Published in final edited form as:

Health Phys. 2016 March ; 110(3): 283–286. doi:10.1097/HP.0000000000000467.

PHYSICAL CONSIDERATIONS FOR UNDERSTANDING RESPONSES OF BIOLOGICAL SYSTEMS TO LOW DOSES OF IONIZING RADIATION: NUCLEOSOME CLUTCHES CONSTITUTE A HETEROGENEOUS DISTRIBUTION OF TARGET VOLUMES

Roger W. Howell*

*Division of Radiation Research, Department of Radiology, New Jersey Medical School Cancer Center, Rutgers, The State University of New Jersey, Newark, NJ 07101

Abstract

Humans are exposed to low doses of ionizing radiation that arise from a variety of sources. The response of biological systems to low doses of ionizing radiation depend on many factors. Some of the physical factors include distribution of the radiation sources, radiation track structure, structure and dimensions of the biological targets, temporal patterns of radiation exposure(s), absorbed dose rate and total absorbed dose. Recent discoveries suggest that assumptions regarding the structure of an important biological target, namely chromatin, may not be correct. It is now believed that chromatin fiber consists of heterogeneous groups of nucleosomes called clutches, and the distribution of clutch sizes differs between somatic cells and stem cells. This shift in paradigm may have implications for radiation target theory and its explanation of observations of clustered DNA damage.

Keywords

DNA; International Commission on Radiation Units and Measurements; radiation; ionizing; x rays

INTRODUCTION

Humans are exposed to a wide variety of sources of ionizing radiation. In the U.S., these include exposure from ubiquitous background radiation, consumer products, miscellaneous radiation sources (industrial, security, medical, educational, and research), exposure of patients from medical procedures, and occupational exposures received in work environments (NCRP 2009). There are numerous factors that affect the response of biological systems to ionizing radiation. These include, but are not limited to, the distribution of the radiation sources, radiation track structure (Goodhead 1994), structure and dimensions of the biological targets (Nikjoo and Girard 2012), temporal patterns of radiation exposure(s), and absorbed dose rate and total absorbed dose (ICRU 2011). This

For correspondence contact: Roger W. Howell, Ph.D., Department of Radiology, Rutgers New Jersey Medical School, Cancer Center, F1028, 205 South Orange Avenue, Newark, NJ 07101-1709, or rhowell@rutgers.edu.

The author declares no conflicts of interest.

forum article will review some of the physical considerations that affect biological responses to ionizing radiation and point out some recent findings in the literature that may have an impact on the understanding of responses to low doses.

Radiation exposures received over a lifetime

Human exposures to low doses of ionizing radiation are commonplace. The average annual effective dose from ubiquitous background radiation received chronically by the U.S. population is 3 mSv y^{-1} (NCRP 1987). The average annual effective dose received by U.S. citizens from all sources is 6.2 mSv y^{-1} , and a large fraction of it comes from medical exposures (NCRP 2009). The current U.S. population now receives radiation doses from diagnostic medical exposures that are about six times higher than the average received two decades ago (NCRP 2009). Much of this increase can be attributed to CT and nuclear medicine procedures. A typical patient may receive 10 mSv acutely from a high-speed whole-body CT, and these imaging procedures are expected to be received periodically throughout the patient's life (NCRP 2009). An average occupational exposure of 1.7 mSv y^{-1} is received by nuclear power employees that receive measureable doses (NUREG 2003). A more highly exposed radiation worker may receive about 10 mSv y^{-1} , which is still well within the U.S. federal regulatory limit (50 mSv y^{-1}). Jet aircraft flight crews generally fly at an altitude of $12,000 \text{ m}$, which leads to an effective dose rate of $7 \mu\text{Sv h}^{-1}$ (NCRP 1995). Assuming an average air time of $1,000 \text{ h y}^{-1}$, flight crews can receive occupational exposures of about 7 mSv y^{-1} . Fig. 1 plots cumulative effective dose over the lifetimes of different groups of citizens within the U.S. population and compares them to exposures received by the population living in the high background area of Kerala, India, where the natural background exposure is about 30 mSv y^{-1} . It is apparent that the human population receives a wide range of low-dose exposures worldwide.

Non-uniform exposures to ionizing radiation

The low-dose exposures to ionizing radiation that persons receive result in nonuniform deposition of energy (Fig. 2). Many diagnostic x-ray procedures involve partial-body irradiation (e.g., projection radiography, CT). Energy depositions can also be nonuniform at the organ, suborgan, multicellular, and cellular levels (Howell 1994). Ultimately this extends even to spatial dimensions at the molecular level. It is widely accepted that energy depositions at the cellular and molecular levels are the events that ultimately drive the capacity of ionizing radiation to cause biological damage. Depending on the radiation type and energy, the energy density can vary by more than two orders of magnitude (Fig. 2c). These differences are primarily responsible for the differences in damage caused by different types of ionizing radiation (ICRU 2011).

Biological targets and target volumes

As discussed in detail in ICRU Report 86 (ICRU 2011), the events that produce biological damage are the ensemble of energy depositions that lie within the target (Fig. 3). Defining the target volume is often a topic of considerable debate. The human body is a complex biological system made up of a variety of fluids, cells, tissues, and organs. While the system may respond as a whole, the initial events that stimulate responses in organs and tissues are initiated at the cellular and molecular levels. Accordingly, the cell or cell nucleus is often

taken as a target that is relevant to biological responses within the irradiated cell as well as bystander cells (ICRU 2011), although there is ample evidence that other targets such as the cell membrane (Pouget et al. 2008; Seideman et al. 2011) and cytoplasm (Wu et al. 1999) play a role. The choice of the cell or cell nucleus as the target is useful in terms of being a defined volume for calculation of absorbed dose; however, radiations with high linear energy transfer (e.g., alpha particles) cause greater biological effect per unit absorbed dose to the cell nucleus than their low-linear energy transfer (LET) counterparts (e.g., electrons). This phenomenon supports the notion of a smaller target volume (for energy deposition), which has been a topic of debate for many decades. DNA-related target volumes such as DNA-segment, nucleosome, and segments of chromatin fiber have been considered as targets relevant to the concept of clustered DNA damage (Goodhead 1992). As stated in ICRU Report 86 (ICRU 2011): “*The products of radiation interactions in various target volumes do not necessarily act independently with respect to the probability of biological consequences. Thus, there might not be a single target volume that is responsible for a given end effect; rather, the consequences of irradiation might depend on the interaction of products arising from the energy deposited in several different size sites. Different aspects of a given biological response might be dependent on energy-deposition concentration in different volumes and can have different dependence on radiation quality and dose rate.*”

Curiously, recent experiments have shown that the dogma regarding the structure of chromatin fiber may not be accurate (Fussner et al. 2011). The textbook model of chromatin is a 30 nm diameter fiber made from “beads on a string” (Fig. 4). The “beads” are 10-nm-diameter nucleosomes that consist of nucleosome cores wrapped with core DNA. The nucleosomes were purportedly spaced equally on a “string” of linker DNA (Fig. 4). Numerous radiation track structure models have appropriately used this description to specify the target volume. However, recent discoveries suggest that the chromatin fiber consists of heterogeneous groups of nucleosomes called clutches (Ricci et al. 2015). Furthermore, the distribution of clutch sizes differs between somatic cells and stem cells. Somatic cells have a distribution of clutch sizes that are substantially larger than stem cells, which tend to have a few nucleosomes per clutch and often only one (Fig. 5). This potential shift in paradigm could have significant implications for radiation target theory. Nucleosome clutches may be the relevant targets for clustered damage. It has been shown that high-LET radiations, which impart clustered damage efficiently, create larger γ -H2AX foci than low-LET radiations (Desai et al. 2005). Therefore, it stands to reason that the large foci may correspond in part to the capacity of high-LET radiation to impart damage to several nucleosomes simultaneously that comprise a clutch. Correspondingly, the distribution in foci size may be related to the distribution of clutch size. The heterogeneity of clutch size is also consistent with the aforementioned ICRU Report 86 statement regarding the distribution of target sizes.

The fact that somatic cells and pluripotent stem cells appear to have very different distributions of clutch sizes may also provide guidance ultimately about differences that these cells may exhibit with respect to their radiosensitivity for various biological endpoints. One can speculate that this configuration may even have evolved as a means to protect the chromatin in pluripotent stem cells. Regardless, these possibilities warrant further research to unravel the role that this new model of chromatin fiber and the corresponding distribution

of clutch sizes may have in defining the significance of risks associated with the biological effects of low doses and low dose rates of ionizing radiation.

Acknowledgments

This study was supported in part by Grant Number 1R01CA198073 from the National Cancer Institute of the National Institutes of Health (NIH).

References

- Desai N, Davis E, O'Neill P, Durante M, Cucinotta FA, Wu H. Immunofluorescence detection of clustered gamma-H2AX foci induced by HZE-particle radiation. *Radiat Res.* 2005; 164:518–522. [PubMed: 16187760]
- Fussner E, Ching RW, Bazett-Jones DP. Living without 30-nm chromatin fibers. *Trends Biochem Sci.* 2011; 36:1–6. [PubMed: 20926298]
- Goodhead, DT. Advances in radiation biology. San Diego, CA: Academic Press; 1992. Track structure considerations in low dose and low dose rate effects of ionizing radiation; p. 7-44.
- Goodhead DT. Initial events in the cellular effects of ionizing radiations: clustered damage in DNA. *Int J Radiat Biol.* 1994; 65:7–17. [PubMed: 7905912]
- Howell RW. The MIRD schema: from organ to cellular dimensions. *J Nucl Med.* 1994; 35:531–533. [PubMed: 8113909]
- ICRU. Quantification and reporting of low-dose and other heterogeneous exposures. ICRU Report No. 86. *J ICRU.* 2011; 11:1–77. [PubMed: 24174422]
- Jönsson B-A, Strand S-E, Larsson BS. A quantitative autoradiographic study of the heterogeneous activity distribution of different indium-111-labeled radiopharmaceuticals in rat tissues. *J Nucl Med.* 1992; 33:1825–1832. [PubMed: 1403151]
- NCRP. Exposure of the population in the United States and Canada from natural background radiation. Bethesda, MD: National Council on Radiation Protection and Measurements; 1987. Report No. 94
- NCRP. Radiation exposure and high-altitude flight. Bethesda, MD: National Council on Radiation Protection and Measurements; 1995. NCRP Commentary No. 12
- NCRP. Ionizing radiation exposure of the population of the United States. Bethesda, MD: National Council on Radiation Protection and Measurements; 2009. Report No. 160
- Nikjoo H, Girard P. A model of the cell nucleus for DNA damage calculations. *Int J Radiat Biol.* 2012; 88:87–97. [PubMed: 22081899]
- NUREG-0713. Occupational radiation exposure at commercial nuclear power reactors and other facilities. Washington, DC: U.S. Nuclear Regulatory Commission; 2003.
- Pouget JP, Santoro L, Raymond L, Chouin N, Bardies M, Bascoul-Mollevi C, Huguet H, Azria D, Kotzki PO, Pelegrin M, Vives E, Pelegrin A. Cell membrane is a more sensitive target than cytoplasm to dense ionization produced by auger electrons. *Radiat Res.* 2008; 170:192–200. [PubMed: 18666820]
- Ricci MA, Manzo C, Garcia-Parajo MF, Lakadamyali M, Cosma MP. Chromatin fibers are formed by heterogeneous groups of nucleosomes in vivo. *Cell.* 2015; 160:1145–1158. [PubMed: 25768910]
- Seideman JH, Stancevic B, Rotolo JA, McDevitt MR, Howell RW, Kolesnick RN, Scheinberg DA. Alpha particles induce apoptosis through the sphingomyelin pathway. *Radiat Res.* 2011; 176:434–446. [PubMed: 21631289]
- Wu LJ, Randers-Pehrson GR, Xu A, Waldren CA, Geard CR, Yu ZL, Hei TK. Targeted cytoplasmic irradiation with alpha particles induces mutations in mammalian cells. *Proc Natl Acad Sci USA.* 1999; 96:4959–4964. [PubMed: 10220401]

Fig. 1.

Cumulative background and occupational exposures to ionizing radiation as a function of age for various types of radiation exposures. U.S. Background = 3 mSv yr^{-1} natural background; U.S. citizen = natural background + one 10 mSv CT scan every five years of life; U.S. citizen occupational 1.7 = natural background + average annual exposure of 1.7 mSv yr^{-1} received by nuclear power employees that receive measurable doses; U.S. citizen airline crew = natural background + dose received by jet aircraft flight crew at an altitude of 12,000 m ($7 \mu\text{Sv h}^{-1}$) for $1,000 \text{ h yr}^{-1}$; U.S. citizen occupational 10 = background exposure plus an average annual exposure of 10 mSv yr^{-1} received by an occupationally exposed individual; Kerala high background population = natural background of 30 mSv yr^{-1} in Monazite sands region in Kerala, India. It should be noted that CT exposures are delivered acutely in a matter of minutes, whereas the other exposures mentioned are delivered chronically.

Fig. 2. Examples of non-uniform deposition of energy by ionizing radiation at macroscopic and molecular dimensions: A) partial body irradiation with diagnostic x rays; B) nonuniform irradiation of regions within organs of mice administered a radiopharmaceutical labeled with ^{111}In , which emits γ -rays and electrons (reprinted from Jönsson et al. 1992); C) non-uniform deposition of energy along the tracks of alpha particles and low energy electrons (reprinted with permission from ICRU 2011).

Fig. 3.
Depiction of initial track, target volume, and event [reproduced from ICRU Report 86 (reprinted with permission from ICRU 2011)].

Fig. 4.
Textbook model of the structure of chromatin fiber.

Fig. 5. Nucleosomes are arranged in clutches. This figure depicts the heterogeneity in sizes of the nucleosome clutches. Reprinted from Ricci MA, Manzo C, Garcia-Parajo MF, Lakadamyali M, Cosma MP. Chromatin fibers are formed by heterogeneous groups of nucleosomes in vivo. *Cell* 160:1145–1158; 2015, with permission from Elsevier.