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Laboratory-Clinic Interface

The role of telomeres in predicting individual radiosensitivity of patients with cancer in the era of personalized radiotherapy

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ABSTRACT

Radiotherapy plays a key role in cancer treatments, but tumor cell death differs from one tumor to another. The response of patients to radiotherapy varies considerably and adverse side effects are difficult to prevent. The mechanisms involved in the heterogeneity of this response are not well understood. In order to enhance the efficacy and safety of radiotherapy, it is important to identify subpopulations most at risk of developing a late adverse response to radiotherapy. Telomeres are composed of multiple repeats of a unique sequence of nucleotides forming a TTAGGG pattern. They protect chromosomes from end-to-end fusion and maintain genomic stability. Telomeres have been shown to be extremely sensitive to radiotherapy especially because of their atypical DNA damage repair response, which includes partial inhibition of the non-homologous end joining repair pathway. Ionizing Radiation (IR)-induced damage to telomere DNA could lead to chromosome instability and the initiation or progression of tumor processes. Telomeres could thus be a reliable marker of IR exposure and as such become a new parameter for predicting radiosensitivity. Furthermore, short telomeres are more sensitive to radiotherapy, which could partially explain differences in tumor cell death and in inter-individual sensitivity to radiotherapy. Telomere length could be used to identify subpopulations of patients who could benefit from higher or lower doses per fraction. Finally, pharmacological interference with tumor-cell telomere biology to reduce telomere length and/or telomere stability could also enhance the effectiveness and safety of radiotherapy. Telomeres could play a key role in radiotherapy in the era of personalized medicine.

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Introduction

Radiotherapy plays a key role in the treatment of many tumors. It is difficult to determine the sensitivity of tumor cells and the fraction of tumor cells that survive after treatment with ionizing radiation (IR). It is also difficult to determine individual response to different schemas of radiation therapy (RT) notably according to the age of patients. It is therefore hard to prevent RT-related toxicity. Mathematical models of radiobiological effects suffer from poor predictive value *in vivo*. New integrative biomarkers must be

Abbreviations: 8-oxodG, 8-oxo-7,8-dihydro-2′-deoxyguanosine; A-NHEJ, alternative non-homologous end joining; ALT, alternative lengthening of telomeres; ATM, ataxia telangiectasia mutated; bp, base pair; C-NHEJ, classical non-homologous end joining; DDR, DNA damage response; DNA, deoxyribonucleic acid; DNA PK, DNA-dependent protein kinases; DSBs, double-strand breaks; HER2, human epidermal growth factor receptor 2; H2AX, H2A histone family, member X; HRR, homologous recombination repair; hTERT, human telomerase reverse transcriptase; IR, ionizing radiation; kb, kilo base; Mre11, meiotic recombination 11 homolog A; MRN complex, Mre11-Rad50-NBS1 complex; NBN/NBS1, NLRP2, NLR family, pyrin domain containing 2; PML nuclear bodies, promyelocytic leukemia nuclear bodies; Pot1, protection of telomere 1; PTEN, phosphatase and tensin homolog; Rad50, eukaryotic homolog of the prokaryotic RecA protein 50; Rap1, repressor-activator protein 1; RNA, ribonucleic acid; RT, radiation therapy; SMC1, structural maintenance of chromosome 1; TERC, telomerase RNA component; Tin2, TRF1-interacting nuclear protein 2; t-loop, telomere loop; TPP1, tripeptidyl-peptidase 1; TRF1/2, telomeric repeat binding factor 1/2; UV, ultra violet; XLF, XCRCC4 like factor; XRCC3/4, X-ray repair complementing defective repair in Chinese hamster cells 3/4.

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investigated to overcome the weaknesses of current models. One promising integrative biomarker could be telomeres. Telomeres, complex nucleoprotein structures located at the ends of chromosomes, have generated considerable interest for many years. Since Blackburn, Greider and Szostak were awarded the Nobel Prize in 2009 for their work on the structure of telomeres [1–6], a great deal of research has been done into the role of telomeres. Indeed, they appear to be involved in various complex diseases and physiological phenomena. One of these areas of research is cancer. Telomeres and the many proteins involved in maintaining them seem to play a key role in the initiation, progression and diversity of tumor response to various currently-used therapies. The optimization of radiotherapy in the management of cancer must pass through a better understanding of the mechanisms involved in the response of telomeres to RT.

The purpose of this article is to review recent work on the impact of ionizing radiation on telomere biology to better understand the mechanisms and paradoxes involved and thus to optimize RT effects on telomeres with the ultimate goal to set up personalized medicine.

Telomeres are resistant to NHEJ repair pathways

Radiotherapy plays a key role in cancer treatments. One principle of IR is to induce DNA double-strand breaks (DSBs) leading to repair, apoptosis or permanent growth arrest (senescence). In mammalian cells, there are three major pathways to repair DNA DSBs, namely homologous recombination repair (HRR), classical non-homologous end joining (C-NHEJ) and alternative non-homologous end joining repair (A-NHEJ) [7]. NHEJ pathways are considered the major mechanisms of IR-induced DNA Damage Response (DDR). In contrast with HRR, NHEJ pathways lead to the loss of nucleotides and potential errors in DNA repair.

Telomeres, which are nucleoprotein structures at the end of eukaryotic chromosomes, are distinct from the rest of the genome in their DNA repair capacity and have been shown to inhibit NHEJ. Indeed, in 1998, Steensel et al. showed that telomeric repeat binding factor 2 (TRF2), a shelterin protein that together with the other proteins of the shelterin complex, namely TRF1, protection of telomeres 1 (Pot1), tripeptidyl-peptidase 1 (TPP1), repressor-activator protein 1 (Rap1) and TRF1-interacting nuclear protein 2 (Tin2) caps telomeres and thus protects them from end-to-end fusion [8]. The most amazing thing is that as well as the shelterin complex, numerous proteins with known roles in DNA repair, such as Ku, MRN complex or ataxia telangiectasia mutated (ATM), are also involved in normal telomere maintenance [9–11]. The most elegant hypothesis is that the shelterin complex forms t-loop structures that make telomeres inaccessible to NHEJ effectors (Fig. 1). However, a recent study published by Bae et al. showed that, even in very short telomeres (fewer than 10 telomeric repeats, which is too short for loop formation), the TRF2/Rap1 complex permits the inhibition of LIG IV and DNA PKs [12]. This suggests that telomere protection requires various pathways. It is well established that telomeres are prone to persistent DNA damage [13,14]. Fumagalli et al. showed that genomes are not uniformly repairable and that some genomic loci, such as telomeres, resist DNA-damage repair [13]. This study also suggested that cellular senescence could be the result of irreparable telomeric DNA-damage and subsequent persistent DDR signaling. In addition, Hewitt et al. showed that the inhibition of NHEJ repair of telomeres to prevent end-to-end fusion might have detrimental consequences in terms of DNA repair capacity [14]. The authors hypothesized that oxidative damage to telomeric DNA could be responsible for the inability of some factors involved in t-loop formation, such as TRF1 or TRF2, to bind to telomere repeats. This hypothesis is

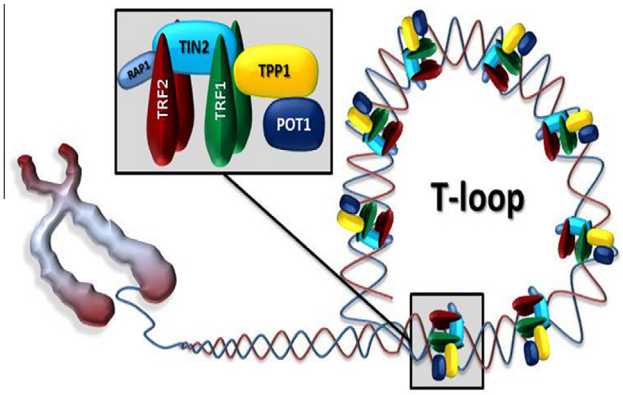

Fig. 1. Partial representation of telomere structure. Telomeres are located at the ends of eukaryotic chromosomes. They form t-loop structures to avoid being recognized as double-strand breaks. The t-loop is maintained by sheltering complex formed by six proteins (TRF1–2, Pot1, TPP1, Rap1 and Tin2).

reinforced by the observation that telomeric repeats (TTAGGG) are rich in guanine, which is remarkably sensitive to oxidation [15]. This oxidation induces conformational modifications that impede normal signaling at telomeres.

Telomere attrition is between 20 and 200 bp with each cell division because of the "end replication problem". This phenomenon occurs in every cell of the body, except in adult stem cells and cells with massive replication potential such as activated lymphocytes [16,17]. Telomere shortening is slowed by dint of telomerase activity, which is the most important mechanism of telomere maintenance. Nevertheless, most somatic cells do not have sufficient telomerase activity to prevent telomere shortening, so their continued proliferation eventually results in senescence. However, a small proportion of cells are able to maintain telomeres without telomerase activity. This phenomenon occurs in about 15% of tumor cells and is known as alternative lengthening of telomeres (ALT) [18–20].

It is therefore important to study links between ionizing radiation and modifications in telomere homeostasis. Because telomeres prevent chromosome end-to-end fusion and thus preserve genomic stability, modifications in telomere structure could lead to genomic alterations and or chromosome rearrangements as discussed below.

Telomere dysfunction, chromosome instability and ionizing radiation

Telomere dysfunction and telomerase reactivation promote tumor initiation and drive tumor progression and aggressiveness

When telomeres are too short to protect the end of the chromosome, somatic cells can eventually develop a state of replicative senescence (when telomeres reach half of their original size, which permits stable cellular physiology [4,21] or apoptosis via p53 and/or p16 pathways [22,23]). The consequences of telomere shortening could be different in cells with compromised cell cycle regulation. Counter et al. [24] demonstrated that transfecting human fibroblasts with viral proteins led to the inactivation of p53 and p16 pathways. Deficiency of p53/p16 proteins leads to "crisis" which is characterized by a high rate of telomere loss and instability in chromosome structure [25–28]. Crisis serves as another line of defense against the development of cancer because the resulting genome instability and DNA-damage signaling induce the death of the vast majority of cells. p16 and p53 are major cellular pathways involved in cellular arrest and oncogene-induced

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