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Review

Fanconi anemia proteins in telomere maintenance

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ABSTRACT

Mammalian chromosome ends are protected by nucleoprotein structures called telomeres. Telomeres ensure genome stability by preventing chromosome termini from being recognized as DNA damage. Telomere length homeostasis is inevitable for telomere maintenance because critical shortening or over-lengthening of telomeres may lead to DNA damage response or delay in DNA replication, and hence genome instability. Due to their repetitive DNA sequence, unique architecture, bound shelterin proteins, and high propensity to form alternate/secondary DNA structures, telomeres are like common fragile sites and pose an inherent challenge to the progression of DNA replication, repair, and recombination apparatus. It is conceivable that longer the telomeres are, greater is the severity of such challenges. Recent studies have linked excessively long telomeres with increased tumorigenesis. Here we discuss telomere abnormalities in a rare recessive chromosomal instability disorder called Fanconi Anemia and the role of the Fanconi Anemia pathway in telomere biology. Reports suggest that Fanconi Anemia proteins play a role in maintaining long telomeres, including processing telomeric joint molecule intermediates. We speculate that ablation of the Fanconi Anemia pathway would lead to inadequate aberrant structural barrier resolution at excessively long telomeres, thereby causing replicative burden on the cell.

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Contents

1. Introduction

1.1. Telomeres are a paradox

Telomeres are chromosome end nucleoprotein structures consisting of short tandem DNA repeats (5′-TTAGGG-3′ in humans and mice) and inherently associated proteins, called the shelterin complex (TRF1, TRF2, POT1, TPP1, TIN2, and RAP1) (Fig. 1A). Telomeres ensure genome stability by capping chromosome termini thereby preventing them from being recognized as broken DNA ends. Such protection of mammalian telomeres has been attributed to (i) the shelterin complex, where TRF2 and POT1 particularly have direct well-defined roles in protecting telomeres from activating ATM and ATR kinase pathways (Fig. 1A); (ii) unusual structures such as the 'T-loop' configuration, where the 3′-telomeric overhang is tucked away in a loop (Fig. 1B); and (iii) other non-shelterin accessory proteins with known functions in DNA

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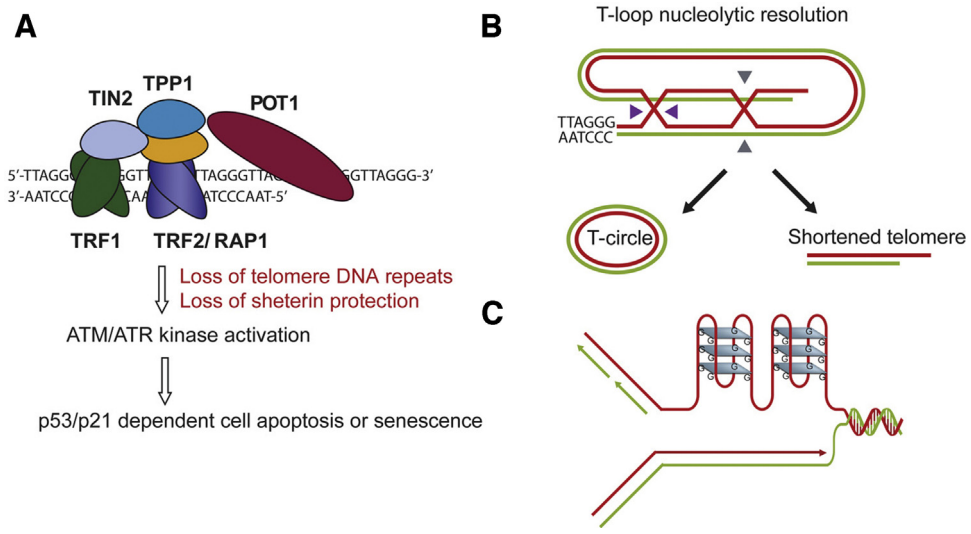

Fig. 1. Consequences of telomere dysfunction and telomeric unique structural and architectural features. (A) Telomeres, bound by the shelterin protein complex cap the chromosome ends against NHEJ, HR, DNA damage signaling, and nuclease degradation. Dysfunctional telomeres can arise due to loss of telomeric DNA repeats or loss of protection of shelterin, which activates ATM or ATR kinase pathways, leading to cell apoptosis and cellular senescence. (B–C) Telomeres present a challenging landscape for DNA metabolism, owing to their T-loop architecture (B) and G-rich sequence that makes it a hotspot for secondary G4 structure formation (C). Resolution of the double HJ in the T-loop would generate a shortened telomere and a circular telomeric DNA [60], a mechanism used for 'trimming' long telomeres in some human cells (B).

repair (including helicases and nucleases that can process/remove unusual structural impediments in telomeric DNA) [1]. Paradoxically, some of the above-mentioned features that enable telomeres to protect DNA ends may also act as impediments in its own maintenance thereby making DNA metabolism processes at telomeres a challenging task. Telomere maintenance entails several components, including length homeostasis (telomerase or ALT-sponsored [2,3]) and replication-recombination-repair. In addition, their G-rich sequence also makes telomeres more susceptible to oxidative DNA damage and formation of replication blocking G-quadruplex structures (G4) [4] (Fig. 1C).

1.2. Chromosomal instability and predisposition to cancer are the common links between FA and telomere dysfunction

Dysregulation of telomere maintenance such as defective length homeostasis (leading to critical shortening or over-lengthening), loss in protective function of shelterin proteins, and other defects in telomere biology leads to ATM/ATR kinase-involved DNA damage response or delays in DNA replication, resulting in genome instability, cell proliferation defects, cellular senescence or cell apoptosis (Fig. 1A) [5,6]. In humans, telomere attrition is associated with replicative cell senescence in culture, ageing populations, and environmental and lifestyle factors that contribute to ageing and ageing-related diseases. Telomere attrition is also linked to human disorders, *e.g.* dyskeratosis congenita (DC), aplastic anemia, and idiopathic pulmonary fibrosis [7–9]. A rare recessive disorder that results in aplastic anemia is Fanconi Anemia (FA) that is characterized by bone marrow failure, congenital abnormalities, increased susceptibility to cancer, and sensitivity to DNA interstrand crosslinking agents [10–12]. Interestingly, FA individuals are also reported to have (i) telomere loss/break in peripheral leukocytes; (ii) increased end-to-end telomere fusions; and (iii) overall shorter telomeres [13–16]. Proposed molecular mechanisms for this shortening include direct breaks at telomere sequences; replicative shortening; and accumulation of breaks due to defective DNA repair at telomeres and impaired response to oxidative stress [17–22]. Although currently there is lack of experimental evidence, as discussed in this review, our current knowledge alludes to a potential direct role of the FA pathway in telomere maintenance.

2. FA proteins in telomere maintenance

2.1. The FA pathway

Mechanistically, the FA syndrome is caused by mutations in genes involved in repair of DNA inter-strand crosslinks (ICLs), with about 19 gene products identified till date [10–12,23](Fig. 2A). Eight FA proteins (FANCA/B/C/E/F/G/L/M) form the FA core complex, and along with the ATR checkpoint kinase, regulate ubiquitination of the heterodimeric FANCD2-I (ID) complex that is recruited to the ICL lesion. The ID complex acts as a platform to coordinate repair activities at the ICL site with several downstream FA proteins (FANCP/J/D1/N/O/S/R/Q and FAN1). This includes bringing multiple nucleases at the lesion via their assembly on FANCP (or SLX4) (discussed below), thus creating nucleolytic incisions at the site, which are then repaired by homologous recombination (HR).

2.2. ID complex players involved in telomere maintenance

The shared genome instability phenomenon in telomere dysfunction and FA suggests possible connection(s) between FA proteins and telomere function. Mammalian telomeres are maintained either via extension by the nucleoprotein complex telomerase or via an alternate lengthening of telomeres (ALT) mechanism that relies on HR to synthesize new telomeric DNA. The key FA player FANCD2 has been shown to colocalize with the inherent telomeric protein TRF1 in ALT cells, in a FANCA, FANCL, and ATR-dependent manner, and depletion of FANCA and FANCD2 causes telomere loss and decrease in telomere sister chromatid exchange [24], suggesting a role for monoubiquitinated FANCD2 in ALT telomere maintenance through telomeric HR. TRF1 that directly binds to double-stranded telomeric DNA is believed to prevent replication defects in telomeres by recruiting the G4 structure resolving helicases BLM and RTEL1 [25,26]. However, TRF1 ribosylation by the telomere-associated poly(ADP-ribose) polymerase Tankyrase 1 (binds to TRF1) displaces TRF1 from telomeric DNA [27,28]. FANCD2 has been shown to interact with Tankyrase 1