Changing seasons and circadian rhythms: e“miR”ging roles of miR-132/212

Samuel Fung[1], Zobia Anwer[1], Nick Lowe[1]

[1]University of Toronto, Canada

The human body is not designed to forgo sleep. The record for continued wakefulness is 11 days and 25 minutes—the equivalent of binge-watching the Titanic 81 times! Luckily, we have evolved intrinsic time-keeping mechanisms that anticipate day-night cycles. Multiple transcription-translation feedback loops (TTFLs) function ubiquitously to regulate circadian rhythms (CRs) in the 20,000 neurons of the suprachiasmatic nucleus (SCN), a central mammalian brain structure that is the central CR oscillator [1]. The SCN receives daily optic light inputs, adjusts individual neuronal oscillation phases, and orchestrates CRs globally by sending temporal information to peripheral tissues and organs [1,2].

Seasonal variations in the length of days, known as the photoperiod, can profoundly affect animal behaviour and physiology. However, the mechanisms behind SCN seasonal adaptations remain to be explored [3]. Recently, Dr. Hai-Ying (Mary) Cheng's laboratory at the University of Toronto discovered that day length variations change the SCN's timing mechanisms and neuronal morphology [3].

Dr. Cheng's laboratory discovered that the conditional knockout (cKO) of *miR-132/212*, a non-coding microRNA gene cluster that regulates post-transcriptional gene expression, impacts SCN dendrite spine morphology and proteomic landscape [3]. They also found that cKO mice adapt faster to shorter "winter" days and adapt slower to longer "summer" days, compared to wild-type mice expressing *miR-132/212* [3]. SCN expression of P*ERIOD2*, a key CR regulator, is noticeably enhanced in cKO mice during shorter days and remains tightly synchronized during longer days, unlike wild-type mice [3]. The authors suggest that deletion of *miR-132/212* changes CR regulation when manipulating day length [3].

SCN responses to environmental changes, such as crossing time zones, depend on neuronal network properties rather than individual neuron behaviour [3]. With new experiences, neuronal networks exhibit functional and structural plasticity [3]. Quantitative mass spectrometry revealed an attenuated time of day-dependent protein expression within the SCN of cKO mice [3]. Deletion of *miR-132/212* affected a group of proteins regulating cytoskeletal organization, which suggested abnormal neuronal morphology in the SCN [3]. Using morphometric analysis, the authors demonstrated that dendrite spine density in the SCN was significantly reduced in cKO mice [3]. They confirmed the link between SCN seasonal adaptation and *miR-132/212* expression using Syrian hamsters [3]. Here, *miR-132/212* levels and dendritic spine density varied according to the photoperiod [3]. Compared to longer days, shorter days elicited a decrease in *miR-132/212* levels and dendritic spine density [3].

Surprisingly, the authors found that knocking out another gene, *MeCP2*, reversed the effects of *miR-132/212* ablation by rescuing cKO dendrite spine density to levels observed in wild-type neurons [3]. The authors suggested that *miR-132/212* affected dendritic morphology by regulating *MeCP2* expression [3]. *MeCP2* is a genetic factor for autism and the causative gene for Rett syndrome, a neurodevelopmental disorder that affects females [3]. Interestingly, both disorders are characterized by strong circadian disruptions [3]. How the *miR-132/212-MeCP2* pathway contributes to circadian disturbances in these diseases remains unknown [3].

Dr. Cheng's laboratory elucidated the novel role of *miR-132/212* encoding day length information by modulating SCN neuronal architecture [3]. The findings of this research raise the possibility that structural neuronal changes strongly impact SCN plasticity across seasons [3]. This discovery sheds light on the roles of specific genes in SCN function, which may further illuminate potential therapeutics for sleep-related disorders [3].

References

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