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CIRCADIAN IMMUNITY AND COVID-19: UNVEILING THE SIRT1 CONNECTION

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Article Info

Abstract

Background: Immunity against infectious diseases, particularly viral infections where antibiotics do not work, plays a key role in their eradication. Therefore, it is essential to identify the natural and biological factors that contribute to a strong immune response to combat COVID-19 and other diseases effectively.

Methodology: In this study, we investigated the relationship between the circadian clock, immune function, and the eradication of COVID-19. Also, we evaluate the past research works for the analysis.

Results: In this analysis, we examine how SIRT1, circadian clocks, and COVID-19 immunity may interact. Considering that the SIRT1 gene controls the circadian clock, and the circadian clock enhances immunity, therefore, the circadian clock, SIRT1, and the body's immune defence against coronavirus influence each other in a mutual relationship.

Conclusion: Maintaining a healthy sleep and wake routine helps regulate the balance between the circadian clock and cellular immune responses, which is crucial for effectively fighting infections and may aid in recovering from illnesses such as COVID-19.

Keywords:

Sirt1, Circadian clock, COVID-19, Immunity, Health.

1. Introduction

The coronavirus outbreak, known as coronavirus disease 19 (COVID-19) caused more than two million deaths globally so far. It may be asymptomatic but sometimes manifests in three clinical phases: an early upper respiratory tract infection, progressing to a pneumonic phase in some patients, and even a few cases, to a hyperinflammatory phase, which may be fatal (1).

Four coronaviruses are known to infect the upper respiratory tract only and cause minor symptoms. These are human coronaviruses 229E, NL63, OC43 and HKU1. But three coronaviruses divide in the lower respiratory tract and cause pneumonia that can be lethal. These include severe acute respiratory syndrome coronavirus (SARS-CoV), Middle East respiratory syndrome coronavirus (MERS-CoV) and SARS-CoV-2. Like the other types, SARS-CoV-2 spreads through respiratory droplets. There is a possibility of faecal–oral transmission route, but it is not confirmed. The average incubation period is about 4-5 days after the infection. However, with 97.5% of patients, symptoms develop within 11.5 days.

The treatment required is to inhibit its replication at an early stage to prevent the progression of the disease to an advanced stage. This treatment may be either prophylactically or therapeutically to prevent the stage where mechanical ventilation (MV) is required, or sometimes significant organ dysfunction occurs (2). Older age, obesity, immunosuppression, non-asthmatic respiratory diseases and chronic diseases such as diabetes, cardiac disease, hypertension and male sex are the independent risk factors for the poor outcome (2,3)

The mammalian SIRT1, a member of the sirtuin family (4), deacetylase enzyme that relies on nicotinamide adenine dinucleotide (NAD^+) and acts on various proteins, including histones, to remove acetyl groups (5). Because of these characteristics, SIRT plays a role in various physiological processes, such as regulating gene expression, metabolism and ageing (5, 6). In the enzymatic reaction catalysed by SIRT, a nicotinamide is released, and the substrate's acetyl group is shifted to the cleaved NAD^+ molecule, and the reaction produces a novel metabolite known as O-acetyl-ADP ribose. In addition to a broad range of functions, the SIRT1 also protect against chronic inflammation. It regulates the acetylation of nuclear factor kappa B (NF-κB), a transcription signalling pathway that plays a key role in the innate immune response (7). In reaction to prolonged genotoxic stress, it limits the replicative life span (8).

There are seven members of Sirtuins (class III histone deacetylases) that are SIRT1-SIRT7 and have different functions and localisations. They regulate many health conditions, including mainly chronic diseases such as cancer, cardiovascular diseases, neurodegeneration, and diseases associated with ageing. The Nad^+ dependent histone/protein deacetylase not only plays a role in epigenetic silencing, heterochromatin formation, metabolism, DNA repair, and cellular stress responses, but also regulates the circadian clocks (9).

Circadian clocks are the biological oscillators that play a role in controlling the behavioural and physiological processes in an organism, including growth, metabolism, temperature homeostasis, blood pressure and hormone production. The mammalian circadian clock is based on the self-regulating transcriptional feedback loop within the cell. This loop regulates circadian processes such as occupancy of transcription factors, recruitment of RNA polymerase II and initiation, nascent transcription and chromatin remodelling. The CLOCK and BMAL are the core clock genes that encode activators, while PER1, PER2, CRY1 and CRY2 encode repressors (10, 11).

During the daytime, the core circadian clock genes—circadian locomotor output cycles kaput (CLOCK) and brain and muscle ARNT-like protein-1 (BMAL1)—form a heterodimer that activates the transcription of repressor clock genes, such as Period (Per1/2/3) and Cryptochrome (Cry1/2). Among these, PER 2

increases the BAMLI1 transcription by inhibiting its repressor, REV-ERBα/β, thus creating a reinforcing positive feedback loop within the circadian clock. In the evening, however, the PER2/CRY complex acts as a repressor, blocking the transcriptional activity of the CLOCK/BMAL1 complex. This creates a self-regulating negative feedback loop, allowing the CLOCK/BMAL1 complex to reset and become active again the following morning (12).

Circadian rhythms have great effects on human health because they maintain coordination between the daily physiological processes, including innate and adaptive immunity. The disruption of circadian clocks in host speeds up the replication and propagation of pathogens, which shows that the severity of acute infections could be significantly influenced by circadian rhythm. Keeping in view that the SIRT1 gene controls the circadian clock, which in turn enhances immunity, the circadian clock, SIRT1, and immune coronavirus response are interconnected through reciprocal regulatory mechanisms. Therefore, this analysis focuses on the potential interactions among SIRT1, circadian rhythms, and immune responses to COVID-19.

2. Circadian clock and general health

Variations in light and temperature are affected by the regular rotation of Earth on its axis. Therefore, life on Earth has evolved through the light and dark periods, manifesting the sleep and wake cycle. Sleep is the biological need of all mammals, and humans, on average, spend one third of their life spend during sleeping (13, 14). The sleep time, duration and quality are associated with health and well-being. Disruptions in all these parameters are linked with many disorders and dysfunctions such as insulin resistance, type 2 diabetes, obesity, metabolic syndrome, cardiovascular diseases and mortality from all causes (15, 16).

Research has shown that the molecular clock is present in various tissues and different cell types in the central and peripheral nervous systems. The main circadian pacemaker is positioned in the suprachiasmatic nuclei in the forebrain bundle of hypothalamus. With the experimental injury of the suprachiasmatic nuclei in the hypothalamus, Serious circadian arrhythmicity and desynchronisation of peripheral oscillators appear (17).

As many homeostatic processes such as feeding, rest, activity, temperature, hormones secretions, innate immunity, cardiac functions, and neurophysiology are control by the rhythmic expression of endogenous biological clock (18), therefore it is not unexpected that the disruption of these clock result in adverse effects on health and behavioural outcomes (19). Studies have shown that non-seasonal major depressive disorder is associated with later phenotypes and delayed sleep onset as compared to the control population (20, 21). Also, yearly changes in the daylight length cause changes in the circadian system, which is also associated with seasonal depression disorders (22). Moreover, the circadian misalignment due to “biological night” time activity increases the risk of various other diseases and also affects their treatment response (23).

3. SIRT 1 and circadian clock

As the SIRT1 plays a role in regulating DNA repair, apoptosis, and circadian rhythm by controlling the expression of p53, PGC-1□, NF-K,□□ □□4□. □it is reported that chronic obstructive pulmonary disease (COPD) patients have a low level of SIRT1 in their lungs. (25). This decreased level of SIRT 1 expression results in increases in the MMP9 (the protein for breakdown of extracellular matrix) in the lungs of these patients (26). Furthermore, the deficiency of SIRT1 protein is shown to cause emphysema in the respiratory epithelium of experimental animals, which is a type of COPD. In contrast, its deficiency

increases cellular senescence in mice lungs (27, 28). Therefore, the SIRT 1 deficiency in the Clara cell may be a factor for COPD.

SIRT1 influences the gene expression of the circadian system by deacetylating and promoting the degradation of PER2 within the CLOCK/BMAL1/PER complex, thereby positively regulating the circadian clock (29). Also, by increased deacetylation of histone 4 it negatively affects PER2 expression. If SIRT1 is lost, PER 2 overexpression results in premature ageing. PER 2 upregulation negatively influences SIRT1 expression by inhibiting CLOCK/BMAL1-driven transcription of the SIRT1 gene. (30).

4. Circadian clock and immune response, and COVID-19

The immune system consists of a complex system of physiological processes to protect the body from foreign entities, including pathogens like bacteria, viruses, and parasites, as well as abnormal cells as those involved in cancer. Most of the immune cells contain circadian clock genes and exhibit extensive gene expression patterns that follow a 24-hour cycle. (31)

Recent studies have indicated that the roles of clock proteins like BMAL1 and REV-ERBα in immune regulation could offer new perspectives on developing infectious and inflammatory diseases. It is well recognised that diseases such as asthma (32), rheumatoid arthritis (33), and atherosclerosis (34) show strong circadian patterns, often worsening during nighttime and early morning hours. Also, there is a close relationship between circadian rhythms and cancer, which is frequently linked to inflammation (35). In healthy individuals, levels of proinflammatory cytokines like TNF-α and IL-6 are highest in the early morning hours around 3 a.m. and 6 a.m., respectively (36).

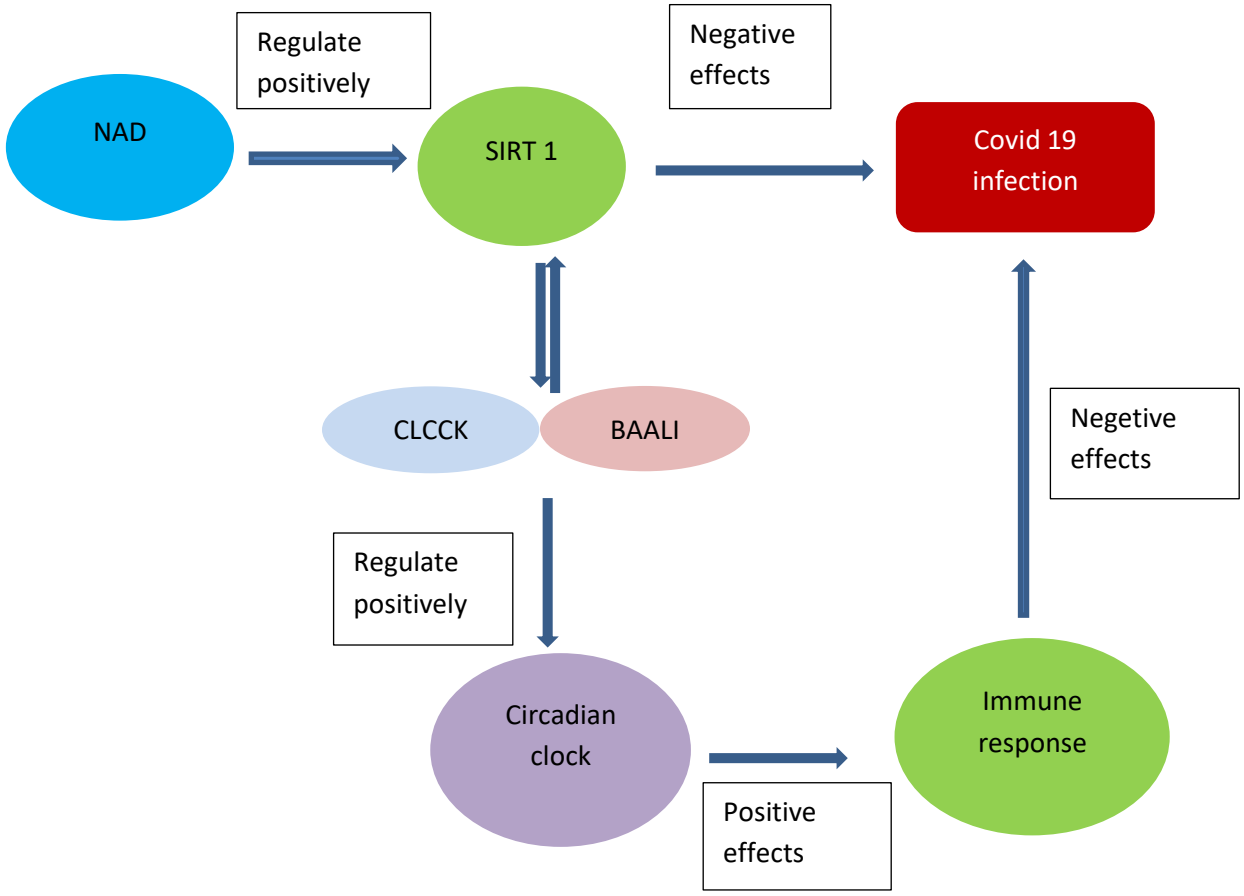

Figure: Controlling effects of SIRT 1 gene on the circadian clock and immunity.

Studies have shown that both acute and chronic models of virus-induced airway inflammation demonstrate that disruption of the day-and-night circadian cycle negatively impacts the onset, progression, and worsening of asthma symptoms. more severe asthma-related airway alterations were apperad by silencing the clock gene BMAL1, it indicated that BMAL1 may be involved in regulating lung-specific antiviral defences and the appearance of asthma symptoms (37). These findings support earlier research by Majumdar et al., which identified BMAL1 as a key regulator of innate immunity. Their study demonstrated that cells lacking BMAL1 were more susceptible to infection by RNA viruses, including respiratory syncytial virus (RSV) and parainfluenza virus type 3 (PIV3) (38).

5. Conclusion:

The NAD-dependent SIRT1 gene plays a crucial role in the regulation of the Circadian clock. The Circadian clock disruption negatively affects the immune system. A weak immune system exposes the body to more adverse effects of pathogens, including SARS-CoV-2 and negatively affects the eradication of COVID-19. Therefore, maintaining a good sleep pattern supports the proper balance between humoral and cellular immune responses, which is essential for effective defence against infection and may help in recovery from various diseases, including COVID-19.

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