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Review article

Impact of oxidative stress on telomere biology

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A B S T R A C T

Telomere integrity is essential for genome stability and it regulates cell proliferation and tissue renewal. Several lines of evidence indicate that telomeres are particularly sensitive to oxidative damage. Moreover, recent studies demonstrate striking inhibitory effects of oxidative damage on telomerase activity. On the other hand, several mechanisms have been uncovered that either counteract oxidative damage at telomeres or remove the modified lesions. Here, we review the current understanding of oxidative damage and protection of telomeric DNA. We discuss how oxidative telomeric lesions impact on telomerase, the regenerative capacity of stem cells and cancer. Finally, we propose how through a better understanding of the involved pathways it may become possible to target telomerase in cancer cells in future cancer therapies.

1. Introduction

Telomeres correspond to the physical ends of eukaryotic chromosomes. They protect chromosomal ends from degradation, DNA recombination, DNA end joining and the DNA damage response (DDR) (Lazzerini-Denchi and Sfeir, 2016; Palm and de Lange, 2008). In vertebrates, the telomeric DNA consists of 5′-TTAGGG-3′ repeats in the strand that contains the 3′ end. Telomeric DNA length is roughly 5,000–15,000 bp long in humans whereas laboratory mice strains have exceptionally long telomeres of more than 30,000 bp. In yeast, telomeres are only approximately 300 bp long. Telomeres are single-stranded at the very end forming a 3′ overhang. Overhangs have a length of 50–200 nucleotides in humans and only 3–5 nucleotides in yeast. Telomere structure and function is mediated by the proteins that are recruited to chromosomal ends through the telomeric DNA and the telomeric long non-coding RNA TERRA. In vertebrates, the six shelterin proteins are abundant at telomeres eliciting many of the telomere functions (Lazzerini-Denchi and Sfeir, 2016; Palm and de Lange, 2008). TRF1 and TRF2 bind as homodimers to the double-stranded telomeric DNA repeats. POT1 binds with high specificity to the single-stranded 5′-TTAGGG-3′ repeat DNA (Baumann and Cech, 2001). TPP1, TIN2 and Rap1 associate to telomeres through protein-protein interactions (Fig. 1A). TRF2 suppresses at telomeres activation and signaling by the ATM checkpoint kinase and it protects telomeres from end joining by the non-homologous end joining machinery (NHEJ) (Denchi and de Lange, 2007). These functions may involve the formation of t-loop structures in which the telomeric 3′ overhang is tucked into the double-stranded part of the telomere (Griffith et al., 1999; Doksani et al., 2013). TRF1 is required for the efficient replication of telomeric DNA recruiting DNA helicases that are involved in DNA replication (Sfeir et al., 2009). The fission yeast Taz1 protein fulfills analogous functions in this organism (Miller et al., 2006). TPP1 which physically interacts with TIN2 and POT1 plays crucial roles for the recruitment of telomerase (Abreu et al., 2010; Schmidt et al., 2016; Zhong et al., 2012). POT1 suppresses RPA binding to the single-stranded G-rich telomeric strand and signaling by the ATR checkpoint kinase (Denchi and de Lange, 2007). In addition to the shelterin proteins, telomeres may contain roughly 200 additional proteins many of which provide crucial functions as mutations of a subset of them lead to telomere syndromes and cancer (Bartocci et al., 2014; Dejardin and Kingston, 2009; Grolimund et al., 2013). In addition, telomeres are transcribed into the long non-coding RNA TERRA which contributes to telomere structure and function regulating the recruitment of chromatin modifiers, telomerase and DNA processing enzymes (Azzalin and Lingner, 2015; Azzalin et al., 2007).

The replication of telomeric DNA by semiconservative DNA replication cannot proceed to the very end of the chromosome leading to continuous shortening of telomeric DNA from the ends with every round of DNA replication in cells that lack telomerase (Soudet et al., 2014). Telomerase, which in humans is expressed only in the germ line, during early embryogenesis and to some extent in stem cells can counteract telomere shortening. It adds telomeric DNA repeats to the 3′ ends of chromosomes using an internal RNA moiety as a template (Greider and Blackburn, 1989). In addition, to the end replication problem, telomere loss can occur in a stochastic fashion as the

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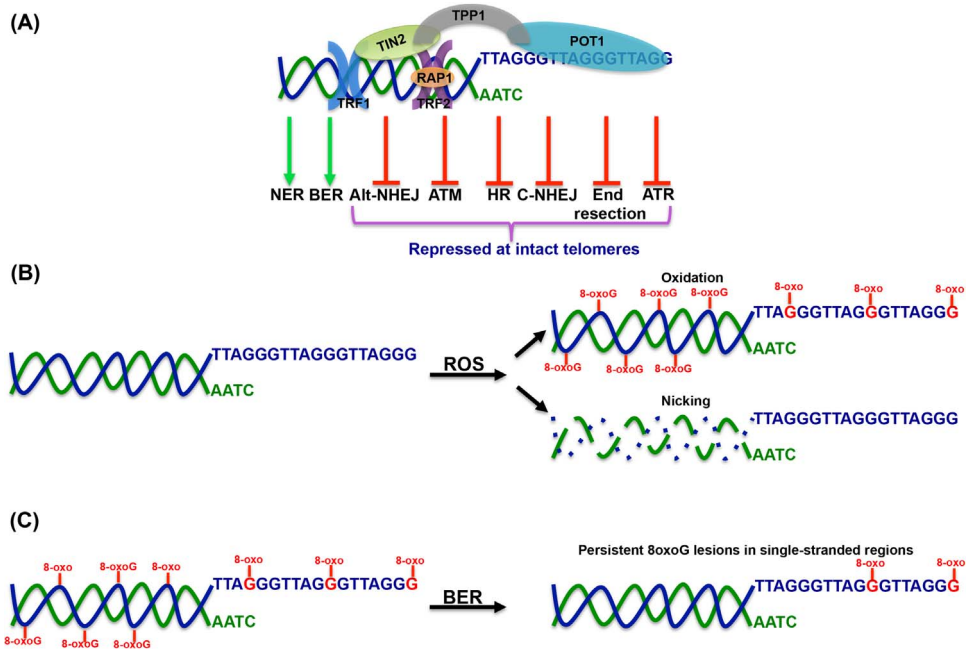

Fig. 1. Susceptibility of telomeres to oxidative damage (A) Suppression of DNA damage response (DDR) and repair pathways at telomeres. Shelterins disguise chromosome ends from DDR pathways and major DNA repair systems. Consequently damaged telomeric DNA may be repaired less efficiently. Nonetheless, double strand breaks within telomeric repeats can be repaired by alt-NHEJ. BER and NER mechanisms can remove oxidized nucleotides and DNA adducts, respectively, from telomeric DNA. **(B)** Intrinsic sensitivity of triplet G (GGG) repeat sequences to ROS-induced damage. The G-rich strand of telomeric DNA accumulates 8oxoG lesions upon exposure to free oxygen radicals and exhibits high frequency of single-strand break formation in the DNA backbone. **(C)** Inability of the BER pathway to remove ROS-generated lesions from single-stranded 3′-ends of telomeres which lack a complementary strand required for template dependent repair.

semiconservative DNA replication poses special difficulties to the replication machinery (Miller et al., 2006; Sfeir et al., 2009). The difficulties in replication are due to first, the propensity that single-stranded TTAGGG-repeats may adopt highly stable G-quadruplex structures during their replication that need to be unwound in order to serve as a template during replication. The DNA helicases Blm, Wrn and Rtel1 have been implicated in unwinding G-quadruplexes (Sfeir et al., 2009; Crabbe et al., 2004; Vannier et al., 2012). Second, the t-loop structures need to be unwound by Rtel1 (Sarek et al., 2015; Vannier et al., 2012). Third, TERRA can form DNA/RNA hybrid structures, which can interfere with replication. The THO-complex as well as RNase H have been implicated in suppressing TERRA/DNA hybrid structures at telomeres in *S. cerevisiae* and humans (Arora et al., 2014; Balk et al., 2013; Pfeiffer et al., 2013). UPF1 and other proteins involved in RNA surveillance also counteract TERRA presence at chromosome ends for telomere replication (Azzalin et al., 2007; Chawla et al., 2011). Forth, telomere replication is driven from origins of replication that are present in the subtelomeric DNA. Origin firing occurs only rarely from within telomeric repeat sequences (Drosopoulos et al., 2012). Therefore, the replication is unidirectional and stalled forks cannot be rescued from converging forks coming from the end of the chromosome.

An additional threat for telomeres is inefficient repair of its DNA when damaged. Double-strand DNA breaks can be repaired by homology directed DNA repair (HDR), NHEJ and alt-NHEJ. NHEJ and to some extent also HDR are repressed at intact telomeres (Sfeir and de Lange, 2012). In contrast, alt-NHEJ can repair double-strand DNA breaks that occur within telomeric repeats (Doksani and de Lange, 2016). The DNA mismatch repair machinery corrects single nucleotide mismatches and small insertions or deletions that arise during DNA replication. It is not known to what extent this pathway suppresses DNA mismatches at telomeres. However, defects in DNA mismatch repair genes have been associated with facilitation of telomere maintenance by DNA recombination in yeast cells in which telomerase had been deleted (Rizki and Lundblad, 2001). Whether this effect is caused by elevated base mismatches or whether other activities of mismatch repair proteins suppress the DNA recombination at telomeres is not clear. Nucleotide excision repair (NER) removes DNA modifications such as cyclobutane pyrimidine dimers (CPD) and pyrimidine 6-4 photoproducts that induce a distortion of the helical structure. This pathway is active at telomeres (Parikh et al., 2015). Base excision repair (BER) removes chemically altered bases from DNA (Jacobs and Schar, 2012). This includes base modifications caused by reactive oxygen species (ROS) such as 8-oxo-7,8-dihydro-guanine (8-oxoG) which frequently mispairs with adenine during DNA replication. In BER, a DNA glycosylase that recognizes a chemically altered base excises the damaged base. OGG1, NTH1, NEIL1, NEIL2, and NEIL3 are the five DNA glycosylases which are specific for removing oxidized DNA bases in human cells (Jacobs and Schar, 2012). OGG1 removes oxidized purines and NTH1 oxidized pyrimidines. Abasic sites or apurinic/apyrimidinic sites are cleaved by an AP endonuclease and processed by short-patch or long-patch base excision repair to replace one or more nucleotides at the site of lesion. BER is active at telomeres and its effects on telomere length will be discussed in further detail below.

In this review, we elaborate on how oxidative damage impacts telomere structure and function. We discuss the effects of ROS on telomeric DNA, protein composition and maintenance by telomerase. We describe which antioxidant enzymes and repair factors counteract oxidative damage. We review how telomere dysfunction may impinge mitochondrial biogenesis which in turn increases ROS and telomere damage. We discuss the effects of ROS and telomere damage on human health and how increased knowledge in this field might be exploited to reduce damage in healthy tissues or target telomere maintenance in cancer cells.

2. Susceptibility of telomeres to oxidative damage

ROS are generated by exogenous and endogenous sources (De Bont and van Larebeke, 2004). Exogenous sources include UV and ionizing radiation and a wide range of chemicals. Mitochondria are a major endogenous source as during oxidative phosphorylation at a low

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