groups, Dbp, Bhlhe41, Picalm, Unc119b, Tcap, Ppfla1, and Mapk4. In addition, there was one intersection between 16-month and 22-month simGCRsim male groups which is the St6galnac3 gene.

The set of upregulated DEGs in male hearts at 16 and 22 months indicate a regulation of negative processes such as abnormal heart morphology, abnormal myocardial fiber morphology, cardiac fibrosis, small heart, decreased heart weight, and abnormal circadian regulation of heart rate. Interestingly, in female mice heart tissue a single gene (Hsd17b4) responsible for the enlarged heart was upregulated at 16 months, suggesting that the heart may be compensating by hypertrophy. In addition, a few genes regulating immune responses were also upregulated in female mice heart tissue.

In summary, our findings suggest significant and long-lasting IR-induced (both, simGCRsim- and ?-IR) gene expression changes in the LV function in both male and female mice, specifically - 1) most of the differentially expressed genes in radiation groups are sex specific; 2) simGCRsim radiation have more impact on the gene expression of left ventricular tissue; 3) the identification of a small number of shared genes in comparisons across different types of IR and sham treatments suggests an insignificant overlap between radiation exposure type and alterations in the transcriptome.

Bibliography Type:

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