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Review

Telomerase and idiopathic pulmonary fibrosis

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ABSTRACT

Idiopathic pulmonary fibrosis (IPF) is the most common manifestation of telomere-mediated disorders. Germline mutations in the essential telomerase genes, *hTERT* and *hTR*, are the causal genetic defect in up to one-sixth of pulmonary fibrosis families. The presence of telomerase mutations in this subset is significant for clinical decisions as affected individuals can develop extra-pulmonary complications related to telomere shortening such as bone marrow failure and cryptogenic liver cirrhosis. There is also evidence that IPF is an ancestral manifestation of autosomal dominant telomere syndromes where, with successive generations, the disease evolves from pulmonary fibrosis into a bone marrow failure-predominant disorder, defining a unique form of genetic anticipation. Here I review the significance of telomere defects for understanding the genetics, disease patterns and pathophysiology of IPF. The importance of this diagnosis for patient care decisions will also be discussed.

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Idiopathic pulmonary fibrosis (IPF) is perhaps the most devastating of the idiopathic disorders in medicine. It is estimated to affect as many as 100,000 individuals in the United States. Characterized by an unrelenting progression of parenchymal lung scarring, its most famous attribute has long been its "idiopathic" or unknown etiology. Recently, genetic clues have opened possibilities for a new understanding of IPF. Here I review the significance of telomere biology to understanding the genetics, pathophysiology and disease patterns seen in IPF patients.

1. Idiopathic pulmonary fibrosis is an age-related disease

IPF has a well-characterized, progressive clinical course. Most individuals are diagnosed after presenting with worsening respiratory complaints. From the time of diagnosis, IPF patients live on average 3 years, although in some individuals, the natural history may be more protracted [1]. Several clinical risk factors are known to be linked with IPF. Age is the biggest with the great majority of individuals diagnosed after the age of 60 [2]. IPF is also diagnosed more frequently in males with a nearly 2:1 ratio [2]. Cigarette smoke is known to accelerate disease onset with those having a smoking history presenting as much as a decade earlier than never smokers [3]. A positive family history is also a major risk factor with up to 20% of IPF patients reporting an affected family member [4]. Understanding the genetics which underlie familial

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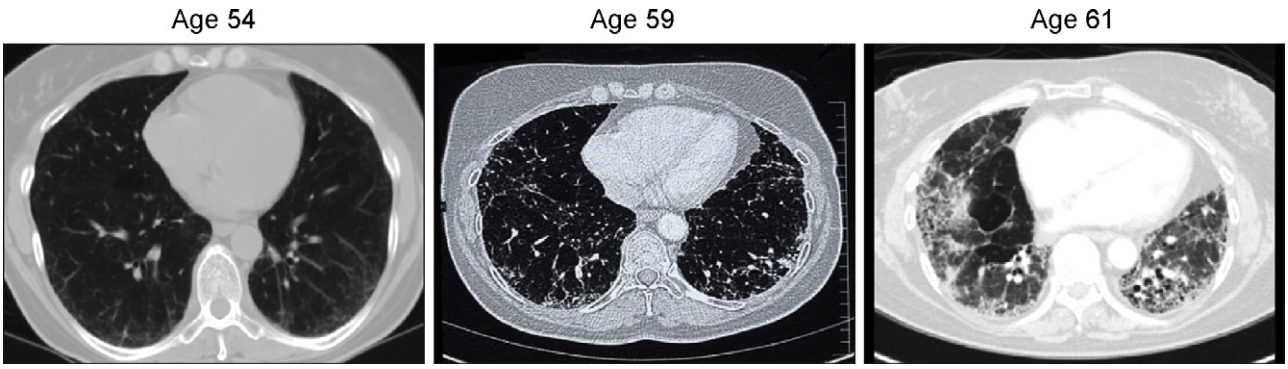

Fig. 1. Pulmonary fibrosis is a progressive disease. Successive computed tomography (CT) lung images from an individual who carried a germline mutation in *hTERT*, the gene for the reverse transcriptase component of telomerase. The images show reticular infiltrates with honeycombing in the basilar and peripheral portions of the lung. The patient's disease was progressive and she died from respiratory failure at the age of 61.

clustering of pulmonary fibrosis has held promise for understanding its etiology.

IPF has a recognizable constellation of clinical findings which are often sufficient to make the diagnosis without the need for lung biopsy [1]. On imaging studies, IPF has a characteristic honeycombing pattern, which preferentially affects the basilar and peripheral areas of the lung (Fig. 1). When available, histology shows a destructive pattern of alveolar architecture, and is classically known as usual interstitial pneumonia [1]. Usual interstitial pneumonia is a histological hallmark of end-stage lung disease, and the "usual" terminology is derived from the fact that IPF/usual interstitial pneumonia is the most common of the interstitial lung diseases [1].

The treatment for IPF is supportive, and there are currently no known therapies that alter its natural history. Patients with IPF do not respond to immunosuppressive drugs, in contrast to fibrotic lung disease that occurs in the setting of autoimmune disorders [1]. In eligible patients, transplant is considered, and since 2007, IPF has become the most common indication for lung transplant in the United States [5]. Transplantation is however limited by organ availability and procedure morbidity. Despite significant advances in transplant medicine, recipients have an average survival of 5 years [6]. A better understanding of its etiology holds promise for advancing therapeutic paradigms in IPF.

2. Telomere length is the effector of telomerase-associated phenotypes

Telomerase is a remarkable enzyme that maintains chromosome ends [7–9]. Mutations in the essential genes coding for the enzyme telomerase are the most commonly identified genetic risk factor in IPF [10]. Telomerase has two essential components: hTERT, the telomerase reverse transcriptase, and hTR, a specialized RNA that contains a template for telomere repeat addition. hTERT uses the template within hTR to add new $(TTAGGG)_n$ repeats onto the 3′ end of chromosomes [11]. In cells, telomerase forms a holoenzyme complex with other proteins. Its biogenesis and stability depend on an essential protein dyskerin which is coded by the X-chromosome *DKC1* gene [12]. Dyskerin binds to an RNA motif within hTR known as the box H/ACA, which is critical for hTR integrity ([13,14], reviewed in [15]). Mutations in *hTERT*, *hTR* and *DKC1* cause telomerase loss of function, and decrease telomerase activity [12,16,17] (Fig. 2). The loss of function accelerates the telomere shortening which normally occurs with age. Syndromes associated with mutant telomerase genes are therefore considered premature aging syndromes.

The consequences of telomerase deficiency were studied in model organisms before telomerase mutations were discovered in the setting of human disease [18,19]. In mouse models where telomerase deletion was engineered, it was initially recognized that telomerase itself is not essential [18,19]. In first generation mice that were null for telomerase, no phenotypic defects could be identified. However, after breeding for successive generations, mice that have short telomeres developed degenerative disease that was most evident in tissues of high turnover [19,20]. For example, the bone marrow has a significant requirement for intact regenerative potential to sustain the high turnover demands, and short telomeres limit the self-renewal capacity of hematopoietic stem cells causing ineffective hematopoiesis [19–21]. The phenotypes of telomerase null mice are identical whether *TR* or *TERT* is deleted, and both *TR* and *TERT* null mice develop phenotypes only when telomeres are short [22,23]. These genetically defined models have established telomere shortening as a mechanism of genetic anticipation, whereby phenotypes worsen in successive generations due to the accumulation of dysfunctional telomeres [16,18,21]. The absence of telomerase alone is therefore not sufficient to mediate degenerative disease, but the short telomere length, which is the primary genetic determinant of phenotype severity.

3. Dyskeratosis congenita (DC) is a familial pulmonary fibrosis syndrome

In the setting of human disease, mutations in telomerase enzyme components were first identified in a rare syndrome dyskeratosis congenita (DC) [12,24]. This disorder, as is delineated below, represents a more severe presentation of a spectrum of telomere syndromes where IPF represents an attenuated form [10]. DC is classically defined based on a triad of mucocutaneous manifestations: reticular skin pigmentation, nail dystrophy and oral mucosal leukoplakia [25]. In childhood, bone marrow failure is the most frequent complication of DC, while pulmonary fibrosis is a frequent cause of mortality in adults [26]. In DC patients with bone marrow failure, pulmonary fibrosis can be precipitated by pulmonary toxic drugs in the setting of bone marrow transplant. For example, the alkylating agent busulfan, which is used in myeloablative conditioning regimens, causes fatal pulmonary fibrosis in DC patients [27]. Attenuated bone marrow transplant regimens that avoid pulmonary toxic drugs and minimize ionizing radiation exposure can delay the onset of this complication [27–29]. Even without precipitating toxins, pulmonary fibrosis is a significant and under-estimated complication of DC. In some large DC kindreds, pulmonary fibrosis is the major cause of premature mortality in the absence of bone marrow failure [26]. Therefore DC can manifest as familial pulmonary fibrosis.

DC is a disease of telomere maintenance. Mutations in the *DKC1* gene cause an X-linked form [24]; while mutations in *hTERT* and *hTR* cause autosomal dominant disease [17,30]. In 40–50% of cases,