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Syndromes of Telomere Shortening

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Abstract

Telomeres and telomerase were initially discovered in pursuit of questions about how the ends of chromosomes are maintained. The implications of these discoveries to age-related disease have emerged in recent years with the recognition of a group of telomere-mediated syndromes. Telomere-mediated disease was initially identified in the context of dyskeratosis congenita, a rare syndrome of premature aging. More recently, mutations in telomerase components were identified in adults with idiopathic pulmonary fibrosis. These findings have revealed that the spectrum of telomere-mediated disease is broad and includes clinical presentations in both children and adults. We have previously proposed that these disorders be collectively considered as syndromes of telomere shortening. Here, the spectrum of these disorders and the unique telomere genetics that underlies them are reviewed. I also propose broader clinical criteria for defining telomere-mediated syndromes outside of dyskeratosis congenita, with the goal of facilitating their diagnosis and highlighting their pathophysiology.

Keywords

cryptogenic liver cirrhosis; stem cell; shelterin; dyskerin; interstitial lung disease

TELOMERASE AND TELOMERES

Telomeres are DNA-protein structures that protect chromosome ends. Telomeres consist of TTAGGG repeats that are bound by a specialized protein complex known as shelterin (54). Because of the end-replication problem (24,52), telomeres shorten successively with each cell division, and short telomeres activate a p53-dependent checkpoint that leads to apoptosis or senescence (Figure 1) (7,11,20,31,34,40,69). Telomerase solves the end-replication problem by synthesizing new telomeres (26,27; for a review see 9,29). Telomerase has two essential components: telomerase reverse transcriptase (hTERT), the catalytic component, and telomerase RNA (hTR, also known as hTERC for telomerase RNA component) which provides the template for telomere addition (21,26–28,42,50).

Telomerase biogenesis requires the assembly of hTERT and hTR into a stable complex that can function at telomeres (13). hTR contains a box H/ACA motif, similar to small nucleolar RNAs, that is required for RNA trafficking and stability (12,46–48). The box H/ACA motif allows hTR to associate with the dyskerin complex, a four-protein core that contains the dyskerin protein as well as three other nucleolar proteins: NOP10, NHP2 and GAR1 (46). Of the six components that make up the telomerase ribonucleoprotein, mutations in five components have been identified in humans with features of a telomere syndrome. More recently, mutations in the shelterin component *TINF2* were also found in DC patients (Figure

DISCLOSURE STATEMENT
I am not aware of any factors that might be perceived as affecting the objectivity of this review.

2;Table 1) (61). The association of essential telomerase and telomere components with disease has brought telomere biology to the forefront in understanding a group of disorders that we have referred to as syndromes of telomere shortening (2,5,6).

DYSKERATOSIS CONGENITA (DC) IS A DISEASE OF SHORT TELOMERES

Disease-associated mutations in telomerase components were first discovered in the context of DC. DC is a rare syndrome of premature aging that was recognized as a clinical entity nearly a century ago (see Reference 74 for a review of the history). It derives its name from features initially recognized by clinicians who coined the term based on a triad of mucocutaneous features that they noted in male children: oral leukoplakia, skin hyperpigmentation, and nail dystrophy/ridging (17). The triad was noted to be associated with premature mortality due to bone marrow failure in aplastic anemia (74). In 1998, the gene encoding dyskerin, *DKC1*, was identified in X-linked families by linkage and positional cloning (33,37a). Homology studies revealed dyskerin to be a putative box H/ACA RNA-binding protein (33). The link with telomerase then came from important insights into telomerase RNA structure. First, it was noted that hTR contains a box H/ACA motif and thereafter, that X-linked DC patients had lower levels of telomerase RNA and short telomeres, consistent with the fact that *DKC1* mutations disrupt hTR maturation and stability (48). When a subsequent linkage study of a large Iowa family with autosomal dominant DC included the telomerase RNA locus at 3q, the *hTR* gene was an important candidate, and this family was found to harbor a large deletion of the 3′ end of *hTR* (72). We subsequently identified a three-generation family, Johns Hopkins Family 1, which carried a functionally null allele in the catalytic domain of hTERT (5). Mutations in *NOP10* and *NHP2*, components of the dyskerin complex, have also been identified in rare autosomal recessive families 71, 77).

Recently, heterozygous mutations in the shelterin component *TINF2*, through yet-unknown mechanisms, were identified in severe cases of DC (61,75). Individuals with *TINF2* mutations have severe manifestations and usually present in childhood. The majority of cases described have spontaneous mutations highlighting the detrimental effect of such mutations and their intolerance across generations (61,75) (Table 1).

HAPLOINSUFFICIENCY OF TELOMERASE LEADS TO ANTICIPATION IN AUTOSOMAL DOMINANT FAMILIES

Over the past decade, it has become evident that DC is a disease of short telomeres. In autosomal dominant families, mutations in *hTR* and *hTERT* lead to haploinsufficiency of telomerase and affected families display genetic anticipation, an earlier and more severe onset of phenotypes with successive generations (5,72,82). The anticipation occurs because of an accumulation of short telomeres across generations and highlights the role of telomere length, and not only telomerase mutations, in determining disease onset and severity (Figure 3) (5,73). Mutations in *hTERT* and *hTR* can thus lead to diverse phenotypes where severity depends on which generation is examined. For example, some family studies point to a pattern where in older generations, mutations in *hTERT* and *hTR* appear clinically as adult-onset pulmonary fibrosis. Later generations more frequently present in childhood with aplastic anemia along with classic features of DC (5,6).

CHILDHOOD PRESENTATIONS OF SYNDROMES OF TELOMERE SHORTENING

Telomere syndromes have multisystem organ presentations that manifest across the age spectrum. This heterogeneity has posed unique challenges to their recognition as well as their nomenclature. The most severe form is Hoyeraal-Hreiderasson syndrome, a rare disorder that

is usually diagnosed in the first months of life. Newborns and children with this condition have impaired pre- and postnatal growth, progressive aplastic anemia, severe immunodeficiency, and cerebellar hypoplasia (37,80). A subset of these patients has identifiable mutations in *DKC1* and *TINF2* (37,75,80). Homozygous mutant *hTERT* alleles have also been identified in consanguineous families who may clinically appear to have autosomal recessive inheritance. However, in these families, parents who are heterozygous mutation carriers have mild disease, whereas homozygous mutation carriers present in childhood with Hoyeraal-Hreiderasson syndrome or DC (43).

Individuals who carry mutations in *DKC1* usually come to medical attention in the first two decades of life (17). According to the International Registry in England, which follows a large cohort of classic DC patients, the most frequent causes of mortality in X-linked patients are aplastic anemia (80%), followed by pulmonary fibrosis and cancer (17). In addition to its role in the biogenesis of telomerase RNA, dyskerin catalyzes uridine to pseudouridine modification in ribosomal RNA, a modification critical for ribosomal RNA maturation and function (Decatur, Lafontaine, Ni and Yang, see numbers on attached sheet). This parallel function of dyskerin has raised the possibility that patients with mutations in *DKC1* may have both telomere and ribosomal defects and may explain the earlier onset compared with patients with mutations in *hTERT* or *hTR* (60). However, defects in pseudouridine modification in ribosomal RNAs have not been detected in cell lines from X-linked DC patients (48,77). Furthermore, mutations in *DKC1* can lead to significant declines in hTR levels, as little as one fifth of wild-type, consistent with the fact that *DKC1* mutations lead to accelerated phenotypes because of a loss of greater than half the dose of available telomerase (48,77). The fact that mutations in the shelterin component *TINF2* lead to severe disease suggests that telomere defects alone are sufficient to mediate early-onset presentations of DC.

APLASTIC ANEMIA ALONE CAN BE A PRESENTATION OF A TELOMERE SYNDROME

Mutations in *hTERT* and *hTR* lead to the most heterogeneous clinical phenotypes. Early on, the finding that aplastic anemia can precede the mucocutaneous features of DC implied that the dermatologic features that originally defined and gave DC its name are not canonical for its diagnosis (5,6,22). Subsequently, screening studies identified germline mutations in *hTR* and *hTERT* in ~3% of adults with so-called acquired aplastic anemia (81,82). Many of these patients had family members with hematologic abnormalities, suggesting that a careful family history could enrich for aplastic anemia patients who carry germline mutations in the essential telomerase genes (82). Nonhematologic manifestations of a telomere syndrome have not been systemically examined in this population. A small subset of patients with familial aplastic anemia and constitutional aplastic anemia, ~5%, also carry mutations in either *hTR* or *hTERT* (18,71).

A SUBSET OF IDIOPATHIC PULMONARY FIBROSIS (IPF) PATIENTS FALLS ON THE SPECTRUM OF TELOMERE SYNDROMES

The early study of syndromes of telomere shortening focused on hematologic manifestations as aplastic anemia was the most common cause of mortality in young patients with classic DC. In our study of Hopkins Family 1, we noted that in addition to anticipation of the aplastic anemia phenotype, pulmonary fibrosis and liver disease manifested earlier and more severely with each generation (5). The genetic anticipation was associated with progressive telomere shortening, implying that telomere length determined the onset of organ failure both within as well as outside of the bone marrow. In Hopkins Family 1, the pulmonary fibrosis phenotype had a pattern identical to a clinical entity known as IPF, a progressive scarring of the lung of

unknown etiology that ultimately leads to respiratory failure (5). Since some individuals in Hopkins Family 1 had their most prominent symptoms in the lung and the IPF phenotype was a dominant trait in this family, we hypothesized that *hTR* and *hTERT* may be candidate genes in familial IPF where the inheritance is also known to be autosomal dominant (6). Using this candidate gene approach, we identified germline mutations in both of the essential components of telomerase in a subset of families with IPF (6). In another study, the *hTERT* locus was identified in a genome-wide linkage study, which led to the characteriztion of hTERT, and subsequently hTR, mutations in families with pulmonary fibrosis (66). Collectively, these studies identified loss-of-function *hTERT* and *hTR* mutations in 8%–15% of families with IPF. Germline mutations in *hTERT* and *hTR* are also present in 1%–3% of apparently sporadic cases of IPF (2,15,66).

SHORT TELOMERES ARE A RISK FACTOR FOR PULMONARY FIBROSIS

To examine the relevance of telomere shortening broadly, we measured telomeres in IPF patients with sporadic disease. IPF patients had short leukocyte and alveolar telomeres, in the range of known telomerase mutation carriers (2). Cronkhite et al. also reported short telomeres in this population (15). Telomere length is a heterogeneous trait across populations (68), and these cross-sectional studies support the idea that the IPF phenotype enriches for individuals with the shortest germline telomeres and that such individuals are at increased risk for developing a telomere-mediated disorder in the lung that manifests as IPF (2). In support of this idea, sporadic IPF patients have a greater than expected incidence of cryptogenic liver cirrhosis, another feature of a telomere syndrome (2). The observation that lung and liver fibrotic disease cluster together suggests that, in at a least a subset of pulmonary fibrosis patients, short telomeres are likely genetic mediators of disease and can predispose to other features of a telomere syndrome in this population (2).

PULMONARY FIBROSIS IS THE MOST COMMON CLINICAL MANIFESTATION OF MUTANT TELOMERASE GENES

In contrast to DC, which is a rare disorder largely limited to reported cases in the literature, and aplastic anemia, which has an incidence of 1 to 5 per million; IPF and related disorders are common and have a prevalence of at least 90,000 with an annual mortality of 15—20,000, similar to common cancers (53,55). The prognosis for patients with IPF is poor, with a median survival of three years from the time of diagnosis (1). Currently, there are no approved therapies, and progress in the area of treatment has been hampered by the poorly understood etiology of IPF, as the label idiopathic implies (1). The presence of detectable telomerase mutations in this population (8–15% of families, 1–3% of sporadic cases) makes pulmonary fibrosis the most common manifestation of a syndrome of telomere shortening (2,6,15,66). This prevalence rate also makes dominant inheritance the most common form of transmission of a syndrome of telomere shortening.

Although mutations in telomerase components have been identified only in a small subset of sporadic patients, the presence of short telomeres broadly may explain, at least in part, the predilection of this disorder to older individuals (2). IPF is a disease of aging and its incidence increases 100-fold from 3 per 1,00,000 in adults less than 35 years to as much as 277 per 1,00,000 in men over 75 years (55). In elderly populations, asymptomatic changes of IPF are also frequently observed on CAT scan, highlighting the fact that the IPF pattern may be a manifestation of aging in the lung (2). That short telomeres mediate pulmonary fibrosis in the setting of IPF provides a rationale for pursuing translational strategies aimed at preventing telomere shortening or its cellular consequences as a therapeutic approach (6).

IPF is the most common of idiopathic interstitial pneumonias, a group of interstitial lung disorders that commonly share a pattern of progressive scarring due to an unknown etiology (1). IPF accounts for 70% cases of all idiopathic interstitial pneumonia. Different subtypes of idiopathic interstitial pneumonia histologies are often diagnosed in the same patient and within a single family, even though the pathophysiology is presumably identical (66, **66b**). Different subtypes have also been observed within families with known telomerase mutations (6,15). Additionally, upper lobe predominant disease has been observed in some families with known telomerase mutations (15). The new insights from genetics may, in the future, play a role in refining the diagnosis and molecular classification of interstitial lung disease.

APLASTIC ANEMIA AND ORGAN FIBROSIS CLUSTER IN PATIENTS AND FAMILIES WITH SYNDROMES OF TELOMERE SHORTENING

The careful clinical study of families who carry telomerase mutations has identified a pattern of disease that has not been previously appreciated: a clustering of aplastic anemia with disorders of fibrosis in the lung and liver. This clustering is best described in families with mutations in *hTERT* and *hTR*. In the majority of cases, IPF probands with telomerase mutations had a family history that was positive only for other cases of pulmonary fibrosis (6). However, in a large family, when we probed the family history, we documented four cases of aplastic anemia in addition to six cases of IPF (6). The clinical observations in this family confirmed that the telomere-related spectrum can include both aplastic anemia and organ fibrosis in the same individual and within a single family. Hopkins Family 1 also embodied these features (5). To our knowledge, no other known syndrome explains the clustering of these features, and the genetics of telomere syndromes now makes it clear that this is a distinct clinical entity. Thus, although the early twentieth century descriptions of DC were limited to children with the most severe manifestations, the clustering of aplastic anemia with organ fibrosis suggests that syndromes of telomere shortening have their most common manifestations in adulthood.

Aplastic anemia is a likely a marker of more severe phenotypes in individuals with mutant telomerase. Mutation carriers who present first with aplastic anemia are generally younger than those who present with IPF. In a family with ten affected individuals, individuals with aplastic anemia were, on average, two decades younger than those with IPF, suggesting that individuals who initially present with IPF may have a more attenuated phenotype compared with those with aplastic anemia (6).

ORGAN FAILURE IN THE BONE MARROW, LUNG, AND LIVER DEFINES A SYNDROME OF TELOMERE SHORTENING

While the incidence of syndromes of telomere shortening is not known, defining their diagnostic criteria will facilitate their recognition and likely reveal that they are more common than previously appreciated. Syndromes of telomere shortening have clinical manifestations in multiple organs; however, three main causes contribute to most of the morbidity and mortality: organ failure in the bone marrow, lung, and liver (Figure 4). I would propose that these three features are sufficient to define a syndrome of telomere shortening in individuals and families who lack the classic DC features. Organ failure in this setting frequently seems idiopathic after a thorough work-up and is often mistaken for an autoimmune process, although it does not respond to immunosuppression. The poor response to immunosuppression has been best documented in aplastic anemia, but IPF is also characteristically unresponsive (1,6,82). Each of these features has its own spectrum of severity that ranges from asymptomatic laboratory abnormalities to decompensated organ failure. I have summarized these features based on the literature and observations from our cohort and clinical experience (Table 2) (2, 5,6,15,38,73). Currently, decompensated organ failure in the setting of syndromes of telomere

shortening is only definitively treated with organ transplant. A thorough personal and family history in individuals with these features is essential for making decisions about diagnostic work-ups, therapeutic options as well as for appropriate genetic counseling.

RECOGNIZING PATIENTS WITH SYNDROMES OF TELOMERE SHORTENING IS CRITICAL TO TREATMENT DECISIONS

Ample evidence from the bone marrow transplant experience reveals that individuals with DC are exquisitely sensitive to DNA-damaging agents in preparative regimens. Importantly, individuals with DC who undergo bone marrow transplant for aplastic anemia most frequently suffer morbidity and mortality from pulmonary fibrosis and liver failure even when they appear to have intact function in these organs at the time of transplant (16,57,79). This observation highlights the limited reserves that patients with short telomeres have in the lung and liver and their poor capacity to repair DNA damage after injury from chemotherapy and radiation. Exquisite toxicity to radiation and chemotherapy has also been documented in mice with short telomeres (30,59,78). Nonmyeloablative bone marrow transplant options should be considered for aplastic anemia patients with known mutations in telomere or telomerase components, and evaluations should be undertaken in specialized centers. Altogether, the clinical experience in bone marrow transplant for aplastic anemia emphasizes the need to identify patients prospectively based on careful personal and family histories for optimal care and risk stratification. The prognostic relevance of mutations in telomerase for IPF patients who undergo lung transplant is an active area of research (15).

PATIENTS WITH DC ARE CANCER PRONE

Cancer predisposition in syndromes of telomere shortening is best described in the setting of DC where as many as 10% of deaths are due to a cancer diagnosis (4). The cancer spectrum has a particular predilection to tissues of high turnover where organ failure also occurs: the skin, oral mucosa, and bone marrow. DC patients are at increased risk of mylodysplasia and acute myeloid leukemia (4, 4b). Since aplastic anemia itself has an associated increased risk for transformation to acute myeloid leukemia, it is unclear whether DC patients with aplasia have an added predisposition. An increased incidence of squamous cell cancers of the skin and head and neck has also been well documented (4, 4b). Although these solid cancers are typically diagnosed in older populations, in DC patients they are diagnosed as early as the second decade of life. Based on a recent literature review, DC patients with cancer have a mean age at cancer diagnosis of 29 and a cumulative incidence of ~40% by the age of 50 (4, 4b). DC patients are also predisposed to other solid tumors, though this spectrum is less well defined (4, 4b).

GENOTYPE-PHENOTYPE CORRELATIONS: TELOMERE LENGTH DETERMINES THE AGE OF ONSET AND SEVERITY OF SYMPTOMS

The fact that short telomeres mediate the severity and age of onset in telomere syndromes implies that telomere syndromes are genetically unique in that a specific gene mutation does not directly mediate the phenotype, but specifically does so by altering another physical heritable change in DNA: the telomere length. Thus in examining syndromes of telomere shortening, we find that the severity of disease depends on the telomere length. For example, children with *TINF2* mutations have the shortest telomeres described in humans to date and in general come to clinical attention in the first few years of life (61,75).

Hypomorphic mutations in *hTR* and *hTERT* lead to the most heterogeneous manifestations but identical syndromes (2,5,6,15,66,72,81,82). Disease-causing mutations in both genes lead to haploinsufficiency and a decrease in the amount of available telomerase that can elongate

telomeres (5,30,72,82). Mutation-intrinsic factors can also contribute to the telomere length. Functionally null mutations can lead to an accelerated rate of telomere shortening and thus an earlier onset of organ failure compared with hypomorphic mutations. Family-dependent factors also likely contribute. For instance, a family with longer initial telomere length that harbors a mutation could have its first affected individuals in later generations compared with a family that has shorter telomeres. Most importantly, the fact that mutations in *hTERT* or *hTR* lead to genetic anticipation implies that even within the same family, variability in the clinical course and phenotype spectrum can exist, with the latest generations being most severely affected.

Several pieces of evidence further support the clinical observation that mutations in *hTERT* and *hTR* lead to a single clinical entity. Mutations in familial IPF, aplastic anemia alone, and DC do not each have a predilection to specific domains in hTERT or hTR. In fact, mutations in either gene have been identified throughout the entire structure of both components of telomerase (http://telomerase.asu.edu/diseases.html) and are associated with the entire spectrum of telomere-mediated disease. As an example, identical mutations in *hTERT* have been identified in unrelated adults with IPF and aplastic anemia, underscoring the potential generation effects on telomere length (15). Haploinsufficiency for *mTERT* and *mTR* also occurs in mice, and yeast are haploinsufficient for telomerase RNA (19,25,30,32,49). Also, in yeast, null strains for the protein and RNA telomerase components have identical phenotypes (41, 64). Thus the clinical evidence, along with telomerase genetics in several species, is consistent with the fact that mutations in *hTERT* and *hTR* lead to identical syndromes.

TELOMERE GENETICS ARE UNIQUE: LESSONS FROM THE TELOMERASE KNOCKOUT MOUSE

The study of the telomerase knockout mouse has provided key insights into the pathophysiology of telomere-mediated disease. Anticipation of phenotypes due to telomere shortening was first described in the $mTR^{-/-}$ mouse where phenotypes only appeared after four generations of breeding (10,40,59). The $mTR^{-/-}$ mouse was initially engineered on the C57BL/6 background where telomeres extend up to 50 kb (longer than human telomeres, which are on average 10 kb). By backcrossing the null allele onto the Castaneus mouse strain, which has telomere lengths and distributions comparable to those of humans, telomere-associated phenotypes can be appreciated in the first $mTR^{-/-}$ generation and Castaneus late-generation $mTR^{+/-}$ mice develop worsening bone marrow failure similar to that in humans with mutations in telomerase components (30).

Other key lessons emerge from the study of the telomerase knockout mouse: (*a*) Short telomere-mediated phenotypes are most prominent in tissues of high turnover. In the mouse, degenerative phenotypes appear in the skin as poor wound healing, apoptotic tubules in the testes, and compromised hematopoietic function (30,40,59). Skin and hematopoietic defects are also prominent in DC. (*b*) The shortest telomere, not the average telomere length, determines phenotypes (35). The shortest telomere thus has a genetically dominant effect and is sufficient to induce a DNA-damage response that determines cell fate and symptom onset (Figure 3). This fact may account for some of the phenotype heterogeneity within a single generation because it adds an additional variable that determines telomere heterogeneity. For example, in an autosomal dominant family with a mutation in *hTERT* or *hTR*, individuals who stochastically inherit the shortest telomeres as well as a mutation may have more pronounced phenotypes than individuals who inherit long telomeres and a mutation. (*c*) Wild-type mice that inherit short telomeres have phenotypes similar to those of $mTR^{+/-}$ mice (30). Clinically affected wild-type relatives from autosomal dominant families with known mutant telomerase genes have not been described, although short telomeres have been noted in these individuals (Figure 3) (23). The observations from mouse studies highlight the importance of telomere length as

a potential unique heritable trait that can contribute to disease risk even when the telomerase locus is wild type.

SHORT TELOMERES CAN BE ACQUIRED: IMPLICATIONS FOR UNDERSTANDING COMMON DISEASE

Short telomeres can also be acquired. Telomere length is a mosaic trait and reflects the replicative history of cells. Mosaicism has been best documented in mature leukocyte subsets (see Reference 8 for a review). For example, within a given individual, granulocytes usually have longer telomeres than total lymphocytes (8). Mosaicism also explains the pronounced penetrance of telomere phenotypes in tissues of high turnover where progenitors rely on telomere reserves. Chronic injury-repair disease states are also associated with telomere shortening in several conditions. For example, chronic exposure to cigarette smoke in the lung and acid reflux in Barrett's esophagus are associated with telomere shortening (44,67,68). Chronic inflammatory processes such as in ulcerative colitis are also associated with regional telomere shortening (51,56). Additionally, telomere shortening can be observed as a consequence of infection in the mouse hematopoietic system (36). In preneoplastic lesions, short telomeres are also acquired somatically (44,45). Chronic injury states will likely have more pronounced consequences in individuals who inherit short telomeres. For example, in families with pulmonary fibrosis, smokers have an earlier onset of lung disease than nonsmokers (65,66). Since telomere length has a broad distribution across populations and since short telomeres can also be acquired, telomere length likely plays an underappreciated role in the epidemiology of chronic disease associated with irreparable organ failure.

SHORT TELOMERES LIMIT THE REPLICATIVE CAPACITY OF HEMATOPOIETIC STEM CELLS

Evidence from animal studies indicates that the decrease in regenerative capacity with age may be a result of cumulative DNA damage in stem cells (58,62,63). Syndromes of telomere shortening provide a clinical context for understanding the consequences of telomere shortening on stem cell function. Aplastic anemia is the prototype of stem cell failure disorders where progressive aplasia occurs as a result of limited replicative capacity of the hematopoietic stem cell (Figure 5). Impaired hematopoietic stem cell function has been documented in late-generation $mTR^{-/-}$ mice (3,14,30). And although hematopoietic stem cells may be enriched for telomerase activity, short telomeres may be sufficient to limit their replicative capacity even when telomerase is present. Although the pathophysiology of scarring in IPF is poorly understood, we have proposed that, at least in a subset, the progressive fibrosis may be a result of regional stem cell failure due to telomere shortening in the lung (5,6). The study of syndromes of telomere shortening thus has important implications for understanding the biology of stem cell failure in age-related disease within and outside of the hematopoietic system.

SUMMARY

In summary, syndromes of short telomeres may be the archetype of premature aging syndromes because short telomeres accumulate universally with aging. Distinct from other progeroid syndromes (e.g., Hutchinson-Gilford), they epitomize a process that occurs in humans as they age, and affected individuals have many features of age-related disease (Table 3). Age-related disease is marked by vascular and degenerative components as well as by cancer predisposition. In at least DC, the latter two aspects are captured. The study of syndromes of telomere shortening thus provides a disease-specific context for understanding the consequences of cumulative telomere attrition and stem cell failure with aging.

The spectrum of syndromes of telomere shortening is broad and encompasses common age-related disorders previously thought to be idiopathic, such as IPF. Recent developments in understanding the genetics of syndromes of telomere shortening allows the recognition of a distinct clinical entity that appears as a clustering of aplastic anemia and fibrosis in the lung and liver. This telomere syndrome often appears in adults and falls on the same spectrum as DC. Recognizing syndromes of telomere shortening as a single entity due to a common pathophysiology will, it is hoped, allow for improved genetic, diagnostic, and therapeutic approaches for affected individuals and families. The study of telomere and telomerase biology and genetics has provided a platform for elucidating the pathophysiology of a group of disorders that have heretofore been poorly understood. Future insights may also provide a basis for rational therapeutic approaches that can attenuate their course.

SUMMARY POINTS

1. Mutations in telomerase and telomere components lead to a broad spectrum of disease that has presentations in children and adults. The extent of telomere shortening determines the onset and severity of these disorders.
2. The study of families with mutations in telomerase components allows the identification of a distinct disease entity marked by organ failure in the bone marrow and a clustering of pulmonary and liver fibrosis. This syndrome frequently appears in adulthood and is distinct from DC, though it falls on the same spectrum.
3. IPF is the most common manifestation of a syndrome of telomere shortening. The causal role implicating short telomeres in IPF provides evidence that short telomeres are sufficient to cause common, age-related disease with manifestations in the lung.
4. Syndromes of telomere shortening are unique among progeroid disorders in that they embody a process that occurs in humans as they age.

FUTURE ISSUES

1. Will the future study of familial IPF and DC implicate other components of telomeres and telomerase in the pathogenesis of this group of disorders?
2. Will the presence of mutations in telomerase components affect prognosis and treatment of patients with IPF and related disorders?
3. What is the true incidence of syndromes of telomere shortening?
4. Can the natural history of syndromes of telomere shortening be attenuated by telomere- and telomerase-based approaches?

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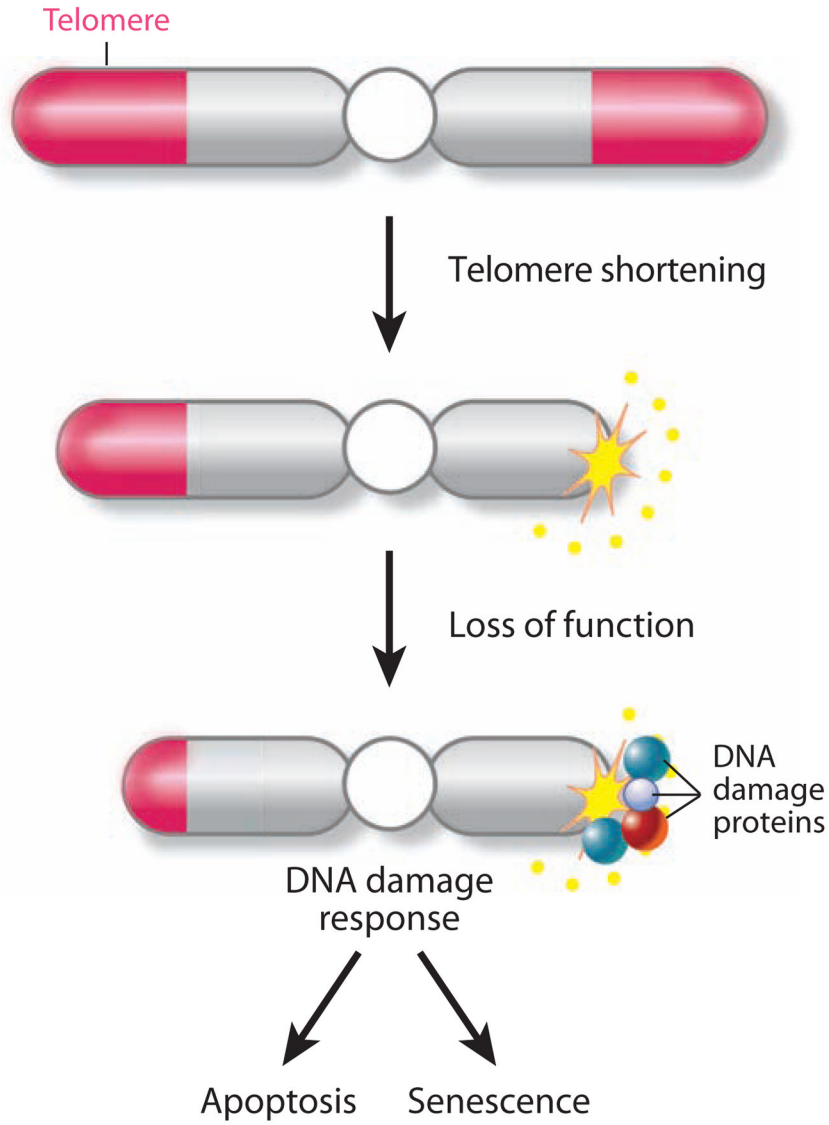

Figure 1.
Short telomeres activate a DNA-damage response that leads to apoptosis and senescence. As cells divide, short telomere accumulate because of the end-replication problem. Critically, short telomeres recruit DNA damage proteins that activate cellular programs of apoptosis or senescence. This cellular response manifests as organ failure in clinically recognizable syndromes of telomere shortening.

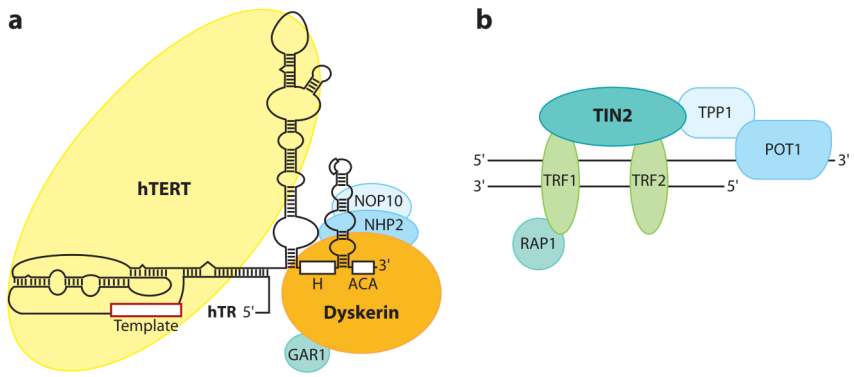

Figure 2.

Mutations in telomerase and telomere components lead to syndromes of telomere shortening. (*a*) The essential telomerase components. hTERT utilizes the template provided by hTR to add new telomeres onto the ends of chromosomes. hTR is a 451 nucleotide RNA which contains a box H/ACA motif at its 3′ end. The box H/ACA motif is essential for hTR stability and for its assembly with hTERT. These functions are mediated by the presence of the box H/ACA-binding dyskerin complex, which is composed of four proteins: dyskerin, NOP10, NHP2 and GAR1. Loss-of-function mutations in *hTR*, *hTERT*, *DKC1*, and likely *NOP10* and *NHP2* lead to a decrease in available telomerase dose and accelerated telomere shortening. (*b*) The shelterin complex is composed of six specialized proteins that bind telomeric DNA. Mutations in the shelterin component *TINF2* explain a subset of severe cases of dyskeratosis congenita. The mechanism by which *TINF2* heterozygous mutations lead to telomere shortening is not known.

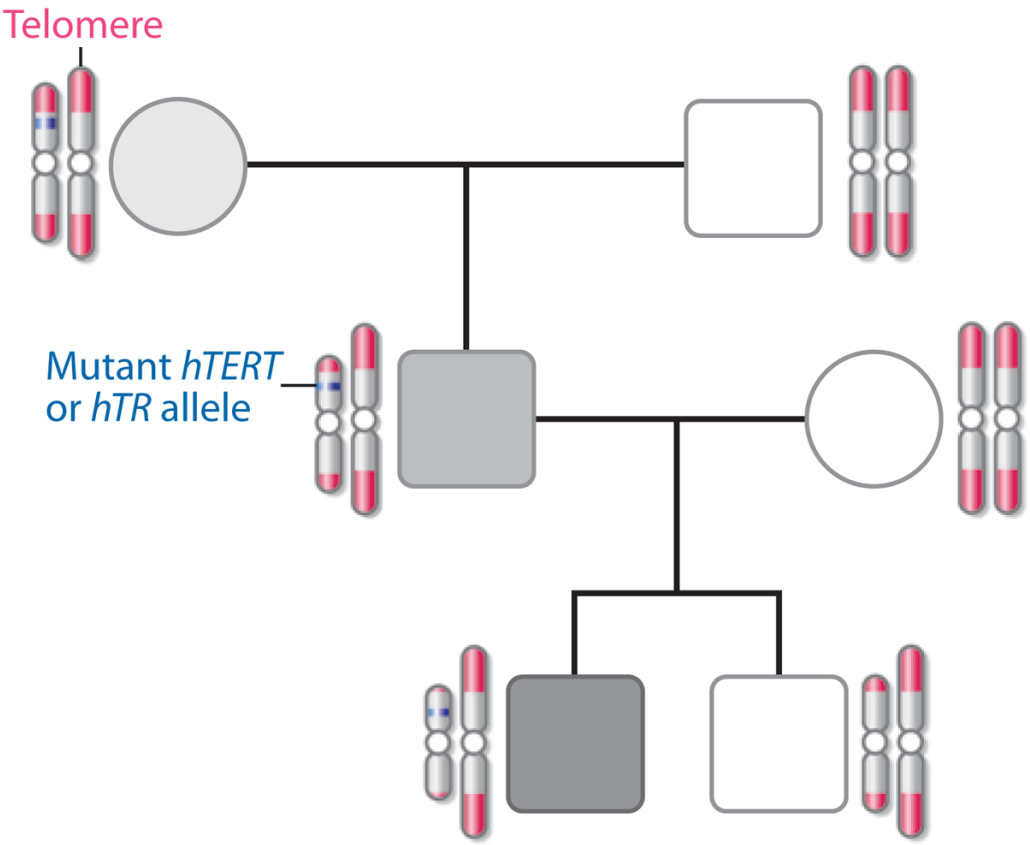

Figure 3.
Telomere length is a unique heritable trait. In autosomal dominant syndromes of telomere shortening, in addition to a mutant *hTERT* or *hTR* allele, short telomeres are inherited across generations. The progressive telomere shortening leads to anticipation of phenotypes, as indicated by the darker shades of black in affected successive generations. Short telomeres can also be inherited in wild-type individuals; however, no telomere-associated phenotypes have been described in these individuals. Wild-type mice who inherit short telomeres have degenerative phenotypes similar to $mTR^{+/-}$ mice (30).

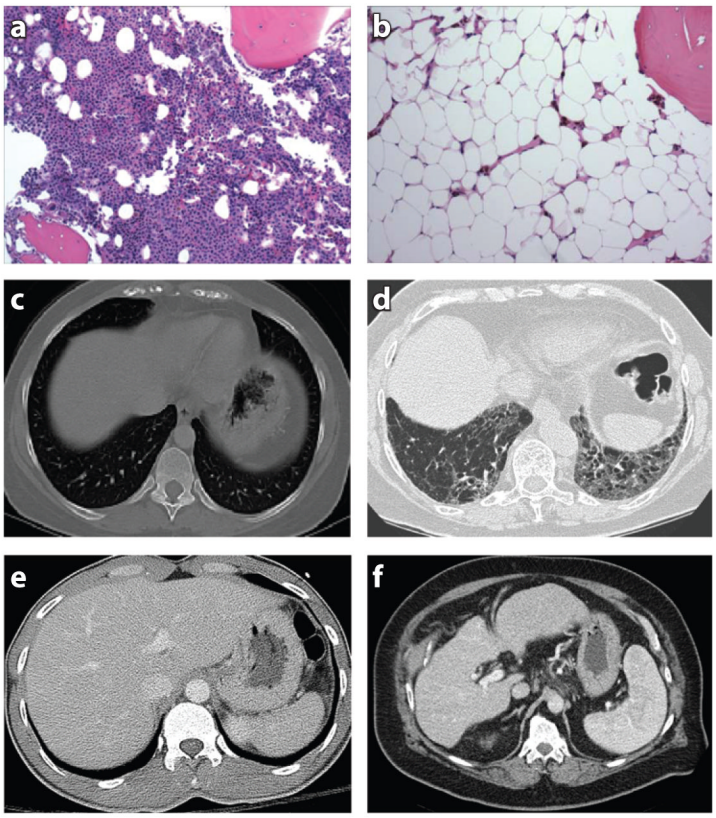

Figure 4.
Syndromes of telomere shortening lead to organ failure in the bone marrow, lung, and liver and define a distinct telomere-mediated entity in the absence of the classic features of DC. Bone marrow biopsy with normal cellularity shown in (*a*) is contrasted with marrow from patient with aplastic anemia in (*b*) where hematopoiesis is absent, and the marrow is replaced with fat. (*c*) Normal CAT scan of the chest with clear lung parenchyma is contrasted with (*d*) showing a CAT scan from a patient with idiopathic pulmonary fibrosis, a disorder classically marked by honeycombing in the peripheral and basilar portions of the lung as shown. (*e*) Normal CAT of the abdomen revealing a healthy liver size and structure. (*f*) CAT scan from a patient with cryptogenic liver cirrhosis due to telomere shortening. The liver is small and atrophic with nodular edges and secondary splenomegaly due to portal hypertension. This patient received a liver transplant after developing progressive symptoms of cirrhosis. Bone marrow micrographs were kindly provided by Dr. Kathleen Burns, Johns Hopkins Department of Pathology.

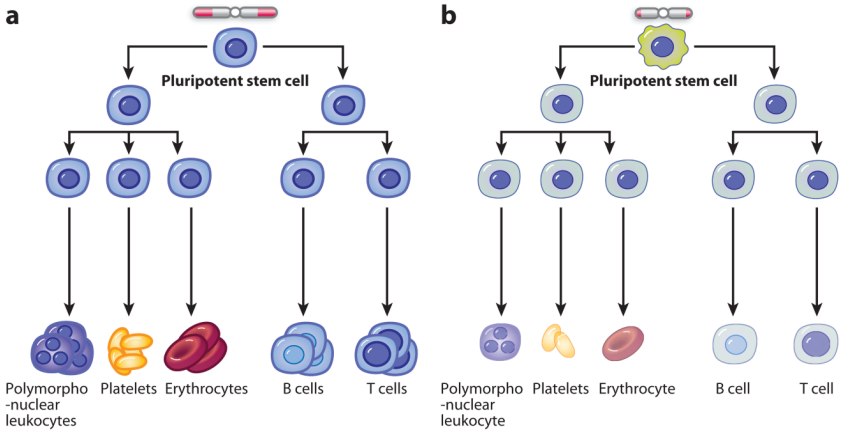

Figure 5.

Short telomeres lead to stem cell failure in the bone marrow. (*a*) Normal hematopoiesis is hierarchical and relies on the intact capacity of a pleuripotent stem cell to self-renew and differentiate. When telomeres are short (*b*), stem cell function is impaired and the impairment leads to a progressive decline in the production of mature blood lineages in aplastic anemia.

Table 1

Mutations in telomerase and telomere genes lead to a broad clinical spectrum of syndromes of telomere shortening.

Gene Name	Diagnosis	Typical age of onset in years
hTR *hTERT*	Sporadic IPF 1–3% Familial IPF[a] 8–15% Sporadic and familial aplastic anemia ~3–5% Autosomal dominant DC[b]	Broad range 5–77
DKC1	X-linked DC Hoyeraal-Hreiderasson	Less than 30 Less than 5
TINF2	Sporadic DC Autosomal dominant DC Hoyeraal-Hreiderasson	Less than 10 - Less than 5
NOP10	Autosomal Recessive DC	-
NHP2	Autosomal Recessive DC	-

[a] IPF refers to idiopathic pulmonary fibrosis.

[b] DC refers to dyskeratosis congenita.

Table 2

Spectrum of bone marrow, lung, and liver disease seen in individuals with syndromes of telomere shortening

Hematologic features
Macrocytosis
Elevated hemoglobin F
Isolated cytopenias (most commonly thrombocytopenia)
Aplastic anemia
Myelodysplasia
Acute myeloid leukemia
Pulmonary fibrosis
Asymptomatic restrictive defects on pulmonary function studies
Idiopathic pulmonary fibrosis/usual interstitial pneumonia
Nonspecific interstitial pneumonia
Idiopathic interstitial pneumonia nonclassifiable on biopsy
Liver disease
Normal or mildly elevated transaminases
Atrophic nodular liver on imaging studies
Splenomegaly
Cryptogenic liver fibrosis/cirrhosis

Table 3

Age-related processes that affect individuals with syndromes of telomere shortening

Premature hair graying/loss
Nail ridging
Idiopathic pulmonary fibrosis
Liver fibrosis
Decreasing bone marrow cellularity and function
Thrombocytopenia
Immune dysfunction
Increased cancer risk
Chemotherapy intolerance
Radiation therapy intolerance