acid produces a fusogenic lipid, or instead functions to recruit Mfn1, Mfn2 or OPA1 to sites of fusion. Experiments with isolated mitochondria will also be critical to resolve whether MitoPLD dimers function in *cis* or *trans*. Interestingly, despite a number of genetic, genomic and proteomic studies, yeast mitochondria do not seem to contain a MitoPLD-like protein. If generation of phosphatidic acid is truly a fundamental step in the all mitochondrial fusion pathways, then either the yeast MitoPLD awaits discovery, or yeast cells generate phosphatidic acid from a lipid other than cardiolipin. Regardless, the discovery of mammalian MitoPLD suggests that despite carrying a unique repertoire of fusion proteins, the basic mechanism of mitochondrial fusion is surprisingly similar to fusion mechanism(s) used by other organelles. □

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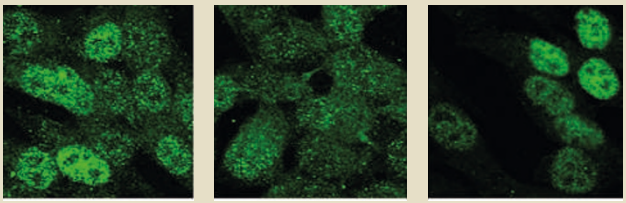
PERing in their sleep

Why are some of us 'night owls' and others 'early birds'? In a report published in *Genes & Development* (**20**, 2660–2672; 2006), Achim Kramer and colleagues address mechanisms underlying the genetic predisposition to dramatic shifts in sleep–wake patterns.

Sleep–wake cycles are regulated by circadian clocks, the internal oscillators that respond to changing environmental cues, such as light and temperature. In patients with familial advanced sleep-phase syndrome (FASPS), the sleep phase is shifted ahead every day so it occurs 4–5 h earlier than in normal individuals. Patients not only go to bed unusually early, but also wake up very early. Previous work had shown that a single point mutation in human PER2, a protein known to be important in controlling circadian rhythm, or in the gene encoding casein kinase Iδ (CKIδ), are associated with FASPS. How either of these mutations results in changes in circadian period was unclear.

Using mouse PER2 as their model, the authors demonstrated that PER2 is extensively phosphorylated *in vivo*, including at Ser 659, which corresponds to the Ser 662 residue that is mutated in FASPS patients. Expression of mutant PER2 where Ser 659 has been mutated to glycine in oscillating cultured cells that also express endogenous PER2 phenocopied the shift in phase observed in FASPS. The authors found that the FASPS-associated mutation led to rapid clearance of PER2 from the nucleus and its subsequent degradation in the cytoplasm. Both effects could be rescued by mutating Ser 659 to asparagine to mimic the phosphorylated state. These data indicated that a phosphorylation defect at Ser 662 of human PER2 is likely to underlie the FASPS phenotype. The authors speculate that PER2 phosphorylation at the FASPS site determines the dynamics of nuclear accumulation of the PER2 protein. A lack of phosphorylation leads to premature nuclear clearance and hence, to earlier release of transcriptional repression. In contrast, CKIε/δ-dependent PER2 phosphorylation at other sites leads to PER2 degradation, therefore, this second phosphorylation event is antagonistic to phosphorylation at the FASPS-associated residue.



The FASPS^{S659G} mutation but not S659N leads to an accelerated nuclear clearance of the PER2 protein (green) in oscillating fibroblasts.

It has been known for some time that mutations in DOUBLETIME, the *Drosophila* homologue of CKIε, can not only shorten but also lengthen the circadian period in flies depending on the specific mutant allele. A *CKIε* mutation in the hamster called *tau* also shortens the circadian period. At least *in vitro*, all three *CKIε* alleles have reduced kinase activity. So, how can they have opposite effects on the length of the circadian period? Using mathematical modelling supported by experimental validation, the authors suggest that specific perturbations of either one or both PER2 phosphorylation events by CKIε may account for the opposite phenotypes of *CKIε* mutant alleles.

By unravelling the complex set of crossregulatory interactions that characterize the circadian clock, this study provides molecular insights into a genetic disorder that results in compulsive early birds.

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