GENE EXPRESSION

Clockwork conductor

Clk
http://flybase.bio.indiana.edu/.bin/fbidq.html?FBgn0023076

tim
http://flybase.bio.indiana.edu/.bin/fbidq.html?FBgn0014396

cry
http://flybase.bio.indiana.edu/.bin/fbidq.html?FBgn0025680

per
http://flybase.bio.indiana.edu/.bin/fbidq.html?FBgn0003068

ey
http://flybase.bio.indiana.edu/.bin/fbidq.html?FBgn0005558

Teamwork is all very well but some intricate tasks, such as the performance of a symphony, need a leader to ensure that all participants start and stop at the right times. Now, new work shows that the symphonic complexities of circadian rhythmicity fall into this category, and, in this case, the transcriptional activator Clock (Clk) is the maestro waving the baton.

Circadian rhythms are amazingly widespread: they affect behaviour, physiology and gene expression in many different tissues, from *Drosophila* to human. In *Drosophila*, a complex series of interdependent feedback loops is involved in circadian gene expression. *Clk* has a role as both transcriptional activator and inhibitor in these loops, and might be the limiting factor for the crucial CLK/CYC heterodimer. This last role marked *Clk* as a potential 'master' circadian control gene.

In their recent study, published in *Cell*, J. Zhao and colleagues performed an ingenious test of this hypothesis. They focused their efforts on the fly brain, in which *Clk*-expressing cells are uncommon but vital for controlling the most prominent circadian rhythm in flies: the daily cycle of rest and activity.

The authors fused binding sites for the yeast transcription factor GAL4 upstream of *Clk* cDNA and, using a GAL4 driver, were subsequently able to misexpress *Clk* in brain cells that did not normally express clock genes. Not only did this misexpression induce circadian gene expression of *timeless* (*tim*), a clock gene directly regulated by *Clk*, but also of *cryptochrome* (*cry*), a gene with a rhythmic expression pattern that is the inverse of that of *tim* and is normally repressed by *Clk*: clear evidence that *Clk* expression was sufficient to induce an ectopic circadian clock.

Transgenic flies in which misexpressed *Clk* induced an ectopic circadian clock had patterns of activity during light–dark cycles that were notably different from those of wild-type flies: instead of two peaks of activity in the morning and evening they had a single daytime peak. So, these data indicate that ectopic clocks generated by misexpressed *Clk* can directly affect circadian rhythms in behaviour.

Zhao *et al.* took this work one step further. They showed that another important clock gene, *period* (*per*), when ectopically expressed in the same way as *Clk*, could not induce rhythmic expression of *tim*. So, it seems that only *Clk* can induce an ectopic circadian clock.

The identification of *Clk* as a master controller in flies has widespread implications. The mammalian system that controls circadian rhythm is similar to that of *Drosophila*, so the mammalian *Clk* orthologue might be equally important.

Even more interesting is the similarity between this discovery and that of master genes that control development, such as *eyeless* (*ey*). Will most complex regulatory networks, including those that underlie complex behaviours, perhaps turn out to have 'conductors' that are sufficient to initiate and organize the performance of the whole programme?

Nick Campbell, Associate Editor,
Nature Reviews Genetics

References and links

ORIGINAL RESEARCH PAPER Zhao, J. *et al. Drosophila* Clock can generate ectopic circadian clocks. *Cell* **113**, 755–766 (2003)
FURTHER READING Young, M. & Kay, S. Time zones: a comparative genetics of circadian clocks. *Nature Rev. Genet.* **2**, 702–715 (2001)