DEVELOPMENT

MicroRNAs mediate synapse development

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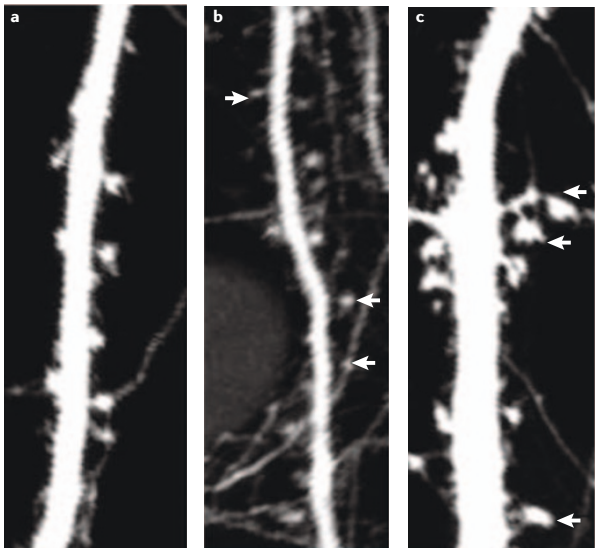
MicroRNAs (miRNAs) are small non-coding RNAs that have a key role in development in a wide variety of organisms. A team led by Michael Greenberg has now identified, for the first time, a particular miRNA — miR-134 — that is crucial for the formation of synapses.

miRNAs can regulate gene expression by attaching to mRNAs and inhibiting their translation. mRNA translation is an important aspect of synaptic development and plasticity, so it is possible that miRNAs are involved in these processes.

Schratt and co-workers investigated the expression and localization of candidate miRNAs in rat hippocampal neurons and found that miR-134 expression is confined to the brain. Intriguingly, this miRNA was more highly expressed in the hippocampus during development, and levels peaked at the time when synapses became mature. *In situ* hybridization and immunostaining revealed that miR-134 was specifically located close to synaptic sites in dendrites, implicating it in synaptic functions.



Dendritic spines in rat hippocampal neurons that express a control construct (**a**), increased levels of miR-134 (**b**) or a miRNA antisense inhibitor (**c**). Arrowheads point to examples of spines that illustrate the reduced spine size in (**b**) and the increased spine size in (**c**).

These researchers then studied the nature of miR-134 involvement in synaptic functions. They found that overexpression of miR-134 led to a marked decrease in the volume of mature spines that was attributed to a decrease in spine width, whereas inhibition of miR-134 resulted in increased volume and width of spines. These data indicate that miR-134 negatively regulates dendritic spine volume.

The next step was to understand how miR-134 influences spine volume. Schratt and colleagues isolated several mRNA targets for miR-134, and focused their explorations on *Limk1* (Lim-domain-containing protein kinase 1) as this is known to be involved in spine development. miR-134 and *Limk1* were co-localized in dendrites both *in vitro* and *in vivo*. In line with the known inhibitory effect of miRNAs on mRNAs, overexpression of miR-134 blocked translation of *Limk1* mRNA, whereas preventing miR-134 activity increased *Limk1* expression, effects that were specific to dendritic compartments. Moreover, co-expression of miR-134 with a mutant form of *Limk1* mRNA that could not bind with miR-134 rescued the decrease in spine volume, whereas the same construct with wild-type *Limk1* did not. These findings suggest that miR-134 mediates its effects on spine volume by disrupting *Limk1* mRNA translation in dendrites.

The translation of dendritic mRNAs at synaptic sites might not be activated until synaptic stimulation triggers the release of extracellular factors such as brain-derived neurotrophic factor (BDNF). Interestingly, Schratt and colleagues found that exposure to BDNF resulted in increased *Limk1* mRNA translation, which suggests that BDNF stimulation can release *Limk1* mRNA translation from inhibition by miR-134.

This comprehensive study not only pin-points a specific miRNA that is important for synaptic development, but also sheds light on its mechanism of action. The development of dendritic spines seems to depend on a fine balance between the inhibitory effect of miR-134 on *Limk1* mRNA translation and, following synaptic activity, the release of this repression by BDNF to allow development to progress. It remains to be seen whether other miRNAs and their target mRNA species are involved in the development of synapses.

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ORIGINAL RESEARCH PAPER Schratt, G. M. *et al.* A brain-specific microRNA regulates dendritic spine development. *Nature* **439**, 183–289 (2006)
FURTHER READING He, L. & Hannon, G. J. MicroRNAs: small RNAs with a big role in gene regulation. *Nature Rev. Genet.* **5**, 522–531 (2004)