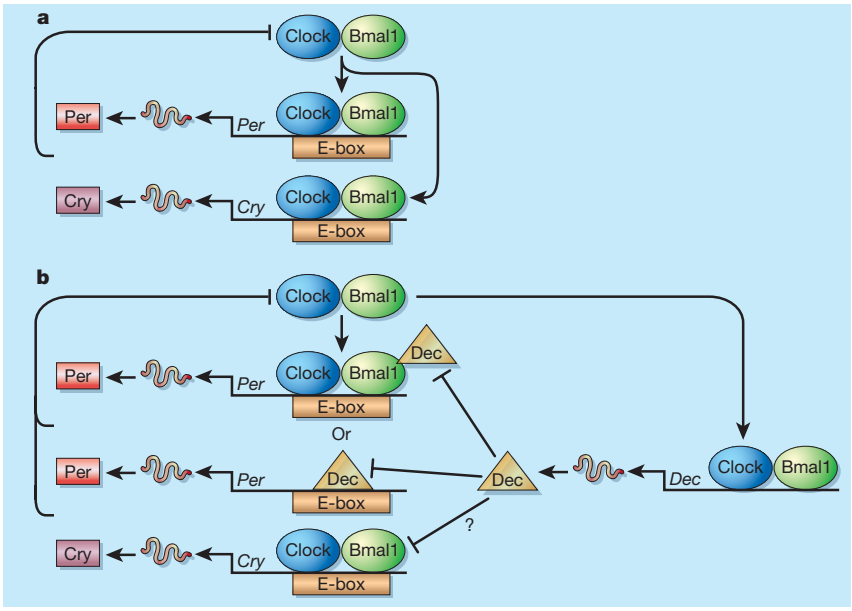

Figure 1 **The circadian clock and its regulation.** a, **The molecular basis of the clock is an oscillatory feedback loop consisting of positive and negative components. The positive components are the proteins Clock and Bmal1, which activate transcription of the negative-component genes, *Period* (*Per*) and *Cryptochrome* (*Cry*), by binding DNA sequences called E-boxes. The Per and Cry proteins repress the activity of Clock and Bmal1. Protein turnover allows the loop to restart.** b, **The Dec proteins, as described by Honma *et al.*[1], repress *Per* transcription by interfering with Clock/Bmal1 activity. The mechanism underlying this interference is not clear — Decs may bind to the E-box or to Bmal1, or to both. It is not known if they repress other genes, such as *Cry*. Transcription of *Dec* genes is reportedly activated by Clock and Bmal1.**

In mammals, the central circadian clock resides in a subset of neurons called the suprachiasmatic nucleus (SCN), which lies in the hypothalamus of the brain[2]. It is based on a cyclical feedback loop that includes two proteins, called Period (Per) and Cryptochrome (Cry)[3]. These are negative components because, when their levels are high, both proteins — but Cry in particular — repress transcription of the genes for the two proteins, resulting in decreased production of Per and Cry. The degradation of Per and Cry over time causes their levels to fall, resulting in relief of the repression and thus restarting the cycle. Both Per and Cry block the action of two positive clock components, Clock and Bmal1, which activate transcription of the *Per* and *Cry* genes. The overall result is oscillatory expression of clock genes and proteins in the SCN (Fig. 1a). Clock-gene expression also oscillates in tissues other than the SCN, so circadian clocks may occur in most organs of the body. These peripheral oscillators may tailor circadian responses to various physiological conditions, such as hunger and hormone release[4].

Honma *et al.*[1] propose that Dec1 and Dec2 are components of the core feedback loop (Fig. 1b). These proteins belong to the basic helix–loop–helix (bHLH) family, members of which dimerize with other family members and affect gene transcription by binding to specific DNA sequences called E-boxes[5]. Clock and Bmal1 are also bHLH proteins and activate transcription by binding E-boxes in the *Per* and *Cry* genes[6]. In contrast, the Decs repress transcription. Structurally, they are related to proteins found in the fruitfly *Drosophila* — Hairy and Enhancer of split — that function in neural development[7]. Honma *et al.* show that *Dec* expression is cyclic in the SCN and in other brain areas, and that Dec1 and Dec2 can strongly repress Clock/Bmal1 activation of the mouse *Per1* gene (one of three forms of *Period*). Moreover, they report that oscillatory expression of the *Dec* genes occurs in peripheral tissues.

The discovery of cyclic *Dec* transcription in the SCN is compelling. But do these genes function in the core feedback loop? Caution is needed here, because microarray experiments have identified hundreds of genes that show cyclic behaviour in the SCN[8,9]; presumably, not all of these are components of the central clock mechanism. A finding that favours a central role for the Decs is that only a small subset of genes cycle both in the SCN and in peripheral tissues, as the *Dec* genes do.

The repressive effect of the Decs on circadian transcription suggests that they are negative clock components. The oscillations in *Dec1* and *Dec2* RNA in the SCN lag slightly behind those of *Per1*, which correlates with the repressive effect on *Per1* transcription. If the Decs are indeed repressors of Clock/Bmal1-mediated transcription of *Per1*, then they would seem to be redundant given that Per and Cry — most notably Cry[10] — have the same function. Perhaps there are extra mechanisms to ensure timely repression of the positive components of the feedback loop. Alternatively, the Decs may regulate the amount of *Per1* synthesized rather than block its expression at a specific time of day. Because *Dec1* expression is upregulated following a light pulse in the middle of the night, it may be involved in the clock's response to light. Notably, *Per1* expression responds similarly to a light pulse. If *Dec1* represses *Per1* expression, it is unclear why both genes would be induced by light. Possibly, *Dec1* limits the *Per1* response and thereby the overall response of the clock to light.

Honma *et al.*[1] have produced some intriguing results. But we're left with many questions. Do the Decs merely repress Clock/Bmal1 activation of *Per1* (and perhaps other Clock/Bmal1 targets), or do they have another function within the clock? Also, how do these proteins accomplish gene repression? The Decs can interact directly with Bmal1, so these proteins may form a large complex on DNA that represses transcription. But the Decs can also bind E-boxes directly, and may inhibit Clock/Bmal1 binding to DNA. Finally, do the Decs function in peripheral clocks, as their oscillatory expression in peripheral organs would suggest? Use of gene-knockout techniques in mice may be needed to answer these questions — work that is probably already under way. ■

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correction

In Russell F. Doolittle's article "The grand assault", commenting on the genome sequence of *Plasmodium falciparum* (*Nature* **419,** 493–494; 2002), the size estimates for the *Dictyostelium discoideum* genome given in Fig. 1 were for its largest chromosome and not the entire genome — which, at around 11,000 genes and 32 megabases, is about four times larger. Labelling on the *x* axis runs as a log scale 1–10,000.