Stress and Radiation Responsiveness

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20.1 The Space Radiation Environment

20.1.1 Introduction

Ionizing radiation is radiation having enough energy to induce cell damage through ionization. This can be in the form of photons such as gammas or X-rays or subatomic particles such as electrons, muons, neutrons, protons, and heavier nuclei. A first important characteristic of radiation is its energy, which is typically in mega-electronvolt (MeV). One electronvolt is the energy an electron gains during acceleration by a one volt potential difference. A second important characteristic of radiation is the linear energy transfer (LET), typically in keV/μm. The LET specifies the amount of energy deposited per unit of length. The higher the LET of the radiation, the more complex the cell damage it creates and the more harmful the radiation is. The LET increases with increasing mass and increasing charge. Therefore, heavy nuclei have high LET and are a very harmful radiation type (Fig. 20.1). A third important characteristic of radiation is its intensity. For radiation protection purposes the radiation intensity is expressed in terms of the effective dose rate, typically in microsievert per hour (μSv/h) (ICRP 2007). The effective dose takes into account the amount of energy the radiation deposits in the different tissues, the harmfulness of the radiation type and the sensitivity of the exposed tissues and is proportional to the chance for developing radiation-induced cancer. Based on epidemiological studies this chance is estimated at about 5% per sievert.

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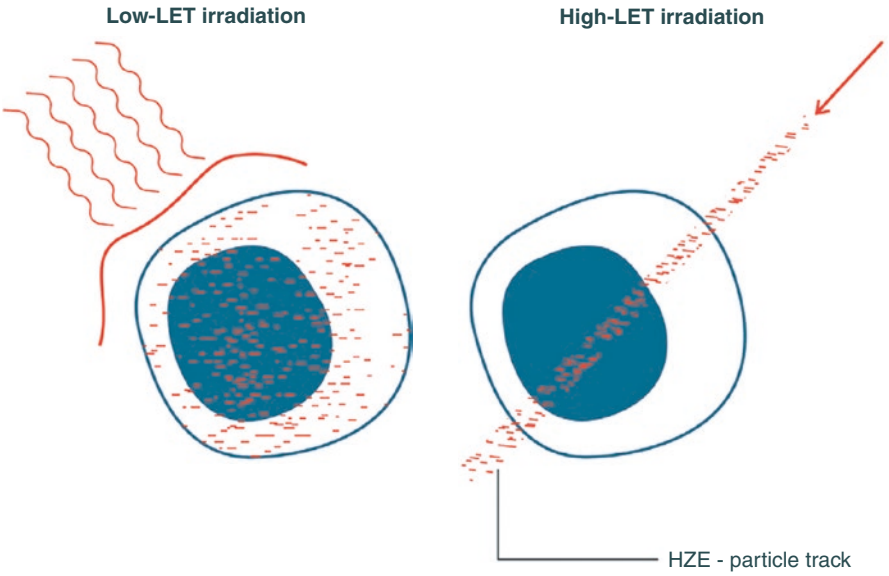

Fig. 20.1 Comparative diagram on DNA damage induced by low- and high-LET radiation. HZE particles, also called "densely ionizing radiation" typically deposit a large amount of their energy along linear tracks referred to as cores, while the remaining energy is deposited radially and uniformly by secondary electrons (i.e. Delta-rays). In contrast, low-LET radiations deposit their energy uniformly and are often referred as "sparsely ionizing radiation" (Cortese et al. 2018)

Ionizing radiation is omnipresent. Even on Earth we are continuously exposed to gamma radiation from natural radionuclides in the soil and to neutrons and muons created in the atmosphere by cosmic radiation from the sun and supernova remnants. The typical dose rate on Earth is about 0.1 μSv/h. This gives rise to a yearly dose due to natural background radiation of about 1 mSv/year. Radiation workers in hospitals and nuclear power plants are exposed to artificial radiation sources with dose rates up to a few μSv/h. However, their yearly dose should remain below the legal effective dose limit of 20 mSv.

In space the dose rate is much higher than on Earth because the protection by the Earth's atmosphere and the geomagnetic field against cosmic radiation is very limited in Low Earth Orbit (LEO) or even absent in deep space (Hassler et al. 2014; Kleiman 2012). In the International Space Station (ISS) the dose rate is typically about 20 μSv/h or 200 times higher than on Earth. For a typical stay of 6 months this leads to a dose of about 100 mSv, which is five times higher than the yearly legal dose limit for radiation workers on Earth. The dose rate on the surface of Mars is slightly higher, about 25 μSv/h or 250 times higher than on Earth. In deep space the dose rate is about 75 μSv/h or 750 times higher than on Earth. A typical manned Mars mission scenario with 180 days transit to Mars, 500 days on the Mars surface and 180 days transit back to Earth would lead to a total dose of about 1 Sv and thus about 5% risk of radiation-induced cancer (Hassler et al. 2014; Cucinotta et al. 2017). During strong solar storms the dose rate in space can temporarily increase a

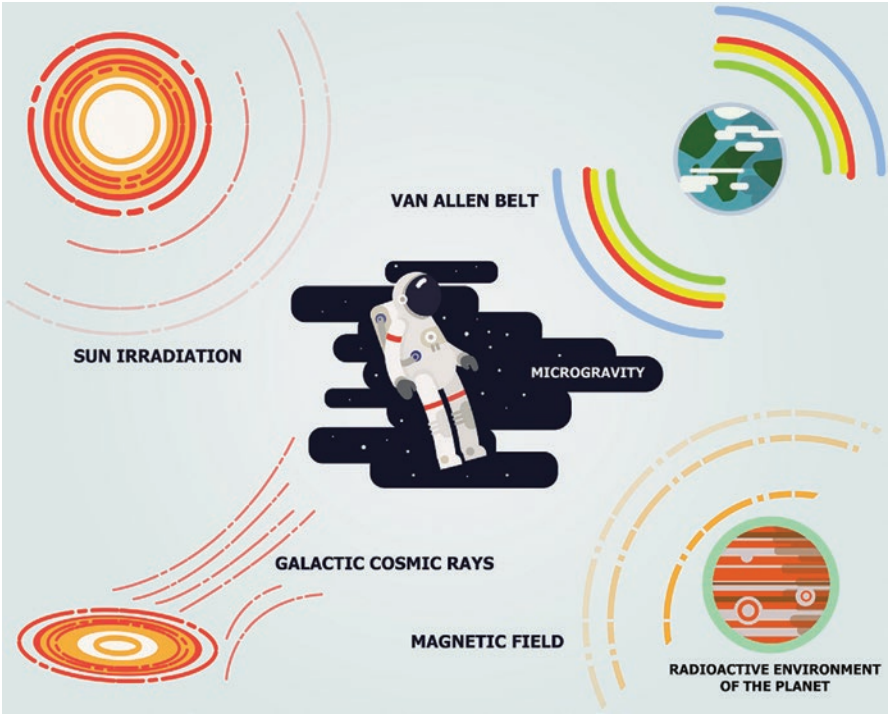

Fig. 20.2 Major sources of space radiation. The space radiation comes from three major sources including galactic cosmic rays, sun radiation, and Van Allen radiation belts of the Earth (Cortese et al. 2018)

few orders of magnitude. Without adequate shielding astronauts on the surface of the moon or Mars or in transit could be exposed to doses leading to serious health effects or even death (Benton and Benton 2001).

The radiation environment in space is also very different from that on Earth (Fig. 20.2) (Benton and Benton 2001). It consists of electrons, muons, neutrons, protons, and heavier nuclei up to extremely high energies. Furthermore, the radiation environment depends strongly on the solar activity, local shielding, and the location in space. This makes it very challenging to predict and monitor radiation doses received by astronauts. There is also much more uncertainty on the radiation-induced health effects because the epidemiological data for exposure to this type of radiation is very scarce.

20.1.2 Primary Cosmic Radiation

There are two primary sources of cosmic radiation: the sun and supernova remnants (Benton and Benton 2001). The sun is continuously emitting energetic electrons, protons, and a limited amount of heavier nuclei. This continuous flux of charged

particles is called the solar wind. Fortunately, the fluence rate and energies of the charged particles in the solar wind are very limited. Therefore, the solar wind is not of concern from radiation protection point of view. Even a small amount of shielding provides sufficient protection against the solar wind. However, the sun is a very turbulent object. Sometimes very energetic events at the surface of the sun such as solar flares and coronal mass ejections (CMEs) lead to temporary strong emissions of very energetic electrons and protons up to typically 100 MeV. Such events are commonly known as solar particle events (SPEs). The solar activity describes an 11-year cycle during which the activity goes from a minimum to a maximum. This can be observed by counting the sun spots. These dark spots on the surface of the sun are a good measure for the solar activity. During solar maximum the chance for an SPE is the highest. But even during solar minimum an SPE can happen. Currently, scientists do not yet fully understand how SPEs develop. Therefore, one cannot really predict SPEs. The best one can do is observe the sun with satellites and look for solar flares and CMEs. In that way one can at least send out a warning to the astronauts several minutes up to a few tens of minutes before the energetic electrons and protons reach them. But even then it is not possible to accurately predict the impact of the SPE. This can range from minor SPEs that will cause no harm up to dramatic events that can kill astronauts in deep space without adequate shielding. Hence, for manned missions to the moon or Mars the SPEs are an important issue. In LEO such as at ISS the dose due to SPEs is very limited due to partial protection by the Earth's magnetic field.

The second source of primary cosmic radiation is supernova remnants. Some stars undergo a very energetic explosion by the end of their life. After such an explosion or supernova very strong electromagnetic fields remain. In these electromagnetic fields charged particles can be accelerated up to extremely high energies. This is probably the most important source of the galactic cosmic radiation (GCR) coming from outside of our solar system. The GCR is a continuous flux of energetic charged particles coming isotropically from all directions. It is composed mainly of protons (85%) and ^{4}He nuclei (12%) and smaller amounts of heavier nuclei (1%) and electron and positrons (2%). The heavier nuclei are also called high-atomic number (Z), high-energy, or HZE particles. Although they are not so numerous, they are important from radiation protection point of view because of their high LET. The GCR energies are extremely high up to 10^{12} MeV with a peak around 1000 MeV. These high energies make it extremely challenging to shield from GCR. The most energetic particles can even penetrate the geomagnetic field. Proper shielding requires a material shield of at least a few meters thick. On Earth our atmosphere provides this protection. In spacecraft it is impossible to shield from GCR because of the weight limits. At ISS about 75% of the radiation dose is coming from GCR. In possible future habitats on the surface of the moon or Mars adequate protection could be provided by using local soil material. The GCR contribution to the dose is easy to predict. It is fairly constant in time. There is only a slight modulation of the GCR due to shielding by the magnetic field carried by the solar wind. The GCR dose rate is highest during solar minimum and lowest during solar maximum.

20.1.3 The Geomagnetic Field and the Van Allen Radiation Belts

Convection currents of molten iron in the Earth's outer core lead to electric currents and the generation of the geomagnetic field. This field is almost a magnetic dipole. The dipole axis is tilted about 11° with respect to the Earth's rotational axis. Also the dipole centre is slightly displaced with respect to the Earth's gravitational centre. The geomagnetic field shields the Earth and its close environment efficiently from cosmic radiation. Charged particles follow the magnetic field lines while gyrating around them with a certain radius. The more energetic the particle, the larger this gyration radius. Only the most energetic particles manage to reach the Earth's atmosphere. Less-energetic particles are captured by the magnetic field lines and diverted towards the poles. The equatorial region is best protected because the magnetic field lines there are parallel to the Earth's surface, while the polar regions are least protected because the magnetic field lines there intersect the Earth's surface. Therefore, the GCR dose rate is higher around the poles and the dose received by spacecraft in LEO increases with the inclination of the orbit.

A second important effect of the geomagnetic field is the creation of the Van Allen radiation belts. Some of the energetic charged particles of the SPEs and the GCR are trapped in the geomagnetic field. These trapped particles form two belts around the Earth that are called the Van Allen belts. The inner belt has its centre around 3000 km above the Earth's surface and contains electrons with energies up to 5 MeV and protons with energies up to 700 MeV. This belt is mainly filled by GCR. Therefore, its size and dose rate are inversely proportional to the solar activity. When spacecraft pass through this belt they are exposed to relatively high dose rates mainly due to the energetic protons. In LEO spacecraft are normally below the inner belt. Only above the coast of Brazil there is a region that is called the South Atlantic Anomaly (SAA) where the inner belt reaches down to 200 km above the Earth's surface. This is caused by the fact that the magnetic axis is not coincident with the rotational axis and does not go through the gravitational centre of the Earth. The ISS has an orbit with a typical altitude of 400 km and thus crosses the inner belt significantly in the SAA. These SAA crossings lead to about 25% of the radiation dose received by the astronauts in the ISS. Therefore, increasing the altitude of the ISS leads to increase of the radiation dose. The total radiation dose received in the ISS is also increasing for decreasing solar activity because both the GCR and SAA contributions are inversely proportional to the solar activity, while the SPEs do not contribute significantly to the radiation dose. Figure 20.3 shows a map of the absorbed dose rate measured in the Columbus module onboard the ISS with the DOSTEL detector in the framework of the DOSIS experiment during solar minimum in 2009 (Berger et al. 2017). This map clearly illustrates the increased dose rate in the SAA and the polar areas. The outer radiation belt has its centre around 22000 km above the Earth's surface and contains electrons with energies up to 7 MeV. This belt is mainly filled by SPEs. Therefore, its size and dose rate are proportional to the solar activity. This belt is only crossed for missions to the moon and Mars and is less of an issue because it only contains relatively low-energy electrons.

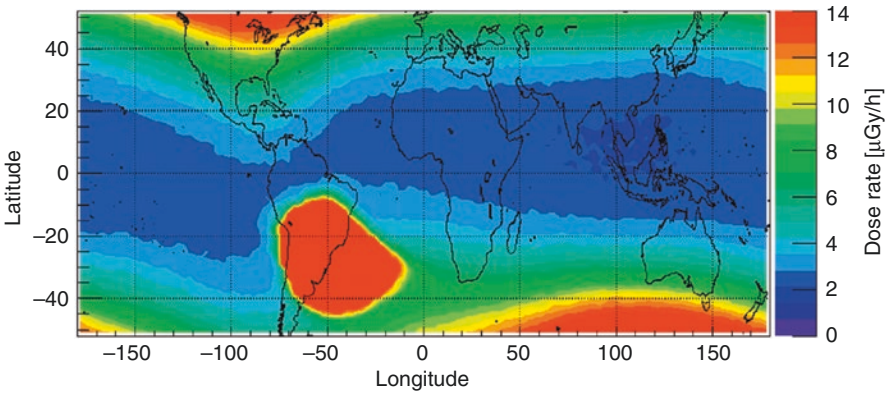

Fig. 20.3 Map of the absorbed dose rate measured in the Columbus module onboard the International Space Station with the DOSTEL detector in the framework of the DOSIS experiment during solar minimum in 2009 (Berger et al. 2017)

20.1.4 Shielding and Secondary Cosmic Radiation

Shielding is one of the primary methods to decrease radiation doses. However, interaction of cosmic radiation with shielding materials does not only attenuate the incoming radiation. Collisions of the very energetic GCR charged particles with the atoms of the shielding also create secondary cosmic radiation by nuclear reactions. This secondary cosmic radiation consists of neutrons, muons, pions, gammas, electrons, protons, and heavier nuclei and thus makes the radiation environment in space even more complex. Especially the secondary heavy nuclei and neutrons typically represent a substantial contribution to the radiation dose of the astronauts. The creation of the secondary cosmic radiation depends strongly on the shielding material composition. Ideally one should use shielding materials containing atoms with low atomic number such as hydrogen. Such materials give the best shielding per unit of mass and create the least secondary cosmic radiation. Constructive materials such as aluminium are thus not optimal with respect to radiation shielding. Using only a few millimetre of aluminium shielding can even increase the radiation dose. So, shielding could be optimized by using also low-atomic number materials. For habitats on the surface of the moon or Mars one could use several meters of soil material to get proper shielding.

20.2 Space Radiation Dosimetry

20.2.1 General Methodology

Radiation dosimetry for astronauts is very different from radiation dosimetry for radiation workers on Earth. Astronauts are exposed to much higher radiation doses and the type of radiation is also very different from the radiation typically

encountered by radiation workers on Earth. Therefore, the very approximate concept of the effective dose is not applicable for astronaut risk assessment. A more precise and personalized risk assessment has to be performed (Dietze et al. 2013).

A detailed risk assessment should be performed before each mission. This risk assessment is based on the expected radiation energy deposition in the different organ in terms of the organ absorbed dose in joule per kilogram (J/kg) or gray (Gy). These organ absorbed doses should be assessed separately for different radiation particles and energies and multiplied with the appropriate quality factors taking into account the radiation harmfulness, the organ sensitivity and the age and sex of the astronaut. This product of the organ absorbed dose with the quality factor is called the organ dose equivalent. For assessing the organ absorbed doses one starts from models of the GCR, Van Allen belts and worst case SPEs. These models are used as input for radiation transport simulations with Monte Carlo codes such as MCNP (MCNP website), FLUKA (FLUKA website), GEANT (GEANT website) and PHITS (PHITS website). These codes simulate how the primary cosmic radiation interacts with the spacecraft structure and the human body and eventually how much energy is deposited in each of the organs by the different radiation types.

However, these calculations should be accompanied by radiation measurements. There are still significant uncertainties in the cosmic radiation models and the interaction cross sections used in the Monte Carlo codes. So, measurements are required to validate and improve the models and the Monte Carlo codes. This can be done by placing radiation detectors in manned and unmanned spacecraft, satellites, and rovers on the moon and Mars. Furthermore, SPEs still cannot be predicted and the radiation dose also depends strongly on the local shielding inside spacecraft. Therefore, ambient radiation detectors and personal dosimeters for astronauts are required to alert in case of abnormally high dose rates due to SPEs and to accurately monitor the actually received dose.

20.2.2 Space-Related Constraints for Radiation Detectors

Radiation detectors used for radiation dosimetry in space are bound by several constraints (Benton and Benton 2001). Because of the high cost of launching equipment into orbit, radiation detectors must be small and of low mass. Furthermore, they should be of a robust design and able to withstand a long period of use without failing. Finally, they need to consume as little power as possible. The types of materials that can be used are also bound by constraints on crew safety, such as the possible outgassing of certain polymers and the limited bandwidth available for the transmission of data to Earth. From a technological point of view it is very challenging to measure the large dynamic range of energies, fluence rates and particle types. During SPEs the fluence rates can increase by several orders of magnitude. Ideally, the detector should be able to distinguish different particles and energies. Currently there is no detector that can fulfil all these requirements. Therefore, the results from different detectors need to be combined with simulations. Measurements are necessary to validate simulations and to allow personalized dose assessment. But also

the other way around, simulations are necessary to interpret radiation measurements. The design and development of space radiation detectors is also assisted by simulations. Furthermore, space radiation detectors are tested and characterized extensively at reference ion beam facilities on Earth such as the Heavy Ion Medical Accelerator in Chiba (HIMAC) in Japan before sending them into space.

20.2.3 Radiation Detectors Used in Space

Radiation cannot be observed directly. Therefore, radiation detectors rely on ionization and excitation effects induced by radiation in the detector material (Knoll 2010). Most radiation detectors are based on collection of radiation-induced charges such as gas ionization chambers and semiconductor detectors or on collection of visible light emitted by radioluminescent materials such as scintillators and optically or thermally stimulated luminescence detectors. There are also detectors in which radiation creates visible changes such as film, plastic nuclear track, and superheated emulsion or bubble detectors.

Different types of radiation detectors are used in space, depending on their purpose. There are active detectors providing real-time dose information and passive detectors that accumulate the dose until they are read out at a certain moment. Some detectors are mounted as ambient monitors somewhere fixed inside or outside a spacecraft or rover to monitor the radiation environment, while other detectors are carried by astronauts as personal dosimeter to monitor their personal dose.

Active detectors typically give the most detailed information because the data are time resolved and typically also give information on the radiation type. However, active detectors require power supply, are typically relatively bulky and expensive and require complex analysis. The oldest active detectors are based on simple gas ionization chambers. The R-16 (Tverskaya et al. 2004) is a combination of two such gas ionization chambers with different shielding. It was used already on board the Mir space station and is still used inside the Russian segment of the ISS. It cannot provide information on the radiation type. A more advanced type of gas ionization chamber used in space is the Tissue Equivalent Proportional Counter (TEPC). It is composed of a chamber of tissue equivalent wall material containing a tissue equivalent gas. The TEPC simulates the radiation energy deposition in a typically 1 or 2 μm diameter sphere of tissue. After appropriate analysis an approximate LET spectrum of the radiation can be derived. With the ISS-TEPC (Badhwar et al. 1996) and the updated version IV-TEPC, NASA currently has two TEPCs operational in the ISS. The newer active detectors are based on telescopes containing several semiconductor silicon diodes. Examples are the MSL-RAD (Mars Science Laboratory—Radiation Assessment Detector) (Hassler et al. 2014) on board the Curiosity rover on the surface of Mars and the DOSTEL (Berger et al. 2017), CPDS (Lee et al. 2007), ISS-RAD (similar to MSL-RAD) and Liulin (Dachev et al. 2015) detectors on board ISS. Such detectors provide more precise LET spectra and give also directional information. Both the gas ionization chambers and silicon telescopes are relatively bulky. Currently, there is a transition towards smaller active detectors. NASA

has the ISS-REM monitoring network on board ISS and is working on the BIRD and HERA detectors for the Orion missions (Kroupa et al. 2015). These detectors are all based on the Timepix technology which consists of a compact pixelated silicon detector that requires limited power and is able to provide even more information on radiation type and angle. Both ESA and NASA are also developing very compact active personal dosimeters to replace the current passive personal dosimeters of the ISS astronauts. These are based on silicon diodes and Direct Ion Storage (DIS) detectors, which are miniature ionization chambers storing the liberated charges on a nonvolatile semiconductor memory cell. However, these active personal dosimeters do not provide detailed information on the radiation type. So, they still need to be complemented with more sophisticated active ambient monitors.

Passive detectors typically give less information because they provide a measurement integrated over time and radiation type. However, they are very compact, cheap and don't require any power. This makes them very complementary to active detectors. They are used for instance to perform detailed mapping of the dose rate such as inside the Columbus module of the ISS in the DOSIS 3D experiment (Berger et al. 2016), to measure inside anthropomorphic phantoms to experimentally assess organ absorbed doses such as in the MATROSHKA experiment (Berger et al. 2013), to monitor radiation doses for biological experiments in space (Vanhavere et al. 2008) and as personal dosimeter for the ISS astronauts. There are three main types of passive radiation detectors used in space. The first type are the optically stimulated luminescence detectors or OSLDs (e.g. Al_2O_3:C) and the thermoluminescent detectors or TLDs (e.g. LiF:Mg,Ti, LiF:Mg,Cu,P, $CaSO_4$:Dy). These detectors absorb the radiation energy and emit it as visible light when stimulated with heat or visible light during read out. The amount of light emitted is proportional with the received dose. There is also the Pille system (Szanto et al. 2015) which allows read out of $CaSO_4$:Dy detectors inside the ISS. It is used by the Russians for dose mapping and personal dose monitoring during Extra Vehicular Activities (EVAs). The disadvantage of the stimulated luminescence detectors is that their sensitivity drops rapidly for radiation with LET above 10 keV/μm. But limited information on the high LET part of the radiation can be obtained by combining different OSLDs and TLDs and by looking at the high temperature signal of the TLDs (Parisi et al. 2017). The second type of passive detectors are Plastic Nuclear Track Detectors (PNTDs). These detectors are based on a polymer, typically polyallyl diglycol carbonate or CR-39. Radiation with high LET creates tracks in this detector that can be visualized under a microscope after chemical etching. The number of tracks, their size, and shape can be used to calculate the dose and even an LET spectrum. The PNTDs are only sensitive for radiation with LET above 10 keV/μm. Therefore, the OSLDs and TLDs are typically combined with the PNTDs such as in the passive dosimeter of the ISS astronauts and the DOSIS 3D experiment. Finally, there are also the superheated emulsion or bubble detectors. These detectors contained small droplets of superheated liquid dispersed in a polymer. Radiation with high LET can deposit enough energy in these droplets to evaporate them into gas bubbles. The number of bubbles is a measure of the dose. The bubble detectors are typically used for neutron measurements (Smith et al. 2016).

20.3 Radiobiology

20.3.1 Introduction

All biological consequences of ionizing radiation on living tissues are a result of the interaction with atoms in a process called ionization. Ionizing radiation has sufficient energy to remove one orbital electron from an atom, thereby creating an ion pair. There are two mechanisms by which radiation ultimately affects cells: either by direct ionization of the target molecule, or indirectly by the production of free radicals which may ultimately affect the target molecule (Fig. 20.4). During direct ionization, radiation transfers energy directly to the atoms of cellular components such as deoxyribonucleic acid (DNA), proteins, and lipids. If a cell is exposed to ionizing radiation, the probability of directly interacting with DNA is low, as it makes up only a small part (1%) of the cell. The main constituent of all cells of the human body is water (up to 80%). Therefore, most of the energy produced by ionizing radiation (particularly photon irradiation) leads to water radiolysis, which results in free radical production that ultimately can lead to indirect DNA damage. Free radicals are highly reactive compounds, such as hydroxyl radicals and superoxide anions, which are characterized by an unpaired electron. In addition, other reactive compounds including hydrogen peroxide and hydroxyl ions can also be produced.

Radiation induces a large spectrum of DNA lesions, including single-strand breaks (SSB), double-strand breaks (DSB), base loss, base changes, and cross-links. The DSB constitute the principle cytotoxic lesion in response to both photon and particle radiation, and is considered to be the critical primary lesion in the formation of chromosomal aberrations. The quantification of DSBs as well as chromosomal aberrations after radiation exposure is frequently used as a biological dosimeter or to evaluate radiosensitivity of individuals (see Chap. 28). DSBs are detected in the

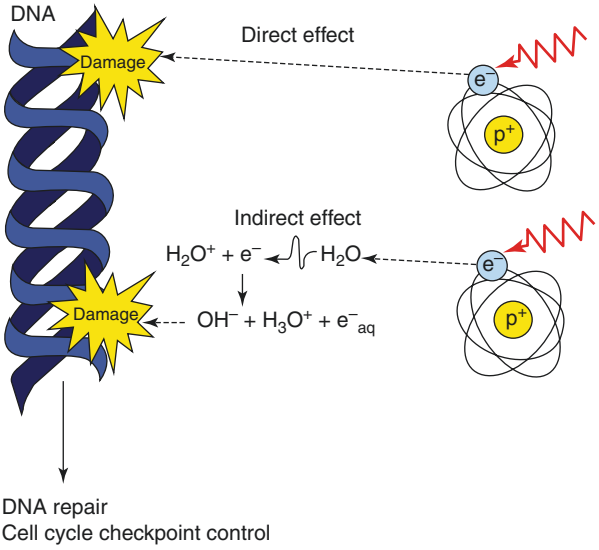

Fig. 20.4 Ionizing radiation induces direct DNA damage and indirect damage through the radiolysis of water (figure is *adapted* from a figure in (Morgan and Sowa 2007))

cell by sensing molecules which activate a signaling cascade by phosphorylating the histone H2AX (γ-H2AX) (Kinner et al. 2008; Rogakou et al. 1998). Repair enzymes will be attracted to the damaged site and the cell will go into cell cycle arrest to allow time for repair. It is well known that the number of γ-H2AX foci is proportional to the amount of DSBs. By immunofluorescent staining of the γ-H2AX foci, quantitative and qualitative evaluation of the amount of DSBs as well as subsequent DNA repair kinetics can be performed (Fig. 20.5) (Ghardi et al. 2012). Substantial evidence indicates that particle radiation such as protons or heavy ions induces DNA damage that is quantitatively and qualitatively different from that caused by photons (Fakir et al. 2006). Particle radiation (especially high-LET) produces dense ionization tracks, thereby inducing a greater number of, and more complex, "clustered" DNA lesions than photon radiation (Hada and Georgakilas 2008; Terato et al. 2008). These clusters contain various types of DNA damage (e.g., SSB, DSB) within a localized region of the DNA molecule and are associated with the increased relative biological effectiveness (RBE) of particle radiation beams (Fakir et al. 2006; Hada and Georgakilas 2008; Cortese et al. 2018).

The global response of a cell to DNA damage triggers multiple pathways involved in sensing DNA damage, activating cell cycle checkpoints, and inducing DNA repair (Su 2006).

However, when the damage is severe, cellular apoptosis can be induced. Failure of DSB repair or misrepair can initiate genomic instability, causing chromosome aberrations and genetic mutations, and may eventually lead to cancer. Besides damaging the DNA molecule, ionizing radiation can cause a number of lesions in other macromolecules as well (e.g., lipid peroxidation, reactive oxygen species). These non-DNA lesions trigger multiple signaling pathways including Protein Kinase C (PKC), Mitogen-activated protein Kinase (MAPK), and c-Jun NH_2-Terminal Kinase (JNK), which are involved in cell cycle control, DNA repair, and apoptosis. In addition, other radiation-induced phenomena have been described. These include nontargeted and delayed effects such as bystander effects, genomic instability, and adaptive response (Averbeck 2010). Bystander effects occur in cells that are not hit directly, but which are affected by signals derived from neighboring irradiated cells. Genomic instability is characterized by the increased rate of acquisition of genomic alterations (e.g., chromosomal aberrations, mutations) of the progeny of an originally irradiated cell appearing several generations after irradiation. On the other hand, the adaptive response model postulates that certain doses of low-dose radiation may be beneficial, and renders cells less susceptible to the damaging effects of radiation.

20.3.2 Biological Effects of Radiation

20.3.2.1 Tissue Reactions and Stochastic Effects of Ionizing Radiation

Radiation risk assessment by advisory bodies such as ICRP (International Commission on Radiological Protection) and NCRP (National Council on

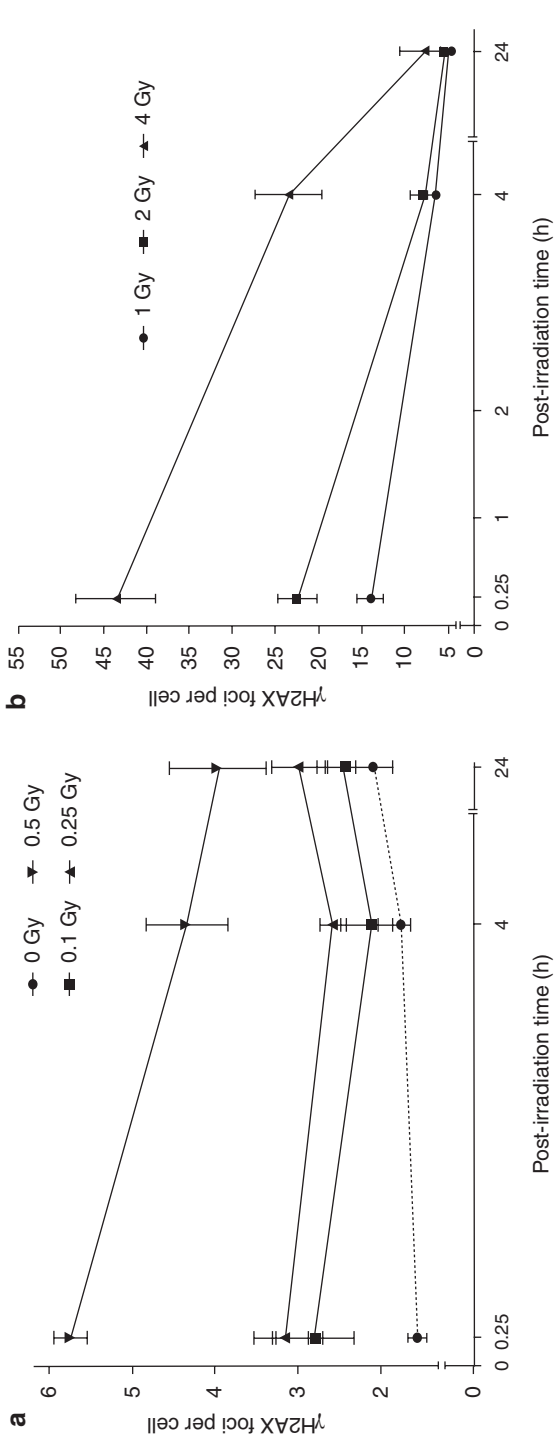

Fig. 20.5 Kinetics of γH2AX foci formation in human lymphocytes analyzed by fluorescence microscopy. Time response curves represent the relative mean of γH2AX foci at different time points after irradiation. (**a**) Low and moderate doses (0.1, 0.25 and 0.5 Gy) or (**b**) high doses (1, 2 and 4 Gy) of X-irradiation. Error bars represent ± SEM ($n = 3$). (Figure from (Ghardi et al. 2012))

Radiation Protection & Measurements) have classified biological effects of radiation as either tissue reactions or stochastic (ICRP 2012). *Tissue reactions*, previously called deterministic effects, are associated with high doses of radiation exposure over a short period of time. The severity of the effects in affected individuals depends on the dose and increases with the magnitude of the radiation. There is a threshold radiation dose, below which the tissue reactions has, so far, not been detected clinically (Fig. 20.6a). *Stochastic* effects are usually associated with exposure to low doses of radiation over a longer period of time, typically like those encountered by astronauts on board the ISS. The probability of inducing the effect, but not the severity of the effect, is dose-related (Fig. 20.6b). Dose-effect curves for these changes are considered to be nonthreshold in type. It is assumed that there is always a small probability of an effect even at very low doses. Low doses can be defined as a dose, and dose rate, at which, on the average, only a fraction of all targets (cell nuclei) is affected by an energy deposition event. In this dose range, the risk for one cell to be transformed is very low. However, the risk to the organism of having one transformed cell depends on the number of cells being hit. The upper limit according to this criterion is 0.020 Gy (ICRP). Increased incidence of cancer after low-dose radiation is an example of a stochastic effect. For the induction of tumors, doses below 0.1 Gy are considered as low doses. The linear nonthreshold model presupposes that the damage caused by ionizing radiation linearly increases in response to the dose. Furthermore, nontargeted as well delayed effects including bystander effects, genomic instability, and adaptive response might be involved in the response to low doses.

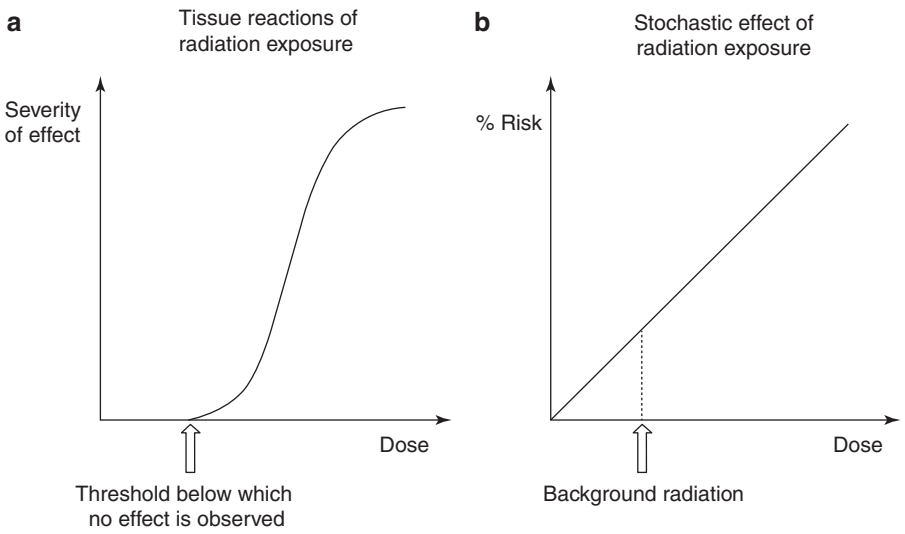

Fig. 20.6 Biological effects of ionizing radiation: (**a**) tissue reactions and (**b**) stochastic effect

20.3.2.2 Early and Late Effects

Radiation effects can appear rapidly, but also after a delay. *Early* or *acute effects* are those occurring within hours, days, or a few weeks following high-dose exposure (>1 Gy) in a short period of time. These effects appear to be threshold phenomena and are classified as *tissue reactions*. Exposure to high doses of ionizing radiation can cause a rapid whole-body response, often referred to as acute radiation syndrome (ARS) or radiation sickness. These high doses tend to kill cells in such a way that tissues and organs become damaged and their functioning impaired. The principal sites of biological action are rapidly proliferating cells from the bone marrow, gastrointestinal cells, skin, and testes. These tissues and organs are classified as radiosensitive organs. ARS is characterized by a sequence of phased symptoms in which the clinical effects develop proportionally to the dose amount (Xiao and Whitnall 2009). Moderate doses (1–7 Gy in humans) induce depression of bone marrow function, known as hematopoietic syndrome. This syndrome leads to decreased resistance to infections and hemorrhage. Higher single doses (about 8 Gy or more) will result in gastrointestinal syndrome leading to small intestinal cell killing. Very severe whole-body exposure (20–40 Gy) is characterized by a deteriorating state of consciousness with eventual coma and death (neurovascular syndrome).

Late or *long-term effects* usually occur after a number of months or years following radiation exposure. For radiation protection purposes, these late effects are classified as being stochastic or tissue reactions in nature. Epidemiological studies have clearly identified an increased risk of several types of cancers induced by ionizing radiation (Preston et al. 2007), rendering *carcinogenesis* as the main somatic *stochastic late effect*. It is generally agreed that DNA damage, including DSB, mutations, and chromosomal rearrangements are the initiating event in the multistep process leading to malignant transformation. In this context, radiation-induced chromosomal aberrations in peripheral blood lymphocytes are considered as a validated biomarker of cancer risk estimation (Durante 2005; Norppa et al. 2006; Boffetta et al. 2007). In addition to an increased risk of carcinogenesis, long-term immune dysfunction should also not be underestimated (Kusunoki and Hayashi 2008). A classic example of a *late tissue reaction* induced by ionizing radiation exposure is cataract formation (reviewed in Kleiman 2012). The eye, and more specifically the crystalline lens, is one of the most radiosensitive organs of the human body. Ocular ionizing radiation exposure causes dose-related, progressive changes in the lens, finally leading to cataract. Since 2012 and 2016, respectively the ICRP and NCRP have reported threshold values for visually disabling cataracts of 0.5 Gy. Furthermore, apart from lens opacity, it has long been realized that high-radiation doses also have the potential to cause effects such as cardiovascular diseases as well as cognitive impairment and that such non-cancer effects at low doses cannot be readily explained by the extrapolation of cancer risk from high to low doses (LNT model), pointing out the need for more experimental (mechanistic) and epidemiological studies to address this particular extrapolation issue to radiation-induced non-cancer effects.

20.4 Biological Effects of Cosmic Radiation

Compared to individuals on Earth, astronauts receive much higher doses of ionizing radiation during spaceflight. Dose estimates for interplanetary space travel indicate that astronauts receive 0.5–1.4 Gy/year. Recently, estimates for a round-trip to Mars show that total cumulative doses of up to 0.662 ± 0.108 Sv are likely (Zeitlin et al. 2013). However, these doses are not expected to result in significant acute radiation effects (thereby assuming no significant SPEs during the mission), but they may increase the long-term health risks that are associated with radiation exposure. Besides this, the type of radiation in space differs from the typical terrestrial radiation (e.g., X-rays, γ-rays), and consists mainly of protons and HZE particles (e.g., iron, oxygen, carbon, and silicon ions). Although protons account for >90% of deep space radiation, charged particles are predicted to account for most of the biological consequences of cosmic radiation exposure, due to their high-LET and their linear track structure (Swenberg et al. 1991; Green et al. 2001). Unfortunately, shielding against this type of ionizing radiation is not feasible. Exposure to high-LET radiation is therefore considered as a major health risk for astronauts and is of major concern during long-term spaceflights.

Cataract formation was the first proven late tissue reaction of space radiation on astronauts. Previous studies showed that an increased risk of cataract with lens doses greater than 8 mGy was observed in astronauts (Cucinotta et al. 2001; Rastegar et al. 2002; Chylack et al. 2009). In addition, a significant association was found between the space radiation doses received by US astronauts, and the progression rate of cortical cataracts (Chylack et al. 2012). The induction of late stochastic effects such as cancer risk after cosmic radiation exposure is so far unknown (Cucinotta and Durante 2006; Durante and Cucinotta 2008). Estimations of cancer risk for space missions are mainly based on epidemiological settings from data obtained from atomic bomb survivors and patients exposed to radiation therapy (Little 2009). However, most of these studies are related to photon radiation types (e.g., X-rays, γ-rays), and do not take into account the important biological differences that exist between photons and particles. As a result, extrapolation of photon data for radiation risk assessment on astronauts can lead to wrong conclusions (Cucinotta and Durante 2006). Therefore, at present, prediction of cancer risk for humans exposed to heavy ions during deep space mission has very large uncertainties since there are no data available that address the risk from extended exposure to complex radiation fields. For this reason, NCRP recommended age and gender-dependent career dose limits based on a 3% excess cancer fatality risk. In order to improve the risk modeling during deep space missions, calculations should be based on biological and mechanistic studies on the effects of different radiation qualities on carcinogenesis (Barcellos-Hoff et al. 2015). Estimation of cancer risk following occupational deep space ionizing radiation exposure could be based on studies performed on cancer patients treated with charged particles including protons and carbon ions (hadron therapy). However, recent studies on patients treated with particle irradiation only reported a few cases of secondary tumors and suffer from a limited follow-up time

and inadequate statistics (Kamran et al. 2016; Eaton et al. 2015). Nevertheless, the increased use of charged particles (protons and carbon ions) for radiotherapy purposes can increase our general knowledge about the biological effects of particles in general. Recently, ground-based studies on animals showed that exposure to particle radiation has a higher carcinogenic effect compared to photon exposure (Weil et al. 2014; Suman et al. 2015; Trani et al. 2010). In addition, our lab performed many in vitro experiments with cancer cells exposed to carbon ions (Suetens et al. 2016, 2014, 2015). Further studies in this field will definitely contribute in reducing the present uncertainties associated with cancer risk estimates on astronauts.

Chromosomal abberations have been used as surrogate endpoints to investigate radiation quality effects related to cancer risk estimation. Caution should be given, however, when extrapolating the number of chromosomal abberations to a cancer risk as it has been observed that the dose response for chromosomal aberrations following particle exposure is nonlinear at lower (<0.1 Gy) doses (Hada et al. 2014). As mentioned before, measurement of chromosomal aberration frequencies in lymphocytes after radiation exposure have been proposed as an indicator of cancer risk (Durante 2005). So far, several papers have described radiation-induced chromosomal damage in astronauts' lymphocytes after missions in low-Earth orbit (Testard et al. 1996; Obe et al. 1997; Yang et al. 1997; George et al. 2001; Durante et al. 2003; Greco et al. 2003; George et al. 2005). Short-duration missions did not result in significant detectable differences in chromosome abnormalities measured before and after flight. In contrast, an increase in post-flight aberrations was found in the case of long-term flights. However, in another study no correlation was found between aberration frequencies and total mission duration or in the cumulative dose equivalent in space for 13 crew members involved in multiple spaceflights (Durante et al. 2003). In addition, it appeared that the post-flight decline in time of chromosomal aberrations was faster than expected and significant heterogeneity was observed among individuals. Besides differences in individual radiosensitivity, the adaptive response mechanism to space radiation might explain these observations. This adaptation might take place after the first exposure, leading to an increased radioresistance in exposed individuals. Recently, the effect of repeated space flight on the yield of translocations in individual crewmembers was analyzed (George et al. 2013). All crewmembers showed a consistent increase in total exchanges and translocations after both the first and second flight. These results support the assumption of addividity of biological doses for ISS crew exposures. The long-term consequences of these persistent chromosomal rearrangements are not well understood so far, and further investigation in this field is definitely needed.

20.4.1 Immune Dysfunction in Space: Impact of Cosmic Radiation?

Immune dysfunction during spaceflight is of paramount concern and can lead to serious health problems. The first study about immune abnormalities in space dates back to the 1970s, where reduced reactivity of peripheral blood lymphocytes in

crew members was observed (Konstantinova et al. 1973). Currently, numerous immune aberrations have been reported in astronauts, cosmonauts, and animals flown in space (reviewed in Gueguinou et al. 2009). Some of these observed alterations include variations in peripheral blood leukocyte populations, changes in function of cells involved in innate immunity, decreased cytokine expression, depression of T cell activation and proliferation, and many others. So far, the precise nature of immune dysregulation related to spaceflight is unknown (see Chaps. 11–19) and multiple underlying causes might be involved. In this context, the impact of cosmic radiation, which is always present during spaceflight, should not be underestimated.

To gain more insight into the specific influence of radiation on the immune system, Earth-based experiments are increasingly used and represent a more reproducible alternative to in-flight experiments. To date, several ground-based studies in animals demonstrated that ionizing radiation influences many aspects of the immune system and can cause immune dysfunction. Until recently, the majority of radiobiology studies were related to photon radiation such as X- and γ-rays (Harrington et al. 1997; Shankar et al. 1999; Gridley et al. 2001; Pecaut et al. 2001; Shearer et al. 2005). However, due to the recent worldwide increase in particle accelerator facilities, several studies investigated the effect of whole-body exposure to particle radiation including protons and heavy ions. In this way, it is possible to expose cells and animals to types of radiation encountered by astronauts during interplanetary space travel. Laboratory studies have shown that whole-body radiation of rodents can result in significant acute and long-term effects on the immune system. Table 20.1 gives a summary of the main papers describing ground-based experiments that investigate acute and chronic immune changes after exposure to photon and particle radiation.

20.4.1.1 Acute Effects

In general, when mice are exposed to a single exposure of up to 3 Gy of protons, photons, or high-LET particles, a clear effect on different immune cell populations is observed. There is a large dose response on day 4 followed by general recovery over the following 2–3 weeks. Independent of the radiation type, relative radiosensitivities of the various lymphocyte populations (B cells > T cells > NK) and T cell subsets ($CD8^+ > CD4^+$) are observed (Kajioka et al. 1999, 2000; Gridley and Pecaut 2006; Pecaut et al. 2006; Gridley et al. 2008; Pecaut and Gridley 2008). Lower doses of high-LET particles (<2 Gy) were shown to induce acute damage to the hematopoietic stem cells and their progenitor cells (Chang et al. 2016, 2017a, b). To better mimic the space radiation environment, experiments with simulated solar particle event (sSPE) were performed (Gridley et al. 2008). For this purpose, mice were exposed to a high dose of sSPE protons over a period of 36 h. The results obtained were compared to γ-ray and proton exposure with the same dose. Acute effects including general immune depression and leukocyte abnormalities were present; however, the damaging effects of sSPE on leukocytes were generally less pronounced compared to the acute photon and proton radiation. Furthermore, it has been demonstrated that inhomogeneity of the proton dose distribution (30–74 MeV) does not affect white blood cell counts (Sanzari et al. 2014). Besides the risk of

Table 20.1 Ground-based studies—impact of photon and particle radiation on the immune system of rodents

Reference	Irradiation source	Animal model	Time point of analysis	Effect
Harrington et al. (1997)	γ-rays: 1–7 Gy	C57Bl/6 mice	Acute (1–4–7 days)	Immune suppression
Kajioka et al. (1999, 2000)	Proton: 3 Gy (0.4 Gy/min)	C57Bl/6 mice	Acute (4–10–15–29 days)	Decrease in lymphocyte populations
	γ-rays: 3 Gy			→ B sens > CD4 > CD8 > NK resist
				Decrease in acute response to antigen
				No significant differences between proton and γ-ray exposure
Pecaut et al. (2001)	γ-rays: 0–0.5–1.5–3 Gy	C57Bl/6 mice	Acute (4 days)	Decrease in lymphocytes populations
	LDR: 1 cGy/min			B sens > CD4 > CD8 > NK resist
	HDR: 80 cGy/min			Immune changes depend more on dose than on dose rate
Gridley et al. (2001)	γ-rays: 0–0.5–1.5–3 Gy	C57Bl/6 mice	Acute (4 days)	Decrease in number of blood cells
	LDR: 1 cGy/min			Decrease in IL-2 secretion by activated spleen cells
	HDR: 80 cGy/min			Changes depend more on the dose, than on the dose rate
Gridley et al. (2002a)	Proton: 0–0.5–1.5–3 Gy (entry region Bragg peak)	C57Bl/6 mice	Acute (4 days)	Decrease in number of lymphocytes
	LDR: 1 cGy/min			NK are more radioresistant
	HDR: 80 cGy/min			Significant dose and dose rate effects
	γ-rays: 3 Gy			Effect of proton irradiation (3 Gy) is larger than γ-ray exposure (3 Gy)
Pecaut et al. (2002)	Proton: 0–0.5–1.5–3 Gy (entry region Bragg peak)	C57Bl/6 mice	Acute (4 days)	Decreased splenocyte response
	LDR: 1 cGy/min			Increased blastogenesis
	HDR: 80 cGy/min			Effects depend on dose (and not dose rate)
	γ-rays: 3 Gy			Effects are more pronounced with proton exposure compared to γ-rays

Gridley et al. (2002b)	Fe ion: 0.1–0.5–2.0 Gy (LET = 148.2 keV/μm)	C57Bl/6 mice	Acute (Fe ion: 4 days)	Acute effects: decrease in lymphocytes (B sens > CD8 > CD4 > NK resist)
	Si ion: 2.0 Gy (LET = 42.1 keV/μm)		Chronic (Fe ion, Si ion: 113 days)	Chronic effects after Fe exposure: high number of B cells, low number of CD8 cells
				Chronic effects after Si exposure: low number of NK
				Immune aberrations persist long after exposure
				Effects depend on radiation type
Pecaut et al. (2003)	Proton: 3–4 Gy (± shielding)	C57Bl/6 mice	Chronic (122 days)	Dose-dependent decrease in lymphocyte populations
Shearer et al. (2005)	γ-rays: 0.3 Gy	Balb/c mice		Decrease in number of immune cells
Pecaut et al. (2006)	Fe ion: 0–0.5–2–3 Gy (LET = 148.2 keV)	C57Bl/6 mice	Acute (4 days)	Decrease in number of lymphocyte populations
				B sens > CD8 > CD4 > NK resist
Gridley et al. (2006)	Fe ion: 0–0.5–2–3 Gy (LET = 148.2 keV)	C57Bl/6 mice	Acute (4 days)	Alterations in leukocyte response and function
Gridley et al. (2006)	γ-rays: 2 Gy	C57Bl/6 mice	Chronic (110 days)	Significant aberrations in immune parameters observed 4 months after exposure
	Proton: 2 Gy			
	C ion: 2 Gy (LET = 12.9 keV/μm)			
	Fe ion: 2 Gy (151.5 keV/μm)			
Gridley et al. (2008)	Fe ion: 0–1–2–4 Gy (LET = 148.2 keV/μm)	SD Rat	Chronic (9 months)	Decrease in number of lymphocytes
Gridley et al. (2008)	SPE protons: 2 Gy (chronic)	C57Bl/6 mice	Acute (4–21 days)	Effects on immune system with SPE protons less pronounced compared to other types of radiation (acute γ-rays or acute protons)
	Protons: 2 Gy (acute)			
	γ-rays: 2 Gy (acute)			
Gridley et al. (2009)	Proton: 0.01–0.05–0.1 Gy	C57Bl/6 mice	Acute (4–21 days)	Changes in CD4 T cell gene expression after low-dose proton irradiation
	LDR: 0.1 cGy/h			
	(delivered over a 2 week period)			LDR enhances CD4 T cell responsiveness

(continued)

Table 20.1 (continued)

Reference	Irradiation source	Animal model	Time point of analysis	Effect
Pecaut and Gridley (2010)	Fe ion: 0.5–2–3 Gy	C57Bl/6 mice	Acute (4–30 days)	Mouse strain influences Fe radio-immune response
		CBA/Ca		
Gridley et al. (2010)	± SPE protons: 1.7 Gy (chronic) ± pre exposure to γ-rays: 0.01 Gy (LDR: 0.179 mGy/h)	C57Bl/6 mice	Acute (4–21 days)	Preexposure to LDR photons does not protect against adverse effects of radiation mimicking a SPE on the immune system
Rizvi et al. (2011)	± SPE protons: 1.7 Gy (chronic) ± pre exposure to γ-rays: 0.01 Gy (LDR: 0.179 mGy/h)	C57Bl/6 mice	Acute (4–21 days)	Protracted exposure to LDR γ-rays modifies effect of SPE protons on lymphocyte signaling proteins and secretion of cytokines
Luo-Owen et al. (2012)	Chronic preexposure to γ-rays: 0.05 Gy (LDR: 0.025 cGy/h) + acute proton irradiation (2 or 3 Gy)	C57Bl/6 mice	Acute (4–17 days)	Preexposure modulates the response to acute proton exposure
Gridley et al. (2013)	2 Gy proton (1 Gy/min) or γ-ray (0.9 Gy/min) + preexposure to γ-rays: 0.01 Gy (LDR: 0.03 cGy/h)	C57Bl/6 mice	Acute/chronic (21–56 post-exposure)	Some immune responses to acute 2 Gy radiation are dependent on radiation quality, time of assessment, and preexposure to LDR γ-rays
Sanzari et al. (2014)	SPE proton radiation (homogenous and inhomogenous dose distribution)	ICR mice	Acute (4–24 h)	Reduced number of blood cells, comparable for both dose distributions
Chang et al. (2015)	1 Gy whole-body proton irradiation (150 MeV/n)	C57BL/6J mice	Chronic (22 weeks)	Persistent reduction of bone marrow hematopoietic stem cells linked to increased oxidative stress, reduced quiescence, and increased DNA damage
Chang et al. (2016)	Low dose of ^{16}O exposure (0.1, 0.25 and 1.0 Gy)	C57Bl/6 mice	Acute (14 days)	Acute damage to hematopoetic progenitor and stem cells

Gridley and Pecaut (2016)	^{56}Fe ion: 0–1–2–3 Gy	C57Bl/6 mice	Chronic (40 days)	Aberrations in a variety of immune parameters
Chang et al. (2017b)	0.5 and 1 Gy whole-body proton irradiation (150 MeV/n)	C57BL/6 mice	Acute (14 days)	Decreased numbers of common myeloid progenitor and $Lin^{-}SCA1^{+}c\text{-}KIT^{+}$ bone marrow stem cells
Chang et al. (2017a)	Low dose of ^{28}Si ions (0.3, 0.6 and 0.9 Gy)	C57Bl/6 mice	Acute (28 days)	Reduced number of hematopoietic stem cells
Wang et al. (2017)	0.05, 0.1, 0.25 and 1.0 Gy whole body ^{16}O (600 MeV/n)	C57BL/6J mice	Chronic (3 months)	Long-term decrease in number of hematopoietic stem cells, primarily via increased intracellular ROS production

LDR low dose rate, *HDR* high dose rate

relatively high-dose exposure (e.g., during an SPE), low dose/low-dose-rate (LDR) radiation must be taken into account when performing research in the context of radiation risks for astronauts. Rizvi et al. (2011) and Luo-Owen et al. (2012) demonstrated that total body LDR γ-radiation can modify the response of leukocytes exposed to simulated SPE protons, thereby increasing cellular tolerance.

In the context of individual radiosensitivity, the potential impact of mouse strains with a genetic background on various immune parameters after acute iron ion exposure was compared. These results showed that the impact of the genetic background on radiation-induced immune aberrations appeared to be minimal, and only included changes in circulating phagocytic populations, erythrocytes, and liver mass (Pecaut and Gridley 2010).

20.4.1.2 Chronic Effects

So far, knowledge about the long-term effects on the immune system after exposure to different types of radiation is limited (Gridley et al. 2002b, 2008, 2013; Pecaut et al. 2003; Gridley and Pecaut 2006, 2016). Summarized in Table 20.1, these studies investigated the potential chronic effects on lymphoid cells 4 months after exposure to a single high dose of photons, protons, iron, silicon, or carbon ion whole-body irradiation (Gridley et al. 2002a, b; Pecaut et al. 2003; Gridley and Pecaut 2006). The first study in this field investigated long-term effects (3 months) after iron and silicon irradiation (Gridley et al. 2002b). In response to Fe ion irradiation animals had significantly increased total lymphocyte and B cell numbers, whereas $CD8^+$ T cell proportions were low, compared with nonirradiated controls. However, whether these changes result in abnormal/compromised immune responses is not clear. Interestingly, these changes could not be observed after exposure to Si ion beams. Long-term changes in mice exposed to Si beams resulted in a lower number of NK. After whole-body exposure to proton irradiation at doses of the order of large SPE, dose-dependent decreases in $CD8^+$ and NK were observed (= depression of peripheral white blood cell count) (Pecaut et al. 2003). In contrast, B and T helper cell numbers in the spleen were significantly elevated following total body irradiation with iron ions (Gridley and Pecaut 2016). Another study showed increases in the number of T cells and a decrease in NK in response to proton and carbon ions (Gridley and Pecaut 2006). Gridley et al. (2008) focused on the impact of a single iron ion 9 months after whole-body irradiation in rats and showed lower numbers of circulating lymphocytes and monocytes, indicating that the intrinsic quality of a particle beam is of importance as well, and can evoke different long-term effects on the immune system. When investigating the priming effect of low-dose radiation on the sensitivity to a subsequent high proton dose, expression of apoptosis and inflammation related genes was still affected on day 56 post-exposure (Gridley et al. 2013). Furthermore, high LET irradiation has been demonstrated to induce a persistent reduction in murine bone marrow hematopoietic stem cells via mechanisms related to oxidative stress, DNA damage and stem cell quiescence (Chang et al. 2015, 2016; Wang et al. 2017).

In summary, several ground-based studies clearly demonstrated acute and long-term changes in the immune system status of whole-body irradiated animals exposed to photon and/or particle radiation. Some of these observed alterations

include changes in the numbers of T- and NK which are important cellular components to suppress infections and kill virus-infected or neoplastic cells. Prolonged deficiency in any of these lymphocyte populations can have serious consequences for astronaut health. In addition this immune cell deficiency can even be exaggerated as a persistent reduction in bone marrow hematopoietic stem cell after radiation exposure has also been observed. However, it still needs to be determined whether these observed immunological aberrations will actually result in impaired immune function.

Another important observation in this field is that results obtained with high-LET are not always similar to those obtained after photon radiation such as X-rays and γ-rays. This clearly demonstrates that caution is important when extrapolating to photon results. In addition, long-term immune changes differ significantly between the various high-LET particles, thereby indicating that the intrinsic quality of the particle beam may be important as well.

Ground-based experiments are increasingly being used and represent a more reproducible alternative to inflight experiments. Although these experiments are a good model to investigate the impact of radiation on the immune system, they most often evaluate the effect of exposure from a single source of radiation. In this context, simultaneous exposure to radiation of different types, thereby better simulating the radiation spectrum to which astronauts are exposed to, might be interesting to decipher whether this might affect a broader range of immunological parameters.

20.4.1.3 Spaceflight-Associated Immune Changes: Examples of Tentative Interaction Between Radiation and Other Space Flight Stressors

To date, it is beyond doubt that spaceflight can induce changes in the immune system. Most, if not all, of these immune alterations have been attributed to both psychological stress and the microgravity (μg) environment. In the context of cosmic ray exposure, it is only after long-term missions that increased levels of cosmic radiation may play a more significant role in this immune dysfunction. However, it is likely that several of the space stressors can interact with one another. These interactions may be additive or synergistic, but can be antagonistic as well, thereby resulting in a final common effect on the immune system that might compromise astronaut resistance to infections and other diseases (see Chap. 3). In the next paragraph an example of a tentative interaction between two spaceflight specific stressors is given.

20.4.1.4 The Combined Effects of μG and Radiation

During spaceflight, μg induces numerous systemic effects including alterations in the musculoskeletal system, cardiovascular system, sensory-motor system, and immune system. With regard to the latter, changes such as decreased number and responsiveness of T lymphocytes, reduced cytotoxic activity of NK, and alterations in cytokine and chemokine activity have been reported (reviewed by Frippiat et al. 2016). However, one might ask whether this reduced gravity can alter the cellular response to ionizing radiation. Experiments performed on living embryonic systems in space showed a synergistic interaction between both space stressors, thereby decreasing cell survival and inducing chromosomal aberrations (Reitz et al. 1989; Horneck 1999).

However, further studies demonstrated that the interplay between both could not be explained by a decreased capacity to repair damaged DNA (Kiefer and Pross 1999; Pross et al. 2000). Therefore, other mechanisms have to be postulated for this synergism. One may hypothesize that immune cells respond to decreased gravity as well as to radiation challenges by activating similar cell signaling pathways (see Chap. 28). In the context of μg, "gravi-sensitive" signal transduction components are present in different cell compartments of immune cells such as on the cell surface (e.g., IL-2 receptor, which can result in a diminished proliferative response of T cells), in the cell cytoplasm (e.g., intracellular signaling pathways), and in the nucleus (e.g., expression of the genes regulating a number of cellular processes including differentiation and proliferation) (Ullrich et al. 2008; Tauber et al. 2015). With regard to intracellular signaling pathways, various kinases such as tyrosine, PKC, and MAPK play important roles in response to μg. Besides μg, it has been shown that radiation also induces changes in the activation of different kinases in immune cells (Varadkar et al. 2003; Varadkar and Krishna 2004; Mitra et al. 2007). Tyrosine kinase, PKC, and MAPK activity increase with increasing dose after irradiation in lymphocytes in vivo. However, in contrast, MAPK activity decreased with an increasing dose in ex vivo irradiated lymphocytes. The effect might become even more complicated when comparing photon data with results obtained after high-LET radiation (Narang et al. 2009). In this context, the hindlimb unloading mice model was used to investigate the combined impact of microgravity and proton radiation on several immune parameters (Sanzari et al. 2013a). Results demonstrated that exposure to combined stressors decreased leukocyte numbers and function. In addition, whole-body proton or γ-ray radiation in a ferret model resulted in a significant reduction in circulating white blood cells (Sanzari et al. 2013b). The importance of the radiation-counterpart in cellular changes in response to physical space stressors such as μg is still not clear, and more research is definitely needed to gain additional insight into this complex matter. Moreover, the differences between the response of a single cell and the one of the whole animal must be considered as well. Once again, several studies underscore that in vitro data cannot be extrapolated indiscriminately to in vivo conditions.

Besides similar cell signaling pathways, μg and radiation can indirectly affect inflammation by influencing components that are essential in mediating the inflammatory response. A crucial step in inflammation is the trafficking of leukocytes from the blood stream into the tissue. This leukocyte–endothelial adhesion involves dynamic interactions between leukocytes and endothelial cells, and is mediated by several families of cell adhesion molecules (CAMs). CAMs that are expressed on the surface of vascular endothelial cells include the selectin family (E-selectin and P-selectin) and the Ig superfamily (e.g., ICAM-1). These CAMs interact with leukocytes to initiate cell extravasation and migration. The impact of both radiation and μg on the induction of cell adhesion molecules on endothelial cells has been studied (Zhang et al. 2008; Hallahan et al. 1996; Romanov et al. 2001). Both E-selectin and ICAM-1 are increased after X-irradiation, whereas VCAM and ICAM-1 also increase under hypogravity conditions. These experiments indicate that leukocyte adhesion (and consequently inflammation) might be promoted both by radiation and μg. Additional experiments are needed to gain more insight into the combined effects of both physical spaceflight stressors.

To gain more fundamental insight into the potential interplay between these two physical space stressors in immune cells, Earth-based experiments that simulate space conditions can be useful. In this light, μg-simulating devices such as rotating-wall bioreactors (clinostat) or the Random Positioning Machine (RPM) are currently used to perform in vitro experiments under hypogravity conditions. Ideally, cells should be exposed to μg and different radiation qualities at the same time. However, only a limited number of studies have yet been performed in which cells are simultaneously exposed to both these physical space stressors (Beck et al. 2014; Pani et al. 2016; Fernandez-Gonzalo et al. 2017). In a recent study simulated μg was found to increase particle radiation-induced apoptosis in B lymphoblast cells (Dang et al. 2014). The combined impact of space radiation and microgravity on DNA integrity is also of a major concern for their impact on astronaut health. Unfortunately, results from either ground-based or inflight studies are ambiguous and require validation in the true space environment (reviewed in Moreno-Villanueva et al. 2017).

20.5 Conclusion

It has become clear that several aspects of the spaceflight environment lead to acute and long-term changes in the immune system. Therefore, to reduce the health risks for astronauts, it is important to better understand the mechanisms responsible for the changes observed in the immune parameters (Dang et al. 2014). Ideally, to discriminate between different factors and their impact on the immune system, data should be obtained e.g., from the same cohort of animals that are exposed simultaneously to different spaceflight stressors. However, various experimental setups (space vs. Earth-based models) are concomitant with different uncontrolled stressors e.g., shipping animals, housing. These conditions may elicit immune system alterations that always make direct comparison problematic. In addition, to study the effect of space radiation on ground-based models, radiation should be delivered at a very low dose rate for extended periods in order to be as relevant as possible to spaceflight. Unfortunately, these conditions are not easy to achieve on Earth due to facility limitations and high demand for beam time. Currently, researchers are starting to elucidate the different effects of cosmic radiation on the immune system. Nevertheless, several important questions remain: Which pathways are responsible for repairing radiation-induced changes? How capable is the irradiated immune system of responding to an immune challenge? How are other metabolic cofactors (see Chaps. 5, 16, 28, 32 and 33), hormones and transmitters affecting this process?

In conclusion, gaining more insight into changes in immune responses after radiation exposure is needed to more accurately predict health risks associated with long-duration spaceflight. This knowledge might not only be relevant to extended ISS missions (more than 1 year) and to future exploration and colonization missions in space but also of significant importance to life on Earth and to patient care, e.g., during cancer radiation therapy, when metabolic effects, the immune system, and the radiation effects are interacting closely on the therapeutic goals of curing and limiting cancer growth, respectively.

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