Role of High-Linear Energy Transfer Radiobiology in Space Radiation Exposure Risks

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Abstract

Many manned missions to the Moon and Mars are scheduled in the near future. However, space radiation presents a major hazard to humans, and astronauts are constantly exposed to radiation, including high linear energy transfer (LET) radiation, which differs from radiation on Earth. Thus, there is thus an urgent need to clarify the biological effects of space radiation and reduce the associated risks. In this review, we consider the role of high-LET radiobiology in relation to space-radiation exposure.

Keywords: radiobiology; space radiation; linear energy transfer; risk assessment

Introduction

Many manned space missions are scheduled in the near future, during which astronauts will be constantly exposed to space radiation [1]. The radiation environment in deep space and low Earth orbit is very different from that at the Earth's surface (**Figure 1**), and space radiation, including high linear energy transfer (LET) radiation, is a serious hazard to people outside the protection of Earth's magnetic field and atmosphere, even at low doses and low dose rates. A lack of knowledge regarding the biological effects of space radiation is considered to be the most important factor limiting the prediction of radiation risk associated with long-term space travel. Accumulating evidence has refuted the classic target theory of radiation biology, and studies have found inverse low-dose-rate effects, an adaptive response, and bystander effects after exposure to low doses of high-LET radiation at a low dose rate [2]. The existence of space-radiation-induced nontargeted effects thus influences our understanding of the health risks associated with exposure to low fluences of high-charge and high-energy particles (HZE).

The present review summarizes the characteristics and environment of space radiation and the biological effects of exposure to high-LET radiation at a low dose rate and considers the status of biological research into space radiation.

Characteristics of Space Radiation

Galactic Cosmic Rays

Galactic cosmic rays (GCRs) come from outside the solar system but generally from within the Milky Way galaxy. The GCR particles consist of about 1% electrons, 85% to 90% protons, 10% to 13% helium ions, and about 1% HZEs [3]. Because the proton flux is generally high compared with the HZE flux, it is assumed that cells are likely to be hit by a proton before being hit by an HZE ion. GCRs include fully stripped ions to uranium; even-

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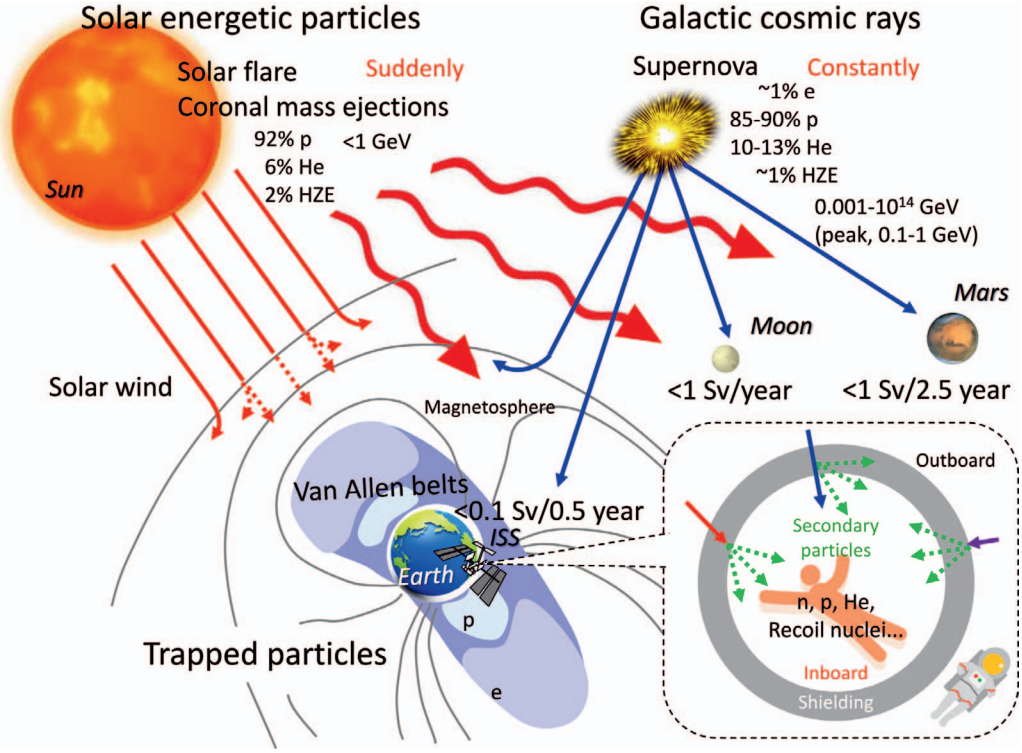

Figure 1. Environment of space radiation with galactic cosmic rays, solar energetic particles, and trapped particles. Abbreviations: e, electron; p, proton; He, helium ion; HZE, high-charge and high-energy particle; n, neutron.

numbered elements, such as carbon, oxygen and iron, are more abundant than odd-numbered elements, although the flux of ions above nickel is low. GCR energy has a wide range from 0.001 to 10^{14} GeV/n, with a peak at 0.1 to 1 GeV/n. Cosmic particles with energies >10 GeV/n do not contribute to the radiation dose because they have a very low flux and are emitted isotropically [4, 5].

Though GCRs are considered to originate from high-energy explosions of supernovae [6], the mechanism of GCR acceleration is unknown. However, GCRs with less than about 10^6 GeV energy are generally accepted to be accelerated by shock waves from supernova explosions within the Milky Way galaxy [7, 8]. A supernova remnant (SNR), which is the structure resulting from a supernova explosion, is bounded by an expanding shock wave and consists of ejected material expanding from the explosion. The main protons of GCRs were recently reported to be accelerated in SNRs [9]. In contrast, GCRs with $>10^9$ GeV energy are believed to originate outside our galaxy [10], having been accelerated to nearly the speed of light within the past few million years and traveled across the galaxy.

The heliosphere shields the solar system from GCRs. The GCRs are pushed back out by the solar wind, such that they are ejected out from the Sun with the magnetic field because the charged GCRs are affected by Lorentz forces. Thus, GCRs are subjected to heliospheric (solar) modulation associated with the 11-year solar activity cycle and show an inverse correlation with solar activity [11].

Solar Energetic Particles

The Sun emits radiation across most of the electromagnetic spectrum, including high-energy γ-rays and x-rays, ultraviolet, visible, and infrared light, microwaves, and ultra-long-wavelength radio waves. The frequencies, but not the sizes, of solar flares (SFs) and coronal mass ejections (CMEs) are related to the cycle of solar activity. A solar radiation storm (solar energy particle [SEP] event) comprises high-energy particles from the Sun originating in SFs and/or CMEs. The exposure durations of the SEPs from SFs are short (several hours) while those from CMEs are longer (a few days). These SEP events are sporadic and difficult to predict. They consist of 92% protons, 6% helium ions, and 6% HZE ions [4], with the proton energy ranging from 0.01 to 10 GeV/n. The peak proton flux of SEP events varies as a function of both SF and CME properties [12].

Trapped Radiation

The rotation of the Earth's molten iron core creates a magnetic field around the Earth that resembles a dipole field. This field traps high-energy protons (10-100 MeV/n) and electrons (0.1-10 MeV) in 2 annular doughnut-shaped zones known as the

inner (1,000-5,000 km) and outer (15 000-25 000 km) Van Allen radiation belts [5]. Although protons and electrons may be produced by solar ultraviolet-induced and x-ray-induced dissociation of hydrogen atoms, the inner-belt protons and electrons are mainly derived from cosmic-ray albedo neutron decay [13]. Because Earth's rotational and magnetic axes are different, the South Atlantic Anomaly is formed by the Van Allen radiation belt dropping to low altitude (about several hundred kilometers) over the south Atlantic Ocean.

Environment of Space Radiation

Low-Earth Orbits and the International Space Station

The International Space Station (ISS) flies at an average altitude of about 400 km above Earth, and the astronauts are exposed to high-energy radiation originating from GCRs and SEPs, largely due to trapped radiation in the South Atlantic Anomaly [14]. The dose rate outside the ISS is greater than that inside the ISS, and the dose inside the ISS depends on the location and overall shielding at the location, which can vary significantly [4]. The radiation field varies spatially and temporally depending on the Earth's magnetic field and the solar cycle. High-energy charged particles of space radiation produce secondary particles, mostly neutrons, through nuclear reactions, when they strike a spacecraft or an astronaut. Exposure doses in the ISS have been estimated to be about 0.5 mSv/day [15, 16], which is about 100 times the dose on the ground, with the dose-equivalent rate remaining below 100 mSv during a 6-month stay on the ISS. However, exposure to 100 mSv is associated with a 0.5% increase in the risk of fatal cancer. The dramatically higher dose rates at solar minimum than at solar maximum are attributed to higher GCR fluxes around several hundred MeV/n, which are affected by solar modulation, particularly in the absence of magnetic shielding [17].

Deep Space, the Moon, and Mars

Deep space refers to space outside Earth's protective magnetic field, and the flow of high-energy charged particles of SEPs and GCRs presents a major problem relating to long-duration manned missions in deep space. Astronauts will be exposed to trapped radiation as they travel through the Van Allen radiation belts before reaching deep space. The GCR dose rate also depends on the solar cycle, and the total dose from SEP particles during an event can be 19.5 mSv/event or higher in a spacecraft traveling through interplanetary space. [18].

The lunar surface is exposed to much higher levels of radiation than the Martian surface because there is little gas in the lunar atmosphere, though the atmosphere of Mars is also much thinner (0.75%) than that of Earth. Nevertheless, the dose rates at the surfaces of the Moon and Mars are still lower than those inside a spacecraft traveling through interplanetary space [17].

It has been recognized that the albedo, or backscattered, radiation environment near the surfaces of the Moon and Mars may pose a biological risk to astronauts. The Mars Science Laboratory's Curiosity Rover measured dose-equivalent rates of GCRs and SEPs of 0.64 mSv/day and 0.025 mSv/event, respectively, on the Martian surface during a period of solar maximum [19]. A Mars mission comprising 360 days return space flight and 500 days on the Martian surface would be associated with a total exposure of around 1 Sv [19], while the exposure rate on the lunar surface has been calculated at 1 Sv/year [20]. Although the total dose exposure during a deep-space mission may vary depending on the solar cycle, an exposure to 1 Sv is anticipated to be associated with a 5% increase in the risk of fatal cancer. Consideration of the radiation environment on the Martian and lunar surfaces also needs to take account of albedo neutrons, but not other secondary reaction products (eg, photons, electrons, positrons, pions.). In general, the contribution of albedo neutrons to the effective radiation dose ranges from 1% to 32%, depending on the environmental model, shielding material, and shielding thickness [21]. The most intense region of the albedo neutron spectrum occurs at low thermal energies ($E < 1$ eV), where the biological risk is smaller [20, 21], while the flux of neutrons is smaller at higher thermal energies (up to hundreds of MeV), but the biological risk is greater due to recoil nuclei and target fragmentation [22].

Detection of DNA Damage Induced by Space Radiation

Space radiation–induced damage to DNA samples during space flight has been observed using 2 methods: postlabeling and immunocytochemistry. Postlabeling detects DNA strand breaks as grains on fixed silver emulsion resulting from β-rays emitted from ^{3}H-atoms in the nuclei of the cells. Fixed cultured human cells spent 9 days onboard the Space Shuttle and 40 days onboard the Mir Space Station in 1997 [23], and space radiation–induced DNA strand breaks were then labeled by enzymatic

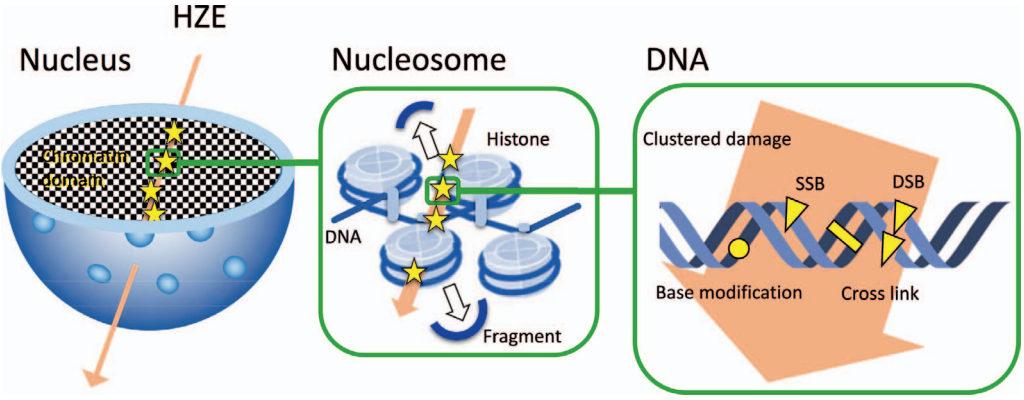

Figure 2. DNA damage due to high-energy particles. High linear energy transfer radiation induces clustered DNA damage, involving 2 or more closely spaced damages (strand breaks, base modifications, or cross links) within 1 or 2 DNA helix turns, as well as small fragments of DNA (<40 base pairs) along the track of particle irradiation in the cell nucleus.

incorporation of [^{3}H]-dATP with terminal deoxyribonucleotidyl transferase. The number of cells with many grains was higher in the Mir Space Station samples compared with the Space Shuttle samples, while virtually no DNA damage was detected in the ground control sample. These results suggest that space radiation causes DNA damage, with the amount of damage depending on the duration of the space flight [23].

Immunocytochemistry detects DNA damage by recognizing phospho-histone H2AX (γH2AX) foci, which has become the gold standard for detecting DNA double-strand breaks. High-LET radiation damages DNA along the track of particle irradiation, leaving fragments of DNA and clusters of DNA damage, including double-strand breaks [24–26] (**Figure 2**). This differs from the damage normally produced by sparse low-LET radiation, such as x-rays or γ-rays, and the differential spatial distribution of the energy deposited along the core and penumbra of the track creates DNA lesions that are complex and difficult to repair [27]. In 2008–2009, human frozen cells spent 133 days in an ISS freezer [28], after which they were cultured for 30 minutes and then fixed. γH2AX was detected in the nuclei in space samples but not in the ground control samples, providing the first report of high-LET space radiation–induced γH2AX tracks in cell nuclei. These results confirmed that space flight damaged nuclear DNA along tracks reflecting the tracks of space-radiation exposure [28]. Other recent studies have reported γH2AX signals in cells flown in space [29], as well as other forms of DNA damage, including chromosome aberrations in astronauts' lymphocytes [30]. High-LET radiation can thus induce permanent genetic changes in somatic and germ cells and is usually more effective per unit of absorbed dose than low-LET radiation.

Biological Effect of a Low Dose Rate of High-LET Radiation

Inverse Dose-Rate Effect

Low-LET radiation received at a low dose rate usually reduces the effectiveness of a given dose [31], but decreasing the dose rate also increases the risk of carcinogenesis and other biological effects (eg, gene mutation, chromosome aberration, and oncogenic transformation). This inverse dose-rate effect [32, 33] has been supported by many in vitro and in vivo studies.

One possible mechanism for this inverse dose-rate effect is that there may be a narrow window during the cell cycle when the cells are particularly sensitive to oncogenic transformation [34], and high-LET radiation, even at a low dose rate, is thought to be able to deposit enough energy to initiate the required effect in cycling cells. Bystander effects, which involve intercellular signaling, are another possible mechanism for the inverse dose-rate effect of high-LET radiation [35, 36].

If the suggested model is realistic, high-LET radiation, such as HZE cosmic rays, would be expected to have relatively little effect, though trapped protons might have an effect on astronauts in Earth orbit [34]. However, the inverse dose-rate effects were reported around 20 years ago and were observed in such end points as cell transformation. Although cell transformation is relevant to cancer risks, the impact of inverse dose-rate effects on risk projections needs to be confirmed in animal studies.

Adaptive Response

The ability of living organisms to resist stress damage through prior exposure to reduced stress levels is referred to as an adaptive response. This adaptive response manifests through decreased levels of cell death, gene mutation, micronuclei

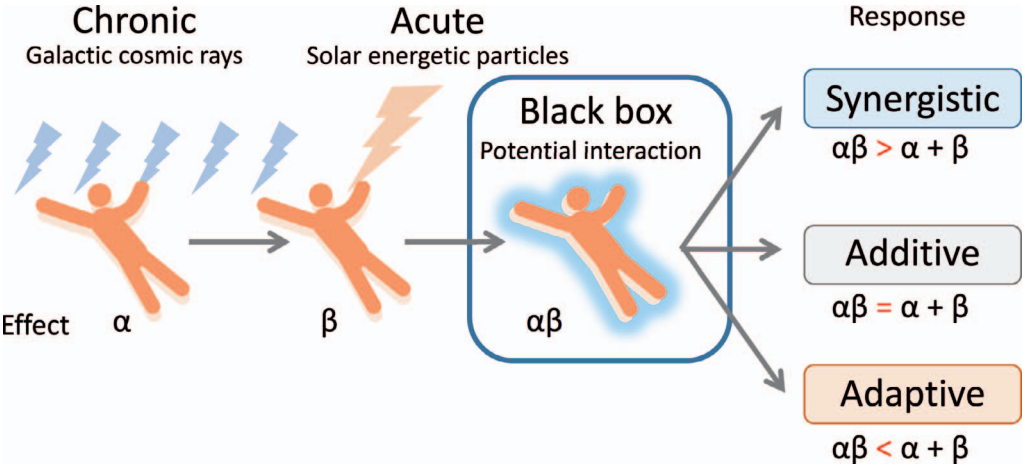

Figure 3. Possibility of adaptation to sudden high doses of radiation due to solar energetic particles after exposure to chronic galactic cosmic rays (based on [50]).

formation, chromosome aberration, and malignant transformation [37, 38]. The dose window (ie, the specific range of doses and/or dose rates) and the interval between conditioning and challenging irradiation are important factors affecting the adaptive response [39].

The possible mechanisms of the adaptive response include the transcription and translation of DNA repair-regulated and cell cycle–regulated genes [40, 41], the activation of poly (ADP-ribose) polymerase [42], protein kinase C [43, 44], p53 [45, 46], and signal transducer and activator of transcription1 [47], and the secretion of nuclear clusterin [48]. Although radioadaptation was assumed to occur only when cells were exposed to a priming dose of low-LET, but not high-LET, irradiation [49], both low-LET and high-LET irradiation have been reported to act as challenging doses for radioadaptation. Although chronic exposure to GCRs was reported to reduce the radiation susceptibility and help to protect astronauts against unpredictable exposure to a sudden and dramatic increase in flux due to SEPs during a mission [50], this finding remains highly speculative (**Figure 3**). This may be particularly important to understanding the radiation risks involved in space travel, because the GCR environment comprises predominantly protons, and it is realistic to expect that cells will be exposed to multiple hits from protons before being traversed by an HZE [51]. Notably unirradiated cells co-cultured with proton-irradiated cells were also significantly protected from the DNA-damaging effects of the challenge dose with iron ions [52], indicating that protective adaptive responses can spread from cells targeted by low-LET space radiation to unirradiated cells in their vicinity.

Human Effect of Space Radiation

Chronic exposure to space radiation on long-duration and exploration spaceflights increases the risk of cancer [53, 54], can lead to tissue degeneration and cataracts [55, 56], and can affect the central nervous system [57–59] and immune function [60]. Furthermore, it was recently shown that the risk of cardiovascular disease may also be increased by traveling into deep space [61], although the study sample was small and the results were not statistically valid [62]. However, this finding is supported by the results of the Radiation Effects Research Foundation studies on a cohort of Japanese atomic-bomb survivors, who showed that low-dose total-body irradiation could be responsible for increased cardiovascular mortality rates [63].

Several factors contribute to the large uncertainties in risk projection and hinder evaluations of the effectiveness of possible countermeasures, including radiation-quality effects at a low dose rate (ie, the inverse dose-rate effect, adaptive response, bystander effect, and cell competition) and microgravity [64]. To allow the assessment and management of human health risks in space, it is necessary to obtain more basic data on the combined effects of radiation under microgravity [30, 65]. To address these serious problems, we developed 3-dimensional clinostat-synchronized heavy-ion and x-ray irradiation systems [66, 67], which are expected to provide significant contributions to space radiation research, as a valuable platform for studies on the relative biological effectiveness and the combined effects of radiation under microgravity.

The basic mechanisms underlying the molecular, cellular, and tissue responses to radiation with different ion species and LET remain under investigation [68, 69]. Although the risks of acute exposure to space radiation with a complicated mixed beam can be estimated, the effects of chronic and fractionated exposures have not yet been resolved. The risks of late tissue effects, including cancer, are important, and further analysis of the effects of mixed radiation beams is required [70]. A GCR

simulator was recently designed in the NASA Space Radiation Laboratory to deliver a mixed radiation field comprising different ions, from protons to iron ions, at energies ranging from about 100 to 1,500 MeV/u for all ions and up to 2,500 MeV for protons [71]. This simulator will become a powerful tool in basic data acquisition for space radiobiology.

Conclusion

The present review clarifies the characteristics and biological effects of space radiation, including charged particles at a low dose and low dose rate. While some effects, such as cataracts, have been observed, others, such as cancer, are still being investigated. Furthermore, some health consequences of spaceflight, such as cardiovascular disease and immune dysfunction, are primarily caused by microgravity, and the contribution of radiation to these effects remains unclear. Further research is necessary to identify these risks of space radiation.

ADDITIONAL INFORMATION AND DECLARATIONS

Conflict of Interest Statement: The authors have no conflicts of interest to disclose.

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