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INTRODUCTION

Clocks and Cycles

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An organism's fitness depends on their ability to adapt to their environment. So perhaps it is no surprise that multicellular organisms ranging from plants to animals--vertebrates and invertebrates alike--live by a daily biological rhythm that is set by the Earth's rotation and orbit around the sun. During the daily 24-hour cycle, an individual's physiology, behavior, and well-being can vary greatly, often in synchrony with environmental changes by a process called entrainment. These organismal-level changes occur due to corresponding fluctuations in cycle-specific molecules, such as proteins aptly named CLOCK and PERIOD, at the cellular level. In 2017, Jeffrey C. Hall, Michael Rosbash, and Michael W. Young were jointly awarded the Nobel Prize in Physiology & Medicine for their efforts in discovering and elucidating key mechanisms underlying circadian (or daily) rhythms. Therefore, we feel that an issue dedicated to the inner workings of circadian cycles in both plants and animals is timely.

It has been shown that proper light entrainment is necessary for optimal health, however, factors that disturb proper entrainment are ubiquitous in our modern world--artificial lighting, night-time shift work, and jet-lag from travel. Not only are our baseline health and normal physiology influenced by circadian rhythms, but the success of medical interventions and the severity of disease states are also dependent on these cycles. In this issue, Abele *et al.* review the daily fluctuations seen in cytokines, chemokines, phagocytic capacity, and immune cell trafficking that influence the immune response in a time-of-day-dependent manner. This has important implications during infection. Experimental evidence has shown that onset of infection at different times in the day can predispose an organism to succumb to that infection, presumably due to daily fluctuations in immune cell function. Importantly, this Review details various considerations for chronotherapy, or therapeutic interventions that use knowledge of circadian rhythms to develop treatment strategies. For example, the authors speak to harnessing knowledge of immune system fluctuations to inform vaccine administration strategies as a way to improve the protective immunity provided by vaccines. On the other hand, an Original Contribution by Di *et al*. shows how disease states can be tracked through noticeable deviations from normal, healthy circadian rhythms. To study vision deterioration during progressive diabetes, they use an electroretinogram to track changes in the retinal circadian cycle as the disease state worsens. This study demonstrates how disease states correlate with aberrant cycles and that cyclical changes that can be detected and tracked by medical instrumentation.

Melatonin is a key molecule whose regulation and release depends on the time of day. In diurnal animals, melatonin is released at low levels in the presence of sunlight which promotes wakefulness in the day and it is released at high levels in darkness which promotes drowsiness and sleep at night. This pattern of fluctuating melatonin secretion is an internal mechanism that animals use to respond to external environmental changes. Christopher DeVera, Kenkichi Baba, and Gianluca Tosini review the retinal

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circadian clock, which processes cues such as sunlight to signal for cyclical melatonin production. However, in cases of blindness, the retina cannot process light and darkness cues to enforce regulated melatonin release. We want to highlight the Case Report provided by Andrew Tubbs, Michael Grandner, and Daniel Combs, which details use of the melatonin receptor agonist, Tasimelteon, to treat non-24-hour sleep-wake disorder in a blind adolescent. This case shows potential benefit in expanding the use of Tasimelteon for blind adolescents, which is important given that Tasimelteon treatment is currently only approved for adults.

One of the goals of this issue is to also feature investigations into circadian rhythms outside humans and mammals. Plants also adapt their physiology based on the time of day and they use specific molecular mechanisms that fluctuate in accordance with environmental changes, resulting in an organismal-level response. A well-known example of a plant response that varies throughout the day is the sun-tracking movement of sunflowers. Initially facing towards the east for sunrise, sunflowers will gradually track the sun as it sets in the west, before repositioning to face towards the east in anticipation of the sunrise of the next day. This movement clearly demonstrates that sunlight is a cue that entrains a response in plants, much like it does in other organisms. Light also affects the cyclical flowering of plants through fluctuations in genes related to flowering. As such, we would like to highlight an Analyses by Hoong-Yeet Yeang, which argues that existing data does not support a model in which the flowering of *Arapidopsis* is entrained to sunrise as previously accepted, but rather to midnight.

In this issue, we hoped to capture all aspects of circadian rhythm in a way that spans both basic, mechanistic research, as well as clinical and translational work. This vision includes discussions about the centralized mammalian clock in the suprachiasmatic nucleus and its relationship to the peripheral clocks in other organ systems like the cardiovascular system. The issue looks at healthy circadian cycles, but it also gives key examples of clock desynchrony, which are central in sleep and metabolic disorders. This is especially relevant today because features of modern life contribute to clock desynchrony. The issue also delves into circadian rhythms outside of mammals, from *Drosophila* to plants. We hope that you enjoy and appreciate how the articles featured in this issue are a testament to the highly integrated cycles that help organisms function and interface with their environment.