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REVIEW ARTICLE

Chronodisruption and Lung Fibrosis: The Role of Circadian Rhythm Disturbances in the Onset and Progression of Idiopathic Pulmonary Fibrosis

Swathy Kuppala G[1*], Muddassir Khalid[2]

[1] Sri Ramachandra Medical College, Porur, Chennai - 600116. Tamil Nadu, India

[2] Nishtar Medical University, Nishtar Rd, Gillani Colony, Multan, 66000, Pakistan

***Corresponding Author:** Swathy Kuppala
Sri Ramachandra Medical College, Porur, Chennai - 600116. Tamil Nadu, India.
Email: drswathykg@gmail.com

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Abstract

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive interstitial lung disease characterized by irreversible scarring and declining lung function. The circadian clock governs a wide array of physiological processes, including inflammation, immune regulation, cellular repair, and metabolism, all of which are implicated in fibrotic lung pathology. This review synthesizes current insights into the molecular crosstalk between circadian rhythm regulators and profibrotic signaling pathways in IPF. We also explore how lifestyle, environmental cues, and shift work may influence lung fibrosis risk through clock gene dysregulation. Furthermore, we examine the potential for chronotherapy and circadian-aligned pharmacological interventions in improving outcomes for IPF patients. Understanding the temporal architecture of fibrosis could offer novel therapeutic targets and a paradigm shift in IPF management.

1. Introduction

Idiopathic Pulmonary Fibrosis (IPF) represents a paradigmatic example of a complex, age-associated, and ultimately fatal fibrosing interstitial lung disease of unknown etiology (Mora et al., 2017). Characterized histologically by usual interstitial pneumonia and clinically by progressive dyspnea, chronic dry cough, and impaired pulmonary function (Ahmad et al., 2017), IPF has historically been regarded through the lens of inflammation-driven models. However, the paradigm has shifted in recent decades, recognizing aberrant wound healing, epithelial injury, fibroblast activation, and extracellular matrix deposition as core processes driving disease progression. Median survival remains a dismal 3 to 5 years from diagnosis despite current antifibrotic therapies (Zheng et al., 2022), emphasizing the urgency to uncover novel pathogenic pathways and therapeutic targets.

Circadian rhythms are intrinsic, near-24-hour oscillations in biological functions that are orchestrated by a central clock located in the suprachiasmatic nucleus of the hypothalamus and supported by peripheral clocks present in virtually every organ, including the lungs (Albrecht, 2012; Morin et al., 2025). These rhythms regulate vital physiological processes such as cell proliferation, apoptosis, DNA repair, metabolism, and immune response (Zhao et al., 2025). Central to these rhythms is a transcriptional-translational feedback loop driven by core clock genes including Brain and Muscle ARNT-Like 1 (BMAL1), Circadian Locomotor Output Cycles Kaput (CLOCK), Period (PER1, PER2) and Cryptochrome (CRY1, CRY2) (Angelousi et al., 2018). These genes not only maintain temporal homeostasis but also influence gene expression in a tissue-specific manner, adapting physiological functions to predictable environmental changes.

Chronodisruption, defined as a misalignment between endogenous circadian rhythms and external environmental cues, can arise from shift work, irregular sleep-wake cycles, chronic jet lag, or even systemic inflammation and aging (Smolensky et al., 2016). Increasing evidence has shown that chronodisruption can exacerbate various pathological conditions including cardiovascular disease, metabolic syndrome, cancer, and most recently, fibrotic diseases (Vitale et al., 2018). In the context of pulmonary biology,

studies have identified time-of-day-dependent variations in lung function, immune responses, and airway resistance, alluding to the presence of an active pulmonary circadian clock (Pearson et al., 2021). More intriguingly, disruption of clock genes such as BMAL1 and PER2 in murine models has been linked to increased susceptibility to fibrosis, exaggerated inflammatory responses, and impaired tissue repair mechanisms in the lung (Chen et al., 2013; Dong et al., 2016).

In IPF, pathological hallmarks such as epithelial cell injury, myofibroblast differentiation, and excessive extracellular matrix deposition are tightly regulated by pathways that exhibit circadian control. Transforming Growth Factor-beta (TGF-β), a master regulator of fibrosis, has been shown to be influenced by circadian components, with evidence suggesting time-of-day variations in TGF-β signaling amplitude and responsiveness (Hahn and Sundar, 2023). Similarly, oxidative stress a known contributor to epithelial apoptosis and fibroblast activation in IPF is modulated by clock-controlled antioxidant defense mechanisms, including nuclear factor erythroid 2-related factor 2 (NRF2), which demonstrates rhythmic expression (Paudel et al., 2021). Disruption in circadian control of these protective pathways may predispose to fibrotic progression through unchecked cellular injury and maladaptive repair.

Additionally, the lung's immune microenvironment, a key player in fibrosis, demonstrates circadian variation in leukocyte trafficking, cytokine release, and inflammatory mediator expression (Shirato and Sato, 2022). For example, macrophage activation and neutrophil infiltration are regulated in a time-dependent manner, and their dysregulation in a state of chronodisruption may promote chronic low-grade inflammation conducive to fibrotic remodeling (Colombini et al., 2022). Given that immune dysregulation is increasingly recognized as a modulator of fibrosis rather than its initiator, understanding how circadian control influences these immune dynamics is crucial. Recent transcriptomic analyses of fibrotic lung tissues have identified altered expression of clock genes (Song et al., 2017), supporting the hypothesis that circadian dysfunction is not merely a bystander but may play a causative role in IPF. Importantly, pharmacologic manipulation of clock gene activity has shown promise in preclinical models, suggesting that restoration of circadian homeostasis could serve as a therapeutic strategy in fibrotic lung disease (Wang et al., 2023). This review aims to synthesize current understanding of the intersection between chronobiology and pulmonary fibrosis, highlighting key mechanisms, evidence from experimental and clinical studies, and the therapeutic implications of targeting the circadian clock in IPF.

2. Molecular Mechanisms Linking Circadian Rhythms to Fibrogenesis

Fibrogenesis in IPF involves a complex interplay of epithelial injury, fibroblast proliferation, and extracellular matrix accumulation. Recent research highlights that these processes are intricately regulated by circadian clock genes. Disruption of circadian regulation termed chronodisruption has been found to intensify fibrotic responses. BMAL1 and CLOCK genes orchestrate the circadian rhythm through a transcriptional translational feedback loop (Trott and Menet, 2018). In pulmonary tissue, these clock genes influence the regulation of TGF-β signaling, a critical driver of fibrogenesis. Evidence shows that in BMAL1-deficient mice, there is increased TGF-β activity, which augments fibroblast to myofibroblast differentiation and extracellular matrix deposition (Sato et al., 2017). Additionally, circadian regulators influence the expression of matrix metalloproteinases (MMPs) and tissue inhibitors of MMPs, affecting extracellular matrix degradation and turnover.

Oxidative stress, an established component of IPF pathophysiology, is also subject to circadian modulation. The NRF2 pathway, a master regulator of oxidative stress response, exhibits rhythmic activation and is controlled by BMAL1 (Early et al., 2018). When circadian rhythm is disrupted, NRF2 signaling diminishes, leading to elevated reactive oxygen species (ROS) and increased epithelial cell damage. Furthermore, autophagy and mitochondrial homeostasis, essential for cellular repair and anti-fibrotic defenses, are regulated by clock genes (Cui et al., 2024). Studies indicate that circadian misalignment impairs these protective mechanisms, thereby fostering a microenvironment conducive to fibrosis (Lin et al., 2024). Overall, the molecular underpinnings linking circadian dysregulation to lung fibrosis provide a compelling rationale for further exploration of clock-targeted therapies.

3. Clock Genes and Immune Regulation in IPF

The immune system exhibits marked circadian fluctuations that affect immune cell trafficking, cytokine secretion, and pathogen recognition. This rhythmic control extends to various immune cells such as macrophages, neutrophils, and lymphocytes. In IPF, where immune-mediated injury contributes to epithelial dysfunction and fibrosis, circadian disruption exacerbates inflammatory responses (Purushothaman and Nelson, 2023). Macrophages play a dual role in lung repair and fibrosis. Clock genes such as BMAL1 and REV-ERBα regulate macrophage polarization and cytokine production. Mice lacking BMAL1 in myeloid cells show elevated levels of IL-6 and TNF-α, cytokines associated with fibrosis initiation (Hand et al., 2019). REV-ERBα downregulates pro-inflammatory signaling, and its reduced activity in chronodisruption states contributes to sustained inflammation (Wang et al., 2025). Neutrophil infiltration, often observed in early IPF, also follows circadian control. Time-of-day variations influence chemokine expression and neutrophil extravasation. Disturbed rhythms enhance neutrophil-driven injury, releasing proteolytic enzymes and ROS that promote fibrosis (Zhu et al., 2023).

T cell subsets like Th17 and Treg cells are modulated by circadian genes such as RORγt and NFIL3 (Zeng et al., 2024). Their balance is critical for immune homeostasis. Disruption favors Th17 dominance, enhancing pro-fibrotic inflammation. Additionally, clock-controlled genes influence

Table 1: Expression Patterns of Key Fibrotic Genes in the Lung

Gene	Function	Peak Expression (Zeitgeber Time, ZT)	Circadian Regulation	Implication in IPF
TGF-β1	Pro-fibrotic cytokine	ZT12–ZT18	YES	Drives fibroblast activation and ECM accumulation
COL1A1	Collagen type I synthesis	ZT18	YES	Elevated in fibrotic foci; major ECM component
MMP-9	ECM remodeling enzyme	ZT6–ZT12	YES	Degrades ECM; imbalance leads to excessive deposition
IL-6	Pro-inflammatory cytokine	ZT0–ZT6	YES	Amplifies inflammatory loops; enhances fibrotic transformation
BMAL1	Core circadian transcription factor	ZT0–ZT6	Core clock gene	Its loss increases susceptibility to lung fibrosis
PER2	Negative circadian feedback regulator	ZT12–ZT18	Core clock gene	Modulates TGF-β response; associated with epithelial damage

antigen presentation and dendritic cell maturation. These changes can distort immune surveillance and contribute to an environment permissive to chronic injury and repair dysfunction. Thus, circadian regulation plays a pivotal role in immune equilibrium, and its disruption is a significant driver of IPF pathogenesis (Table 1).

4. Chronotherapeutics in Pulmonary Fibrosis

Chronotherapeutics refers to the alignment of medical treatment with the body's biological rhythms to optimize efficacy and minimize side effects (Colita et al., 2024). In the context of IPF, targeting circadian biology holds promise for improving treatment outcomes. Existing evidence suggests that the timing of drug administration could profoundly affect the pharmacodynamics and therapeutic impact in fibrotic lung disease. Antifibrotic drugs such as nintedanib and pirfenidone, currently used in IPF management (Finnerty et al., 2021), may have variable effects depending on the time of administration. Chronopharmacology studies have shown that drug-metabolizing enzymes, inflammatory mediators, and fibrotic signaling pathways fluctuate throughout the day (Weger et al., 2023). Aligning treatment schedules with peak activity of these targets may enhance drug efficacy and reduce toxicity.

Moreover, experimental therapies targeting circadian genes are emerging. REV-ERB agonists have been shown to suppress fibrosis in murine models by downregulating profibrotic cytokines and modulating immune responses (Raza et al., 2022). Similarly, pharmacologic modulation of BMAL1 and CLOCK activity has demonstrated the potential to restore oxidative balance and inhibit fibroblast activation (Takaguri et al., 2025). Timing of corticosteroid administration, often used for inflammation, is another area of interest. Administering steroids at times when endogenous cortisol levels are low can enhance efficacy and reduce adrenal suppression. Non-pharmacologic strategies, including light therapy and sleep interventions, may also re-entrain disrupted circadian rhythms and support lung repair mechanisms. Future clinical trials should incorporate time-of-day variables to assess their role in optimizing outcomes. Chronotherapeutic approaches offer an innovative frontier for IPF management.

5. Circadian Disruption and Oxidative Stress in IPF

Oxidative stress is a pivotal factor in the initiation and progression of IPF, contributing to epithelial cell injury, fibroblast activation, and extracellular matrix remodeling. Increasing evidence indicates that circadian rhythms intricately regulate oxidative stress pathways, and chronodisruption significantly amplifies oxidative damage in pulmonary tissues (Sundar et al., 2018). Central to this regulation is the transcription factor NRF2, a master regulator of antioxidant defense. NRF2 activity follows a circadian pattern driven by core clock components such as BMAL1 and CLOCK (Sun et al., 2021). In normal conditions, rhythmic NRF2 expression ensures timely activation of genes encoding antioxidant enzymes, including heme oxygenase-1 (HO-1), superoxide dismutase (SOD), and glutathione peroxidase (Chhunchha et al., 2020). However, in states of circadian misalignment, this protective rhythm is blunted, leading to impaired detoxification of ROS and heightened

Table 2: Human Circadian Disruptors Potentially Linked to Increased Pulmonary Fibrosis Risk

Circadian Disruptor	Mechanism of Circadian Misalignment	Epidemiological Evidence in Pulmonary Disease	Potential IPF Relevance
Night Shift Work	Desynchronization of sleep-wake and hormonal rhythms	Associated with higher rates of asthma, reduced lung function	May amplify fibrotic signaling via chronic inflammation
Chronic Jet Lag	Frequent trans-meridian travel affecting melatonin	Increased oxidative stress and systemic inflammation	Could worsen epithelial damage and repair capacity
Blue Light Exposure at Night	Suppression of melatonin secretion	Linked to sleep disorders, immune dysregulation	Disrupts NRF2 pathways and immune balance in lung tissue
Social Jet Lag	Disparity between workday and weekend sleep patterns	Associated with metabolic syndrome and reduced lung function	May impair circadian-controlled lung regeneration pathways
Sleep Apnea	Intermittent hypoxia and arousals during sleep	Causes oxidative stress and inflammation	Known contributor to fibrotic remodeling in alveolar tissue

vulnerability of alveolar epithelial cells.Mitochondrial dysfunction, another source of ROS in IPF, is also circadian-regulated. Disruption in mitochondrial biogenesis and autophagy cycles due to clock gene dysregulation further promotes ROS accumulation and subsequent fibroblast activation. Moreover, clock genes influence redox-sensitive signaling pathways such as TGF-β and p38 MAPK, which are crucial mediators of fibrotic responses (Samarakoon et al., 2013) (Table 2).

6. Sleep Disturbance, Chronotype, and Pulmonary Fibrosis Risk

Sleep disturbances and altered chronotypes are increasingly recognized as non-genetic contributors to circadian misalignment and chronic disease susceptibility, including IPF. Epidemiological studies have linked poor sleep quality, excessive daytime sleepiness, and shift work with increased incidence of pulmonary disorders (AlShareef, 2020), possibly through the disruption of physiological rhythms that maintain lung homeostasis. In IPF patients, sleep-disordered breathing, reduced REM sleep, and fragmented sleep cycles are commonly observed and correlate with worse disease severity and reduced quality of life (Milioli et al., 2016).

Chronotype, an individual's innate preference for timing of sleep and activity, influences circadian gene expression and hormonal regulation. Evening chronotypes are more prone to circadian misalignment, which may amplify the effects of environmental stressors, systemic inflammation, and oxidative stress factors implicated in fibrotic lung remodeling (Joshi and Sundar, 2023). Additionally, chronic sleep restriction or irregular sleep-wake cycles impair the rhythmic secretion of melatonin and cortisol, both of which play roles in immune modulation and antioxidant defense (Szataniak and Packi, 2025). Behavioral and occupational factors such as rotating shift work, long working hours, and social jet lag contribute to chronic misalignment between endogenous rhythms and external cues. These disruptions may sensitize lung tissues to injury, impair repair mechanisms, and foster a fibrotic milieu (Figure 1). Understanding the role of sleep and chronotype in pulmonary fibrosis pathogenesis could inform behavioral interventions and risk stratification. Integrating chronobiological assessment into clinical evaluation may help identify high-risk individuals and support preventive strategies that restore circadian alignment through sleep hygiene, light exposure, and work schedule optimization.

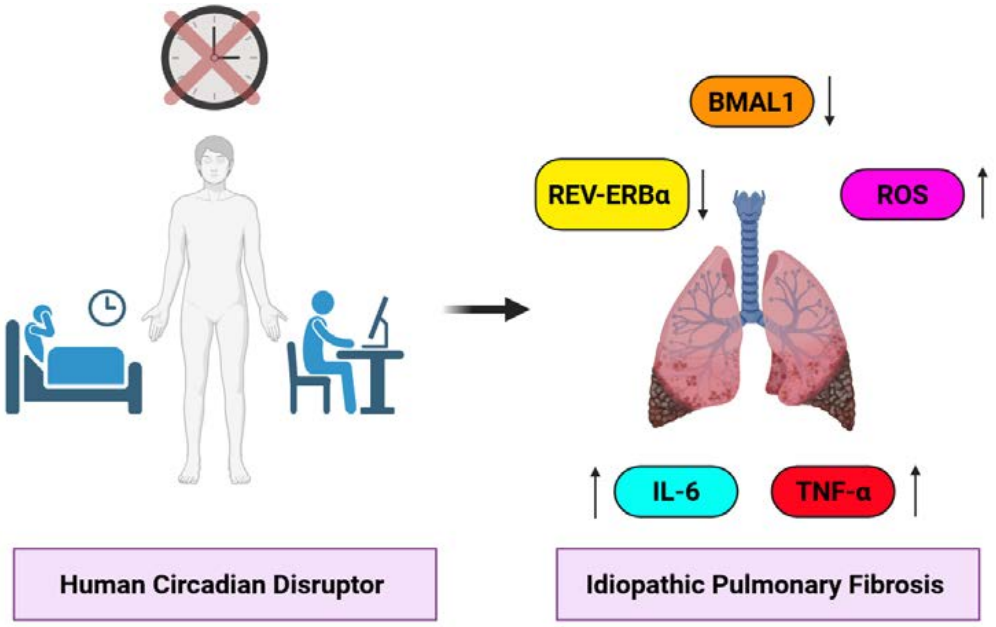

Figure 1: Key circadian proteins (BMAL1, REV-ERBα) modulate oxidative stress (ROS) and inflammation (IL-6, TNF-α), driving fibroblast activation and collagen deposition in IPF. Human circadian disruptors (Sleep apnea, Night shift work) are implicated as potential accelerators of fibrotic remodeling.

7. Future Perspectives

Future research should focus on elucidating the detailed mechanisms through which circadian rhythms impact pulmonary fibrosis and how these pathways can be targeted for therapeutic gain. With advancements in chronobiology, omics technologies, and systems biology, a more integrative understanding of time-dependent gene regulation in lung tissue is emerging. This opens the possibility of developing personalized treatment regimens based on an individual's chronotype or circadian profile. Large-scale cohort studies that incorporate circadian metrics such as sleep-wake cycles, melatonin levels, and actigraphy could help identify patients at risk of chronodisruption-induced fibrosis. Additionally, longitudinal studies assessing the effect of shift work, jet lag, and social jet lag on IPF incidence may provide valuable epidemiological insights. On the therapeutic front, drug development efforts could pivot toward identifying clock gene modulators that exert anti-fibrotic effects. The application of gene-editing technologies like CRISPR-Cas9 to correct aberrant clock gene expression in fibroblasts and epithelial cells may also become feasible. Another promising avenue is the use of wearable technologies and digital health tools to monitor circadian alignment and respiratory function in real-time, allowing for dynamic treatment adjustments. Collaborative efforts between pulmonologists, chronobiologists, and pharmacologists will be crucial in translating these insights into clinical practice. Integrating circadian biology into IPF research is not just an academic exercise—it has the potential to reshape diagnostics, prognostics, and treatment paradigms in fibrotic lung diseases.

8. Conclusion

The intersection of circadian biology and pulmonary fibrosis represents a frontier in understanding the temporal dimensions of chronic lung disease. As evidence mounts linking disrupted circadian rhythms with enhanced fibrogenesis, immune dysregulation, and oxidative stress, the need for incorporating chronobiological perspectives into IPF research and therapy becomes apparent. Molecular clock genes such as BMAL1, CLOCK, PER, and CRY are not only temporal regulators but also pivotal mediators of cellular homeostasis.

Chronodisruption, whether environmentally induced or genetically programmed, alters key signaling pathways such as TGF-β, NRF2, and immune modulators, facilitating fibrotic progression. Addressing these disruptions through chronotherapeutic interventions, pharmacological agents, or behavioral modifications may offer new hope for patients with IPF. While current antifibrotic therapies provide symptomatic relief and modestly slow disease progression, they do not reverse fibrosis. Circadian-based strategies could enhance their efficacy or serve as adjuncts, targeting upstream regulatory nodes. The future of IPF management may thus lie in aligning treatment with time personalized to the patient's biological rhythm.

Declarations

Ethics approval statement

Not applicable

Consent to participate

Not applicable

Consent to publish

Not applicable

Data Availability Statement

The data are available from the corresponding author upon reasonable request

Competing Interests

The authors declare that they have no conflict of interest

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During the preparation of this work the authors used AI-assisted technology QuillBot, in order to check the grammar and spell in some sentences

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