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Targeted and non-targeted effects of ionizing radiation

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ABSTRACT

For a long time it was generally accepted that effects of ionizing radiation such as cell death, chromosomal aberrations, DNA damage, mutagenesis, and carcinogenesis result from direct ionization of cell structures, particularly DNA, or from indirect damage through reactive oxygen species produced by radiolysis of water, and these biological effects were attributed to irreparable or misrepaired DNA damage in cells directly hit by radiation. Using linear non-threshold model (LNT), possible risks from exposure to low dose ionizing radiation (below 100 mSv) are estimated by extrapolating from data obtained after exposure to higher doses of radiation. This model has been challenged by numerous observations, in which cells that were not directly traversed by the ionizing radiation exhibited responses similar to those of the directly irradiated cells. Therefore, it is nowadays accepted that the detrimental effects of ionizing radiation are not restricted only in the irradiated cells, but also to non-irradiated bystander or even distant cells manifesting various biological effects.

1. Introduction

All living organisms are daily exposed to radiation. In addition to diagnostic and therapeutic medical exposures, we are exposed chronically to background radiation from cosmic rays, radioactive waste, radon decay, nuclear tests, and accidents. The contribution to dose from naturally occurring radionuclides is much larger. In recent years, it has become evident that inhalation of the short-lived decay products of ^{222}Rn is one of the more important sources of natural exposure. The diagnostic applications of ionizing radiation (IR) in medicine include the use of X-rays and radioisotopes in diagnostic imaging. Natural radiation and radioactivity in the environment, along with diagnostic medical exposure, make up the very largest part of the accumulated annual dose to human beings who are not occupationally exposed to ionizing radiation from other sources during their daily work activity.

Despite the vast benefits derived from various medical applications, radiation can be harmful and is well established as a carcinogen to living organisms (Little, 2003). The adverse effects of radiation are grouped into two categories: deterministic effects and stocohahstic effects. Deterministic effects are based on cell killing and characterized by a threshold dose. Below the threshold dose there is no clinical effect. Stochastic effects are associated with long-term, low-level (chronic)

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exposure to radiation. With exposures above the threshold dose the severity of the injury increases with dose. The probabilities of experiencing detrimental effects from exposure to low-dose radiation are estimated by extrapolating from data obtained after exposure to high-dose radiation, using a linear model without a threshold (the LNT model). Using this model, possible risks from exposure to low dose ionizing radiation (below 100 mSv) are estimated by extrapolating from data obtained after exposure to higher doses of radiation (Matsumoto, Tomita, Otsuka &, Hatashita, 2009). The LNT model has been widely used to establish international rules and standards of radiation protection (ICRP). It follows the notion that increases in the physical energy deposition of IR linearly increases the carcinogenic risk with increasing dose.

The conventional model, based on direct targeted effects of radiation, has developed in radiobiology and it has been extended to apply to radiation health risks and to guide radiation protection practice. The radiation effects have been explained using target theory. According to this, deleterious effects of IR, such as mutation and carcinogenesis, are attributed to damage to a cellular target, usually identified as nuclear DNA *via* direct absorption of radiation energy, the consequences of which are expressed in the surviving irradiated cells (UNSCEAR 1993).

Although this model is applied carefully and conservatively, there is room for concern about the validity of the low dose exposure risks obtained in this way because a number of findings have accumulated which cannot be explained by the classical "target theory" of radiation biology. Specific cellular responses observed in response to low dose and/or low dose-rate radiation have been described as the radioadaptive response, the radiation-induced bystander response, low-dose hyper-radiosensitivity, and genomic instability. All of these phenomena are considered to be responses to radiation which involve non-targeted molecules or molecules which have not interacted directly with radiation (Waldren 2004). The propagation of damaging effects from irradiated to non-irradiated bystander cells would, presumably, result in supra-linear dose–response relationships. In contrast, the expression of adaptive responses that mitigate the initial damaging effects induced by radiation would suggest an infra-linear dose–response relationship or the existence of a threshold dose, below which there would be no risk.

2. Conventional interactions of ionizing radiation with biological matter

2.1. *Interaction types*

Ionizing radiation is energetic and penetrating. Many of its chemical effects in biological matter are due to the geometry of the initial physical energy deposition events, referred to as the track structure. Ionizing radiation exists in either particulate or electromagnetic types. The particulate radiation interacts with the biological tissue either by ionization or excitation. The ionizations and excitations that it produced tend to be localized, along the tracks of individual charged particles. Whereas the photon can penetrate matter without interacting, it can be completely absorbed by depositing its energy, or it can be scattered (deflected) from its original direction and deposit part of its energy as follows:

1. Photoelectric interaction: a photon transfers all its energy to an electron located in one of the atomic shells, usually the outer shell. The electron is ejected from the atom and begins to pass through surrounding matter.
2. Compton scattering: only a portion of the photon energy is absorbed and a photon is scattered with reduced energy. The photon that is produced leaves in a different direction than that of the original photon with different energy.
3. Pair production: the photon interacts with the nucleus in such a way that its energy is converted to matter producing a pair of particles, an electron and a positively charged positron. This only occurs with photons with energies in excess of 1.02 MeV. (Hall & Giaccia, 2011)

3. Direct and indirect effect

Radiation damage to the cell can be caused by the direct or indirect action of radiation on the DNA molecules. In the direct action, the radiation hits the DNA molecule directly, disrupting the molecular structure. Such structural change leads to cell damage or even cell death. Damaged cells that survive may later induce carcinogenesis or other abnormalities. This process becomes predominant with high-LET radiations such as α-particles and neutrons, and high radiation doses. In the indirect action, the radiation hits the water molecules, the major constituent of the cell, and other organic molecules in the cell, whereby free radicals such as hydroxyl (HO•) and alkoxy (RO2•) are produced.

Free radicals are characterized by an unpaired electron in the structure, which is very reactive, and therefore reacts with DNA molecules to cause a molecular structural damage. Hydrogen peroxide, H_2O_2, is also toxic to the DNA molecule. The result of indirect action of radiation on DNA molecules is the impairment of function or death of the cell. The number of free radicals produced by ionizing radiation depends on the total dose. It has been found that the majority of radiation-induced damage results from the indirect action mechanism because water constitutes nearly 70% of the composition of the cell (Saha, 2013).

In addition to the damages caused by water radiolysis products (i.e. the indirect effect), cellular damage may also involve reactive nitrogen species (RNS) and other species (Wardman, 2009), and can occur also as a result of ionization of atoms on constitutive key molecules (e.g. DNA). The ultimate result, of direct and indirect effects, is the development of biological and physiological alterations that may manifest themselves seconds or decades later. Genetic and epigenetic changes may be involved in the evolution of these alterations (Koturbash, 2008).(Fig. 1)

X-ray and γ-ray photons deposit energy in tissue in a highly dispersed manner, characterized as low "linear energy transfer" (LET). IR can be either low LET (sparsely ionizing) or high LET (densely ionizing). Photons are low LET radiation, displaying a very broad energy distribution in tissue, and the peak dose is located relatively close to the surface. Heavy