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Review Article

Carcinogenesis induced by space radiation: A systematic review ☆

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Abstract

The carcinogenic risk from space radiation has always been a health risk issue of great concern during space exploration. In recent years, a large number of cellular and animal experiments have demonstrated that space radiation, composed of high-energy protons and heavy ions, has shown obvious carcinogenicity. However, different from radiation on Earth, space radiation has the characteristics of high energy and low dose rate. It is rich in high-atom-number and high-energy particles and, as it is combined with other space environmental factors such as microgravity and a weak magnetic field, the study of its carcinogenic effects and mechanisms of action is difficult, which leads to great uncertainty in its carcinogenic risk assessment. Here, we review the latest progress in understanding the effects and mechanisms of action related to cell transformation and carcinogenesis induced by space radiation in recent years and summarize the prediction models of cancer risk caused by space radiation and the methods to reduce the uncertainty of prediction to provide reference for the research and risk assessment of space radiation.

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Keywords: Carcinogenesis, Heavy ions, Risk assessment, Space flight, Space radiation

Introduction

The first artificial satellite was launched in 1957, which was a pioneering event in the exploration of space and marked the beginning of the space age [1]. In 1961, Yuri Gagarin orbited Earth in Vostok 1, which opened the prelude to manned space flight [2,3]. To date, more than 4000 satellites have been launched into space, of which about 800 are in orbit, and a number of space laboratories and space stations have been established. Space technology is developing continuously, new discoveries in the field of space science are emerging frequently, and human space exploration is progressing at a substantial rate. Space science is gradually affecting human life on Earth, and leading to a view of the universe and nature [4–8].

The rapid development of space science and technology has unlocked many mysteries of the universe and brought many favorable conditions to human life, such as space breeding [9], communication satellite, and production of new materials [10–12]. However, the health risk of astronauts is a problem that must be faced in the development of deep spaceflight, especially that of space radiation [13–15]. Human space exploration is gradually stepping from low Earth orbit (LEO) to the Moon, Mars and beyond. Missions in LEO benefit from the protection of the Earth's magnetosphere, but upcoming exploration missions beyond LEO will expose astronauts to higher doses of space radiation [16]. As early as 2008, the US National Research Council summarized five potential health problems caused by space radiation in human deep space exploration: carcinogenesis, neurocognitive impairment, degenerative and cardiovascular diseases, decreased immunity and acute radiation syndrome [17]. The risk of radiation carcinogenesis has a high probability of occurring and is likely to adversely affect the long-term quality of post-flight life [18]. Prior to long duration missions beyond LEO, it is important to accurately estimate and effectively reduce the risks caused by space radiation, especially the carcinogenic risk. Space radiation is complex and includes high-energy protons and heavy ions. Compared with common terrestrial radiation, such as X-rays and γ-rays, space radiation is more effective in causing biologically relevant damage [19–21]. However, due to difficulties in simulating the effects of space radiation, the lack of accurate data, and individual differences between astronauts such as age, sex and genetic background [22], there is great uncertainty in space radiation risk prediction.

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Space radiation environment

The space radiation environment consists of a variety of charged particles with a wide energy range spanning multiple orders of magnitude, including protons and electrons with an mean energy of around 10 MeV, as well as high-energy heavy ions and high-energy protons with energies in the order of GeV. The main sources of particles in the space radiation environment include the following [23–26]:

(1) Galactic cosmic radiation (GCR): Galactic cosmic radiation consists of high-energy protons, helium ions, electrons and heavy ions. Although heavy ions account for only 1% of the total mass, they belong to high linear energy transfer (LET) radiation, which can seriously damage human cells, tissues and organs. Moreover, the damage caused by high-LET radiation is difficult to repair, causing great harm to the health of astronauts. Shielding against GCR is very difficult, and ordinary physical shielding methods cannot achieve effective protection of astronauts. In space flight, GCR are the main source of radiation and the main contributor to the biological effects of space radiation.
(2) Solar particle events (SPEs): These events occur at the peak of solar activity. A large number of high-energy charged particles are released during the outbreak of solar flares or coronal mass ejections. SPEs are divided into two categories, small events with relatively short duration, known as flares; and larger events, known as coronal mass ejections. The energy generated by coronal mass ejections is enough to damage aeronautical equipments such as satellites. Most of the particles released by SPEs are medium-energy or high-energy protons, thus SPEs are also known as "solar proton events". The occurrence of SPEs is random, but is related to the solar cycle. They are more likely to occur during a period of intense solar activity, the intensities and frequencies of which are related to the solar cycle.
(3) Earth's trapped radiation belt (ERB): This belt mainly consists of protons and electrons. The geomagnetic field captures protons and electrons in a circular radiation belt, which is also known as the Van Allen radiation belt. ERB is divided into an inner and outer radiation belt; high-energy protons mainly exist in the inner radiation belt, while high-energy electrons mainly exist in the outer radiation belt. These radiation belts are located at the equator and at a distance from the Earth's surface between 200 km and 60,000 km. The intensity of the proton belt reaches a peak value at a distance of about 5000 km (for 10 MeV protons), while the intensity of inner and outer electron belts reach peak values at distances of 3000 km and 20,000 km, respectively. Generally, the spacecraft hull can shield particles with low energy. As ERB is mainly composed of protons and electrons with energy of around 10 MeV, the spacecraft hull can shield it effectively.

In LEO, due to the protection of the Earth's magnetic field and atmosphere, the contribution of radiation dose mainly comes from ERB and GCR. Heading for deep space means leaving the protection from the Earth's magnetic field and atmosphere. During deep space missions, the main radiation sources of space radiation are GCR and SPEs. Space radiation has the characteristics of high energy, high LET and high relative biological effectiveness (RBE), which is thought to cause destructive and irreparable biological damage to astronauts at lower dose and dose rate than low-LET radiation, but this depends partly on the energy, charge and velocity of the particles, as well as the endpoint being examined. Space radiation also has the characteristics of low dose (defined as doses $<$100 mGy) and low dose rate. Effective dose rate for astronauts on the International Space Station (ISS) is about 0.4 mSv/day, accumulating to about 0.072 Sv for half a year [27]. Effective dose for a 180-day lunar mission is about 0.17 Sv [28]. On travelling to Mars, the effective radiation dose during flight is about 1.84 mSv/day, and about 0.64 mSv/day on the surface of Mars, amounting to a total effective dose of $\sim$1.01 Sv for a round trip to Mars with 180-day one-way flight and 500-day stay at the surface of Mars [29]. Besides, the space radiation field is a complex mixed field, composed of many different types of radiation and affected by concurrent exposure to other stressors such as microgravity, and day-night transformation [30]. Therefore, it is difficult to study the radiobiological effects of space radiation, and more attention should be paid to the prediction and assessment of the space radiation risk.

The National Aeronautics and Space Administration (NASA) categorizes the carcinogenic risk of radiation exposure as one of the four type I risks [31]. The four type I risks induced by space radiation are (1) carcinogenesis, (2) acute radiation syndromes, (3) acute or late central nervous system effects and (4) degenerative tissue disease. The concept of type I risk is a risk that has been proved to be serious and without effective countermeasures, and which is a potential obstacle to long-term space flight. Carcinogenesis is of interest because it is more likely to occur at lower doses than neurocognitive or cardiovascular effects and is therefore dose limiting. NASA sets the acceptable level of cancer risk from space radiation as a 3% fatal cancer risk at the upper 95% confidence interval [32], radiation risk levels above 3% are unacceptable for safety reasons. Of note, the recent NASEM (National Academies of Sciences, Engineering, Medicine) consensus study report recommends a flat dose limit similar to that of most other space agencies [33]. It remains to be seen if the recommendation will be adopted.

The role of space radiation in carcinogenesis

The occurrence of cancer is a multi-stage and long-term process, which involves gene mutation, genomic instability, overactivation of oncogenes, inactivation of tumor suppressors, changes in genetic material and abnormal cell metabolism [34,35]. It is generally believed that the occurrence of cancer includes three stages: initiation, promotion and progression [36]. Initiation is a rapid and irreversible process, while promotion is a long-term and reversible process. Radiation has both initiating and promoting effects, and thus is considered to be a complete carcinogen [37]. Radiation-induced DNA damage and subsequent mutations are generally considered to be the initial events of radiation-induced cancer. Radiation can induce DNA strand breaks, resulting in gene mutations or chromosome aberrations in cells, and these cytogenetic changes can eventually lead to malignant transformation of cells, and subsequent carcinogenesis [38]. Park *et al.* found that irradiated human mammary epithelial cells exhibited disrupted cell–cell communication, aberrant cell–extracellular matrix interactions, and loss of tissue-specific architecture, which are indicative of neoplastic progression [39]. Kumar *et al.* found that space radiation up-regulated Wnt/β-catenin signaling, downregulated cell division cycle 42 (Cdc42), myosin light-chain kinase (Mlck), partitioning defective 3 (Par3), and E-cadherin, leading to DNA damage and chronic oxidative disease in intestinal epithelial cells [40]. Besides, a previous review has highlighted the impact of cell cycle G2/M checkpoint on genomic instability and cancer induction [41]. The above-mentioned work demonstrated that radiation-induced activation of proto-oncogenes, inactivation of tumor suppressor genes and imbalance of expression of important genes involved in cell cycle regulation play roles in radiation-induced malignant transformation of cells. Space radiation is rich in high-atom-number and high-energy (HZE) particles, which can induce complex clustered DNA damage [42,43], and its biological effect is often several times that of X-rays [20,44].

Afshinnekoo *et al.* summarized fundamental biological features of spaceflight, including oxidative stress, DNA damage, mitochondrial dysregulation, epigenetic/gene regulation changes, telomere length alterations, and microbiome shifts [45]. Exposure to space radiation can lead to elevated oxidative stress, which is one of the main responses to space-flight conditions that can trigger DNA damage. da Silveira *et al.* reported increased 8-oxo-guanosine levels in 59 astronaut's urine [46]. 8-oxo-guanosine is a biomarker of cellular oxidative stress related to DNA repair and a risk factor for cancer [47]. Mitochondrial dysfunction is also heavily

linked to oxidative stress [46]. In the recent NASA Twins Study, a range of effects of space radiation on the human genome have been revealed. Many epigenetic and gene expression changes were detected during Scott Kelly's year-long mission, but most of them returned to normal upon return to Earth [48]. Altered telomere length is linked to age-related pathologies, including dementia, cardiovascular disease, and cancer [49]. The NASA Twins Study showed astronauts suffered DNA damage and telomere length dynamics after long space missions. The frequency of chromosomal translocations and inversions increased during flight and remained elevated after flight, while telomere length rapidly (within 48 h after returning to Earth) became shorter than preflight [48]. A similar study on eleven unrelated astronauts showed that irrespective of mission duration, the telomere lengthened during spaceflight and shortened rapidly upon return to Earth. And overall astronauts had shorter telomeres after spaceflight than they did before [50]. Bisserier *et al.* identified 27 differentially expressed long non-coding RNAs (lncRNAs) by RNA-seq in exosomes isolated from the blood plasma of three astronauts who flew short ISS missions as early as 3 days post-landing [51]. LncRNA dysregulation may induce aberrant gene expression and trigger the development of cancer [52].

According to the dose-effect relationship of radiation, the biological effect of radiation can be divided into deterministic and stochastic effects [53]. The severity of the former is related to the radiation dose, while the occurrence probability of the latter increases with the increase of the radiation dose, although the severity has little to do with the radiation dose. Indeed, a radiation dose lower than the deterministic effect threshold can cause stochastic effects. Among the stochastic effects induced by space radiation, much attention has been paid to the carcinogenic risk, which is affected by a variety of factors, such as radiation type, radiation dose/dose rate, type of cancer, as well as the sex, age and genetic sensitivity of the astronauts.

Experimental studies in vitro

Some researchers have conducted *in vitro* experiments using animal cells. As early as 1978, Borek *et al.* have found that high-energy neutrons and argon ions have a higher ability to induce the malignant transformation of golden hamster embryo cells than X-rays [19]. In 1998, Han and Suzuki *et al.* used Syrian hamster embryo cells to compare the malignant transformation of cells induced by carbon and silicon ions of different LET. The results showed that carbon and silicon ions can induce malignant transformation of cells more effectively than X-rays, and their RBE increased with the increase of LET. When LET reached 100 keV/μm, the RBE reached a maximum value of about 7 [54]. Usually, astronauts are exposed to low doses of space radiation, and the low-flux ionized particles directly target only a few cells. It is estimated that an individual cell in an astronaut will be traversed by protons once every three days, helium nuclei once every three weeks and HZE nuclei once every three months [55]. However, the stress effects produced by these cells under radiation spread to neighboring cells, creating the so-called bystander effect [56,57]. The bystander effect induced by radiation is related to cellular contact, communication signals and metabolic properties, and so on [58,59]. Buonanno *et al.* conducted experiments with mouse embryonic fibroblasts and irradiated them with 0.25 Gy high-energy iron ions or 1 Gy protons. It was found that the malignant transformation frequency of bystander mouse embryo fibroblasts co-cultured with iron ion-irradiated cells increased significantly, rather than that co-cultured with proton-irradiated cells [60]. This biological end point associated with the carcinogenic effects of radiation suggests that the bystander effect induced by space radiation is caused by high-LET radiation.

Some researchers also used human cells to conduct experiments. Lee *et al.* reported that in human lymphocytes, complex chromosome exchanges produced by carbon ions involved more breaks and more chromosomes than those induced by isodoses of X-rays at the first post-irradiation mitosis, which are responsible for the increased effectiveness of high-LET ions [61]. Ding *et al.* found that some growth-related pathways in human bronchial epithelial cells were significantly up-regulated after exposure to high-energy iron ions and silicon ions, including hypoxia inducible factor-1α (HIF-1α), mammalian target of rapamycin (mTOR), insulin-like growth factor-1 (IGF-1), ras homolog family member A (RhoA) and extracellular regulated protein kinases/mitogen-activated protein kinase (ERK/MAPK), indicating that heavy ions increased the potential risk of lung cancer [62]. Li *et al.* found that 1 Gy of HZE ions have the ability to stimulate the exosome release by about 4-fold from human bronchial epithelial cells relative to 10 Gy reference γ-rays [63]. Exosome-derived miRNAs are confirmed to transmit non-targeted radiation effects *in vitro*, including genomic and telomeric instability [64]. As reported by Li *et al.*, the presence of miRNAs which are relevant to the development of lung cancer were detected, including miR-1246, miR-1290, miR-23a, and miR-205 [63]. Wang *et al.* found that heavy ions could enhance the transformation of epithelial cells to mesenchymal cells mediated by transforming growth factor beta (TGF-β). TGF-β has been found to be a key regulator of epithelial-mesenchymal transition (EMT), and can regulate cell proliferation, differentiation and apoptosis. Furthermore, it plays an important regulatory role in the late stage of tumorigenesis [65]. EMT has been shown to be an important process in the development of cancer, and is activated when a large number of mutations or abnormal signal transduction occur. During space travel, heavy ions are one of the main sources of ionizing radiation that threatens the health of astronauts. Research has shown that even low doses of heavy ions can induce the expression of TGF-β, which can cause the occurrence of EMT and increase the risk of tumor development and metastasis [66]. Andarawewa *et al.* further studied the effect of radiation dose on TGF-β-mediated EMT. The results showed that TGF-β-mediated EMT is a non-targeted radiation effect and has little to do with the radiation dose [67]. Shao *et al.* used human salivary gland tumor cells to study the bystander effect. It was found that cell colony formation and cell proliferation were enhanced after carbon ion irradiation, which was related to both LET and the radiation dose [68]. The space radiation field is also affected by other environmental factors, among which microgravity is one of the main environmental factors in human spaceflight. Hada *et al.* conducted experiments with human fibroblasts and simulated the microgravity environment in space with a 3D clinostat. The results showed that compared with cells exposed to radiation alone, exposure to simulated microgravity and space radiation at the same time increased the rate of chromosome aberrations [69]. These results show that great attention should be paid to the bystander effect induced by space radiation and the carcinogenic effect of space radiation combined with other space environmental factors (Table 1).

Experimental studies in vivo

Roentgen discovered X-rays in 1895, and from then on, medical researchers quickly recognized the carcinogenic risks of ionizing radiation. Epidemiological studies of atomic bomb survivors in Japan have also shown that whole-body radiation exposure increases the risks for some types of tumors, especially those of the lung [79–82]. Terrestrial radiation is mainly composed of low-LET radiation such as X-rays, β-particles and γ-rays. Different from terrestrial radiation, space radiation is composed of a variety of high-LET particles, and there is no typical epidemiological data to estimate the cancer incidence; therefore, most studies rely on animal experiments. Wang *et al.* detected the incidence of lung cancer in wild-type C57BL/6 mice after exposure to radiations of different LET, including iron, silicon, oxygen ions and X-rays. The results showed that the incidence of lung cancer induced by HZE particles (iron, silicon and oxygen ions) was higher than that induced by X-rays, and that HZE particles induced more invasive lung tumors [83]. Mishra *et al.* found that exposure to iron ions caused ovarian DNA damage, oxidative damage and apoptosis, resulting in premature ovarian failure [84]. Weil *et al.* evaluated the incidence of acute myeloid leukemia (AML) and

Table 1

Experimental studies *in vitro*.

Experimental materials	Radiation condition					Major biological consequences	Refs
	Type of radiation	Energy	LET	Dose	Dose rate		
Golden hamster embryo cells	neutrons	430 keV	-	0.001-1.5 Gy	0.1-0.8 Gy/h	Compared with X-ray, high-energy neutrons and argon ions had higher ability to induce malignant transformation of cells.	[19]
	argon ions	429 MeV/u	-	0.01 or 0.1 Gy	-		
	X-rays	250 kVp	-	0.75-3 Gy, 0.01-0.1 Gy	0.13-0.6 Gy/min		
Syrian hamster embryo cells	carbon ions	290 MeV/u	13, 50, 100 keV/μm	0001, 0.025, 0.05, 0.1, 0.2 Gy	0.04-0.2 Gy/min, 1-2 Gy/min	The RBE of heavy ions first increased with the increase of LET, and reached the maximum value of about 7 at 100 keV/μm.	[54]
	silicon ions	490 MeV/u	150, 240, 400 keV/μm	0.025, 0.05, 0.1, 0.2 Gy	0.04-0.2 Gy/min, 1-2 Gy/min		
	X-rays	250 kVp	2.5 keV/μm	0.05, 0.1, 0.2 Gy	0.5 Gy/min		
Human bronchial epithelial cells	iron ions	996.8 MeV/u	151 keV/μm	0.5, 1 Gy	-	Some growth-related pathways in cells were significantly up-regulated.	[62]
	silicon ions	990 MeV/u	44 keV/μm	0.5, 1 Gy	-		
	γ-rays	0.661 MeV	-	1, 3 Gy	-		
Immortalized human esophageal epithelial cells, Lung epithelial cells of non-transformed mink	silicon ions	170 MeV/u	99 keV/μm	0-2 Gy	0.25-1 Gy/min	0.1 Gy silicon ions or iron ions could induce EMT, and 2 Gy rays could induce EMT more obviously.	[66]
	iron ions	600 MeV/u	180 keV/μm	0-2 Gy	0.25-1 Gy/min		
Mouse embryo fibroblasts	iron ions	1 GeV/u	151 keV/μm	0.25 Gy	0.5 Gy/min	The malignant transformation frequency of bystander progeny cells irradiated by iron ions increased significantly.	[60]
	protons	1 GeV/u	0.2 keV/μm	1 Gy	1 Gy/min		
Human salivary gland tumor cells	carbon ions	290 MeV/u	13, 100 keV/μm	1, 2, 3, 4, 5 Gy	-	The abilities of colony formation and proliferation of bystander cells were enhanced.	[68]
Human fibroblasts	carbon ions	290 MeV/u	50 keV/μm	0.5-3 Gy	0.03 Gy/min	Simultaneous exposure to microgravity and space radiation increased the rate of chromosome aberration.	[69]
	X-rays	200 kVp	-	0.5-3 Gy	0.03 Gy/min		
Immortalized human mammary epithelial cells	iron ions	-	-	-	-	Low-dose-rate heavy ions could induce malignant transformation of cells.	[70]

(*continued on next page*)

Table 1 (*continued*)

Experimental materials	Radiation condition					Major biological consequences	Refs
	Type of radiation	Energy	LET	Dose	Dose rate		
Mouse embryo fibroblasts	X-rays	225 kVp	-	0-1.2 Gy	-	The malignant transformation of cells induced by heavy ions was mostly a direct effect, and with the increase of LET, the cell damage became difficult to repair.	[71]
	γ-rays	1.25 MeV	-	0-12 Gy	0.005, 0.04, 1, 100, 1000 cGy/min		
	argon ions	400, 330 MeV/u	120, 140 keV/μm	0-6 Gy	0.01, 1 Gy/min		
	protons	240 MeV/u	-	0-12 Gy	-		
	iron ions	600 MeV/u	200 keV/μm	0-8 Gy	-		
	neon ions	425 MeV/u	32 keV/μm	0-10 Gy	0.02, 2 Gy/min		
Immortalized human bronchial epithelial cells	iron ions	1 GeV/u	-	0-4 Gy, 0.06 Gy	-	Iron ions or α-particles could induce genomic instability and malignant transformation of human bronchial epithelial cells.	[72]
	α-particles	-	150	0-2 Gy, 0.06 Gy	-		
	γ-rays	-	-	0-10 Gy	-		
Immortalized human bronchial and mammary cells	iron ions	1 GeV/u	-	0.06 Gy	-	The malignant transformation was related to the repair of DNA damage and the expression of cell cycle regulatory genes.	[73]
	α-particles	-	150 keV/μm	0.06 Gy	-		
V79-4 Chinese hamster cells	α-particles	3.26 MeV	121 keV/μm	0.36, 0.56, 0.69, 1.39, 2.23 Gy	0.008, 0.154, 0.28 Gy/h	The induction of chromosomal aberrations exhibited a linear relationship with dose and showed evidence of significant conventional dose-rate dependence.	[74]
Human neonatal primary fibroblasts	iron ions	1 GeV/u	-	-	$\leq$ 1 Gy/min	Silicon ions were more likely to induce malignant transformation than protons.	[75]

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Table 1 (*continued*)

Experimental materials	Radiation condition					Major biological consequences	Refs
	Type of radiation	Energy	LET	Dose	Dose rate		
	silicon ions	600 MeV/u	-	-	$\leq$ 1 Gy/min		
	protons	235, 188 MeV/u	-	0.05 Gy	-		
	X-rays	250 kVp	-	-	$\leq$ 1 Gy/min		
Human neonatal primary fibroblasts	iron ions	1.005 GeV/u	151.3 keV/μm	0.02 Gy	$<$ 1 Gy/min	The frequency of malignant transformation induced by sequential irradiation was related to the time interval between the two kinds of particle irradiation.	[76]
	titanium ions	1.007 GeV/u	108.1 keV/μm	0.02 Gy	$<$ 1 Gy/min		
	protons	1 GeV/u	0.22 keV/μm	0.02 Gy	$<$ 1 Gy/min		
Human fibroblasts	protons	0.05, 1 GeV/u	1.25, 0.2 keV/μm	0.2 Gy	0.1 Gy/min	Low-dose proton irradiation could protect human fibroblasts which are subsequently irradiated by iron ions.	[77]
	iron ions	1 GeV/u	151 keV/μm	0.5 Gy	0.5 Gy/min		
Human lymphoblastic cells	X-rays	200 kVp	-	0.5, 1, 1.1, 1.5 Gy	0.03 Gy/min	The combination of microgravity and GCR can increase chromosome aberrations.	[78]
	carbon ions	290 MeV/u	50 keV/μm	0.25, 0.5, 0.75, 1 Gy	0.03 Gy/min		
Immortalized human bronchial epithelial cells	titanium ions	230, 1000 MeV/u	200, 108 keV/μm	1 Gy	-	1 Gy of HZE ions have the ability to stimulate the exosome release by about 4-fold from human bronchial epithelial cells relative to 10 Gy reference γ-rays.	[63]
	silicon ions	65, 148 MeV/u	200, 100 keV/μm	1 Gy	-		
	oxygen ions	35 MeV/u	100 keV/μm	1 Gy	-		
	γ-rays	0.661 MeV	-	3, 10 Gy	1.5 Gy/min		
Human lymphocytes	X-rays	250 kVp	-	1-6 Gy	1-2 Gy/min	Complex chromosome exchanges are responsible for the increased effectiveness of carbon ions compared to X-rays at the first post-irradiation mitosis.	[61]
	carbon ions	9.5 MeV/u	175 keV/μm	1, 2 Gy	1-2 Gy/min		

hepatocellular carcinoma (HCC) induced by 1 GeV ^{56}Fe ions in male CBA/CaJ mice. The results showed that the incidence of AML induced by 1 GeV ^{56}Fe ions did not increase significantly compared with γ-rays. However, for HCC, the incidence induced by 1 GeV ^{56}Fe ions was significantly higher than that of γ-rays, and the RBE was found to be approximately 50 [85]. The results suggested that there may be differences in the mechanism of radiation-induced solid tumors and leukemia. Some studies have shown that during the induction of leukemia, a small number of mutations and epigenetic changes could cause leukemia; relatively speaking, the occurrence of solid tumors required more mutations and genetic alterations [79,86,87]. Weil's team further used male C3H/HeNCrl mice, between 8 and 10 weeks old, to evaluate the incidence of AML and HCC induced by 300 MeV/u ^{28}Si ions and 600 MeV/u ^{56}Fe ions, and obtained similar results, that is, compared with γ-raysirradiated mice, the incidence of AML in mice irradiated with ^{28}Si and ^{56}Fe ions did not increase significantly, while that of HCC did [88]. In a mouse model for irradiation-induced HCC, Nia *et al.* found a large number of transcripts differentially expressed after irradiation of ^{56}Fe, ^{16}O, and ^{28}Si ions, including peroxisome proliferator-activated receptor α (PPARα), B cell receptor (BCR), Insulin-like growth factor-1 (IGF-1) [89]. These findings may help to understand biological mechanisms underlying risks for HZE ions-induced HCC. Of note, a recent research has identified common molecular pathways between mouse and human HCC through transcriptomic analysis [90]. Watanabe *et al.* compared the carcinogenic effects of carbon ion and X-ray irradiation on B6C3F1 mice. The results showed that the tumor incidence rate of mice irradiated with 0.426 Gy carbon ions was lower than that of mice irradiated with 5 Gy X-rays, but was significantly higher than that of mice irradiated with 0.5 Gy X-rays [91]. High-LET heavy ions often cause genetic instability, which can lead to mutations in cancer-related genes. Imaoka *et al.* found that carbon ions induce breast cancer in rats with an RBE of about 2, which may be higher in the low dose range [92]. Illa-Bochaca *et al.* found that silicon ions could cause breast cancer in a microenvironment-dependent manner. Compared with low-LET radiation, silicon ion-induced breast cancer was found to be more invasive and had a higher degree of malignancy [93,94]. However, other studies have different results. Udho *et al.* used murine models of mammary and liver cancer to compare the impact of exposure to 0.2 Gy of 300 MeV/u silicon ions, 3 Gy of γ-rays or no radiation. The results showed that tumors formed in the silicon ions irradiated mice were not more invasive than those arising from exposure to low-LET γ-rays or those formed spontaneously [95]. Patel *et al.* examined the effect of protons or silicon ions on the hematopoietic system in a genetic mouse model of aging, and found that the incidence of lymphomas is related to radiation quality while the phenotype of the tumors is independent of LET [96].

Epidemiological studies of atomic bomb survivors and workers exposed to radiation have shown an increase in the incidence of colorectal cancer in those exposed to radiation compared with those who have not been exposed to radiation. However, this radiation exposure is mainly composed of low-LET radiations such as γ-rays. By contrast, there are always some high-energy charged heavy ions in the space environment, such as ^{56}Fe, ^{28}Si and ^{16}O, which have a large dose contribution to space radiation. Unlike low-LET radiation, there is great uncertainty in predicting the risk of colorectal cancer induced by heavy ions due to a lack of data. Trani *et al.* compared the incidence of intestinal tumors in mice exposed to 5 Gy γ-rays and 4 Gy iron ions, and found that the incidence of intestinal tumors in the iron ion irradiation group was significantly higher than that in the γ-ray irradiation group, and was accompanied by dysplasia [97]. Datta *et al.* studied tumor incidence in APC$^{Min/+}$ mice exposed to iron ions at a dose of 1.6 Gy or 4 Gy. The results showed that compared with γ-rays, iron ions induced a higher frequency and stage of intestinal tumors regardless of the dose [98]. The mechanism may be related to the activation effect of iron ions on β-catenin [99]. Suman *et al.* compared colorectal cancer induced by carbon, silicon and iron ions in APC$^{1638N/+}$ mice. It was found that the largest number of tumors was induced by silicon ions, followed by iron ions and carbon ions, and the incidence of tumors per unit of radiation was higher at low doses, indicating that tumorigenesis reached the saturation point at high doses [100]. The team further studied the mechanism of intestinal tumorigenesis induced by heavy ions and found that a decrease of RXRα may play a key role in this process [101]. Recently, the results of a survey of cancer incidence and mortality in US astronauts were presented, which showed that in comparison to the US general population, US astronauts have increased incidence of prostate cancer and melanoma skin cancer, although only melanoma shows a significant increase in mortality. Lung cancer and colon cancer had reductions in both incidence and mortality. The increased incidence of melanoma is speculated to be related to ultraviolet radiation or lifestyle factors, rather than any astronaut specific exposure [102] (Table 2).

According to the above results both *in vivo* and *in vitro*, space radiation can induce carcinogenesis through a variety of mechanisms, including accumulated DNA damage, expression of TGF-β and β-catenin, and the bystander effect. And compared with common low-LET radiations on Earth, such as X-rays, the heavy ion components in space radiation tend to induce more invasive and higher incidence of some tumors. However, the issue is that human epidemiological data with high-LET radiation are lacking, and many of the mechanisms underlying carcinogenesis induced by heavy ions are not clear.

Cancer risk assessment of space radiation

Cancer risk has long been recognized as the most serious late impact of exposure to complex space radiation during spaceflight. Prior to widespread manned space missions, it is necessary to effectively evaluate and reduce the carcinogenic risk of space radiation. However, there is a high degree of uncertainty in the prediction and evaluation of space radiation, and the reasons for its high uncertainty mainly include the following five points [104]: (1) the difference in radiation quality between space radiation and low-LET radiation, which leads to increased biological damage; (2) the difference in the dose rate between space radiation and terrestrial radiation, which is the key factor affecting DNA repair, cell regulation and biological response; (3) prediction of SPEs, including their time, energy spectrum and size, (4) translation of experimental data to real life applications; and (5) individual radiosensitivity factors, including genetics [105] and diet [106]. According to a report, the overall uncertainty of space radiation carcinogenic risk prediction is about five times that of the median risk prediction at the 95% confidence interval [107]. Therefore, it is an important and urgent task to reduce the uncertainty of predicting the risk of cancer caused by space radiation.

Cancer risk prediction model of space radiation

Since the 1960s and 1970s, NASA has observed the geomagnetic trapped belt through satellite probes, obtained the relevant data of the geomagnetic trapped belt and established the spatial distribution model of proton and electron fluence rates in the trapped belt based on the data. According to the acquired database of solar particle events, the SPE model was established. Based on the data obtained, NASA has developed the Monte Carlo program HZETRN for simulating the GCR radiation field, and the GERMCode Monte Carlo program for the Mars program [32,108-110]. On this basis, Cucinotta *et al.* proposed the U.S. NASA Space Cancer Risk Model for American astronauts, which is used to assess whether a specific space mission has caused serious harm to astronauts and whether astronauts can safely complete the mission. The model uses epidemiological survey data of Japanese atomic bomb survivors, combined with American cancer epidemiological survey data, and is adjusted by the Dose and Dose Rate Effectiveness Factor. Finally, the risk assessment result of cancer fatality rate is obtained [69,107,108,111,112]. At present, NASA still uses the 95% confidence interval and 3% limit of Radiation Exposure Induced

Table 2

Experimental studies *in vivo*.

Experimental materials	Radiation condition					Major biological consequences	Refs
	Type of radiation	Energy	LET	Dose	Dose rate		
C57BL/6 mice	X-rays	320 kVp	-	1 Gy or 0.2 Gy × 5	0.5-1 Gy/min	The incidence and invasiveness of lung cancer induced by iron, silicon and oxygen ions were higher than that of X-rays.	[83]
	iron ions	600 MeV/u	175 keV/μm	1 Gy or 0.2 Gy × 5	0.5-1 Gy/min		
	silicon ions	300 MeV/u	70 keV/μm	1 Gy or 0.2 Gy × 5	0.5-1 Gy/min		
	oxygen ions	600 MeV/u	17 keV/μm	1 Gy or 0.2 Gy × 5	0.5-1 Gy/min		
ACI, F344, Wistar and Sprsage-Dawley rats	carbon ions	290 MeV/u	40-90 keV/μm	0.05-2 Gy	0.1-1 Gy/min	Carbon ions significantly induced breast cancer in rats.	[92]
	γ-rays	0.661 MeV	-	0.05-2 Gy	0.6 Gy/min		
Male CBA/CaJ mice	iron ions	1 GeV/u	150 keV/μm	0.1, 0.2, 0.4, 1 Gy	-	The incidence of liver cancer induced by iron ions was much higher than that induced by γ-rays, and the RBE was about 50.	[85]
	γ-rays	0.661 MeV	-	1, 2, 3 Gy	-		
Male C3H/HeNCrl mice	silicon ions	300 MeV/u	64 keV/μm	0.1, 0.2, 0.4, 1 Gy	-	Silicon and iron ions were not more effective than γ-rays in inducing AML, but the incidence of liver cancer induced by them was much higher than that induced by γ-rays or protons.	[88]
	iron ions	600 MeV/u	181 keV/μm	0.1, 0.2, 0.4, 1 Gy	-		
	Protons	30-80 MeV/u	-	1, 2 Gy	-		
	γ-rays	0.661 MeV	-	1, 2, 3 Gy	-		
$APC^{Min/+}$ and $APC^{1638N/+}$C57BL/6J mice	γ-rays	0.661MeV	-	5 Gy	-	The incidence of intestinal tumor induced by iron ions was significantly higher than that induced by γ-rays.	[97]
	iron ions	1 GeV/u	-	4 Gy	-		
Trp53-deficient BALB/c mice	γ-rays	0.661 MeV	-	1 Gy	-	Silicon ions could cause more invasive breast cancer compared with γ-rays.	[103]

(*continued on next page*)

Table 2 (*continued*)

Experimental materials	Radiation condition					Major biological consequences	Refs
	Type of radiation	Energy	LET	Dose	Dose rate		
	silicon ions	350 MeV/u	64 keV/μm	0.11, 0.3, 0.81 Gy	-		
$APC^{1638N/+}$C57BL/6J mice	carbon ions	290 MeV/u	13 keV/μm	0.1, 0.5, 2 Gy	-	The RBE of colorectal cancer induction by silicon ions was the highest, and the RBE was even higher at low dose.	[100]
	iron ions	1000 MeV/u	148 keV/μm	0.1, 0.5, 1.6 Gy	-		
	silicon ions	300 MeV/u	69 keV/μm	0.1, 0.5, 1.4 Gy	-		
	γ-rays	0.661 MeV	-	0.1, 0.5, 2 Gy	-		
B6C3F1 mice	carbon ions	290 MeV/u	60-210 keV/μm	0.426 Gy	0.4 ± 0.2 Gy/min	The incidence of tumor induced by 0.426 Gy carbon ions was significantly higher than that induced by 0.5 Gy X-rays.	[91]
	X-rays	250 kVp	-	0.5 or 5 Gy	0.1 or 1 Gy/min		
$APC^{Min/+}$C57BL/6J mice	γ-rays	0.661 MeV	-	2 or 5 Gy	1 Gy/min	The frequency and grade of intestinal tumors induced by iron ions were significantly increased compared with the γ-rays.	[98]
	iron ions	1000 MeV/u	148 keV/μm	1.6 or 4 Gy	1 Gy/min		
Mlh1$^{+/-}$ mice (B6.129-$Mlh1^{tm1Rak}$/NCI)	Protons	1000 MeV/u	0.23 keV/μm	0.1 or 1 Gy	0.05-0.5 Gy/min	Although the incidence of lymphomas is related to radiation quality, and increased due to loss of *Mlh1*, the phenotype of the tumors is independent of LET.	[96]
	silicon ions	300 MeV/u	70 keV/μm	0.1 or 1 Gy	0.05-0.5 Gy/min		
C3B6F1-AFP and C3H-AFP mice	silicon ions	300 MeV/u	-	0.2 Gy	0.2 Gy/min	Tumor aggressiveness is independent of radiation quality in murine hepatocellular carcinoma and mammary tumor models.	[95]
	γ-rays	0.661 MeV	-	3 Gy	1.43 Gy/min		
C3H/HeNCrl mice	iron ions	600 MeV/u	-	0.2 Gy	-	A large number of transcripts were found differentially expressed post-HZE irradiation.	[89]
	oxygen ions	1 GeV/u	-	0.2 Gy	-		
	silicon ions	350 MeV/u	-	0.2 Gy	-		
C57BL/6J female mice	iron ions	600 MeV/u	179 keV/μm	0.05, 0.3, 0.5 Gy	0.135-0.186 Gy/min	Exposure to iron ions caused ovarian DNA damage, oxidative damage and apoptosis.	[84]

Death recommended by the NRC and the National Council on Radiation Protection as the criteria for whether astronauts can carry out missions [31]. However, as the well-known space environmental health risk assessment model in the world, its uncertainty is as high as 500%. Cucinotta and Saganti have applied the NASA Space Cancer Risk-2020 model to make the first predictions of age-dependent space radiation cancer risks for several US populations of different races and ethnicities. Results suggested that white females have the overall highest radiation risk in this group. Females have larger risks of lung, stomach and bladder, and males have larger risks of colon and brain.

Cancer is a typical stochastic effect. As mentioned earlier in this paper, the dose-effect relationship of the stochastic effect is usually linear-no-threshold (LNT), which encompasses the traditional LNT hypothesis. At present, the traditional LNT model is often used to extrapolate the risk of low-dose radiation [113–115]. According to this traditional model, the carcinogenic risk of space radiation is proportional to the radiation dose and has a linear relationship. However, some cellular non-target effects such as the bystander effect and genomic instability induced by low-dose radiation do not fit well in the LNT model [116].

The heavy ion components in space radiation can cause many biological changes at the tissue, cellular and molecular levels. Among them, some sensitive biomarkers can be used as indicators to predict individual cancer risk, such as chromosome aberrations, DNA single-strand or double-strand breaks and micronuclei [117]. Several biomarkers can be used to predict long-term effects. Considering the uncertainty of cancer risk assessment and the long incubation period of cancer development, using some biomarkers related to carcinogenesis to build models to predict cancer risk is an important and effective strategy. For example, DNA damage has been modeled using Monte Carlo trajectory structure code and water as a substitute for biological tissue, which can accurately predict the trajectory behavior of charged particles in water [118]. The DNA damage model shows that a decrease of charged particle energy will lead to more complex DNA damage. However, it is not clear how these early biological changes relate to the effects of long-term radiation exposure on cells and tissues.

Chromosome aberrations are a recognized marker of carcinogenesis. Feiveson *et al.* investigated whether the radiosensitivity determined by the *in vitro* dose response of the pre-flight chromosome aberration rate (CAR) is valuable for predicting post-flight CAR caused by space radiation exposure during flight. The authors collected blood samples of astronauts before and after the mission, respectively. The pre-flight samples were irradiated with different doses of γ-rays, and the post-flight samples were collected several months after the astronauts returned. The chromosome aberration analysis of these samples was carried out to estimate the space radiation dose received by the astronauts. The results showed that under the same conditions, the individuals with higher radiation sensitivity had higher levels of chromosome damage after carrying out the mission. The frequency of chromosome aberration after the flight can be determined by radiosensitivity determined before the mission, combined with the dose received during the mission [119]. Chromosome aberrations can also be effectively detected by new techniques, such as fluorescence *in situ* hybridization (FISH) [120]. FISH technology uses specific DNA probes to color specific chromosomes, which can quickly and effectively detect the structural aberrations associated with these chromosomes, and greatly improve the detection rate of chromosome aberrations, especially translocations. However, because the detection resolution of this technique is limited to the range of Mb, it is impossible to evaluate all types of chromosome rearrangements with high resolution at the same time. A new model named biological damage by stochastic tracks (BDSTRACKS) has been used to make up for this deficiency, as it can simulate smaller translocations at the theoretical level. The sensitivity of chromosome aberration detection can be improved by using this model, which is of great significance for evaluating the biological effects of high-LET radiation, especially the carcinogenic effects [121]. Recently, Edmondson *et al.* used a mouse model to prove that the mechanism of tumorigenesis in mice after exposure to HZE particles and γ-rays may be similar, especially susceptible genes. The results showed that a cancer risk model of space radiation can be established by relying on the epidemiological data of human γ-ray exposure, after which the risk of cancer caused by space radiation can be predicted and estimated [122].

Methods to reduce the uncertainty of predictions

Uncertainty is a major obstacle in assessing the lifetime cancer risk of human exposure to space radiation. In view of the five main causes of high uncertainty, research can be carried out from the following aspects to reduce uncertainty: (1) accurate calculation of the RBE of radiation of different quality; (2) in-depth and systematic study of low dose-rate radiation biological and epidemiological data; (3) establishment of an accurate application model for the prediction of SPEs; (4) enhancement of ground simulation study of space radiation for more accurate research data; and (5) accurate prediction of individual space radiation sensitivity through biomarkers.

As early as 1999, Peterson and Cucinotta have given a Monte Carlo mixture model to reduce the uncertainty of assessing the lifetime cancer risk of radiation exposure in space flight. In order to estimate the uncertainty of high-LET radiation risk, they considered the uncertainty of the radiation weighting factor and folded the low-LET radiation risk uncertainty model into a probability density function. The probability density function of high-LET radiation quality and dose rate may be better than the traditional risk assessment methods [123]. In the prediction of cancer risk caused by space radiation, the two biggest uncertainty factors are radiation quality and the dose rate effect. In NASA's classical quality factor (QF risk) model, the ratio of the radiation QF to the dose and dose rate reduction effectiveness factor (DDREF) is used to measure the organ dose of cosmic ray protons and HZE particles and the risk rate of γ-rays from human epidemiological data. The experimental data of low-dose γ-ray risk are highly uncertain, which affects the estimation of the RBE_{max}. In 2015, Cucinotta developed an alternative model, QF γ Acute, which is built relative to higher doses (0.5 to 3 Gy) of acute γ-rays. The alternative model reduces the dependence on DDREF in cancer risk prediction. The results show that the upper confidence interval of the space mission risk prediction of QF γ Acute, a QF model based on acute γ-ray dose response, is about 50% lower than that of the RBE-based QF model [124]. Recently, Simonsen and Slaba proposed a new method to evaluate uncertainty, which extends the current NASA radiation carcinogenic risk model to a multi-model integrated framework. This method can be used to evaluate the uncertainty of sub-model parameters, including radiation QF, DDREF, latency function and excess risk function. This modeling method also takes into account the uncertainty of different theoretical or empirical models [125].

The study of Japanese atomic bomb survivors has served as the primary basis for estimates of radiation-related disease risks. The issue is that there are less epidemiologic data on low dose-rate exposures than acute exposures, particularly for space relevant dose rates (~0.5 mSv/day). Currently, the International Nuclear Workers Study (INWORKS) and Million Person Study (MPS) results are being published, which should increase our understanding of low dose-rate effects in humans. INWORKS is a collaborative epidemiological study of mortality among nuclear workers in France, the United Kingdom, and the United States. The study provided direct estimates of associations between low dose-rate external radiation exposure and mortality due to a range of categories of cause of death, including leukemia and solid cancer [126–129]. The Million Person Study consists of five categories of workers and veterans exposed to radiation from 1939 to the present. Different from the case for Japanese atomic bomb survivors, MPS is to provide scientifically valid information on the level of radiation risk when exposures are received gradually over time and not within

seconds [130,131]. INWORKS and MPS provide an illuminating insight into the possible range and assessment of carcinogenic effects following low dose-rate radiation exposure.

Simulating space radiation environment on Earth is challenging because it involves chronic, prolonged exposure to mixed radiation fields at low dose rates. Historically, the majority of research on ground to understand the health risks caused by space radiation has been performed using the same total dose of acute single-exposures, such as γ-rays and X-rays [132]. However, the space radiation environment consists of a variety of ion species over a wide energy range. Space radiation is simulated on Earth with the GCR simulator beam at the NASA Space Radiation Laboratory (NSRL) and individual components of space radiation are generated by research accelerators and proton and hadron therapy centers. A recently developed method for a ground-based GCR simulator in NSRL has shown promising results. It has been possible to expose cells or small animals to 33 sequential beams, including a number of heavy ions, protons, and helium of different energies [133]. Moreover, the effects of space radiation exposure can be more accurately simulated by performing biological experiments under more realistic conditions, such as simulating GCR exposure concurrently with simulated microgravity [134]. Studies have shown that the combination of microgravity and GCR can increase chromosome aberrations in human lymphoblastic cells [78].

To sum up, over the years, with the efforts of many radiation researchers, some space radiation carcinogenic risk prediction models and methods to reduce the prediction uncertainty have been developed and designed. However, thus far, there is no accurate or fully applicable prediction model. It is therefore the long-term goal of space science research to predict the risk of cancer caused by space radiation and reduce its uncertainty, and to find effective countermeasures to reduce the risk of cancer caused by space radiation.

Summary and prospect

The space radiation field is complex, and compared with terrestrial radiation, it shows higher carcinogenic effects. Effective assessment and reduction of carcinogenic risks from space radiation is an important prerequisite to ensure the health and safety of astronauts during deep space flight. However, due to the lack of ground simulation conditions and the limitations of animal models, a great many obstacles to the study of the effects of high-energy and low-dose-rate radiation remain. At present, there are still limitations in the understanding of the effects of space radiation regarding human tumor morbidity and mortality.

There are still many unsolved mysteries regarding the relationship between space radiation and human tumorigenesis, while the pace of human space exploration is increasing. In order to have a deeper understanding of the risk of cancer caused by space radiation, to assess the risk of cancer caused by space radiation more accurately, and to reduce the uncertainty of risk assessment and radiation health risk of astronauts, future research should be carried out to (1) accurately calculate the RBE of different types of radiation to predict the space radiation quality factor; (2) strengthen the ground simulation of space radiation, and perform an in-depth and systematic study of radiation biological and epidemiological data dependent on the dose rate; (3) establish an accurate application model of SPE prediction to prepare carefully for different solar activities; (4) deeply explore the mechanisms underlying carcinogenesis, especially the carcinogenic mechanism of heavy ions, and explore potential representative early tumor biomarkers; (5) screen and identify specific space radiation sensitive biomarkers; (6) optimize the space mission plan to avoid prolonged manned space missions; (7) design and develop effective radiation protection materials and devices to achieve better radiation shielding effects; and (8) strengthen radiation-related medical care for astronauts, including diet, exercise and necessary medical treatment.

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Author contributions

Wentao Hu and Zi Guo conceived the idea for this review. Zi Guo carried out literature research, wrote the manuscript and prepared the tables. Wentao Hu and Guangming Zhou revised the manuscript, and Wentao Hu edited the final version of this manuscript. All authors have read and approved the final manuscript.

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