International Journal of Biology and Life Sciences
ISSN: 2957-9511 | Vol. 13, No. 1, 2026

Clinical Research Progress on the Correlation between Thyroid Hormones and Idiopathic Pulmonary Fibrosis

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Abstract: Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive, fatal interstitial lung disease with unknown etiology, characterized by lung parenchymal scarring and progressive lung function decline, and poor prognosis. Its pathogenesis remains unclear. Recent studies have confirmed a significant correlation between thyroid hormones (THs) and IPF's occurrence and development. This article systematically reviews relevant clinical research progress: (1) Epidemiological studies show a significantly higher incidence of thyroid dysfunction in IPF patients; (2) Mechanistic studies indicate THs affect IPF progression by regulating glucose metabolism, improving mitochondrial function, inhibiting inflammation, modulating alveolar epithelial repair, and suppressing fibroblast activation; (3) Clinical intervention studies suggest thyroid function management may improve IPF prognosis. These findings provide new insights for IPF diagnosis and treatment, and this article further discusses the potential value of thyroid hormone replacement therapy in IPF management.

Keywords: Thyroid Hormones; Idiopathic Pulmonary Fibrosis; Glucose Metabolism; Mitochondria; Inflammation; Alveolar Epithelial Cells; Fibroblasts; Myofibroblasts; Macrophages.

1. Introduction

Pulmonary fibrosis (PF) results from various lung injuries, featuring lung parenchymal destruction, extracellular matrix deposition, and phenotypic changes in fibroblasts and alveolar epithelial cells[1]. IPF, a chronic progressive subtype of PF, presents with persistent cough and exertional dyspnea, with a 5-year survival rate of 70%-80% after diagnosis and no cure available [2]. Known risk factors include age, smoking, and gastroesophageal reflux, necessitating novel therapeutic strategies.

Thyroid hormones (THs) have complex physiological effects, and thyroid and lung share an embryonic origin from endodermal Nkx2.1 cells [3]. Hypothyroidism correlates with increased fibrosis risk in the liver, heart, and lungs via collagen gene upregulation and TGF-β pathway activation [4] [5], and TH replacement alleviates this progression[6]. Multiple animal studies confirm THs' protective role in IPF by regulating glucose metabolism, mitochondrial function, and inflammation[7]. This review summarizes the TH-IPF correlation based on recent literature.

2. TH Deficiency and IPF

Thyroid transcription factor-1 (TTF-1), encoded by Nkx2.1, regulates surfactant protein expression and is critical for lung development [8]. Hypothyroidism (HT) patients have higher rates of respiratory symptoms[9], and perinatal TH deficiency impairs neonatal respiratory function, which is reversible with levothyroxine (LT4) supplementation[10] [11]. HT is more common in women and the elderly (>65 years), often coexisting with autoimmune diseases [12], and its prevalence in IPF patients is significantly higher than in COPD patients and the general population—HT is independently associated with IPF and predicts mortality[13]. Severe HT can induce reversible lung fibrosis-like changes, reversed by LT4[14]. IPF patients show increased lung expression of DIO2 (type 2 deiodinase), a compensatory mechanism enhancing local T4-to-T3 conversion—DIO2 deficiency exacerbates bleomycin-induced fibrosis in mice[15] [16]. The thyroid gland mainly secretes T4 (over 90% of total secretion), which is converted to active T3 via tissue-specific deiodinases[17]. The deiodinase system (DIO1/DIO2 for activation, DIO3 for inactivation) regulates tissue-specific TH bioavailability, with DIO2 upregulation maintaining alveolar epithelial cell (AECs) mitochondrial function in fibrotic lungs[15]. DIO2 also reduces inflammation and maintains tissue repair in lung injury [18]. Exogenous active THs (e.g., nebulized T4, selective TRβ agonist sobetirome) improve established fibrosis with targeted efficacy [16].

3. Mechanisms of TH Affecting IPF

3.1. Mitochondrial Dysfunction

Mitochondrial dysfunction, a hallmark of cellular aging, contributes to IPF via increased reactive oxygen species (ROS), energy metabolism abnormalities, and cell senescence[19]. IPF patients exhibit mitochondrial imbalance (impaired biogenesis, fusion/fission dysregulation) and metabolic reprogramming (enhanced glycolysis) in lung cells, accelerating fibroblast activation and collagen deposition[20]. Downregulation of PINK1 in lung epithelial cells aggravates mitochondrial damage, endoplasmic reticulum stress, and pro-fibrotic factor release[21], while aging-related cellular changes (autophagic defects, telomere shortening) converge on mitochondrial dysfunction to increase IPF susceptibility[22]. THs (especially T3) localize to mitochondria, with thyroid hormone receptors (TRα/TRβ) regulating mitochondrial function [23]. TRβ1 and ESRRα coordinately regulate mitochondrial energy metabolism[24]. T3 directly regulates mitochondrial function via receptor p43 and indirectly via nuclear receptors (e.g., TFAM)[25], and

exerts anti-apoptotic effects by modulating Bcl2 family proteins [26]. TH-induced autophagy enhances mitochondrial activity [27]. In IPF mouse models, aerosol T3 or selective TRβ agonist sobetirome improves survival and reduces fibrosis by enhancing AECs mitochondrial function [15].

3.2. Glucose Metabolism

IPF lung tissue exhibits enhanced glycolysis, a core energy source for activated myofibroblasts—HIF-1α-mediated upregulation of key enzymes (HK2, PKM2, PFKFB3) drives fibroblast transdifferentiation[20] [28] [29]. Fructose-1,6-bisphosphate (FBP) alleviates fibrosis by regulating extracellular matrix deposition[30]. THs regulate glucose metabolism by coordinating macronutrient synthesis and catabolism[31], and activating mitochondrial hexokinase (mt-HK) [32] [33]. As a PKM2 inhibitor, TH reduces ATP production in fibrotic cells[34]. In silica-induced lung fibrosis mice, T3 downregulates glycolytic enzymes, decreases lactate levels, and alleviates collagen deposition[35]. Lactate accumulation activates TGF-β1, forming a pro-fibrotic feedback loop[36], and T3 antagonizes TGF-β/SMAD signaling to suppress pro-fibrotic gene expression[37]. Nebulized T3 mitigates radiation-induced lung fibrosis by inhibiting the TGF-β1/SMAD3 pathway[38]. TH efficacy depends on thyroid hormone receptors (TRα/TRβ), whose expression is restored by T3 intervention[35].

3.3. Immune Regulation

IPF involves immune dysregulation, including macrophage phenotype switching and lung microbiota alterations[39] [40]. Viral infections (e.g., HCV, EBV) and dysbiotic microbiota accelerate fibrosis[41] [42] [43] [44]. THs regulate innate and adaptive immunity[45], with innate immune cells as key TH targets[46]. IPF acute exacerbation is associated with alveolar inflammation and microbiota disturbance[47]. T3 reverses abnormal inflammatory gene expression in D2KO mice[18] and reduces pro-inflammatory cytokines (IL-1β, IL-6, TNF-α) in silica-exposed models[48]. TRs deficiency increases inflammatory responses[49], and T3 inhibits SiO_2-induced inflammation via T3/TRα signaling, downregulating NF-κB and NLRP3 inflammasome activity[48]. The detailed interaction between THs, immunity, and fibrosis requires further clarification.

4. Summary and Outlook

Current IPF standard treatments (nintedanib, pirfenidone) delay disease progression, combined with pulmonary rehabilitation and oxygen therapy[50]. Novel therapeutic targets have been identified with ongoing development[51]. Nintedanib inhibits VEGFR/FGFR/PDGFR pathways[52], while pirfenidone exerts anti-fibrotic, anti-inflammatory, and antioxidant effects[53]. However, both have limitations (no lung function improvement, gastrointestinal/hepatic side effects). Notably, nebulized T3 shows comparable anti-fibrotic efficacy in IPF mice without systemic cardiovascular side effects[15]. THs hold potential as IPF therapeutic targets by regulating mitochondrial function, glucose metabolism, and inflammation. However, current evidence mainly comes from preclinical studies, and their exact mechanism in human IPF remains unclear. Future research should clarify THs' molecular targets and explore clinical translation strategies to improve IPF outcomes.

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