CIRCADIAN REGULATION

Bridge of time

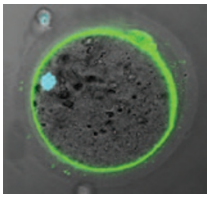
Cell **157**, 1203–1215 (2014)

The redox state of a cell is thought to be under circadian control, but the exact impact of redox regulation on the circadian clock transcriptional program remains unclear. Members of this program, Period (PER) and Cryptochrome (CRY) proteins, form a complex that represses the CLOCK/BMAL1–mediated activation of clock genes. Schmalen *et al.* determined the crystal structure of the photolyase domain of mouse CRY1 with a C-terminal fragment of PER2. Among the dimer interfaces observed, the authors identified a three-cysteine and one-histidine arrangement that coordinates a zinc ion. Interestingly, the previously reported apo-CRY1 crystal structure contained a disulfide bridge in the vicinity of the zinc interface, and CRY1 undergoes oxidation in cells. This bridge then undergoes reduction upon CRY1–PER2 complex formation. Mutation of the CRY1 residues involved in the zinc interface resulted in decreased PER2 binding, whereas loss of disulfide bond formation slightly increased PER2 binding, suggesting that the transition from the disulfide bond to zinc coordination ensures PER2–CRY1 complex formation. Consistent with this, decreased PER2–CRY1 binding resulting from the loss of the zinc interface can be rescued by preventing disulfide bond formation. Finally, zinc directly interacted with and enhanced CRY1–PER2 complex formation and was dependent on the presence of the zinc-coordinating residues for binding. The release of zinc promoted the oxidation of CRY1 and restoration of the disulfide bonds. These results provide an intriguing link between redox regulation and circadian clock activity. *GM*

RECEPTORS

Sperm meets egg

Nature **508**, 483–487 (2014)



NATURE

During mammalian fertilization, sperm are believed undergo the acrosome reaction when coming into contact with the extracellular matrix—the zona pellucida—of egg cells. This exposes the Izumo1 receptor on sperm, which is essential for recognition of the egg. Despite knowing the identity of this sperm component of the interaction, the receptor on eggs that recognizes Izumo1 has been difficult to identify. One clue about the receptor is that removing glycophosphatidylinositol (GPI) linkages from cell surface proteins renders eggs incapable of being fertilized. Bianchi *et al.* now used an Izumo1 ectodomain probe and a mouse oocyte cDNA library to identify Folr4, a member of the folate receptor family, as the egg receptor for Izumo1. Folr4, which the authors renamed 'Juno' after the Roman goddess of marriage, is GPI anchored and does not bind folate. Antibodies against Juno blocked binding of the Izumo1 probe to oocytes and blocked *in vitro* fertilization (IVF). SPR showed the Izumo1-Juno interaction to be highly transient. Female but not male *Juno*-deficient mice were infertile despite ovulating morphologically normal eggs that could be penetrated by sperm. Subsequent IVF experiments and experiments where nonfusing cells were separately transfected with the receptors suggested that the Izumo1-Juno interaction is necessary for adhesion, but not fusion, between sperm and egg. Finally, the authors found that cell-surface Juno was rapidly lost into extracellular vesicles after fertilization, providing a mechanism for the membrane block to polyspermy, the ability of eggs to regulate the fusion with one—and only one—sperm. *MB*

PHOTOCHEMISTRY

Light my way

Angew. Chem. Int. Ed. Engl.
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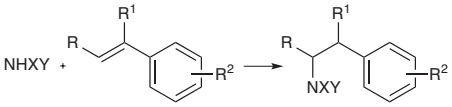

Nitrogen atoms are important mediators of biomolecular interactions, but installing them at desired positions in a chemical scaffold is not always straightforward. Previous research showed that the Fukuzumi acridinium photoredox catalyst along with a hydrogen atom donor and an appropriate light source could mediate formation of an intramolecular C-N bond at the *anti*-Markovnikov position, but the generality of this strategy was unknown. Nguyen *et al.* now substantially expand the scope to include intermolecular reactions between nitrogen-containing compounds and substituted alkenes, focusing on phenethylamines as a medicinally relevant chemical class. The authors first confirmed that the odorless solid diphenyl disulfide could be used in place of the toxic thiophenol as a hydrogen donor. Testing of alkene analogs demonstrated that variations in aryl substituents were well tolerated, with electron-rich rings reacting most quickly. Substrates featuring extensions from the β-position were also converted in good yields, including nonaromatic substrates and one bearing a free alcohol group. Sulfonamide- or Boc-substituted nitrogens were unsuccessful as nucleophiles, though several other heterocycles could be used. The complete *anti*-Markovnikov selectivity observed in these reactions suggested a mechanism in which the light source excites the acridinium catalyst, causing oxidation of the alkene to form a radical and directing attack of the nitrogen at the less-substituted position. This study provides a compelling use of light to access chemically challenging materials. *CG*

ION CHANNEL SIGNALING

Kinase cut-and-run

Cell **157**, 1061–1072 (2014)

TRPM7, an essential cation-conducting channel that is involved in embryonic development, is unusual in having a C-terminal serine/threonine kinase domain with an unknown function. A new study by Krapivinsky *et al.* now reveals that the kinase domain is cleaved from the membrane channel and acts in the nucleus by phosphorylation of chromatin proteins. Examination of the expression levels of TRPM7 across cell and tissue types identified specific proteolytic fragments of TRPM7 that were localized to the nuclei of cells and contained an active kinase domain (M7CK). Affinity purification and co-immunoprecipitation revealed that M7CKs bind to but do not appear to phosphorylate several nuclear proteins involved in chromatin remodeling, including RYBP, a zinc-finger protein. These M7CK–chromatin protein complexes lead to phosphorylation of Ser10 of histone H3 (H3S10p), either directly or in concert with other kinases. H3S10p modification perturbs the abundance of other histone marks and leads to specific regulation of TRPM7-responsive genes. To relate channel function to this nuclear role of M7CKs, the authors showed that TRPM7 actively increases cytoplasmic Zn^{2+} concentrations and that M7CK binding to RYBP and other zinc finger–containing proteins was Zn^{2+} dependent. Though the proteases involved in M7CK release remain uncharacterized and may vary by cell type, the current study suggests a new mechanism to transmit ion channel signals at the membrane to rapid changes in gene expression in the nucleus. *TLS*