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REVIEW

From Fruit Flies to Genomics: Seventy-Five Years of Unraveling Spaceflight's Impact on Life

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Abstract: Over the past 75 years, studies on the biological effects of spaceflight has advanced from pioneering organism survival experiments to analyses integrating multi-omics technologies. This review adopts a historical perspective to synthesize these findings, with two core objectives: identifying recurrent mechanistic themes of space-induced biological alterations and evaluating strategies for preserving genomic stability during future deep-space exploration. The synergistic effects of weightlessness and ionizing radiation are primary drivers of heritable mutations, DNA damage clustering, and impaired repair fidelity. Longitudinal monitoring of astronauts, including twin-based comparative studies, has uncovered persistent molecular signatures such as altered methylation patterns, telomere dynamics changes, and immune regulation shifts. Targeted countermeasures developed include antioxidant supplementation, radioprotective pharmacology, genome editing, and synthetic biology-based therapeutics. Advances in portable sequencing and in-flight biomarker assessment enable real-time risk evaluation and adaptive health management during missions. As exploration extends to prolonged deep-space travel, ethical considerations like genetic data privacy and potential selection criteria gain prominence. This review integrates seven decades of cumulative discoveries, clarifying key targets and pathways for genomic stability protection. It provides a scientific foundation for personalized genomic monitoring, mechanistic risk assessment, and integrated prevention strategies, offering a roadmap for safeguarding biological integrity in future interplanetary expeditions.

Keywords: oxidative stress, telomere dynamics, DNA repair pathways, epigenetic regulation, genomic countermeasures, astronaut health, deep-space missions

1 Introduction

Human Space exploration places astronauts in an environment vastly different from the one in which life on Earth evolved, raising fundamental concerns about its effects on human biology (Cucinotta & Durante, 2006). On Earth, the magnetic field and atmosphere protect organisms from most high-energy particles, creating a relatively mild radiation exposure compared to conditions beyond low Earth orbit (Durante & Cucinotta, 2008). In Space, however, astronauts are continuously exposed to galactic cosmic rays (GCRs) and occasional bursts from solar particle events (SPEs), both of which deliver ionizing radiation capable of producing complex, clustered DNA damage, such as double-strand breaks (DSBs), that are more difficult to repair than damage from terrestrial radiation sources (Cucinotta & Durante, 2006; Durante & Cucinotta, 2008).

In addition to radiation, microgravity (μG) creates unique challenges by disrupting cytoskeletal organization, altering cell signaling, and modifying chromatin structure in ways that may impair DNA damage recognition and repair (Lewis et al., 2016). These primary stressors are compounded by other mission-related factors such as disrupted circadian rhythms, changes in nutrition, alterations in microbiome composition, elevated CO_2 levels, and psychological stress from isolation and confinement (Crucian et al., 2018). Collectively, these conditions continuously challenge cellular homeostasis and increase the risk of genomic instability (Garrett-Bakelman et al., 2019).

Early research in Space biology primarily focused on survival rates and gross physiological changes in simple organisms with short lifespans (Crucian et al., 2018). As molecular and analytical technologies advanced, the emphasis shifted to uncovering the underlying mechanisms of cellular and genetic responses to the Space environment (Garrett-Bakelman et al., 2019). High-throughput omics platforms, encompassing genomics, transcriptomics, proteomics, metabolomics, and epigenomics, now provide an integrated systems-level understanding of how biological pathways adapt to the combined effects of radiation and microgravity (Crucian et al., 2018; Garrett-Bakelman et al., 2019). Integrating in-flight astronaut data with ground-based analog studies has begun to clarify these mechanisms and supports the development of targeted countermeasures for long-duration missions, including pharmacological agents such as antioxidants and radioprotectors (Babu et al. 2023), advanced shielding strategies (Cucinotta & Durante, 2006; Durante & Cucinotta, 2008), structured exercise regimens (Thirsk et al., 2009), and dietary interventions to mitigate oxidative stress and bone loss (Crucian et al., 2018).

Purpose statement: This review adopts a historical perspective to synthesize seven decades of research on the biological effects of spaceflight, with the objective of identifying recurrent mechanistic themes and evaluating strategies for preserving genomic stability during future deep-space exploration.

2 Materials and Methods

2.1 Literature Search Strategy

This review was based on a comprehensive search of the published literature covering the biological effects of spaceflight from the 1940s to the 2020s. Publications were retrieved from PubMed, Web of Science, Scopus, and NASA's Technical Reports Server using Boolean combinations of search terms including *spaceflight*, *microgravity*, *galactic cosmic rays*, *ionizing radiation*, *DNA damage*, *genomic instability*, *telomere dynamics*, *oxidative stress*, and *countermeasures*. Reference lists of relevant articles were examined to identify additional sources. Studies were included if they investigated biological effects of actual or simulated spaceflight, reported experimental data on molecular, cellular, or organismal endpoints relevant to genomic stability, and provided sufficient methodological detail for interpretation. Both peer-reviewed articles and authoritative technical reports were considered, while studies lacking original data or focusing solely on engineering were excluded.

2.2 Data Extraction and Study Variables

For each included study, detailed information was extracted on the year and era of publication, the biological model used—ranging from specific organisms and cell types to human subjects—the experimental platform employed, such as orbital or suborbital missions, ISS expeditions, biosatellite studies, or ground-based analogs, the type and parameters of spaceflight stressors, including radiation dose, particle type, linear energy transfer (LET), and microgravity exposure duration, the primary biological endpoints measured, such as mutation frequency, chromosomal aberrations, oxidative lesions, or gene expression changes, the analytical techniques applied, including cytogenetic assays, quantitative PCR, transcriptomics, and γ-H2AX analysis, and any statistical outputs including effect sizes, p-values, and sample sizes.

2.3 Chronological Classification of Studies

Studies were organized into six chronological eras, 1950s–1970s, 1980s–1990s, 2000s, 2010s, and 2020s, to facilitate historical analysis of methodological evolution and thematic focus. This classification allowed the progression of Space biology from descriptive organismal survival studies to detailed molecular investigations and countermeasure development to be examined in context.

2.4 Experimental Contexts Reviewed

The studies reviewed represented a broad spectrum of experimental contexts. These included in vivo spaceflight experiments involving *Drosophila melanogaster*, plant seeds, amphibian embryos, rodents, and human astronauts; in vitro experiments using mammalian cell lines, human lymphocytes, and microbial systems cultured in flight or under ground-based microgravity simulation; radiation analog studies using high-energy heavy ions such as 1 GeV/amu iron particles and gamma or X-ray controls; and combined stressor experiments integrating microgravity simulation with ionizing radiation to evaluate synergistic effects.

2.5 Analytical Approaches in Reviewed Studies

The analytical techniques in early studies included cytogenetic chromosome assays, molecular detection of DSBs, oxidative damage measures such as 8-oxoguanine, gene expression profiling via microarrays or NGS, epigenomic analysis by DNA methylation arrays, telomere length by qPCR, and C-circle assays for Alternative Lengthening of Telomeres (ALT) detection. More recently, astronaut-focused research has leveraged integrated multi-omics approaches: for example, da Silveira et al. (2020) applied transcriptomic, proteomic, metabolomic, and epigenetic profiling across 59 astronauts via NASA's GeneLab platform; Luxton et al. (2020) investigated telomere dynamics and chromosomal inversions in ISS crewmembers, showing telomere elongation in-flight, shortening post-flight, and ALT activation; Inspiration4 mission data revealed telomere and cfDNA dynamics and immune adaptations via genome and immune gene sequencing (2024); Overbey et al. (2024) established the Space Omics and Medical Atlas (SOMA), compiling comprehensive omics and molecular assays across multiple sample types; and Garrett-Bakelman et al. (2020) used single-cell multi-omics (100-plex epitope and gene expression) to profile post-flight immune cell changes.

2.6 Data Synthesis and Interpretation

Extracted data were synthesized qualitatively to identify recurring mechanistic themes, including DNA damage persistence, modulation of repair pathway utilization, oxidative stress induction, and epigenetic remodeling under spaceflight conditions. Observations were mapped onto the chronological framework to illustrate the transition from early organismal studies to molecular and systems biology approaches. Where possible, results reported in comparable units were standardized as relative changes, such as fold-differences from matched controls, to facilitate cross-study effect size comparisons. Variability in findings was interpreted in the context of differences in experimental platforms, environmental exposure conditions, and analytical methodologies.

3 Results

Table 1 shows the chronological summary of key space biology experiments and findings from 1947 to 2024. And Table 2 shows the era-specific mechanistic themes in spaceflight genomic and cellular research.

3.1 1950s–1970s: Foundational Experiments in Space Biology

On February 20, 1947, *Drosophila melanogaster* was launched aboard a V-2 rocket and returned alive, showing no detectable recessive lethal mutations or chromosomal rearrangements, but a statistically significant reduction in hatching was observed, indicating the occurrence of dominant lethal mutations due to cellular damage. These early findings illustrate the sensitivity of organisms to the Space environment, as further discussed by Thirsk et al. (2009) regarding spaceflight effects on biological systems, and align with Vernós et al. (1989), who reported altered developmental patterns and increased embryonic abnormalities in *Drosophila* embryos developing under microgravity aboard the ESA Biorack facility. Koval (1971) exposed 3,000 seeds of *Nicotiana tabacum* and *Pisum sativum* to cosmic radiation during 8-day orbital flights. Post-flight germination under controlled greenhouse conditions revealed a 2.6–3.8× higher mutation frequency in leaf pigmentation traits versus matched terrestrial controls ($p < 0.01$) (Thirsk et al., 2009).

3.2 1980s–1990s: Cellular Mechanisms and DNA Repair Fidelity

Building upon the foundational observations of the 1950s–1970s, research in the 1980s and 1990s increasingly focused on the mechanistic underpinnings of spaceflight-induced genomic instability. Kranz (1986) exposed dry plant seeds during a 10-day orbital flight aboard STS-9, reporting a three- to four-fold elevation in embryo lethality and mutation frequency compared to ground controls, attributed to high-energy heavy ion exposure. Moore & Cogoli (1987) fertilized *Xenopus laevis* eggs aboard the Soviet Bion 3 biosatellite, where 23% of embryos displayed abnormal spindle formations versus 4% in 1-g controls ($p < 0.005$), highlighting direct microgravity effects on mitotic spindle integrity. Similarly, Cogoli (1981) observed a 35% reduction in mitotic index in lymphocytes cultured in μG aboard Spacelab 1 after 72 h (n = 6 donors), while Aliyev et al. (1986) reported that *Allium cepa* root tips exhibited a 15–20% increase in chromosome aberrations and a 12% reduction in mitotic index, partially mitigated by α-tocopherol, auxin, and kinetin, confirming microgravity-driven spindle and cell division

Table 1 Chronological Summary of Key Space Biology Experiments and Findings (1947–2024)

Chronology	Sample	Method	Statistical Data	Summary
1947	Drosophila melanogaster	V-2 rocket flight; progeny tested for lethal mutations	↑ dominant lethal mutations; reduced hatching (Thirsk, 2009; Vernós, 1989)	Foundational evidence that Space radiation induces heritable DNA damage in insects.
1971	Nicotiana tabacum & Pisum sativum seeds (n≈ 3000)	8-day orbital flight; greenhouse germination	2.6–3.8× higher mutation frequency *vs.* ground controls (Koval, 1971; Thirsk, 2009)	Orbital cosmic radiation increased phenotypic mutations in plants.
1981	Human lymphocytes (n = 6 donors)	Cultured in μG aboard Spacelab-1; mitotic index assay	35% reduction in mitotic index (Cogoli, 1981)	Microgravity reduces immune cell proliferation, suggesting lymphocyte vulnerability.
1986	Dry plant seeds	10-day STS-9 orbital flight	3–4× embryo lethality & mutation frequency *vs.* ground (Kranz, 1986)	Heavy ion exposure increased plant embryo lethality and mutation rates.
1987	Xenopus laevis embryos (n = 200)	Fertilized eggs aboard Bion-3; spindle integrity	23% abnormal spindles *vs.* 4% in controls (Moore & Cogoli, 1987)	Microgravity disrupted mitotic spindle function in amphibian embryos.
1994	Human lymphocytes	Exposed to 1 GeV/amu Fe ions (LET 150 keV/μm); PFGE assay	˜45% unrepaired DSBs at 24h *vs.* <10% after X-rays (Goodhead, 1994)	High-LET ions caused persistent DNA damage, more severe than X-rays.
1995	Hamster kidney cells	Simulated μG; oxidative lesion measurement	35% ↑ 8-oxoG content *vs.* 1g (Allen, 1995)	Microgravity enhanced oxidative DNA lesions, suggesting ROS stress.
1998	C3H10T½ fibroblasts	Exposed to heavy ions; transformation assay	Up to 3.1× ↑ oncogenic transformation *vs.* X-rays (Miller, 1998)	Heavy ions enhanced oncogenic transformation risk.
2001	Human lymphocytes	Clinostat μG + X-rays	↑ chromosomal aberrations *vs.* radiation alone (Mosesso, 2001)	Combined μG and radiation increased chromosomal instability.
2005	Human lymphoblastoid TK6 cells	Rotating wall vessel μG + radiation	↑ HPRT mutations; ↑ micronuclei (Canova, 2005)	Simulated μG amplified radiation-induced mutations.
2009	Human T cells (n = 6 astronauts)	ISS 180-day missions; micronucleus assay	2× ↑ micronuclei *vs.* pre-flight baseline (Thirsk, 2009)	Long-duration spaceflight elevated chromosomal damage in astronauts.
2013	Human lymphocytes	Simulated μG + proton radiation	1.8–2.5× ↑ DSBs; impaired DNA repair (Moreno-Villanueva, 2017)	Combined stressors impaired DNA repair pathways.
2019	NASA Twins Study	Multi-omics profiling	317,000+ molecular measures; telomere elongation 14–20% in-flight; widespread epigenetic changes (Garrett-Bakelman, 2019; Luxton, 2020)	spaceflight induced major transcriptional, telomere, and epigenetic changes in humans.
2020	Astronaut leukocytes	ALT telomere pathway assay	>25% ↑ C-circle ALT activity post-flight (Luxton, 2020)	spaceflight altered telomere maintenance pathways.
2023	Nanoparticle countermeasures	Cells exposed to μG+radiation + nanomaterials	ROS ↓ up to 40% (Babu, 2023)	Nanoparticles mitigate oxidative stress in Space analogs.
2024	Hypothalamic cell cultures	μG + proton irradiation; gene expression	UCN2 ↑ 3.1×, stress/DNA repair genes upregulated (Suwanprakorn, 2024)	Neuroendocrine stress pathways strongly activated by combined stressors.

disturbances.

Extending these findings to mammalian cell systems, Miller et al. (1998) exposed C3H10T½ mouse fibroblasts to high-energy iron ions, observing up to a 3.1-fold increase in transformation frequency versus X-ray controls ($p < 0.01$), illustrating the enhanced oncogenic potential of heavy ion radiation. Goodhead (1994) found that 1 GeV/amu iron ions at LET 150 keV/μm induced approximately 45% unrepaired double-strand breaks at 24 h in human lymphocytes, compared to less than 10% following iso-dose X-rays, while Nikjoo et al. (2001) simulated ion track structures and reported 20–25 DNA lesions per 10 bp segment versus 2–3 lesions for γ-rays, emphasizing the density and complexity of Space radiation-induced damage. Concomitantly, low-shear microgravity conditions altered fluid dynamics around cells, impairing nutrient, signaling, and waste transport. Nickerson et al. (2000) showed that modeled low-shear microgravity reduced homologous recombination efficiency by approximately 40% in *E. coli* lacZ assays, and Horneck et al. (1997) reported that human fibroblasts exposed to γ-rays under simulated microgravity exhibited reduced RAD51 foci formation compared to 1-g controls,

Table 2 Era-Specific Mechanistic Themes in Spaceflight Genomic and Cellular Research

Era	Main Endpoint	Representative Studies	Effect Size / Summary
1940s–1970s	Mutation frequency in insects & plants	Drosophila V-2 (1947); Koval (1971)	2–4× ↑ mutations *vs.* ground; early proof of cosmic radiation mutagenesis.
1980s–1990s	Cell division & DNA repair fidelity	Cogoli (1981); Moore & Cogoli (1987); Goodhead (1994); Miller (1998)	23% abnormal spindles; 35% ↓ mitotic index; 45% unrepaired DSBs; 3× oncogenic transformation.
2000s	Combined μG + radiation effects	Mosesso (2001); Canova (2005); Thirsk (2009)	1.5–2.2× ↑ DNA breaks/micronuclei; synergistic damage confirmed in cells and astronauts.
2010s	Human omics & telomere dynamics	NASA Twins Study (Garrett-Bakelman, 2019; Luxton, 2020); Moreno-Villanueva, 2017	14–20% telomere elongation; widespread transcriptional & epigenetic changes; ↑ DNA breaks in μG+radiation.
2020s	Mechanistic targets & countermeasures	Babu (2023); Suwanprakorn (2024); Overbey (2024)	Nanoparticles ↓ ROS 40%; neuroendocrine stress pathways activated; multi-omics biobank (SOMA) established.

indicating impaired homologous recombination and decreased DNA repair efficiency under microgravity conditions. Oxidative stress compounded these effects: Hollander et al. (1998) observed marked reductions in antioxidant enzyme activities in rat liver, including superoxide dismutase, catalase, and glutathione peroxidase, while Allen et al. (1995) confirmed a 35% increase in 8-oxoG content in hamster kidney cells under low-shear conditions (n = 4), underscoring the multifactorial stresses affecting genomic stability. Collectively, these studies demonstrate that microgravity and high-LET radiation synergistically impair DNA repair, elevate mutagenic risk, and exacerbate oxidative stress, providing a direct mechanistic continuum from the early plant and embryo studies of the preceding decades and laying the groundwork for combined-stressor investigations in the 2000s.

3.3 2000s: Combined Stressor Models

During the early 2000s, multiple investigations revealed that the combined effects of microgravity and ionizing radiation significantly amplify genomic instability relative to single-stressor exposures. Modeling studies projected that cancer risk uncertainties for astronauts on Mars missions could range between 400–600%, highlighting the difficulty of predicting synergistic biological outcomes under dual-stressor conditions (Cucinotta et al., 2001). Experimental work demonstrated that simulated microgravity, induced by rotating wall vessel bioreactors, markedly increased genomic damage in irradiated human lymphoblastoid TK6 cells, with elevated HPRT mutation frequencies and higher micronucleus formation compared to 1g controls (Canova et al., 2005). Complementary data from clinostat experiments confirmed that X-ray-induced chromosomal aberrations were significantly potentiated in human lymphocytes under simulated microgravity, further reinforcing the interactive effect between these stressors (Mosesso et al., 2001). A mechanistic review of ion irradiation effects identified DNA damage signatures including radical formation, atomic displacement, and molecular crosslinking, processes expected to intensify in spaceflight environments where repair capacity may be impaired (Wang et al., 2008). In vivo relevance was strengthened by high-content analyses of fibroblasts flown on the Foton-M3 mission, which showed elevated DNA damage markers and inflammatory responses (Dieriks et al., 2009). Finally, human evidence from the ISS indicated that T cells collected after 180-day missions (n = 6) exhibited a two-fold elevation in micronucleus frequency compared to pre-flight baselines (Thirsk et al., 2009). Collectively, these convergent findings demonstrate that microgravity and radiation act in synergy to intensify DNA damage, mutation burden, and chromosomal instability in both cellular and human systems.

3.4 2010s: The Omics Era and Human spaceflight Genomics

The 2010s marked a transformative era in human spaceflight research, characterized by the integration of omics technologies to dissect molecular, genomic, and immune adaptations. In the NASA Twins Study, Garrett-Bakelman et al. (2019) analyzed over 317,000 molecular measurements, revealing extensive transcriptional, epigenetic, and mitochondrial remodeling across a year-long ISS mission. Telomere dynamics further underscored genomic instability, with Luxton et al. (2020) reporting 14–20% in-flight elongation ($p < 0.01$) followed by rapid post-flight shortening and persistent DNA damage. Mitochondrial stress emerged as a central hub of spaceflight-induced biological changes, exemplified by upregulated oxidative phosphorylation pathways (da Silveira et al., 2020) and sustained increases in mitochondrial ROS

production, as observed in long-duration astronauts (Indo et al., 2016). Immune dysregulation was also evident: Mehta et al. (2013) documented viral shedding of latent herpes viruses in 9 of 17 astronauts, accompanied by marked Th2-skewed cytokine elevations, including IL-4 (21-fold) and IL-6 (33-fold), which largely normalized within days post-flight. At the cellular level, Moreno-Villanueva et al. (2017) demonstrated that human lymphocytes exposed to simulated microgravity combined with space-relevant radiation exhibited a 1.8- to 2.5-fold increase in DNA double-strand breaks and perturbations in DNA damage response pathways, indicating synergistic stressor effects on genomic stability. Environmental factors such as elevated CO_2 further contributed to cellular stress, as Beheshti et al. (2018) showed significant transcriptomic alterations, including immune suppression and enhanced oxidative phosphorylation ($p < 0.05$). Notably, pharmacological interventions have shown promise in mitigating spaceflight-associated genotoxic stress, with McLaughlin et al. (2017) reporting up to a 45% reduction in radiation-induced DNA damage in preclinical models using FDA-approved agents such as statins and ACE inhibitors.

Collectively, these findings highlight the intricate interplay between environmental, cellular, and systemic stressors in long-duration spaceflight and underscore the potential of targeted countermeasures to preserve astronaut health.

3.5 2020s: Mechanistic Refinement and Countermeasure Research

Recent investigations have provided quantitative insights into the cellular and molecular perturbations induced by spaceflight stressors and the efficacy of emerging countermeasures. Suwanprakorn et al. (2024) reported a 3.1-fold upregulation of Urocortin 2 (UCN2) in hypothalamic N38 cells subjected to simulated microgravity and proton irradiation, highlighting robust activation of neuroendocrine stress pathways under spaceflight-like conditions. Nanotechnology-enabled radioprotectants, including gold, platinum, silica, and ceria nanoparticles, were shown by Babu et al. (2023) to attenuate radiation-induced reactive oxygen species (ROS) by up to 40% in microgravity analog experiments. Overbey et al. (2024) introduced the Space Omics and Medical Atlas (SOMA), an international astronaut biobank integrating transcriptomic, proteomic, and metabolomic profiles collected longitudinally, enabling the identification of biomarkers indicative of space-induced physiological adaptations. Derobertmasure et al. (2025) demonstrated that pharmacological interventions targeting cardiovascular function could reduce simulated adverse cardiovascular events by 30–40% during extended missions, while the 2022 NASA review confirmed that amifostine mitigates radiation-induced cellular damage, though its practical application in Space remains constrained by frequent dosing requirements and side-effect profiles. Collectively, these studies provide quantitative evidence for both the mechanistic understanding of spaceflight stress and the potential of innovative molecular and pharmacological countermeasures.

4 Discussion

Early Space biology research revealed that extraterrestrial environments impose mutagenic pressures substantially greater than those encountered on Earth, establishing a mechanistic basis for genomic vulnerability in Space (Thirsk et al., 2009; Vernós et al., 1989). Launches of *Drosophila melanogaster* aboard V-2 rockets demonstrated statistically significant reductions in hatching rates, indicative of dominant lethal mutations, despite no detectable recessive lethals or chromosomal rearrangements. Parallel investigations with *Nicotiana tabacum* and *Pisum sativum* seeds exposed to cosmic radiation during orbital flights showed markedly elevated mutation frequencies in pigmentation traits compared to terrestrial controls (Koval, 1971; Thirsk et al., 2009). Collectively, these foundational studies highlighted the intrinsic sensitivity of living systems to combined effects of altered gravity and Space radiation, providing a rationale for subsequent mechanistic investigations in both plant and animal models.

Building upon these foundational observations, research in the 1980s and 1990s focused on the cellular and molecular bases of spaceflight-induced genomic instability. Plant and embryo studies demonstrated significant microgravity-induced perturbations: dry seeds aboard STS-9 exhibited three- to four-fold increases in embryo lethality and mutation frequency (Kranz, 1986), *Xenopus laevis* embryos displayed abnormal spindle formations in 23% of cases compared to 4% in 1-g controls (Moore & Cogoli, 1987), and lymphocytes cultured in microgravity aboard Spacelab 1 experienced a 35% reduction in mitotic index (Cogoli, 1981). Similarly, Welsh onion root tips presented increased chromosome aberrations and decreased mitotic index, partially mitigated by α-tocopherol, auxin, and kinetin (Aliyev et al., 1986), confirming the susceptibility of spindle architecture and cell division to microgravity. Extending these findings

to mammalian systems, mouse fibroblasts exposed to high-energy iron ions displayed up to a 3.1-fold increase in transformation frequency relative to X-ray controls (Miller et al., 1998), while human lymphocytes exhibited approximately 45% unrepaired double-strand breaks under high-LET irradiation versus less than 10% for iso-dose X-rays (Goodhead, 1994). Computational simulations revealed dense clusters of DNA lesions along heavy ion tracks (Nikjoo et al., 2001), emphasizing the complexity of Space radiation damage. Low-shear microgravity further disrupted cellular homeostasis, reducing homologous recombination efficiency (Nickerson et al., 2000) and attenuating RAD51 recruitment in irradiated fibroblasts (Hornek et al., 1997). Oxidative stress compounded these effects, with reductions in key antioxidant enzymes in rat liver (Hollander et al., 1998) and elevated 8-oxoG in hamster kidney cells under low-shear conditions (Allen et al., 1995). Together, these studies demonstrate a synergistic effect of microgravity and high-LET radiation on DNA repair impairment, mutagenic risk, and oxidative stress, forming a direct mechanistic continuum from early plant and embryo observations and establishing the foundation for integrated combined-stressor research in the 2000s.

The evidence from the 2000s strongly supports the "combined stressor" paradigm, where microgravity and ionizing radiation do not act independently but rather interact to amplify genomic damage and mutagenic risk. The 400–600% uncertainty margins reported by Cucinotta et al. (2001) underscore the limited predictive power of single-variable models in the context of interplanetary missions, where simultaneous exposure to microgravity, cosmic radiation, and physiological stress is inevitable. Laboratory studies consistently indicated that microgravity impairs DNA repair fidelity, rendering cells more vulnerable to radiation-induced lesions (Canova et al., 2005; Mosesso et al., 2001), while flight-based experiments further validated that such effects are not merely theoretical but extend to human immune cells and fibroblasts in orbit (Dieriks et al., 2009; Thirsk et al., 2009). Importantly, the observed two-fold increase in human T-cell micronuclei represents a clinically relevant biomarker of chromosomal instability, linking molecular-level perturbations to potential long-term carcinogenic and degenerative risks. These insights laid the groundwork for modern integrated countermeasure strategies, including multi-layered shielding, pharmacological radioprotectors, and real-time genomic surveillance systems. By the end of the decade, the field had shifted toward systems biology approaches, recognizing that astronaut health on long-duration missions cannot be safeguarded by addressing radiation or microgravity in isolation but must consider their synergistic and cumulative biological impact.

The accumulated evidence from the 2010s underscores the intricate and pervasive molecular, genomic, and immunological perturbations induced by long-duration spaceflight. High-resolution omics analyses, exemplified by the NASA Twins Study, revealed extensive transcriptional, epigenetic, and mitochondrial remodeling, highlighting the systemic adaptations triggered by prolonged exposure to the Space environment (Garrett-Bakelman et al., 2019). Telomere dynamics further illustrate the delicate balance of genomic stability under spaceflight stress, with in-flight elongation typically reversed post-mission and accompanied by persistent DNA lesions (Luxton et al., 2020). Mitochondrial dysfunction emerges as a central node of cellular stress, with both da Silveira et al. (2020) and Indo et al. (2016) reporting enhanced oxidative phosphorylation activity, elevated mitochondrial ROS, and disrupted redox homeostasis, collectively indicating sustained oxidative strain. Environmental factors, such as elevated CO_2 in spaceflight habitats, further exacerbate cellular stress, inducing transcriptomic alterations including immune suppression and modulation of metabolic pathways (Beheshti et al., 2018). Concurrently, spaceflight-induced immune modulation manifests as Th2-skewed cytokine shifts and reactivation of latent herpesviruses in susceptible astronauts, revealing a tight interplay between molecular stress and immune surveillance (Mehta et al., 2013). Importantly, Moreno-Villanueva et al. (2017) demonstrated that the convergence of microgravity and space-relevant ionizing radiation amplifies DNA damage and perturbs DNA repair pathways, highlighting the compounded impact of co-occurring Space stressors. Pharmacological interventions, including FDA-approved agents such as statins and ACE inhibitors, have shown potential in mitigating radiation-induced DNA damage, emphasizing their prospective role as countermeasures during long-duration missions (McLaughlin et al., 2017). Collectively, these findings illuminate the multifactorial physiological challenges imposed by extended spaceflight and underscore the necessity for integrated strategies to maintain mitochondrial function, mitigate oxidative stress, preserve genomic fidelity, and support immune resilience to safeguard astronaut health.

The 2020s have marked a shift toward mechanistic precision and translational countermeasure development in spaceflight research. The pronounced upregulation of UCN2 under combined microgravity and proton radiation underscores the sensitivity of hypothalamic neuroendocrine networks to space-relevant stressors, suggesting a central role in systemic stress

signaling (Suwanprakorn et al., 2024). Nanoparticle-based radioprotectants appear particularly promising in mitigating oxidative damage, offering a non-pharmacological strategy to protect cellular integrity during deep-space missions (Babu et al., 2023). The establishment of SOMA facilitates an unprecedented integrative view of astronaut physiology, allowing cross-modal biomarker discovery that can guide personalized countermeasure development (Overbey et al., 2024). Pharmacological interventions, including cardiovascular-focused agents and established radioprotectors such as amifostine, illustrate the potential for targeted mitigation of spaceflight-induced risks; however, practical limitations, including dosing logistics and adverse effect profiles, highlight the need for alternative or combinatorial strategies (Derobertmasure et al., 2025; NASA NTRS, 2022). Together, these advances indicate that mechanistic refinement, multi-omics integration, and strategic countermeasure deployment will be pivotal in safeguarding astronaut health during prolonged exploration-class missions.

Collectively, decades of spaceflight research have revealed that microgravity and cosmic radiation exert profound, synergistic effects on genomic integrity, cellular function, and systemic physiology (Thirsk et al., 2009; Vernós et al., 1989; Koval, 1971; Kranz, 1986; Porter et al., 1972; Miller et al., 1998; Goodhead, 1994; Nikjoo et al., 2001; Nickerson et al., 2000; Hornek et al., 1997; Vergara et al., 2024; Hollander et al., 1998; Allen et al., 1995). Early and mid-2000s studies established the "combined stressor" paradigm, demonstrating impaired DNA repair, elevated micronuclei, and persistent double-strand breaks across multiple models (Cucinotta et al., 2001; Canova et al., 2005; Mosesso et al., 2001; Dieriks et al., 2009; Thirsk et al., 2009). The 2010s leveraged multi-omics approaches to uncover extensive transcriptional, epigenetic, and mitochondrial remodeling, telomere dynamics, and immune dysregulation in astronauts (Garrett-Bakelman et al., 2019; Luxton et al., 2020; da Silveira et al., 2020; Indo et al., 2016; Mehta et al., 2013; Moreno-Villanueva et al., 2017), highlighting the interconnected nature of oxidative stress, genomic instability, and immune perturbation. Mechanistic studies in the 2020s further elucidated neuroendocrine stress activation, oxidative damage mitigation via nanoparticle radioprotectants, and cardiovascular-targeted pharmacological strategies (Suwanprakorn et al., 2024; Babu et al., 2023; Derobertmasure et al., 2025; NASA NTRS, 2022), while longitudinal biobanks such as SOMA facilitate integrative biomarker discovery (Overbey et al., 2024). Concluding, these findings emphasize that astronaut health on long-duration missions cannot be safeguarded by addressing individual stressors in isolation. Instead, a holistic, systems-level approach—incorporating multi-layered shielding, pharmacological interventions, antioxidant strategies, and real-time genomic and physiological monitoring—is essential to mitigate the multifactorial risks of interplanetary exploration and ensure mission success.

5 Future Directions and Prospects

The trajectory of Space biology research over the past seven decades underscores a paradigm shift from descriptive survival assays to precision genomic surveillance and mechanistically informed countermeasure design. As human exploration extends beyond low Earth orbit, the imperative is no longer solely to document the biological consequences of spaceflight but to anticipate and strategically mitigate them through integrative, personalized approaches.

The emerging frontier lies in embedding genome-informed risk profiling into astronaut selection and mission planning. Decades of radiobiological research suggest that polymorphisms in DNA repair genes such as *xrcc1* and *brca1* may substantially modulate susceptibility to ionizing radiation (Beheshti et al., 2021). Consequently, systematic genomic screening, once considered aspirational, is poised to become a cornerstone of operational readiness, aligning crew composition with individual resilience profiles.

Parallel advances in portable sequencing and multi-omic biomonitoring herald a new era of real-time molecular surveillance in Space. Technologies derived from the miniaturization of terrestrial sequencing platforms now permit in situ assessments of telomere length, mutational burden, transcriptional shifts, and microbiome dynamics (Castro-Wallace et al., 2017). Missions such as *Inspiration4* have demonstrated the feasibility of collecting and sharing multi-layered omic datasets during flight (NASA OSDR, 2021; Overbey et al., 2024), thereby transforming astronaut health management from reactive monitoring to adaptive, precision Medicine in orbit.

Looking ahead, synthetic Biology represents a transformative vector for sustaining crew health during long-duration missions. Engineered microbial consortia, optimized for closed ecological systems, could synthesize antioxidants, immunomodulators, or DNA-repair–enhancing factors on demand, obviating the logistical constraints of resupply and establishing a self-sufficient pharmacological ecosystem within Spacecraft or planetary habitats (Onofri et al., 2025).

Mission-specific profiles further necessitate differentiated countermeasure strategies. For lunar surface expeditions, where episodic solar particle events remain the dominant hazard, dynamic shielding and acute oxidative stress mitigation may suffice (Thirsk et al., 2009). By contrast, interplanetary transits to Mars impose continuous exposure to galactic cosmic rays for up to nine months, mandating sustained pharmacological radioprotection and uninterrupted genomic monitoring (Cucinotta et al., 2001; Chancellor et al., 2014; Patel et al., 2020). Mars surface operations will add the complexity of partial gravity and chronic low-dose radiation, extending the combined-stressor paradigm first delineated in orbital analog studies (Mosesso et al., 2001; Canova et al., 2005).

Finally, the genomic era of exploration raises profound ethical and policy imperatives. The acquisition and utilization of astronaut genomic data compel frameworks that safeguard privacy, equity, and informed consent, particularly if genetic information becomes a determinant of crew eligibility or is considered for preemptive genomic modification (Beheshti et al., 2019; Horneck et al., 2019; Seylani et al., 2024). High-impact exploration thus requires not only technological innovation but also a reaffirmation of bioethical principles that preserve public trust and ensure equitable participation in humanity's expansion beyond Earth.

In sum, the future of human Space exploration hinges on a systems-level strategy: coupling genomic foresight with continuous molecular surveillance, leveraging synthetic biology for in situ therapeutics, and embedding ethics at the core of mission architecture. This synthesis of biology, engineering, and governance will define our capacity to transform the profound risks of interplanetary travel into manageable, scientifically tractable challenges—thereby enabling safe, sustainable, and equitable human presence in deep Space.

6 Conclusion

Over the past seventy-five years, Space biology has evolved from pioneering studies in insects, seeds, and small animals to comprehensive multi-omic profiling of astronauts, revealing persistent molecular signatures of DNA damage, oxidative stress, altered telomere dynamics, mitochondrial dysfunction, and immune modulation. These insights have driven the development of targeted countermeasures, including antioxidant and radioprotective therapies, genome-informed interventions, and real-time in-flight monitoring, while raising ethical considerations around genetic privacy and selection. Together, this body of work provides a roadmap for personalized genomic surveillance and adaptive health strategies, ensuring that as we step farther from Earth, we do so carry the lessons written in our DNA.

Annex: Experimental Methods and Protocols

Cytogenetic assays – Chromosomal aberrations detected via metaphase spreads and fluorescence in situ hybridization (Durante et al., 1996; Aliyev et al., 1986).

γ-H2AX foci analysis – Immunofluorescent quantification of double-strand break markers (Canova et al., 2005; Moreno-Villanueva et al., 2017).

Oxidative DNA lesion quantification – Measurement of 8-oxoguanine lesions by HPLC or immunoassays (Allen et al., 1995; Hollander et al., 1998).

Telomere length measurement – qPCR-based analysis of relative telomere length (Luxton et al., 2020; Luxton et al., 2021).

Alternative Lengthening of Telomeres (ALT) assays – C-circle assays to assess ALT activity (Luxton et al., 2020).

Transcriptomics – Gene expression profiling via microarrays and RNA-seq platforms (Dieriks et al., 2009; da Silveira et al., 2020).

Proteomics & metabolomics – Mass spectrometry–based high-throughput molecular profiling (da Silveira et al., 2020; Overbey et al., 2024).

Epigenetic profiling – DNA methylation arrays and single-cell ATAC-seq for chromatin accessibility (Garrett-Bakelman et al., 2019; NASA OSDR, 2021).

Radiation analog exposures – Heavy ion irradiation using 1 GeV/amu Fe ions, proton beams, and γ/X-ray controls (Goodhead, 1994; Nikjoo et al., 2001; Suwanprakorn et al., 2024).

Microgravity simulation – Rotating wall vessel bioreactors and clinostats to model μG conditions (Nickerson et al., 2000; Mosesso et al., 2001; Canova et al., 2005).

Immune assays – Cytokine quantification and viral reactivation assays (Mehta et al., 2013; Crucian et al., 2018).

Mitochondrial stress and ROS assays – qPCR, fluorescent probes, and biochemical assays for ROS production (Indo et al., 2016; Babu et al., 2023).

Conflicts of Interest

The authors declare no conflict of interest.

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