GENES AND BEHAVIOUR

Live fast, die young

Sleep deprivation, as any new parent or college student can attest, leads to considerable impairments in behaviour. Even fruitflies need to sleep, but a study published in *Nature* shows that a mutation in a potassium channel can allow them to function normally on just a third as much sleep as wild-type flies.

Clearly, sleep serves some essential function, in species from humans to *Drosophila melanogaster*. Remarkably, however, it remains unknown what this function is, or how sleep is homeostatically controlled so that the pressure to sleep increases with time awake.

The study by Cirelli and colleagues describes a mutant line of *D. melanogaster* named *minisleep* (*mns*). These flies sleep for only about one-third of the duration for which wild-type flies sleep (4–5 h compared with 9–15 h). Despite this dramatic reduction in the length of each sleep episode, the number of bouts of sleep and general periodic locomotor activity were similar to those of wild-type flies. The authors conclude that the mutation does not influence the circadian clock system, which ensures that animals sleep at appropriate times.

Surprisingly, the mutant flies seem to behave normally despite this lack of sleep, and, unlike their wild-type relatives, are not impaired by further sleep deprivation.

The mutation that leads to this unusual phenotype was found to be in a conserved region of the well-studied *Shaker* gene, which encodes a voltage-dependent potassium channel that is involved in membrane polarization and presynaptic transmitter release. Taking advantage of the powerful tools available in *D. melanogaster* genetics, the authors showed that the phenotype is specific to the *Shaker* locus and does not depend on genetic background. Furthermore, other ion channel mutations did not cause abnormal sleep phenotypes.

The results might pave the way for a greater understanding of how the need for sleep is measured and controlled, much as early genetic studies of *period* and other mutations in *D. melanogaster* led to an understanding of the circadian clock. Clearly this is just the beginning of

NEUROGENESIS

Nervous beginnings

Although proneural genes are known to regulate the differentiation, position and identity of neurons during the early development of a wide range of organisms — from flies to humans — it is unclear which genes lie immediately downstream of them. A series of experiments using transgenic mice, reported in *Development*, show, for the first time, a conclusive link between a proneural gene and its direct target, and the authors link this interaction to a specific neuronal fate.

Proneural genes encode basic helix–loop–helix (bHLH) proteins, which activate transcription by binding to the E-box regulatory sequence of their target gene. In the developing spinal cord of the mouse, cells adjacent to the roof plate express the proneural gene *Math1* and also a Bar-class homeobox gene *Mbh1*. Previous work has shown that *Math1* is involved in controlling the number of dI1 cells and commissural neurons, that dI1 cells express *Mbh1*, and that *Mbh1*-positive cells give rise to commissural neurons. However, until now, the functional relationship between the two genes and their influence on neuronal cell fate was unclear. Now Saba and colleagues have shown that *Mbh1* is a direct downstream target of MATH1 and that MBH1 confers commissural neural identity in the spinal cord.

Using a series of deletions and a *LacZ* reporter gene, the authors discovered that the *Mbh1* enhancer contains an E-box that is well conserved among mice, rats and humans, and showed that a mutation known to disrupt the binding of MATH1 to this site abolishes *Mbh1* expression. This proved that *Mbh1* expression in the dorsal spinal cord requires an E-box, as might be expected if MATH1 binds directly to regulate *Mbh1* expression. The relationship between *Mbh1* and MATH1, which was indicated by other studies, was then confirmed by knockout and overexpression studies. *Mbh1* expression was absent from *Math1*-knockout embryos, and expressing MATH1 on the sides of the dorsal cord led to the ectopic expression of *Mbh1* in these regions.

Biochemical assays reinforced the conclusion drawn from the *in vivo* experiments. An anti-MATH1 antibody specifically immunoprecipitated *Mbh1* enhancer DNA fragments that contain the E-box, thereby showing that endogenous MATH1 bound the enhancer at the binding site. Similar results were obtained for misexpressed MATH1. But what does *Mbh1* do? Evidence obtained from chimaeric proteins of MBH1 showed that the protein requires a transcriptional-activator domain to inhibit the generation of commissural neurons by MATH1, which indicates that MBH1 is a transcriptional repressor.

This is the first demonstration that an aspect of neuronal identity is determined immediately downstream of a bHLH protein, and reveals a chain of events leading to specific commissural neural identity in the spinal cord.

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References and links

ORIGINAL RESEARCH PAPER Saba, R. *et al*. Commissural neuron identity is specified by a homeodomain protein, Mbh1, that is directly downstream of Math1. *Development* **132**, 2147–2155 (2005).