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Human Cells' Genomic Changes as a Result of Microgravity

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ABSTRACT: Humans are at risk in the space environment, which is made up of a complicated mixture of various forms of ionising radiation and changing gravity. Particularly, the risk of space radiation carcinogenesis is directly correlated with individual radiation sensitivity. Therefore, in order to increase the safety of space exploration and in light of upcoming missions to the Moon and Mars, it is necessary to quantify each individual's risk from space exposure as precisely as feasible. In this review, we examine how ionising radiation and microgravity, the two primary physical elements of the space environment, interact to change the genetics and epigenetics of human cells in both real and simulated space conditions. The possible use of data gathered from studies on human cells to calculate each person's own risk of radiation carcinogenesis from exposure to space is addressed.

KEYWORDS: space radiation; microgravity; OsaD; genetic and epigenetic changes; radiation carcinogenesis risk

I. INTRODUCTION

For human travel and permanent habitation beyond of the sphere of protection provided by the magnetosphere, the space environment poses a significant risk. During the past 60 years of manned spaceflight, reports of cellular and tissue changes brought on by exposure to the space environment have been made. Epidemiological data gathered from astronauts provides the first proof of human body changes, displaying muscle weakening, weight loss, bone degeneration, cardiovascular disease, and immunological suppression [1]. Additional information has been gathered from more recent satellite missions [2-4] and is available on the National Aeronautics and Space Administration (NASA) website (accessed on September 23, 2021). Space radiation, isolation, separation from Earth, gravitational fields, and hostile/closed habitats are the five categories into which NASA's Human Research Program (HRP) has divided dangers for astronauts. The danger resulting from space exposure is difficult to identify because all of these risks are present simultaneously during a space mission. According to NASA's HRP, assessing the risk of radiation carcinogenesis is regarded as a top research priority for upcoming space missions that intend to permanently settle people on Mars and the Moon. Before beginning deep space missions, the "huge" risk of radiation carcinogenesis resulting from spaceflight must be considered. One such concern is the possibility of developing cancer in the years following a space flight. Currently, NASA has defined the acceptable limit of risk at 3% [5]. The danger of radiation-induced DNA damage and reactive oxygen species (ROS) generation may, however, be higher for astronauts due to a number of unique hereditary characteristics than the threshold of radiation risk generally acknowledged. Genotype, age, nutrition, diabetes, and other factors all affect how sensitive an individual is to radiation [6,7]. However, research on how space circumstances affect human molecular pathways as well as information on how space radiation affects the human genetic and epigenetic landscape are still in their infancy. Peripheral blood lymphocytes (PBLs) from astronauts on 3-6 month missions were shown to have genomic abnormalities in the form of chromosomal damage [8]. However,

there have only been a few studies on genetic changes in human cells that have been into space due to a lack of data from long-duration missions. The NASA Twins Study, which involved two monozygotic twin astronauts, found gene expression differences between the astronaut who spent 340 days on the International Space Station and his Earthbound twin [3]. Malkani et al. [9] have discovered a miRNA profile in mammalian cells that is related with spaceflight. This is why genomic research has so enormous potential for analysing how cells react to an environment in space. However, predicting danger in space is fraught with numerous unknowns, chiefly brought on by cosmic radiation and changed gravitational fields. Here, we provide a summary of the research on the modification of genetic and epigenetic pathways in human cells subjected to actual or simulated space environments.

II. ENVIRONMENTAL RADIATION IN SPACE

Long-term human exploration is at danger in a number of ways, one of which being the radiation environment in space. Astronauts and cosmonauts are exposed to a number of radiation sources when in Low-Earth Orbit (LEO), such as the International Space Station (ISS), which has an orbital inclination of 51.6 degrees and an altitude of around 400 kilometres. This comprises low-energy (typically 50 MeV/n) protons from solar energetic particles (SEP), medium-energy (250 MeV/n) protons trapped in the Van Allen Belts, and high-energy radiation from protons to high-atomic number iron nuclei known as galactic cosmic rays (GCR) [10,11]. GCRs and trapped protons are projected to contribute around half of the dosage in LEO; the Earth's magnetic field affects all of these sources. Furthermore, the combination of these particles creates a complicated radiation environment within and around a LEO. The orbital parameters (orbital inclination and altitude), the solar cycle, and spaceship shielding all affect how complicated these radiations are. At solar maximum and lowest, the radiation rates within the ISS range from 0.3 to 0.4 mSv/day [12]. These radiation rates are several hundred times greater than those found on Earth at sea level. High-energy charged particles from SEPs and GCRs have a significant impact on astronauts' and cosmonauts' dosimetry outside of the Earth's magnetic field. In transit between planets, on the surface of the moon, or on Mars, the cosmic-ray dosage rates are approximately 0.4, 0.3, or 0.2 mSv/day at solar maximum and 1.1, 0.9, or 0.5 mSv/day at solar minimum, respectively [12]. The likelihood of a solar particle event (SPE), which might be very dangerous, increases during the solar maximum period even though increasing solar activity greatly decreases the dosage from cosmic rays. Space-based research to look into the health consequences of space radiation have significant constraints, despite the fact that the impacts of GCRs are quite alarming. Studies conducted on the ground are crucial for collecting data that are statistically significant. Ground-based accelerators with high-energy ion beams have been used to conduct extensive research with a single beam or beam combinations, including the BEVALAC at Lawrence Berkeley National Laboratory (LBNL), the Helmholtz Center for Heavy Ion Research (GSI), NASA's Space Radiation Laboratory (NSRL) at Brookhaven National Laboratory (BNL), and the Heavy Ion Medical Accelerator (HIMAC) at the National Institute of Radiological Sciences (NIRS). Rapid switching technology has recently been used by the NSRL to create SPE and GCR simulated beams for diverse ion species and energies [13]. Additionally, animals are exposed to neutrons from a panoramic Californium-252 source in a concrete-shielded structure on the Colorado State University campus [14] at a low dosage rate of 1 mGy per day. When astronauts come into contact with GCRs while on missions beyond the Earth's magnetosphere, it might pose a risk to their health. Although only a tiny part of GCRs are neutrons, secondary neutrons that are expelled as a result of the interaction of GCRs with shielding components are important [15,16]. The effects of high-LET radiation on cells and animals have been widely researched in ground-based facilities, but microgravity, another significant environmental stressor in space, is absent from these settings. Takahashi's team has created a special mechanism in order to comprehend the impacts of space radiation combined with microgravity settings [17–19]. These technologies enable the simultaneous exposure of samples to neutrons, carbon ions, or X-rays while in a microgravity simulation.

III. THE GENERATION OF OXIDATIVE STRESS AND DAMAGE (OSAD) IN THE SPACE ENVIRONMENT

Ionizing radiation (IR) exposure causes cells to have a complicated reaction that is fueled by several proteins from various biological pathways that work together to protect cells from the cytotoxic and genotoxic assault. The cellular context (cell type and proliferative status) as well as the energy and LET of the radiation as well as dose-rate, final dosage, exposure period are all directly connected to the biological response to infrared radiation (IR) [20, 21]. Different types of cellular damage linked to both the direct and indirect impacts of IR are caused by the mixed nature of

space radiation. GCRs have a strong ionising power and severely damage DNA molecules because they are made up of high-energy protons and high-charge (Z) and energy (E) nuclei (HZE) [5]. Single-strand breaks (SSBs) and double-strand breaks (DSBs) occur when IR interacts with the DNA molecule. When radiation enters the cell and causes DSBs, the upstream signalling protein kinase ataxia telangiectasia mutated (ATM) is activated to start the DNA-Damage Response, which results in chromatin remodelling and a series of protein phosphorylations (DDR). The DDR pathway's ultimate purpose is to overcome DNA damages in order to preserve genomic integrity and guarantee cell survival. Given the potentially hazardous force of space radiation, this is a difficult task. The DDR pathway is dependent on the function of numerous proteins that, after being phosphorylated by ATM, participate in sensing/transducing the DNA damage signal to effector proteins that are in charge of the DNA-repair machinery, cell cycle checkpoints (if cells are proliferating), and cell death by apoptosis [22–24]. Additionally, ATM mediates modifications in the RNA metabolic pathways, including as mRNA production and miRNA biogenesis, brought on by DNA damage [25, 26]. The PARP family of proteins, which bind to DNA SSBs and DSBs and catalyse the ADP-ribosylation of chromatin proteins, initiate DNA repair [22]. However, because water makes up the majority of cells, water radiolysis results in the formation of many reactive oxygen species (ROS). High amounts of free radicals, including hydrogen peroxide, the hydroxyl radical, and the superoxide anion, are produced as a result, and these radicals may harm many organic molecules, including lipids, proteins, and nucleic acids. Highly reactive nitrogen species (RNS), which are a result of the early activation of nitric oxide synthases in irradiated cells, also cause harm to the same biological targets [27]. The production of ROS and RNS as well as the kind, dosage, and dose-rate of radiation all affect how much oxidative DNA damage occurs. Oxidative stress and damage (OsaD) is a condition caused by the increase in oxygen and nitrogen reactive species that radiation causes, which changes the physiological equilibrium between reduction and oxidation [28]. OsaD causes a tightly controlled defensive response that, while working with the DDR pathway, on the one hand activates antioxidant enzymes such superoxide dismutase, catalase, and glutathione s-transferase and low molecular weight antioxidants. Despite the fact that only a small number of proteins are shared by the OsaD and DDR Pathway [31,32]. The majority of oxidised bases seen in oxidative DNA damage are 8-Oxo-7,8-dihydro-2'-deoxyguanosine (8-oxodGuo), which is also employed as a biological biomarker of oxidative stress [33]. In addition to purines, pyrimidines are also broken down by ROS, resulting in oxidised pyrimidine derivatives including thymine glycol (Tg) and 5,6-dihydroxyuridine (DHU), which can inhibit DNA and RNA polymerases [33]. While RNS mostly leads to protein changes in the form of tyrosine nitration and S-nitrosylation of cysteine that disrupt the normal action of proteins [29], ROS also produces oxidised base-derived apurinic/apyrimidinic sites and SSBs [34]. Several physiological activities are regulated by intracellular signalling cascades that involve reactive oxygen and nitrogen species [35]. In this context, a number of transcription factors can activate certain signalling pathways and are sensitive to variations in ROS/RNS levels [29]. A non-targeted (bystander) impact can result from cells that were not directly exposed to radiation, and the quantity of direct and indirect DNA damage is tightly correlated with the radiation quality and dosage [27,36]. In the presence of oxidative stress, ribosomal RNA also sustains oxidative damage [37]. Particularly noteworthy is the role that mitochondria play in the rise in oxidative stress by producing mitochondrial ROS during cellular respiration. Numerous studies have shown that OsaD significantly affects human physiology because it acts as a plasma biomarker [39] and because the oxidative levels of irradiated cells can fluctuate for days after exposure, causing long-term consequences [38]. The space environment is characterised by lower gravity, which adds additional stress, in addition to radiation. Numerous studies have shown that oxidative stress is brought on by microgravity, whether it be actual or artificially created on Earth [40]. Therefore, a real or simulated environment of low gravity that affects the OsaD response can amplify the impacts of space radiation. Particularly for long-duration missions where a situation of chronic exposure develops, the combination of the two stressors might exacerbate the negative effects of the space environment. Regarding this, research using cosmonaut and space-flew rat cell samples have demonstrated an increase in oxidative stress, inflammation, lipid peroxidation, and a reduction in various blood antioxidants [4,41,42]. When exposed to a different gravitational environment, macrophages and T cells showed changes in the human immune system's transcriptional profile [43]. The amount of oxidative stress-induced gene expression alterations between the microgravity/hypergravity samples and their corresponding control cells was determined to be significant by the authors. Similar findings were made by Overbay et al. [44], who discovered oxidative damage and altered gene expression in the retina of mice that had spent 35 days in space. Three unrelated astronauts who were sent on two 6-month space missions had persistent DDR activation, as well as mitochondrial and oxidative stress, chromosomal abnormalities, and telomere lengthening [4,42]. Cancer is one of



many human illnesses caused by loss of function or imbalance in DDR proteins, which is a danger for astronauts exposed to space radiation.

IV. REPAIR OF DNA REPAIR DAMAGE CAUSED BY SPACE ENVIRONMENT

DNA damage was discovered in space-flown cell nuclei using the TdT post-labeling experiment, which was dependent on the duration of the spaceflight [45], and the creation of -H2AX foci allowed researchers to see the tracks of double strand breaks. The many forms of DNA damage brought on by space radiation and changed gravity are correctly repaired in accordance with their characteristics. Different repair processes are active and well-known for nuclear DNA [3]. Non-proliferating (G0) cells use the non-homologous end joining (NHEJ) pathway, which is the main method to repair radiation-induced DSBs across all cell cycle stages (G1-S-G2). NHEJ is split into two types in mammalian cells: CANONICAL NHEJ (c-NHEJ) and ALTERNATE NHEJ (alt-NHEJ), which depend on the activity of many distinct proteins. NHEJ is a non-conservative pathway overall, but c-NHEJ typically restores sequence integrity, whereas alt-NHEJ has low fidelity end-joining activity and frequently occurs in microhomologies [48]. At proliferating cells, homologous recombination (HR) predominates in the mid-S and mid-G2 cell cycle stages when the sister chromatid is able to conservatively repair DSBs [49]. Base excision repair (BER), which activity employs DNA glycosylases to remove damaged bases and create abasic sites, is used to repair SSBs that were either directly or indirectly caused by radiation. These abasic sites are then filled and repaired by DNA polymerase beta and DNA ligase IIIa (reviewed in [50]). Along with the mismatch repair (MMR) pathway, BER also participates in the repair of oxidative DNA damage [34,51–53]. It's interesting to note that oxidised DNA base damage and BER activation encourage the development of G4 structures, which control gene expression and play a part in transcription, replication, and other critical biological processes [54]. Chromosome translocations in *Drosophila melanogaster* [55] and larval deformities in *Carausius morosus* [56] were significantly more common in the space environment as a result of microgravity and radiation exposure. Recent studies on bacteria, yeast cells, and human fibroblasts suggest that a disruption of cellular repair processes in the microgravity environment might not be a complete explanation for the reported synergism of radiation and microgravity, despite the hypothesis that these synergistic effects may be caused by an interference of microgravity with DNA repair processes [57-60]. Alternative explanations for the effects of microgravity should be taken into account because they may be caused by modifications to signal transduction, metabolic/physiological states, chromatin structure at the cellular level, self-assembly, intercellular communication, cell migration, pattern formation, or differentiation at tissue level [61]. While mtDNA repair mechanisms are less well characterised, mitochondrial DNA (mtDNA) is likewise damaged by the direct and indirect effects of radiation. According to data, the same proteins involved in BER activity in the nucleus are also primarily involved in repairing oxidised bases and AP sites in mitochondria [62]. Mammalian mitochondria also have proteins for the NHEJ, HR, and nucleotide excision repair (NER) processes, however it is yet unknown exactly what these pathways do in terms of repair. Mammalian mitochondria have been shown to contain MMR proteins, however it is still unclear if this route is active [63].

V. GENETIC AND EPIGENETIC MODIFICATIONS IN HUMAN CELLS IN SPACE:

The genetic environment can change as a result of the combined direct and indirect impacts of IR and the OsaD state encountered during space missions. The immune system, cardiovascular system, endothelium system, bone maintenance, and metabolism are among the cellular systems that OsaD is known to contribute to the dysregulation of [28]; however, the molecular underpinnings of OsaD pathway regulation in space remain little understood. The maintenance of the human epigenome is put at risk when human cells exposed to the space environment experience genetic changes and changes to epigenetic factors like chromatin structure, DNA methylation, histone post-translation modifications (PTMs), and non-coding RNAs (ncRNAs). These changes can have an impact on gene regulation. An individual's reaction to genotoxic stress can be influenced by genetic variation in the form of single nucleotide polymorphisms (SNP) in genes in the DDR pathway. In *Staphylococcus aureus* and other research, short-term spaceflight settings were found to cause genetic alterations [64, 65]. Specific SNPs were shown to have been impacted by spaceflight in the NASA Twin research, which is one factor in space radiation damage. In particular, it has been demonstrated in the clinic that five SNPs discovered in risk alleles might predict possible development of ophthalmic disorders in connection to Neuro-ocular issues that arise during spaceflight [66]. Six of the nine risk alleles were shown to be present in the NASA Twin research [67]. This is one illustration of how space radiation may affect genetic polymorphisms and the necessity of considering protection against it. According to a recent study [68], chromatin is a

dynamic structure whose alterations are influenced by a number of variables including chromatin remodelers, chromatin modifying/binding enzymes, and non-coding RNAs. It is anticipated that space microgravity can alter nuclear shape and chromatin structure with significant ramifications for the control of gene expression. Mechanical forces applied at the cell surface may operate distantly to enhance mechanochemical conversion in the nucleus [69]. In comparison to 1-g in-flight and ground controls, the chromatin structure of human breast cancer cells displayed greater and more instances of low density under weightlessness circumstances [70]. Despite the fact that the period of time was brief (48 hours after launch), it is an indication of structural alterations that are inextricably tied to genome organisation. After lengthy space missions lasting many months, it has been observed that the yield of chromosomal abnormalities increases in lymphocytes from astronauts and cosmonauts [71-75]. Although background chromosomal aberration rates and individual radiosensitivity are very varied, an *ex vivo* dose-response in astronauts' pre-flight blood samples can be utilised to forecast the rate of chromosome aberration during the voyage [76]. Chromosome exchanges, particularly translocations, have a significant correlation with several malignancies [77,78], hence they provide an excellent biomarker for determining the astronauts' cancer risk. Studies conducted on the ground also revealed that exposure to radiation and simulated microgravity at the same time enhanced chromosomal abnormalities [79–81]. Human chromosomes have telomeres that protect the integrity of the genome at their ends. Researchers have used lymphocytes from astronauts' blood to study telomere length. Regardless of the length of the expedition, telomere length increased during spaceflight, and it swiftly decreased upon return to Earth. Overall, telomere length decreased in astronauts following spaceflight [3,4,42]. There are possible dangers associated with ageing as well as general health and illness, even if the precise mechanism and health impacts of telomere length dynamics have not yet been established. The primary epigenetic method for controlling gene expression is DNA methylation, however histone post-translational modifications (PTMs) also play a role in the epigenetic regulation of gene activity. Human blood-derived stem cells (BDSCs) that spent 48–72 hours in low gravity on the ISS showed changes in histone H3 methylation [82]. Particularly, ground-based incubated cells but not space-flew cells exhibit epigenetic changes at H3K4me3, H3K27me2/3, and H3K9me2/3 residues, which are implicated in the control of gene expression and cellular reprogramming. Human T cells launched into hypergravity showed decreased histone H3 acetylation [83]. DNA methylation of blood cells was investigated during the year-long NASA twin research expedition. DNA methylation alterations in pathways associated to the immune system and oxidative stress were found, despite the fact that genome-wide modifications were proven to be negligible [3]. A huge number of genes were differently methylated in the mouse retina that had spent 37 days in space. The ECM/cell junction and cell proliferation/apoptosis signalling in the retina were shown to be two crucial biological processes where the impacts were particularly severe [84]. Non-coding RNAs (ncRNAs) are crucial components that interact with histone-modifying complexes to support epigenetic maintenance and serve as scaffolds for chromatin-modifying complexes involved in the DDR pathway. Numerous ncRNAs with various sizes have been identified, including ribosomal RNA (rRNA), which ranges in size from 120 to 4500 nucleotides, transfer RNA (tRNA), which ranges from 76 to 90 nucleotides, small nuclear RNA (snRNA), which ranges from 100 to 300 nucleotides, small nucleolar RNA (snoRNA), which ranges from 60 to 400 nucleotides. There is little understanding of how these ncRNAs are affected by space and, more especially, by space radiation, despite the fact that many of these ncRNAs are being researched in illnesses. MicroRNAs (miRNAs) are a subclass of ncRNAs that regulate post-transcriptional gene expression by physically interacting with their target mRNAs, inhibiting their translation and/or causing their instability and degradation [86, 87]. MiRNAs are the ncRNAs that have been investigated the most in terms of space biology. Numerous human miRNAs have been discovered to be dysregulated in human space-flown cells [2,88], and a work by Hughes-Fulford et al. [89] conducted in human T cells activated with mitogens provides the first proof that the space environment controls miRNA expression. The expression of 85 genes linked to T-cell activation as well as miRNAs related in immunological function were dysregulated during the 11 days spent in space. Human fibroblasts did not differ from ground controls in another brief (>1 month) expedition on board the ISS in terms of their gene and miRNA expression patterns [90]. However, in order to get more useful information, gene expression assessments have been combined with studies of changes in miRNA expression in the space environment. A spaceflight miRNA signature was discovered by Beheshti et al. [91] using transcriptome data from NASA's GeneLab platform. In this study, scientists examined transcriptome data from mice that had been sent to space on a variety of missions, including both older Space Shuttle flights and more contemporary ISS investigations. A group of 13 miRNAs were expected to be linked with space environment degradation and elevated health risks based on this research. TGF was also discovered to be the primary target of the miRNAs. Additional research was done by Malkani

et al. [9] to confirm the existence of these circulating miRNAs in rodents and people exposed to space. These results show that these miRNAs will not only be a good biomarker to assess health risks in space, but also factors that can be developed into potential countermeasures. They also inhibited the portion of the miRNAs associated with cardiovascular health risks in space and were able to mitigate space radiation damage. According to Zhang et al. [90], compared to ground controls, the 3 or 14-day space environment has no effect on the gene expression alterations in human normal non-dividing fibroblasts. Similar to what was shown for gene expression, 3 and 14 days of ISS culture had no impact on the miRNA expression profile of human non-proliferating fibroblasts. Let-7a and miR-29 were the only two alterations seen, and they were both down-regulated on day 3. It's interesting to note that let-7a also has similarities with the spaceflight miRNA profile that Malkani et al. [9] found and confirmed. The space environment has an impact on gene expression in human cells, and these results are distinct [92]. Numerous crucial biological processes, such as immunological response, endothelial function, cardiovascular function, bone and muscle dynamics, cell growth and death, and oxidative stress response, are all governed by transcripts that have been discovered to be considerably changed. Versari et al. [93] found alterations in focal adhesion, over-expression of the TXNIP gene, which codes for the thioredoxin-interacting protein, and oxidative phosphorylation in HUVEC cells cultured for 10 days on the ISS. These changes result in an oxidative stress condition that encourages DNA damage and inflammation. Camberos et al. [94]'s transcriptome investigations of human adult and neonatal cardiovascular progenitors grown for 30 days on the ISS revealed considerable oxidative stress gene changes, with the superoxide dismutase 2 (SOD2) gene highly upregulated. Additionally, pathways for cardiovascular development, stemness, senescence, and cell proliferation and survival were enriched. In the human myelomonocytic cell line U937 during the 19th DLR Parabolic Flight Campaign [95], where the component of cosmic radiation is restricted in comparison to that of deep space, differential gene expression has also been found. In order to explain the normal immunosuppression seen in astronauts returning to Earth, Chang et al. [96] showed the downregulation of genes involved in the activation of human T cells. As compared to pre-flight samples, the transcriptional profiling of a subset of stress response genes in whole blood from six astronauts who spent 10 to 13 days on a space shuttle [97] revealed substantial gene changes in oxidative stress (GPX1, which codes for glutathione peroxidase), DNA repair (XRCC1, HHR23A), and chaperones (HSP27, HSP90AB1). In human endothelium cells exposed to weightlessness from 31 parabolic flights, the PRKAA1 gene was dramatically increased in the research by Grosse et al. [98]. Given that this gene encodes for a protein involved in the antioxidant state of endothelial cells, it may have a protective function. In comparison to 1.2-fold in simulated microgravity, the SOD gene was 4-fold more strongly activated in actual space [99]. After a 4 days, 23 hours in space, alterations in the expression of genes involved in the oxidative stress response, DNA repair pathways, cell cycle, apoptosis, and energy metabolism were found in human fibroblasts [100]. The outcomes of the NASA Twin Study are what determines how lengthier space voyages (>4 months) affect molecular dysregulation in human cells [3]. In this study, gene expression patterns showed substantial differences between the twin astronaut's peripheral blood cells at the end of his year-long mission aboard the International Space Station and those of his twin brother back on Earth. Adaptive immune system, innate immune response, and natural killer cell-mediated immunity are only a few of the immune-related pathways that have undergone substantial modification. Inflammatory pathways have also evolved dramatically (higher levels of cytokines that remained elevated during the 6-months after return to Earth). It's interesting to note that within 6 months after the journey, 91% of the differentially expressed genes reverted to normal levels. In this work, RNA sequencing revealed increased quantities of mitochondrial RNA inflight compared to pre- and post-flight. Da Silveira et al. [32] showed that mitochondrial dysregulation was the primary route that was dysregulated in space by performing pathway analysis on multi-omics datasets from NASA's GeneLab platform obtained from human cells that had been sent into space. Subsequent investigation in this work showed that fatty acid metabolism, cell cycle, oxidative stress, immunological suppression, and malfunction were all impacted by the mitochondrial dysfunction. This could mean that the upstream mitochondrial dysfunction discovered in this study is what is causing the observations from the other studies that were previously discussed. Many laboratories throughout the world have conducted research by imitating microgravity on Earth due to the limitations of executing experiments in genuine space conditions. However, there is little information on the interaction of simulated microgravity with ionising radiation on human cells, and the majority of research only looked at the effects of microgravity. Here, we provide an overview of recent findings about genetic and epigenetic changes found in human cells when simulated microgravity was applied alone or in conjunction with IR, by examining the link with the OsaD response. For the first time, the in vivo mutant frequency at the hypoxanthine-guanine phosphoribosyl transferase (HPRT) locus in human T-lymphocytes from monozygotic twins has been

examined to determine the relative contribution of simulated weightlessness to the development of mutation [102]. The scientists showed that personal genetics have a significant role in determining mutation rates, even if the impacts of simulated weightlessness had no influence on the mutant frequency. In comparison to those grown in 1 g, the mutation frequency at the HPRT locus considerably increased in human PBLs incubated in MMG during the repair phase following 1 Gy and 2 Gy of γ - or X-irradiation [103]. In γ -irradiated TK6 cells incubated in MMG compared to 1 g, HPRT mutant frequency also rose dramatically up to 4 Gy [104]. Interestingly, compared to healthy, unexposed participants, the prevalence of the HPRT mutant was 2–5 times greater in cosmonauts from various space missions [105]. Single nucleotide polymorphisms are another element of genetic diversity (SNPs). A few recent research provided significant data regarding genetic polymorphism connected to a DNA damage response. In a healthy population that had both professional and personal exposure to genotoxic substances like radiation, Niazi et al. [106] investigated the relationship between DNA repair gene polymorphisms and chromosomal abnormalities. The findings of the testing of 607 people for 153 DNA repair genes revealed SNP correlations with chromosomal aberration frequency within 14 genes that play important roles in preserving genomic integrity. Ten of the 14 SNPs affected the expression of the target DNA repair gene, and all of them were found in a region of active transcription. As a result, it is anticipated that SNPs and gene expression are related. In patients receiving radioiodine treatment, SNPs in the DNA repair genes for the HR and MMR pathways, which are important in repairing IR-induced DNA damage, are strongly related with DNA damage manifested as the production of micronuclei [107]. The connection between BER gene polymorphisms and individual radiosensitivity was also validated by correlation studies of SNPs in the BER pathway with DNA damage, DNA repair, and mRNA expression in healthy donors [108]. Based on these findings, it is anticipated that specific genetic traits would impact the DDR after exposure to radiation from space. The accessibility of several proteins, including transcription factors and DNA repair proteins, is influenced by chromatin architecture, which also has an impact on gene expression and cellular signalling pathways. The competence of repair proteins in the BER and NER systems is influenced by the DNA sequence and local structure around the 8-oxoG lesion, which is largely caused by ROS [109]. Differential OsaD response activity may result from changes in the chromatin accessibility for the various DDR pathway proteins. Human endothelial cells treated for 72 hours in an environment simulating microgravity showed chromatin condensation and margination along with alterations in the expression of genes involved in the Bcl2-apoptosis pathway and proteins involved in the PI3K/Akt pathway [110]. In addition, in human breast epithelial cells cultivated in simulated microgravity, genes whose expression is dependent on the linker of the nucleoskeleton and cytoskeleton (LINC) complex, connecting chromatin with the nuclear surface, were changed [111]. Important epigenetic alterations known as histone PTMs regulate the chromatin architecture and gene expression. According to Wang et al. [112], human embryonic cells subjected to shear flow in vitro undergo an increase of histone H2B acetylation, which controls chromatin dynamics. Furthermore, oxidative stress has been shown to change a number of histone PTMs [82,113], therefore it stands to reason that simulated microgravity, which produces both oxidative and mechanical stress, might impact histone PTMs. Human mesenchymal stem cells cultured in simulated microgravity showed a reduction in H3K27me3 when histone H3 methylation at promoter regions of certain genes was analysed [114]. Oxidative stress affects the activity of chromatin remodelers such histone acetyltransferase (HAT) p300 [113]. Chromosome level effects can result from variations in the expression of histone deacetylase (HDAC) genes in microgravity. The expression of HDAC1 decreased after 7 days in human T cells cultured in simulated microgravity, which was connected with genome-wide DNA hypomethylation [115]. Human cancer cells were cultured for 24-72 hours in a microgravity simulation before the HDAC1 and HDAC3 genes were shown to be dysregulated (downregulated and upregulated, respectively) [116]. Based on their physical makeup, telomeric DNA and mitochondrial DNA should be more vulnerable to oxidative stress and damage [117]. In newborn cardiac progenitors, transcripts for the telomerase reverse transcriptase (Tert) gene, whose protein maintains telomere ends, and RAD50, whose protein is essential for telomere maintenance, were shown to be upregulated in simulated microgravity [118]. Recently, bulk blood and sorted cells from two astronauts were used to map chromatin and epitope alterations at a single-cell level (Gertz et al., 2020). In particular for monocytes and dendritic cell precursors, our multi-omic (100-plex epitope profile, ATAC-seq, and gene expression) data on PBMCs revealed alterations in blood cell composition and gene expression post-flight. It had been in line with the stress on the immune system and cytokines brought on by flight, followed by skeletal muscle regeneration in reaction to gravity. A foundation for high-resolution immune cell activity during spaceflight is also provided by these results [119]. Modulation of gene expression can be significantly impacted by changes in histone PTMs and DNA methylation patterns. Human T cells cultured in

simulated microgravity were shown to have altered DNA methylation and histone acetylation [115]. Particularly, DNMT1, DNMT3a, and DNMT3b gene expression levels were time-dependent, rising during 72 h of simulated microgravity incubation and falling throughout 7 days of incubation in comparison to 1g-incubated controls. The work by Chowdhury et al. [120] examined the relationship between changes in gene expression and DNA methylation patterns brought on by simulated microgravity in human lymphoblastoid TK6 cells. Comparing cells that were treated for 48 hours in a simulation of microgravity to static controls, a large number of genomic locations displayed changes in methylation (either an increase or a decrease). In particular, genes with differential expression that were enriched for the p53 pathway, the PI3-kinase pathway, and the activation of the T/B cell pathway showed hypermethylation, whereas genes with differential expression that were enriched for the EGF receptor signalling pathway, apoptosis, and FGF signalling showed hypomethylation. Even while the scientists were unable to identify a general pattern linking changes in the genome's pattern of 5-methylcytosine (5-mC) and 5-hydroxymethylcytosine (5hmC) with variations in gene expression brought on by simulated microgravity, they were nonetheless able to profile the DNA methylation state of specific transcriptionally up- or down-regulated genes. For instance, two genes (TSPAN5 and SPG20, both up-regulated) and three genes (PLIN2, MAP3K13, and FBXO1, all down-regulated) were linked to loss-of-5mC at their promoters. Given the conventional assumption that increases in promoter methylation enhance gene activity, this suggests that the link between transcriptional activity and DNA methylation is more nuanced than anticipated. Although the expression of the PLIN2 gene, which codes for the Perilipin-2 protein related to the production of lipid droplets, has been found to be significantly increased in human HepG2 cells experiencing oxidative stress induced by H₂O₂, these differentially expressed genes were implicated in the mechano-stress response [121]. The downregulation of PLIN2 shown in Chowdhury et al. [120] may be due to the distinct cell type and a lower amount of oxidative stress brought on by microgravity than by H₂O₂. Non-Coding RNAs and Changes in Gene Expression MiRNAs are the focus of the majority of studies on the dysregulation of ncRNAs in simulated microgravity, radiation exposure or not. Numerous studies have combined the transcriptome and microRNAome of the same kind of cells taken from normal or tumour samples to get insight into changes in gene expression. The miRNA expression patterns were considerably changed in human peripheral blood lymphocytes (PBLs) cultivated in normal gravity (1g) or simulated microgravity (MMG) throughout the repair period following -irradiation (2 Gy) [122]. In particular, the combined effects of radiation and MMG led to the dysregulation of several miRNAs (let-7i, miR-7, miR-7-1, miR-27a, miR-144, miR-200a, and miR-650), as well as a reduction in the number of radiation-responsive miRNAs when compared with 1g conditions (32 vs. 52 miRNAs, respectively). The DDR pathway, which includes the p53 pathway, underwent significant changes. The biological categories "reaction to DNA damage stimulation", "DNA damage response", and "apoptotic mitochondrial alterations" were significantly enriched in Gene Ontology (GO) words, but only in 1g conditions for PBLs. These findings are consistent with the biological response seen in PBLs incubated with MMG, which included increased apoptosis, a delay in DSB repair, and an increase in mutant frequency [103,123]. Human lymphoblastoid TK6 cells were exposed to the same amount (2 Gy) of gamma rays in the work by Fu et al. [124] and then cultured for 24 hours in a microgravity simulation. They demonstrated changes in the quantity of long-ncRNAs (lncRNAs) that were connected with differentially expressed genes in the immune/inflammatory response and apoptotic process that were stressor-specific. However, miRNA profiles showed relatively little variation, and this difference is likely due to the studied cells' normal or tumoral condition, which represents various genomic responses to genotoxic chemicals. It is significant to note for this study that the microgravity assessment was conducted using low LET (gamma) irradiation. According to Malkani et al. [9], it has been demonstrated that miRNAs associated with the response to high-LET space radiation function quite differently from those associated with low-LET. Future investigations to examine the impacts of space radiation should take into consideration the differences with low- and high-LET irradiation as they might be one explanation for the variations seen with miRNAs. Only in 1g settings for PBLs were the biological categories "reaction to DNA damage stimulation," "DNA damage response," and "apoptotic mitochondrial changes" considerably enriched in Gene Ontology (GO) terms. These results are in line with the physiologic effects of MMG incubation on PBLs, which included increased apoptosis, a postponement of DSB repair, and an increase in mutant frequency [103,123]. In the study by Fu et al. [124], human lymphoblastoid TK6 cells were treated to the same quantity (2 Gy) of gamma rays before being cultivated for 24 hours in a microgravity simulation. They showed modifications in the abundance of long-ncRNAs (lncRNAs) that were linked to differentially expressed genes in the immune/inflammatory response and the stressor-specific apoptotic pathway. When examining the effects of simulated microgravity on the miRNA and gene expression patterns in human cells, significant changes have been found. Although the oxidative

stress response appears to develop after an incubation duration of >24 h in simulated microgravity, the changed miRNA-mRNA pairings enhanced identical biological pathways depending on the cell type. Using lymphoblastoid TK6 cells, Mangala et al. [125] discovered seven miRNAs whose expression was substantially different from control cells cultured in 1g after being incubated for 72 hours in simulated microgravity. The majority of the biological categories of the immune response, including the NF- κ B pathway, apoptosis, and survival, were enriched in the genes that these miRNAs targeted. Human colorectal cancer cells and lymphoblast leukemic cells that were cultured for 72 hours in simulated microgravity were found to have significantly different miRNAs targeting genes related to cell cycle and proliferation, DNA repair, apoptosis, and the Notch signalling pathway from the counterpart cells cultured in static 1 g [116]. Additionally, in human PBLs treated for 24 hours in MMG, a collection of miRNA-mRNA pairings associated with immunity, cell proliferation, and death were discovered [126]. Many of the genes and miRNAs that have been identified to be dysregulated have a role in biological processes such as signal transduction, programmed cell death/proliferation, the immune/inflammatory response, and the NF- κ B pathway. Interestingly, HUVEC cells treated in simulated microgravity during a brief period of time (i.e., 2 h) showed significant alterations in gene and miRNA expression in pathways of NF- κ B, cell proliferation, and inflammation [127]. Dysregulated miRNAs targeted apoptotic genes when the same cells were cultivated in microgravity for a longer time (i.e., 48 h) [128]. Human mesenchymal stem cells' expression of genes associated to apoptosis, cell survival, and proliferation were changed by a one-week incubation in microgravity [129]. Chowdhury et al. [120] found 370 differentially expressed genes primarily involved in the biological categories of "oxidative stress response," "carbohydrate metabolism," and "regulation of transcription" in their genome-wide study on human lymphoblastoid TK6 cells exposed for 48 h to simulated microgravity. 3-5 days of incubation in simulated microgravity caused changes in the VEGF, MAPK, and PAM signalling pathway genes in prostate cancer cells [130]. Even though the alterations in gene expression seen in genuine microgravity are distinct, many of the genes that have been discovered to be differently expressed in human cells that have been cultured in simulated microgravity also change in real microgravity. This is not true for all cell types, as shown by the observation that dysregulated genes in human neural crest stem cells cultivated in actual or simulated microgravity belong to distinctly diverse pathways [131]. As an example, the superoxide dismutase (SOD) gene was upregulated 4.1-fold in space microgravity compared to 1.2-fold in a rotating wall vessel (RWV) [99] and cells exposed to both real and simulated space conditions generally reported less pronounced gene expression changes in simulated than in space conditions.

VI. RADIATION CARCINOGENESIS RISK ASSOCIATED WITH GENETIC AND EPIGENETIC CHANGES

Radiation carcinogenesis is one of the most significant health issues that can arise from exposure to the space environment. The tremendous destructive force of cosmic radiation and each person's unique genetic landscape, which might affect the radiation response, are to blame for this danger. The physical properties of cosmic rays are one of several variables that affect the radiation carcinogenesis risk linked to deep-space exposure. High-LET radiation (protons and HZE ions) that makes up GCRs causes chromosome abnormalities including intrachromosomal inversions that continue to increase post-flight [3] and direct DNA damage in the form of clustered and complicated lesions that are challenging to repair [5,132]. The complex DNA lesions, oxidative DNA damage, and unintended side effects of ionising radiation all work together to increase the risk of carcinogenesis. It's significant because genomic modifications relate not only to the environment of spaceflight but also to certain genetic traits that affect the effectiveness of the DDR pathway. In the past several years, new information on the genetic and epigenetic changes that radiation exposure causes in human cells has been available thanks to genome-wide investigations. Whole blood from astronauts showed high variability in the expression of the GPX1 gene, which is crucial for oxidative stress, and the DNA repair genes XRCC1 and HHR23A [97]. Similar to this, -irradiated single donor-derived PBLs incubated in MMG dramatically altered the expression of numerous DDR pathway genes [122], while similar genes were unaffected when PBLs were examined as collections of various donors [123]. This demonstrates that an individual DDR to IR does exist, as has been suggested in prior investigations. According to Pariset et al. [133], people with low basal levels of DNA damage are both more sensitive to radiation-induced DNA damage and less vulnerable to its adverse effects. They also have a larger number of repair foci. Better therapeutic results and a larger potential for DNA repair are conferred by these two traits. Other research found variations in DNA repair ability at four SNPs in the BER genes hOGG1, APEi, XRCC1, and LIGASE1 that are connected to a person's genotype [108]. The results show a link

between gene polymorphism and DNA damage capability despite the drawback of a limited sample size, allowing for the separation of radiosensitive donors from those who have a radio-adaptive response. In human peripheral blood cells from a population exposed to chronic low-level radiation, SNPs in the BER genes (LIG1 and NEIL1) or DNA repair genes in the NHEJ pathway (XRCC5, XRCC6, and XRCC7) were shown to be correlated with individual radiosensitivity [134]. Notably, when radiation-induced DSBs were repaired, mouse embryonic fibroblasts showed signs of genomic instability due to replication stress-induced DSB accumulation brought on by oxidative DNA damage [135]. Cells were more likely to experience single nucleotide variations (SNV), including SNVs linked to radiation, under these circumstances. Human cells exposed to space radiation would suffer from a similar mutagenesis impact, although cosmonauts have been shown to have an increased frequency of mutant HPRT genes [105]. As a result, it is also anticipated that the combined effects of radiation and microgravity may cause mutations in the genes involved for the carcinogenic process. The quality and amount of space radiation have previously been used to evaluate the cancer risk during space missions. The research by Cucinotta and Smirnova [136] made an effort to evaluate the risk of human radiation-induced leukaemia. By employing a radiation dosage and dose rate that matched the mean dose rates of continuous irradiation of nuclear workers and radiotherapy patients, the scientists created a dynamic model of radiogenic leukaemia. The modelling outcomes show the model's ability to forecast outcomes; but, by disregarding the effects of microgravity, it might potentially overestimate the danger to astronauts. Particularly, immune system abnormalities brought on by stresses related to space flight must be taken into account when evaluating the probability of cancer mortality [137]. According to studies, normal mice underwent hind-limb unloading (HU) showed considerably more splenic and thymic atrophy, tumour development, and metastasis than controls [138,139]. HU was created to make it possible to examine the negative effects of space travel, although it might not be a precise representation of microgravity. Therefore, studies conducted in space will be required to confirm these findings. Measuring clonal hematopoiesis (CH), which was first noted in astronauts in 2020 [140], is one of the most promising research directions for longitudinal and ongoing assessments of risk for haematological malignancies or cardiovascular disease. Numerous studies have focused on reducing the oxidative stress brought on by RNS and ROS as a way to save important targets including DNA, RNA, and other biological components. Animal models have been used to test several dietary supplements for their ability to reduce oxidative stress on various biological endpoints [141,142]. N-acetyl cysteine (NAC), ascorbic acid (vitamin C), vitamin E succinate, coenzyme Q10, folic acid, glutathione, alpha-lipoic acid, selenomethionine, and a pro-tease inhibitor produced from soybeans are a few examples of these (Bowman-Birk inhibitor, BBI). When C57BL/6J male mice subjected to 56Fe brain irradiation received treatment with alpha-lipoic acid, the impairment of spatial memory retention was less severe [143]. After 56Fe ion radiation, vitamin A dramatically decreased neoplasms in a Sprague-Dawley skin model and prevented the expression of genes associated to inflammation. The reduction in serum or plasma levels of total antioxidants after exposure to gamma radiation or 1GeV/n of the 56Fe ion was reversed by a diet high in selenomethionine, whether it was combined with sodium ascorbate, NAC, alpha-lipoic acid, vitamin E, or coenzyme Q10 [145]. In CBA/JCrHsd animals fed with a BBI concentrate or an antioxidant mixture of selenomethionine, NAC, ascorbic acid, coenzyme Q10, alpha-lipoic acid, and vitamin E succinate, a decrease in 56Fe radiation-induced cataracts as evaluated by lens opacification was demonstrated [146]. According to a recent study, adding 25% dried plum to the diet protected mice from gamma radiation or sequential proton and 56Fe ion exposure by lowering the expression of genes linked to bone resorption and cancellous bone loss. This is likely because dried plum has a high polyphenol content and antioxidant capacity. Additionally, this study was expanded to look at how exposure to ionising radiation interacted with lower gravity caused by hind-limb unloading. Increases in indicators for bone resorption, inflammation, and oxidative stress were avoided in hind-limb unloaded C57BL/6J mice given 137Cs gamma-ray irradiation and fed a dried plum-enriched diet [148]. These kinds of findings imply that dietary supplements may guard against the harmful effects of oxidative stress when in space. Additionally, pre-, in-flight, and post-flight space missions have long used physiological countermeasures owing to microgravity [149]. Exercise was also found to have a mitigating impact on 68 of 72 pertinent outcomes that lowered DNA damage, oxidative stress, and inflammation following radiation exposure in a recent assessment of 22 research [150]. Although it is unlikely, radiation exposure from a solar particle event (SPE) might cause acute radiation syndromes (ARS), which would need the use of medical countermeasures (reviewed by [151]). Hematopoietic failure is due to a possibly fatal exposure in the lowest dosage levels (H-ARS). Physical shielding serves as the main component of an efficient defence against these exposure levels. But should a radioactive exposure happen, the prodromal phases of H-ARS, or early symptoms, include nausea, vomiting, anorexia, and

diarrhoea. There are medications that may be used to treat these symptoms, such as 5-HT₃ serotonin antagonists for nausea or Imodium® for diarrhoea. Currently, three medications have been created and received FDA clearance to improve patients' chances of survival after receiving acute myelosuppressive radiation doses. Filgrastim (Neupogen® from Amgen) and the sustained release version peg-filgrastim or Peg-G-CSF (Neulasta® from Amgen) are made of recombinant granulocyte colony stimulating factor (G-CSF), which has been shown to successfully reduce neutropenia from SPE-like proton irradiation in a mouse model [152]. Last but not least, recombinant human granulocyte macrophage colony stimulating factor (rhGM-CSF), also known as Sargramostim (Leukine® from Partner Therapeutics), is used to treat both adult and paediatric patients who have received myelosuppressive radiation doses [153]. Numerous experimental considerations have been made for the combined consequences of oxidative stress brought on by microgravity and exposure to space radiation in relation to several tissue types, including the immune system [157], central nervous system [156], and cardiovascular system [154,155]. Astronauts have previously shown post-flight carotid arterial stiffness [158]. Pentoxifylline, a phosphodiesterase inhibitor, and -tocopherol have been used to treat a rat model of radiation-induced heart disease, despite the fact that there is little study on pharmacological countermeasures (vitamin E). This medication enhanced left ventricular function and myocardial fibrosis, which may lessen cardiac in-jury [159]. The prevention of immune system dysregulation is a significant obstacle to maintaining astronauts' health. Research is now being done on potential defences, such as pharmacological, probi-otic, prebiotic, and medical treatment plans employing antibiotics or antivirals. The effective development and use of innovative nutritional and pharmacological countermeasures will help to reduce the overall risk related to exposure to the space environment for long-duration spaceflights.

VII. CONCLUSION

The cellular reaction to radiation and the likelihood of getting cancer or other disorders are directly correlated with specific genetic characteristics. Because healthy people's DNA repair genes have genetic variations that alter their ability to repair DNA damage, radiosensitive people are more likely to develop cancer when exposed to space radiation. Additionally, each person's genomic characteristics should determine the degree of epigenetic modifications caused by the space environment. Determining the best methodological way to detect the molecular fingerprints of those people who are more likely to acquire radiation sensitivity, prior to their employment in long-duration space missions, is therefore one of the study objectives. The most effective method to evaluate inter-individual variations in the physiological response to space environment is next-generation genomics and integrative analyses, according to recent significant findings derived from multi-omics data from astronauts employed in long-duration missions on the ISS.

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