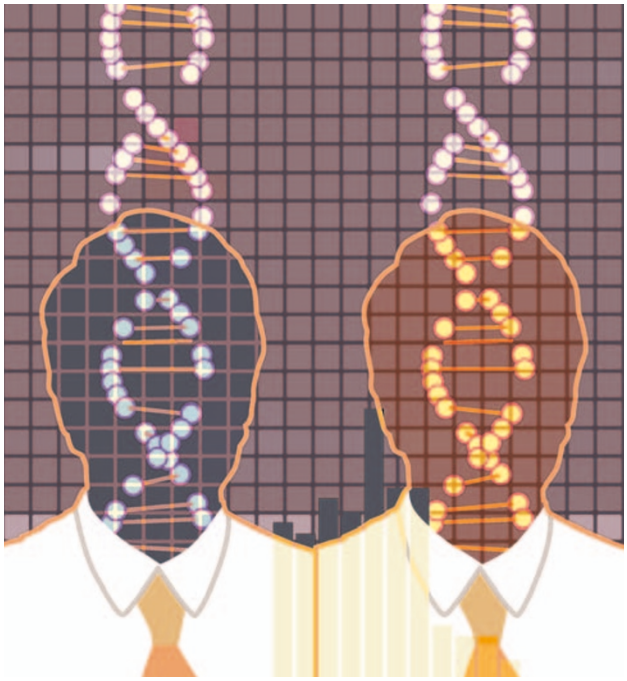
NEURODEGENERATIVE DISORDERS

Mapping multiple sclerosis genes



It is well established that multiple sclerosis is a heritable disease. Nevertheless, the susceptibility genes for this common condition have so far eluded researchers. Two studies reported in *Nature Genetics* now take us a step closer to unravelling the genetic risk factors that underlie this disorder.

The only known genomic region that has been linked to multiple sclerosis is the major histocompatibility complex (MHC) on chromosome 6, a large region that is involved in immune responses. Lincoln and colleagues used this as the starting point for their large-scale search for multiple sclerosis risk genes.

These researchers genotyped two independent samples of individuals with multiple sclerosis from Canada and Finland using a dense panel of single nucleotide polymorphisms (SNPs) that cover the MHC region. They confirmed the associations between this genomic region and multiple sclerosis. Moreover, they narrowed the candidate region to *HLA-DRB1* as the most promising susceptibility locus.

In the second study, Reich and colleagues used high-powered admixture mapping — a technique that identifies genomic regions with disease genes by exploiting differences in genetic marker frequency among different populations. Populations with combined ancestry have different frequencies of susceptibility genes that reflect the extent to which each original population has contributed to each individual's genome. As multiple sclerosis is more prevalent among European Americans than African Americans, genomic regions that contain risk genes would therefore be associated with a greater European than African contribution in African American individuals with multiple sclerosis.

Reich *et al.* studied a large group of African Americans and found a

ADDICTION

Brainwashing

For recovering addicts, the sight of drug-taking paraphernalia and other reminders of drug use can trigger intense cravings and relapses. Now, two studies report that it is possible to impair rats' memories associated with taking cocaine and that such treatments significantly reduce their drug-seeking behaviours.

Both studies are based on the belief that retrieval of some forms of memory are followed by an active 'refiling' process, known as memory reconsolidation. If this process is disrupted, memories might be weakened or even lost.

In the first study, Lee and colleagues trained rats to self-administer cocaine by nosepoking, thereby establishing a strong addiction. The animals then learned the association between nosepoking, cocaine infusion and the illumination of a light. This was followed by a 'reactivation' session, in which nosepoking resulted only in the light coming on. Before this session, the researchers blocked transcription of *Zif268* — a gene involved in reconsolidation — by infusing the antisense oligodeoxynucleotides into the amygdala. A few days later, the rats were taken to the same chamber, but this time two levers had been installed in it: pressing one lever lit the light associated with cocaine use, whereas pressing the other did nothing. Rats that had received the antisense treatment pressed the lever that illuminated the light significantly fewer times than their control counterparts.

In the second study, Miller and Marshall used the model of conditioned place preference, in which rats learned to associate the rewarding effects of cocaine with one chamber where the drug was provided, and later preferred to stay in that chamber even when no cocaine was available. Interestingly, the researchers found that this phenomenon was associated with activation of ERK, CREB, ELK1 (a member of the ETS oncogene family) and Fos in the accumbens core, which is involved in the initiation and maintenance of drug-seeking behaviours, but not in the accumbens shell, which mediates the primary rewarding effects of drugs. Infusion of an inhibitor of the ERK pathway, U0126, into the accumbens core blocks the activation of ERK, CREB, ELK1 and Fos as well as the animals' preference for the cocaine chamber.

As only drug-related memories were being recalled when the inhibitors were given, the resulting amnesia might be specific to those memories rather than having a general effect on all memories. These findings hint at an exciting new approach that might help addicts kick the habit.

Jane Qiu

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strong association between the extent of European ancestry and multiple sclerosis around the centromere of chromosome 1. However, they did not discover admixture associations elsewhere on the genome, including the MHC region.

Although further large-scale studies will be required to reconcile these findings and to further refine our knowledge of the particular genes that confer risk for multiple sclerosis, these studies highlight promising candidates for future exploration. Moreover, the success of admixture mapping suggests that it could be a powerful tool for identifying genetic risk factors in other complex disorders.

Alison Rowan

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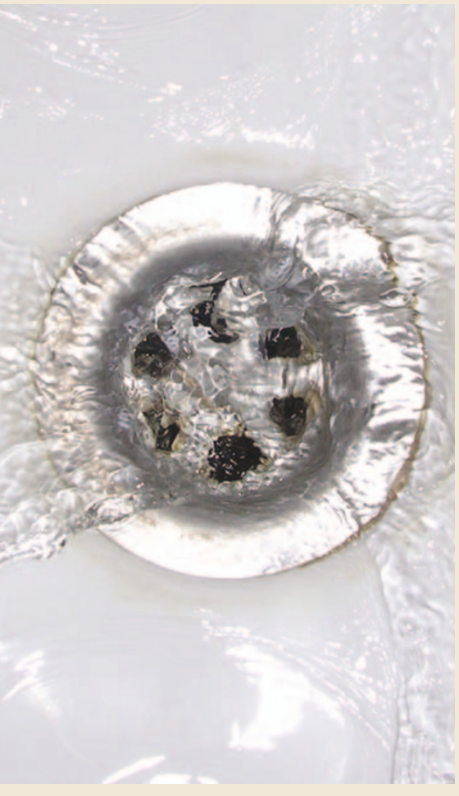

DEVELOPMENT

Throwing light on photoreceptor development

Colour vision in *Drosophila* depends on the responses of two types of colour-sensitive photoreceptor, R7 and R8. Two new studies provide important insights into the mechanisms that govern the cell fate and synaptic specificity of these neurons.

The compound eye is made up of 800 'unit eyes' or ommatidia, each of which contains eight photoreceptors (R1–R8) that project retinotopically to their targets in the optic ganglia. The centre of the unit eye is occupied by photoreceptors R7 and R8, which share the same optic path. These neurons express one of four rhodopsins — Rh3, Rh4, Rh5 or Rh6 — in three subtypes of ommatidium: p (pale), y (yellow) and DRA (dorsal rim area).

Colour vision depends on the p and y ommatidia, which discriminate long and short wavelengths, respectively. If R7 chooses the p fate, it expresses UV-sensitive Rh3 and instructs R8 to commit to the same fate, expressing the blue-sensitive Rh5. In the absence of a signal from R7, as when R7 commits to the y fate and expresses UV-sensitive Rh4, R8 defaults to the y fate and expresses the green-sensitive Rh6.

Desplan and colleagues explored the question of how R8 commits unambiguously to a p or y cell fate. They found that *warts* (*wts*, encoding large tumour suppressor, LATS) and *melted* (*melt*, encoding a pleckstrin homology (PH)-domain protein) have opposite roles in establishing pR8 or yR8 cell fates. *wts* is necessary and sufficient for yR8 specification, whereas *melt* suppresses *wts*, allowing *rh5* expression and preventing *rh6* induction. By repressing each other's transcription, *wts* and *melt* form a bistable loop that guarantees a firm commitment of R8 to a single fate. The authors propose that in the absence of an instruction from R7, the loop is biased in favour of *wts* expression, and that the system can amplify this signal to ensure that cell fate is unambiguous.

A report from Zipursky's group shows that the mechanisms underlying the synaptic specificity of photoreceptors are no less remarkable. The first step of R7 targeting requires the cell-adhesion molecule N-cadherin. Given that alternative splicing generates 12 isoforms of N-cadherin, which could explain how this widely expressed protein contributes to the differential cell recognition that leads to synaptic specificity, Zipursky and colleagues reasoned that isoform-specific mutants affecting only some N-cadherin functions probably exist.

They found that different subsets of N-cadherin isoforms act at early and late stages of R7 targeting. A mutant allele that eliminates the six isoforms containing alternative exon 18A was shown to disrupt the connections of R7 neurons. Whereas isoforms containing exon 18B were sufficient for the projection of R7 to a temporary target layer, 18A isoforms were necessary for R7 to terminate in the appropriate synaptic layer — M6 in the medulla — during the second phase of development.

These studies reveal some of the striking ways in which the cell fate and synaptic specificity of neurons are determined. They highlight the value of using relatively accessible invertebrate systems for studying the mechanisms of neurodevelopment.

Rebecca Craven

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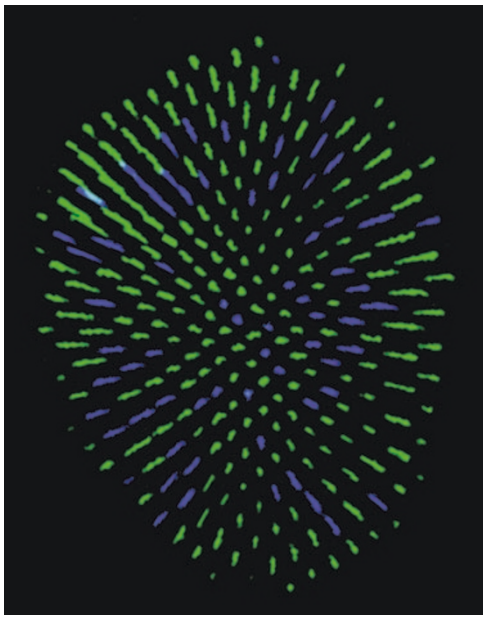

A *Drosophila* retina stained for R8 rhodopsins: blue-sensitive Rh5 (blue) and green-sensitive Rh6 (green). Image courtesy of C. Desplan, New York University, USA.