CHAPTER 18.

Ionizing radiation

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Introduction

The carcinogenic risk associated with exposure to ionizing radiation has been evaluated previously in the *IARC Monographs*: radon in Volume 43 (IARC, 1988), X-rays, γ-rays, and neutrons in Volume 75 (IARC, 2000), and some internally deposited radionuclides in Volume 78 (IARC, 2001). An updated review on all carcinogenic types of radiation, also including solar and ultraviolet radiation, was published as Volume 100D (IARC, 2012).

For certain types of ionizing radiation, the evidence of carcinogenicity in humans is clear, but in other cases the data are few or non-existent. However, the overall conclusion reached in Volume 100D of the *IARC Monographs* was that all types of ionizing radiation should be considered as *carcinogenic to humans* (Group 1). The rationale for this was that all types of ionizing radiation transfer their energy to biological material in clusters of ionization and excitation events, primarily through a mechanism mediated by free electrons. In addition, DNA damage is a common biological outcome of exposure to all ionizing radiation; energy deposition results in a wide variety of molecular damage, such as base damage and single- and double-strand breaks, some of which may be clustered to form complex lesions. Subsequent processing of these lesions may lead to chromosomal aberrations and mutations. The generality of induction of and response to radiation damage is discussed for all types of ionizing radiation in greater depth later in this chapter.

In addition to the above-mentioned reviews in the *IARC Monographs*, there have been many major national and international reviews of the literature on radiation, as well as radiation risk estimates. These include the publications of the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR, 2000, 2008, 2010) and the reports from the United States National Research Council (NRC, 1999, 2006), the United States National Council on Radiation Protection and Measurements (NCRP, 1993, 1999, 2001, 2005), and the International Commission on Radiological Protection (ICRP, 2003, 2007; Valentin, 2005).

Two major issues faced when studying radiation carcinogenesis is that radiation-induced cancers are indistinguishable from those that occur naturally, and that risk estimates rely on epidemiological data for which statistical significance is reached only at high doses. The existing data

are not powerful enough to enable comment on the shape of the dose–response curve and the associated risks at doses associated with typical human exposures. Many of the in vitro and in vivo studies investigating the mechanisms underlying cancer risk from exposure to ionizing radiation have concentrated on low-dose exposures, typically of 0.1 Gy (= 0.1 J/kg) and below.

The nature of ionizing radiation

Ionizing radiation is a term used for any radiation that is capable of ionizing (i.e. removing electrons from) atoms or molecules of the medium being traversed. Ionizing radiations are usually classified as either electromagnetic or particulate.

X-rays and γ-rays are both electromagnetic radiations. They do not differ in nature, but their designation reflects their origin; X-rays are produced by extranuclear processes and γ-rays by intranuclear processes. These types of radiation are often classified as indirectly ionizing, because the chemical and biological damage is dominated by the charged particles (mainly electrons) produced as a result of interactions within the medium. Neutrons are also classified as indirectly ionizing. They deposit energy and cause damage through recoil protons, α-particles, and nuclear fragments that result from neutron interactions.

Particulate radiations include electrons, positrons, protons, neutrons, α-particles, and other ions. With the exception of neutrons, all of these particles are charged and are classified as directly ionizing (if they have sufficient energy) because they directly ionize the medium they are traversing, producing chemical and biological damage.

The human body can be irradiated either from external sources or through internal exposure as a result of ingestion, inhalation, dermal absorption, or injection of radionuclides. The effects of radiation are directly related to the dose received by individual cells or organs, and by the radiation quality. Therefore, these effects can vary significantly, depending on the resulting dose distribution or distribution of radionuclides throughout the body. The dose distribution may vary from being essentially uniform after whole-body exposure to being highly heterogeneous in the case of non-uniform distribution of internal radionuclides that emit short-range α-particles or β-particles. Medium- to high-energy X-rays, γ-rays, and neutrons are typically highly penetrating and will traverse the body, whereas α-particles and β-particles typically have a short range (for α-particles, less than 100 μm, and for β-particles, from less than 1 μm to several millimetres). In general, the penetration range of charged particles can vary significantly depending on their energy and the type of particle.

Genotoxicity and the importance of radiation track structure

Ionizing radiation interacts within cells and tissues by depositing energy in highly structured tracks of ionization and excitation events that are stochastic in nature. On average, these events are relatively sparsely distributed for high-energy X-rays and γ-rays, which deposit energy via electrons with relatively low linear energy transfer (LET), where LET corresponds to the energy loss per unit track length. For example, cobalt-60 γ-rays have an LET of about 0.25 keV/μm (where 1 eV = 1.602×10^{-19} J). The ionization and excitation events are much closer together for low-energy charged particles, which are considered to be high-LET radiation. For example, an α-particle with an energy of 2 MeV has an LET of about 180 keV/μm.

All types of ionizing radiation induce a wide range of damage and effects, including DNA damage, chromosomal aberrations, mutations, cell transformation, and cell killing (NRC, 1999, 2006; UNSCEAR, 2000; ICRP, 2003, 2007). The efficiency in causing damage and subsequent biological effects is related not only to the amount of energy transferred per unit mass (the absorbed dose, expressed in units of gray, where 1 Gy = 1 J/kg) and the rate of energy transfer (the dose rate) but also to the microdistribution of energy, which is determined by the type of radiation and the associated track structure.

The relative biological effectiveness is defined as the inverse ratio of the dose required to produce a given biological effect to the dose required by a reference radiation to produce the same effect. The relative biological effectiveness typically increases with the LET value of the radiation, and it reaches a peak at about 100–200 keV/μm for a range of biological end-points. Whereas the absorbed dose unadjusted for attenuation by the body is expressed in units of gray (Gy), the weighted organ dose (the equivalent or effective dose) is expressed in sieverts (Sv) or millisieverts (mSv), which are also the units in which radiation exposure limits are given.

For many biological effects, nuclear DNA is a critical target of ionizing radiation (UNSCEAR, 1993).

Ionizing radiation can cause DNA damage either by direct ionization of the constituent atoms in the DNA or indirectly by reactions with free radicals produced by interactions with water molecules (most notably the hydroxyl radical, which can induce DNA strand breakage or base damage), or by a combination of direct and indirect effects. In the cell, hydroxyl radicals will typically only diffuse a few nanometres (< 6 nm), thus preserving the spatial structure of the radiation tracks.

Ionizing radiation can thus induce a range of different types of molecular damage in DNA, such as base damage (including apurinic/apyrimidinic sites), strand breaks, DNA–protein cross-links, and combinations of these within a few base pairs of each other. Examples are double-strand breaks (DSBs) and non-DSB clusters (two or more base damages and/or strand breaks within about 10 base pairs, but not resulting in a DSB). The pattern and frequency of these lesions are determined by the clustering of ionization and excitation events on the nanometre scale, which ultimately produces clustering of damage over the dimensions of the DNA helix and larger.

Theoretical analyses show that clustered DNA damage that is more complex than a single-strand break can occur at biologically relevant frequencies with all types of ionizing radiation (Goodhead 1987, 1994; Brenner and Ward, 1992). Such clustered damage in DNA is produced mainly within a single track, with a probability that increases with increasing ionization density (LET). Calculations show that a dose of greater than 10 000 Gy is required for a second track to have a reasonable chance of contributing to the local complexity of DNA damage (Nikjoo and Goodhead, 1991). These more complex forms of damage are essentially unique to ionizing radiation and are not seen spontaneously or with other DNA-damaging agents.

The number of DSBs induced in DNA is approximately 20–40 per cell per gray for low-LET X-rays and γ-rays, and a similar number is observed for α-particles in standard assays. However, the percentage of complex DSBs (with extra strand breaks and/or associated base damage within 10 base pairs) is about 30–50% for electrons (similar to the percentage produced by X-rays and γ-rays) based on Monte Carlo calculations, and this percentage increases with increasing ionization density (LET) of the radiation, to about 90% for 0.3 MeV protons and about 96% for high-LET 2 MeV α-particles (Nikjoo et al., 1991; Goodhead, 2006). In addition to this increase in the frequency of complex DSBs with increasing LET, there is also an increase in the overall complexity of the damage spectrum produced. Clustering of damage is not confined to DNA but can occur in all biomolecules.

Complex non-DSB damage has been shown to be a significant component of the lesions induced by radiation, occurring 4–8 times as frequently as direct DSB formation. Whereas isolated lesions (e.g. base damage or single-strand breaks) are repaired quickly and generally with high fidelity, for non-DSB clusters the rate of repair is typically impaired by the presence of additional lesions within the cluster. The delay and the ultimate consequence depend on the types of lesion and their relative positions. The longer lifetime of these clusters also results in an increased probability that the damage will be present during DNA replication, which ultimately leads to stalled replication forks that may give rise to DSBs or mutations. Therefore, non-DSB clusters are potentially highly mutagenic and are likely to play a more important role at low doses of low-LET radiation; because non-DSB damage is produced at a higher frequency than DSBs at these lower doses, more cells will contain non-DSB clustered damage compared with DSBs (reviewed by Eccles et al., 2011).

DNA is wrapped around histone proteins to form nucleosomes, which are organized into 30 nm chromatin fibres that are typically arranged in loops. As a result of the sequence of ionization events along individual radiation tracks, especially in the case of densely ionizing high-LET particles such as α-particles, these tracks can lead to multiple correlated DSBs over short sections of DNA arranged in these structures. Conventional DSB assays (e.g. pulsed-field gel electrophoresis and γH2AX assays) are not able to resolve these additional DSBs and therefore typically underestimate the absolute yields (Friedland et al., 2008). However, experimental and theoretical data have demonstrated the existence of these short fragments for these particles, showing a significant deviation from a random distribution (Rydberg et al., 1998; Friedland et al., 2008). Whereas viable radiation-induced mutations are rarely associated with visible chromosomal exchanges observed by use of fluorescence in situ hybridization (FISH), molecular analysis of these sites shows that high-LET particles can induce gene mutations of greater complexity than simple deletions or point mutations,

consistent with the correlation of damage along the radiation track (Singleton et al., 2002).

The pattern of energy deposition is also important on the cellular or nuclear scale (over distances in the micrometre range). When an α-particle traverses a cell, the dose distribution of the energy deposited is highly heterogeneous across the cell, with a greater probability of correlated damage and DSBs within a single chromosome or adjacent chromosomes. Studies with multiplex FISH (mFISH) have shown that commonly four and up to a maximum of eight different chromosomes may be involved in rearrangements after the nuclear traversal of a human peripheral blood lymphocyte by an α-particle (Anderson et al., 2002, 2006); a similar response was seen in human CD34-positive haematopoietic stem cells (Anderson et al., 2007). This is in contrast to the production of mainly simple rearrangements between two chromosomes observed for low doses of low-LET X-rays. Complex rearrangements have been observed in radiation workers with a large body burden of α-particle-emitting plutonium (Anderson et al., 2005). Stable intrachromosomal rearrangements were also found in lymphocytes of former nuclear weapons workers who were exposed to plutonium (Hande et al., 2003), although not consistently for all cases of in vivo high-LET exposures (reviewed by Hada et al., 2011).

Other potential mechanisms for modifying cancer risk from radiation exposure

Ionizing radiation also produces a whole range of effects with potential implications for carcinogenesis (UNSCEAR, 2012). For example, the patterns of gene and protein expression are critical in determining cellular function and response. Ionizing radiation has been shown to modulate protein phosphorylation (Yang et al., 2006) and gene expression in a dose- and dose rate-dependent manner (Ding et al., 2005; Fachin et al., 2009). Epigenetic changes can also result in modifications in gene expression, and ionizing radiation produces DNA methylation (Kovalchuk et al., 2004), histone methylation (Pogribny et al., 2005), and chromatin modification (Kim et al., 2009; Luijsterburg et al., 2009; Nagarajan et al., 2009; Pandita and Richardson, 2009), along with modulation of microRNA expression (Templin et al., 2011).

Intercellular communication and the bystander effect

Within tissues of multicellular organisms, cells do not act in isolation; intercellular signalling is vital for maintaining the multicellular organization of the tissue and for normal functioning of the constituent cells (Park et al., 2003). These cellular interactions and the microenvironment are also important in influencing the growth and development of cancer cells.

Radiation can initiate stress-inducible signals, which can perturb this signalling and affect not only irradiated cells but also non-irradiated cells. Many studies have shown a wide range of responses in non-irradiated “bystander” cells, including induction of DNA damage, chromosomal aberrations, delayed genomic instability, mutations, oncogenic transformation, and cell killing (Morgan, 2003a, b).

Signalling has been demonstrated to occur via intercellular gap junctions and media-borne factors. Several signalling pathways have been implicated, and these typically result in the modulation of reactive oxygen species and reactive nitrogen species as a result of signalling through molecules such as nitric oxide, peroxidase, and the cytokine transforming growth factor beta (TGF-β) and other inflammatory markers (Burdak-Rothkamm et al., 2007; Han et al., 2007; Portess et al., 2007; Coates et al., 2008). Radiation is capable of perturbing intercellular signalling down to very low doses (on the order of 2 mGy for γ-rays and 0.3 mGy for α-particles), which are directly relevant to typical human exposures (Portess et al., 2007).

Reactive oxygen species are expected to be important in initiating and maintaining the inflammatory process (Barcellos-Hoff et al., 2005; Mantovani et al., 2008). In addition, radiation can lead to a modification in the immune response; at high whole-body doses, this results in immunosuppression, whereas at low doses and dose rates, this can lead to either suppression or stimulation of the immune response (UNSCEAR, 2008).

There is increasing evidence to suggest that radiation-induced perturbation of intercellular signalling and of the microenvironment may play a role in modulating cancer risk. However, the relative importance of these effects to cancer induction after human exposure is unclear, and it is not generally known whether the dominant consequences of these effects are beneficial or detrimental.

Radiation-induced genomic instability

In addition to being capable of producing mutations directly in the irradiated cell, ionizing radiation can also lead to genomic instability, resulting in the cell and its progeny having a

reduced ability to replicate the genotype faithfully and therefore showing a permanently increased rate of acquisition of alterations in the genome (Kadhim et al., 1992, 1994; Little, 2000; Morgan, 2003a, b; Barcellos-Hoff et al., 2005). This may lead to an increased probability that the cell and its progeny will undergo the various genetic and epigenetic changes necessary in multistage carcinogenesis. It is thus possible that the instability phenotype plays a major role in radiation-induced cancer, especially because genomic instability is a well-recognized feature in many tumours (Bielas et al., 2006).

Radiation-induced genomic instability typically becomes manifest several cell generations after irradiation and can be detected via a range of end-points, including chromosomal and chromatid aberrations, micronuclei, changes in ploidy, gene mutations and amplifications, and mini- and microsatellite instabilities. The frequency of genomic instability was observed to be too high to be explained by the induction of a mutator genotype. Several mechanisms have been proposed, including dysfunctional telomeres (Goytisolo et al., 2000; McIlrath et al., 2001; Williams et al., 2009) and inflammatory (free radical) responses (Barcellos-Hoff et al., 2005; Natarajan et al., 2007; Coates et al., 2008; Lorimore et al., 2008), along with DNA damage and response, for example long-term response to directly induced DNA damage and reduced ability to handle subsequent damage or cell division (Snyder and Morgan, 2005; Maxwell et al., 2008; Toyokuni et al., 2009).

Epigenetic modification has been implicated as playing an important role in the promotion and maintenance of transmissible instability (Kadhim et al., 2004; Barber et al., 2009; Filkowski et al., 2010; Rugo et al., 2011). Genomic instability has also been observed in non-irradiated cells that were in the neighbourhood of irradiated cells, demonstrating the importance of intercellular signalling in initiating this instability response (Lorimore et al., 1998). Although genomic instability is a plausible mechanism for cancer induction, its precise role, if any, remains to be proven.

The importance of dose distribution with respect to tumour sites

The passage of ionizing radiation through the body results in the deposition of energy within the irradiated tissue volume. External irradiation with photons is typically highly penetrating and will often result in all cells and tissues in the radiation field being irradiated. In contrast, emission from internalized radionuclides typically occurs from specified locations occupied by the emitting nuclide source. This will often lead to a non-uniform dose distribution in the body, especially if the emitted radiation has only a short range (e.g. for α-particles and β-particles).

The biological effects of deposited radionuclides in the body depend on the amount and activity of the radionuclide deposited, the type of radiation emitted, the physical half-life of the isotope, the mode of entry, the organs and tissues in which the radionuclide is retained, the duration of retention, and the rate of excretion from the body. The chemical characteristics of the radionuclide (or the compound in which it is incorporated) along with its physical properties (such as size and shape) determine its behaviour, including absorption and transport within the body, elimination route and rate, and uptake and retention in organs. In some cases, for example for radioactive heavy metals, the health effects and carcinogenic potential may also be related to, and potentially dominated by, the chemical properties rather than the radiation emitted.

In some cases, a radionuclide may spread throughout the whole body; in other cases, it will concentrate in specific organs or locations within the body. If the emitted radiation has a short range (e.g. for α-particles and β-particles), this can lead to significant heterogeneity in the resulting dose distribution, with certain organs receiving a significant dose while for others the radiation dose is minimal. Biokinetic models (ICRP, 1989, 1993, 1994, 1995a, b, c, 2001) are used to estimate the spatial and temporal uptake of radionuclides as well as their subsequent distribution and ultimate excretion. Dosimetry models (Eckerman, 1994) are then used to calculate the resulting dose distribution over the body and organs, based on the physical characteristics of the radionuclides.

The ability of internal radionuclides to produce a biological response and ultimately cancer in various organs is related to the biodistribution of these emitters within the body (which will depend on the chemical and physical properties of the particles and the route of entry). Examples are iodine-131, which concentrates largely in the thyroid, and strontium-90 and plutonium-239, which are deposited mainly in the bone. The same radionuclide may result in a different range of tumours if it is delivered in such a way as to produce a different biodistribution pattern. In addition, there may be

confounding factors, such as chemical toxicity, that may contribute to or even dominate the cancer response.

Human exposures to ionizing radiation typically occur at low dose and low dose rate

The effects of radiation are most notable at the high doses (above a few gray) that are usually associated with significant radiation accidents and radiotherapy treatments, and that are observed in atomic bomb survivors. These effects include erythema, oedema, ulceration, necrosis, fibrosis, telangiectasia, inflammation, immunosuppression (through bone marrow depletion), and pneumonitis (HPA, 2007; Stewart et al., 2012). Although there is clear evidence from epidemiological data for significant cancer risks associated with high-dose exposures, the existing data for the low-dose range are limited, such that below approximately 0.1 Gy – doses associated with typical human exposures – the data are not powerful enough to enable comment on the shape of the dose–response curve and the associated risks.

For an average annual environmental background exposure of approximately 0.001 Gy for low-LET radiation, individual cells may receive no track at all or only single tracks, well isolated in time. The nucleus of each cell in a tissue will experience on average one electron track per year from background radiation, assuming a spherical nucleus of 8 μm diameter. Exposure from diagnostic procedures can vary from 0.005 Gy for dental exposures to approximately 0.01 Gy for typical exposures from computed tomography (CT), or occasionally up to 0.1 Gy for some procedures over a short period (Brenner and Hall, 2007, 2012). Individuals are also exposed to high-LET α-particles as a result of naturally occurring radon gas. With typical residential levels of radon gas, the cell nuclei in the bronchial epithelium of the inhabitants are estimated to receive on average between 0.15 and 0.6 α-particle traversals per year (NRC, 1999). However, for those cell nuclei that are occasionally traversed, the dose to the traversed nucleus is significant (on the order of 0.1–0.5 Gy).

For the high doses associated with radiotherapy or significant accidental exposures, it is expected that classical direct effects of radiation are likely to dominate the response, as a result of radiation-induced DNA damage. However, at the very low doses associated with typical human exposures, where only a small fraction of cells have a DNA DSB, it is possible that other mechanisms for cancer induction or modulation of cancer incidence (such as radiation-induced genomic instability or effects associated with perturbation of intercellular signalling) may play a more important role.

Generality of response after exposure to different types of ionizing radiation

All types of ionizing radiation ultimately lead to clusters of ionization and excitation events, along with the production of electrons, through which energy is deposited. Interaction of X-rays and γ-rays with tissues generates fast electrons that interact with atoms or nuclei, producing additional electrons as they slow down and deposit energy. Charged particles such as α-particles and protons also interact with tissue, producing primary ionization and excitation events, and also a trail of secondary electrons along the path of the primary particle. Uncharged neutrons also interact with tissue and deposit energy via lower-energy charged particles such as protons, deuterons, α-particles, and heavy-ion recoils, ultimately leading to energy deposition via secondary electrons.

Therefore, energy deposition by way of electrons is common to all ionizing radiation. Indeed, isolated track ends of low-energy electrons (produced by all ionizing radiations) have been shown not only to be capable of affecting a wide range of genotoxic end-points but to do so with a high efficiency per unit dose (Goodhead and Nikjoo, 1990; Hill et al., 2001; Hill, 2004; HPA, 2007). Because of their increased local ionization density, these track ends of low-energy (0.1–5.0 keV) electrons have been proposed as the biologically critical component of low-LET radiation, rather than the isolated ionization and excitation events along the path of fast electrons (Goodhead and Nikjoo, 1990; Botchway et al., 1997).

In addition, α-particles emitted by radionuclides, irrespective of their source, produce the same pattern of secondary ionizations and the same pattern of localized damage to biological molecules, including DNA, and ultimately the same biological effects. Therefore, due to the communality in their interactions within the body and in the biological responses induced, all types of ionizing radiation have been classified by IARC as *carcinogenic to humans* (Group 1), even though in some cases direct evidence is weak or non-existent, with the risk of cancer depending on dose and radiation quality. Although internal radionuclides can vary significantly in the range of cancers and cancer sites observed, the cancer response is ultimately dominated by the biodistribution of these emitters within the body.

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