Mutation Research 761 (2014) 6–14

Contents lists available at ScienceDirect

Mutation Research/Reviews in Mutation Research

journal homepage: www.elsevier.com/locate/reviewsmr
Community address: www.elsevier.com/locate/mutres

Review

# Low dose effects of ionizing radiation on normal tissue stem cells

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ARTICLE INFO

*Article history:*
Received 12 August 2013
Received in revised form 3 February 2014
Accepted 13 February 2014
Available online 22 February 2014

*Keywords:*
Normal stem cells
Irradiation
Low dose
Carcinogenesis

ABSTRACT

In recent years, there has been growing evidence for the involvement of stem cells in cancer initiation. As a result of their long life span, stem cells may have an increased propensity to accumulate genetic damage relative to differentiated cells. Therefore, stem cells of normal tissues may be important targets for radiation-induced carcinogenesis.

Knowledge of the effects of ionizing radiation (IR) on normal stem cells and on the processes involved in carcinogenesis is very limited. The influence of high doses of IR (>5 Gy) on proliferation, cell cycle and induction of senescence has been demonstrated in stem cells. There have been limited studies of the effects of moderate (0.5–5 Gy) and low doses (<0.5 Gy) of IR on stem cells however, the effect of low dose IR (LD-IR) on normal stem cells as possible targets for radiation-induced carcinogenesis has not been studied in any depth. There may also be important parallels between stem cell responses and those of cancer stem cells, which may highlight potential key common mechanisms of their response and radiosensitivity.

This review will provide an overview of the current knowledge of radiation-induced effects on normal stem cells, with particular focus on low and moderate doses of IR.



**Contents**



*Abbreviations:* APE1, Apurinic endonuclease; ATM, ataxia telangiectasia mutated; BER, base excision repair; CSC, cancer stem cell; DNA DSB, DNA double strand break; ESC, Embryonic stem cell; EMT, Epithelial-to-Mesenchymal Transition; HD-IR, high doses of ionizing radiation; HR, homologous recombination; HSC, hematopoietic stem cell; HPC, hematopoietic progenitor cells; iPSC, induced pluripotent stem cell(s); I, ionizing radiation; LD-IR, low doses of ionizing radiation; NHEJ, non-homologous end joining; SC, stem cell(s); Sv, sievert; γ-H2AX, phospho-serine 139-histone variant 2AX.

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http://dx.doi.org/10.1016/j.mrrev.2014.02.003
1383-5742/

## 1. Introduction

### 1.1. Conventional models of radiation-induced carcinogenesis

There is extensive evidence from animal and human exposures describing the risk of many cancer types, following acute radiation exposures [1,2]. The epidemiological data from the Atomic Bomb survivor cohort collected over 60 years supports a linear dose response relationship for intermediate doses, however for low dose exposures the evidence is less reliable due to lack of statistical power for cancer induction at low doses (<100 mSv) [3].

Conventional radiobiological models assume that cellular responses to radiation occur as a result of direct damage to nuclear DNA by a radiation track (known as 'target theory'). A further assumption is that damage is proportional to the number of tracks (which is related to dose) and therefore any dose no matter how small, can result in potentially mutagenic DNA damage.

These assumptions along with the epidemiology data for intermediate doses underpin the most frequently employed model for estimating radiation risk, the Linear No Threshold (LNT) model. This model only accounts for direct irradiation of cell nuclei. Therefore based on the LNT model, for all doses <1.5 Gy, the dose-response curve for excess cancer risk is linear. This is a conservative model that assumes any dose confers an excess cancer risk. In the low dose region this model is also supported by studies of *in utero* exposures in the order of 10 mGy that showed an increase in childhood cancers in exposed individuals [3].

There has been extensive debate concerning the suitability of this model for doses below 100 mSv and experimental studies in that dose region have provided evidence for a non-linear dose-response curve. This may impact on risk estimations after low dose occupational or medical exposures.

### 1.2. The new paradigm in radiation biology

Evidence from *in vitro* and *in vivo* studies in the last two decades has highlighted several issues that are not considered by conventional radiation carcinogenesis theories [4,5]. Firstly, the precise initiation event is difficult to pin point for radiation and is generally observed to be a stochastic process.

Secondly, a cancer outcome following radiation is most likely affected by the microenvironment, signalling between irradiated and non-irradiated cells and inflammatory responses. Finally, controversial 'abscopal effects' have been observed *in vivo* at sites distant from the irradiated area. These issues highlight the fact that mutation and subsequent cancer development cannot be explained by direct energy deposition in DNA only.

Low dose and targeted radiation studies have identified cellular phenomena that do not fit the traditional model as they elicit responses in cells that were not directly traversed by radiation tracks. These phenomena include genomic instability and bystander effects. Genomic instability describes an increased frequency of mutations and chromosome aberrations in the progeny of irradiated cells [6–8]. Radiation induced bystander effect describes the response of unirradiated cells to the irradiation of their neighbours. Radiation induced bystander effects have been observed for a range of biological endpoints including: apoptosis [9], DNA damage and up regulation of proteins in the DNA damage response, [6,10,11], micronucleus induction [12,13], cell proliferation [14], cell survival [15–17] and genomic instability [18,19].

These processes have been found to saturate at low doses and to have non-linear dose responses. They are also often cell and radiation type specific and their existence indicates the need for better understanding of the mechanisms involved in radiation carcinogenesis and the development of alternative models for this complex process. Some more recent papers have described models of radiation effects that incorporate bystander signalling [20–26].

### 1.3. Stem cells as the target for the initiation of radiation carcinogenesis

Stem cells are undifferentiated cells, possessing the potential for unlimited replication and differentiation to many cell types (pluripotency). Key to this is the ability of stem cells can undergo symmetrical or asymmetrical division. Whilst in the first case two copies of the original stem cells are formed; the second case results in one daughter progenitor cell and one undifferentiated stem cell. Thereby stem cells can both self-renew and produce daughter cells capable of differentiating into one or more types of mature cell. The decision to divide by either route is stringently regulated by endogenous signalling and exogenous micro-environmental factors [27]. Stem cell fate is influenced by multiple convergent signal-transduction pathways the outcome of which is ultimately controlled by cell/tissue type specific 'master' regulators [28–30]. Key players in the decision for self-renewal or differentiation are the JAK/STAT and Hedgehog pathways as well as members of the transforming growth factor beta (TGF-β) family. TGF-β has an important impact on processes such as proliferation, differentiation, regeneration and homeostasis [31]. In cancer, TGF-β has a tumour-suppressive effect on premalignant cells. However, in the later stages of cancer, TGF-β promotes invasion because of its role in epithelial to mesenchymal transition [32]. This process is also influenced by epigenetic regulation [33].

In mammals, there are two types of normal stem cells: embryonic stem cells (ESCs), which are isolated from the inner cell mass of the blastocyst, and can differentiate to form all cells of the three main germ layers (pluripotent). The second type of normal stem cells are adult stem cells. They act as a repair mechanism replenishing mature cells at a rate dependent on the requirement of the specific organ. Adult stem cells are typically slow cycling cells and, in general, can only differentiate into the cell types found in the tissue of origin although there are exceptions to this via reprogamming. They are defined as being multipotent. As a result of their long life span adult stem cells are thought to have an increased propensity for the accumulation of genetic mutations.

## 2. Are stem cells involved in cancer initiation?

Traditionally the development of cancer has been described to occur in three steps–initiation, promotion and progression. Carcinogenesis is now understood to be a complex process that occurs in a multiple stages, which have not been understood in any depth [34]. However, the fact that exposure with ionizing radiation (IR) can induce cancer has been known for over a century [35]. In recent years there has been increasing evidence to indicate the involvement of stem cells in cancer initiation, progression and tumour maintenance. The development of cancer and the possibility that cancers could arise from stem or stem-like cells (Cancer stem cells (CSCs)) is not a new idea, in fact this was proposed in the 18th century [36,37]. However it was not possible until the mid-1990s to isolate stem cell-like populations from a human cancer [38]. A good overview of the milestones contributing to the understanding of normal and cancer stem cells, has been published by Nguygen and co-workers [36]. As a result of the many investigations in this context, the 'Cancer Stem Cell' hypothesis was born [37,39,40]. This theory assumes that normal stem cells can be transformed into CSCs (Fig. 1) and progenitor cells can be modified into cancer progenitor cells, which are able to generate differentiated cells that make up the bulk of the tumour. The key question that remains for the radiation protection and radiation biology communities is, what role radiation exposure plays in