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Telomeres and aging

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Telomeres (the TTAGGG repetitive DNA at the ends of linear chromosomes) are part of the 3D spatial organization of the nuclear genome. Long-range 3D chromatin interactions also establish specific patterns of regulated gene expression. An emerging area of interest is the role of telomere 3D looping with interstitial telomeric sequences (ITS) through interactions with telomere shelterin proteins. Telomeres form interstitial telomere loops (ITL) that interact with ITS and modify gene expression at distal genomic regions. Human laminopathies and telomeropathies often correlate with short telomeres. Since telomeres progressively shorten with increased turnover and chronological age in dividing somatic cells, ITLs may also change and have functional roles in normal and pathophysiological processes. Overall, telomeres help stabilize the nuclear genome with high fidelity throughout early adult life but diminish in post-reproductive age-associated pathology.

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Introduction

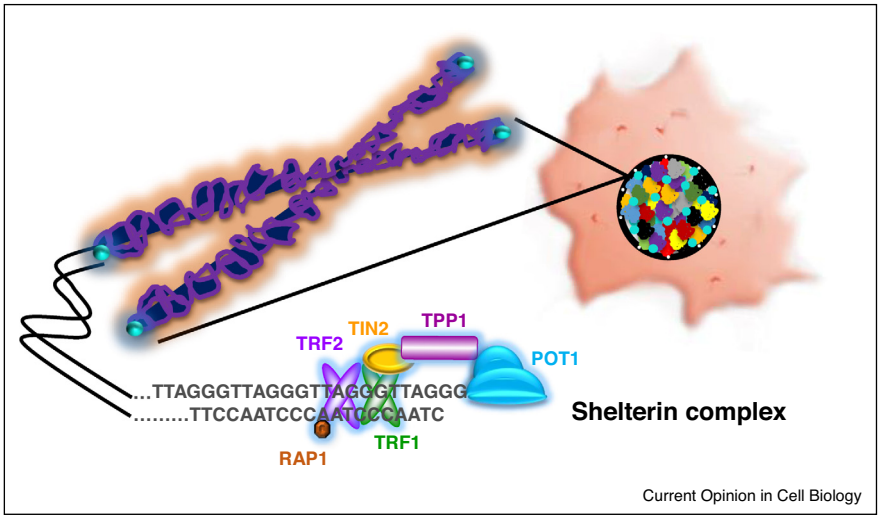
Three-dimensional (3D) chromatin looping mediate long-range interactions that bring distal genomic segments into close spatial proximity between enhancers and promoters that are linked to the regulation of gene expression [1•,2–4]. There are both cell type-specific and constitutive classes of genes that are regulated by 3D chromatin looping interactions. The ability to fold the entire human genome into the small volume of a typical nucleus involves occupancy of proteins such as CTCF (CCCTC-binding factor) and cohesion to form and maintain the chromatin loops resulting in insulated neighborhoods that are thought to protect genes from aberrant gene activation [1•,2–4]. However, the genome-wide landscape of long-range looping interactions and their dynamic properties across most lineages in humans remain largely uncharacterized. How progenitor cells differentiate through coordinated expression and repression of complex chromatin interactions remains an area of intense study. Even less well studied are the ends of linear chromosomes that are capped by thousands of hexameric telomeric $(TTAGGG)_n$ repeats [5] that also form 3D looping interactions. These types of interactions are particularly interesting since telomeres progressively shorten with increased aging and thus may provide a 'clocking' mechanism for gene regulation over long periods of time without initiating a DNA damage signaling response. A better understanding of the topological chromatin interactions at telomeres may provide new insights into how the genome and epigenome act in concert to regulate cell fate determinations during early human development and later in life as part of normal aging and disease progression.

Telomeres

Mammalian telomeres are repetitive DNA sequences, associated with the multimeric protein shelterin complex that facilitates formation of a lariat-like structure to shield the exposed ends of telomeric DNA from the DNA damage machinery [5,6]. The six member shelterin protein complex (Figure 1) includes TRF1 (telomeric repeat-binding factor 1) that binds to the canonical TTAGGG double-stranded telomeric repeats and interacts with TIN2 (TRF1-interaction nuclear factor 2). Another shelterin protein is TRF2 that also binds to double-stranded telomeric repeats and interacts with RAP1 (repressor/activator protein 1). POT1 (protection of telomeres 1) binds to single-stranded TTAGGG repeats and connects to TRF1 and TRF2 though a binding partner, TPP1, that also associates with TIN2. Information on how the complex of shelterin proteins maintain telomeres and preserve genomic integrity was recently reviewed [7•].

Due to incomplete lagging strand DNA synthesis, oxidative damage and other factors, progressive telomere shortening eventually results in cellular growth arrest and has been proposed as an initial proliferative barrier to tumor formation [8,9]. However, when the growth arrest initiated by a few shortened telomeres is bypassed due to loss of tumor suppressors and oncogenic changes, telomeres can continue to shorten eventually leading to chromosome bridge-fusion-breakage cycles that can result in genomic instability and an increased risk of cancer [9,10]. Eventually a mechanism is engaged to maintain telomeres as part of cancer development and this is almost universally accomplished by the reactivation of the telomerase reverse transcriptase (*TERT*) that produces

Figure 1



Human telomeres are repetitive DNA sequences at the ends of linear chromosomes. Telomeres function in nuclear architecture, chromosome positioning, and are often associated with the nuclear envelope. Telomeres also protect the linear ends of chromosomes from being recognized as DNA damage needing repair which occurs by interactions with the complex of six shelterin proteins. The very end of telomeric DNA consists of a single strand G-rich overhang that loops back and strand invades into the duplex TTAGGG repeats forming a T-loop. However, during replication the telomeres must unfold so the free end is accessible to the replication machinery. In total the telomere ends only account for ~1/6000th of the total genomic DNA in a cell. Telomeres progressively shorten with each cell division in the absence of a telomere maintenance mechanism eventually leading to a proliferation arrest that can be considered an initial potent tumor suppressor mechanism in large and long-lived mammals. However, loss of telomere protection can lead to telomere crisis and rare cells that escape crisis can promote cancer progression by almost universally activating telomerase.

telomerase enzymatic activity when associated with other essential components to form a ribonucleoprotein complex [11,12]. Telomerase synthesizes telomeric DNA using the integral or template telomerase RNA component (*TERC*). During early human development telomerase is active but becomes silenced between 12 and 18 weeks of gestation [13,14]. There is evidence that *TERT* alternative splicing may be involved in silencing telomerase [13–15] thus limiting the maximal length of human telomeres. In addition to alternative splicing other mechanisms such epigenetic changes involving telomere 3D looping may also be involved.

Mechanisms regulating telomere length and telomerase

There are heterochromatin-associated histone marks (H3K9 and H4K20) associated with nucleosomes at the canonical TTAGGG telomeres and the non-canonical subtelomeric degenerative repeats that are similar but not identical to the histone marks present in constituitive heterochromatin [16]. Thus, telomeres have more compacted nucleosomes (altered spacing) potentially silencing genes in the vicinity of the telomeres. Similar to yeast and fly chromosome ends, mammalian telomeres can transcriptionally silence nearby genes through a process known as TPE (Telomere Position Effects) supporting the concept there are multiple epigenetic modifications at mammalian telomeres that organize them into a unique chromatin structure [16,17]. TPE in humans is influenced by telomere length that involves histone hypoacetylation that can be disrupted by treatment with deacetylase inhibitors [17]. Thus, the length of telomere repeats may influence heterochromatin assembly at telomeres and in part regulate gene expression changes. The first human disease in which the TPE model of continuous heterochromatin spreading that declines with distance from the telomere was FSHD (facioscapulohumeral muscular dystrophy) [18]. In another study the *ISG15* gene located 1 megabase from the end of chromosome 1p was reported to be regulated by telomere length [19]. Because genes between *ISG15* and the telomere were not regulated by telomere length a different mechanism of gene regulation by telomeres was clearly involved.

Recently, telomere 3D organization has been implicated in cellular processes in addition to the well-established telomere role in end protection (Figure 2). Telomeres are also involved in a process known as interstitial telomere loops (ITLs) or telomere position effects over long distances (TPE-OLD) [20,21,22••,23,24••,25]. Understanding the mechanisms that regulate the maximal length of human telomeres during human embryonic development and the mechanisms of how progressive telomere shortening leads to epigenetic alterations and changes in gene expression associated with human aging and pathologies is a current area of interest.