Editorial

miRNA-211 stops the clock

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The endoplasmic reticulum (ER) is an essential mediator of cellular homeostasis and stress responses; it influences secreted protein synthesis, post-translation modification, and peptide folding (1). Environmental cues such as limited carbon sources, reduced oxygen, viral infections, metabolic imbalances, and cancer-related signaling may induce ER stress (2). ER stress results in accumulation of improperly folded proteins, and the unfolded protein response (UPR) is triggered to overcome the stress conditions (2). UPR signaling is initiated by three ER membrane-associated proteins: double-stranded RNA-dependent protein kinase PERK, the transcription factor ATF6, and the transmembrane kinase/endoribonuclease IRE1 (1). Stimulation of these transducers leads to translational attenuation, up-regulation of ER chaperones, protein degradation, and clearance of misfolded proteins by the proteasome (1). When the UPR pathway is insufficient to overcome the ER stress and fails to restore cellular homeostasis, the apoptosis system is activated (1).

Dysregulation of the UPR machinery is involved in diabetes and inflammatory and cardiovascular diseases (3). Further, the UPR has an established role in carcinogenesis and tumor progression, as it sustains proliferation and promotes resistance to cell death. The UPR is also an inducer of metabolic changes, angiogenesis, and inflammation (4).

The circadian clock controls the daily regulation of biological functions and cellular homeostasis by driving rhythmic gene expression and protein translation (5). The heterodimeric transcription factors CLOCK and BMAL1 are the main coordinators of the circadian clock (5), and their mis-regulation, which leads to desynchronization of cellular rhythms, has been linked to metabolic pathologies (6) and cancer progression (7).

Although the UPR and the circadian clock serve similar physiological functions as cellular homeostasis keepers, whether or not there is a crosstalk between the circadian clock and the UPR is not clear. It was previously shown that the circadian clock rhythmically activates IRE1a to facilitate liver metabolism (8). A reciprocal relationship between the two systems, by which ER stress influences the clock, had not been demonstrated until recently when Bu *et al.* characterized a feedback regulation, governed by miRNA-211, from the UPR back to the circadian clock (9).

This worked started with the observation that ER stress results in a phase shift in central circadian clock regulators BMAL1 and CLOCK. A similar circadian phase shift was demonstrated in livers of *PERK* conditional knockout mice compared to wild-type mice, indicating that the circadian phase shift is PERK-dependent. Bu *et al.* found that genes downstream of the UPR exhibited a circadian oscillation pattern of expression, which strengthened their hypothesis of crosstalk between the two systems. Dark/light reversal activates UPR signaling, as demonstrated by alteration of expression in PERK-related genes, including miRNA-211 (10). It also perturbs the circadian oscillations of BMAL1 and CLOCK. Bu *et al.* hypothesized that miRNA-211 is the link between UPR and circadian oscillation. Indeed, they found that inhibition of miRNA-211 activity de-represses BMAL1 and CLOCK expression and restores circadian oscillation under the UPR condition. Further, miRNA-211 was found to directly repress the expression of both *Bmal1* and *Clock3*.

Whereas *Clock3* is repressed by miRNA-211 via the

canonical post-transcriptional mechanism, *Bmal1* is regulated at the transcriptional level. The promotor of *Bmal1* contains miRNA-211 binding seed sequences, which leads to RNA-induced transcriptional silencing (RITS) (11). RITS is a newly discovered mechanism, best characterized in yeast and plants, by which miRNAs facilitate the recruitment of epigenetic modifiers to gene promotors leading to repression of gene expression. Bu *et al.* nicely demonstrated that miRNA-211 recruits Argonaute to the *Bmal1* promotor, enhances H3K27me3 modification, and reduces RNA polymerase II occupancy, leading to transcriptional repression of *Baml1*. To prove a bi-directional communication between the UPR and circadian clock, the authors demonstrated that in response to ER stress, expression of *Bmal1* inhibits UPR-dependent protein translation inhibition.

The authors also investigated the UPR-miRNA-211-circadian axis in the context of tumorigenesis. miRNA-211 has a well-established role in various pathologies (12-14) and plays a major role in melanoma development (15-18) and in development of other types of cancer including leukemia (19), glioblastoma (20), and breast cancer (21). In Burkitt's lymphoma, a Myc-driven tumor, *Bmal1*/*Clock* and miRNA-211 expression patterns are inversely correlated. Treatment with a PERK inhibitor or anti-miRNA-211 restores circadian oscillation of *Bmal1* and *Clock* and enhances expression of metabolic genes. From a physiological perspective, Baml1 re-expression increases cell sensitivity to ER stress, resulting in cell death. Bu *et al.* nicely showed that the newly discovered axis of ER stress-miRNA-211-circadian genes is relevant in various cancers including mammary carcinoma, neuroblastoma, cervical, colon, lung, and more. Patients with relatively high *Bmal1* expression have a better survival rate than those with lower levels. The demonstration of this axis, the link between the UPR and the circadian clock, suggests new approaches to tumor therapy.

Melanoma is a melanocyte origin neoplasm, and miRNA-211 plays a key role in melanoma initiation and progression that may be related to its genomic location embedded within the intron of a lineage-restricted transporter gene (16,17). Sun exposure at a young age dramatically increases the risk for melanoma (22); however, the mechanism is not fully understood. The demonstration that miRNA-211 mediates crosstalk between the UPR and the circadian clock and is sensitive to dark/light reversal, suggests the possibility that miRNA-211 may have an as-yet uncharacterized role in melanoma initiation due to early sun exposure. Along the same lines, miRNA-211 might play a role in other light-sensitive medical conditions.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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