REVIEW ARTICLES

Telomeres in lung disease

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Telomeres are DNA-protein structures that cap the ends of chromosomes; telomerase is the enzyme that ensures their integrity. Telomere biology has recently been implicated in the pathogenesis of a variety of lung diseases, including idiopathic pulmonary fibrosis, chronic obstructive pulmonary disease/emphysema, and lung cancer. This review highlights recent discoveries pertaining to the role of telomere biology in lung disease. (Translational Research 2013;162:343–352)

Abbreviations: COPD = chronic obstructive pulmonary disease; IPF = idiopathic pulmonary fibrosis; *TERC* = telomerase RNA component; TERT = telomerase reverse transcriptase

The 2009 Nobel Prize in Physiology or Medicine was awarded for the discovery of how chromosomes are protected by telomeres and the enzyme telomerase.[1-3] Telomeres are repetitive DNA sequences and associated proteins located at the ends of linear chromosomes.[4-6] The ends of linear DNA cannot be replicated by DNA polymerase (end-replication problem); telomeres protect these DNA ends from the iterative shortening of critical chromosomal DNA that would otherwise occur.[7] Telomeres also help prevent fusion events between chromosomes.[1-3,8-15]

Telomerase is the enzyme complex that generates and maintains telomeres. It has 2 essential components, telomerase reverse transcriptase (TERT) and an RNA template, telomerase RNA component (*TERC*).[16-23] A number of additional proteins, including dyskerin, associate with the core complex of TERT and *TERC*.[24,25] Telomerase is expressed mainly in embryonic and adult stem cells; however, lymphocytes and select epithelial and testicular cells also express telomerase.[26] Over time, somatic tissue telomeres shorten, eventually triggering cell senescence and apoptosis.[14-28]

Human telomere lengths are often measured in leukocytes for reasons of convenience, but they can also be measured directly in lung or other tissues. Human telomeres are generally 5 kbp–15 kbp in length[29] and shorten progressively with age at a rate of 9 bp/y–92 bp/y.[30-37] Telomere lengths can exhibit large population-level heterogeneity[38,39]; length differences are also present in individual chromosome ends within the same cell.[14] The shortest telomeres are expected to activate cellular responses leading to senescence and apoptosis.[40]

In this review, we discuss the role of telomeres and telomerase in lung diseases, including idiopathic pulmonary fibrosis (IPF), chronic obstructive pulmonary disease (COPD)/emphysema, and lung cancer.

IDIOPATHIC PULMONARY FIBROSIS

IPF is a devastating form of interstitial lung disease and the most common idiopathic interstitial

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Conflicts of interest: None.

Submitted for publication January 14, 2013; revision submitted April 2, 2013; accepted for publication April 3, 2013.

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1931-5244/$ - see front matter

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http://dx.doi.org/10.1016/j.trsl.2013.04.001

pneumonia.[41,42] This chronic, progressive, fibrosing interstitial pneumonia is typically associated with the histopathologic and radiographic pattern of usual interstitial pneumonia.[43] IPF is estimated to have a U.S. prevalence of between 14 cases/100,000 and 63 cases/100,000, depending on whether narrow or broad case definitions are used[44-47]; median survival after diagnosis is only 3.5 years.[48] IPF affects approximately 5 million people worldwide[42]; the incidence increases with age and, in most countries, males are more likely to be affected than females.[44] For the most part, the pathogenesis of IPF remains uncertain; however, it is now known that some cases result from mutations in telomerase genes.

Clues from dyskeratosis congenita. Dyskeratosis congenita is a rare disorder defined initially in the early 20th century by a triad of mucocutaneous abnormalities: nail dystrophy, mucosal leukoplakia, and pigmentary changes of the skin.[49-52] By the 1960s, pancytopenia and a predisposition to cancer were recognized as associated findings.[53-55] It was not until the 1990s that pulmonary fibrosis was reported frequently in patients with dyskeratosis congenita, especially after bone marrow transplantation.[56-60] Subsequently, mutations in the telomerase components dyskerin, *TERT*, and *TERC* were identified, establishing dyskeratosis congenita as a disorder of telomere biology.[61-69] Affected individuals exhibit great phenotypic heterogeneity, and liver cirrhosis, premature hair graying, osteoporosis, avascular necrosis, hypogonadism, and immunodeficiency have all been described.[70,71] More important, some families lack the classic cutaneous features of dyskeratosis congenita; indeed, pulmonary fibrosis was the only manifestation in 1 *TERT* mutation carrier.[68] These data, along with whole-genome linkage data from 2 large kindreds, led to the hypothesis that mutations in telomerase components could cause familial and possibly sporadic IPF.[72,73]

***TERT* and *TERC* in IPF.** Two studies published in 2007 demonstrated that specific mutations in the telomerase components *TERT* and *TERC* result in IPF.[72,73] Congruent with these findings, a genome-wide association study identified a common intronic single-nucleotide polymorphism in *TERT* that was associated with susceptibility to IPF.[74] It is now recognized that mutations in *TERT* and *TERC* are present in 8–15% of patients with familial pulmonary fibrosis and 1–3% of patients with sporadic IPF.[9,31,72,73,75,76] IPF due to *TERT* and *TERC* mutations can be transmitted in an autosomal dominant manner, with the mutations causing disease through haploinsufficiency.[9,68,77-79] In addition, genetic anticipation–the observation that the phenotype is present at an earlier age in subsequent generations–occurs in families affected by *TERT* or *TERC* mutations.[9,68,75,80-82] *TERT* and *TERC* mutations associated with interstitial lung disease are listed in Table I[31,46,68,72,73,76,79,81,82,83-88,118] and illustrated in Fig 1. From a clinical standpoint, it is important to recognize that patients with IPF who have an underlying *TERT* or *TERC* mutation may also exhibit or develop premature hair graying, liver cirrhosis, and hematologic abnormalities such as bone marrow failure.[68,72,73,75,76,79-88]

Telomere lengths in IPF. Patients with IPF that have a *TERT* or *TERC* mutation generally have leukocyte telomere lengths below the 10th percentile relative to age-matched control subjects.[31,72,75,76,80-83] Patients with sporadic IPF and familial pulmonary fibrosis who do not have mutations in *TERT* or *TERC* can have telomeres of normal length but often have shorter telomeres when compared with age-matched control subjects.[31,76] In one study, 20%–25% of IPF patients without mutations in *TERT* or *TERC* had telomere lengths below the 10th percentile.[31] Short telomeres observed in some patients may be the result of genetic polymorphisms (such as the *TERT* intronic polymorphism described earlier), leading to decreased expression of *TERT* or *TERC*. Alternatively, environmental factors—such as smoking, which is a well-established risk factor for IPF[43]—could be responsible. Interestingly, men have shorter telomeres than women, which could explain in part the male predominance of IPF.[31,90]

Mechanism of disease in IPF. The mechanism by which telomerase deficiency contributes to the development of IPF is a matter of speculation. One longitudinal study showed that in 2 sisters with *TERT* mutations, alveolar inflammation and activated alveolar macrophages were present many years before the onset of overt pulmonary fibrosis,[84,91] suggesting that persistent inflammation could contribute to eventual fibrosis. It has also been hypothesized that senescence and depletion of alveolar epithelial stem cells may contribute to the development of pulmonary fibrosis.[72] A better understanding of potential mechanisms by which telomerase deficiency leads to the development of pulmonary fibrosis could improve the development of therapies for IPF.

Treatment of IPF. There are currently no approved therapies for IPF that are directed specifically at reversing telomerase deficiencies in patients with *TERT* or *TERC* mutations. Furthermore, no clinical trial involving patients with IPF has examined treatment outcomes by telomere length or telomerase mutation status. Recently, the PANTHER-IPF study showed that

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