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REVIEW

Telomere-associated non-malignant pulmonary diseases: Pathogenic mechanisms and therapeutic strategies

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Abstract Telomeres and telomerase have been extensively implicated in the cellular processes of aging and inflammation. Recent studies have shown that telomere length (TL), the shelterin complex, and telomerase dysfunction are closely related to non-malignant pulmonary diseases, including interstitial lung diseases (ILD), chronic obstructive pulmonary disease (COPD), and asthma. Short telomere defects with or without mutations in telomere maintenance genes and telomerase are relatively common, affecting the progression of non-malignant pulmonary diseases, explaining disease susceptibility, and revealing clinically relevant manifestations. In this review, we examine the biological characteristics and functions of telomeres and telomerase, and investigate the intricate relationship between changes in TL and mutations in telomerase genes in non-malignant pulmonary diseases after a detailed associated literature review. Subsequently, we focus on the clinical features of non-malignant pulmonary diseases related to dysfunctional telomeres/telomerase, as well as the potential molecular mechanisms underlying these associations, along with the current status of therapeutic interventions. Finally, we delineate current knowledge gaps and transformative opportunities in telomere biology research, with a focus on bridging molecular discoveries to clinical innovations for telomere-associated non-malignant pulmonary diseases, aiming to accelerate the development of precision diagnostic tools and mechanism-based therapeutics.

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1. Introduction

Human lungs, as a major internal organ requiring continuous bidirectional exchange with the external environment through the respiratory tract, endure various biological, chemical, mechanical, and immunological stresses throughout an individual's lifetime. Pulmonary diseases are responsible for millions of deaths worldwide each year, and pulmonary function continues to decline with age and environmental exposures, especially among the elderly[1]. To date, at least 40 distinct cell types have been identified in the lung[2]. Emerging technologies such as single-cell transcriptomics and *in vivo* lineage tracing have helped uncover cellular diversity and clarify lineage hierarchies[3]. In the aging lung, diverse cell populations undergo distinct structural and functional declines, broadly classified into four categories: respiratory epithelium, lung progenitor cells, pulmonary immune cells, and interstitial compartment[1]. These alterations collectively impair pulmonary function. Specifically, aging respiratory epithelium exhibits quantitative and qualitative deficits, such as a loss of specific cell types and reduced mucociliary clearance[4]. Lung-resident stem cells face a diminished capacity for tissue repair and regeneration with age, while pulmonary immune cells, such as alveolar macrophages, display various functional deficits, like impaired phagocytic clearance and weakened antiviral responses[5,6]. Concurrently, the aging interstitial compartment contributes to tissue remodeling and fibrosis[7,8]. However, the upstream drivers of lung aging, its comprehensive impact on the pulmonary cellular landscape, and the reason why premature senescence increases the susceptibility to non-malignant pulmonary diseases remain unclear. Therefore, it is urgent to elucidate the role and mechanisms of lung aging in relation to organ aging for a comprehensive understanding of non-malignant pulmonary disease development.

Telomeres are specialized chromatin structures that protect the ends of chromosomes from detrimental degradation, fusion, or aberrant DNA repair responses. In most somatic cells, telomeres undergo progressive shortening due to the "end replication problem (ERP)"[9]. That is, DNA polymerases are unable to completely replicate chromosome ends, resulting in the loss of DNA at the chromosome ends during each replication cycle. In the absence of telomere maintenance mechanisms such as the expression of telomerase or recombination among telomeres, cumulative telomere attrition across successive cell divisions ultimately induces replicative senescence, a state of permanent growth arrest defined by the Hayflick limit[10]. Furthermore, telomeres are highly vulnerable to oxidative stress due to their G-rich sequence, which favors the formation of 8-oxo-7,8-dihydro-2′-deoxyguanosine[11]. Compounding this inherent susceptibility, the compact heterochromatin structure of telomeres hinders the access and efficiency of key DNA damage repair pathways, leaving oxidative lesions inadequately repaired[12]. This damage directly disrupts DNA replication, leading to accelerated telomere shortening[13]. Consequently, telomere shortening is recognized as a biomarker of cumulative oxidative damage and cellular senescence. Nowadays, a spectrum of methodologies exists for assessing telomere length (TL) in human cells, each presenting distinct advantages and drawbacks[14] (Fig. 1). Recent studies have revealed that telomere shortening exerts a substantial influence on the progression of non-malignant pulmonary diseases[15]. It is now clear that telomere shortening is not merely a marker of aging but a dynamic and influential driver of disease pathogenesis across a spectrum of conditions, including interstitial lung diseases (ILD), chronic obstructive pulmonary disease (COPD), and asthma[16−20]. This pervasive role is evidenced by the significantly shortened telomeres observed in peripheral blood cells of patients with specific subtypes of ILD[21] as well as in alveolar epithelial cells, endothelial cells, fibroblasts, and smooth muscle cells of COPD patients[22,23]. The mechanisms linking telomere shortening to pathology are multifaceted, encompassing genomic instability[24], cellular senescence[25], compromised immune function[26], senescence-associated secretory phenotypes (SASP)[27], and mitochondrial impairment[28]. In light of these mechanisms, telomerase activation therapy, gene editing, and antioxidant/anti-senescence therapies emerge as promising therapeutic strategies to address telomere dysfunction in non-malignant pulmonary diseases (Fig. 1).

This review is therefore constructed around a central scientific thesis: while telomere shortening represents a fundamental pathogenic element in non-malignant pulmonary diseases, its specific pathological manifestation, ranging from progressive fibrosis in ILD to inflammatory tissue destruction in COPD and immune-mediated remodeling in asthma, is determined through precise molecular mechanisms within distinct cellular microenvironments. To substantiate this thesis, we first present an overview of telomere biology, highlight the intricate interplay between TL changes and telomerase function, and explore the connection between telomere (TL or the shelterin complex) and telomerase dysfunction with age-related non-malignant pulmonary diseases. Then, we discuss the potential molecular mechanisms of telomere shortening in the pathogenesis of non-malignant pulmonary diseases and a comparative analysis of disease-specific molecular mechanisms, identifying how divergent signaling pathways and distinct SASP translate telomere shortening into discrete pathological programs across different diseases. Subsequently, we critically evaluate the current therapeutic strategies and drug status for treating non-malignant pulmonary diseases associated with telomere-dependent senescence. Finally, we delineate the persistent gaps in our mechanistic understanding of telomere biology and its clinical translation. These limitations, primarily stemming from the complexity of telomere−environment interactions and the incomplete characterization of regulatory networks, highlight critical opportunities to refine diagnostic frameworks and therapeutic strategies for telomere-associated non-malignant pulmonary diseases.

2. The connection of telomeres and telomerase with age-related non-malignant pulmonary diseases

2.1. Characteristics and biological functions of telomeres and telomerase

Telomeres, protective structures located at the ends of chromosomes in eukaryotes, consist of repetitive DNA sequences

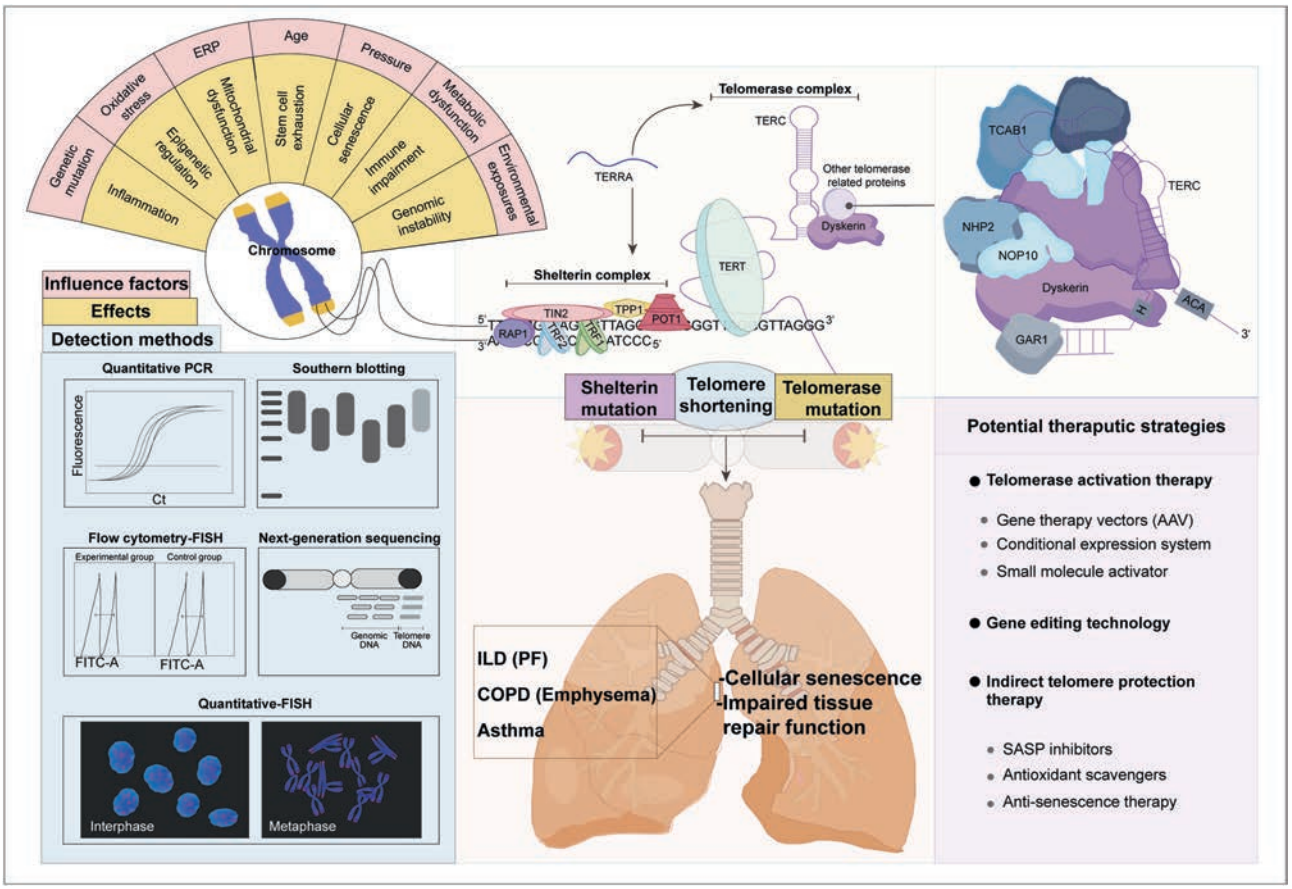

Figure 1 Schematic diagram of telomeres and telomerase, and the relationship between telomere-related dysfunction and non-malignant pulmonary diseases. Fan-shaped pink area: the factors that affect telomere length. Fan-shaped yellow area: the effects that are caused by telomere shortening and the potential mechanisms of telomere shortening in non-malignant pulmonary diseases. Blue area: the methods for evaluating telomere length. Purple area: potential therapeutic strategies for telomere dysfunction-associated non-malignant pulmonary diseases. Abbreviations: ERP, end replication problem; ILD, interstitial lung diseases; PF, pulmonary fibrosis; COPD, chronic obstructive pulmonary disease; TERC, telomerase RNA component; TERT, telomerase reverse transcriptase; TRF1, telomeric repeat-binding factor 1; TRF2, telomeric repeat-binding factor 2; RAP1, repressor/activator protein 1; TIN2, TRF1-interacting nuclear factor 2; TPP1, TINT1/PTOP/PIP1; POT1, protection of telomeres 1; TERRA, telomeric repeat-containing RNA; PCR, polymerase chain reaction; AAV, adeno-associated virus; SASP: senescence-associated secretory phenotype.

(TTAGGG) and a six-protein complex (shelterin). Among the shelterin components, telomeric repeat-binding factors 1 and 2 (TRF1 and TRF2) bind to telomeric double-stranded DNA as dimers, playing critical roles in maintaining telomere structural stability and regulating TL. TRF1 primarily mediates the negative regulation of TL, while TRF2 is essential for protecting telomere ends from being recognized as DNA damage sites and facilitating the formation of telomere loops. Another protein, repressor/activator protein 1 (RAP1), interacts with TRF2 to enhance the specificity of TRF2's binding to telomeric DNA sequences and regulate its localization at chromosome ends. Protection of telomeres 1 (POT1) binds to a single-stranded sequence and interacts with TRF1 and TRF2 through TINT1/PTOP/PIP1 (TPP1), while also binding to TRF1-interacting nuclear factor 2 (TIN2)[16,29–33]. The shelterin complex has an immensely complex role in safeguarding exposed telomeric DNA ends from damage and fusion (solving the end protection problem), and regulating telomerase recruitment to control TL changes (solving the end replication problem)[34–37].

Telomerase, a special enzyme responsible for synthesizing new telomere repeats, mainly consists of telomerase reverse transcriptase (TERT), telomerase RNA component (TERC), and dyskerin. Telomerase counteracts some of the telomere shortening acquired during cell replication. However, telomerase expression exhibits stringent cell type-specificity, and it is usually active mainly in stem cells and germ line cells[38]. The epigenetic silencing of its activity in somatic cells induces progressive telomere attrition. Once reaching the genomic stability threshold, this process ultimately triggers replicative senescence through the DNA damage response (DDR) machinery[10]. Pulmonary epithelial stem cells, including an identified population of distal bronchiolar alveolar epithelial cells with self-renewal and differentiation capacity, are crucial for maintaining tissue homeostasis and mediating repair after injury[39]. The functional integrity of these cells is critically dependent on telomerase, which maintains TL homeostasis by synthesizing telomeric repeats to counteract their progressive erosion. This telomerase-mediated maintenance of telomeres is essential for the sustained regenerative capacity of the pulmonary epithelium, and its dysfunction is a key driver of age-related tissue decline[40]. TL serves as an indicator of cellular fitness, with its attrition rate varying across different cell types, which is potentially linked to differential telomerase activity and

the efficacy of antioxidant defense mechanisms[41]. In addition to age and ERP, lung-specific stressors such as chronic inhalation of airborne pollutants, oxidative stress, recurrent respiratory infections, pressure, metabolic dysfunction such as obesity, and genetic vulnerabilities such as *TERT/TERC* mutations and shelterin complex defects could lead to sustained DNA damage and subsequent telomere shortening in pulmonary or immune cells, the manifestation of which is clinically evident in a variety of non-malignant pulmonary diseases[25,41,42] (Fig. 1).

2.2. *Association between telomere shortening and non-malignant pulmonary diseases*

Emerging evidence reveals that telomere attrition exhibits disease-specific patterns in non-malignant pulmonary disorders such as ILD, COPD, and asthma. These patterns directly link telomere dysfunction to cellular senescence, impaired alveolar regeneration, and persistent tissue inflammation, highlighting the critical role of telomere biology in lung pathophysiology.

However, changes in TL are also heterogeneous, and what are the primary factors influencing this? And what is the specific correlation between TL changes and telomerase regulation? The heterogeneity of TL changes in non-malignant pulmonary diseases arises from three hierarchical determinants: 1) intrinsic drivers such as genetic variants and initial inherited TL; 2) extrinsic modifiers such as environmental exposures and TL attrition from therapeutic interventions for underlying diseases over the years; 3) disease-stage feedback loops wherein progressive telomere crisis amplifies tissue dysfunctional events and perpetuates pulmonary epithelial injury[43,44]. Additionally, TL dynamics are primarily regulated by the activity of telomerase, but also exhibit complex modulation through telomerase recruitment efficiency, regulation of shelterin complex, and cell proliferation rate, collectively shaping TL changes in a cell type- and stress-dependent manner[45]. Genetic mutations that impact the expression or function of telomerase, as well as subtle metabolic, environmental, or systemic changes, can influence TL and increase susceptibility to non-malignant pulmonary diseases[15]. Notably, even when telomerase is normally expressed, not all telomeres undergo extension during each cell cycle[46]. Therefore, there exists a complex interplay between TL and telomerase activity. Revealing this relationship will greatly enhance comprehension of the role of telomere dysfunction in the pathogenesis of non-malignant pulmonary diseases (Fig. 1).

2.2.1. *Interstitial lung diseases*

Short telomeres are a common defect in ILD, characterized by inflammation and fibrosis within the interstitial space, as well as impaired gas exchange[47,48]. Numerous studies have demonstrated that maintaining TL is crucial in some ILDs, exhibiting signs of telomere shortening[21,49,50]. For example, shortened peripheral blood leukocyte telomere length (PBL-TL) has been associated with the presence of ILD in both rheumatoid arthritis-associated interstitial lung disease (RA-ILD) and systemic sclerosis-associated interstitial lung disease (SSc-ILD), correlating with disease severity[51,52]. Variability in telomere shortening exists among different forms of ILD, which can be categorized as congenital defects in telomere biology and stress-induced acquired telomere shortening. Although acquired telomere shortening is a common feature of many non-malignant respiratory diseases, patients with idiopathic pulmonary fibrosis (IPF) have significantly shorter TL than those with other forms of ILD, including nonspecific interstitial pneumonia, cryptogenic organizing pneumonia, hypersensitivity pneumonitis, and sarcoidosis[21,44]. Therefore, congenital defects in telomere biology are crucial in IPF. Genetic factors associated with telomere biology are fundamental to telomere shortening in IPF patients, with IPF being the phenotype most closely linked to germline defects in telomere maintenance. The subsequent section will delve into pulmonary fibrosis (PF) and its related molecular mechanisms.

Telomere-associated mutations underlie the inheritance of familial pulmonary fibrosis (FPF). However, patients with sporadic IPF also exhibit generally shortened telomeres in multiple lineages, including lymphocytes, granulocytes, lung fibroblasts, and alveolar epithelial cells. This supports the idea that the short telomere in IPF is systemic[15,50,53]. Notably, telomerase mutations could occur independently of a telomere-mediated family history, further complicating genotype−phenotype correlations in telomere-associated non-malignant pulmonary diseases[54]. Meanwhile, mutations in telomere-related genes such as *TERT*, poly (A)-specific ribonuclease (*PARN*), and regulator of telomere elongation helicase 1 (*RTEL1*) were also present in RA-ILD, suggesting a contribution of FPF-related genes to susceptibility for RA-ILD and partially shared genetic pathogenic mechanisms[55].

Overall, these diverse clinical phenotypic observations and genetic clues support that IPF is the most common manifestation of telomere dysfunction in non-malignant pulmonary diseases, but not the only one. This indicates phenotypic heterogeneity and has important implications for making accurate diagnoses, providing effective genetic counseling, anticipating genetic risks, adjusting drug dosages, and guiding therapeutic decisions[56,57].

2.2.2. *Chronic obstructive pulmonary disease*

Short telomeres serve as a predictive marker of COPD progression, marked by progressive and irreversible airflow limitation, including chronic obstructive bronchiolitis and emphysema. TL is indicative of all-cause mortality risk, disease progression, survival expectancy, and quality of life in COPD[58]. Compared to smokers with normal lung function, patients with COPD experienced more significant telomere shortening in circulating leukocytes[59,60]. Shorter TL was also observed in alveolar epithelial and endothelial cells of emphysema patients, leading to accelerated cellular senescence[61]. A longitudinal study revealed that smoking significantly accelerated lung function decline in subjects with shorter TL[62]. Moreover, COPD patients with shorter TL had a worse prognosis[63]. A 10-year study of TL dynamics in COPD patients revealed that those experiencing accelerated telomere shortening exhibited diminished lung gas exchange capacity, excessive lung expansion, and extrapulmonary lesions during follow-up[64]. These findings suggest that TL may serve as an effective biomarker for assessing the progression of COPD. However, while TL is influenced by lifestyle and environment, its variability depends more on genetic factors. Baseline TL is genetically determined, and changes in TL during diseases are closely associated with age-adjusted baseline TL. Telomere shortening was accelerated in COPD patients, but the shortening rate of telomeres was negatively correlated with baseline TL, which could be explained by negative feedback regulation in the dynamics of telomere shortening[65]. However, the association between dynamic TL changes in pulmonary structural and immune cells and long-term lung function changes remains unclear. This may require a larger sample size and a longer study period to draw definitive conclusions.

Emphysema is another pulmonary phenotype strongly associated with telomere dysfunction[66]. Telomerase mutations mediate a

unique gene−environmental interaction that increases smokers' susceptibility to emphysema[67]. In the COPD cohort, approximately 1% of COPD patients were found to carry *TERT* mutations, which significantly reduce telomerase activity, impact TL, and correlate with the severity of emphysema[68]. The study by Ding et al.[69] demonstrated that single-nucleotide polymorphisms (SNPs) in *TERT* are associated with an increased risk of COPD in certain populations, suggesting that the interaction of *TERT* gene loci may be more important than a single locus. Additionally, SNPs near *TERC* could independently influence the risk of COPD, regardless of TL[70]. These findings provide deeper insights into the heterogeneity of COPD across different populations and offer crucial information for assessing risk and identifying novel candidate genes.

2.2.3. Asthma

Short telomeres are an etiological mediator of asthma, often accompanied by airway hyperresponsiveness and reversible airflow limitation. A meta-analysis revealed a negative correlation between TL and asthma, while a positive correlation was found between TL and lung function indicators, such as forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC), and FEV_1/FVC[19]. This suggests that TL-indicated accelerated senescence may be involved in the pathogenesis of asthma and inter-individual variability in lung function. The TL of bronchial fibroblasts was shorter in mild asthma patients than in healthy individuals, which was associated with elevated β-galactosidase levels[71]. Severe therapy-resistant asthma is strongly related to different clinical and inflammatory phenotypes, with severely shortened telomeres and up-regulated eotaxin-1 levels[72,73]. These findings indirectly suggest that cellular senescence may contribute to the pathogenesis of asthma and potentially increase susceptibility to early asthma. Furthermore, the end-stage of telomere shortening not only accounts for the limited cell proliferation and premature senescence in asthma patients but also highly correlates with the clinical features and severity of asthma. Research has confirmed that telomere shortening in bronchial fibroblasts is associated with airway hyperresponsiveness and reduced forced expiratory flow[71,74]. Moreover, shorter telomeres may serve as indicators of asthma persistence throughout life, possibly through systemic eosinophilic inflammation[75]. TL could also reflect the therapeutic effect of medication on asthma, as patients receiving steroid therapy experienced less telomere shortening compared to untreated patients[76].

3. Potential molecular mechanisms of telomere shortening in non-malignant pulmonary diseases

Genetic defects in telomere maintenance and accelerated telomere shortening are recognized as important drivers of chronic lung pathologies through their dual impact on cellular function and tissue microenvironment. By impairing alveolar regeneration, perpetuating fibrotic signaling, and amplifying inflammaging, these telomere-centric alterations create a self-reinforcing loop that exacerbates disease progression. Identifying the pathogenic mechanisms of telomere shortening in non-malignant pulmonary diseases and exploring novel therapeutic approaches represent pressing and complex challenges, which can suggest prognosis and provide a theoretical basis for drug research and therapy selection.

3.1. Interstitial lung diseases

3.1.1. Genetic features of telomere/telomerase-mediated ILD

Approximately one-third of patients with FPF carry pathogenic mutations in telomerase or other telomere maintenance genes[15]. To date, 17 genes have been implicated in telomere biology disorders, each contributing to telomere dysfunction through distinct mechanisms, such as impaired telomere maintenance, disrupted telomeric structure, loss of protective capping function, or altered telomerase abundance and activity (Fig. 2)[77]. A common hallmark across most telomere biology disorders is accelerated telomere shortening, which underlies key clinical features, including genetic anticipation. In affected families, offspring with genetic mutations and shorter TL exhibit earlier and more severe disease onset[57]. Notably, the genetically expected pattern of offspring may display phenotypic heterogeneity within the same family, manifesting as different pathologies of idiopathic interstitial pneumonitis[57]. This suggests that underlying genetic factors can increase susceptibility to PF but not to a specific subtype of pathology. As a result, it is more accurate to describe the phenotype of some families as FPF rather than familial IPF[24,78].

Telomerase components (partial). *TERT* mutations are the most common genetic defect in IPF, accounting for 15% of familial inheritance. These mutations span the entire gene and lead to diminished telomerase activity, compromising its conserved catalytic function[78,79]. NOP10, as part of the H/ACA ribonucleoprotein complex, plays a critical role in stabilizing *TERC*[80]. A monoallelic variant in *NOP10* was recently reported in a family with adult-onset PF and short telomeres, although the precise pathogenic mechanism remains to be elucidated[81]. Additionally, heterozygous mutations in *NHP2*, a contributing component of the telomerase holoenzyme, have been identified in three unrelated patients with PF[82]. Telomere Cajal body protein 1 (TCAB1), encoded by *WRAP53*, influences trafficking of telomerase to Cajal bodies, recruitment of telomerase to telomeres, and folding of the TERC domain, which are essential for telomerase activation[83,84]. Moreover, TCAB1 has also been involved in DNA repair[85]. To date, whether the disruption of this function contributes to the telomere-associated clinical phenotype remains unknown. Notably, TRiC chaperonin complex functions as an integral component of telomere maintenance by properly folding and stabilizing TCAB1. Recent work has identified right open reading frame kinase 2 as an upstream transcriptional regulator, whose deficiency downregulates mRNA expression of both TRiC and dyskerin complex subunits that impairs telomerase activity and triggers telomere shortening in IPF[86].

***TERC* biogenesis and stability factors**. Another class of genes associated with FPF mainly influences the integrity, biogenesis, and catalytic function of *TERC*, including *TERC*, *DKC1*, *NAF1*, *ZCCHC8*, and *PARN*. These mutations predominantly result in autosomal dominant disease, except for *DKC1* mutations, which manifest as X-linked disease in males[15,47]. Mutations in the *TERC* gene itself often disrupt its structural integrity and the base pairings required for TERT to perform its catalytic functions. Another mutant gene, *DKC1*, encodes dyskerin, a protein essential for stabilizing cassette H/ACA RNA such as TERC, and mutations that impair this interaction compromise TERC maturation and stability, leading to decreased telomerase activity and accelerated telomere shortening[87]. *DKC1* mutations could lead to an overall lack of dyskerin, resulting in PF manifestation in adults[15,88,89]. *NAF1* encodes a ribonucleoprotein whose mutations affect TERC transport and nucleolar

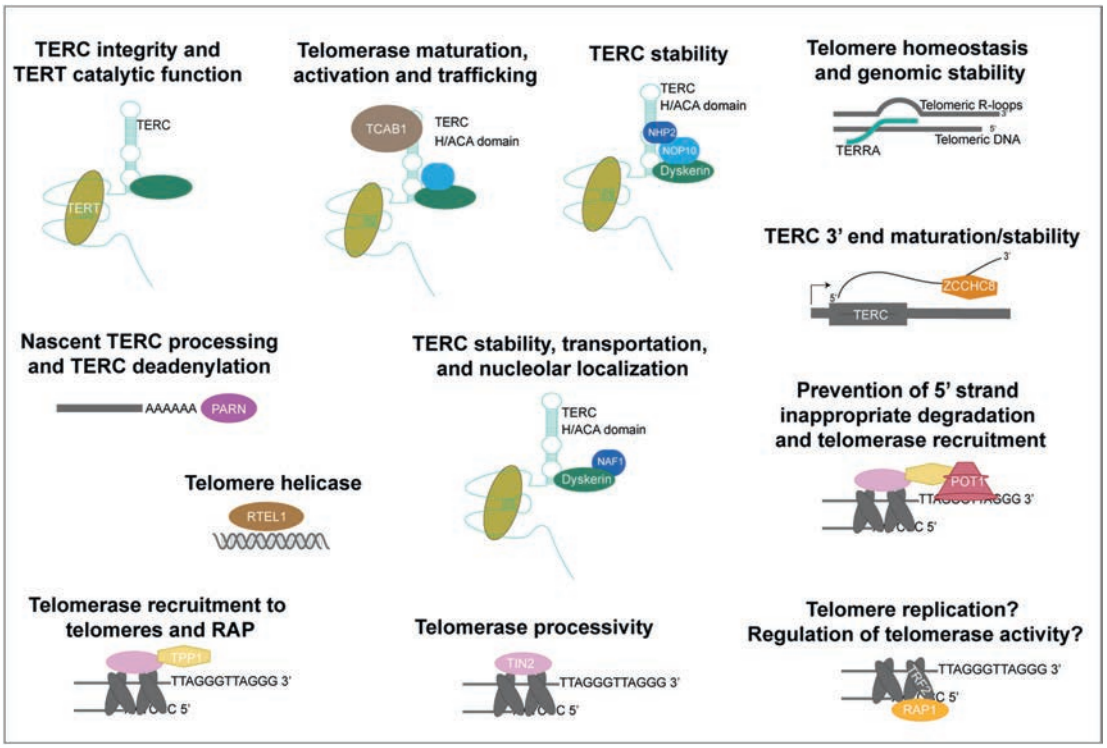

Figure 2 Mechanisms linking telomere biology disorders to pulmonary fibrosis. Multiple factors involved in global genome integrity play critical roles at telomeres by facilitating telomere replication, participating in 3′G-overhang production, affecting TERC or its biogenesis and localization, and promoting telomerase recruitment. Mutant components are highlighted in color. Abbreviations: RAP, repeat addition processivity.

localization, resulting in PF and emphysema[90]. The defective function of ZCCHC8, a targeting component of nuclear RNA exosomes, affects TERC 3′ end post-transcriptional maturation, leading to FPF[91]. Similarly, *PARN* mutations disrupt the processing of nascent and adenylated TERC, impacting their stability and enhancing susceptibility to PF[92,93].

Telomeric accessory factors. RTEL1, an essential DNA helicase, safeguards telomere replication by unwinding G-quadruplexes and disassembling the telomere loop structure. *RTEL1* mutations tightly link FPF to telomere shortening, but the precise mechanisms require further investigation[92]. The single-strand DNA-binding protein RPA1, critical for DNA replication and repair, is also integral to telomere maintenance. Monoallelic *RPA1* variants have recently been identified in four unrelated individuals, presenting with short telomeres and telomere biology disorder manifestations, including PF[94]. Recently, a study revealed that UBQLN1 could regulate TL by shutting RPA1 off from the replication fork. The deficiency of UBQLN1 causes a replication problem and telomere shortening. Moreover, knocking down *UBQLN1* in lung cells of the IPF model would accelerate senescence and aggravate PF, indicating that the UBQLN1−RPA1 axis plays a vital role in telomere maintenance and the pathogenesis of IPF[95]. Other telomeric accessory factors, such as DCLRE1B, CTC1, and STN1, play a crucial role in regulating the telomeric 3′ G-overhang[77]. However, whether they play a causative role in PF has yet to be elucidated.

Shelterin factors. TIN2 is a telomerase-recruiting factor, and *TINF2* mutations may affect telomerase processivity, leading to telomere shortening. Although *TINF2* mutations represent a relatively rare etiology of adult-onset PF, the observed depletion of TIN2 in fibrotic lungs suggests a broader role in disease pathogenesis. The extent to which this loss impairs local telomerase function and contributes to alveolar maintenance failure represents a significant gap in our mechanistic understanding of fibrotic progression[96−98]. The shelterin component TPP1, encoded by *ACD*, serves as a key regulator of telomere stability and telomerase recruitment. Importantly, disease-causing mutations in *ACD* have been identified in patients with PF, implicating disrupted telomere maintenance as a contributing mechanism in the disease[99]. Another shelterin protein, POT1, interacts with TPP1 to form a complex that orchestrates the protection of telomeric 3′ G-overhang, while also recruiting telomerase to telomeres and regulating its activity and repeat addition processivity[100]. Disruption of these critical functions is exemplified by the recently identified *POT1* (L259S) mutation. Functionally, this mutation causes telomere shortening, lagging-strand defects, telomere-induced DNA damage, and premature senescence with irreversible G1 arrest[101].

3.1.2. Telomeric repeat-containing RNA (TERRA) expression regulates the course of ILD

Long non-coding RNA (lncRNA) is a type of RNA molecule lacking protein-coding ability and exhibiting specificity in tissue and cell type. It is closely related to epigenetic regulation of genes in physiological and pathological processes[102,103]. Cao et al.[104] found that the expression profile of lncRNA was significantly altered in PF tissues, correlating with multiple signaling pathways such as PPAR, JAK−STAT, and chemokines. Telomere-associated lncRNA, TERRA, is a telomeric repeat-containing RNA transcribed from the sub-telomeric region. It can invade the telomeric

DNA double-strand and form an RNA: DNA heteroduplex with the template strand (R-loop structure)[105]. This structure is essential for the recognition of shelterin and regulation of biological processes in DNA to maintain telomere homeostasis[77,105–107]. Increased expression of TERRA has been reported to correlate with susceptibility to oxidative stress and apoptosis in type II alveolar epithelial cells (AT2) from ILD patients and PF mice[108]. Furthermore, its overexpression inhibits telomerase activity and induces cellular senescence in the specific absence of telomere maintenance[109]. Additionally, TERRA can be delivered *via* exosomes and exists in a cell-free form. It promotes intercellular communication and activates the innate immune response by stimulating the secretion of IL-6, TNF-α, and CXCL10, suggesting that TERRA may serve as a tool for inducing a specific inflammatory microenvironment in non-malignant respiratory diseases[41]. TERRA may also be released into circulation from the lungs through exosomes and impact other organs by stimulating the production of inflammatory factors and senescent cells, which could explain the co-morbid mechanisms of chronic lung diseases, such as the extrapulmonary phenotype of ILD[18,41,110]. Moreover, exosomes isolated from bronchoalveolar lavage fluid of IPF patients were found to contain WNT-5a, a protein that induces fibroblast proliferation[111]. Therefore, could TERRA delivered *via* exosomes be used as an indicator of an inflammatory environment or a marker for cellular senescence? These questions require further exploration.

3.1.3. Telomere dysfunction initiates the program of alveolar epithelial senescence and pulmonary fibrosis

Epidemiological and molecular studies consistently show that germline mutations in telomere-related genes predispose offspring to critically short TL. However, children and young adults with severe telomere shortening typically develop non-malignant pulmonary diseases only after the age of 40, which suggests that short telomeres alone are insufficient to cause non-malignant pulmonary diseases[57,78,112]. This discovery is further supported by the observation that late-generation telomerase-knockout mice did not spontaneously develop PF[113]. As a result, secondary hits are required for the onset of telomere-mediated non-malignant pulmonary diseases, including endogenous factors such as endoplasmic reticulum stress[57,78], and DNA damage[41], as well as exogenous factors such as cigarette smoking[21], pneumonia[78], and viral infections[114–117], thereby lowering the threshold for these diseases due to cumulative damage. Therefore, characteristics of short telomeres may simply underlie genetic susceptibility to age-related fibrotic diseases. The interplay between genes and both the internal and external environment is critical for disease progression.

AT2 are crucial for maintaining alveolar homeostasis and serve as progenitor cells for self-renewal and differentiation into type I alveolar epithelial cells (AT1)[15,118–120]. Notably, regarding the general importance of epithelial injury as an initiator in fibrosis, genetic polymorphisms confer susceptibility to premature senescence in alveolar epithelial cells, while environmental exposures accelerate this process by inducing oxidative stress and DNA damage[121]. During this phase, the cyclic GMP–AMP synthase (cGAS)–stimulator of interferon genes (STING) pathway is activated by cytoplasmic DNA, reinforcing the senescence program and amplifying local inflammatory responses[122]. When lungs are subjected to secondary injurious stimuli, AT2 cells exhibit severe functional defects, manifested as enhanced cellular stress responses, increased activation of apoptotic pathways, and impaired progenitor function[118,119]. Senescence of alveolar epithelial stem cells impairs the re-epithelialization of the alveolar basement membrane after injury[123]. This denuded state stimulates pathways involved in the normal wound healing response, thereby promoting the activation and transformation of fibroblasts into myofibroblasts[124]. At this stage, the TGF-β/Smad pathway emerges as the core driver of fibrosis. TGF-β ligands bind to their receptors, phosphorylate Smad2/3, which then form complexes with Smad4 and translocate into the nucleus to directly upregulate the transcription of genes such as collagen and alpha-smooth muscle actin. Concurrently, aberrant activation of the Wnt/β-catenin pathway, through inhibition of GSK-3β, leads to cytoplasmic accumulation and nuclear translocation of β-catenin. There, it cooperates with β-catenin–T-cell factor/lymphoid enhancer-binding factors (TCF/LEF) to promote fibroblast proliferation and suppress apoptosis[122]. Additionally, recruited monocyte-derived alveolar macrophages, neutrophils, or lymphocytes contribute to the profibrotic milieu by synthesizing and locally secreting profibrotic growth factors. The collagens and extracellular matrix (ECM) proteins secreted by activated fibroblasts and myofibroblasts alter the composition and stiffness of the lung parenchyma, thereby creating a sustained profibrotic stimulus[125]. The progressive deposition of ECM and resultant stiffening of the lung parenchyma activate mechanotransduction pathways. The pathological matrix stiffness is primarily sensed through the integrin–focal adhesion–YAP/TAZ axis. The ensuing signaling cascade promotes the nuclear translocation of YAP/TAZ to initiate a potent pro-fibrotic gene program[126]. Consequently, once initiated, the fibrotic process becomes self-propagating through this mechanobiological framework, thereby perpetuating disease progression. Furthermore, telomere-mediated senescence within specific cellular niches, particularly AT2 cells and fibroblasts, drives pathological lung remodeling. Critically, SASP acts as the key executor of this pathology. These senescent cells secrete distinct and highly active SASP molecules, enriched with key mediators such as TGF-β and IL-1α. It is primarily through this paracrine SASP that a dual pathological effect is exerted, by which a senescence-like phenotype is induced and telomere damage exacerbated in neighboring cells, while pathogenic reprogramming, including epithelial–mesenchymal transition (EMT) and fibroblast-to-myofibroblast differentiation, is simultaneously driven[118,127]. Together, the SASP-mediated bystander effect and cellular reprogramming establish a self-amplifying positive-feedback loop. The autonomous propagation of the SASP within this dysregulated microenvironment ultimately drives the progressive destruction of lung architecture, irreversible scar formation, and consequent impairment of gas exchange[18,127].

The pulmonary vasculature also undergoes significant changes in PF, where endothelium and smooth muscle cells acquire a pathologically activated phenotype[128,129]. Activated endothelial cells can undergo endothelial-to-mesenchymal transition (EndMT), which contributes to the myofibroblast pool[130]. Concurrently, the loss of endothelial barrier function facilitates the recruitment of circulating immune cells, thereby amplifying the pro-fibrotic inflammatory milieu[131]. Additionally, the loss of functional capillaries may create localized hypoxia, stabilizing hypoxia-inducible factor-1α, which in turn transcriptionally upregulates key fibrotic genes, establishing a self-perpetuating cycle of vascular drop-out and scar formation[132] (Fig. 3).

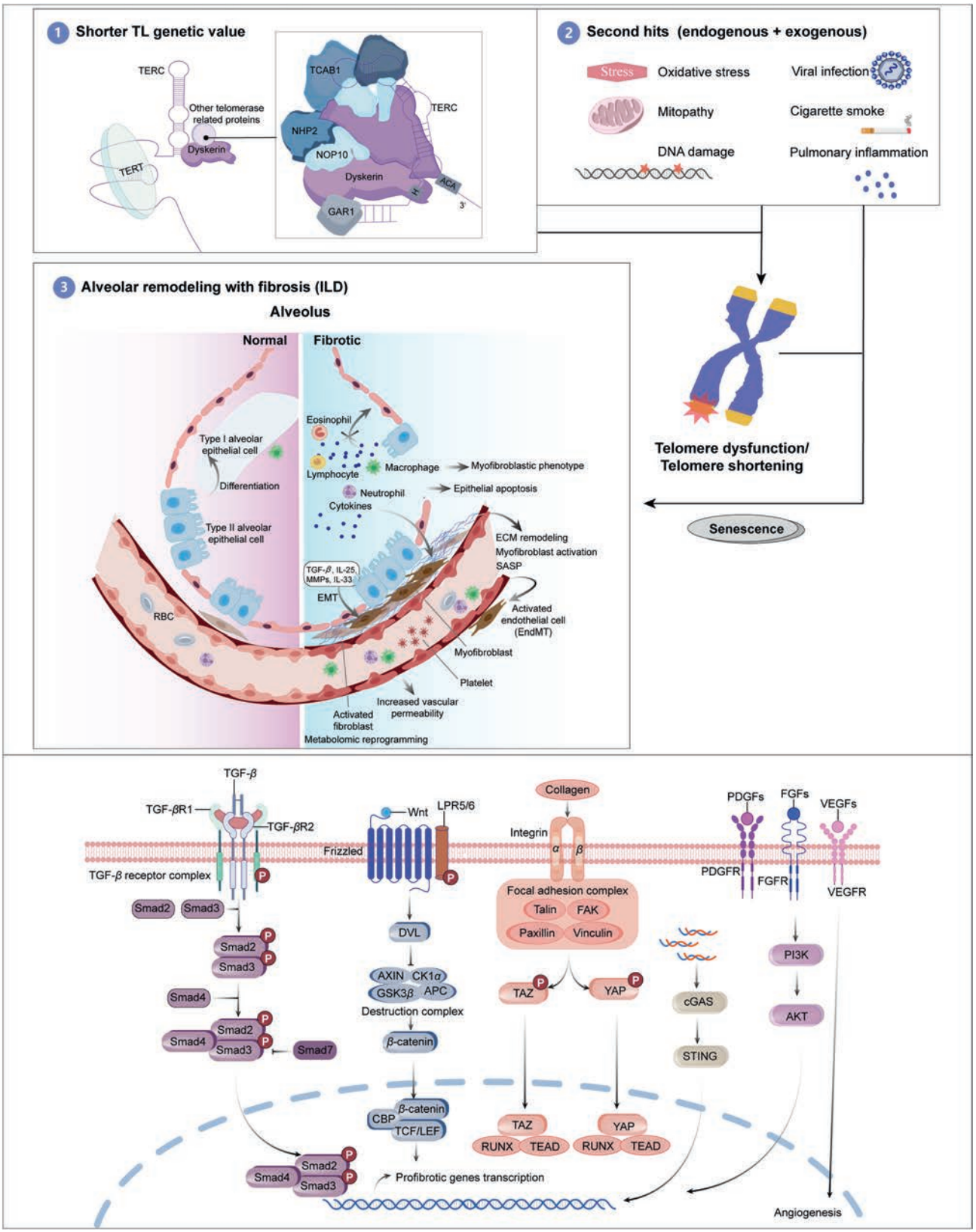

Figure 3 Multifactorial pathogenesis of telomere-driven ILD (primarily PF) and an overview of molecular signaling pathways. This schematic diagram illustrates the pathogenic progression from telomere dysfunction to established fibrosis, driven by genetic susceptibility and environmental "second hits". Initiation: genetic polymorphisms and cumulative environmental exposures induce severe dysfunction and premature senescence in AT2 cells. Amplification: dysfunctional AT2 cells interact with immune cells, amplifying initial damage events and promoting mesenchymal expansion, which can be supplemented by epithelial-mesenchymal crosstalk (*via* EMT). Fibrogenesis: the failure of

3.2. Chronic obstructive pulmonary disease

3.2.1. Telomerase mutations and SNPs underlie the genetics of COPD pathogenesis

Although smoking is a significant risk factor for COPD, only 10%−15% of smokers eventually develop COPD, implying that genetic mutations, as well as epigenetic and post-translational modifications, also increase the risk for certain individuals[133]. Section 2.2.2 has presented that mutations in telomerase genes are susceptibility factors for COPD and may enhance an individual's vulnerability to it. SNPs at loci near telomerase-related genes have also been associated with an increased risk of developing COPD. Therefore, mutations in telomerase genes contribute disproportionately to COPD disease mechanisms despite their low prevalence in affected individuals.

3.2.2. Short telomeres combined with other aging features contribute to COPD progression

COPD is a disease of accelerated lung aging. Telomere shortening, one of the hallmarks of aging, interacts with other aging features such as mitochondrial dysfunction, cellular senescence, epigenetic changes, metabolic reprogramming, and microRNA profiles to promote disease progression[59]. With each cell division, telomeres undergo progressive attrition. When they reach a critical length, a DDR is triggered, resulting in the activation of p53 (replicative senescence). In addition, exposure to exogenous stressors such as cigarette smoke or endogenous factors such as reactive oxygen species (ROS) can activate $p16^{INK4a}$ (stress-related senescence). These pathways may converge to activate $p21^{CIP1/WAF1}$, leading to irreversible cell cycle arrest. The activation of $p21^{CIP1/WAF1}$ initiates the SASP response, thereby activating pathways such as mitogen-activated protein kinases (MAPKs), JAKs, and nuclear factor-κB (NF-κB)[18]. Despite ceasing to divide, senescent cells remain metabolically active and undergo a profound shift in metabolic reprogramming, which deeply influences the neighboring non-senescent cells through SASP[134−136]. The senescence-mediated secretome is highly heterogeneous, cell context- and cell type-dependent, being released either directly or through macrovesicles/exosomes, acting as primary mediators of the senescent state's influence on the tissue microenvironment[137]. A critical and detrimental consequence is the paracrine propagation of telomere dysfunction. Senescent cells release ROS and pro-inflammatory cytokines like IL-6 and TNF-α, which induce oxidative stress in neighboring cells, directly damaging their telomeric DNA and accelerating telomere attrition[138,139]. Furthermore, these SASP factors potently activate the DDR in adjacent cells, a process molecularly evidenced by the formation of telomere-associated DNA damage foci (TAFs) and the subsequent activation of the p53−p21 pathway, thereby driving them into a senescent state[17]. This senescence-by-stander effect creates a self-amplifying and feed-forward loop of senescence that spreads through the pulmonary architecture. In COPD, senescent airway epithelial cells release SASP factors that recruit and activate immune cells like neutrophils, which in turn release proteases like matrix metalloproteinase-9 (MMP9) that destroy the alveolar walls and generate more ROS, further fueling the cycle of epithelial damage and telomere attrition in adjacent epithelial cells[134,140−142]. Ultimately, these intricate SASP-mediated interactions result in the recruitment and sustained activation of inflammatory cells, perpetuate the chronic low-grade inflammation known as inflammaging, disrupt lung tissue homeostasis, and directly promote the local tissue destruction and aberrant repair that characterize COPD pathology.

Immune cells in the COPD microenvironment also exhibit significant metabolic alterations[143]. In macrophages, for instance, activation, polarization, and energy metabolism are intrinsically linked to their inflammatory status[144]. The spectrum of macrophage phenotypes is broadly categorized into two distinct subsets with different functions and metabolic patterns: the pro-inflammatory, glycolytic M1 macrophages and the anti-inflammatory, pro-resolving oxidative M2 macrophages[134]. However, under senescent conditions, M2 macrophages accumulate dysfunctional mitochondria with increased membrane permeability, impairing ATP production, shifting M2 macrophages toward a more pro-inflammatory phenotype. Similarly, M1 macrophages also experience functional damage, characterized by lysosomal permeabilization and leakage of lipids and trace elements into the cytosol[134]. These changes lead to impaired phagocytosis, diminished microbicidal capacity, and an overall ineffective immune response, creating a critical vulnerability in the lungs. While these cells fail to adequately clear pathogens and apoptotic debris, their persistent basal inflammatory activity continues to release proteases and ROS. This paradoxical state establishes a self-perpetuating cycle of tissue injury and impaired repair: the inability to resolve microbial invasions leads to recurrent infections that exacerbate inflammation, while the ongoing inflammatory milieu further damages lung parenchyma and amplifies emphysematous destruction. Iron metabolism adds another regulatory layer to the immunometabolic dysfunction of COPD macrophages[145]. Cigarette smoke delivers inherent iron-rich particles and triggers alveolar microhemorrhages that release heme, thereby loading alveolar macrophages with iron[146]. Excess iron catalyzes the Fenton reaction, potentiating oxidative injury and telomere dysfunction[147]. This telomere attrition, particularly in alveolar epithelial cells and macrophages, accelerates cellular senescence and reinforces SASP. Simultaneously, iron-dependent lipid peroxidation drives ferroptosis in epithelial cells, which is increasingly recognized as a significant pathological mechanism in COPD[148]. The ensuing cell death and inflammation are further amplified by iron-laden macrophages, which propagate tissue damage and create a pro-inflammatory microenvironment that sustains this destructive cycle, ultimately driving disease progression through combined genomic instability and inflammatory tissue destruction.

In addition, neutrophils that accumulate in the lower airways of COPD patients also undergo metabolic adaptations with reduced glycolytic activity, diminished lactate production, and an impaired capacity to utilize glutamine for gluconeogenesis[149]. This energy

re-epithelialization of the basement membrane and sustained senescence signaling activate fibroblasts (*via* EndMT and other pathways, including TGF-β/Smad, Wnt/β-catenin, cGAS−STING, integrin-focal adhesion-YAP/TAZ, and PI3K−AKT axis) into collagen-producing myofibroblasts, driving progressive fibrosis. Additionally, endothelial cell activation triggers vascular leakage and initiates the clotting cascade, which activates platelets and promotes fibrin deposition. Abbreviations: SASP, senescence-associated secretory phenotype; MMPs, matrix metalloproteinases; TGF-β, transforming growth factor-β; ECM, extracellular matrix; EMT, epithelial−mesenchymal transition; EndMT, endothelial-to-mesenchymal transition; RBC, red blood cell.

crisis, evidenced by critically low ATP and NADH levels, underlies their functional impairment and senescent phenotype, which includes decreased phagocytosis, bacterial killing, chemotaxis, and apoptosis, as well as increased release of elastolytic proteases[150]. Neutrophil elastase contributes directly to emphysematous destruction by degrading key components of the lung ECM and disrupting epithelial cadherin integrity, thereby accelerating alveolar tissue loss and disease progression[151,152]. The breakdown of ECM can generate tripeptide neutrophil chemoattractant *N*-acetyl Pro-Gly-Pro, which acts as a structural homology of chemokines to orchestrate neutrophil chemotaxis and superoxide production through engagement of C−X−C motif chemokine receptors[153]. Additionally, the proteolytic activity of neutrophils further compromises innate immunity *via* cell-type-specific receptor cleavage. Elastase and cathepsins cleave C−X−C motif chemokine receptor 1 on the neutrophil surface, thereby blunting its phagocytic and inflammatory responsiveness[154]. Concurrently, these proteases target the IL-22 receptor expressed in the lung mucosa, disrupting a critical STAT3 signaling axis for antimicrobial defense and tissue repair[155]. Beyond its direct proteolytic activity, neutrophil elastase instigates a self-sustaining inflammatory circuit by activating bronchial epithelial receptors to upregulate IL-8 transcription, thereby fueling further neutrophil influx into the airways[156,157]. Unopposed neutrophil elastase activity also drives goblet cell hyperplasia and mucus hypersecretion by inducing MUC5AC mucin expression through a protein kinase C (PKC)−ROS−TNF-α−converting enzyme signaling cascade in human airway epithelial cells[158]. Consequently, the senescent and metabolically imbalanced microenvironment in COPD creates a dysfunctional state characterized by a loss of protective immunity but a persistence of tissue-destructive capacity, thereby directly driving disease progression (Fig. 4).

The phosphoinositide-3-kinase (PI3K)−mammalian target of rapamycin (mTOR) signaling pathway, a central regulator of growth and metabolism, is important for regulating anti-aging processes[159]. Increased PI3K activation, as assessed by phosphorylation of its downstream kinase AKT, has been observed in the lungs and peripheral blood mononuclear cells of COPD patients[160]. Inhibition of this pathway could extend lifespan across a diverse range of model organisms[159]. Sirtuins, a family of nicotinamide adenine dinucleotide (NAD^+)-dependent histone deacetylases implicated in aging and longevity, play key roles in telomere maintenance, DDR, inflammatory homeostasis, and metabolic adaptation[1,59,161]. MicroRNAs are short non-coding single-stranded RNAs that regulate post-transcriptional gene expression[162]. Oxidative stress can upregulate microRNA-34a in peripheral lung and epithelial cells through the PTEN−PI3K−mTOR pathway, resulting in reduced protein levels of sirtuin-1 (SIRT1) and sirtuin-6 (SIRT6)[18]. Another microRNA, microRNA570, can inhibit SIRT1 expression through the activation of p38 MAPK−cJun−activator protein 1. Reduced levels of SIRT1 and SIRT6 have been found in COPD patients[163,164]. On one hand, decreased SIRT1 accelerates senescence by increasing the acetylation of proteins, including Ku70 (which plays an important role in DNA repair), p53 (which induces cellular senescence), NF-κB (which regulates SASP and MMP9), FOXO3a (which has a positive feedback on oxidative stress), and critically, PGC-1α (which leads to mitochondrial dysfunction)[18]. The mitochondrial dysfunction resulting from PGC-1α dysregulation creates a demand for quality control *via* mitophagy, the selective autophagy of damaged mitochondria regulated by the PTEN-induced kinase 1 (PINK1)-parkin RBR E3 ubiquitin protein ligase (PRKN) pathway. Research highlighting this link has shown that Arylsulfatase K counteracts airway epithelial cell senescence in COPD by enhancing PRKN-mediated mitophagy, underscoring a promising therapeutic strategy[165]. Furthermore, SIRT1's role extends to telomere maintenance. The shelterin component TPP1 interacts with and is deacetylated by SIRT1. Cigarette smoke disrupts this interaction, leading to TPP1 acetylation, degradation, and subsequent telomere damage and cellular senescence[166]. This mechanism provides a theoretical foundation for targeting shelterin complexes to alleviate cellular aging in COPD. On the other hand, the reduction of SIRT6 can directly induce telomere shortening, leading to cellular senescence and impaired autophagy. Moreover, it can also inhibit the activity of nuclear factor erythroid-2-related factor 2, a key regulator of antioxidant genes, thereby potentiating oxidative stress. This interplay constitutes a detrimental feedback loop that exacerbates the progression of COPD[59] (Fig. 4).

In summary, while telomeres and telomerase are undeniably central to COPD pathogenesis, their precise and individual mechanistic contributions remain elusive. The research has not yet fully deciphered their isolated roles; rather, the prevailing paradigm integrates telomere dysfunction as a critical node within a complex network of interconnected aging hallmarks. This system-level approach has been instrumental in revealing the accelerated aging phenotype of COPD. To propel the field forward, several pivotal questions demand exploration. First, is telomere attrition a primary causative driver or a critically exacerbated consequence within the COPD aging network? Second, how do cell-type-specific telomere maintenance mechanisms dictate distinct pathological outcomes, such as emphysema or airway remodeling? Finally, beyond maintaining TL, what non-canonical roles does telomerase play in modulating inflammation and metabolism in COPD? Addressing these questions will be crucial for moving from association to mechanism and for translating our understanding of telomere biology into targeted therapies for COPD.

3.3. Asthma

3.3.1. Short telomere-associated senescence is involved in the development of asthma

In asthma, telomere shortening serves as a critical nexus, where diverse pathological stimuli, such as oxidative stress, mitochondrial dysfunction, and inflammation, converge to accelerate cellular senescence. The process is initiated when asthma-related risk factors, such as allergens and pollutants, induce oxidative damage to telomeric DNA, leading to the functional disruption of the shelterin complex and exposure of telomeric ends. This exposure is perceived as double-strand breaks, triggering a persistent DDR mediated by the ATM/ATR kinases, which stabilizes p53 and upregulates p21, enforcing cell cycle arrest and initiating cellular senescence[20,167]. A pivotal mechanism involves the cGAS−STING pathway: chromatin rupture from dysfunctional telomeres releases telomeric fragments into the cytosol, where they are sensed by cGAS, which activates STING and subsequently drives the production of type I interferons and pro-inflammatory cytokines through NF-κB and IRF3-mediated pathways, thereby directly linking a nuclear telomere crisis to innate immune activation. This process could be synergistically amplified by a feedforward loop. In this loop, mitochondrial dysfunction impairs biogenesis and causes a ROS burst, which in turn exacerbates telomeric damage and thereby reinforces the senescent program[167−171]. The senescent cell then orchestrates tissue damage through the SASP by activating nucleotide-binding

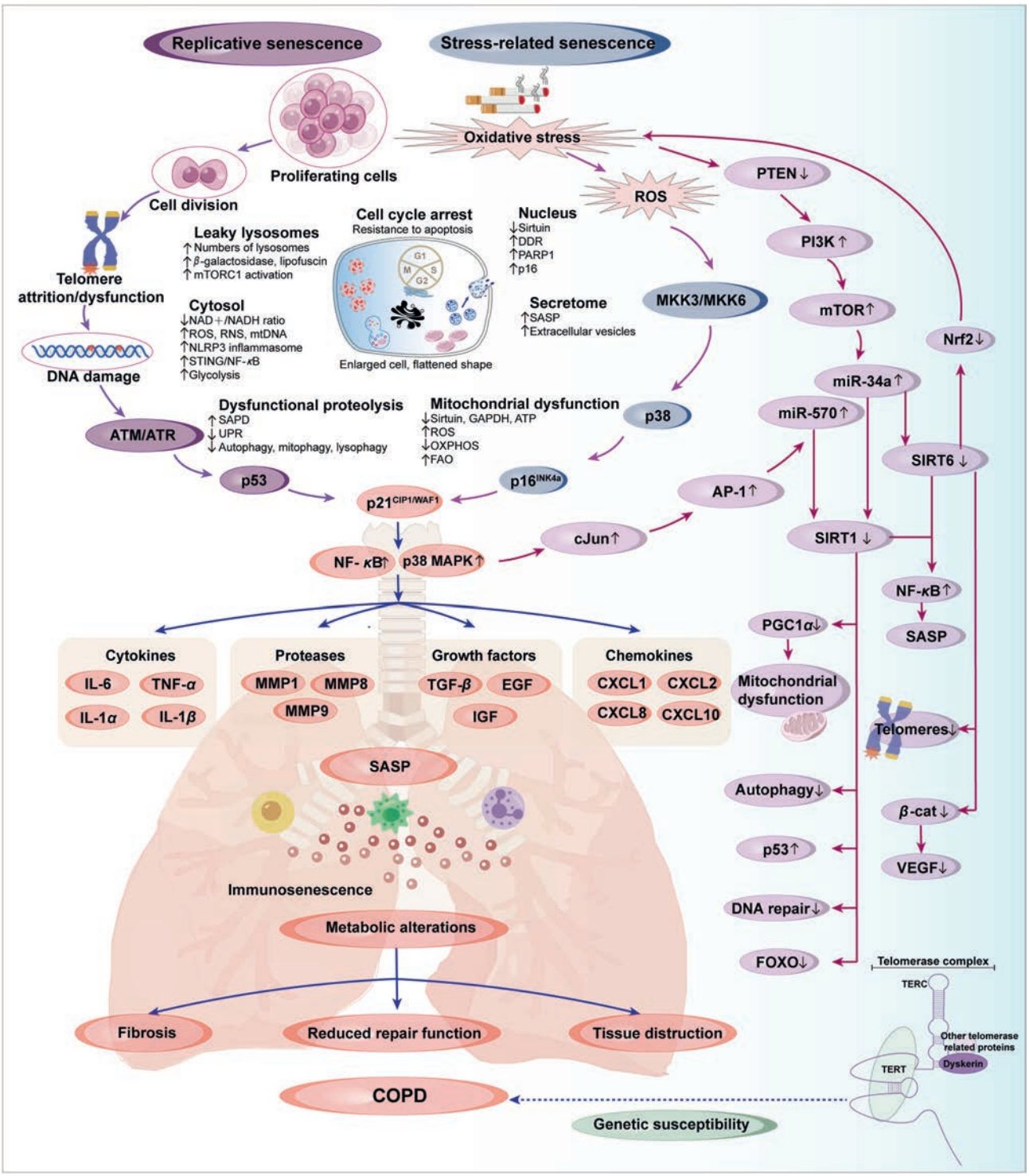

Figure 4 Signaling pathways of cellular senescence in COPD pathogenesis. The integrated pathogenic cascade initiates with core senescence pathways, as replicative and stress-induced senescence trigger cell cycle arrest and metabolic alterations. These changes lead to dysfunctional lysosomes and mitochondria that exacerbate macromolecular damage. Subsequently, senescent cells activate NF-κB and p38 MAPK signaling, driving secretion of multiple pro-inflammatory cytokines, termed SASP, which promotes destructive lung structural changes, including fibrosis, tissue destruction, and functional decline. This process is further integrated with oxidative stress pathways that modulate microRNAs *via* PTEN−PI3K−mTOR and p38 MAPK−cJun−AP-1 pathways, impacting mitochondrial and telomere homeostasis, while telomere-related mutations constitute an important genetic component within this pathogenic network. Abbreviations: ROS, reactive oxygen species; SIRT1, sirtuin-1; SIRT6, sirtuin-6; MAPK, mitogen-activated protein kinase; NF-κB, nuclear factor-κB. miR-570, microRNA-570; miR-34, microRNA-34; PTEN, phosphatase and tensin homolog; PI3K, phosphoinositide-3-kinase; mTOR, mammalian target of rapamycin; AP-1, activator protein-1; UPR, unfolded protein response; SAPD, senescence-associated protein degradation; OXPHOS, oxidative phosphorylation; FAO, fatty acid oxidation; EGF, epidermal growth factor; IGF, insulin like growth factor; Nrf2, nuclear factor erythroid-2-related factor 2.

domain, leucine-rich repeat, and pyrin domain-containing family protein 3 inflammasome and releasing inflammatory cytokines such as IL-6, TNF-α, IL-1β, and MMPs that perpetuate chronic inflammation, recruit immune cells, induce paracrine senescence, and compromise the epithelial barrier[20,172].

3.3.2. The impact of telomeres being triggered in asthma differs from IPF and COPD

Some features of asthma differ from IPF and COPD, suggesting that telomeric damage may be triggered or have different effects on the disease. Firstly, asthma mostly develops in childhood, indicating that patients may experience premature senescence, potentially initiated by environmental stressors during critical developmental stages, including neonatal hyperoxia, air pollutant inhalation, and childhood/adolescent allergen challenges[173–175]. Previous research has delineated a correlation between asthma and telomere attrition. However, the question remains whether short telomeres at birth precipitate asthma and its progression, or if asthma causes damage at the cellular and molecular level that induces telomere shortening? A causal relationship has not yet been elucidated. According to the study by Belsky and colleagues[75], there are two possible mechanistic pathways: either an accelerated telomere shortening, which may be influenced by genetic factors or/and early developmental processes, contributes to chronic disease phenotypes; or significant telomere shortening results from the persistence of active symptoms from childhood into adulthood and the associated inflammatory processes. Notably, premature senescence may only occur in specific cell types and be caused by specific inflammatory factors.

Secondly, the heterogeneous inflammatory phenotypes of asthma are closely linked to telomere shortening-induced senescence, with underlying molecular mechanisms revealing a new dimension of immunosenescence. Asthma is primarily classified into eosinophilic (Th2-high) and neutrophilic (Th2-low) subtypes based on the predominant type of immune cells that infiltrate the airways[167]. Emerging evidence indicates that telomere dysfunction plays a pivotal role in driving this process. Telomere shortening-driven senescence and the consequent SASP collectively foster a chronic pro-inflammatory microenvironment. Concurrently, the decline in repair capacity of senescent airway epithelial progenitor cells compromises the airway barrier, facilitating allergen penetration. This not only causes persistent epithelial damage and substantial release of IL-25, IL-33, and thymic stromal lymphopoietin (TSLP) but also leads to sustained activation of the Th2 immune pathway, which characterizes the Th2-high asthma endotype[176]. Moreover, the SASP can also propel the Th2-low phenotype. The specific immune polarization is strongly influenced by the immunomodulatory effects of SASP. A microenvironment shaped by factors like TGF-β and IL-6 promotes Th17 lineage commitment by activating the SMAD/STAT3−RAR-related orphan receptor γt (RORγt) signaling cascade[177,178]. In contrast, the SASP may promote a microenvironment that leads to the production of IL-12, which could skew differentiation towards the Th1 pathway, activating STAT1 and inducing the key transcription factor T-bet[179,180]. Notably, the microenvironment shaped by telomere shortening-induced senescence may converge with impaired autophagy and mitochondrial dysfunction to disrupt the Th1/Th2 immune balance, thereby promoting lung aging and immunosenescence, which contributes to asthma progression[181]. In addition, Th17/Treg bias is more common in asthma, a phenomenon that could be affected by immunosenescence[182] (Fig. 5).

Beyond modulating immune responses, SASP contributes critically to airway remodeling. This process is sustained by a paracrine network of senescent cells across the airway microenvironment. Senescent epithelial cells secrete remodeling factors such as TGF-β, EGF, and MMPs, which directly promote airway hyperresponsiveness and tissue restructuring[167]. These epithelial signals further activate adjacent resident interstitial cells. In addition, lung fibroblasts also release SASP molecules and exosomes, which stimulate epithelial hyperplasia and impaired repair, thereby entrenching a maladaptive remodeling cycle[183]. Furthermore, senescent immune cells amplify this cascade by producing MMPs, leading to airway wall thickening, fibrosis, and ultimately exacerbating airflow obstruction[167]. Collectively, airway remodeling in asthma can be conceptualized as a propagating cascade initiated and sustained by SASP-mediated crosstalk among epithelial, interstitial, and immune cells, creating a self-reinforcing cycle that perpetuates asthma progression. However, the mechanistic links connecting telomere dysfunction and cellular senescence to both immune skewing (Th1/Th2, Th17/Treg) and SASP-mediated structural pathologies remain largely unexplored.

Thirdly, the molecules and pathways involved in telomere shortening-induced senescence in asthma may differ from those in IPF and COPD, depending on stimulus source, senescence time, environment, and cell types. Different types of senescent cells or tissues predispose to various non-malignant pulmonary diseases. Specifically, senescence of bronchial and alveolar epithelial cells may correlate with acute or chronic respiratory infections; senescence of alveolar epithelial progenitor cells may cause IPF; and senescence of mesenchymal stem cells may lead to COPD[178]. In addition, it is crucial to determine how changes in different genes are connected to telomeres, senescence, and diseases. Integrin B4 may be a key gene linking epithelial cellular senescence to asthma pathogenesis[184]. Moreover, significant interest has been garnered regarding the potential role of telomere-induced cellular senescence in the pathogenesis of asthma. Consequently, further investigations should focus on examining the impact of mutations in telomere-related genes on the diverse phenotypes of asthma, as well as the underlying molecular mechanisms.

3.3.3. Understanding the role of telomerase-mediated inflammation and immune response in asthma

Despite the nascent understanding of telomerase in asthma, emerging evidence suggests that telomerase activity and its interaction with shelterin complexes may contribute to the physiopathology of the disease. Asthma patients have significantly thickened airway smooth muscle (ASM) cell layers in the airways that secrete various chemokines, with the NF-κB transcription factor playing a central role in this inflammatory process[25,185,186]. Telomerase and PIN2/TERF1 interacting-telomerase inhibitor 1 were found to regulate NF-κB activity and chemokine expression in ASM cells, indicating that the telomerase and shelterin complexes are important in modulating inflammation in airway cells and represent potential targets for anti-inflammatory therapy in asthma[185]. Furthermore, a study of memory T lymphocytes in asthma revealed that telomerase activity was up-regulated during antigen-specific immune response, with an increased response to house dust mite allergens[187]. This may contribute to the persistent allergen-specific tendency observed in asthma patients, suggesting a potential role for telomerase inhibitors in controlling atopic asthma. Overall, these results indicate that the telomerase/shelterin complex may play a critical role in the development of asthma.

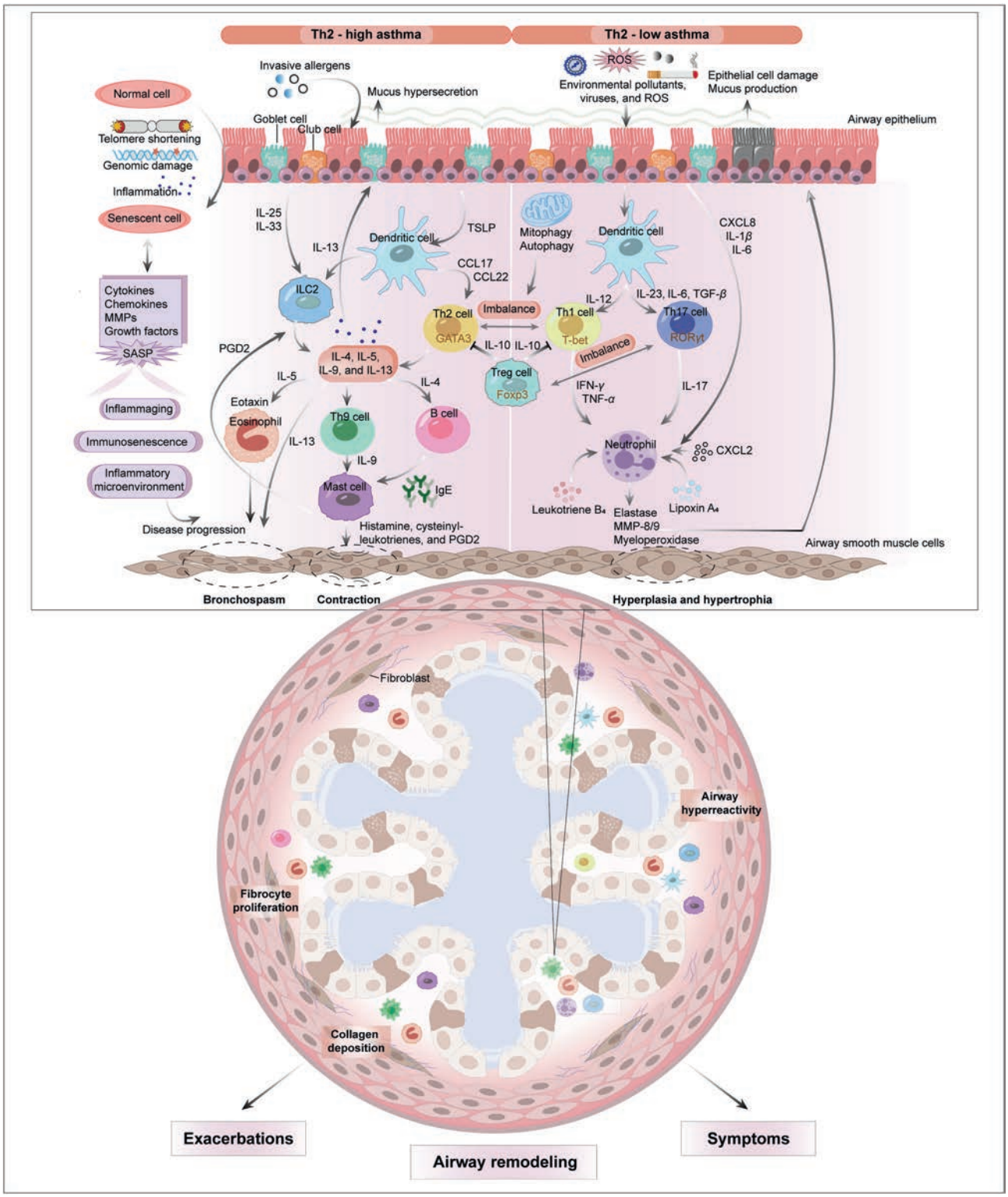

Figure 5 Potential role of telomere-associated cellular senescence in asthma. Multiple stimuli, including pollutants, viruses, and allergens, induce telomere damage, oxidative stress, and mitochondrial dysfunction, collectively driving senescence in airway epithelial, mesenchymal, and immune cells. These senescent cells amplify their effect through SASP, establishing a pro-inflammatory microenvironment characterized by inflammaging and immunosenescence. In this context, damaged epithelial cells release alarmins (TSLP, IL-25, IL-33), activating dendritic cells (DCs) and group 2 innate lymphoid cells (ILC2s). DCs further promote the differentiation of naïve T cells into Th2 lymphocytes, which, together with ILC2s, secrete type 2 cytokines (IL-4, IL-5, IL-9, IL-13) to initiate and sustain inflammation. Simultaneously, environmental triggers stimulate the epithelium to release IL-1β, IL-6, and neutrophil-attracting chemokines such as IL-8. DCs further recruit neutrophils and amplify

3.4. Comparative perspective

Telomere dysfunction operates across a pathogenic spectrum in non-malignant pulmonary diseases, ranging from a core genetic etiology to a perpetuating amplifier and finally a consequential biomarker, with distinct causal contributions and temporal sequences defining each disease (Fig. 6).

In ILD, telomere shortening acts as an upstream and initiating cause. Germline mutations in telomerase or shelterin complex genes set a genetically low ceiling for alveolar epithelial replicative capacity, creating a vulnerable cellular substrate. Critically, the clinical manifestation of disease typically requires additional environmental "second hits". These exposures inflict direct damage on the epithelium, overwhelming its repair capacity and precipitating the onset of the senescence-fibrosis cascade. Although germline defects establish a near-linear genetic-to-pathologic causal chain, which is strongly supported by the Mendelian randomisation study, environmental factors act as essential triggers that determine the timing and possibly the rate of disease progression. In COPD, telomere shortening functions as the central amplifier within a self-perpetuating vicious cycle. While not a direct genetic cause, as in ILD, a genetic predisposition, such as a shorter baseline TL, lowers the threshold for damage from environmental stimuli. These stimuli induce oxidative stress and chronic inflammation, accelerating telomere attrition. This attrition then induces cellular senescence and a distinct pro-inflammatory/proteolytic SASP, such as IL-8 and MMPs, which further exacerbates tissue destruction (emphysema) and inflammation. Critically, this sustained inflammatory milieu regenerates oxidative stress, thereby closing the loop and reinforcing the cycle of telomere damage and disease progression. In asthma, however, the evidence positions telomere shortening primarily as a downstream consequence and an integrative biomarker. It results from the combined effects of environmental factors and chronic inflammation-induced cellular stress. This telomere dysfunction may contribute to a local senescence microenvironment that potentiates airway remodeling and therapeutic refractoriness, thereby amplifying disease severity and chronicity in a feed-forward manner. The evidence remains largely associative, highlighting its role as a severity marker rather than a primary initiator.

Therefore, deciphering the causal hierarchy and temporal sequences of telomere dysfunction across this spectrum provides a powerful lens for developing mechanistically grounded therapies tailored to the unique pathogenesis of each disease.

Additionally, to provide a more systematic and in-depth elucidation of the core mechanistic differences in telomere dysfunction across distinct pulmonary disease subtypes, current evidence and understanding regarding the primary causes of telomere shortening, key effector cells, causal link, most relevant SASP factors, and core signaling pathways in conditions such as ILD, COPD, and asthma have been integrated. These details are summarized in Table 1[18,19,21,50–52,61,65,68,71,73,76,113,122,130,167,188–203].

4. Therapeutic interventions targeting telomere-associated senescence

Emerging technologies link the most prominent manifestations of telomere and telomerase dysfunction to the etiology of non-malignant pulmonary diseases, deepening our understanding of the pathogenic mechanisms underlying these conditions. The increasing discovery and utilization of drugs and novel therapeutics with anti-senescence properties through modulation of TL and telomerase activity will significantly impact the progression of chronic lung diseases and the future of "health span".

4.1. Telomere gene therapy

Telomere shortening is a prevalent defect in non-malignant pulmonary diseases, which raises potential therapeutic approaches involving telomerase-targeted gene therapy and CRISPR editing to lengthen TL. One potential therapeutic strategy involves the application of non-integrating and replication-incompetent adenoviral vectors, specifically adeno-associated viruses (AAVs). AAV9 has been utilized for delivering *TERT* into murine models, resulting in an extension of their lifespan without increasing the risk of cancer[204,205]. Treatment with AAV9-*TERT* could also potentially reduce lung DNA damage, delay senescence, and lower susceptibility to non-malignant pulmonary diseases[195,196]. However, pre-existing or therapy-induced immunity against the AAV capsid may provoke inflammatory responses and limit redosing efficacy[206]. Current mitigation strategies include engineering novel capsids with enhanced pulmonary specificity and employing tissue-specific promoters to restrict transgene expression to target cells, thereby improving the safety profile[207].

Another novel approach is the targeted insertion of transgenes into specific chromosomal sites, where the transgenes can be stably expressed in relevant tissues without adversely affecting endogenous gene structure and expression[205]. The *CLYBL* gene on chromosome 13 holds therapeutic promise as a "safe Harbor" locus in human cells, with transgenes inserted into this locus showing high levels of expression and less localized effects on genes[208]. The primary challenge lies in the critical dependence on precise gene-editing machinery, and off-target editing remains a non-negligible risk, as unintended genomic alterations could lead to deleterious consequences. In cellular gene therapy, it is crucial to avoid cellular immortalization. Transient ectopic expression of *TERT* mRNA consisting of modified nucleotides has been reported to enhance telomerase activity and increase TL without immortalizing the cells. This approach may target disease-specific cells such as stem or progenitor cells, representing a major advancement in the field of biological research and medicine[209]. However, despite its designed transient nature, a paramount concern remains the intrinsic oncogenic risk of even systemic temporary telomerase activation. As telomerase reactivation is a hallmark of approximately 90% of human cancers, there is a justified apprehension that enhancing its activity systemically could inadvertently promote the proliferation of pre-neoplastic cells or accelerate the growth of undiagnosed microtumors[210,211]. Therefore, the development of tissue-specific or cell-type-specific delivery systems is not merely an optimization goal but a critical safety prerequisite. Strategies such as inhalation delivery of mRNA or nanoparticle-based vectors could potentially confine telomerase activity to the lung epithelium, thereby minimizing systemic exposure and off-target risks[212–214]. Beyond safety, significant pharmacological hurdles remain[215]. For interventions aimed at lung aging, achieving efficient and sustained delivery to

inflammation through Th1 and Th17 pathways, contributing to chronic airway inflammation, immune dysregulation, and structural remodeling in asthma. Abbreviations: Treg, regulatory T cell; TSLP, thymic stromal lymphopoietin; PGD2, prostaglandin D2.

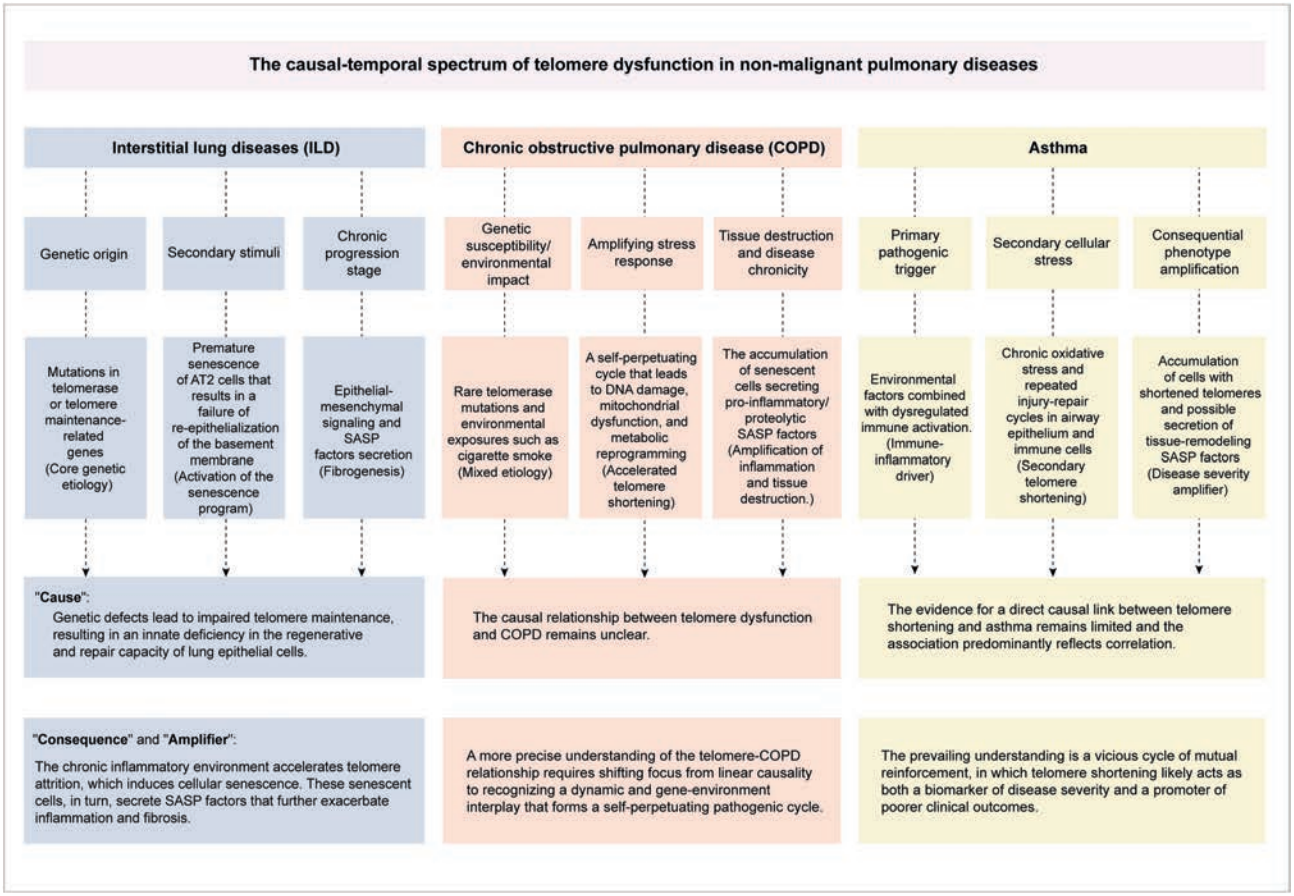

Figure 6 The causal-temporal spectrum of telomere dysfunction in non-malignant pulmonary diseases. The conceptual framework outlines a unifying causal-temporal spectrum to comparatively analyze the role of telomere shortening in non-malignant pulmonary diseases. It highlights that telomere dysfunction is not a uniform entity but varies fundamentally across diseases in its causal primacy (primary cause or secondary consequence) and its temporal position within the disease pathogenesis timeline.

the target cell populations, such as AT2 cells, resident stem cells, or specific immune cells, presents a formidable challenge. The development of novel delivery platforms, such as lipid nanoparticles, viral vectors with lung tropism, and branched-tail ionizable lipidoids, is essential to overcome biological barriers and ensure expression efficiency or sufficient biodistribution to diseased areas, particularly in fibrotic lungs where tissue architecture is severely compromised[215–218].

In addition, several intrinsic obstacles in telomere biology raise concerns about the safety, feasibility, and efficacy of the aforementioned methods. First, effective telomere elongation is strictly dependent on the cell cycle, specifically the S phase, during which the telomeric conformation is permissive for extension. However, the lung epithelium exists largely in a state of relative quiescence and is innate. Thus, the mere reintroduction of telomerase is unlikely to achieve its goal in these predominantly non-cycling cells, presenting a primary challenge to feasibility. The second challenge is the limited and transient efficacy of telomerase; its elongation is often insufficient to overcome inherited short telomere defects, and a significant corrective lag in TL is consistently observed despite functional restoration of telomerase, questioning the durability of the intervention[15,219]. Furthermore, the distinct temporal nature, multifactorial and multistep pathogenesis of telomere-mediated pulmonary diseases indicate that the pathology results from damage accumulated over decades. This implies even if the short telomere defect is corrected, the decades of accumulated damage and the established pathological microenvironment may prevent the full restoration of normal tissue function[15]. Therefore, despite the prevalence of telomere defects in non-malignant pulmonary diseases, significant challenges still exist for approaches to reverse telomere defects and aging phenotypes. A deeper understanding of lung biology, immunology, and regenerative technologies is required to explore innovative therapies for telomere-associated non-malignant pulmonary diseases.

In conclusion, while the path forward is fraught with challenges, the compelling preclinical evidence warrants a concerted effort to innovate solutions. Overcoming these hurdles will pave the way for harnessing telomere biology to combat age-related non-malignant pulmonary diseases, ultimately shifting the paradigm from symptom management to targeting a fundamental driver of aging.

4.2. Pharmacotherapy

Therapeutic interventions targeting key molecules or signaling pathways of telomerase and telomere-related senescence show significant promise in delaying aging and alleviating telomere-associated non-malignant pulmonary diseases. These approaches can be broadly organized into a multi-level framework addressing distinct aspects of telomere biology (Table 2[44,220–228]).

Table 1 A telomere dysfunction-centric comparative analysis of non-malignant pulmonary diseases.

Disease	Telomere shortening/dysfunction					Core signaling pathway	Animal models	Ref.
	Primary causes	Specific mechanisms	Key effector cells/ tissues (correlative link)	Causal link	Most relevant SASP factors			
ILD	Genetic factors	Mutations in telomerase complex genes (*e.g.*, *TERT*, *TERC*) or telomere maintenance-related genes (*e.g.*, *RTEL1*, *PARN*) result in an inability to maintain normal TL.	In humans: PBL (various ILDs, such as RA-ILD, SSc-ILD, IPF), Alveolar epithelium (IPF), Lung fibroblasts (IPF), Lung tissue (ILD). In mice: AT2 (PF).	In human: a Mendelian randomisation study infers a causal link between TL and IPF. In mice: telomerase re-expression in a telomerase-deficient model and overexpression in wild-type mice can ameliorate pulmonary profibrotic pathologies.	IL-1α, IL-1β, IL-6, IL-8, IL-11, TGF-β, PDGF, IFN-γ, CCL2, MMP1, MMP3, MMP7, MMP10	Canonical TGF-β/ Smad pathway, IL-11 pathway, PI3K/AKT pathway, YAP/TAZ pathway, canonical WNT/β-catenin pathway, cGAS −STING pathway	Late-generation telomerase-deficient ($Tert^{-/-}$ or $Terc^{-/-}$) mice treated with low dose bleomycin, mice with inducible *Trf1* or *Trf2* knockout in AT2 cells.	21,50-52, 113,122, 130,188-196
	Cellular autonomy mechanism	Natural aging: telomeres naturally shorten with repeated cell divisions during aging.						
	Acquired/ Secondary factors	(1) Endogenous (*e.g.*, oxidative stress, mitochondrial dysfunction) and exogenous (*e.g.*, cigarette smoking, viral infection) stressors accelerate telomere damage. (2) SASP mediates autocrine and paracrine effects, creating a milieu that accelerates telomere shortening. (3) Unknown autoantibodies that disrupt telomere/ telomerase function or an increased rate of leukocyte replication that leads to accelerated telomere attrition and immune cellular senescence may exist in autoimmune diseases (*e.g.*, SSc-ILD).						
COPD	Genetic predisposition	Mutations in telomerase complex genes (*e.g.*, *TERT*, *TERC*) result in inherently accelerated telomere attrition (low prevalence).	In humans: Circulating leukocytes (COPD), AT2 cells (emphysema), Endothelial cells (emphysema), Small airway epithelial cells	−	IL-1α, IL-1β, IL-6, TNF-α, MMP1, MMP8, MMP9, TGF-β, VEGF, IGF, CXCL1, CXCL2, CXCL8, CXCL10, PAI-1, CCL2	DDR/p53 pathway, p38 MAPK pathway, PI3K/mTOR pathway, AMPK/mTOR pathway, NF-κB pathway, Nrf2 pathway	Late-generation telomerase-deficient mice ($Terc^{-/-}$), wild-type mice exposed to cigarette smoke	18,61,65, 68,197-199
	Acquired factors/ Cellular senescence (vicious cycle)	(1) Replicative senescence: telomeres shorten to a critical length after repeated cell divisions, triggering						

		permanent cell cycle arrest. (2) Stress-related senescence (endogenous and exogenous stressors): telomere shortening is triggered by oxidative and inflammatory stress (*e.g.*, cigarette smoke, ROS). (3) SASP-mediated bystander effect: senescent cells secrete factors (*e.g.*, IL-6, IL-8) that induce telomere dysfunction and senescence in neighboring cells.	(COPD, increased TAFs, but not telomere shortening), Bronchoalveolar lavage cells (COPD). In mice: Small airway epithelial cells (COPD, increased TAFs).					
Asthma	Environmental/ Acquired factors	Chronic oxidative stress from inflammation and environmental triggers (*e.g.*, allergens, pollutants) generates ROS, damaging telomeric DNA and accelerating shortening.	In humans: Bronchial fibroblasts, Peripheral blood, Circulating leukocyte, ASM cells (increased TAFs).	−	Eotaxin-1 (CCL11), IL-13, TGF-β, IFN-γ, IL-1β, IL-6, IL-8, TNF-α, EGF, MMPs	cGAS−STING pathway, JAK/STAT pathway	−	19,71,73,76, 167,200-203
	Secondary/ Disease treatment-related factors	(1) Cellular senescence and SASP: the SASP creates a detrimental microenvironment to induce telomere dysfunction and a senescent state in nearby cells. (2) The impact of disease therapies (*e.g.*, glucocorticoids) on TL is context-dependent, representing a balance between their anti-inflammatory, potentially protective effects and their dose-dependent, potentially senescence-promoting adverse effects.						

Abbreviations: RA-ILD, rheumatoid arthritis-associated interstitial lung disease; SSc-ILD, systemic sclerosis-associated interstitial lung disease; PBL, peripheral blood leukocyte; IPF, idiopathic pulmonary fibrosis; PF, pulmonary fibrosis; AT2, type II alveolar epithelial cells; ASM, airway smooth muscle; TAFs, telomere-associated DDR foci; SASP, senescence-associated secretory phenotype; PDGF, platelet-derived growth factor; EGF, epidermal growth factor.

Table 2 Mechanisms of therapeutic interventions for anti-aging or treating non-malignant pulmonary diseases by regulating telomeres/telomerase.

Therapeutic intervention	Disease	Mechanism	Effect	Ref.
TERT activator compound	–	Enhances *TERT* transcription through MEK/ERK/AP-1 cascade.	In primary human cells and naturally aged mice, it could promote telomere synthesis, attenuate tissue senescence features, reduce cellular senescence and inflammatory cytokines, and repress $p16^{INK4a}$ expression.	220
Small molecule PAPD5 inhibitors (BCH001, RG7834)	PF	Target TERC and upregulate telomerase based on the physiological expression of *TERT* in stem cells.	Restoration of TL in cells from patients with genetic "telomeropathies" and human blood stem cells xenotransplanted into mice.	221
Molecular hydrogen therapy (Drinking hydrogen-rich water, HRW)	RA-ILD, PF, COPD, asthma	Delays telomere shortening rate, attenuates mitochondrial impairment and regulates cellular senescence by inhibiting inflammation and oxidative stress.	Clinically, the inflammatory level in the patients' airways was attenuated; at the animal level, the number of inflammatory cells in the BALF was reduced, along with alleviation of small airway remodeling and goblet cell hyperplasia.	222
Danazol	PF	Inhibits telomere attrition by inducing *TERT* gene expression.	PF patients with shorter telomeres increased TL and maintained pulmonary function.	44,223,224
Melatonin	–	Blocks TERRA–PARP-1-mediated SASP secretion by protecting telomeres.	Melatonin treatment reduced SASP release stimulated by TERRA –PARP-1 interaction by 67.9% (in terms of IL-8).	225
Small molecule telomerase activator (GRN510)	PF	A mechanism dependent upon telomerase activation.	Suppressed the development of fibrosis and accumulation of senescent cells in the lung in the model of bleomycin-induced fibrosis.	226
Cycloastragenol (CAG)	–	Affects the expression of aging-related *Klotho* genes.	Exerts anti-aging effects on human embryonic lung fibroblasts.	227
TA-65	SAR	Affects many important cellular processes such as gene expression, mitochondrial function, cell survival, and stress resistance through non-obligatory extra-telomeric functions.	Potential protective effects on cigarette smoke-induced SAR models.	228
Epimedium brevicornu	–	Possible protection of TL by inhibiting the expression of the *p16* gene and promoting the production of phosphorylated Rb protein.	Significantly extended the population doublings of human diploid fibroblasts and improved the TL without telomerase activation.	227

Abbreviations: AP-1, activator protein-1; PF, pulmonary fibrosis; TL, telomere length; RA-ILD, rheumatoid arthritis-associated interstitial lung disease; COPD, chronic obstructive pulmonary disease; BALF, bronchoalveolar lavage fluid; SASP, senescence-associated secretory phenotype; IPF, idiopathic pulmonary fibrosis; SAR, small airway remodeling.

Firstly, telomerase activity can be modulated directly or indirectly. A TERT activator compound has been identified that enhances *TERT* transcription through the MEK/ERK/AP-1 cascade[220]. PAPD5 is an atypical polymerase that oligomerizes adenylate and destabilizes TERC, with its specific inhibitors BCH001 and RG7834 to modulate TERC levels, thereby restoring telomerase activity and TL in patient-induced pluripotent stem cells[221]. Moreover, estrogen and androgens have been reported to induce *TERT* gene expression[44,223,224]. Concurrently, interventions aimed at protecting telomeres from exogenous/endogenous damage are being explored. Molecular hydrogen protects telomeres by counteracting oxidative stress, a key driver of telomere attrition[222]. Furthermore, targeting the downstream inflammatory consequences of telomere dysfunction represents a third strategy, as demonstrated by melatonin, which may protect telomeres by blocking PARP-1 and TERRA-mediated SASP events[225]. This discovery established a new epigenetic paradigm for understanding aging-related diseases involving inflammation.

Beyond these targeted strategies, natural products and their derivatives constitute a structurally and mechanistically diverse source of potential therapeutics. For instance, the synthetic derivative GRN510 suppresses the accumulation of senescent cells and the development of PF phenotype in IPF mice by activating telomerase[226]. Cycloastragenol (CAG) could affect *Klotho* expression and exerts anti-aging effects on human embryonic lung fibroblasts, while flavonoid from *Epimedium brevicornu* may maintain TL through the Rb/p16 pathway without direct telomerase activation[227].

Collectively, these approaches delineate a multifaceted framework for tackling telomere-driven lung aging, but their clinical translation necessitates further validation of long-term safety and efficacy.

5. Conclusion and future perspective

In recent years, significant advancements have been made in the understanding of telomeres and telomerase in non-malignant pulmonary diseases. Telomere shortening with or without mutations in telomere maintenance genes and telomerase is relatively prevalent in non-malignant pulmonary diseases such as ILD, COPD, and asthma. This impacts the progression, prognosis, and survival outcomes of these respiratory conditions. Mutations in telomerase and telomere maintenance genes have potential value in predicting, diagnosing, and targeting therapies for non-malignant pulmonary diseases.

However, the relationship between telomeres/telomerase and non-malignant pulmonary diseases is mostly limited to characterization phenomena, and the understanding of specific causal relationships and underlying molecular mechanisms remains poorly understood. Moreover, there are more obstacles from basic research to clinical translation, especially regarding the precise effects of TL, mutations in telomere maintenance genes and telomerase on various lung and immune cells (cellular heterogeneity), as well as their impact on relative susceptibility to different non-malignant pulmonary diseases. Looking forward, resolving cellular heterogeneity presents a fascinating frontier. Future investigations employing single-cell multi-omics, such as single-cell RNA sequencing coupled with an assay for transposase-accessible chromatin using sequencing and spatially resolved transcriptomics, are poised to not only identify the key responder cell types but also reconstruct the transcriptional networks and cell−cell communication events that drive the pathophysiology. Furthermore, leveraging lung organoids or precision-cut lung slices could empower a targeted and cell-type-specific manipulation of these pathways, moving beyond correlation to definitive causation. Such a deep and mechanistic dissection is the next critical step toward understanding lung homeostasis and diseases with unprecedented resolution, ultimately informing the development of highly targeted diagnostic and therapeutic strategies.

To bridge these foundational insights into clinical application, several key translational challenges should be addressed. The immediate priority lies in establishing robust clinical standards for TL assessment, particularly regarding disease-specific and clinical samples threshold values and precise measurement standardization. The current absence of universal diagnostic cutoffs necessitates contextual interpretation based on age, genetic background, and disease etiology. In clinical practice, TL below the 10th age-adjusted percentile demonstrates high positive predictive value in ILD, especially when combined with pathogenic telomere-related gene mutations, whereas in COPD and asthma, it may serve better as a prognostic indicator of disease severity and progression[50,229]. Methodological standardization across techniques, such as qPCR and Flow-FISH, demands the establishment of length standards and disease-specific reference ranges. Future directions should advance beyond single measurements toward dynamic monitoring of telomere attrition rates and development of integrated "senescence burden indices" combining TL with complementary markers such as specific SASP factors or $p16^{INK4a}$ expression.

Moreover, the translation of TL measurement into clinical practice is fundamentally constrained by the choice of biological sample, a decision that pits clinical feasibility against biological precision. Current research primarily utilizes two sample sources: readily accessible PBL and specific tissue samples that directly capture lesion pathology, each defining distinct pathways for biomarker interpretation and application. PBL-TL reflects the average telomeric status of the hematopoietic system, integrating the influence of age, genetics, inflammation, and lifestyle. Thus, PBL-TL serves as a biomarker for assessing an individual's systemic aging burden and risk of multisystem age-related diseases[230]. However, it often weakly correlates with telomere dynamics in disease-relevant somatic tissues, such as lung epithelia. Therefore, while PBL-TL efficiently answers "is there a systemic risk?", it poorly addresses "where is the pathology localized?". Conversely, specific tissue samples (from lung biopsy) offer direct mechanistic insight into the target organ's replicative history and stress exposure. This is essential for directly linking telomere attrition to local pathophysiology. However, this specificity is compromised by invasive collection, sampling bias, and limited suitability for repeated monitoring, rendering such samples impractical for screening or longitudinal tracking. Moving forward, establishing a reliable correlative model between TL derived from these two sample types, along with the development of novel non-invasive techniques such as liquid-biopsy-based approaches that measure TL in cell-free DNA from specific cellular origins, may be key to advancing the translation into precise clinical practice.

With this foundation in place, advancing along the precision medicine pathway also requires systematically addressing the following key issues. Who constitutes the target population for screening? Which specific indicators should be tested (telomerase-related genes, telomere length, or both)? And crucially, how can we discover and select therapeutic drugs targeting telomeres based on target efficacy with off-tumor toxicity (telomerase activation in latent malignancies)? By delving deeper into these scientific inquiries, more valuable references and insights can be provided for respiratory diagnosis and treatment.

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Author contributions

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Conflicts of interest

The authors declare no conflicts of interest.

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