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Seeing the light

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Despite the enormous progress that has been made in recent years towards unravelling the autoregulatory transcriptional feedback loops that underlie circadian rhythms in organisms ranging from cyanobacteria to man, many mysteries remain. As discussed at the Novartis Foundation Symposiumon 'Molecular clocks and light signalling' in London this week, not least among the unknown factors for many organisms is the identity of the photopigment that transmits signals about light and dark in such a way that each organisms' internal circadian clock becomes synchronized with night and day.

In mammals, evidence from mice lacking rod and cone photoreceptors crystallised the view that there must be a photo pigment other than rhodospin that signals to the circadian clock. Prime candidates include the cryptochromes, homologs of blue-light receptors in *Arabidopsis* and circadian photoreceptors in the *Drosophila*brain, and melanopsin, which is a member of the same family as rhodospin but is found in retinal cells that are quite distinct from the rods and cones that underlie image-based vision. It is not yet possible to identify either one as the definitive mammalian circadian photopigment, however.

Mice lacking both cryptochrome genes behave normally when housed in daily cycles of light and dark but display no circadian rhythms of behaviour when kept in constant darkness, implicating cryptochromes in circadian photoreception (Russell van Gelder, Washington University School of Medicine, St Louis, USA). Yet the spectrum of light that is optimally active in eliciting non-rhodopsin-based circadian responses is quite distinct from that of flavoproteins such as cryptochrome (Russell Foster, Imperial College. London, UK). A novel opsin, VA-opsin, may underlie non-retinal photoreception in teleosts, but such an opsin has not (at least as yet) been found in mammals. Melanopsin certainly seems to have a role in circadian rhythmicity, and is found in retinal cells that respond to light, yet it has not been definitively shown to function as a signal-transducing photopigment, and it remains possible that melanopsin will prove to function on the circadian light-sensing pathway in some other way than as a signalling photosensor - perhaps as a photoisomerase, like some other members of the opsin family.

Although eagerly anticipated melanopsin-knockout mice may shed light on this thorny issue, experience with studies of other molecules on circadian pathways suggests that multiple, somewhat redundant components are each able to operate and compensate for one another under slightly different conditions. It is therefore likely that debate will rage until all possible components are identified and analysed in mammals, following the completion of mouse and human genome sequences. The good news is that at least for *Neurospora*, a fungus that has served as a stalwart of circadian studies for many decades, the photoreceptor has been definitively identified as White Collar 1, a DNA-binding transcription factor that is also directly light-sensitive (Jay Dunlap, Dartmouth Medical School, Hanover, USA).

The meeting proceedings will be published as a book by John Wiley & Sons Ltd. In spring of 2003.

References

1. Molecular bases of circadian rhythms. Harmer SL, Panda S, Kay SA. *Annu Rev Cell Dev Biol* 2001, 17:215-53.

2. The Novartis Foundation, [http://www.novartisfound.org.uk]

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