Editorial

Lungs can tell time—a highlight from 2016 ATS session on clock genes, inflammation, immunology, and sleep

Michael T. Y. Lam[1], Michael A. Grandner[2], Atul Malhotra[3]

[1]Department of Internal Medicine, UCSD, San Diego, CA 92103, USA; [2]Department of Psychiatry, University of Arizona, Tucson, Arizona 85724-5002, USA; [3]Division of Pulmonary, Critical Care & Sleep Medicine, La Jolla, CA 92037, USA

Correspondence to: Atul Malhotra, MD. Division of Pulmonary, Critical Care & Sleep Medicine, 9300 Campus Point Drive, #7381 La Jolla, CA 92037, USA. Email: amalhotra@ucsd.edu.

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Circadian rhythms represent endogenous processes that regulate physiological and cellular functions in a 24-hour cyclical pattern (1). These rhythms are thought to be an evolutionary strategy for adaptation to diurnal changes in the environment. Sleep-wake cycle, core body temperature, endogenous release of glucocorticoid and melatonin are a few of the many physiological processes with circadian properties. The central circadian pacemaker resides in the Suprachiasmatic Nucleus (SCN) of the hypothalamus. It synchronizes the endogenous peripheral clocks that exist in almost every single cell of the body (2). Within each cell, the clock consists of transcriptional-translational anti-regulatory loops that generate molecular oscillation of core clock genes. These core clock genes—including *Clock*, *Bmal I*, *Crytochromes*, *Period*, *Rev-erb*—in turn regulate expression and production of "output genes" that give rise to the diurnal function of each cell (3). Disease processes such as myocardial infarction, ischemic stroke, and epilepsy exhibit rhythmic day-night variance (4). In animal models, disruptions of circadian rhythm recapitulate chronic disease states such as metabolic syndrome (5). Evidence is emerging supporting the role of circadian biology in diseases.

At the 2016 American Thoracic Society Conference, a panel of physicians and scientists gathered to discuss the relevance of circadian rhythm in pulmonary biology. Dr. Steven Shea from Oregon Health and Science University highlighted the diurnal patterns in pulmonary function. Serial 2-hour interval measurements of FEV1 in young healthy subjects showed a circadian nadir of FEV1 at biological sleep time. Importantly, subjects were awake the entire time under conditions devoid of any time cues (e.g., constant low light, no clock, identical meal every 2 hours). This experiment demonstrated that the endogenous circadian pacemaker, instead of sleep-wake cycle or environmental changes, drives diurnal pulmonary function (6). The circadian nadir of pulmonary function also coincides with nocturnal attacks in patients with asthma, as pointed out by Dr. Jeffrey Haspel from Washington University. Bronchial lavage at this time point showed considerable infiltration of macrophages, neutrophils, and T cells in alveolar tissues (7,8). In obstructive sleep apnea, the duration of apnea/hypopnea events also appears to be regulated in a circadian fashion (9). A better understanding of these mechanisms offers new targets for therapy and refinement of current treatments in these diseases.

Circadian rhythmicity of physiological responses is intricately regulated at the molecular level by circuitry of core clock genes. Dr. Andrew Loudon from University of Manchester shared some of his work on circadian biology in lung inflammation. Many physiological processes such as cell proliferation, inflammation, or insulin-signaling pathways have different levels of activity at specific times of the day, a concept referred to as circadian gating. The lung's innate response to bacterial endotoxin—which involves upregulation of chemokines leading to neutrophils recruitment—exhibits a diurnal pattern. Using club cell-specific genetic targeting of the molecular clock genes, Dr. Loudon's group showed that the circadian gating of neutrophil recruitment is predominantly mediated by chemokine *Cxcl5*. The expression of *Cxcl5* upon inflammation, in turn, is regulated by core clock gene *Rev-erb*α. The variance of *Rev-erb*α activity at different circadian times dictates diurnal

regulation of *Cxcl5* and its subsequent inflammatory cascade.

Environmental exposure can interact with the molecular clock. Cigarette smoking, as highlighted by Dr. Irfan Rahman from University of Rochester, affects the activity of Sirtuin-1. As mentioned above, the core clock genes *Bmal I* and *Clock* are transcription factors that form a transcription unit and drives cyclic expression of circadian genes. Sirtuin-1 binds to the Bmal I: Clock complex and affects its activity by post translational modifications (10,11). Cigarette smoking led to decreased Sirtuin-1 activity leading to altered Bmal I: Clock activity (12). This finding may be a contributing factor for increased inflammation seen in smokers with COPD (13).

While animal models are excellent tools to dissect molecular function of the circadian clock, the effect of circadian disruption in humans is less clear. Dr. Karen Gamble from the University of Alabama at Birmingham addressed this question by examining circadian rhythm in shift workers. In shift work the hours of work and sleep switch repetitively between day and night. During such drastic time-shifts the central clock attempts to synchronize peripheral clocks. The duration required for clocks to adjust, however, varies between different tissues. Thus the timing of rhythm between different organ systems can be "misaligned" in shift works. Gamble's group focuses on characterizing biological parameters of circadian rhythmicity—including level of activity, core body temperature, melatonin levels, and transcriptome of peripheral nucleated blood cells—and compared between day-shift and night-shift nursing staff. As expected, circadian rhythmicity was robust in staff with regular day-shift schedules. The night shift staffs work three consecutive nights with four days off when they revert to a day schedule. The circadian amplitudes of night shift nurses were significantly blunted in all measured rhythmic parameters. Interestingly, the transcriptome analysis was performed on day 3 after the end of the night shift, showing that the circadian rhythm of white blood cells had not readjusted even when the staff had switched back to "normal" diurnal sleep time. They are also one day away from the next night shift. This notion implies that circadian clocks are chronically misaligned in shift workers. In epidemiological studies, shift-work is associated with predisposition of chronic diseases such as metabolic syndrome and cancer (14,15). Understanding circadian misalignment and its impact on health is thus important, with future implications on public health policy, work-hour regulation, and societal norms on work.

Discussions of circadian biology in pulmonary physiology, immunology, and sleep at this ATS session were refreshing, engaging, and captivating. The sessions confirmed a high level of interest and excitement in this research community emerging in pulmonary medicine. This session was only the tip of an iceberg, as studies in multiple areas begin to emerge. These priorities include sleep in the ICU, chronotherapy, and cancer biology to name a few (16,17).

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Footnote

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