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FURTHER INFORMATION
Biology of the Mammary Gland Web Site: http://mammary.nih.gov/
Cancer Biomedical Informatics Grid: https://cabig.nci.nih.gov/
Cancer Genome Anatomy Project: http://cgap.nci.nih.gov
Cancer Models: https://cancermodels.nci.nih.gov/
Cell Type Ontology: http://obofoundry.org/cgi-bin/detail.cgi?id=cell
Festing's Listing of Inbred Strains of Mice: http://www.informatics.jax.org/external/festing/search_form.cgi
International Mouse Strain Resource: http://www.findmice.org/
The Jackson Laboratory: http://www.jax.org/
JAX® Mice Web Site: http://jaxmice.jax.org/
MMHCC: http://emice.nci.nih.gov/
MMHCC Mouse Repository: http://mouse.ncifcrf.gov/
Mouse Genome Informatics: http://www.informatics.jax.org/
Mouse Nomenclature Home Page: http://www.informatics.jax.org/nomen
Mouse Phenome Database: http://www.jax.org/phenome/
Mouse Tumor Biology database: http://tumor.informatics.jax.org/
PathBase: http://www.pathbase.net/
Tumor Frequency Grid movie: http://tumor.informatics.jax.org/media/MTB-TumorFrequencyGrid.mov
UC-Davis Center for Comparative Medicine Image Archive: http://imagearchive.compmed.ucdavis.edu/
Zoomify: http://www.zoomify.com/
Zoomify movie: http://tumor.informatics.jax.org/media/MTB-Zoomify.mov

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SCIENCE & SOCIETY

Heavy ion carcinogenesis and human space exploration

Marco Durante and Francis A. Cucinotta

Abstract | Before the human exploration of Mars or long-duration missions on the Earth's moon, the risk of cancer and other diseases from space radiation must be accurately estimated and mitigated. Space radiation, comprised of energetic protons and heavy nuclei, has been shown to produce distinct biological damage compared with radiation on Earth, leading to large uncertainties in the projection of cancer and other health risks, and obscuring evaluation of the effectiveness of possible countermeasures. Here, we describe how research in cancer radiobiology can support human missions to Mars and other planets.

Space radiation, isolation (psychosocial problems) and microgravity-induced physiological changes are the main health problems for the exploration of the Solar system. Among the various health risks, carcinogenesis caused by exposure to space radiation is now generally considered the main hindrance to interplanetary travel for the following reasons: large uncertainties are associated with the projected cancer risk estimates, no simple and effective countermeasures are available, and the large uncertainties prevent determining the effectiveness of countermeasures. Optimizing operational parameters such as the length of space missions and crew selection for age and gender, or applying mitigation measures, such as radiation shielding or use of biological countermeasures, can reduce risk, but these approaches are clouded by uncertainties.

Space radiation is comprised of high-energy protons and high charge (Z) and energy (E) nuclei (HZE), whose ionization patterns in molecules, cells and tissues, and the resulting initial biological insults, are distinct from typical terrestrial radiation. Terrestrial radiation is largely characterized by low linear energy transfer (LET) radiation (X-, β- or γ-rays), with the exception of the dose localized to the lungs caused by low-energy α-particles from radon gas. HZE nuclei dominate the exposure in deep space (interplanetary travels), whereas trapped protons also contribute to the equivalent dose absorbed by crews in low-Earth-orbit (Space Shuttle flights or International Space Station). BOX 1 and FIG. 1 provide a physics primer on space radiation types and the differences in energy deposition in biomolecules, cells and tissues. The relationships between the early biological effects of HZE nuclei and the probability of cancer in humans are poorly understood[1–3], and it is this missing knowledge that leads to large uncertainties in projecting cancer risks (BOX 2 and FIG. 2) during space exploration.

In this Perspective, we will first discuss the issue of radiation risk in space: what is an 'acceptable' risk, how we can estimate it and what are the associated uncertainties. We will then discuss heavy-ion radiobiology, the key research field needed to reduce risk uncertainty. Finally, we will deal with the problem of countermeasures, both physical (shielding), biomedical (radioprotectors) and genetic (screening of radiosensitive individuals).

Acceptable levels of risk for astronauts

Space exploration is a high-risk endeavour, given the prospects of vehicle or life-support-system failure[4,5]. Acceptable levels of risk must take into account the value of the mission for humanity and science, the stakeholders for risk acceptance, which include astronauts and their loved ones, tax-payers and the scientific community, and the risk–benefit ratio[6]. A goal of <1% mission failure risk is used in the design of launch, life-support and crew-return systems. Radiation risks must also be considered, including cancer morbidity and mortality that would be projected to occur years after the mission. The National Aeronautics and Space Administration (NASA) sets risk acceptance levels at 3% risk of exposure-induced death

Box 1 | **Basic radiation physics**

Astronauts are exposed to protons and high energy and charge (HZE) ions, along with secondary radiation including neutrons and recoil nuclei that are produced by nuclear reactions in spacecraft or tissue. The nuclear charge of the galactic cosmic radiation (GCR) extends from hydrogen to uranium; however, nuclei heavier than iron (Z=26) are infrequent (FIG. 1a). The energy spectrum of the GCR peaks at about 85% of the speed of light, or 1 GeV per nucleon in energy units, and consequently these particles are so penetrating that shielding can only partially reduce the doses absorbed by the crew. The number of nuclei per unit area is denoted by the fluence, F. The large ionization power of HZE ions with Z>2 makes them the major contributor to the risk, in spite of their lower fluence than protons. The absorbed dose (D; measured in Gy) is the amount of energy deposited per unit mass of material and is calculated from the fluence by multiplying it by the linear energy transfer (LET), L, such that $D = F \times L$.

Because the types of radiation in space are diverse in how they deposit energy, absorbed dose is a poor descriptor of biological effects. If the same biological effect (for example, same cell survival or mutation frequency) is induced by a reference radiation (for example, X-rays) dose D_x and by a dose D_t of a test radiation (for example, HZE ions), then the ratio D_x/D_t is defined as relative biological effectiveness (RBE) of the test radiation. The RBE depends on several parameters, including LET, particle velocity and charge, dose and dose-rate, biological endpoint and oxygen concentration. To estimate biological effects it is customary to scale the absorbed dose by a quality factor Q(LET), which is estimated from the measured RBE values for late effects. Q ranges from 1 at low LET (<10 keV/μm) to 30 at high LET (around 100 keV/μm), and then decreases at very high LET values because of what is called over-kill or wasted energy. The quantity $H = D \times Q$ is called the dose equivalent and is measured in sievert (Sv).

(REID) for radiation carcinogenesis. This level is several times higher than other mission design risk levels. However, this may be appropriate because the life loss for cancer death, at least for low-LET radiation, is estimated at about 15 years, compared with the remainder of life for a mission failure. Risk levels much higher than 3% would be difficult to accept owing to safety concerns, but also because other fatal radiation risks such as heart and digestive diseases[7] become likely at higher exposure levels, making the radiation risk even more problematic. Furthermore, overall uncertainties in space radiation cancer projections are about five-fold higher at the 95% confidence level[8,9] than the median risk projection and it is therefore not possible, with the current state of knowledge of cancer biology, to judge if risks are higher or lower than safety standards.

Estimating space cancer risk

The differences in physical characteristics and biological effects of celestial versus terrestrial radiation make the usefulness of γ- or X-ray exposure data in predicting heavy ion effects extremely limited. The scaling of mortality rates for space radiation risks to astronauts from atomic bomb survivors and patients exposed to therapeutic radiation introduces many uncertainties[1,2,8] into risk estimates (BOX 2, FIG. 2). A key assumption in current methods of projecting cancer risk is that radiation-induced cancer mortality rates based on epidemiological studies of the atomic bomb survivors can be scaled to other populations, dose rates and radiation types. Two scaling parameters with large uncertainties are the dose and dose-rate effectiveness factor (DDREF), which scales for reduced dose and dose rate (<0.05 Gy/h), and, especially, the 'radiation quality factor', Q, which estimates the increased effectiveness of HZE nuclei compared with γ-rays for the same dose. Risks for extended missions to the Moon and the Mars exploration mission exceed 3% for most scenarios with upper 95% confidence levels near 15% risk of death[9]. However, there are important questions with regard to the correctness of any scaling approach because of qualitative differences between the biological effects of HZE ions and γ-rays.

Biological effectiveness of HZE nuclei

Energy deposition. The initial biophysical events induced by radiation in biomolecules, cells and tissues are key to understanding differences between γ-rays and the heavy ions in space. Energy deposition by HZE nuclei consists of a localized high-LET contribution along the trajectory of each particle and lateral extension of low-LET energetic electrons (δ-rays) many microns from the ion's path[10,11]. The dose deposited in a biomolecule is described by microdosimetry concepts (FIG. 1). For radiation effects on small DNA segments, heavy ions are several times more effective than X-rays[11,12]. Differences between radiation types also occur at the level of chromosomal loops or whole chromosomes, leading to distinct spatial patterns of DNA lesions for HZE nuclei and X-rays[13].

DNA damage. DNA damage and consequent mutations are generally accepted as the initiating event of the multi-step carcinogenic process, although recent evidence demonstrates the importance of non-targeted effects independent of DNA lesions[1]. Among the many radiation-induced lesions, DNA double-strand breaks (DSBs) are considered the key precursors of most early and late effects. There are qualitative differences between high- and low-LET radiation both in the induction and repair of DNA damage[14–17]. The number of DNA single-strand breaks (SSBs) and DSBs produced by radiation varies little with radiation type, but for high-LET radiation a higher fraction of DNA damages are complex, that is, are clusters containing mixtures of two or more of the various types of damages (SSB, DSB and so on) within a localized region of DNA. Complex damage is uncommon for endogenous damage or low-LET radiation, and has been associated with the increased relative biological effectiveness (RBE, see BOX 1) of densely ionizing radiation[18,19].

The repair of DSBs is known to occur through the non-homologous end-joining (NHEJ) and homologous recombination (HR) pathways[20–23]. Foci experiments using immunohistochemistry for antibodies to important NHEJ and HR repair proteins have been performed recently with X-rays and HZE nuclei. Key differences between X-rays and HZE nuclei are rapidly apparent, including dynamic and larger foci sizes in the first 2 h after irradiation for HZE nuclei compared with X-rays[24], the appearance of streaks of foci indicating the path of a particle track, and the persistence and slower removal of foci for HZE nuclei[25]. DNA damage response proteins[26–28], such as ataxia-telangiectasia mutated (ATM), ataxia-telangiectasia and Rad3-related (ATR)[29], Artemis (also known as DCLRE1C) and NBS1 (also known as NBN), might have a large role in the repair of complex DSBs and are an important focus of current space radiation research.

Live-cell imaging of DNA repair proteins induced with high-intensity laser microbeams is now widely used to study the kinetics of DNA damage responses[30–32]. Live-cell imaging with heavy ions has shown that DNA repair proteins are recruited to sites of heavy ion hits in cell nuclei of fibroblast cells

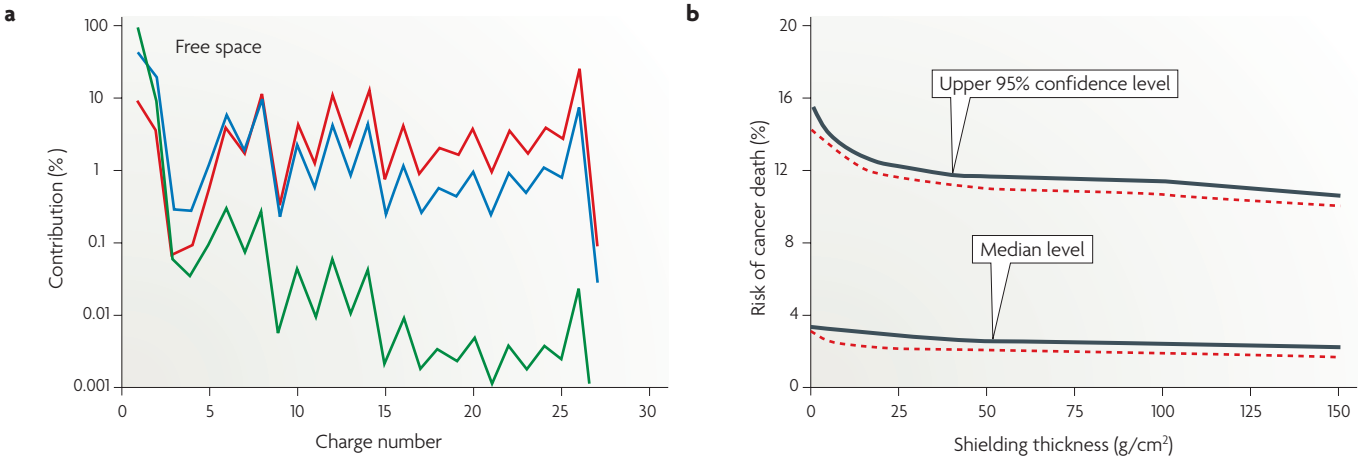

Figure 1 | **Space radiation environment and shielding. a** | The contribution in fluence (green), dose (blue), and dose equivalent (red) of different nuclei in galactic cosmic radiation. **b** | How the cancer risk for a mission to Mars varies for increasing amounts of shielding materials after considering the tissue shielding of the human body. Red and black lines represent water and aluminium shields, respectively. Lower curves are median estimates, and upper curves provide the upper 95% confidence limits. This calculation shows that even heavy shields will not be able to reduce the risk by a large factor.

within seconds. No large-scale chromatin movements are associated to the repair activity[33], yet some movement is observed in the repair protein foci. Image analysis of γ-H2AX and TP53BP1 protein dynamics in human epithelial cells fixed following exposure to Fe ions suggests that DNA lesions do indeed move to nuclear sub-domains for more efficient repair[34].

To date, there is no experimental evidence that different repair pathways are invoked following exposure to heavy ions or sparsely ionizing radiation. However, emerging evidence does suggest significant differences in gene expression at early times after irradiation[35], and that LET has an influence on the dynamics of chromatin movements following irradiation[36–37]. More studies comparing HZE nuclei and X-rays are necessary to assess the recruitment kinetics of different proteins at sites of DNA damage.

Chromosomal aberrations. DNA DSBs misrepaired or left unrepaired eventually appear as chromosomal aberrations[38]. Heavy charged particles are effective at producing chromosomal exchanges with RBE values exceeding 30 in interphase (as visualized using premature chromosome condensation) and 10 at the first post-irradiation mitosis for energetic heavy ions[39]. However, lower values are observed *in vivo*[40–41]. Besides, cytogenetic studies reveal a much higher level of complexity of chromosomal rearrangements induced by heavy ions compared with sparsely ionizing radiation (FIG. 3) — that is, rearrangements induced by heavy ions involve a higher number of chromosomes and breakpoints[42], and include both intra- and inter-chromosomal exchanges[43,44]. However, most of these complex rearrangements ultimately lead to cell death. In fact, only a few complex exchanges are found in the bone marrow of mice after 1 week of exposure to Fe ions[41], and the fraction of aberrant cells in the progeny of human lymphocytes exposed to heavy ions is close to the frequency observed in samples exposed to γ-rays[45] (FIG. 3e).

Interestingly, chromosomal aberrations can be measured in the blood lymphocytes of astronauts returning from long-term space flights and can then be used to test dose and risk estimates from current models[46]. In fact, chromosomal aberrations in blood lymphocytes are considered a validated biomarker of cancer risk[46–48], and can be used as biodosimeters to estimate equivalent dose in exposed individuals[49]. Biodosimetry studies performed by NASA[50–51] and in Russian cosmonauts[52] show that the measured chromosomal rearrangements in crew members returning from space flight are consistent with current models, although the biological results are also affected by a large experimental uncertainty at low doses. However, yields of translocations and dicentrics decrease as a function of time after exposure during the space mission, and it is unclear what the influence of time since test should be on risk estimates[51]. For cosmonauts involved in multiple spaceflights, the final yield of aberrations does not seem to be additive[46]. Further, in experienced cosmonauts with a total of about 2 years in space, the total yield of the aberrations is close to the measured background before the first flight[52]. The real significance of these findings remains to be elucidated.

New approaches to cancer risk estimates

The fundamental problem in space radiation research is the absence of sufficient evidence that models of cancer risk sufficiently describe the biology of tumour formation from HZE nuclei. Animal studies generally demonstrate that HZE nuclei have a higher carcinogenic effectiveness than low-LET radiation[53–56], but RBE values are difficult to quantify because of statistical uncertainties, which in many experiments prevents a definitive conclusion regarding the risks at low doses or dose rates. Additionally, the large variety of radiation types in space precludes an extensive study of tumour types in different strains of mice with different ion or dose regimes.

Tissue effects not dependent on direct DNA damage that have been associated with cancer initiation or progression include genomic instability[57–61], extracellular matrix remodeling[62], persistent inflammation[63] and oxidative damage[64–66]. Research on carcinogenesis continues to debate what is cause and what is effect[67]; that is, is the cause DNA damage and mutation leading to genomic instability, or is it extracellular matrix remodelling and other non-targeted effects? Space research benefits from these studies, but they must be extended to test the effects of HZE nuclei. HZE nuclei can modify these responses, as well as others that include DNA changes, in ways distinct from other radiation types or carcinogens, which complicates our ability to estimate and design effective mitigations.

Major radiation-induced solid cancer sites include breast, thyroid, colon and lung[68]. Lung cancer makes up about one-third of the cancers attributable to radiation

Box 2 | **Key issues in projecting space radiation cancer risks**

Ionizing radiation is a well-known carcinogen on Earth. The risks of cancer for X-rays and γ-rays have been established at doses above 100 mSv, but there are large uncertainties and ongoing scientific debate about cancer risk at lower doses and at low dose rates (<50 mSv/h).

The major uncertainties in risk prediction for space radiation are as follows:

- The effect of radiation quality on biological damage because of the qualitative and quantitative differences between space radiation and γ-rays.
- The dependence of risk on dose rates in space and their effects on the biology of DNA repair, cell regulation and tissue or organism responses.
- Predicting solar-particle events, including temporal, energy spectrum and size predictions.
- Extrapolation from experimental data to humans.
- Individual radiation-sensitivity factors including genetic, epigenetic, dietary or 'healthy worker' effects.

The minor uncertainties in risk prediction are as follows:

- Data on galactic cosmic radiation environments.
- The physics of shielding assessments based on the transmission properties of radiation through materials and tissue.
- Microgravity effects on biological responses to radiation.
- Errors in human data (statistical, dosimetry or recording inaccuracies).

observed in the atomic-bomb survivors[68] and nuclear-reactor workers[69]. However, risk estimates are confounded by the use of tobacco by a large fraction of the exposed, and the large tobacco risk often precludes identification of the radiation effect with high accuracy[68]. A small number of astronauts have smoked in the past and virtually none do so currently. A new experimental model that allows the study of individual or combinations of mutations in lung cancer progression has been recently developed[70]: a three-dimensional co-culture of telomerase reverse transcriptase (TERT)-immortalized bronchial epithelial cells interacting with a stroma layer. Over 30 primary lines have been immortalized to study how specific genetic components influence radiation-induced transformation. The results illustrate the extreme inefficiency with which X-rays transform primary cell lines. Studies using the three-dimensional co-culture models with Fe nuclei are being conducted and will be especially important owing to the limitations in animal models of human lung carcinogenesis[71].

Research on the mechanisms of radiation-induced mammary carcinogenesis has highlighted the importance of tissue regulation modifications in the development of cancer. Transforming growth factor β1 (TGFβ) acts as a tumour suppressor during cancer initiation and as a promoter during progression[72]. Recent studies of the role of TGFβ in tumorigenesis highlight how tissues can control a broad range of cellular responses, including how TGFβ-null epithelial cells, or cells treated with a small-molecule inhibitor of TGFβ, show downregulation of DNA damage responses, as evidenced by almost complete abrogation of γ-H2AX foci[73], and induction of an epithelial to mesenchymal transition[74] after ionizing radiation exposure in a primary human cell culture model.

Countermeasures

Even if risk projections and their uncertainties are reduced in the next few years, effective countermeasures to reduce the biological damage produced by ionizing radiation remains a long-term goal of space research. Such countermeasures might not be necessary for a lunar base, but will probably be needed for the Mars mission, and most definitely for exploring Jupiter or Saturn's moon Titan or the nearby satellites[2]. In all basic radioprotection textbooks, it is stated that there are three means to reduce exposure to ionizing radiation: increasing the distance from the radiation source, reducing the exposure time and shielding. Distance has no role in space, as space radiation is omnidirectional. Time in space is likely to be increased rather than decreased given plans for exploration and colonization. Shielding remains a plausible countermeasure, albeit a prohibitively costly one in light of current launch mass capabilities. Furthermore, the present uncertainties in risk projection prevent us from determining the true benefit of shielding. Other strategies can be effective in reducing exposure and the effects of radiation in space, including the choice of an appropriate time of flight, administration of drugs or dietary supplements to reduce the radiation effects, and crew selection.

Radioprotective agents. The search for efficient radioprotectors is a major goal of research in radiation protection and therapy. Both radiation injury and oxygen poisoning occur through the formation of reactive oxygen species; therefore, antioxidants can be efficiently used to prevent the damage[75].

Phosphorothioates and other aminothiols, which are usually administered shortly before exposure, are so effective in tissue protection against ionizing radiation that one specific compound (Ethyol, also known as amifostine or WR-2721) is approved in many countries for clinical use during chemotherapy and radiotherapy cancer treatments[76]. Unfortunately, amifostine and other thiols have significant side effects, including nausea, vomiting, vasodilatation and hypotension[77], precluding their use in space flights, except in case of an intense solar-particle event, which could produce acute radiation syndromes and even be life-threatening for an unprotected crew. Naturally occurring antioxidants are less effective than phosphorothioate agents in protection against high-dose acute radiation burden. However, nutritional antioxidants have a low toxicity, can be used for prolonged periods of time and seem to have a key role in the prevention of cancer[78–79]. A diet rich in fruit and vegetables significantly reduced the risk of cancer in the atomic-bomb survivor cohort[80]. Retinoids and vitamins (A, C and E) are probably the best-known and most-studied natural radioprotectors, but hormones (for example, melatonin), gluthatione, superoxide dismutase (SOD), phytochemicals from plant extracts (including green tea and cruciferous vegetables) and metals (especially selenium, zinc and copper salts) are also under study as dietary supplements for individuals overexposed to radiation[81], including astronauts. In addition, there is evidence of reduced antioxidant capacity during spaceflight, as shown by reduced SOD levels and total antioxidant activity in some astronauts returning from missions on the International Space Station[82].

Understanding the effectiveness of antioxidants in space is complicated by the presence of HZE particles. Whereas most of the DNA damage induced by γ- or X-rays is mediated by free radicals produced in the water surrounding the biological molecules (indirect effect), for densely ionizing radiation the direct effect predominates, that is, atoms in the DNA are directly ionized. Therefore, in principle, antioxidants should provide reduced or no protection against the initial damage from heavy ions, because

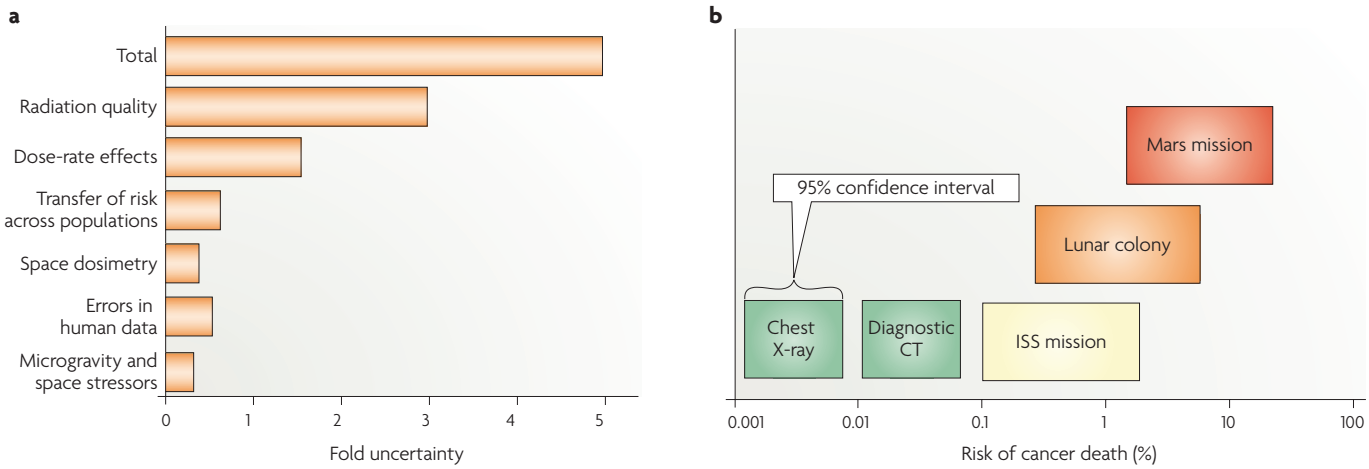

Figure 2 | **Uncertainties in space and terrestrial radiation exposures.** **a** | Estimates of uncertainties in projecting cancer risks for space from terrestrial exposures. Several factors, such as radiation-quality effects, space physics and microgravity, do not contribute on Earth and lead to large increases in risk projections. Predicting risks to individuals is difficult as there are few quantitative measures of individual sensitivity. Only a select few individuals enjoy space travel and projecting risks for them rather than populations will be of utmost importance for space missions to Mars. The extrapolation from experimental models to humans is perhaps the greatest challenge to cancer risk assessments. **b** | The uncertainties are larger for astronauts in space than for typical exposures on Earth; the figure shows the current estimates[9] of cancer risks and 95% confidence bands for adults of age 40, the typical age of astronauts on space missions for several terrestrial exposures and missions, on the International Space Station (ISS), a lunar colony and the projections for a Mars mission. CT, computed tomography.

scavenging of free radicals will not preserve the DNA molecule. However, there is an expectation that some benefits should occur for persistent oxidative damage related to inflammation and immune responses[67]. Some recent experiments suggest that, at least for acute high-dose irradiation, efficient radioprotection can be achieved by dietary supplements even in cases of exposure to high-LET radiation. Ascorbate reduces the frequency of mutations in human–hamster hybrid cells exposed to high-LET C ions[83]. Vitamin A strongly reduces the induction of fibroma in rats exposed to swift Fe ions[84]. Dietary supplementation with Bowan–Birk protease inhibitors[85], L-selenomethionine or a combination of selected antioxidant agents[86] could partially or completely prevent the decrease in total antioxidant status in the plasma of mice exposed to proton or HZE particle radiation, as well as neoplastic transformation of human thyroid cells *in vitro*. There is evidence that dietary antioxidants (especially those in strawberries) can protect the central nervous system from the deleterious effects of high doses of HZE particles[87]. However, because biological effects are varied for low dose-rate compared with acute irradiation, new studies for protracted exposures will be needed to understand the potential benefits of biological countermeasures.

Even if antioxidants can act as radioprotectors, this does not necessarily translate as an advantage for cancer risk. If antioxidants protect cells by rescuing them from apoptosis, then this may allow the survival of damaged cells, which eventually can initiate tumour progression. Concern about this possibility is sustained by a recent meta-analysis of the effects of antioxidant supplements in the diet of normal subjects[88]. The authors did not find statistically significant evidence that antioxidant supplements have beneficial effects on mortality. On the contrary, they concluded that β-carotene, vitamin A and vitamin E seem to increase the risk of death. Concerns include rescuing cells that not only sustain DNA damage, but also those with altered methylation patterns following radiation, which can also result in genomic instability[89]. An approach to target damaged cells for apoptosis might be advantageous for chronic exposures to galactic cosmic rays (GCR). Radioprotectors tested for acute exposures at high doses should be used with care — rescuing damaged cells may make the problem worse in the long term.

Individual susceptibility. Studying the mechanisms and pathways of genetic radiosensitivity provides important insights into radiation risks to astronauts. Studies of historical data sets such as the atomic-bomb survivors would need to be re-analysed if subsets of the exposed cohorts were found to have higher than average radiation risks[90,91].

Therapeutic misadventures involving ataxia telangiectasia patients have dramatically demonstrated the importance of genetic susceptibility to radiation damage in cancer treatment. ATM homozygotes only represent a small fraction of the extremely radiosensitive patients, although they appear to be the most sensitive. ATM heterozygotes, who are also cancer-prone, are suspected to represent a large fraction of the extremely radiosensitive patients[92]. It has been shown that cells heterozygous for ATM mutations are slightly more sensitive to radiation-induced neoplastic transformation than the wild-type[93]. An increased sensitivity of ATM heterozygotes has also been demonstrated *in vivo* by measuring induction of cataracts in ATM homozygotes, heterozygotes and wild-type mice exposed to 0.5–4 Gy X-rays[94].

Besides ATM there is the issue of whether or not other low-penetrance genes can also help determine sensitivity to radiation-induced cancer. Genes other than ATM can confer radiosensitivity in the heterozygous state, for instance, Rad9 (REF. 95), BRCA1 and BRCA2 (REF. 96). In addition, cells from unaffected parents of retinoblastoma (Rb) patients are radiosensitive, and although the parents do not carry the mutant Rb allele, the hypersensitivity is similar to that observed in those heterozygous for ATM[97]. A recent study on subjects exposed to high-radiation doses to treat ringworm of the scalp (tinea capitis) in Israel revealed a strong familial risk of radiation-induced meningioma[98], suggesting that radiation carcinogenesis might be an issue for genetically predisposed

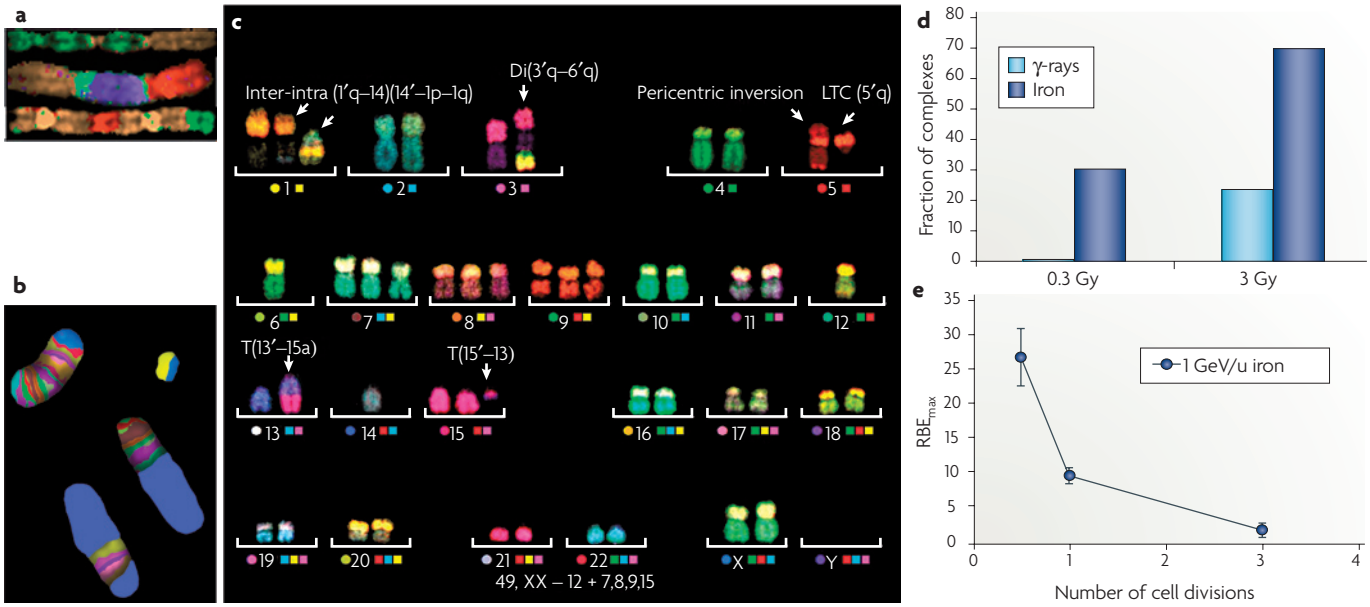

Figure 3 | **Chromosomal aberrations induced by heavy ions.** Examples of complex-type aberrations induced by energetic Fe ions in human peripheral blood lymphocytes. Complex rearrangements involve a minimum of two chromosomes and three breakpoints. **a** | Polycentric chromosomes visualized by multicolour fluorescence *in situ* hybridization (mFISH)[42]: from top to bottom, a quadricentric involving both chromosomes 1, chromosome 9 and chromosome 6; a dicentric of chromosome 1 and 9, with an insertion of chromosome 3; a tricentric involving both chromosomes 6 and chromosome 1. **b** | A complex rearrangement in chromosome 5 visualized by multicolour banding fluorescence *in situ* hybridization (mBAND; courtesy of M. Horstmann). One normal chromosome 5 is visible on the bottom, whereas the other is broken into three pieces. Breakpoints can be mapped on chromosome 5 using mBAND. **c** | A multi-aberrant karyotype, including inter- and intra-changes in the progeny of lymphocytes exposed to Fe ions visualized by arm-specific mFISH (courtesy of D. Pignalosa). Arm-specific mFISH and mBAND show that complex rearrangements can involve both inter- and intra-chromosomal exchanges. **d** | The fraction of complex-type exchanges in lymphocytes following exposure to γ-rays or Fe ions. Aberrations were measured by mFISH in prematurely condensed chromosomes. Clearly, Fe ions induce a high fraction of complex-type rearrangements. **e** | However, many of these rearrangements are lethal: in fact, the relative biological effectiveness (RBE) for the induction of aberrant cells decreases from interphase (prematurely condensed chromosomes) to first mitosis, and to later cell cycles (progeny of irradiated cells). Many of the chromosomal rearrangements induced by heavy ions are not transmitted to the progeny of surviving cells, albeit a higher fraction of complex rearrangements is still observed in the survivors. Part **d** is modified, with permission, from REF. 42 © Radiation Research Society (2002).

subgroups of the general population, rather than a random event[99].

It is not known whether individuals displaying hypersensitivity to low-LET radiation will also be universally hypersensitive to HZE nuclei, or if findings at high dose and dose rates will hold at low dose rates and doses. Mice heterozygous for the ATM gene are more sensitive to cataractogenesis than wild type, not only after exposure to X-rays, but also after localized irradiation with high-energy Fe ions[100]. However, these and other studies show that high-LET irradiation has a reduced dependence on genetic background compared with low-LET irradiation[2].

A predictive assay capable of identifying radiation-hypersensitive or cancer-prone individuals could be very useful in crew selection for long-term space flights. However, this assay is neither scientifically achievable, nor within society norms in most countries at the present time. Ultimately, however, for a high-risk and high-cost endeavour such as a mission to Mars, screening prospective astronauts for increased resistance to space radiation might be completely appropriate in order to reduce both the risk and the cost associated with the mission.

Shielding. For terrestrial radiation workers, additional protection against radiation exposure is usually provided through increased shielding. Unfortunately, shielding in space is problematic, especially when considering GCR. High-energy radiation is very penetrating: a thin or moderate shielding is generally efficient in reducing the equivalent dose, but as the thickness increases, shield effectiveness drops (see cancer risk estimates as a function of shielding thickness in FIG. 1). This is the result of the production of a large number of secondary particles, including neutrons, caused by nuclear interactions of the GCR with the shielding material. These particles generally have lower energy, but can have higher quality factors than the incident cosmic primary particle.

Contrary to the shielding of photons on Earth, for which heavy elements such as lead are preferred, in space shielding effectiveness per unit mass is the highest for hydrogen, and decreases with increasing atomic number. This has been confirmed by computer models such as HZETRN[101–102], used by NASA, or Geant4 (REF. 103), used by the European Space Agency (ESA), and accelerator[104–106] or space-flight measurements[107]. Although liquid hydrogen would display the maximum performance as shield material, it is not at all practical, being a low-temperature liquid. Polyethylene could be a good compromise, and has been installed in the sleeping quarters of the International Space Station. Unfortunately, most biologically dangerous secondary radiation is produced in tissue by high-energy GCR nuclei even behind hydrogen shielding. With current technology, active (magnetic) shielding is not yet feasible[108–109]; passive (bulk) shields may be able to reduce the exposure, but they are not likely to solve the problem.

Future directions

Ground-based experimentation is the key to understanding the risks associated with space radiation exposure; flight experiments are difficult, expensive and poorly reproducible, the dose rate is too low to get useful data in reasonable time, and experiments in the past have yielded no major findings[110–111]. The NASA-funded Space Radiation Health Program[112] is built upon the capabilities of the NASA Space Radiation Laboratory at the Brookhaven National Laboratory (Upton, New York, USA), and has produced experimental data in the past few years of great relevance for reducing uncertainty on risk assessment. To foster European research in the field, the ESA has also recently initiated a ground-based radiobiology program[113], which will be located at the high-energy synchrotron of the Gesellschaft für Schwerionenforschung in Darmstadt, Germany.

Research in this field is also essential for heavy-ion cancer therapy (hadrontherapy) on Earth, in which beams of high-energy carbon ions are used to sterilize solid cancers[114–115]. One major problem related to this treatment is the risk of secondary cancer, especially for paediatric patients[116–117]. Information on heavy-ion cancer risk sought by researchers in space radiation is also essential for estimating the incidence of secondary malignancies in these patients, and therefore the two research fields share many common issues and concerns[118].

Although translation from basic research to cancer risk assessment is far from straightforward, for Moon base activities cancer risk does not appear to be a showstopper, but the uncertainty is still too high for a go or no-go decision on the mission to Mars. Cosmic radiation exposure certainly presents a major hurdle for extended space exploration, but it can be better understood and therefore mitigated. A fruitful NASA–ESA collaboration in accelerator-based research should be fostered in future years, in order to reach a consensus on radiation cancer risk for a Mars mission within the next 10 years or so. Intensified research on countermeasures will be needed in order for such a mission to become a reality.

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DATABASES

Entrez Gene:
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene
ATM | ATR | BRCA1 | BRCA2 | DCLRE1C | H2AX | NBN | Rad9 | TERT | TGFβ | TP53BP1

National Cancer Institute: http://www.cancer.gov/
ataxia telangiectasia | lung cancer | meningioma | retinoblastoma

National Cancer Institute Drug Dictionary:
http://www.cancer.gov/drugdictionary/amifostine

FURTHER INFORMATION

M. Durante's homepage:
http://www.gsi.de/forschung/bio/index_e.html

F. A. Cucinotta's homepage: http://hacd.jsc.nasa.gov/projects/space_radiation.cfm

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