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Introduction to Special Issue: Circadian regulation of metabolism, redox signaling and function in health and disease

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The origin of a special issue in *Free Radical Biology and Medicine* dedicated to circadian rhythms originated in 2016 at a jointly sponsored conference of The Physiological Society and the American Physiological Society held in Dublin. Several of the authors in this issue participated in a symposium dedicated to circadian rhythms and it was evident that research in circadian rhythms is on the brink of explosion, being facilitated by the marriage between modern genetic research and fundamental physiology. The timing of this issue is particularly fortunate given the most recent awarding of the 2017 Nobel Prize in Physiology or Medicine to three pioneers in the circadian biology field, namely Michael Rosbash, Jeffrey C. Hall and Michael W. Young. The discovery of a distinct set of transcription factors that function to temporally orchestrate gene expression and resulting physiological processes have opened up a new field of discovery throughout the world of biology.[1] No area of biological research is immune to the impact of circadian rhythms, including that of free radical biology. Therefore, this issue is devoted to providing broad insight into circadian control of metabolism and related physiologic functions, with particular emphasis on areas relevant to the journal's overall focus.

A starting point when introducing the relation between redox biology and circadian biology would be the review of Nagy and Reddy, where they review the most recent information on rhythms within redox control systems.[2] The authors highlight that therapeutic approaches targeting reactive oxygen species have been slow to develop, which may have been hampered to some extent by the lack of appreciation of how biological rhythms impact production of reactive oxygen species, molecular oscillations of key components of redox biology, drug metabolism/efficacy (i.e., chronopharmacology).

When one thinks about circadian rhythms, daily fluctuations in behavior are often considered. This topic is reviewed in a comprehensive manner by Heyde and colleagues who highlight the complex interplay between sleep and circadian rhythms, disruption of which likely contributes towards various pathologies plaguing human health.[3] Such concepts lead to questions regarding whether redox biology forms an intrinsic mechanistic link between circadian and neural biology, the topic of the article by Kinoshita et al, who review evidence suggesting that circadian clocks directly modulate glutathione levels within the central nervous system, thereby impacting susceptibility to stresses over the 24-hr day.[4] Ishii and colleagues look at the regulation of brain-derived neurotrophic factor by Nrf2, an important redox regulator.[5] This has implications for understanding metabolism in astrocytes, which are key in regulating the milieu of neurons in the brain. Following on from this, Bothwell and Gillette review how the circadian and redox systems interact to regulation another key aspect of brain function – neuronal excitability.[6] They particularly focus on the suprachiasmatic nucleus, a key pacemaker in the brain that drives rhythms in other regions of the brain.

Of note, circadian oscillations are not limited to the brain or to in vivo conditions, or even to mammals. Indeed, the origins of circadian biology were born from observations in plants. In their review, Karapetyan and colleagues show how plant physiology and immune defense is regulated by the circadian clock.[7] In particular, they discuss the intersection between redox systems and the clock, and how this shapes the immune response of plants to attackers. The 2017 Nobel Prize winners carried out pioneering studies focused on the molecular machinery of circadian clocks largely in the fruit fly. In this issue, Giebultowicz and colleagues discuss the regulation of metabolism and health span in fruit flies.[8] The fly is an ideal organism to look for the interaction between these two aspects of life, enabling assessment in a relatively short period of time compared to mammalian systems.

In mammals, metabolism must be coordinated with the homeostatic needs of the body, but also with the external environment. Disruption of circadian systems invariably result in a host of cardio metabolic diseases, including obesity, diabetes mellitus, and cardiomyopathy. With regards to diabetes, Lee et al. review convincing evidence that circadian clocks within pancreatic β-cells are critical for normal glucose homeostasis.[9] These authors provide a logical argument for how circadian misalignment can contribute to metabolic dysfunction, resulting in diabetes. 1. Peliciari-Garcia, Darley-Usmar, and Young delineate the dramatic oscillations that occur in the cardiovascular system over the course of a day, with a particular focus on the heart itself.[10] Importantly, a range of redox and metabolic processes are regulated in a circadian pattern, illustrating the importance of 24-hour patterning in cardiac physiology. In terms of overall cardiovascular health, Khaper and colleagues provide a broader overview of the importance of circadian control systems in the cardiovascular system in general, as well as implications for timing of cardiovascular events such as myocardial infarction.[11]

The kidney is a key tissue that regulates many vital functions, most notably electrolyte balance and blood pressure. Clinically, loss of 24-hour rhythms in blood pressure, for example, leads to adverse outcomes, and may also impact kidney disease. Johnston and Pollock assess evidence for circadian regulation of kidney function, looking at both the basic science and its clinical application.[12] Douma and Gumz provide a unique overview of clock gene regulation in various tissues known to participate in blood pressure regulation.[13] A wide range of mouse models with clock gene deletions have blood pressure phenotypes that have yet to be fully resolved. Another important aspect of blood pressure regulation is vascular function. Rodrigo and Herbert review much of the evidence for circadian control of vascular function including endothelial derived NO and H_2O_2.[14] As readers of this journal would know, the interaction of NO with other reactive oxygen species is well established, which makes circadian control relatively unappreciated in a great deal of previous work in the field.

Circadian regulation of reactive oxygen species production and activity appear to be important in cardio metabolic disease risk. The same is true for the pulmonary system. As reviewed by Sundar and colleagues, an interrelationship exists between redox and circadian biology in the lung, which becomes disrupted during chronic airway diseases.[15] This likely contributes towards the organ dysfunction and pathology, through enhanced inflammation, DNA damage, and fibrosis. The associations between circadian disruption and disease lead to questions regarding how clock function can be enhanced (and whether such strategies have therapeutic potential). Of course, light is not the only way to reset clock gene function. Tahara and Shibata review how food, exercise, and stress can impact circadian control of physiological and pathophysiological systems.[16]

We expect the material reviewed in this issue will provide the basis for future research in the field of free radical biology. Considerable attention has been paid in recent years to rigor and reproducibility within basic and clinical science and much of this discussion has included aspects of experimental design and authentication of biological resources. However, as should be evident from the current issue, time of day and circadian factors should now be elevated to a level of consideration for most all investigators going forward.

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