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# *Telomere Dysfunction in Idiopathic Pulmonary Fibrosis: A Comprehensive Review*

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***Abstract:*** Telomere dysfunction has emerged as a critical determinant in the pathogenesis of various diseases, particularly in age-related disorders such as idiopathic pulmonary fibrosis (IPF). This review delves into the telomere hypothesis, elucidating the function and composition of telomeres, while also acknowledging their intricate relationship with cancer, albeit not as the primary focus. This study employs a comprehensive literature review approach to elucidate the mechanisms linking telomere dysfunction to IPF. The review focuses on the genetic mutations associated with telomere shortening, the role of cellular senescence, and the potential of telomerase activation and TGF-β pathway modulation. Telomere dysfunction is a pivotal determinant in the pathogenesis of IPF, providing new insights into disease etiology and therapeutic targets. The intricate interplay between telomere shortening, cellular senescence, inflammation, and fibrosis underscores the complexity of IPF and highlights the need for multifaceted therapeutic approaches. Future research should focus on elucidating the molecular mechanisms underlying telomere dysfunction in IPF, identifying novel biomarkers for early disease detection, and developing safe and effective telomere-targeted therapies.

***Keywords:*** Telomere dysfunction, Idiopathic pulmonary fibrosis, Telomere hypothesis, Cancer, Telomere length, Genetic mutations

## 1. Introduction

The telomere hypothesis, first proposed several decades ago, postulates that telomeres, the protective caps at the ends of chromosomes, play a pivotal role in aging and disease development. Telomeres are composed of repetitive DNA sequences (TTAGGG in humans) bound by a complex of shelterin proteins that maintain genomic stability by preventing end-to-end fusions, degradation, and inappropriate DNA damage responses (DDR) [1]. Their primary function is to safeguard the genetic material during cell division, as telomeres shorten with each cell cycle due to the "end replication problem" [2]. This attrition serves as a molecular clock, ultimately limiting cellular replicative potential and contributing to cellular senescence.

This paper explores the impact of telomere dysfunction on disease based on the role of telomere dysfunction in the pathogenesis of idiopathic pulmonary fibrosis (IPF), a chronic, progressive and fatal interstitial lung disease of unknown etiology. This study used a comprehensive literature review approach that synthesised findings from genetic, molecular and clinical studies to elucidate the mechanisms linking telomere dysfunction to IPF. The review also explores recent advances in

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telomere-targeted therapies, highlighting their potential to address the underlying causes of IPF and improve patient prognosis. The aim of this review is to provide a detailed understanding of how telomere dysfunction contributes to IPF and to highlight the potential of telomere-targeted therapies in controlling the disease. By exploring the role of genetic mutations associated with telomere shortening, cellular senescence, and the potential for telomerase activation and regulation of the TGF-β pathway, this review aims to provide insights into novel therapeutic strategies for IPF. The significance of this study lies in its potential to improve the clinical management of IPF, which has limited treatment options and a poor prognosis.

## 2. Telomere Function and Composition

Telomeres are not merely passive structures but actively participate in regulating cellular processes, including cell proliferation, apoptosis, and genomic stability. The shelterin complex, consisting of six core proteins (TRF1, TRF2, TIN2, TPP1, POT1, and RAP1), plays a vital role in telomere protection. TRF1 and TRF2 bind to the double-stranded telomeric DNA, while POT1 associates with the single-stranded overhang, forming a protective cap that shields telomeres from DDR activation [3]. In addition, telomerase, a ribonucleoprotein complex, can elongate telomeres by adding telomeric repeats to their ends, thereby counteracting telomere shortening in certain cell types, such as stem cells and cancer cells [4]. However, the regulation of telomere function is more complex than previously thought. For example, the activity of telomerase is not only determined by the components of the telomerase complex itself, but also influenced by various signaling pathways and epigenetic modifications.

Telomere dysfunction is an abnormality in the structure or function of telomeres that results in a cell's inability to properly maintain the integrity of its chromosome ends. This dysfunction can be caused by a variety of factors, including excessive shortening of telomeres, mutations in telomere-related genes, and failure of telomere protection mechanisms. Telomere dysfunction is one of the important mechanisms of cellular aging, genomic instability, and cancer development. It affects normal cellular function and tissue homeostasis by activating multiple intracellular signalling pathways and triggering genomic instability.

Cellular senescence due to telomere dysfunction accumulates gradually and these senescent cells release pro-inflammatory factors that further exacerbate tissue damage and functional decline. In addition, telomere dysfunction affects stem cell proliferation and function, leading to stem cell depletion. This is particularly evident in tissues with high regenerative needs (e.g., skin, gut, and blood), ultimately leading to organ atrophy. As well, telomere dysfunction is an important factor in cancer development. Telomere shortening and genomic instability promote the formation and proliferation of cancer cells. Telomere shortening has long been considered a tumor suppressor mechanism, as it limits the proliferative capacity of cells and promotes senescence. However, cancer cells often overcome this barrier by reactivating telomerase or adopting alternative lengthening of telomeres (ALT) mechanisms, enabling indefinite proliferation [5]. Recent studies have further illuminated the complexity of this relationship, suggesting that telomere dysfunction, beyond mere shortening, can contribute to genomic instability and cancer initiation [6]. For instance, dysfunctional telomeres can lead to chromosomal rearrangements and aneuploidy, which are common features of cancer cells. Moreover, research is now focused on improving telomere-based cancer cell detection and developing potential therapies that inhibit telomerase activity in cancerous cells.

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## 3. Telomere Dysfunction in Idiopathic Pulmonary Fibrosis (IPF)

Idiopathic Pulmonary Fibrosis (IPF) is a chronic, progressive, and fatal interstitial lung disease of unknown etiology, characterized by the excessive accumulation of extracellular matrix in the lung parenchyma, leading to scar formation and compromised lung function [7].

### 3.1. Mechanisms affecting the pathogenesis of IPF

Recent genetic and molecular studies have implicated telomere dysfunction as a crucial determinant in IPF pathogenesis, affecting the disease process through three main mechanisms.

#### 3.1.1. Genetic Mutations and Telomere Shortening

Mutations in telomere-associated genes are more common in patients with idiopathic pulmonary fibrosis (IPF), especially in the genes encoding the shelterin complex and telomerase, and these mutations play an important role in the development and progression of the disease.

Telomerase is a key enzyme in the maintenance of telomere length and consists of the catalytic subunit TERT and the RNA template subunit TERC. Studies have shown a high prevalence of mutations in the TERT and TERC genes in patients with familial IPF. These mutations lead to reduced telomerase activity, accelerated telomere shortening, and ultimately telomere dysfunction [8]. Borie et al. found that patients with TERT and TERC mutations tended to have an earlier age of onset and more severe disease progression. In addition, telomerase mutations are strongly associated with the prognosis of IPF patients. Patients carrying these mutations may have a worse prognosis after lung transplantation, including a higher incidence of infection and risk of drug toxicity.

Second, POT1 is an important component of the telomere protective protein complex, a key protein complex that maintains telomere structure and function, and mutations in the POT1 gene have been strongly associated with the development of IPF, as they disrupt the protective mechanisms of telomeres and lead to telomere dysfunction. Studies have shown that POT1 mutations lead to telomere shortening and cellular senescence, further exacerbating pulmonary fibrosis [9].

Telomere dysfunction not only affects telomere length, but also disrupts lung homeostasis through multiple mechanisms. Telomere shortening activates the DNA damage response (DDR), leading to cellular senescence and apoptosis. These processes of cellular senescence and apoptosis release pro-inflammatory factors and chemokines that further contribute to pulmonary fibrosis. In addition, telomere dysfunction affects the function of alveolar stem cells, particularly type II alveolar epithelial cells (AEC2s). These cells play a key role in maintaining lung tissue repair and regeneration, and telomere dysfunction impairs their regenerative capacity, further exacerbating lung fibrosis.

#### 3.1.2. Cellular Senescence and IPF

Telomere dysfunction triggers cellular senescence, an irreversible state of growth arrest accompanied by altered secretory characteristics and a pro-inflammatory response.

Hallmarks of cellular senescence include cell cycle arrest, altered cell morphology, and increased expression of senescence-associated β-galactosidase (SA-β-Gal).

In the case of IPF, alveolar epithelial cells (AECs), particularly type II AECs, have been shown to undergo telomere-dependent senescence, leading to disease progression [10]. In IPF, senescence of AECs is closely associated with the secretion of several pro-inflammatory factors, factors including PAI-1, P21 and TGF-β. These factors further exacerbate inflammation and fibrosis through autocrine and paracrine effects [11]. Treatment with the curcumin analogue EF24 was found to significantly reduce senescence markers (e.g. SA-β-Gal and PAI-1) in senescent AECs induced by bleomycin and inhibit fibroblast activation induced by senescent AECs or TGF-β.

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TGF-β is a pleiotropic cytokine that plays a central role in fibrosis, including IPF. Telomere dysfunction in AECs enhances TGF-β signaling, leading to the activation of myofibroblasts and the excessive deposition of extracellular matrix components. In addition, activation of the TGF-β signalling pathway further exacerbates the inflammatory response and promotes the development of pulmonary fibrosis. This process is further exacerbated by the infiltration of innate immune cells, such as macrophages and neutrophils, which release additional profibrotic mediators [12].

### 3.2. Recent Advances in Telomere-Targeted Therapies

Given the central role of telomere dysfunction in IPF, therapeutic strategies targeting telomeres and associated pathways are being actively explored. These strategies aim to address the underlying mechanisms of telomere shortening and cellular senescence, which are key drivers of IPF progression. One promising approach involves activating telomerase in alveolar epithelial cells (AECs) to counteract telomere shortening and senescence. Telomerase activation can restore telomere length and improve cellular function, thereby mitigating the effects of telomere dysfunction. However, systemic telomerase activation carries the risk of promoting cancer development, as telomerase is often upregulated in cancer cells. To address this challenge, researchers are developing cell-specific delivery systems to ensure targeted telomerase activity in the lungs, thereby minimizing off-target effects. [13].

Another strategy involves modulating the TGF-β signaling pathway, which plays a central role in fibrogenesis and inflammation in IPF. Several clinical trials are underway, evaluating the efficacy of TGF-β inhibitors in IPF patients. Early results are promising, with some studies showing reduced fibrosis and improved lung function in treated patients. However, long-term safety and efficacy data are still awaited, as the chronic use of TGF-β inhibitors may have unintended effects on tissue repair and immune function [14].

Additionally, recent advances in telomerase-based therapies include the development of telomerase-specific vaccines, which aim to harness the immune system to target cells with high telomerase activity. For example, GV1001 is a telomerase peptide vaccine derived from the human telomerase reverse transcriptase (hTERT) protein. This vaccine has shown potential in preclinical and early clinical studies, with effects including reduced cancer cell growth and fibrosis. While the primary focus of telomerase vaccines has been on cancer treatment, their potential application in fibrotic diseases like IPF is an area of active research.

Overall, recent advances in telomere-targeted therapies hold promise for addressing the underlying mechanisms of IPF. Ongoing research and clinical trials are essential for refining these approaches and ensuring their safe and effective application in clinical practice.

## 4. Conclusion

Telomere dysfunction has emerged as a pivotal determinant in the pathogenesis of IPF, providing new insights into disease etiology and therapeutic targets. The intricate interplay between telomere shortening, cellular senescence, inflammation, and fibrosis underscores the complexity of IPF and highlights the need for multifaceted therapeutic approaches. Future research should focus on elucidating the molecular mechanisms underlying telomere dysfunction in IPF, identifying novel biomarkers for early disease detection, and developing safe and effective telomere-targeted therapies. However, this paper discussed telomere dysfunction only based on the pathogenesis of IPF, without considering other diseases and related therapeutic options, and with relatively limited reference to the literature. In the future, we will try to broaden the scope of the discussion and increase the knowledge base to enrich the discussion.

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