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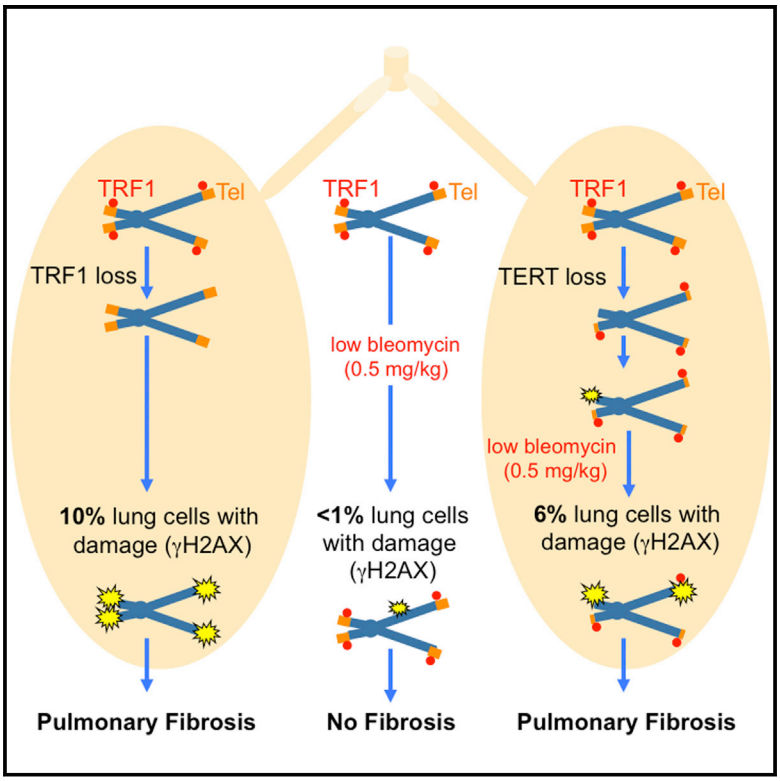
Mice with Pulmonary Fibrosis Driven by Telomere Dysfunction

Graphical Abstract



Highlights

- *Trf1* deletion alone in alveolar type II cells induces pulmonary fibrosis in mice
- Short telomeres and low-dose bleomycin induce pulmonary fibrosis in mice
- These mouse models are instrumental for the development of new therapeutic strategies

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In Brief

Povedano et al. show that persistent telomeric damage induced by telomere dysfunction (either by shelterin disruption or by telomerase deficiency) triggers pulmonary fibrosis in mice. These mouse models are instrumental for the development of new therapeutic strategies to treat pulmonary fibrosis associated with telomere dysfunction.

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Mice with Pulmonary Fibrosis Driven by Telomere Dysfunction

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SUMMARY

Idiopathic pulmonary fibrosis (IPF) is a degenerative disease of the lungs with an average survival post-diagnosis of 2–3 years. New therapeutic targets and treatments are necessary. Mutations in components of the telomere-maintenance enzyme telomerase or in proteins important for telomere protection are found in both familial and sporadic IPF cases. However, the lack of mouse models that faithfully recapitulate the human disease has hampered new advances. Here, we generate two independent mouse models that develop IPF owing to either critically short telomeres (telomerase-deficient mice) or severe telomere dysfunction in the absence of telomere shortening (mice with *Trf1* deletion in type II alveolar cells). We show that both mouse models develop pulmonary fibrosis through induction of telomere damage, thus providing proof of principle of the causal role of DNA damage stemming from dysfunctional telomeres in IPF development and identifying telomeres as promising targets for new treatments.

INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is a life-threatening lung degenerative disease that lacks current effective treatments (King et al., 2011). The mean survival time upon diagnosis is only 2 to 3 years (King et al., 2011). The clinical course of the disease is characterized by a progressive decline in exercise capacity, difficulty breathing, recurrent infections, and severe impairment in lung function, which makes the patients dependent on long-term oxygen treatment. IPF is characterized by the presence of lung scarring, immune infiltrates, and inflammation, which in the past two decades has led to the exploration of inflammation as a therapeutic target for treatment of the disease (Selman et al., 2001). Unfortunately, recent clinical trials for IPF patients based on immune suppression had to be interrupted owing to the toxicity of the treatment (Martinez et al., 2014). More recently, IPF has been proposed to be the result of repetitive epithelial cell injury and defective regeneration, but the precise molecular cause of damage or defective regeneration remains unclear (Hinz et al., 2007; Ryu et al., 2014). To date, lung transplantation is the only therapeutic option for less than 5% of IPF patients with very severe disease (Lama, 2009).

IPF is an age-associated disease, with a mean age at onset between 50 and 70 years (Armanios, 2013; King et al., 2011), and affects men more frequently than women (2:1 ratio) (King et al., 2011). Environmental factors known to inflict damage to lung epithelial cells, such as smoking, are known to increase the risk of developing IPF (Armanios, 2013; King et al., 2011).

One of the hallmarks of aging in mice and humans is the progressive shortening of telomeres with increasing age (López-Otín et al., 2013). Mammalian telomeres are protective structures at the ends of chromosomes (Blackburn, 2001; de Lange, 2005) that consist of TTAGGG repeats bound by a six-protein complex known as shelterin (de Lange, 2005). A minimum length of telomeric repeats is necessary for shelterin binding and telomere protection (Blackburn, 2001; de Lange, 2005). Telomerase (*Tert*, telomerase reverse transcriptase) is an enzyme capable of compensating the telomere attrition produced by telomere degradation and/or by the incomplete replication of telomeric repeats associated with each DNA replication cycle through de novo addition of TTAGGG repeats to the chromosome ends. To this end, telomerase uses an associated RNA component as replication template (*Terc*, telomerase RNA component) (Greider and Blackburn, 1985). In mice and humans, telomerase is silenced after birth, leading to progressive telomere shortening associated with cell division throughout the lifespan (Canela et al., 2007; Flores et al., 2008; Harley et al., 1990; Vera et al., 2012). When telomeres reach a critically short length, this triggers activation of a persistent DNA damage response at telomeres and the subsequent induction of cellular senescence or apoptosis. In the case of adult stem cells, critical telomere shortening impairs their ability to regenerate tissues both in mice and humans, leading to many different age-related pathologies (Flores et al., 2005). Interestingly, telomere shortening has been shown to be influenced both by genetic factors (ie., mutations in genes necessary for telomere maintenance) and environmental factors (ie., cigarette smoke has a negative effect) (Armanios, 2013; King et al., 2011).

Compelling evidence that telomere shortening contributes to aging and age-related disease comes from the study of humans