Circadian clock: each tissue has its own rhythm

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Albano C. Meli received his PhD in Neurobiology at the Faculty of Pharmacy in Montpellier (France) in 2007. He then worked as a postdoctoral research scientist at Columbia University Medical Center in New York City (USA) for 4 years where he got mainly trained in basic cardiology. He was granted a European Marie-Curie Fellowship (2011) and a European Society of Cardiology grant (2012) to build up a team on human pluripotent stem cell-derived cardiomyocytes at Masaryk University Faculty of Medicine in Brno (Czech Republic). Albano was recruited as a permanent researcher by the French National Institute for Health and Medical Research (INSERM) in 2014. He has experience in basic cardiac physiology, calcium handling, ion channel biophysics as well as in human pluripotent stem cell-derived cardiomyocytes to model inherited cardiac arrhythmias. He is also a nucleus member of the Scientist of Tomorrow of the European Society of Cardiology.

Commentary on 'Diurnal transcriptome atlas of a primate across major neural and peripheral tissues' by Mure *et al.*, *Science*, 2018.[1]

Major biological functions follow a circadian rhythm, enabling organisms to adapt to daylight cycles. In 2017 the Nobel Prize in Physiology or Medicine was awarded to Jeffrey C. Hall, Michael Robash, and Michael W. Young for their achievements on elucidating the molecular mechanisms regulating the circadian rhythms. Their seminal work allowed a better understanding of the internal clock, which regulates key biological processes that oscillate during a 24-h period in animals and plants. However, this work was predominantly performed on flies and mice.

Following up on these monumental discoveries, Mure *et al.*[1] recently provided for the first-time, a detailed spatiotemporal mapping of the tissue-specific gene expression in primates (i.e. baboon or *Papio anubis*) through a 24-h period. The authors analysed a total of 768 samples, collected every 2 h, across a 24-h day. They observed that 80% of genes regulated by circadian cycle, including the so-called ubiquitously expressed genes (UEG), code for proteins involved in basic cellular functions including proteolysis, RNA processing, DNA replication and repair, protein homeostasis and metabolism. In fact, 10 989 transcripts were found to be common to all 64 analysed tissues and organs.[1] However, analysis of this transcriptome revealed high variability of other transcripts present in the tissues over 24 h.

This 10-year study revealed that the number of genes regulated by circadian mechanisms is highly specific for each tissue and far more complex than anticipated. The rhythmic transcriptome is not regulated by spatial gene expression signatures, but by organ-specific regulation. Specifically, 3000 genes were identified as being cycle-dependent in glutaeal muscle, 2318 in myocardium, and <200 in lateral hypothalamus. Two expression peaks shared a common expression pattern between the rhythmic transcriptome of the 64 diurnal baboon tissues. The predominant peak appears 6–8 h following awakening and includes more than 11 000 genes, and the second peak of ~5000 genes occurs at the beginning of the evening. This expression pattern in primates distinguishes it from the rhythmic transcriptome of mice, which are nocturnal animals. In the heart, 47% of common rhythmic genes cycle with <6-h phase difference between mouse and baboon. Furthermore, the primary circadian regulated genes (i.e. *Ciart*, *Bmal1*, and *Per*) are expressed differently with 12 h between the diurnal baboon and the nocturnal mouse.[2,3]

This study highlights the importance of tissue-specific gene expression regulation over time. The extent of rhythmic function of the primate organs is impressive. Up to two thirds of coding genes identified are

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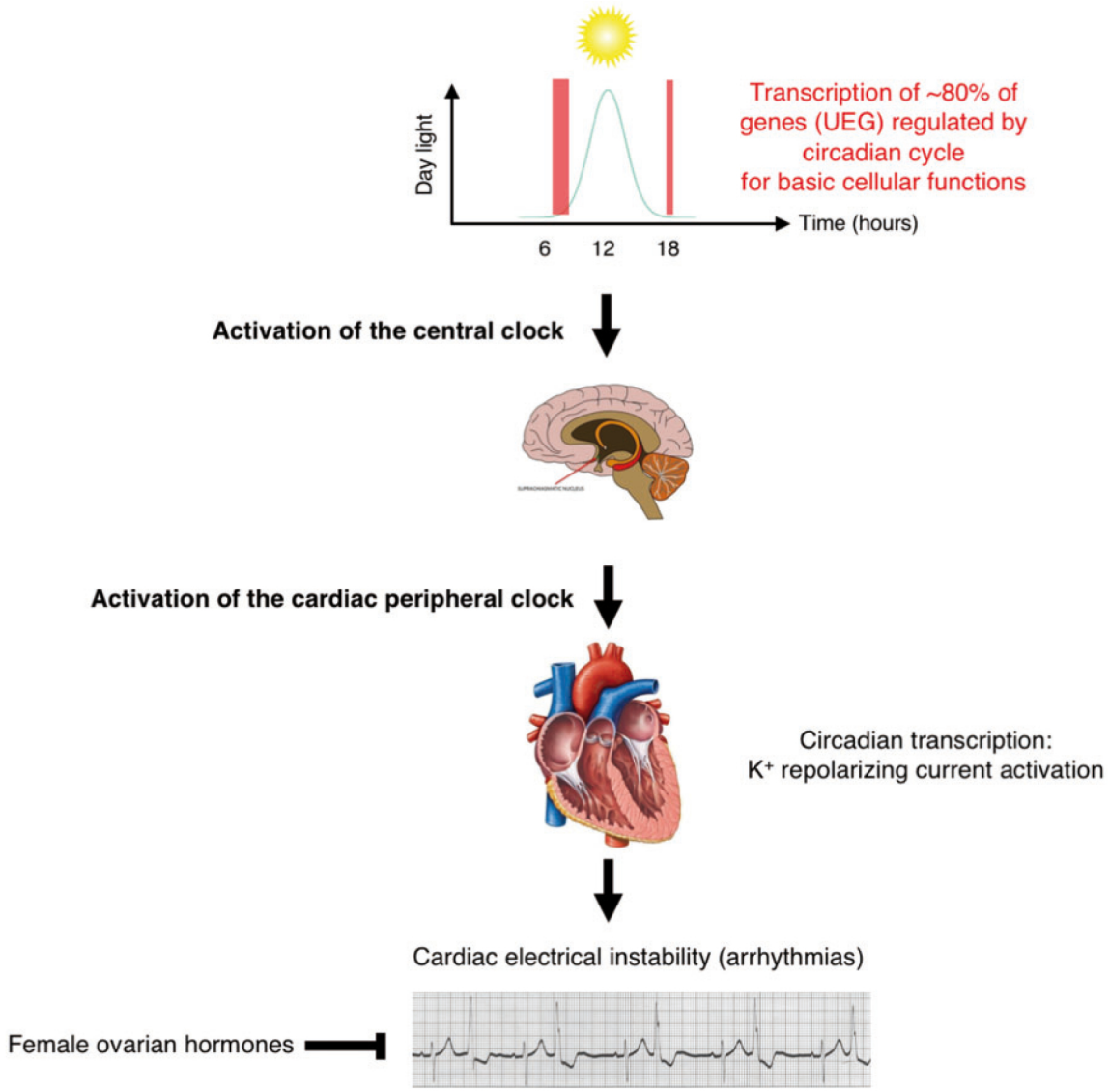

Take home figure Overview figure summarizing some of the main findings.

highly rhythmic and 82% of them code for proteins targeted by current or future therapies. These results support the importance of incorporating biological clock data of each organ/tissue when administering therapeutic drugs. Importantly, this can improve therapeutic efficacy, improve tolerability, and reduce side effects. This important work provides a chronobiologic atlas of gene activity and is available for each tissue and organ across 24 h.

The centre of the biological circadian clock is located within the hypothalamic suprachiasmatic nucleus while each organ has its own 'peripheral' clock. Heart rate, blood pressure and adrenocorticotropic system are modulated by circadian rhythmicity, with a peak in the early morning.[4] It is known that cardiovascular disorders such as myocardial infarction, stroke, and atrial and ventricular arrhythmias can exhibit temporal variation. Some of these episodes are more likely to occur in the morning, due to triggering that is dependent on diurnal secretion of catecholamines by the adrenal glands.

The occurrence of sudden cardiac death also follows a distinct diurnal pattern.[5] Jeyaraj *et al.*[6] highlighted this concept by linking circadian cycles and susceptibility to cardiac electrical instability via a clock-dependent transient outward potassium current (Ito) activation. Using a mouse model, the authors revealed a clock-dependent oscillator that regulates potassium flow out of the cardiomyocytes throughout the day which leads to diurnal variation in arrhythmias.

Mizrak *et al.*[7] reached an opposite conclusion, where cyclic electrical activity generated by the pacemaker neurons in flies modulate circadian gene expression and diurnal transcriptome to control rhythmic behaviour. Their unexpected findings revealed that electrical activity in circadian pacemaker neurons controls the circadian rhythmic transcriptome throughout the day and through the cyclic adenosine monophosphate response element-binding protein family members to regulate the circadian clock. Thus, the ways to decipher the circadian cycle regulation appears more complex.

How does understanding the biological circadian clock improve patient care? One possible answer could be from a recent study by Montaigne *et al.*[8] The authors compared outcomes over 500 days for patients who underwent morning or afternoon surgery for aortic valve replacement. Interestingly, surgery performed in the afternoon led to better outcomes with lower perioperative myocardial injury and better hypoxia-reoxygenation tolerance. These findings suggest that human myocardium exhibits an intrinsic morning-afternoon variation in ischemia/reperfusion tolerance. Using a mouse model, the authors identified the *Rev-Erbα* gene as a potential therapeutic target for cardioprotection. Hence, by considering the circadian clock and timing for cardiac surgery, physicians may be able to decrease major adverse cardiovascular events.

Sex-based differences in cardiovascular outcomes have been well-recognized. Does it have anything to do with circadian rhythm? Alibhai *et al.*[9] has identified difference in circadian clock regulation between male and female mice. In their study, the authors perturbed the circadian cycles of old mice with a genetic 'clock' mutation. Surprisingly, aging transgenic female mice which lack circadian clock function were protected from the development of age-dependent cardiomyopathy while male transgenic mice were not. However, this advantage disappeared in ovariectomized female mice, suggesting a role for female hormones in protecting the heart.

We have just started understanding the physiologic and pathologic consequences of circadian rhythmicity (*Take home figure*). The observations reported in this study on tissue-specific rhythmic regulation have large and exciting applications. However, how multiple clocks work together to give rhythm in the whole organism remains unclear. Further investigation is needed to elucidate the impact of the biological circadian clock on the effectiveness of medications and other interventions. More work is needed to study the expression profile of each gene over a 24-h period and to explore the new avenues for translating this understanding to improving patient outcomes.

Conflict of interest: none declared.

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