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Review Article

Rev-Erbα: A Chronobiological Approach to Inflammation and Lung Disease Management: A Comprehensive Review

Sayyed Mateen, Aafreen Qureshi*, Amit Sharma, Vikas Gupta

Department of Pharmacology, Oriental College of Pharmacy, University of Mumbai, Sanpada, Navi Mumbai, Maharashtra, INDIA.

ABSTRACT

The circadian cellular clock partially reduces macrophage inflammatory response by interacting with the nuclear receptor Rev-erbα. Disruption of circadian rhythm can result in diabetes, metabolic issues and fibrosis. Rev-Erb clock repressor is expressed in the brain, skeletal muscles, liver, heart & lungs. Rev-Erb reduces lung fibrosis and inflammation by acting on NF-κB. Agonists of Rev-Erb lead to a decrease in fat mass specifically in adipose tissue. These agonists also reduce pulmonary fibrosis by preventing myofibroblast differentiation in the lung. A decrease in REV-ERBα levels makes the lungs more sensitive to pro-fibrotic triggers, worsening fibrosis progression. Overproduction of collagen as well as lysyl oxidase due to TGFβ can be stopped by GSK4112, an agonist of Rev-erbα in human lung fibroblasts while an opposite impact is shown by the antagonist. Progression of Lung Adenocarcinoma is contributed by the downregulation of REV-ERBα. Agonists of REV-ERBα such as SR9009 and GSK4112, have therapeutic potential in reducing lung inflammation caused by cigarette smoke-induced COPD. GSK4112 (agonist) and GSK1362 (inverse agonist) target REV-ERBα to reduce pulmonary inflammation, with GSK1362 offering superior efficacy by stabilizing REV-ERBα protein. Based on these findings, there is hope for the therapeutic development of Rev-Erbα agonists for lung fibrosis, thus, further research and clinical trial.

Keywords: Circadian rhythm, COPD, Fibrosis, Inflammation, Rev-Erbα.

Correspondence:
Ms. Aafreen Qureshi
Department of Pharmacology, Oriental College of Pharmacy, University of Mumbai, Sanpada, Navi Mumbai-400705, Maharashtra, INDIA.
Email: aafreenwq@gmail.com

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INTRODUCTION

Idiopathic Pulmonary Fibrosis (IPF) is an irreversible and progressive condition characterized by the stiffening of lung tissue, leading to breathing difficulties for the patient.[1] It is mainly after the failed healing of injured tissues.[2] It can also be promoted by events such as emitting air pollution, some drugs, or infections such as flu or COVID-19 among others.[3] Attempts to find a cure for the said disease are still limited in the current literature and there is still so much that science has not fully explored about the actual process of idiopathic pulmonary fibrosis development and progression.[4] FDA has approved nintedanib and pirfenidone for the treatment of pulmonary fibrosis currently. However, the assistance offered is consultation only the goal of which is to halt the spread of the disease.[5] Fortunately, a promising lead has emerged: Rev-erbα, a molecule showing great potential in helping us better understand and combat fibrosis.[6] REV-ERBα has its action in the nucleus to perform transcriptional corepressor activity for the mRNA transcriptions having rhythmicity, metabolism and inflammation response.[7]

The global mortality rate is a consequence of Chronic Obstructive Pulmonary Disease (COPD) affecting the world's population by 10%. Various causes of COPD are noxious gases, environmental pollutants and cigarette smoke, with cigarette smoke posing a significant threat.[8] There are not many treatments available and fully understood for comprehensive treatment.[9] Earlier reports have shown that acute cigarette smoke exposure in mice increases lung inflammation and damage, leading to the acute exacerbation of emphysema and COPD.[10] This condition can be further worsened by Influenza A virus infection.[11] In earlier times, researchers considered Epithelial-Mesenchymal Transition (EMT) as an important mechanism in the development of COPD.[12] Smokers and patients with COPD display lower REV-ERBα expression levels compared to healthy individuals; similarly LPS-induced Peripheral Blood Mononuclear Cells (PBMCs) had decreased levels of REV-ERBα mRNA.[13]

Lung cancer continued to be the most common and lethal form of cancer globally in 2019.[14] Majority of lung cancer cases (about 80%) are of Non-Small Cell Lung Cancer (NSCLC). Subtypes of NSCLC are: i) Lung Adenocarcinoma (LUAD) and ii) Lung Squamous Cell Carcinoma (LUSC).[15] LUAD's significant tumor heterogeneity contributes to short-term recurrence and treatment

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resistance.[16] Recent studies have underscored the critical involvement of circadian control genes in cancer development.[17] Cancer cells' autonomous circadian clocks can orchestrate a complex network of physiological processes in numerous ways.[18] Circadian clock elements play a crucial role in various important pathways related to tumor growth, indicating that targeting these components with drugs might offer a hopeful and targeted approach to cancer treatment. A decrease in REV-ERBα activity can advance lung cancer by regulating of signaling pathway of NF-κB. This suggests that targeting REV-ERBα might be a promising approach for developing new treatments for lung cancer.[19]

CIRCADIAN RHYTHM

Circadian rhythms are daily biological patterns that follow a roughly 24 hr cycle. These rhythms are regulated by an internal biological clock that continues to function even without external cues, a state known as "free-running." In this state, the internal clock establishes the subjective "night" and "day" periods. Daily changes in heart rate, temperature, blood pressure and the sleep-wake cycle are seen in Circadian rhythms. Also, energy-using processes occur during the active or the wakeful state of the organism while energy-conserving processes occur during the rest state. The role these rhythms play is to coordinate the activities of organisms with those of the outside world especially the period of light and darkness due to the emergence of the sun and setting of the same.[20]

Suprachiasmatic nuclei of the hypothalamus are the main circadian clock seen in mammals. This clock collects information associated with light and regulates the body's internal rhythms, such as sleep/wake cycles and day/night patterns (Figure 1). It then triggers several other 'peripheral oscillators' all over the body using neuroendocrine signals; these have not been well explained fully. These peripheral oscillators decode information from the master clock and consist of even other entrainment factors like feeding rhythm. They modulate local circadian clocks in functions of various physiological messes at the cellular level, intermediaries and metabolisms including NAD+/NADH and rate control enzymes in unique regional metabolic regulation. Some of these are lipid and carbohydrate turnover, secretion of various hormones like insulin, leptin, cortisol, growth hormone and finally, transcription of different genes. This complex organization guarantees the efficiency of even physiological cycles within 24 hr and prepares the organism for constant changes in the environment.[21] Changes to these interactions, like those brought on by shift work, long-distance flights, poor diets, frequent snacking and inconsistent meal times, are commonly linked to issues with the central nervous system, metabolic disorders, heart diseases and even cancer (Figure 2).[22]

THE MOLECULAR CLOCK

The Suprachiasmatic Nucleus (SCN) beneath the hypothalamus in the brain, is where the circadian rhythm, or biological clock, resides, operating on a 24-hr cycle. This cycle helps synchronize wakefulness with the day-night pattern, being influenced by light and temperature. Key proteins involved in maintaining these cellular clocks include ii) CLOCK (Circadian Locomotor Output Cycles Kaput) ii) PER (Period) iii) BMAL1 (Brain and Muscle Arnt-like 1) iv) CRY (Cryptochrome) v) Rev-ERBα vi) RORα (Retinoid-related Orphan Receptor α). Interacting by a network of feedback loops, these proteins regulate the timing of gene expression, ensuring the proper functioning of circadian rhythms within cells (Figure 3).[23]

GRASPING THE MOLECULAR FOUNDATION OF CIRCADIAN RHYTHM

The molecular structure of the central and peripheral oscillators that constitute the circadian clock is remarkably conserved across different species. These oscillators play in the regulation of circadian rhythms through both transcriptional and post-translational modifications. The proteins responsible for these rhythms function through similar mechanisms. In mammals, the core circadian clock consists of a heterodimer formed by CLOCK, CLOCK counterpart NPAS2 and BMAL1. This complex activates the transcription of genes like Per and Cry.[24]

Counterintuitively, Cry and Per negatively regulate CLOCK/Bmal1-driven transcription, marking the beginning of a new cycle (Figure 4). Another feedback loop involves Rev-erb-α and RORα, which strengthens the primary feedback loop. Rev-erb-α is transcribed in a manner initiated by CLOCK/BMAL1 and exhibits daily fluctuations in its levels. The oscillation in Rev-erb-α levels inhibits Bmal1.[25]

ROR-α is a nuclear receptor.[26] It is distinct from Rev-erb-α which interacts with the Bmal1 promoter RORE and is involved in its activation of transcription in the core molecular clock.[27] Additionally, PGC-1α, a metabolic regulator and nuclear receptor cofactor with fluctuating levels in the muscle and liver, has been found to boost ROR-α's activation of Rev-erb-α and BMAL1 transcription, adding more complexity to the regulation of circadian rhythms.[28]

REV-ERBα- A CIRCADIAN REPRESSOR

Two important proteins in the nuclear receptor superfamily i) Rev-Erbα (Nr1d1) and ii) Rev-Erbβ (Nr1d2) are key players in controlling circadian rhythms, regulating metabolism and affecting immune system function.[29] These receptors are distinct from other members of their family due to a specific structural feature: their ligand-binding domain at the C-terminus lacking Activation Function-2 (AF2) at the C-terminus. This region is

usually important for co-activator binding and transcriptional activity.[30]

Rev-Erb proteins continuously repress circadian transcription through two main methods. One way they do this is by competing with ROR for binding to ROR Response Elements (RORE). Secondly, they actively recruit the NCoR-HDAC3 corepressor complex to suppress gene expression.[31] The influence of Rev-Erb proteins extends beyond circadian regulation. They are essential for regulating the metabolism of glucose and lipids, homeostasis, the maturation of fat cells and inflammatory response (Table 1). Their extensive impact emphasizes their critical role in maintaining overall physiological balance and well-being.[32]

Table summarizes the diverse functions of REV-ERBα/β across various organs, tissues and cells. In muscle, REV-ERBα/β enhances mitochondrial function but inhibits myogenesis. In the liver, it reduces lipogenesis while promoting bile acid synthesis. In adipose tissue, it suppresses adipogenesis and in the heart, it decreases cardiac hypertrophy and cytokine production. In the kidneys, REV-ERBα/β is linked to increased kidney injury and fibrosis. In macrophages, it reduces inflammation, while in the lungs, it inhibits myofibroblast differentiation and collagen secretion, highlighting the regulatory roles of REV-ERBα/β in a wide range of physiological processes.

REV-ERBα-A CLOCK GENE AND A NUCLEAR RECEPTOR

Rev-erb-α is found in the adipose tissue, muscle, liver and pancreas, playing a key role in regulating metabolism. It is stored in fat, where it influences immune system inflammation and impacts lipid, glucose and bile acid metabolism. Rev-erb-α likely communicates circadian information to help regulate inflammation and other metabolic processes, while also receiving feedback from these processes.[33]

REV-ERBα IN PULMONARY FIBROSIS

Peter S. Cunningham *et al.*, (2020) demonstrated that fibrotic lungs in mice exhibit disrupted and out-of-phase circadian rhythms, primarily regulated by myofibroblasts. When the REVERBα component was genetically knocked out, it resulted in a severe pulmonary fibrotic response following bleomycin instillation in mice. Molecularly, *in silico* and *in vitro* analysis revealed that REVERBα knockdown enhanced the myofibroblast differentiation via the TBPL1-mediated level of integrinβ1 focal-adhesion formation. The DNA-binding region of the REVERBα gene was removed while keeping its activity controlled by the Pdgfrb gene revealing a significantly stronger scarring reaction in the lungs following exposure to bleomycin, a substance known to induce lung damage. This exaggerated response was characterized by a notable elevation in the myofibroblasts number, identifiable by the presence of the αSMA (α-smooth muscle actin) protein responsible for the formation of scar tissue. Researchers have found that REVERBα can decrease the differentiation of myofibroblasts and the amount of collagen secretion (Figure 5).

DOWN-REGULATION OF REV-ERBα LINKED TO PROGRESSION OF LUNG ADENOCARCINOMA (LUAD)

Zhang *et al.*, (2022) investigated various clinical samples for the expression of REV-ERBα by Immunohistochemistry. REV-ERBα was down-regulated in lung cancer tissues compared to the

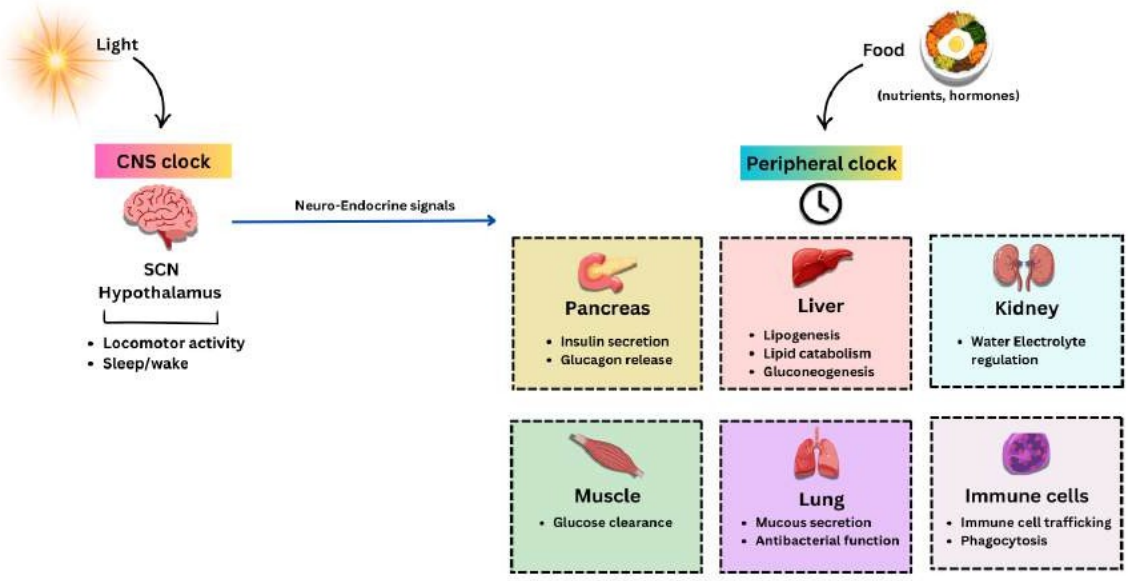

Figure 1: The Role of the Master Clock in Regulating Body Rhythms. The primary or "master" clock is found in the suprachiasmatic nuclei in the hypothalamus. This clock manages and synchronizes the sleep/wake cycle, physical activity and eating patterns, while also influencing other bodily rhythms like liver metabolism, heart function and hormonal responses. Additionally, food acts as a significant signal for the peripheral clocks in the body.

normal tissues. For investigating the levels of REV-ERBα in LUAD patients' samples, 66 samples including 33 tumor samples and their adjacent healthy tissues were collected for IHC staining. These samples also comprised LUAD tissues as well as matching conjunctiva tissues. Down-regulation of REV-ERBα expression in LUAD was analyzed with fewer intensities of staining in the nucleus of the cancer tissues than normal tissue samples. Of increased IHC classification of REV-ERBα, 54 paired LUAD tissues had impaired levels compared to the normal tissues (81%) while the other 12 samples had equal or higher expression levels in LUAD than in their normal tissues (18.2%). According to the findings, the downregulation of REV-ERBα can cause tumorigenesis (Figure 6).

Table 2 summaries the clinical status of study patients. For the 26 females, 24 showed reduced REV-ERBα expressions. Again, this reduction appeared to significantly be observed on younger ages, particularly age fifty. The correlation with the downregulation of REV-ERBα and T stage is another point noted during this study; 31 of 33, meaning all T3 and T4 had downregulation in the tumor tissues. Those with distant metastasis had also low expression in the nuclear REV-ERBα. The study found notable links between low expression levels of REV-ERBα in tumor tissue and the Epidermal Growth Factor Receptor (EGFR) mutation status in patients. This suggests that when REV-ERBα is downregulated, it positively correlates with the growth and aggressiveness of LUAD, particularly regarding how cancer cells proliferate and migrate.

REV-ERBα - A KEY IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD) MANAGEMENT

Yao *et al.*, (2015) demonstrated that REV-ERBα levels were reduced in patients with COPD and smokers when compared to healthy individuals, as well as in LPS-treated peripheral blood mononuclear cells. When both acute mouse models and sub-chronic mouse models were exposed to Cigarette Smoke (CS), there was a link between REV-ERBα and CS-induced Epithelial-Mesenchymal Transition (EMT). Research indicates that REV-ERBα is involved in the activation of mesenchymal cells following CS exposure in mice. Furthermore, agonists of REV-ERBα such as SR9009 and GSK4112, demonstrated therapeutic benefits potential to modulate fibroblast characteristics, with SR9009 treatment leading to a decrease in acute lung inflammation caused by CS. Analysis of NanoString data revealed that targets of circadian clock genes were influenced by subchronic CS exposure, which may play a role in EMT and hindered repair processes in the initial phases of CS-induced lung injury.[34]

OPPOSING EFFECTS OF REV-ERBα AGONISTS AND INHIBITORS ON TGFB- MEDIATED FIBROBLAST DIFFERENTIATION

The Rev-erbα agonist has been shown to decrease the levels of lysyl oxidase, collagen types 1 and 4, αSMA and fibronectin, while these levels rise when Rev-erbα is antagonized. Research

Table 1: Various functions of REV-ERBα/β in organs, tissues or cells.

Organ/tissue/cell	Function of REV-ERBα/β
Muscle	↑ Mitochondrial function ↓ Myogenesis
Liver	↓ Lipogenesis ↑Bile acid synthesis
Adipose tissue	↓ Adipogenesis
Heart	↓ Cardiac hypertrophy ↓ Cytokine
Kidney	↑ Kidney injury ↑ Fibrosis
Macrophages	↓ Inflammation
Lungs	↓ Myofibroblast differentiation ↓ Collagen secretion

Figure 2: Factors Influencing Circadian Dysregulation and Associated Diseases. Internal conditions including age and internal clock genes and external conditions such as sleep deprivation, changes in eating patterns and shift work lead to dysregulation of circadian rhythm. Disturbances in the oscillations are regarded as the precursors of cardiometabolic diseases, disorders of the CNS and neoplastic diseases.

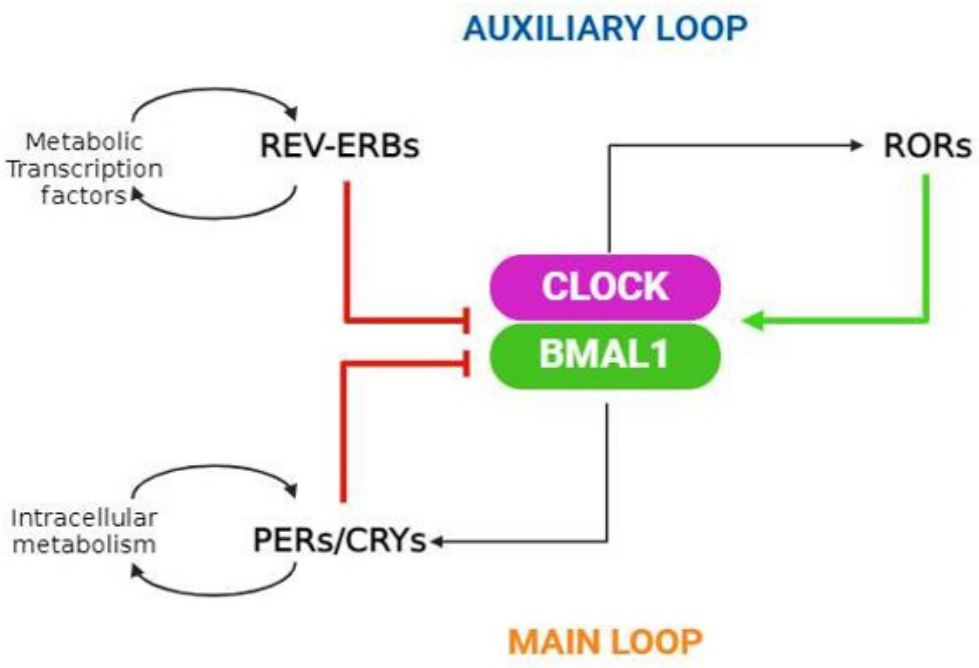

Figure 3: Regulatory Feedback in Circadian Rhythm. Clock and Bmal1 kick off two negative-feedback loops that include Per/Cry and Rev-Erbα/β along with ROR homologs. These loops function by blocking the activation of Per/Cry by Bmal1/Clock and either reducing BMAL1 expression through Rev- Erbα/β or enhancing BMAL1 expression through ROR.

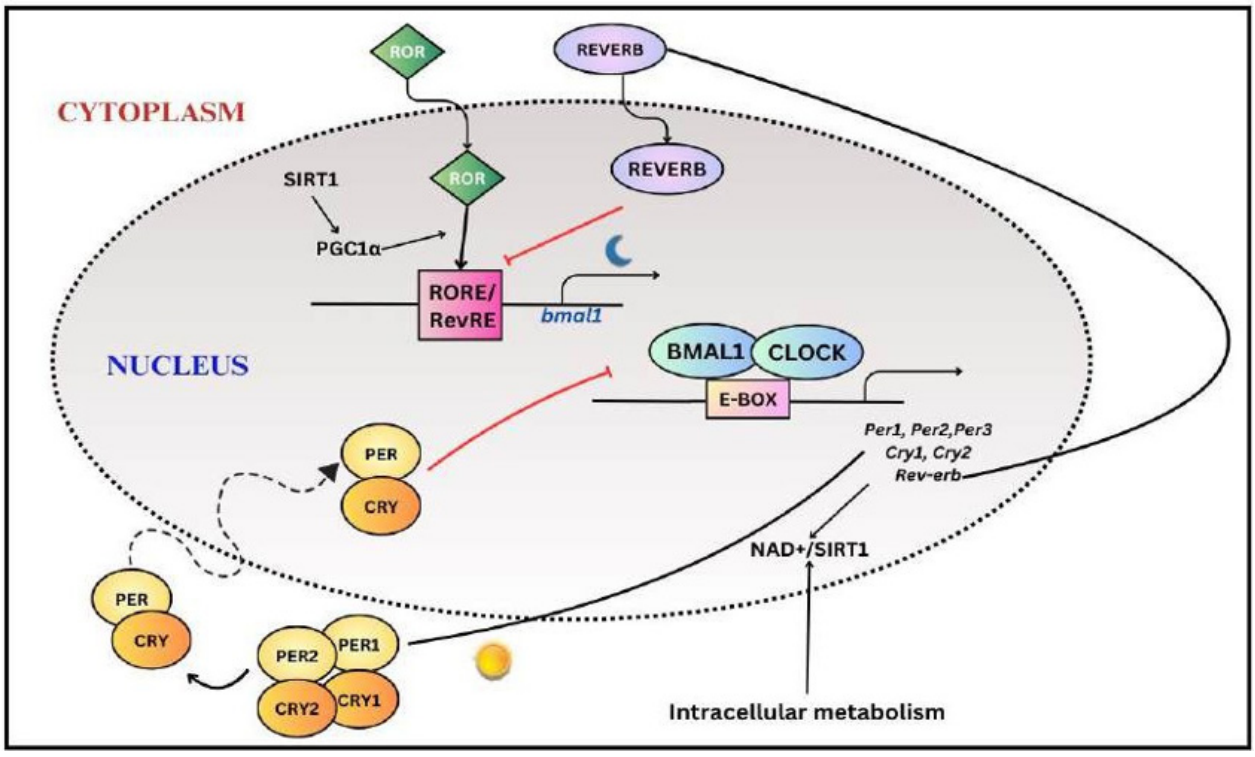

Figure 4: Mechanisms of Circadian Control: Transcriptional Feedback and Post-Translational Modifications.1 Circadian rhythms are kept in check by complex feedback loops that involve both the transcription and translation processes. When CLOCK and BMAL1 come together, they attach to E box elements in the promoter regions of the Per and Cry genes, kicking off their transcription. PER and CRY proteins produced then create a repressive complex that dampens the activity of the CLOCK/BMAL1 dimer, which in turn lowers the levels of these activators. Rev-erb-α and ROR-α regulate Bmal1 expression by competing at RORE/RevRE sites, either turning down or turning up its transcription, adding another layer to the feedback loop. The rhythmic expression of Rev-erb-α means it binds to these sites periodically. Various post-translational modifications like phosphorylation, ubiquitination, acetylation and proteasome degradation are key to keeping the circadian clock on schedule. Plus, metabolic processes and nutrients inside the cell interact with nuclear receptors, further influencing this regulation.

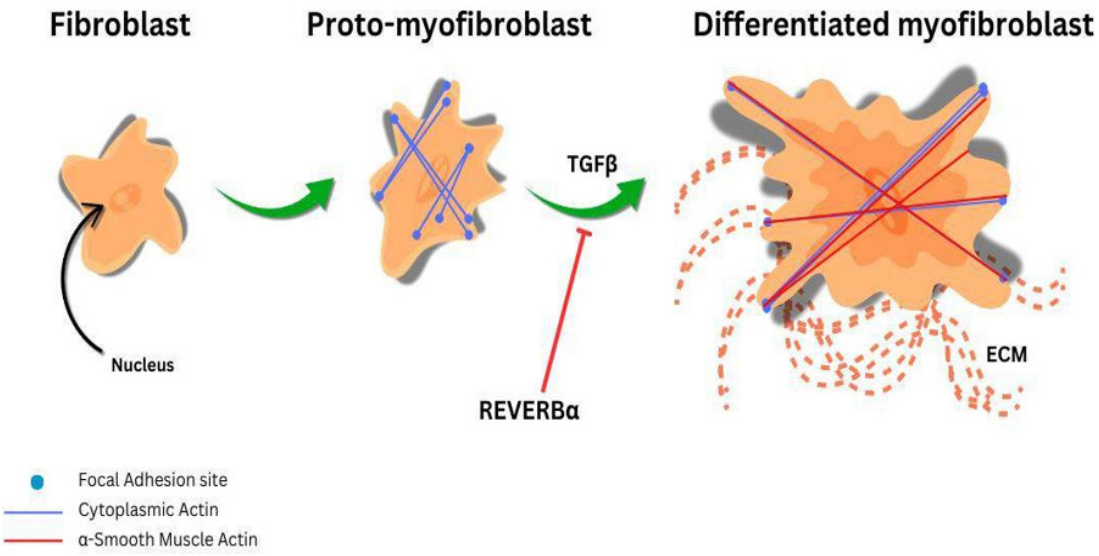

Figure 5: Effect of REVERBα on Myofibroblast and Collagen Regulation in Lung Fibrosis. Knocking down REVERBα led to the activation of myofibroblasts in lung fibroblast cells. REVERBα reduces levels of differentiated myofibroblasts and collagen of the cultured fibroblasts and lung slices in lung fibrosis patients.

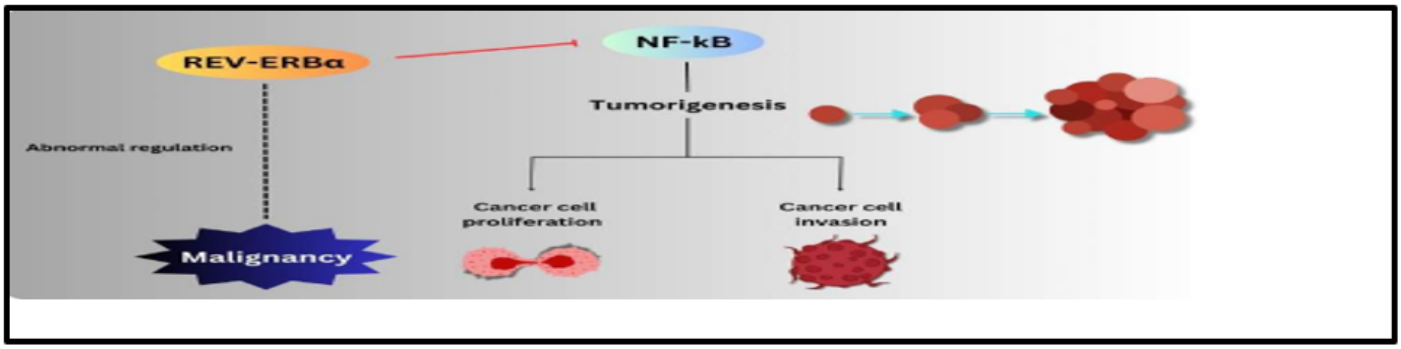

Figure 6: Impact of REV-ERBα on Cancer Growth and Invasion. The "map work" of REV-ERBα's function in the advancement of cancer is illustrated. REV-ERBα is associated with cancer malignancy. When REV-ERBα is low, results have shown that cancer cell growth and invasion can be promoted through activating nuclear factor-κB (NF-κB).

indicated that treatment with the Rev-erbα agonist (GSK4112) led to a significant reduction in mRNA and protein expression of collagen induced by TGFβ. Furthermore, it was found that Rev-erbα might be involved in reducing the progression of fibrosis through its interaction with lysyl oxidase, which helps stabilize collagen levels. Conversely, the Rev-erbα antagonist, SR8278, was found to be ineffective in this context, as it promotes myofibroblast differentiation and increases the levels of collagen, lysyl oxidase and fibronectin (Figure 7).[35]

REV-ERBα IN LUNG INFLAMMATION

REV-ERBα is essential for the regulation of lung inflammation, serving as a link between the circadian clock and innate immune responses. GSK1362, a novel oxazole-based inverse agonist of REV-ERBα, prevents its degradation and enhances its functionality. By obstructing the degradation of REV-ERBα induced by inflammatory cytokines, GSK1362 significantly diminishes lung inflammation. GSK4112, a synthetic agonist of REV-ERBα, plays a significant role in controlling inflammation by modulating the circadian regulation of immune responses. By stabilizing REV-ERBα function, GSK4112 effectively suppresses NF-κB-mediated inflammatory pathways, reducing pulmonary neutrophilic infiltration. Both GSK4112 and GSK1362 are synthetic ligands targeting REV-ERBα, but they exhibit different mechanisms in controlling pulmonary inflammation (Table 3).[36]

Table 3 compares the features of GSK4112 and GSK1362. Both target REV-ERBα to reduce pulmonary inflammation, but act through different mechanisms. GSK4112, an agonist, enhances REV-ERBα activity by promoting repressor recruitment, thereby suppressing proinflammatory cytokines like IL-6 and CXCL5. However, it has low *in vivo* efficacy and off-target effects on LXR receptors. In contrast, GSK1362, an inverse agonist, is more effective as it prevents REV-ERBα degradation, leading to prolonged suppression of inflammation. While GSK1362 is more selective, its pharmacokinetic limitations currently restrict clinical use.

Table 2: Clinical characteristics of 66 patients with lung adenocarcinoma.

Variable		Total cases	REV-ERBα downregulation in LUAD (%)
Age			
	≤50	16	14 (87.5)
	>50	50	40 (80.0)
T stage			
	Tx	1	0 (0.0)
	T1	12	7 (58.3)
	T2	20	16 (80.0)
	T3	31	29 (93.5)
	T4	2	2 (100.0)
M stage			
	Mx	3	1 (33.3)
	M0	58	48 (82.8)
	M1	5	5 (100.0)
EGFR mutation			
No		30	22 (73.3)
Yes		36	32 (88.9)
Gender			
Male		40	30 (75.0)
Female		26	24 (92.3)

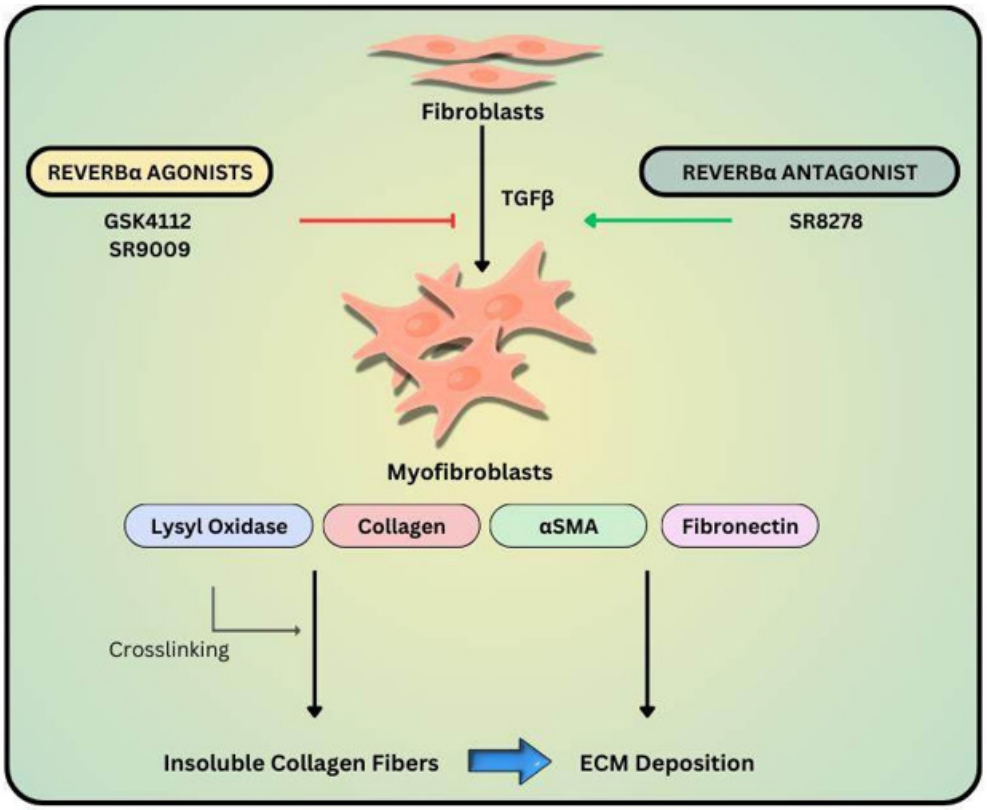

Figure 7: Effects of Rev-erbα Agonist and Antagonist on ECM in TGFβ-Exposed Lung Fibroblasts. A diagram illustrating the roles of both Rev-erbα activator and inhibitor in regulating ECM accumulation in TGFβ- induced lung fibroblasts. Human primary lung fibroblasts exposed to TGFβ (2 ng/mL) in combination with either the Rev-erbα agonist (GSK4112, 20 μM) or antagonist (SR8278, 20 μM) for a duration of 2 days.

Table 3: Comparison of GSK4112 and GSK1362 in Reducing Pulmonary Inflammation.

Feature	GSK4112 (Agonist)	GSK1362 (Inverse Agonist)
Mechanism of Action	Enhances REV-ERBα activity by promoting recruitment of repressor proteins (NCoR1 and SMRT2), leading to suppression of proinflammatory cytokines.	Blocks inflammatory signaling by stabilizing REV-ERBα, preventing its degradation via SUMOylation and ubiquitination.
Effect on Inflammatory Cytokines	Reduces IL-6 and CXCL5 expression by inhibiting NF-κB activation in macrophages and epithelial cells.	Suppresses IL-6, CXCL5 and other neutrophil chemokines by preventing REV-ERBα degradation in response to inflammatory stimuli.
Stability of REV-ERBα Protein	Does not significantly alter REV-ERBα protein stability.	Increases REV-ERBα protein levels by preventing degradation.
Impact on Pulmonary Inflammation	Suppresses airway inflammation by reducing neutrophilic infiltration and chemokine expression.	More potent in reducing inflammation due to sustained REV-ERBα stabilization, leading to prolonged suppression of proinflammatory pathways.
Limitations	Low *in vivo* efficacy, off-target effects on LXR receptors.	More selective for REV-ERBα, but lacks favorable pharmacokinetics for clinical use.

CONCLUSION

Recent studies identified the link between Rev-Erbα and suppression of lung fibrosis has created fresh hope to treat this fatal affliction. With the knowledge of how specifically Rev-Erbα influences inflammation, collagen deposition and myofibroblast conversion and differentiation, it is now feasible to examine the creation of fresh drugs focusing on this 'clock maker'.

Based on the conclusions of the present research, it might be possible to use Rev-Erbα agonists, including GSK4112, to alleviate other symptoms of lung fibrosis in addition to suppressing collagen deposition and other fibrotic biomarkers. This is especially important because the existing therapies such as pirfenidone and nintedanib are not very effective and may entail severe complications.

Also, studies of COPD and lung cancer prove that Rev-Erbα is extremely important to the wellness of the lungs. Thus, because Rev-Erbα is downregulated in patients with COPD and lung cancer, this protein may be a target of these diseases' prevention and treatment. Furthermore, the information about the connection between Rev- Erbα and the clock and the effects observed in lung fibrosis allows to consider the issue of interaction between the organism's biological clock and the pathology in more depth. Rev-Erbα is associated with the circadian clock and knocking out its expression leads to lung fibrosis, implying that other proteins associated circadian clock might also be involved in the pathology of various diseases.

Both GSK4112 (agonist) and GSK1362 (inverse agonist) effectively suppress pulmonary inflammation by enhancing REV-ERBα's regulatory role. However, GSK1362 is superior as it prevents REV-ERBα degradation, ensuring prolonged anti-inflammatory effects. Despite its advantages, GSK1362 has pharmacokinetic limitations, while GSK4112 has off-target effects, highlighting the need for more selective and clinically viable REV-ERBα modulators.

In conclusion, the recently discovered avenue in the understanding of Rev-Erbα as well as its function for lung fibrosis and its relationship to COPD and lung cancer might mark a new era in handling these diseases. More research is still required to get the full insight of how Rev-Erbα influences lung health and to understand how Rev-Erbα can be targeted as a therapy with efficacy. However, the results of the current work should present a new trend for the synthesis of new remedies for lung fibrosis and other similar ailments.

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CONFLICT OF INTEREST

The author declares that there is no conflict of interest.

ABBREVIATIONS

TBPL1: TATA box:binding protein:like protein 1; **Pdgfrb:** Platelet:derived growth factor receptor beta; **NF:kB:** Nuclear Factor Kappa B; **TGFβ:** Transforming Growth Factor Beta; **IHC:** Immunohistochemistry; **Alk5:** Activin receptor:like kinase:5; **LPS:** Lipopolysaccharide; **N:CoR:** Nuclear receptor corepressor; **HDAC3:** Histone deacetylase 3; **CXCL5:** C:X:C motif chemokine ligand 5; **IL:6:** Interleukin 6; **NCoR1:** Nuclear Receptor Corepressor 1; **SMRT2:** Silencing Mediator of Retinoid and Thyroid Hormone Receptor 2; **LXR:** Liver X receptors.

SUMMARY

This review explores the crucial function of the nuclear receptor Rev-Erbα in regulating circadian rhythms, inflammation, and various pulmonary disorders, including pulmonary fibrosis, COPD, and lung cancer. Rev-Erbα plays a vital role in mitigating lung inflammation and fibrosis by modulating NF-κB and inhibiting the conversion of cells into myofibroblasts. Evidence suggests that reduced levels of Rev-Erbα may facilitate the progression of Lung adenocarcinoma (LUAD), positioning it as a promising target for novel therapeutic strategies. Compounds such as GSK4112 and SR9009, which activate Rev-Erbα, have shown promise in treating lung fibrosis and COPD associated with cigarette smoke. Additionally, GSK1362, an inverse agonist, enhances anti-inflammatory effects by stabilizing Rev-Erbα. The review highlights the detrimental impact of circadian rhythm disruptions on lung health and underscores the therapeutic potential of targeting Rev-Erbα. However, further research and clinical trials are necessary to explore the therapeutic possibilities associated with this pathway fully.

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