The role of clock genes in cardiometabolic disease

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Almost all organisms ranging from single cell bacteria to humans, exhibit a variety of behavioral, metabolic, and physiological circadian rhythms (5, 9, 12). The presence of a molecular clock within the cells of both central and peripheral tissues provides the necessary timekeeping for anticipation of daily changes in environmental/external conditions (5, 12). The molecular clock is comprised of a set of genes, referred to as “clock genes,” which generate the interlocking transcription-translation feedback loops necessary for maintenance of 24 h periodicity (5, 12, 14). Studies using rodent models in which clock genes are altered through genetic and/or environmental means implicate disruption of this molecular mechanism as a significant contributing factor in the pathogenesis of metabolic and cardiovascular diseases (4, 8, 14, 16). These observations have also been translated into human health. For example, Scheer et al. (11) recently reported that when circadian misalignment is imposed in humans there are significant changes in mean arterial blood pressure and indexes of metabolic diseases.

The cardiometabolic syndrome is characterized by a complex clustering of cardiovascular risk factors, which include obesity, insulin resistance, dysglycemia, dyslipidemia, and hypertension (1). It is believed that these cardiovascular and metabolic pathologies individually and interdependently lead to a substantial increase in cardiovascular disease morbidity and mortality, establishing the cardiometabolic syndrome as a strong risk factor for premature and severe cardiovascular disease and stroke.

The reviews included in this Highlighted Topic series were chosen to provide an overview of the state of knowledge linking the expression of clock genes with factors associated with cardiometabolic disease. Specifically we chose reviews to cover the known associations between clock genes with cardiovascular physiology and pathophysiology, the current understanding of the interplay between clock genes, metabolism, and function of peripheral tissues, with a final set of reviews selected to provide understanding of the key molecular components that likely link the circadian clock and metabolic regulation.

The first set of review articles in this series will cover the topic of the influence of clock genes on cardiovascular function and dysfunction. Young (17) provides a review of what is currently known regarding modulation of myocardial gene expression, β-adrenergic signaling, lipid metabolism, and ischemia/reperfusion tolerance by the cardiomyocyte circadian clock. The review from Rudic and Fulton (10) provides a focused look at the link between clock genes and the regulation of blood pressure with insights into hypertension and vascular disease. Sole and Martino (13) evaluate studies and provide links between the clock factors and pathogenesis of cardiovascular function with applications to human myocardial hypertrophy and heart failure.

The second set of review articles will cover the role of clock genes in peripheral tissues with links to systemic metabolic homeostasis. Zhang, Dube, and Esser (18) begin this series by summarizing recent insight into the molecular clock in skeletal muscle and known circadian changes in skeletal muscle performance and metabolism. Gimble and Floyd (3) review the state of knowledge in the area of clock genes and adipose biology. In particular, the authors discuss the interplay between the core circadian regulatory factors and adipose in the context of energy, fat, and glucose metabolism. The final review in this set is from Marcheva, Ramsey, Affinati, and Bass (7). This review discusses the growing recognition that factors regulating both circadian and metabolic systems exhibit significant overlap and that disruption to one leads to reciprocal disturbances in the other.

The third set of reviews will cover the topic of molecular links between clock genes and metabolism. This set of reviews focuses more on the identity of specific transcription factors and cofactors/activators and their interplay in both circadian and metabolic systems. Li and Lin (6) review the molecular crosstalk between metabolism and the circadian system with a particular focus on the role of the PGC-1 transcriptional coactivators. In the review from Teboul, Grechec-Cassiau, Guillamond and Delaunay (15), the role of a number of nuclear receptors, including REV-ERB, estrogen receptor, and retinoic acid receptor, are discussed as an integral part of the circadian timing system. Duez and Staels (2) focus their review on the nuclear receptor and core clock component, REV-ERBα, and discuss the contribution of this transcription factor as a critical gatekeeper that coordinates the circadian metabolic response.

We feel that this series of mini-reviews highlights the importance of the rapidly growing field of circadian biology and human health. While the focus of this series is on clock genes and cardiometabolic health we feel that the insights provided by this set of reviews have wide ranging significance for applied physiology, such as the understanding of both acute and chronic metabolic and cardiovascular responses to physical activity.

REFERENCES