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Review

Non-targeted effects of ionising radiation—Implications for low dose risk

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ABSTRACT

Non-DNA targeted effects of ionising radiation, which include genomic instability, and a variety of bystander effects including abscopal effects and bystander mediated adaptive response, have raised concerns about the magnitude of low-dose radiation risk. Genomic instability, bystander effects and adaptive responses are powered by fundamental, but not clearly understood systems that maintain tissue homeostasis. Despite excellent research in this field by various groups, there are still gaps in our understanding of the likely mechanisms associated with non-DNA targeted effects, particularly with respect to systemic (human health) consequences at low and intermediate doses of ionising radiation. Other outstanding questions include links between the different non-targeted responses and the variations in response observed between individuals and cell lines, possibly a function of genetic background. Furthermore, it is still not known what the initial target and early interactions in cells are that give rise to non-targeted responses in neighbouring or descendant cells. This paper provides a commentary on the current state of the field as a result of the non-targeted effects of ionising radiation (NOTE) Integrated Project funded by the European Union. Here we critically examine the evidence for non-targeted effects, discuss apparently contradictory results and consider implications for low-dose radiation health effects.

Contents

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1. Introduction

Non-DNA targeted effects (NTE) of ionising radiation, which include genomic instability (GI), and a variety of bystander effects (BE) including abscopal effects and bystander mediated adaptive response, have raised concerns about human risk at low doses.

In this paper we provide a brief overview of the conventional framework of biological effects of radiation exposure and explore the background to the development of the concept of NTE with respect to key radiobiological mechanisms. We shall critically examine the evidence for non-targeted effects in the radiobiology research literature, some apparently contradictory results in the field and consider the implications for low-dose health effects. Although it has been argued that NTE have implications for cancer radiotherapy (RT) (as recently reviewed [1–3]), here we limit discussion to normal tissue responses and effects of low doses, *i.e.*, those typically encountered from occupational, environmental and medical diagnostic exposures. Other more selective reviews of the current work in this area have been published recently, as for example by Salomaa et al. [4].

1.1. Classical radiation paradigm: target theory (Box 1)

For clarity, throughout this paper the following definitions will apply:

Very high – doses above 15 Gy
High – doses of 5–15 Gy
Medium – doses of 0.5–5 Gy
Low – doses of 0.05–0.5 Gy
Very low – doses below 0.05 Gy

Risks associated with ionising radiation have been known for almost as long as ionising radiation itself. Within a year of the discovery of X-rays by Röntgen skin burns had been reported by Stevens [5] and Gilchrist [6] and within 7 years a case of skin cancer was observed by Frieben [7], in all cases associated with high dose X-ray exposure. In general, risks associated with ionising radiation can be divided into those defined as *stochastic effects* (genetic risks in offspring, somatic effects (cancer) in directly exposed population), and those termed *tissue-reaction* (formerly *deterministic*) effects. The probability of occurrence of stochastic effects but not their severity is assumed to be a function of dose, without a threshold. For the class of tissue-reaction effects defined by the International Commission on Radiological Protection (ICRP) [8], it is assumed that there is a threshold dose, below which there is no effect, and the severity of effect increases with increasing dose above that point. Tissue-reaction effects are assumed to ensue when a sufficiently large number of cells are damaged within a certain critical time period such that the body cannot replace them; biologically it is therefore much more likely that there is a threshold for tissue reaction effects than for stochastic effects [9].

As outlined by Harris [10] and also United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) [11], there are biological data to suggest that cancer arises from a failure of cell differentiation, and that it may be largely unicellular in origin. Canonically, cancer is thought to result from mutagenic damage to a single cell, *via* direct DNA damage, which in principle could be caused by a single radiation track [11].

Conventionally, radiation effects have been explained using target theory [12]. According to this, deleterious effects of ionising radiation, 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 [11]. Therefore the progeny of a single irradiated cell would be expected to show radiation-induced genetic changes in all descendant cells, *i.e.*, the change would be clonal (Box 2).

The classic framework for radiobiology has been generally well validated by numerous interlinked experimental and theoretical studies. Although confirmation of some key assumptions remains elusive, in particular the link between the initial damage and cancer, it forms a logical basis for the standard set of models describing risk of cancer and heritable effects, and has been widely used to establish international rules and standards of radiation protection by the ICRP [8]. Although partly based on human epidemiological data for health effects, in particular those derived from the cancer incidence and mortality follow-up of the Japanese atomic bomb survivors Life Span Study (LSS) cohort [13,14], the regulatory framework derived by the ICRP [8] relies on a number of biological assumptions and models to extrapolate to the low dose and low dose-rate regime of most interest for radiological protection. In particular, the main assumptions made by ICRP [8] and other bodies in relation to estimating stochastic effects are: (1) of targeted damage to nuclear DNA, the yield of which increases

Box 1. Target theory

The *target theory* of radiation induced effects [11] postulates that cells contain at least one critical site or *target* that must be hit by radiation in order to kill a cell or produce an effect. Therefore, radiation damage outside of the target should not cause cell death (effect). It is widely accepted that nuclear DNA is the critical target for radiation induced cell death as well as for non death-related effects.

Box 2. Conventional biological effects of ionising radiation

DNA damage occurs during or very shortly after irradiation of the nuclei in targeted cells. The potential for biological consequences can be expressed within one or two generations.