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The Short and Long Telomere Syndromes: Paired Paradigms for Molecular Medicine

Susan E. Stanley^{1,2} and Mary Armanios^{1,3}

¹Department of Oncology and Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University School of Medicine Baltimore, MD 21287

²Medical Scientist Training Program, Johns Hopkins University School of Medicine Baltimore, MD 21287

³McKusick Nathans Institute of Genetic Medicine, Johns Hopkins University School of Medicine Baltimore, MD 21287

Summary

Recent advances have defined a role for abnormally short telomeres in a broad spectrum of genetic disorders. They include rare conditions such as dyskeratosis congenita as well pulmonary fibrosis and emphysema. Now, there is new evidence that some familial cancers, such as melanoma, are caused by mutations that lengthen telomeres. Here, we examine the significance of these short and long telomere length extremes for understanding the molecular basis of age-related disease and cancer.

The origins of telomere human genetics

Telomeres and telomerase were first discovered in *Tetrahymena thermophila*, a protozoan of no obvious clinical significance[1,2]. Genetic models in yeast, mice, and human cells subsequently established a framework for how chromosome ends are maintained before disease connections crystallized[3]. Now, abnormally short telomeres are appreciated to mediate common age-related disorders such as pulmonary fibrosis and emphysema[4]. While the clear connection between short telomeres and degenerative disease may have suggested a hypothetical benefit for long telomeres, new discoveries have uncovered a potential link between *long* telomeres and familial cancer syndromes[5–7]. Here, we review how extreme telomere length abnormalities, both short and long, inform understanding the molecular basis of diseases associated with aging as well as cancer.

Correspondence. Mary Armanios, M.D., 1650 Orleans St., CRB 1 Room 186, Baltimore, MD 21287, 410-502-3817, phone 410-502-6240 fax, marmani1@jhmi.edu.

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Telomere length is a “molecular clock” mechanism

Telomere shortening is considered one of the best-characterized mechanisms of cellular aging[4]. This claim builds on the fact that telomere length predicts the onset of replicative senescence[8,9]. Telomeres also shorten in humans with age, and in the past decade, it has become clear that abnormally short telomeres can cause several age-related disease phenotypes[4]. The progressive shortening of the TTAGGG telomeric sequence occurs because DNA polymerases cannot fully copy to chromosome ends[10]. Telomerase offsets this ‘end replication problem’ by synthesizing new telomere sequences[2,11,12]. When telomeres become critically short, they activate a DNA damage response[13], which provokes cellular senescence or apoptosis[14–18]; these responses underlie the progressive natural history of disorders that share the short telomere defect as a driving mechanism.

Several safeguards restrict telomere elongation in favor of net shortening with aging. They include a tight regulation of telomerase levels, as well as intrinsic factors at telomeres that limit excessive elongation by telomerase[19–21]. The expression of the reverse transcriptase component of telomerase, TERT, is also repressed in most adult tissues. In hematopoietic as well as other somatic stem cells, even though telomerase is expressed, its low levels do not offset the telomere shortening that normally occurs with aging[19,22–24]. As we will discuss here, genetic defects that disturb this telomere length homeostasis cause highly penetrant disease phenotypes.

The mammalian short telomere phenotype was first studied in telomerase null mice[14,15,25]. While telomerase loss alone has no clinical consequences in the first generation, late-generation telomerase null mice accumulate short telomeres[14,15,18,25,26]. The short telomeres cause degenerative organ failure indicating that the telomere length, and not telomerase loss, is the primary driver of the phenotype. Late-generation mice with short telomeres develop a stem cell failure phenotype, which is prominent in highly proliferative tissues such as the bone marrow and intestinal tract where the replicative potential of stem cells is critical for homeostasis[14,15,18,25,26]. The human short telomere syndromes recapitulate these phenotypes[21,27].

THE SHORT TELOMERE SYNDROMES

The human short telomere phenotype in high turnover tissues

Studies over the past decade have linked the human short telomere phenotype to a broad spectrum of disease[21]; it spans the entire age spectrum from infancy to adulthood (Figure 1). While at onset their clinical and histopathologic classification may show few shared features, there is growing appreciation for their unified natural history[28]. Their recognition as a single syndromic spectrum is critical for treatment decisions, because even though a single organ presentation may arise initially, the systemic telomere defect complicates treatment. Because some of these complications can be averted, the molecular grouping of disease across organs under the short telomere syndrome umbrella exemplifies a molecular medicine paradigm that directly impacts patient care[27,29,30].

The short telomere phenotype in children and young adults represents more severe disease[4]. Bone marrow failure is its most common first manifestation, and stem cell transplantation alleviates this condition pointing to a stem cell-autonomous defect in this compartment[21,31–34]. Affected individuals are also prone to developing intestinal villous atrophy, immunodeficiency and infertility[21,27,35]. Pediatric presentations may also be recognized in historically defined syndromic entities. Dyskeratosis congenita was the first disorder to be linked to telomerase mutations and short telomeres[36,37]; it is classically defined by abnormalities in the skin, mucosa and nails[38,39]. Hoyeraal-Hreidarsson syndrome manifests in infancy and is characterized by developmental delay, enterocolitis, and immunodeficiency[27,40–42]. The criteria for recognizing Hoyeraal-Hreidarsson syndrome and dyskeratosis congenita may be specific; but they identify only a small subset of all short telomere syndrome presentations[43].

The slow turnover phenotype in short telomere syndromes

Lung disease is the most common presentation of short telomere syndromes and it represents an attenuated, adult-onset phenotype (Figure 1)[43]. Two types of lung disease have been linked to mutant telomerase and telomere genes. Idiopathic pulmonary fibrosis and the related interstitial diseases are marked by progressive lung scarring. Familial pulmonary fibrosis is a common manifestation of short telomere syndromes[43], and six mutant telomerase and telomere genes explain one-third of cases[44–49]. Telomerase mutations have also been recently linked to the risk of emphysema[50]. The frequency of telomerase mutations in severe emphysema rivals alpha-1 antitrypsin deficiency, which until recently was its only known Mendelian cause[50]. In families with telomerase mutations, emphysema appears in smokers, while pulmonary fibrosis is the predominant pathology in never smokers[50]. This apparent phenotypic heterogeneity points to a profound gene-environment interaction in a Mendelian disorder in which a single mutation causing telomere shortening provokes fibrotic scarring in never smokers and emphysematous airspace destruction in smokers[50]. In animal models, telomere dysfunction in alveolar stem cells triggers cellular senescence and recapitulates many features of the human lung pathology including recruitment of an inflammatory response[51]. The fibrosis-emphysema caused by short telomeres may therefore be driven by alveolar stem cell failure, and this biology points to potential new approaches to their treatment[4,51]. Pulmonary fibrosis and emphysema are estimated to affect 100,000 and 5 million individuals, respectively, in the United States alone[52,53]. Their disease burden, along with their close association with telomere genetics, makes the short telomere syndromes the most prevalent among the premature aging disorders.

Cancer in the short telomere syndromes

Although the majority of the premature mortality in the short telomere syndromes is caused by degenerative organ failure, there is also an increased risk for cancer. Cancer is estimated to affect 10% of dyskeratosis congenita cases, and when it arises, it is diagnosed at a younger age than the general population[54]. The basis of the cancer prone state in the short telomere syndromes is not understood, but its predilection appears to be for high turnover tissues where stem cell failure also occurs. Short telomere syndromes are associated with an increased incidence of non-melanoma skin cancers, as well as squamous cell carcinomas of

the head and neck[54], but the highest risk is for myelodysplasia and acute myeloid leukemia. These latter bone marrow-derived malignancies are sometimes a first manifestation of telomere-mediated disease[54,55]. In the bone marrow, the stem cell failure state and progressive stem cell dropout may cause replication errors in surviving stem cells that could lead to a clonal advantage. Short telomere patients may also have impaired cancer surveillance because of immunosenescence[21]. All in all, even though the rate of some types of cancers in short telomere syndromes is higher than in the general population, its overall incidence is dwarfed by organ failure which accounts for 90% of the mortality[38].

The genetics of short telomere syndromes

Short telomere syndromes show Mendelian inheritance, and as of this writing, 11 genes have been identified[34,36,48,56–67] (Figure 2). Together, they explain 50–70% of the short telomere Mendelian phenotype. Mutations in these genes disturb telomere homeostasis by impairing telomerase biogenesis, affecting its catalytic functions, its recruitment by shelterin, or the stability of telomere replication machinery components (Figure 2). The predominant phenotype and age of onset do not depend on the gene or the mutation type, but is determined by the extent by which a given mutation causes telomere shortening[68]. The most prevalent cause of short telomere syndromes is heterozygous loss-of-function mutations in *TERT*, which manifest in adults as autosomal dominant familial pulmonary fibrosis[4] (Figures 3A). In rare cases, biallelic *TERT* mutations have also been described and they are associated with more severe short telomere defects and early-onset disease[69]. Mutations in *RTEL1* and *PARN* also show a similar pattern of adult- and pediatric-onset disease depending on whether one or two alleles are affected, respectively[48,63,70].

Genetic anticipation and the evolving disease pattern in the telomere syndromes

Two features distinguish the genetics of autosomal dominant short telomere syndromes from other Mendelian disorders. They also explain the unique natural history of these disorders. The first is that autosomal dominant families with short telomere syndromes show genetic anticipation, an earlier and more severe onset of disease in successive generations[57,71] (Figure 3A). Telomere shortening is a second established molecular mechanism for genetic anticipation in addition to trinucleotide repeat expansion. The successive telomere shortening eventually precipitates severe pediatric disease and/or infertility, leading to loss of the mutation in that lineage[46,68]. Telomere gene mutations thus tend to be private to each autosomal dominant kindred, leading to significant allele heterogeneity. In addition to the earlier onset in later generations, the disease evolves from slow-turnover tissues in older generations (e.g. pulmonary fibrosis-emphysema) to a high-turnover phenotype in younger generations (e.g. bone marrow failure)[68]. The rate of genetic anticipation and disease evolution within a family depends on the extent of telomere shortening caused by a given mutant allele across a generation[72]. As we will highlight below, cancer prone families with mutations that conversely promote telomere lengthening also show evidence of genetic anticipation.

THE LONG TELOMERE SYNDROMES

The price of long telomeres in an increased risk of melanoma

The premature aging phenotypes caused by abnormally short telomeres may intuitively suggest that long telomeres confer an advantage for health and lifespan. However, there is increasing evidence that such a view may be overly simplistic. In the past two years, mutations that appear to lengthen telomeres have been linked to an increased risk of cancer. It is these familial cancer syndromes that we posit here are *long* telomere syndromes (Figures 1). They are also caused by mutations in telomerase and shelterin genes and two of these genes have been implicated also in the short telomere syndromes (Figures 2 and 3). The cancer spectrum in these putative long telomere syndromes is not yet fully defined, but so far it appears to be particularly enriched for melanoma and glioma[5–7,73,74]. Notably, these cancers are different from the squamous cell and hematologic malignancies that arise in the short telomere syndromes.

Mutations in telomere genes that cause familial cancers

Evidence that mutant genes that may promote telomere lengthening cause familial cancer came first from a large melanoma kindred that carried an activating mutation in the *TERT* promoter[5]. This mutation creates an E-twenty-six (ETS) binding site that turns on *TERT* transcription[5,75,76]. Such a mechanism contrasts with the *TERT* loss-of-function mutations seen in the short telomere syndromes that impair the enzyme's catalytic functions[57] (Figure 3A). Somatic *TERT* promoter mutations are also found in 70% of melanomas[75] as well as a number of other solid tumors[77]. Their high prevalence makes *TERT* promoter mutations some of the most common somatic mutations seen in human cancer and points to telomerase abundance as critical in cancer initiation and progression.

Since the initial description of a *TERT* promoter mutation in a family with melanoma, germline mutations in three other telomere gene, all encoding shelterin components, have been linked to familial melanoma and glioma[6,7,73,74] (Figure 2). They include *POT1*, *TPP1* and *RAP1*[6,7] (Figure 2). Like *TERT*, mutations in *TPP1* can cause both short and long telomere syndromes. *TPP1* is a shelterin component that has been implicated in telomerase recruitment, but it also functions to prevent telomerase access to the telomere[78–80]. Its dual functions explain the contrasting net effect of *TPP1* mutations on telomere length. The *TPP1* single amino acid deletion falls in the TEL patch domain; this impairs telomerase recruitment resulting in net shortening[61,62]. The resulting disease phenotype is marked by stem cell failure and a small increased cancer risk. In contrast, *TPP1* nonsense mutations in cancer prone families disrupt protein stability, and are predicted to allow improved telomerase access and promote telomere elongation[62,73,80]. Based on the genetic anticipation documented for short telomere syndromes, it would be expected that long telomere length may similarly be expected to be inherited across generations[18,26,57,81]. A close examination of the published pedigrees interestingly shows a pattern of genetic anticipation for the age of melanoma-related diagnosis and mortality[6,7,73]. While it is theoretically possible that lead time bias (i.e. the earlier detection of cancers because of earlier screening) could explain this pattern, the fact that this genetic anticipation occurs for the age at death as well as diagnosis favors a model where

progressively longer telomeres promote an earlier, more aggressive cancer course in later generations (Figure 3B).

How would abnormally long telomeres predispose to melanoma?

Studies over the past two decades in animal models shed light on how long telomeres may promote cancer-related mortality. Although mice with short telomeres show limited survival because of their stem cell failure phenotypes, in cancer prone contexts they show a paradoxical advantage in overall survival[82–85]. This benefit has been reproduced across several cancer prone models, including oncogene-driven cancers, such as *Myc* and *K-ras*, as well as those driven by loss of tumor suppressors such as *Apc* and *Ink4a*[82–85]. The survival advantage is seen despite the fact that short telomere mice accumulate more micro-tumors, because short telomeres provoke apoptosis and senescence checkpoints in pre-cancers[83,86]. Thus, short telomeres confer an overall benefit at the organismal level in animal models where cancer is induced by a single driving mutation.

Evidence from population studies also supports an association between long telomeres and cancer risk. This association is best documented in cutaneous malignant melanoma[87–90], an intriguing observation in light of the cutaneous melanoma-rich phenotype documented in the long telomere syndromes. Cutaneous malignant melanoma is marked by some of the highest mutation burdens among human cancers because of the mutagenic effects of ultraviolet light[91]. Its clustering in families and individuals who have long telomeres underscores an important role for the telomere-mediated replicative senescence checkpoint in suppressing tumors where mutagenesis is environmentally induced. Unrestricted proliferation when telomeres are long would increase the likelihood of sustaining driver mutations that eventually promote a clonal advantage and metastasis. The role of long telomeres in promoting cancer is however nuanced, and the association with cancer risk may be tissue and cell type specific. For example, the risk of non-melanoma skin cancers (e.g. squamous cell carcinoma) is associated with short telomere length[92]. The available evidence thus suggests that distinct cancer phenotypes are associated with both short and long telomere syndrome extremes, and that a melanoma-rich phenotype will be a hallmark of long telomere syndromes.

SUMMARY AND LOOKING AHEAD

Emerging discoveries have painted a rich mosaic of how telomere length abnormalities at the extremes play a role in disease. The short telomere syndromes unite a group of stem cell failure disorders that share a single molecular pathology. Their grouping informs treatment and pathogenesis paradigms for common, poorly understood conditions especially lung disease. The short telomere phenotype overlaps with diseases that are normally acquired with aging, and it is associated with a modest cancer risk. At the other extreme, the long telomere syndromes manifest as a highly penetrant cancer-prone state. They are enriched for cutaneous melanoma presumably because in the setting of environmentally induced mutagenesis, the loss of the replicative senescence checkpoint promotes carcinogenesis. Both disease extremes point to the importance of a telomere length equilibrium in maintaining stem cell homeostasis with aging while simultaneously minimizing cancer risk.

The profound disease phenotypes caused by extreme telomere length disturbances raise the possibility that targeting telomere length may be a plausible therapy strategy. In the short telomere syndromes, replenishing defective stem cells, such as is currently done with bone marrow transplantation, or aiming to elongate telomeres, could be clinically beneficial. In contrast, for long telomere-associated cancers, inhibiting telomerase could be effective in preventing or treating cancer. How much leeway is available to exploit this delicate system therapeutically remains to be determined, and any treatment approach will have to consider these multiple safeguards at telomeres that favor moderation over excess.

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Figure 1. Telomere length extremes and their predominant clinical manifestations

Telogram showing the telomere length range across the age spectrum with percentile lines defining the normal range at every age. The short telomere syndromes have typical manifestations that are represented by the red circles at the typical age of onset. Familial melanoma and glioma have been linked to mutations that putatively cause long telomeres.

Figure 2. Telomerase and telomere components mutated in both short and long telomere syndromes

The 'S' subscript indicates a link to short telomere syndromes ($n = 11$ genes), while the 'L' superscript indicates a link to long telomere syndromes ($n = 4$ genes). Mutant components are shown in color and gray denotes telomere components not known to be linked to disease. These mutations affect telomerase catalytic activity or processivity (TERT and TR), telomerase biogenesis (dyskerin encoded by *DKC1*), NOP10 and NHP2, or telomerase trafficking (TCAB1 also known as WRAP53). Mutations in telomere syndromes may also fall in the shelterin components: TIN2 (encoded by *TINF2*), TPP1 (encoded by *ACD*), POT1, or RAP1 (encoded by *TERF2IP*). CTC1 and RTEL1 affect lagging strand synthesis and telomere replication, respectively. PARN is involved in RNA processing and deadenylation.

Figure 3. Genetic anticipation in the autosomal dominant short and long telomere syndromes
(a) In the short telomere syndromes, successive telomere shortening across generations manifests in disease that shows an earlier age of onset. There is also an evolving pattern with ancestors developing lung disease and their progeny having a higher incidence of high turnover phenotypes such as bone marrow failure. **(b)** Long telomere syndromes appear to also show genetic anticipation of the melanoma phenotype; this is presumably caused by inheritance of long telomeres (right panel). Mutations in *TERT* have been linked to both syndromes with short telomere syndromes being caused by loss-of-function mutations (a), while familial melanoma is caused by promoter gain-of-function mutations that turn on *TERT* transcription (b).