SYNAPTIC PLASTICITY

Micro-level disruption

Genome-wide association studies have linked several single-nucleotide polymorphisms (SNPs) in the non-coding region of the microRNA (miRNA) gene *mir-137* to schizophrenia, although the biological effects of variation at these sites are not known. Tsai and colleagues now show that induced human neurons with disorder-associated, minor alleles for these SNPs exhibit high levels of miR-137 and that elevated levels of this miR can impair presynaptic plasticity and hippocampus-dependent learning and memory in mice.

Four SNPs at the *mir-137* locus have been associated with schizophrenia. The authors obtained human fibroblast lines that were homozygous for either the major *mir-137* allele (that is, the most common variant in the population) or the disorder-linked, minor allele for all four SNPs. Using a cell-reprogramming strategy, they directly converted these cells to neurons and found that among the induced neurons, those harbouring the minor allele had higher levels of miR-137 than those with the major allele.

To examine the functional effects of increased miR-137 levels, the authors first explored the targets for this miRNA. From an *in silico* screen for potential miR-137 gene targets, they identified various genes with roles in presynaptic trafficking — a function not previously ascribed to miR-137, which has been implicated in dendritic development. Moreover, they found that the mRNA levels for several presynaptic proteins — namely, complexin 1, *N*-ethylmaleimide-sensitive fusion protein, synapsin 3 and synaptotagmin 1 (SYT1) — were downregulated in neuroblastoma cell lines overexpressing a miR-137 mimic and in the induced neurons harbouring the minor allele. These findings suggest that expression of the minor *mir-137* allele could affect presynaptic vesicle trafficking and synaptic transmission.

To assess the functional effects of high levels of miR-137 *in vivo*, the authors virally overexpressed this miRNA in the dentate gyrus — in which it is enriched — in 8-week-old male mice. The expression of all four of the presynaptic proteins mentioned above was subsequently reduced in this region. Moreover, electron microscopy revealed that mossy fibre terminals of the dentate gyrus granule cells had an abnormal distribution of synaptic vesicles, with more vesicles located further away from the release site, in line with a possible role for miR-137 in presynaptic function.

Recordings from hippocampal slices taken from these animals revealed reductions in the amplitude of postsynaptic responses at mossy fibre–CA3 synapses and, in response to high-frequency stimulation of granule cells, deficits in mossy fibre long-term potentiation. Moreover, the mice overexpressing miR-137 showed deficits in two hippocampus-dependent learning and memory tasks: namely, fear conditioning and the Morris water maze. Thus, high levels of miR-137 can cause deficits at the synapse and the behavioural level in mice.

Complementing the results highlighted above, expression of a miR-137 'sponge' sequence, to compete with the endogenous targets of this miRNA, markedly reversed the synaptic and behavioural deficits in miR-137-overexpressing mice. Moreover, restoring SYT1 expression alone partially rescued such deficits, providing evidence that miR-137 targeting of *Syt1* is crucial for presynaptic function.

> “These findings suggest that expression of the minor *mir-137* allele could affect presynaptic vesicle trafficking and synaptic transmission”

This study shows in mice that high levels of miR-137 can disrupt presynaptic function in the dentate gyrus and impair hippocampus-dependent learning and memory by decreasing the expression of various proteins involved in synaptic vesicle trafficking. Thus, variants of *mir-137* that lead to increased miR-137 levels may affect cognitive function through such a mechanism.

Darran Yates

ORIGINAL RESEARCH PAPER Siegert, S. *et al.* The schizophrenia risk gene product miR-137 alters presynaptic plasticity. *Nat. Neurosci.* http://dx.doi.org/10.1038/nn.4023 (2015)
FURTHER READING Issler, O. & Chen, A. Determining the role of microRNAs in psychiatric disorders. *Nat. Rev. Neurosci.* **16**, 201–212 (2015)