

Analysis Of DNA-Damage And Cancer-Related Gene Expression Following Space-Radiation Exposure Using NASA Open Science Data

Dr. Ohmini Krishnamurthy Rajendran

Consultant Radiologist, KIMS Hospital and Research Centre Bengaluru, India. Orcid id- 0009-0006-1516-5002

Abstract

Space exploration exposes astronauts to unique radiation environments that differ fundamentally from terrestrial radiation. Galactic cosmic rays (GCR), solar particle events (SPE), and high-energy heavy ions produce complex DNA damage that may increase long-term risks of cancer, cardiovascular disease, neurodegeneration, and accelerated aging. As human spaceflight progresses toward prolonged missions to the Moon and Mars, understanding the molecular consequences of space radiation has become a major priority in space biology and precision medicine. Recent advances in NASA's Open Science initiative have enabled researchers worldwide to access extensive genomic, transcriptomic, radiation dosimetry, and biological datasets generated through experiments conducted aboard the International Space Station (ISS), ground-based radiation simulators, and spaceflight analog studies. These openly available datasets provide unprecedented opportunities to investigate DNA-damage signaling, genome instability, oxidative stress, immune dysregulation, apoptosis, and cancer-related gene expression following exposure to the unique space radiation environment. High-throughput sequencing technologies, bioinformatics pipelines, systems biology, artificial intelligence, and network-based computational analyses have substantially improved the interpretation of these complex datasets by enabling identification of radiation-responsive molecular pathways, biomarkers, and regulatory networks. This review provides a comprehensive overview of DNA-damage mechanisms induced by space radiation, NASA Open Science resources, computational approaches for transcriptomic analysis, major cancer-associated signaling pathways, current biological discoveries, translational applications, and future directions for precision space medicine.[1]

Keywords: Space radiation, NASA Open Science, DNA damage, Gene expression, Cancer biology, Transcriptomics, Spaceflight, Galactic cosmic rays, Bioinformatics, Precision medicine.

1. Introduction

Human exploration beyond low-Earth orbit represents one of the greatest scientific and technological challenges of the twenty-first century. Missions planned for the Artemis program, the Lunar Gateway, and future expeditions to Mars will expose astronauts to prolonged periods of deep-space radiation unlike any encountered on Earth. While advances in spacecraft engineering continue to improve mission safety, biological exposure to ionizing radiation remains one of the principal health risks limiting long-duration human spaceflight.[2]

Unlike terrestrial radiation, which primarily consists of low-linear energy transfer (LET) photons such as X-rays and gamma rays, the space environment contains highly energetic charged particles capable of producing dense ionization tracks throughout biological tissues. Galactic cosmic rays contain high-energy protons, alpha particles, and high atomic number high-energy (HZE) ions such as iron, silicon, oxygen, and carbon nuclei. Solar particle events

additionally generate bursts of energetic protons capable of delivering substantial radiation doses during relatively short periods. Together, these radiation sources create complex biological injuries that are difficult to reproduce under conventional laboratory conditions.[3]

DNA is among the primary cellular targets of ionizing radiation. High-energy particles induce single-strand breaks, double-strand breaks, clustered DNA lesions, oxidative base modifications, chromosomal rearrangements, telomere dysfunction, and persistent genomic instability. Although cells possess sophisticated DNA repair systems, repeated or inefficient repair may result in mutations that accumulate over time, increasing susceptibility to malignant transformation. Consequently, understanding radiation-induced DNA damage has become central to both astronaut health research and radiation oncology.[4]

Modern molecular biology has revolutionized the study of radiation responses through genome-wide transcriptomic technologies. RNA sequencing, microarrays, single-cell sequencing, epigenomic profiling, and proteomics now allow comprehensive investigation of cellular responses following radiation exposure. These technologies reveal dynamic changes in thousands of genes simultaneously, providing insights into DNA repair pathways, inflammatory signaling, oxidative stress responses, immune regulation, apoptosis, senescence, and cancer-associated biological processes.[5]

NASA has accelerated these investigations through its Open Science initiative, which promotes transparent access to spaceflight research data, computational tools, standardized metadata, and reproducible analytical workflows. Public repositories containing transcriptomic datasets from astronaut samples, cultured human cells, rodents, organoids, microorganisms, and plant systems have become valuable resources for biomedical researchers seeking to understand the molecular consequences of spaceflight and radiation exposure.[6]

Analysis of these publicly available datasets provides opportunities not only to improve astronaut safety but also to advance terrestrial medicine. Space radiation induces biological mechanisms that overlap with cancer development, aging, tissue degeneration, and radiation therapy responses observed in clinical oncology. Consequently, discoveries emerging from space biology increasingly contribute to precision medicine, biomarker discovery, and development of novel radioprotective interventions.[7]

2. Space Radiation Environment and Biological Characteristics

The radiation environment encountered during spaceflight differs substantially from natural background radiation on Earth because Earth's atmosphere and magnetic field normally shield living organisms from most high-energy cosmic particles. Beyond these protective barriers, astronauts are continuously exposed to ionizing radiation originating from both galactic and solar sources.[8]

Galactic cosmic rays constitute one of the most significant contributors to chronic radiation exposure during deep-space missions. These particles originate from distant supernovae and other high-energy astrophysical events. Approximately eighty-five percent of galactic cosmic rays consist of protons, while helium nuclei account for roughly fourteen percent. The remaining fraction comprises heavy charged ions, commonly referred to as HZE particles, including iron, nickel, oxygen, silicon, and carbon nuclei. Although relatively rare, HZE particles produce disproportionately severe biological damage because of their extremely high linear energy transfer.[9]

Solar particle events represent another major radiation hazard. These unpredictable events occur during periods of intense solar activity and may expose astronauts to large proton doses over relatively short durations. The biological consequences depend upon the magnitude of the event, shielding effectiveness, and mission location. Unlike galactic cosmic rays, solar particle events may produce acute radiation syndromes if protective measures are insufficient.[10]

Secondary radiation further complicates biological exposure. High-energy particles interacting with spacecraft materials generate secondary neutrons, gamma rays, and other charged particles that contribute additional radiation doses. Consequently, accurate estimation of astronaut exposure requires sophisticated radiation transport models capable of accounting for both primary and secondary particle interactions.[11]

The biological effects of space radiation differ markedly from those produced by conventional medical radiation. Low-LET radiation generally produces isolated DNA lesions that cells frequently repair efficiently. In contrast, HZE ions create densely clustered DNA damage involving multiple double-strand breaks, oxidative lesions, and chromosomal fragmentation within localized genomic regions. Such clustered lesions are considerably more difficult for cellular repair systems to resolve accurately, increasing mutation frequency and chromosomal instability.[12]

Another defining characteristic of space radiation is chronic low-dose exposure. Rather than receiving a single therapeutic dose, astronauts experience continuous radiation accumulation over weeks, months, or years. The resulting biological responses involve persistent oxidative stress, chronic inflammation, mitochondrial dysfunction, altered cellular metabolism, immune dysregulation, and long-term genomic instability that may continue long after exposure has ended.[13]

Individual susceptibility also contributes substantially to radiation risk. Genetic polymorphisms affecting DNA repair enzymes, antioxidant defense systems, inflammatory mediators, and cell-cycle regulation influence how efficiently different individuals respond to radiation-induced injury. Personalized risk assessment therefore represents an increasingly important component of future astronaut selection and medical monitoring.[14]

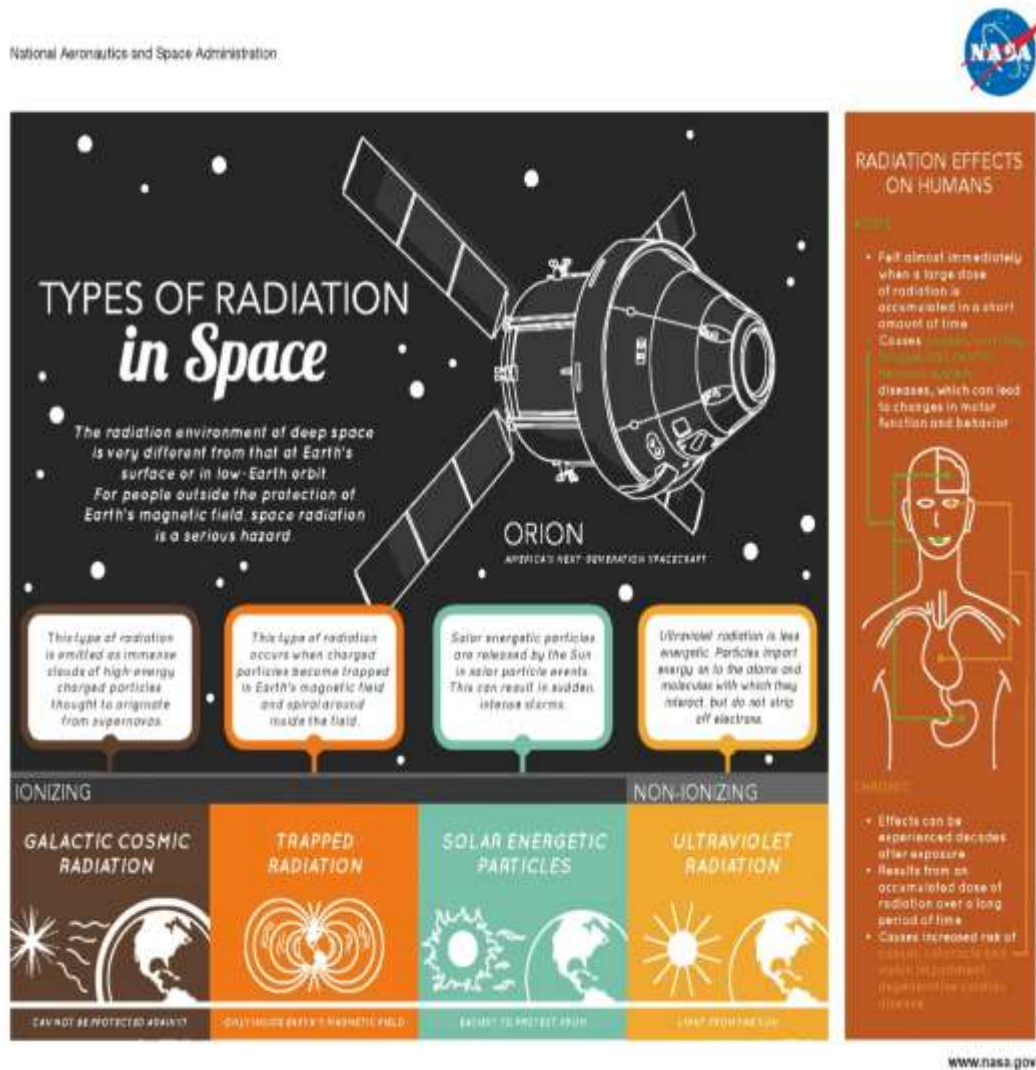


Figure 1. Major sources of radiation encountered during spaceflight. The deep-space radiation environment includes galactic cosmic rays, solar energetic particles, trapped radiation, and secondary particles generated through interactions with spacecraft materials. High-energy charged particles can penetrate biological tissues and induce complex molecular damage. Image credit: NASA/JPL.

3. NASA Open Science Data Resources for Space Biology

The growing emphasis on open science has fundamentally transformed biomedical research by promoting transparency, accessibility, reproducibility, and collaborative discovery. NASA has become a global leader in this movement by making large collections of biological, genomic, physiological, imaging, and environmental datasets publicly available through multiple coordinated platforms.[15]

One of the most important resources is NASA GeneLab, an open-access omics repository specifically developed to support space biology research. GeneLab contains transcriptomic, genomic, proteomic, metabolomic, and epigenomic datasets generated from numerous organisms exposed to actual spaceflight, simulated microgravity, and ground-based radiation experiments. These datasets include standardized metadata, experimental protocols, quality-control information, and processed analytical outputs that facilitate reproducible computational analysis.[16]

Gene expression datasets encompass a broad spectrum of biological models including cultured human cells, stem cells, immune cells, endothelial cells, fibroblasts, mouse tissues, rat models, plant systems, fungi, bacteria, and other experimental organisms. Such diversity enables investigators to compare radiation responses across multiple biological systems while identifying conserved molecular mechanisms associated with DNA damage and cancer development.[17]

NASA's Open Science Data Repository further integrates experimental metadata with radiation dosimetry, environmental monitoring, physiological measurements, and mission-specific information. Researchers can therefore investigate how radiation exposure interacts with microgravity, altered circadian rhythms, confinement, nutritional changes, and psychological stress to influence gene expression during spaceflight.[18]

Open computational workflows accompany many publicly available datasets. Standardized bioinformatics pipelines reduce analytical variability by applying consistent methods for sequence alignment, quality assessment, normalization, differential expression analysis, pathway enrichment, and functional annotation. These standardized approaches improve reproducibility while allowing investigators worldwide to generate comparable biological conclusions from shared datasets.[19]

The availability of openly accessible molecular data has substantially accelerated international collaboration. Academic institutions, government laboratories, hospitals, computational scientists, and biotechnology companies can independently validate findings, develop new analytical algorithms, identify candidate biomarkers, and integrate multiple datasets through systems biology approaches. This collaborative ecosystem increases scientific rigor while maximizing the value obtained from costly spaceflight experiments.[20]

NASA Open Science resources also support educational initiatives by providing students and early-career researchers with authentic biological datasets suitable for computational training. Through reproducible workflows and openly available documentation, investigators can develop expertise in transcriptomics, machine learning, network biology, and precision medicine while contributing to ongoing discoveries in space health research.[21]

4. Mechanisms of DNA Damage Following Space-Radiation Exposure

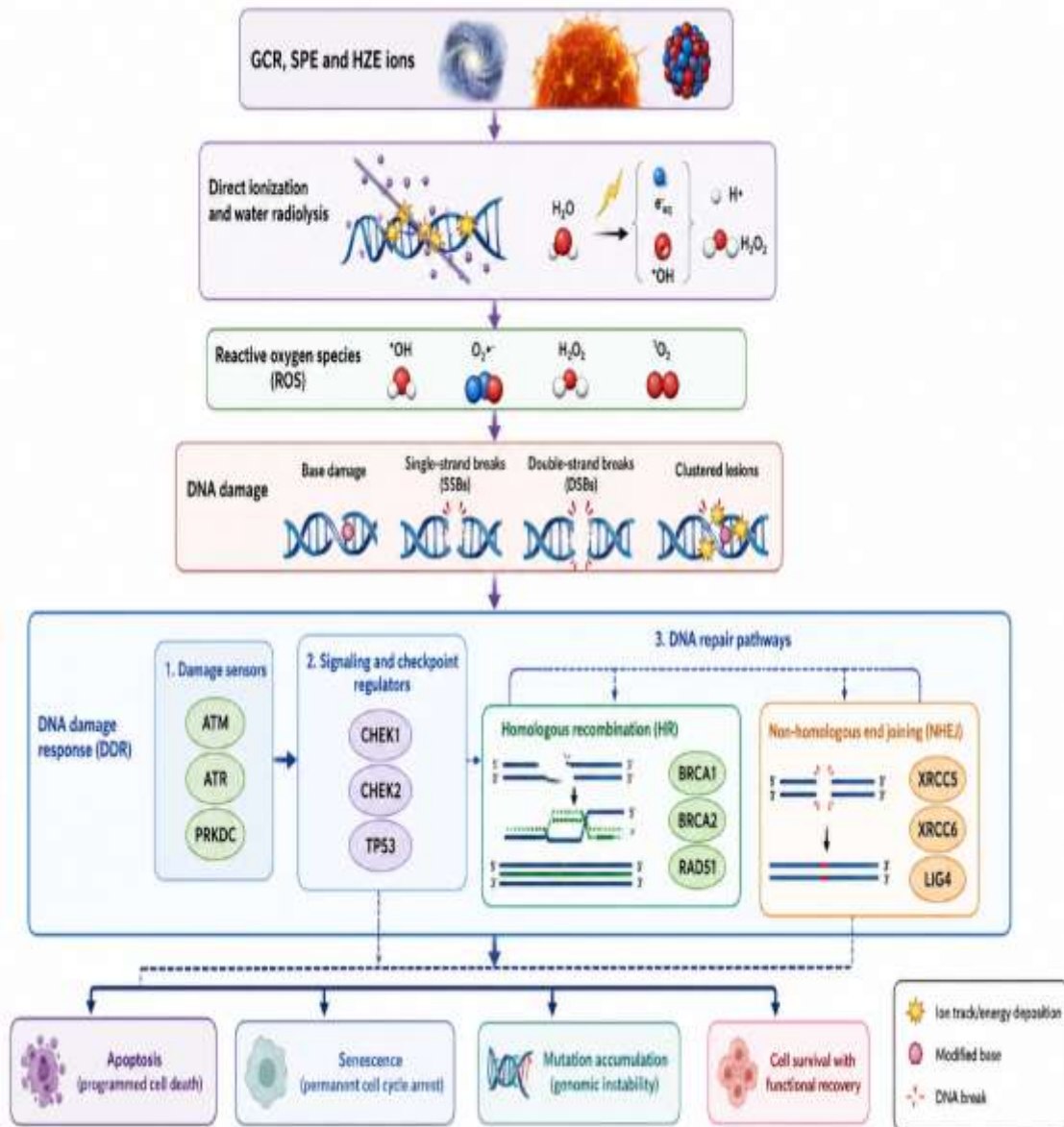


Figure 2. Molecular mechanisms linking space-radiation exposure to DNA damage and carcinogenic risk. Direct particle interactions and radiation-induced reactive oxygen species generate simple and clustered DNA lesions. Cellular outcomes depend on damage recognition, checkpoint activation, repair fidelity, apoptosis and senescence. Inaccurate repair or survival of damaged cells may promote mutation accumulation and genomic instability.

DNA damage represents one of the earliest and most critical biological consequences of ionizing radiation. High-energy charged particles deposit energy directly into DNA

molecules while simultaneously generating reactive oxygen and nitrogen species through radiolysis of intracellular water. These complementary mechanisms produce diverse forms of genomic injury that activate complex cellular stress responses.[22]

Single-strand DNA breaks occur frequently following radiation exposure and are generally repaired efficiently through base excision repair pathways. However, simultaneous damage occurring on opposing DNA strands generates double-strand breaks, which are considerably more hazardous because they threaten chromosomal integrity. Improper repair may produce deletions, inversions, translocations, amplifications, or permanent mutations that contribute to carcinogenesis.[23]

Space radiation is particularly effective at generating clustered DNA lesions in which multiple forms of damage occur within a few helical turns of DNA. These complex lesions often contain combinations of strand breaks, oxidized bases, abasic sites, and crosslinks that overwhelm conventional repair pathways. Persistent clustered damage increases replication errors and genomic instability, hallmarks of malignant transformation.[24]

Oxidative stress provides an additional mechanism of genomic injury. Radiation-induced reactive oxygen species attack nucleic acids, proteins, membrane lipids, and mitochondria. Oxidized DNA bases such as 8-oxoguanine accumulate following exposure and, if unrepaired, promote mutagenesis during DNA replication. Persistent oxidative stress further amplifies inflammatory signaling and accelerates cellular aging.[25]

Cells respond rapidly to DNA damage by activating highly conserved signaling pathways collectively known as the DNA damage response. Sensor proteins including ATM, ATR, and DNA-dependent protein kinase detect genomic lesions and initiate phosphorylation cascades that coordinate cell-cycle arrest, DNA repair, apoptosis, or cellular senescence. Activation of tumor suppressor proteins such as p53 enables damaged cells to either repair their genomes or undergo programmed cell death when injury becomes irreparable.[26]

Repair mechanisms include non-homologous end joining and homologous recombination, which repair double-strand breaks through distinct molecular pathways. Although homologous recombination generally maintains higher genomic fidelity, non-homologous end joining predominates in many differentiated cells and may introduce small insertions or deletions that accumulate over repeated radiation exposure.[27]

Persistent DNA damage may also alter chromatin organization and epigenetic regulation. Radiation influences DNA methylation, histone modifications, chromatin accessibility, and non-coding RNA expression, producing long-lasting changes in gene regulation even after physical DNA lesions have been repaired. These epigenetic alterations increasingly appear to contribute to radiation-induced cancer susceptibility and long-term biological adaptation following spaceflight.[28]

5. Transcriptomic Analysis of Radiation-Responsive Gene Expression

Transcriptomic analysis provides a comprehensive approach for investigating how space-radiation exposure alters cellular activity. RNA sequencing and microarray technologies measure the expression of thousands of genes simultaneously, allowing researchers to identify molecular pathways activated or suppressed after irradiation. Publicly available NASA datasets can therefore be used to compare exposed biological samples with matched controls and determine the magnitude, direction, and duration of radiation-associated transcriptional changes.[29]

A typical analytical workflow begins with evaluation of raw sequencing quality, removal of technical artifacts, alignment of sequencing reads to a reference genome, and quantification

of gene-level expression. Normalization is subsequently performed to account for differences in sequencing depth and sample composition. Differential-expression algorithms then identify genes showing statistically significant changes between experimental groups.[30]

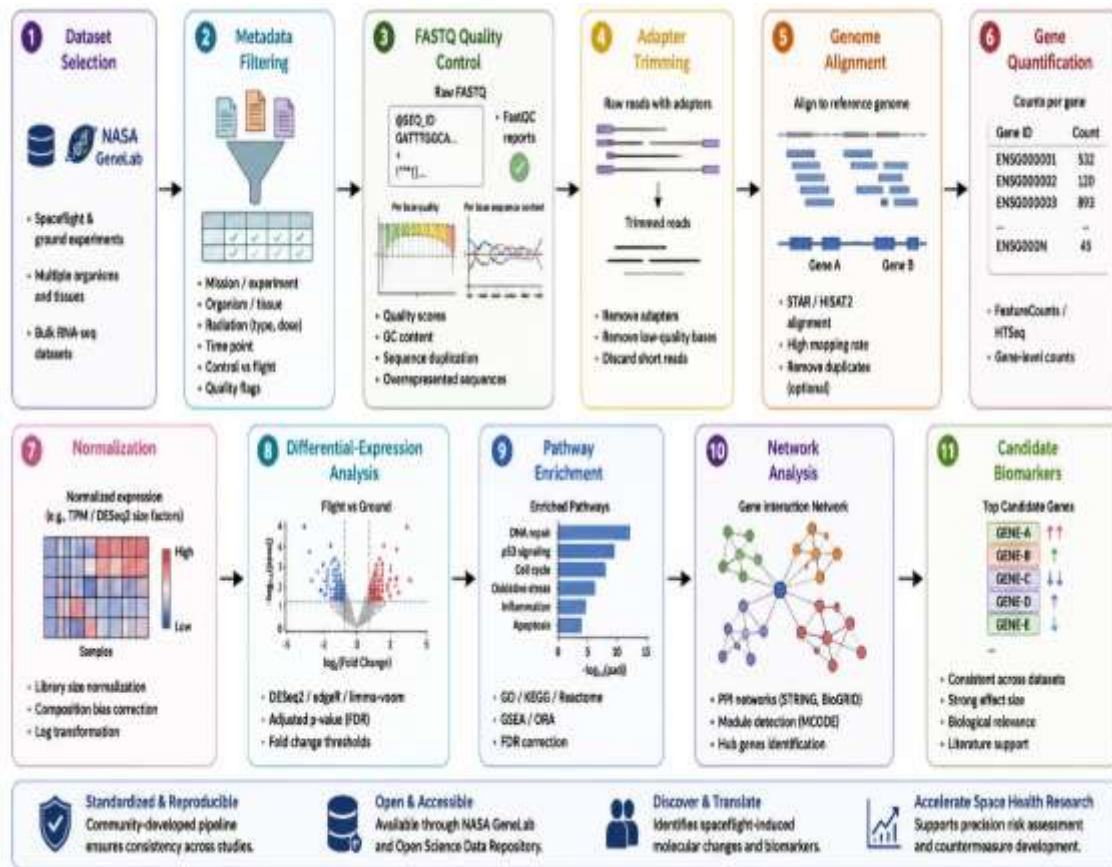


Figure 3. Proposed bioinformatics workflow for analysis of radiation-responsive gene expression using NASA OSDR data. After dataset and metadata selection, sequencing data undergo quality control, alignment, quantification and normalization. Differentially expressed genes are subsequently evaluated using enrichment, network and biomarker-discovery approaches.

Radiation-response studies frequently apply thresholds based on adjusted probability values and fold changes to prioritize biologically meaningful genes. However, individual genes should not be interpreted in isolation. Pathway enrichment, gene-set analysis, network modeling, and functional annotation are required to determine whether groups of altered genes participate in common processes such as DNA repair, oxidative stress, inflammation, apoptosis, senescence, or tumorigenesis.[31]

Batch effects represent an important concern when integrating datasets obtained from different missions, laboratories, sequencing platforms, tissues, or radiation conditions. Computational correction methods can reduce technical variability, but biological differences must be preserved. Careful examination of experimental metadata—including

radiation type, dose, dose rate, exposure duration, organism, tissue, age, sex, and collection time—is therefore essential for reliable interpretation.[32]

Longitudinal transcriptomic analysis is particularly valuable because radiation responses evolve over time. Early transcriptional changes may reflect immediate DNA-damage sensing and cell-cycle arrest, whereas later alterations may indicate persistent inflammation, tissue remodeling, immune dysfunction, or genomic instability. Repeated sampling helps distinguish transient adaptive responses from sustained molecular changes that may contribute to cancer risk.[33]

6. Major DNA-Damage Response Genes

Space-radiation exposure influences numerous genes responsible for detecting DNA lesions, coordinating repair, regulating the cell cycle, and eliminating severely damaged cells. Among the most important are ATM, ATR, PRKDC, TP53, CHEK1, and CHEK2, which form central components of the cellular DNA-damage response.[34]

ATM is predominantly activated by DNA double-strand breaks and initiates signaling pathways that regulate repair, checkpoint activation, and apoptosis. ATR responds strongly to replication stress and regions of single-stranded DNA generated during stalled replication. PRKDC encodes the catalytic component of DNA-dependent protein kinase, which plays a major role in non-homologous end joining.[35]

Downstream checkpoint genes temporarily inhibit cell-cycle progression, preventing damaged DNA from being replicated or transmitted to daughter cells. CHEK1 and CHEK2 regulate transitions between cell-cycle phases by modifying proteins involved in DNA synthesis and mitosis. Failure of these checkpoints may allow genetically unstable cells to continue dividing.[36]

The TP53 tumor-suppressor gene occupies a central position in radiation biology. Following DNA damage, p53 regulates genes involved in cell-cycle arrest, repair, senescence, metabolism, and programmed cell death. Increased expression of CDKN1A, which encodes the p21 checkpoint protein, commonly reflects activation of the p53 pathway. Persistent disruption of this regulatory system is strongly associated with malignant transformation.[37]

Genes involved in homologous recombination—including BRCA1, BRCA2, RAD51, and PALB2—help restore damaged DNA using an intact homologous template. Other genes, such as XRCC5, XRCC6, LIG4, and DCLRE1C, contribute to non-homologous end joining. Altered expression or reduced activity of these pathways may increase chromosomal rearrangements and mutation accumulation following exposure to high-LET particles.[38]

7. Oxidative Stress and Mitochondrial Dysfunction

Radiation-induced reactive oxygen species produce damage that extends beyond the initial particle track. Mitochondria are particularly vulnerable because they generate cellular energy, regulate apoptosis, and contain their own DNA. Damage to mitochondrial membranes and respiratory-chain components may increase the production of additional reactive oxygen species, creating a self-amplifying cycle of oxidative injury.[39]

Genes regulated by the transcription factor NRF2, encoded by NFE2L2, contribute to antioxidant defense by increasing the expression of detoxification enzymes. Radiation-associated alterations may be observed in genes such as HMOX1, NQO1, SOD2, CAT, GPX1, and members of the glutathione metabolic pathway. Their activation may indicate an adaptive attempt to restore redox balance.[40]

Persistent mitochondrial dysfunction may alter cellular metabolism, ATP production, calcium signaling, and apoptotic regulation. These changes are relevant to carcinogenesis because cancer cells frequently undergo metabolic reprogramming that supports survival under stressful conditions. Transcriptomic evidence of disrupted oxidative phosphorylation, glycolysis, fatty-acid metabolism, or mitochondrial biogenesis may therefore reveal connections between radiation injury and cancer-associated cellular adaptation.[41]

Mitochondrial DNA is especially sensitive to oxidative damage because it is located near the electron-transport chain and possesses more limited protective organization than nuclear DNA. Accumulated mitochondrial mutations may contribute to chronic inflammation, altered immune signaling, tissue degeneration, and abnormal cell proliferation.[42]

8. Cell-Cycle Regulation, Apoptosis, and Senescence

Cell-cycle control is essential for preventing damaged cells from undergoing division. Radiation exposure commonly changes the expression of cyclins, cyclin-dependent kinases, checkpoint proteins, and mitotic regulators. Suppression of genes controlling DNA replication and mitosis may represent protective cell-cycle arrest, whereas inappropriate activation may indicate checkpoint failure.[43]

Genes associated with apoptosis include BAX, BAK1, BCL2, MCL1, CASP3, CASP8, CASP9, and APAF1. The balance between pro-apoptotic and anti-apoptotic signaling determines whether an irradiated cell survives or undergoes programmed death. Cells that evade apoptosis despite severe genomic injury may retain mutations capable of promoting future malignancy.[44]

Radiation may also induce cellular senescence, a stable state of proliferative arrest accompanied by extensive changes in gene expression. Senescent cells frequently secrete inflammatory cytokines, growth factors, and extracellular-matrix proteins collectively described as the senescence-associated secretory phenotype. Although senescence can prevent damaged cells from proliferating, the accumulation of senescent cells may produce chronic inflammation and create tissue environments that support tumor development.[45] Potential senescence-associated markers include CDKN1A, CDKN2A, GLB1, and genes encoding inflammatory mediators such as IL6, IL1B, and CXCL8. Because no single marker definitively establishes senescence, transcriptomic findings should be interpreted together with cellular, biochemical, or histological measurements.[46]

9. Inflammation, Immune Dysregulation, and Cancer Risk

The immune system is highly sensitive to both spaceflight stress and ionizing radiation. Radiation can reduce lymphocyte viability, alter immune-cell composition, modify cytokine production, and impair immune surveillance. These effects may influence the body's ability to recognize and eliminate transformed cells.[47]

Transcriptomic datasets may reveal altered activity in interferon signaling, nuclear factor kappa B pathways, Toll-like receptor responses, antigen presentation, T-cell activation, and inflammatory cytokine networks. Genes such as STAT1, STAT3, IRF7, NFKB1, RELA, JAK1, and JAK2 may participate in these responses.[48]

Inflammation has complex effects on cancer development. Acute inflammatory signaling can support tissue repair and removal of damaged cells, whereas persistent inflammation may promote oxidative stress, angiogenesis, genomic instability, and abnormal cellular proliferation. Chronic inflammatory mediators may also remodel the tissue microenvironment, enabling damaged cells to survive and expand.[49]

Changes in antigen-processing genes, major histocompatibility complex molecules, cytotoxic T-cell markers, and natural-killer-cell pathways may indicate reduced tumor immune surveillance. Conversely, excessive immune activation may contribute to tissue injury and long-term inflammatory disease. Integrating transcriptomic data with blood-cell counts, cytokine measurements, and physiological observations can provide a more complete assessment of radiation-associated immune risk.[50]

10. Cancer-Related Signaling Pathways

Cancer development usually results from progressive disruption of multiple regulatory systems rather than alteration of a single gene. Space-radiation datasets should therefore be analyzed for coordinated changes across oncogenic and tumor-suppressive pathways.[51]

The PI3K–AKT–mTOR pathway regulates cellular growth, metabolism, survival, and protein synthesis. Abnormal activation may allow damaged cells to resist apoptosis and continue proliferating. The RAS–RAF–MEK–ERK pathway similarly influences growth-factor signaling and cell division. Radiation-associated alterations in either pathway may contribute to adaptive survival or malignant transformation.[52]

The WNT– β -catenin pathway regulates stem-cell behavior, differentiation, and tissue renewal, while NOTCH and Hedgehog signaling influence cellular identity and developmental programs. Dysregulation of these pathways may promote cancer stem-cell characteristics, abnormal regeneration, and treatment resistance.[53]

The transforming growth factor beta pathway has context-dependent functions. It can suppress early tumor development by limiting proliferation, but in established tumors it may promote invasion, immune evasion, fibrosis, and metastasis. Radiation-induced expression of extracellular-matrix genes and epithelial–mesenchymal transition markers may indicate tissue remodeling associated with this pathway.[54]

Angiogenesis-related genes, including VEGFA, HIF1A, and their downstream targets, may also respond to radiation-induced hypoxia and oxidative stress. Persistent activation of hypoxia signaling can promote vascular remodeling, metabolic adaptation, and survival of genetically abnormal cells.[55]

11. Network and Pathway-Based Interpretation

Differential-expression lists alone provide limited biological insight because genes function within interconnected regulatory networks. Pathway-enrichment analysis identifies biological processes that are statistically overrepresented among altered genes, while protein-interaction networks reveal highly connected regulatory hubs.[56]

Co-expression analysis can group genes showing similar expression patterns across samples. These modules may correspond to DNA repair, immune activity, mitochondrial function, cell-cycle regulation, or tissue-specific responses. Associations between gene modules and radiation dose, particle type, or exposure duration can help identify molecular signatures of biological risk.[57]

Graph-based methods are particularly useful for integrating transcriptomic data with protein interactions, transcription-factor networks, epigenetic information, and known cancer pathways. Central genes identified through network analysis may serve as candidate biomarkers or therapeutic targets, although computational findings require experimental validation.[58]

Cross-dataset comparison further strengthens interpretation. Genes repeatedly altered across different tissues, organisms, missions, or radiation experiments may represent

conserved radiation-response mechanisms. In contrast, tissue-specific changes may reveal organ-dependent vulnerabilities relevant to leukemia, lung cancer, gastrointestinal malignancy, brain tumors, or other radiation-associated conditions.[59]

12. Machine Learning and Predictive Biomarker Discovery

Machine-learning algorithms can analyze high-dimensional NASA datasets to identify combinations of genes that distinguish irradiated samples from controls. Supervised models may also classify radiation quality, estimate dose, predict recovery, or identify samples with persistent DNA-damage signatures.[60]

Feature-selection methods reduce thousands of genes to smaller biomarker panels with potential diagnostic value. However, small sample sizes and large numbers of molecular variables create a substantial risk of overfitting. Nested cross-validation, independent test datasets, dimensionality reduction, and external validation are therefore necessary for credible performance estimates.[61]

Interpretable machine-learning methods can identify which genes contribute most strongly to a prediction. Such transparency is important when proposed biomarkers are linked to astronaut medical monitoring or cancer-risk assessment. Predictions should also be evaluated across sex, age, ancestry, tissue type, and mission conditions to reduce algorithmic bias.[62]

Multimodal models may ultimately combine gene-expression profiles with radiation dosimetry, clinical measurements, immune markers, physiological monitoring, and individual genetic susceptibility. These integrated systems could support personalized evaluation of radiation injury more effectively than transcriptomic data alone.[63]

13. Experimental Validation and Biological Interpretation

Computational analysis of open datasets generates hypotheses but does not independently establish causation. Candidate genes should be validated using quantitative polymerase chain reaction, protein-expression assays, immunofluorescence, chromosomal-damage measurements, or functional DNA-repair experiments.[64]

Gene-expression changes do not always correspond directly to protein abundance or biological activity. Post-transcriptional regulation, protein degradation, phosphorylation, cellular localization, and metabolic conditions may substantially modify the final functional response. Integration with proteomic, metabolomic, epigenomic, and phenotypic data can therefore improve biological interpretation.[65]

Experimental models must also reflect the complexity of space radiation. Many studies use acute exposure to a single particle type, whereas astronauts experience chronic mixed-field radiation combined with microgravity and other environmental stressors. Findings obtained from simplified models should consequently be interpreted cautiously before being translated into human risk estimates.[66]

14. Translational Importance for Astronaut Health and Terrestrial Oncology

Radiation-responsive gene signatures may contribute to personalized astronaut monitoring by identifying individuals who develop unusually persistent DNA damage, oxidative stress, immune dysfunction, or inflammatory activation. Such information could guide mission-specific surveillance, shielding strategies, nutritional interventions, pharmaceutical countermeasures, and postflight follow-up.[67]

The same findings may benefit terrestrial oncology. Genes involved in radiation sensitivity are relevant to radiotherapy response, normal-tissue toxicity, tumor resistance, and secondary-cancer development. NASA datasets may therefore provide complementary evidence for discovering biomarkers that predict how cancer patients respond to therapeutic radiation.[68]

Space-biology research may also support development of radioprotective agents targeting antioxidant pathways, DNA repair, inflammation, mitochondrial dysfunction, or senescent-cell accumulation. Candidate interventions would require rigorous evaluation to ensure that protection of healthy tissues does not unintentionally promote survival of genomically damaged or malignant cells.[69]

By combining openly accessible molecular data with reproducible computational methods, space-radiation research creates a bridge between astronaut health, cancer biology, aging research, and precision medicine. This interdisciplinary framework provides the foundation for more accurate risk assessment and development of individualized countermeasures for future long-duration missions.[70]

15. Challenges in the Analysis of NASA Open Science Data

Although NASA Open Science resources provide valuable opportunities for investigating radiation-associated gene expression, several methodological limitations must be considered. Spaceflight experiments commonly contain relatively small sample sizes because launching biological materials, maintaining experimental conditions, and collecting specimens in space are technically difficult and expensive. Limited sample numbers reduce statistical power and increase the possibility that isolated findings may result from biological variability rather than reproducible radiation effects.[71]

Radiation exposure is also difficult to separate from other components of the space environment. Microgravity, confinement, altered atmospheric composition, disrupted circadian rhythms, psychological stress, nutritional changes, and spacecraft-specific environmental conditions may independently affect gene expression. Consequently, molecular differences between flight and ground-control samples should not automatically be attributed exclusively to radiation.[72]

Ground-based radiation studies provide more controlled exposure conditions but cannot completely reproduce the complex radiation fields encountered in space. Astronauts are exposed to mixtures of protons, secondary particles, and HZE ions delivered at low dose rates over extended periods. In contrast, laboratory experiments frequently employ one particle type administered over a relatively short duration. These differences may influence DNA-damage complexity, repair kinetics, inflammatory responses, and long-term carcinogenic risk.[73]

Tissue selection represents another important limitation. Radiation responses vary among blood cells, epithelial tissues, the nervous system, the gastrointestinal tract, bone marrow, lungs, liver, and reproductive organs. Findings obtained from one tissue or cultured cell line cannot necessarily be generalized to the entire human body. Cell-culture systems may also lack the immune, vascular, stromal, and hormonal interactions that influence radiation responses in living organisms.[74]

Technical variation may arise from differences in sample preservation, RNA extraction, sequencing platforms, library preparation, bioinformatics software, genome annotations, and statistical thresholds. Standardized NASA processing pipelines improve comparability,

but investigators should still inspect metadata, experimental protocols, sequencing quality, and potential batch effects before combining datasets.

16. Statistical Considerations and Reproducibility

Genome-wide expression studies test thousands of genes simultaneously, increasing the likelihood of false-positive findings. Multiple-testing correction methods, such as control of the false-discovery rate, are therefore required. Statistical significance should be interpreted alongside fold change, biological relevance, pathway consistency, and independent validation.[75]

Low sample numbers create additional challenges for machine-learning applications. Complex algorithms may memorize characteristics of the training data rather than learn generalizable biological patterns. This problem can produce apparently high accuracy that declines substantially when the model is evaluated using samples from another experiment. Researchers should separate training, validation, and testing datasets whenever sufficient samples are available. Cross-validation must be performed at the biological-sample level rather than the individual sequencing-read level. External validation using an independent NASA dataset, ground-based radiation experiment, or terrestrial clinical cohort provides stronger evidence that a proposed biomarker is reproducible.

Transparent reporting is essential for open-science research. Investigators should document dataset accession numbers, inclusion criteria, preprocessing procedures, normalization methods, statistical models, software versions, parameter settings, and gene-annotation resources. Analytical code and intermediate results should be shared whenever possible to allow other researchers to reproduce the findings.

Negative findings also have scientific value. Reporting only statistically significant genes may exaggerate the consistency of radiation-associated effects. Complete reporting of tested hypotheses, effect sizes, uncertainty estimates, and sensitivity analyses provides a more accurate representation of the evidence.

17. Ethical, Privacy, and Governance Considerations

Human spaceflight omics data may contain sensitive information regarding genetic susceptibility, disease risk, immune function, treatment response, and reproductive health. Even when personal identifiers are removed, genomic information may potentially be linked to individuals through comparison with other datasets. Appropriate access controls and responsible data-governance frameworks are therefore required.[76]

Genetic findings related to cancer susceptibility must be interpreted cautiously. A radiation-responsive gene signature does not necessarily indicate that an astronaut will develop cancer. Communicating uncertain risk estimates without adequate clinical context could cause unnecessary anxiety or influence occupational decisions unfairly.

Policies should protect astronauts from genetic discrimination while enabling medically appropriate monitoring. Decisions concerning mission eligibility, career progression, insurance, and long-term medical surveillance should not be based solely on unvalidated molecular predictions.

Informed consent is particularly important when astronaut samples are reused for secondary analyses that differ from the objectives of the original study. Participants should understand how their molecular data may be stored, shared, integrated with other information, and analyzed using emerging computational technologies.

International missions will require governance frameworks that address differences in privacy legislation, data ownership, informed consent, and research oversight. Transparent policies developed collaboratively by astronauts, scientists, physicians, ethicists, space agencies, and regulatory authorities will be essential for maintaining public confidence.

18. Development of Radiation Countermeasures

Molecular analysis of radiation-responsive pathways may support the development of biological countermeasures for future missions. Potential strategies include antioxidant supplementation, anti-inflammatory therapies, mitochondrial protectants, DNA-repair modulators, senolytic agents, and compounds that reduce oxidative injury.[77]

Countermeasure development must balance tissue protection against potential cancer-promoting effects. For example, broadly suppressing apoptosis could allow cells with severe DNA damage to survive, while excessive stimulation of DNA repair pathways might produce inaccurate repair. Similarly, antioxidant interventions may reduce normal-tissue injury but could disrupt beneficial signaling required for immune function and adaptation.

Timing and dosage are therefore critical. Some interventions may be most effective before exposure, whereas others may reduce delayed inflammation or tissue degeneration after exposure. Transcriptomic monitoring could help determine whether a countermeasure normalizes harmful pathways without suppressing necessary protective responses.

Physical approaches remain equally important. Improved spacecraft shielding, storm shelters, mission-duration management, solar-event forecasting, and optimized vehicle design can reduce exposure. Biological countermeasures should complement rather than replace engineering controls.

Personalized intervention strategies may eventually account for genetic variation, baseline antioxidant capacity, immune status, age, sex, previous radiation exposure, and mission-specific dosimetry. Such approaches represent an important goal of precision space medicine.

19. Integration with Multi-Omics and Systems Biology

Transcriptomic information provides only one layer of the radiation response. Comprehensive biological interpretation requires integration with genomics, epigenomics, proteomics, metabolomics, microbiome data, physiological monitoring, imaging, and radiation dosimetry.[78]

Genomic analysis identifies inherited variants and acquired mutations that influence radiation sensitivity. Epigenomic profiling reveals changes in DNA methylation, histone modifications, and chromatin accessibility that regulate gene expression. Proteomic analysis measures functional molecular products, while metabolomics captures alterations in energy production, oxidative stress, lipid metabolism, and cellular signaling.

Single-cell sequencing provides additional resolution by identifying cell-specific responses that may be obscured in bulk tissue measurements. A blood sample, for example, contains multiple immune-cell populations with distinct radiation sensitivities. Changes in bulk gene expression may therefore result either from altered activity within cells or from shifts in cell-type proportions.

Spatial transcriptomics may further reveal how radiation responses are organized within tissues. Mapping DNA-damage signaling, inflammation, vascular injury, and immune-cell infiltration could improve understanding of how local tissue environments influence carcinogenesis.

Systems-biology models can connect these molecular layers into integrated networks. Rather than identifying one radiation-associated gene, researchers can characterize coordinated changes in DNA repair, metabolism, inflammation, and cell-cycle regulation. Such models may ultimately support individualized simulations of radiation risk and recovery.

20. Future Research Directions

Future studies should prioritize experiments that more accurately reproduce the chronic mixed-field radiation environment expected during lunar and Martian missions. Long-duration exposure models are necessary to determine whether low-dose radiation produces cumulative damage, adaptive responses, or persistent molecular abnormalities.[79]

Larger biological cohorts will be required to investigate individual variability. International data-sharing initiatives could increase sample sizes by integrating compatible datasets from multiple space agencies and research institutions. Harmonized metadata, radiation measurements, sample-collection protocols, and sequencing procedures would substantially improve cross-study comparison.

Organoids and tissue-engineered systems may provide more realistic experimental models than conventional cell cultures. Patient-derived organoids can reproduce aspects of tissue architecture, cellular diversity, and individual genetic background while allowing controlled radiation exposure.

Longitudinal studies should examine molecular profiles before, during, and after spaceflight. Such designs can distinguish pre-existing differences from flight-associated changes and determine whether altered pathways return to baseline after landing. Extended follow-up is also required because radiation-associated cancers may develop many years after exposure. Artificial intelligence may assist in detecting complex molecular signatures, but models should remain interpretable and clinically validated. Future algorithms should quantify uncertainty, identify the evidence supporting each prediction, and indicate when a sample differs substantially from the data used to train the model.

Integration of radiation dosimetry with molecular measurements will be especially important. Linking particle type, absorbed dose, dose rate, and tissue exposure with gene-expression changes could support biologically informed risk models that are more precise than estimates based solely on physical dose.

21. Discussion

Analysis of NASA Open Science data provides a powerful framework for investigating the molecular consequences of space-radiation exposure. Publicly accessible transcriptomic datasets allow researchers to examine DNA-damage signaling, oxidative stress, mitochondrial dysfunction, immune alteration, cell-cycle regulation, apoptosis, senescence, and cancer-associated pathways without requiring direct access to spaceflight facilities.

The principal strength of these resources lies in their potential for reuse and integration. A dataset originally generated to investigate muscle loss, immune function, or microgravity adaptation may contain valuable information regarding cancer-related gene expression. Combining multiple studies can reveal conserved molecular responses that may not be evident in an individual experiment.

Nevertheless, spaceflight-associated gene-expression changes should not be interpreted as direct evidence of cancer development. Carcinogenesis is a multistage process involving mutation accumulation, clonal selection, altered tissue environments, immune evasion, and

many years of biological evolution. Transcriptomic abnormalities represent indicators of molecular stress or pathway disruption rather than definitive clinical outcomes.

Reliable interpretation therefore requires integration of gene-expression findings with DNA-damage measurements, chromosomal aberrations, mutation analysis, protein activity, tissue pathology, radiation dose, and long-term health observations. Experimental validation remains essential before candidate biomarkers are incorporated into astronaut medical monitoring.

NASA's commitment to standardized open data has created an important foundation for this work. GeneLab and the Open Science Data Repository support access to curated omics data, environmental information, experimental metadata, analytical workflows, and radiation measurements, enabling investigators worldwide to participate in space-biology research.[80]

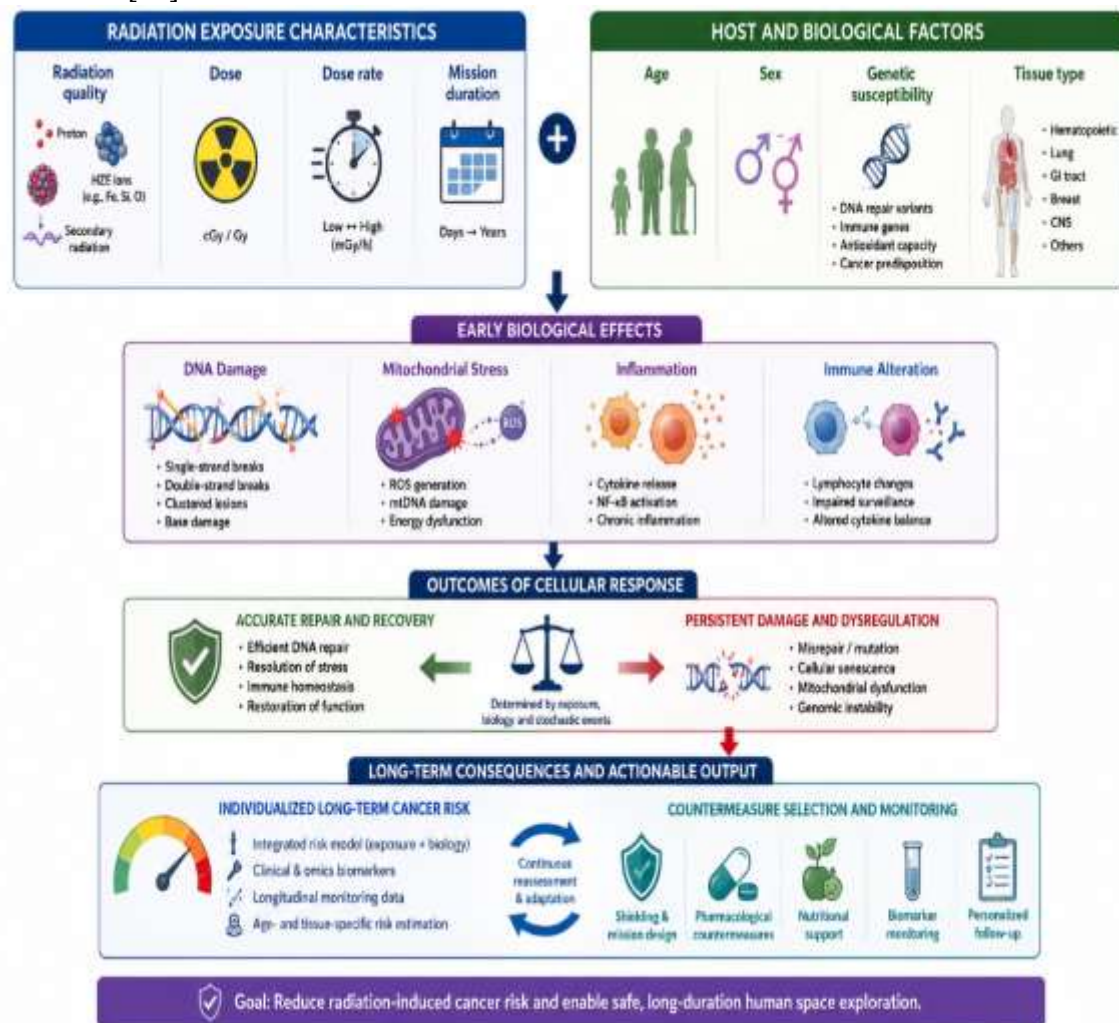


Figure 4. Integrated framework for space-radiation-associated cancer risk. Physical exposure characteristics interact with individual susceptibility and tissue-specific responses to determine whether radiation injury resolves or develops into persistent genomic and

inflammatory abnormalities. Integrated omics and dosimetry may support personalized monitoring and countermeasure development.

22. Conclusion

Space radiation represents a major biological challenge for long-duration human exploration. Galactic cosmic rays, solar energetic particles, secondary radiation, and HZE ions can produce complex DNA lesions, oxidative stress, mitochondrial dysfunction, immune dysregulation, chromosomal instability, and persistent changes in gene expression.

NASA Open Science resources enable systematic investigation of these effects through publicly accessible transcriptomic and multi-omics datasets. Bioinformatics analysis can identify differentially expressed genes, enriched pathways, regulatory networks, and candidate biomarkers associated with radiation response and cancer-related biological processes.

Genes involved in ATM–ATR signaling, p53 regulation, homologous recombination, non-homologous end joining, antioxidant defense, apoptosis, inflammation, senescence, and oncogenic signaling are particularly relevant to radiation-associated risk. However, isolated gene-expression changes should be interpreted cautiously because spaceflight includes multiple interacting environmental stressors and because transcriptional alterations do not necessarily lead to malignant disease.

Future progress will depend on larger longitudinal studies, realistic mixed-field radiation models, multi-omics integration, standardized analytical methods, experimental validation, transparent artificial intelligence, and responsible governance of astronaut genomic information.

By combining open NASA datasets with systems biology and reproducible computational research, investigators can improve understanding of radiation carcinogenesis while developing more effective monitoring tools and countermeasures. These advances will support safer exploration of the Moon and Mars and may also generate important insights for radiation oncology, cancer prevention, aging research, and precision medicine on Earth.

References

1. Gebre SG, Saravia-Butler AM, Costes SV, et al. NASA Open Science Data Repository: open science for life in space. *Scientific Data*. 2024;11:1363.
2. National Aeronautics and Space Administration. Human Research Program: Space Radiation Element. NASA; 2024.
3. Durante M, Cucinotta FA. Physical basis of radiation protection in space travel. *Reviews of Modern Physics*. 2011;83(4):1245–1281.
4. Cucinotta FA, Durante M. Cancer risk from exposure to galactic cosmic rays: implications for space exploration by human beings. *Lancet Oncology*. 2006;7(5):431–435.
5. Garrett-Bakelman FE, Darshi M, Green SJ, et al. The NASA Twins Study: a multidimensional analysis of a year-long human spaceflight. *Science*. 2019;364(6436):eaau8650.
6. Ray S, Gebre S, Fogle H, Berrios DC, Tran PB, Galazka JM, Costes SV. GeneLab: omics database for spaceflight experiments. *Bioinformatics*. 2019;35(10):1753–1759.
7. Afshinnekoo E, Scott RT, MacKay MJ, et al. Fundamental biological features of spaceflight: advancing the field to enable deep-space exploration. *Cell*. 2020;183(5):1162–1184.
8. Chancellor JC, Scott GBI, Sutton JP. Space radiation: the number one risk to astronaut health beyond low Earth orbit. *Life*. 2014;4(3):491–510.

9. Durante M, Cucinotta FA. Heavy ion carcinogenesis and human space exploration. *Nature Reviews Cancer*. 2008;8(6):465–472.
10. Townsend LW. Implications of the space radiation environment for human exploration in deep space. *Radiation Protection Dosimetry*. 2005;115(1–4):44–50.
11. Zeitlin C, Hassler DM, Cucinotta FA, et al. Measurements of energetic particle radiation in transit to Mars on the Mars Science Laboratory. *Science*. 2013;340(6136):1080–1084.
12. Mavragani IV, Nikitaki Z, Souli MP, et al. Ionizing radiation and complex DNA damage: from prediction to detection challenges and biological significance. *Cancers*. 2019;11(11):1789.
13. Sridharan DM, Asaithamby A, Bailey SM, et al. Understanding cancer development processes after HZE-particle exposure: roles of reactive oxygen species, DNA-damage repair and inflammation. *Radiation Research*. 2015;183(1):1–26.
14. Chistiakov DA, Voronova NV, Chistiakov PA. Genetic variations in DNA-repair genes, radiosensitivity to cancer and susceptibility to acute tissue reactions in radiotherapy-treated cancer patients. *Acta Oncologica*. 2008;47(5):809–824.
15. National Aeronautics and Space Administration. NASA Open Science Data Repository. NASA Biological and Physical Sciences Division.
16. Ray S, Gebre S, Fogle H, et al. GeneLab: omics database for spaceflight experiments. *Bioinformatics*. 2019;35(10):1753–1759.
17. McDonald JT, Stainforth R, Miller J, et al. NASA GeneLab platform utilized for biological response to space radiation in animal models. *Cancers*. 2020;12(2):381.
18. Berrios DC, Galazka J, Grigorev K, et al. NASA GeneLab: interfaces for the exploration of space omics data. *Nucleic Acids Research*. 2021;49(D1):D1515–D1522.
19. Overbey EG, Kim J, Tierney BT, et al. The Space Omics and Medical Atlas and international astronaut biobank. *Nature*. 2024;632:1145–1156.
20. National Academies of Sciences, Engineering, and Medicine. *Open Science by Design: Realizing a Vision for 21st Century Research*. Washington, DC: National Academies Press; 2018.
21. Bezdan D, Grigorev K, Meydan C, et al. Cell-free DNA and RNA alterations following spaceflight: implications for open space-omics research. *Cell Reports*. 2020;33(10):108458.
22. Ward JF. DNA damage produced by ionizing radiation in mammalian cells: identities, mechanisms of formation, and reparability. *Progress in Nucleic Acid Research and Molecular Biology*. 1988;35:95–125.
23. Jackson SP, Bartek J. The DNA-damage response in human biology and disease. *Nature*. 2009;461(7267):1071–1078.
24. Hada M, Sutherland BM. Spectrum of complex DNA damages depends on the incident radiation. *Radiation Research*. 2006;165(2):223–230.
25. Azzam EI, Jay-Gerin JP, Pain D. Ionizing radiation-induced metabolic oxidative stress and prolonged cell injury. *Cancer Letters*. 2012;327(1–2):48–60.
26. Blackford AN, Jackson SP. ATM, ATR, and DNA-PK: the trinity at the heart of the DNA-damage response. *Molecular Cell*. 2017;66(6):801–817.
27. Scully R, Panday A, Elango R, Willis NA. DNA double-strand-break repair-pathway choice in somatic mammalian cells. *Nature Reviews Molecular Cell Biology*. 2019;20(11):698–714.

28. Miousse IR, Kutanzi KR, Koturbash I. Effects of ionizing radiation on DNA methylation: from experimental biology to clinical applications. *International Journal of Radiation Biology*. 2017;93(5):457–469.
29. Michalettou TD, Michalopoulos I, Costes SV, Hellweg CE, Hada M, Georgakilas AG. A meta-analysis of the effects of high-linear-energy-transfer ionizing radiation on gene expression. *Life*. 2021;11(2):115.
30. Love MI, Huber W, Anders S. Moderated estimation of fold change and dispersion for RNA-sequencing data with DESeq2. *Genome Biology*. 2014;15(12):550.
31. Subramanian A, Tamayo P, Mootha VK, et al. Gene-set enrichment analysis: a knowledge-based approach for interpreting genome-wide expression profiles. *Proceedings of the National Academy of Sciences of the United States of America*. 2005;102(43):15545–15550.
32. Leek JT, Scharpf RB, Bravo HC, et al. Tackling the widespread and critical impact of batch effects in high-throughput data. *Nature Reviews Genetics*. 2010;11(10):733–739.
33. Garrett-Bakelman FE, Darshi M, Green SJ, et al. The NASA Twins Study: a multidimensional analysis of a year-long human spaceflight. *Science*. 2019;364(6436):eaau8650.
34. Ciccio A, Elledge SJ. The DNA-damage response: making it safe to play with knives. *Molecular Cell*. 2010;40(2):179–204.
35. Maréchal A, Zou L. DNA damage sensing by the ATM and ATR kinases. *Cold Spring Harbor Perspectives in Biology*. 2013;5(9):a012716.
36. Smith J, Tho LM, Xu N, Gillespie DA. The ATM–Chk2 and ATR–Chk1 pathways in DNA-damage signaling and cancer. *Advances in Cancer Research*. 2010;108:73–112.
37. Kasthuber ER, Lowe SW. Putting p53 in context. *Cell*. 2017;170(6):1062–1078.
38. Ceccaldi R, Rondinelli B, D’Andrea AD. Repair-pathway choices and consequences at the double-strand break. *Trends in Cell Biology*. 2016;26(1):52–64.
39. da Silveira WA, Fazelinia H, Rosenthal SB, et al. Comprehensive multi-omics analysis reveals mitochondrial stress as a central biological hub for spaceflight impact. *Cell*. 2020;183(5):1185–1201.e20.
40. Ma Q. Role of Nrf2 in oxidative stress and toxicity. *Annual Review of Pharmacology and Toxicology*. 2013;53:401–426.
41. Wallace DC. Mitochondria and cancer. *Nature Reviews Cancer*. 2012;12(10):685–698.
42. Van Houten B, Hunter SE, Meyer JN. Mitochondrial DNA damage induced autophagy, cell death, and disease. *Frontiers in Bioscience*. 2016;21:42–54.
43. Matthews HK, Bertoli C, de Bruin RAM. Cell-cycle control in cancer. *Nature Reviews Molecular Cell Biology*. 2022;23(1):74–88.
44. Elmore S. Apoptosis: a review of programmed cell death. *Toxicologic Pathology*. 2007;35(4):495–516.
45. Campisi J. Aging, cellular senescence, and cancer. *Annual Review of Physiology*. 2013;75:685–705.
46. Gorgoulis V, Adams PD, Alimonti A, et al. Cellular senescence: defining a path forward. *Cell*. 2019;179(4):813–827.
47. Crucian BE, Choukèr A, Simpson RJ, et al. Immune-system dysregulation during spaceflight: potential countermeasures for deep-space exploration missions. *Frontiers in Immunology*. 2018;9:1437.
48. Sonnenfeld G. The immune system in space and microgravity. *Medicine and Science in Sports and Exercise*. 2002;34(12):2021–2027.

49. Grivennikov SI, Greten FR, Karin M. Immunity, inflammation, and cancer. *Cell*. 2010;140(6):883–899.
50. Kim J, Tierney BT, Ryon K, et al. Single-cell multi-ome and immune profiles of the Inspiration4 crew reveal conserved, sex-dependent, and crew-specific responses to spaceflight. *Nature Communications*. 2024;15:4322.
51. Hanahan D. Hallmarks of cancer: new dimensions. *Cancer Discovery*. 2022;12(1):31–46.
52. Porta C, Paglino C, Mosca A. Targeting PI3K/Akt/mTOR signaling in cancer. *Frontiers in Oncology*. 2014;4:64.
53. Sanchez-Vega F, Mina M, Armenia J, et al. Oncogenic signaling pathways in The Cancer Genome Atlas. *Cell*. 2018;173(2):321–337.e10.
54. Batlle E, Massagué J. Transforming growth factor- β signaling in immunity and cancer. *Immunity*. 2019;50(4):924–940.
55. Semenza GL. Hypoxia-inducible factors in physiology and medicine. *Cell*. 2012;148(3):399–408.
56. Reimand J, Isserlin R, Voisin V, et al. Pathway enrichment analysis and visualization of omics data using g:Profiler, GSEA, Cytoscape and EnrichmentMap. *Nature Protocols*. 2019;14(2):482–517.
57. Langfelder P, Horvath S. WGCNA: an R package for weighted correlation-network analysis. *BMC Bioinformatics*. 2008;9:559.
58. Szklarczyk D, Kirsch R, Koutrouli M, et al. The STRING database in 2023: protein-protein association networks and functional-enrichment analyses for any sequenced genome. *Nucleic Acids Research*. 2023;51(D1):D638–D646.
59. Barcellos-Hoff MH, Mao JH. HZE-radiation non-targeted effects on the microenvironment that mediate mammary carcinogenesis. *Frontiers in Oncology*. 2016;6:57.
60. Glaab E, Bacardit J, Garibaldi JM, Krasnogor N. Using rule-based machine learning for candidate disease-gene prioritization and sample classification of cancer gene-expression data. *PLoS ONE*. 2012;7(7):e39932.
61. Vabalas A, Gowen E, Poliakoff E, Casson AJ. Machine-learning algorithm validation with a limited sample size. *PLoS ONE*. 2019;14(11):e0224365.
62. Lundberg SM, Lee SI. A unified approach to interpreting model predictions. In: *Advances in Neural Information Processing Systems*. 2017;30:4765–4774.
63. Acosta JN, Falcone GJ, Rajpurkar P, Topol EJ. Multimodal biomedical artificial intelligence. *Nature Medicine*. 2022;28(9):1773–1784.
64. Bustin SA, Benes V, Garson JA, et al. The MIQE guidelines: minimum information for publication of quantitative real-time PCR experiments. *Clinical Chemistry*. 2009;55(4):611–622.
65. Vogel C, Marcotte EM. Insights into the regulation of protein abundance from proteomic and transcriptomic analyses. *Nature Reviews Genetics*. 2012;13(4):227–232.
66. Simonsen LC, Slaba TC, Guida P, Rusek A. NASA's first ground-based galactic cosmic-ray simulator: enabling a new era in space radiobiology research. *PLoS Biology*. 2020;18(5):e3000669.
67. National Academies of Sciences, Engineering, and Medicine. *Health and Medicine in Space: A Decadal Survey for 2024–2033*. Washington, DC: National Academies Press; 2023.

68. Baumann M, Krause M, Overgaard J, et al. Radiation oncology in the era of precision medicine. *Nature Reviews Cancer*. 2016;16(4):234–249.
69. Cortese F, Klovov D, Osipov A, et al. Vive la radiorésistance!: converging research in radiobiology and biogerontology to enhance human radioresistance for deep-space exploration and colonization. *Oncotarget*. 2018;9(18):14692–14722.
70. Chancellor JC, Blue RS, Cengel KA, et al. Limitations in predicting the space-radiation health risk for exploration astronauts. *NPJ Microgravity*. 2018;4:8.
71. Thirsk R, Kuipers A, Mukai C, Williams D. The space-flight environment: the International Space Station and beyond. *CMAJ*. 2009;180(12):1216–1220.
72. Demontis GC, Germani MM, Caiani EG, Barravecchia I, Passino C, Angeloni D. Human pathophysiological adaptations to the space environment. *Frontiers in Physiology*. 2017;8:547.
73. Norbury JW, Schimmerling W, Slaba TC, et al. Galactic cosmic-ray simulation at the NASA Space Radiation Laboratory. *Life Sciences in Space Research*. 2016;8:38–51.
74. Durante M, Snijders AM, Cucinotta FA. Biomarkers of space-radiation risk. *Radiation Research*. 2017;188(5):559–572.
75. Benjamini Y, Hochberg Y. Controlling the false-discovery rate: a practical and powerful approach to multiple testing. *Journal of the Royal Statistical Society, Series B*. 1995;57(1):289–300.
76. National Academies of Sciences, Engineering, and Medicine. *The Health Effects of Space Radiation: Ethical, Legal, and Social Considerations*. Washington, DC: National Academies Press.
77. Kennedy AR. Biological effects of space radiation and development of effective countermeasures. *Life Sciences in Space Research*. 2014;1:10–43.
78. Schmidt MA, Goodwin TJ. Personalized medicine in human spaceflight: using omics-based analyses to develop individualized countermeasures. *Metabolomics*. 2013;9(6):1134–1156.
79. Simonsen LC, Slaba TC, Guida P, Rusek A. NASA's first ground-based galactic cosmic-ray simulator: enabling a new era in space radiobiology research. *PLoS Biology*. 2020;18(5):e3000669.
80. National Aeronautics and Space Administration. *NASA Open Science Data Repository: GeneLab, Ames Life Sciences Data Archive, and Biological Institutional Scientific Collection*. NASA Biological and Physical Sciences Division.