determine gene function on a genome-wide scale, as recently shown in *C. elegans*. The findings of Elbashir *et al.* have important consequences for those investigating gene function in mammalian cells. But before these applications become practical in mammalian systems, it will be essential to establish easy and efficient ways of delivering siRNA into mammalian cells and rapid phenotypic screens. Questions regarding the biological role of endogenous dsRNAs in gene regulation also remain to be answered.

Magdalena Skipper

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BEHAVIOURAL GENETICS

Watching the clock

The identification of the *Drosophila period* (*per*) locus — published in 1971 by Ronald Konopka and Seymour Benzer — was a singular landmark in behavioural genetics research. They were the first to show that genetics could be used to dissect behaviour, in this case the internal clock, or circadian rhythm, that underlies many aspects of behaviour in diverse organisms. Since then, many more genes involved in circadian rhythms have been identified (at least nine in mammals); the basic molecular mechanism of the clock has been defined; and the general features of the clock are known to be conserved in most living organisms. But little is known about the connections between the cellular workings of the clock and the patterns of behaviour that it influences. Two new studies provide valuable insights into how such knowledge might be obtained.

The study by Zheng *et al.* begins with an analysis of the mouse gene *Per* (*mPer1*) — one of three mammalian *per* homologues. By knocking out *Per*, the authors show that its clock functions differ from those of *Per2* (*mPer2*). This reinforces the idea that the core mechanism of the mammalian clock is more complex than in *Drosophila*. To investigate further the different roles of *Per* and *Per2*, the authors used microarray studies to identify genes that might be regulated by the clock in *Per*, *Per2* and double-knockout mutants. They found 16 genes with reproducible circadian expression that was dependent on *Per*, *Per2*, or both genes. Two genes in particular showed circadian expression and were dependent on both *Per* and *Per2*: *Alas1* and *Alas2*, which encode rate-limiting enzymes involved in haem

biosynthesis. Because haem is an essential part of many proteins, such as metabolic and signalling proteins, the authors speculate that the circadian regulation of these genes might feed into a range of physiological processes.

In the second study, Shimomura *et al.* used a quantitative genetics approach to identify loci that underlie the difference in circadian rhythms (as measured by wheel-running behaviour) between two inbred mouse strains. Their phenotypic analysis measured five aspects of circadian behaviour, such as the length of the circadian cycle and the phase angle of entrainment — how the onset of activity relates to the light–dark cycles. In addition to searching for independent quantitative trait loci, the authors also looked for epistatic interactions between loci, by incorporating a genome-wide search for loci that had an effect only in combination with another locus. They found 14 loci that had a significant effect on circadian behaviour, including several that interacted epistatically. Importantly, most of these loci mapped to regions outside those containing known mammalian circadian genes.

In the 30 years since *period* was first identified, geneticists have built on the sound foundations laid by the pioneers of this field, but before the vision of Benzer and his colleagues can be realized, a good deal more work needs to be done. Both of these new lines of research hold great promise for finding new genes that function somewhere between the cellular clock and its output — circadian behaviour.

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