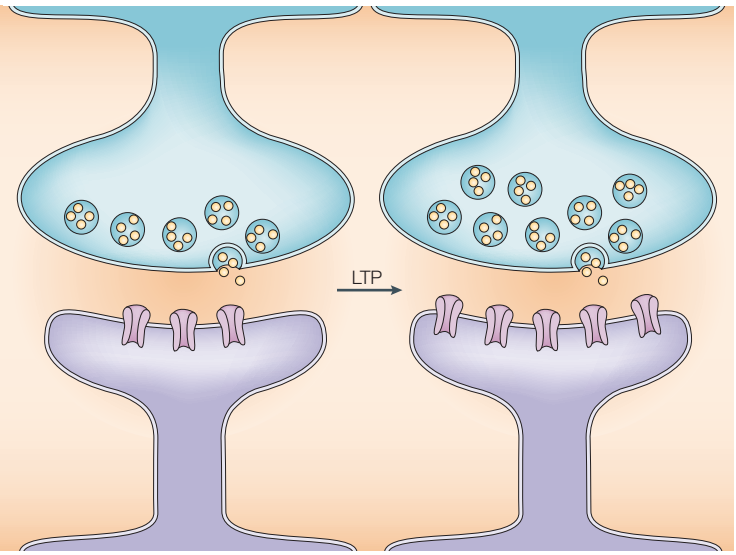
SYNAPTIC PHYSIOLOGY

Putting receptors in their place



The protein postsynaptic density 95, or PSD95, has been implicated in the control of receptor trafficking during synaptic plasticity. In *The Journal of Neuroscience*, Ehrlich and Malinow show that PSD95 controls the incorporation of AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid) receptors into the postsynaptic membrane during plasticity both *in vitro* and *in vivo*.

It was previously shown that expression of PSD95 in hippocampal neurons in slice culture could mimic long-term potentiation (LTP) by increasing the recruitment of AMPA receptors to the synapse, and that it also prevented the induction of further LTP, indicating that the two phenomena probably shared a mechanism. Now, Ehrlich and Malinow have confirmed these findings and taken them further by showing that PSD95 is also important for a different form of plasticity *in vivo*.

The authors investigated whether PSD95 was involved in experience-driven plasticity in the barrel cortex of young rats. At synapses between layer IV and layer II/III pyramidal neurons in neonatal rats, sensory experience from the whiskers causes an increase in AMPA receptors and consequently strengthens synaptic transmission. When the rats are deprived of sensory experience because their whiskers are trimmed, this recruitment process is reduced. Ehrlich and Malinow found that expression of a PSD95–GFP (green fluorescent protein) construct in barrel cortex neurons in rats with trimmed whiskers mimicked the AMPA receptor recruitment that is normally induced by sensory experience. Expression of PSD95 also occluded experience-dependent recruitment of AMPA receptors to synapses, and a dominant-negative form of the protein blocked receptor recruitment.

It is unclear how PSD95 drives the recruitment of AMPA receptors to the synapse. The authors found that mutations that prevented either its association with the cell membrane or its binding to proteins with PDZ

STEM CELLS

Matrix revolutions in 3D

Three-dimensional bioactive scaffolds hold great promise as substrates for generating tissue from stem cells *in vitro* and for promoting tissue regeneration *in vivo*. As reported in *Science*, Silva and colleagues have developed a remarkable new nanofibre matrix that assembles spontaneously when it comes into contact with cells, and can be engineered to promote neuronal differentiation.

The authors constructed a molecule called IKVAV-PA, which included the five-amino-acid motif IKVAV (isoleucine–lysine–valine–alanine–valine). This motif occurs in the extracellular matrix component laminin, and it has been shown to induce and direct the growth of neurites. The IKVAV-PA molecules carried a net negative charge, and mutual repulsion prevented them from aggregating in solution at pH 7.4. However, when they were exposed to positive ions — for example, in living tissue — they formed nanofibres and assembled into a gel-like matrix.

The authors added mouse neural progenitor cells to a solution of IKVAV-PA, prompting the formation of a matrix that encapsulated the cells. The resulting scaffold had a high water content, which allowed efficient diffusion of nutrients. A high proportion of the progenitors differentiated rapidly into neurons, as indicated by the expression of specific marker genes and neurite outgrowth. By contrast, there was little evidence of astrocytic differentiation. A control molecule — EQS-PA — in which the laminin motif was replaced by the non-physiological sequence glutamic acid–glutamine–serine (EQS), was also capable of self-assembly, but failed to induce neuronal differentiation.

Interestingly, the IKVAV-PA nanofibres were also effective at promoting neuronal differentiation when they were presented to neural progenitors as a two-dimensional substrate on a culture dish. The authors proposed that the key to the success of the matrix is the high density of IKVAV epitope that is presented to the cells, rather than the three-dimensional conformation. A soluble IKVAV peptide added to an EQS-PA matrix was far less efficient at stimulating neuronal differentiation than the IKVAV-PA scaffold, indicating that the epitope needs to be integrated into the nanofibres to be appropriately presented.

Silva *et al.* found that the matrix could also be induced to assemble if it was injected into tissue, raising the tantalizing possibility that it could be used to stimulate the regeneration of injured nerves *in vivo*. As the matrix assembles on contact with tissue, it could be injected as a fluid at the injury site, which would be far less invasive than implanting a pre-formed scaffold. Also, because the IKVAV-PA scaffold seems to suppress astrocytic differentiation, it is unlikely to exacerbate the injury by inducing glial scar formation. Further investigations should uncover the full potential of this intriguing material.

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References and links

ORIGINAL RESEARCH PAPER Silva, G. A. *et al.* Selective differentiation of neural progenitor cells by high-epitope density nanofibers. *Science* 22 January 2004 (doi:10.1126/science.1093783)

FURTHER READING Silver, J. & Miller, J. H. Regeneration beyond the glial scar. *Nature Rev. Neurosci.* **5**, 146–156 (2004)