Mutation Research 760 (2014) 1–17

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

Crosstalk between telomere maintenance and radiation effects: A key player in the process of radiation-induced carcinogenesis☆

Grace Shim [a,b], Michelle Ricoul [a], William M. Hempel [a], Edouard I. Azzam [b], Laure Sabatier [a,*]

[a] Commissariat à l'Energie Atomique (CEA), DSV/IRCM/SRO – Laboratory of Radiobiology and Oncology, 18 route du Panorama, 92265 Fontenay-aux-Roses, France
[b] Department of Radiology, Rutgers New Jersey Medical School Cancer Center, 205 South Orange Avenue, Newark, NJ 07103, USA

ARTICLE INFO

Article history:
Received 6 August 2013
Received in revised form 14 January 2014
Accepted 22 January 2014
Available online 31 January 2014

Keywords:
Telomeres
Ionizing radiation
Bystander effect
Radiosensitivity
Chromosomal instability

ABSTRACT

It is well established that ionizing radiation induces chromosomal damage, both following direct radiation exposure and via non-targeted (bystander) effects, activating DNA damage repair pathways, of which the proteins are closely linked to telomeric proteins and telomere maintenance. Long-term propagation of this radiation-induced chromosomal damage during cell proliferation results in chromosomal instability. Many studies have shown the link between radiation exposure and radiation-induced changes in oxidative stress and DNA damage repair in both targeted and non-targeted cells. However, the effect of these factors on telomeres, long established as guardians of the genome, still remains to be clarified. In this review, we will focus on what is known about how telomeres are affected by exposure to low- and high-LET ionizing radiation and during proliferation, and will discuss how telomeres may be a key player in the process of radiation-induced carcinogenesis.

Contents

* Corresponding author. Tel.: +33 1 46 54 83 51; fax: +33 1 46 54 87 58.
E-mail addresses: graceshim1@gmail.com (G. Shim), michelle.ricoul@cea.fr (M. Ricoul), william.hempel@cea.fr (W.M. Hempel), azzamei@njms.rutgers.edu (E.I. Azzam), laure.sabatier@cea.fr (L. Sabatier).

1383-5742/$ – see front matter © 2014 The Authors. Published by Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.mrrev.2014.01.001

1. Introduction

We are all constantly exposed to ionizing radiation (IR) from natural sources such as cosmic rays, radon decay products in the air, and various radionuclides found in food and water. We may also be exposed to low doses of IR released to the environment from man-made sources, including fallout from nuclear weapons testing, discharges of radioactive waste, and consumer products. In addition, individuals may be exposed to IR during occupational activities related to nuclear technology, mining, high altitude airline travel, and deep space exploration [1]. In particular, with the explosive growth in the use of diagnostic radiology, increasing numbers of individuals are being repeatedly exposed to IR. The use of different irradiation modalities remains an effective and widely used means to treat cancer and other pathological conditions [2]. Therefore, exposure to IR is an inevitable part of the environment, and increasingly of modern life.

During cancer radiotherapy, both malignant and normal cells are exposed to IR. Radiation-induced damage, particularly in tissues irradiated with high doses, induces systemic effects that affect the whole body during, or a short time after, exposure. Importantly, delayed effects are also sometimes observed many years after the end of treatment, as illustrated by a higher incidence of secondary malignancies and a variety of degenerative conditions in long-term cancer survivors. Strikingly, in patients receiving radiation treatment, significant biological changes have been observed in tissues that are widely separated from the irradiated area, and treatment directed at a tumor at one site may profoundly affect tumors and/or normal tissues located elsewhere in the body. These non-targeted effects can therefore be either detrimental or beneficial (if they lead to shrinkage of distant tumors), and have been termed "abscopal effects." These diverse physiological effects of IR illustrate the in vivo occurrence of radiation-induced "*bystander*" responses [3–5].

The spread of IR-induced effects among irradiated cells, between irradiated and non-irradiated cells, and their persistence in progeny of both targeted and non-targeted cells, can therefore have profound implications for long-term human health risks. The emergence of secondary cancers and other pathobiological conditions after radiotherapy [3] and the possibility of delayed effects following occupational radiation exposure in miners, nuclear workers, and astronauts directly impact the formulation of cancer treatment strategies and the establishment of occupational radiation protection guidelines [6,7]. Conversely, understanding the mediating mechanisms of IR exposure may help in devising approaches to alleviate its detrimental effects.

Over the last two decades, as will be discussed in the following chapters, increasing evidence has been gathered that shows that the long-term effects of IR exposure are due to oxidative changes leading to the continuous accumulation of DNA damage in the progeny of both irradiated and non-irradiated bystander cells. Strong evidence indicates that these effects are dependent on radiation quality, dose, dose-rate, genetic susceptibility, and age, for example. Based on previous studies in our laboratory, we postulate that the emergence of late radiation effects in directly irradiated or bystander cells may be due to delayed chromosomal instability caused by telomere dysfunction.

2. Telomeres

2.1. Background

The critical role of telomeres in maintaining chromosomal stability was first described in the 1930s by Barbara McClintock in maize [8] and Hermann Muller in fruit flies [9]. Telomeres are specialized nucleoprotein structures located at the ends of linear eukaryotic chromosomes [10]. They consist of tandem repeats of 5′-TTAGGG-3′ (T_2AG_3) DNA sequences and several associated proteins. Together, they form a protective cap called the shelterin complex, which protects chromosome ends from being recognized as DNA double strand breaks (DSBs), and prevent unwanted activation of DNA damage checkpoints and DSB repair pathways [11]. The complex is found in the form of a T-loop, which is formed when the double-stranded telomeric DNA regions fold back to interact with the 3′ single-stranded portion with the help of the shelterin proteins [12,13]. Because of the G-rich nature of the single-stranded telomeric DNA, this region may also form G-quadruplexes, which are formed from a series of G-quartets each containing four guanine bases arranged in a helical fashion [14,15].

The shelterin complex in humans includes six proteins that are associated with telomeric DNA, named TRF1, TRF2, TIN2, POT1 (POT1a/b in rodents [16]), TPP1, and RAP1. Each of these proteins has evolved specific functions for telomere maintenance, including the regulation of telomerase access and activity as well as the interaction with many DNA repair/recombination factors. In this way, telomeres play a critical role as the guardians of genomic stability and integrity. Generally, TRF1 and TRF2 bind to the double-stranded telomeric DNA, while POT1 binds the single-stranded overhang and interacts with the other shelterin proteins via the linker proteins TIN2 and TPP1 [17]. Multiple POT1–TPP1 molecules were shown to coat long stretches of telomeric single stranded DNA and form compact ordered structures that may serve to protect this region from telomerase access and/or DNA damage response (DDR) factors [18,19]. TIN2 stabilizes both TRF1 and TRF2 on the double stranded DNA region [20] and TPP1/POT1 on the single stranded portion [21]. Finally, RAP1, which interacts with TRF2, has been shown to be non-essential for the functions of TRF2, but is important for the repression of DDR factors at the telomeres [22].

2.2. Mechanisms of telomere maintenance in normal human cells

Telomere length (TL) varies between organisms; in humans, the length of the double-stranded end can be 2–20 kb, while the length of the single-stranded G-rich overhang can be 50–500 nucleotides. TL also varies on individual chromosome arms [23], and this inherent heterogeneity of TL is conserved during life [24]. TL in somatic proliferative tissues naturally declines with each cell replication cycle at a rate of approximately 20–300 base pairs per population doubling (varying with cell type) [25] due to the incomplete replication of telomere ends by conventional DNA polymerases, a situation known as the 'end replication problem' [26]. After many rounds of cell division, telomeres eventually become critically short and dysfunctional. In normal cells with intact p53 functions and cell cycle checkpoints, these dysfunctional/uncapped telomeres are sensed as DNA damage and trigger DDR pathways, forming telomere dysfunction-induced foci, termed TIFs [27]. Indeed, induction of DDR factors (such as ATM and gamma-H2AX) was inversely correlated with TL and shelterin protein levels [28–30]. An important recent study suggested that normal human cells are able to tolerate small numbers of dysfunctional telomeres, and cells can continue to proliferate without significant induction of telomere fusions and chromosomal instability until a threshold of five TIFs per cell is reached [31]. At this point, these DDR signals prevent the cell from further division [32], and cells enter a stage of permanent growth arrest called "replicative senescence" [33]. The lack of chromosomal fusions in pre-senescent cells may indicate that sufficient levels of shelterin proteins are present at the telomeres to retain their protective roles. However, in cells that are unable to senesce due to the loss of cell cycle checkpoint proteins such as p53 or p16, senescence is temporarily bypassed, and cells continue to proliferate with further telomere shortening, until "telomeric crisis" is reached