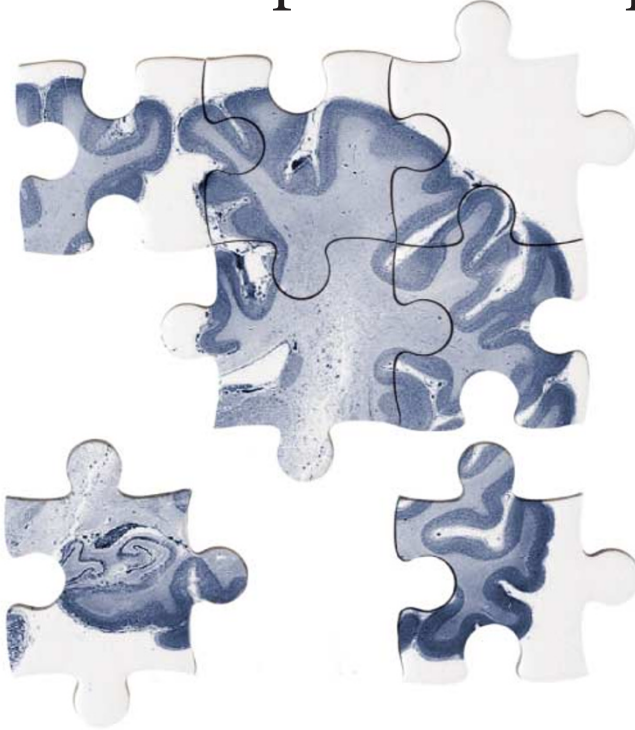


NEURODEGENERATIVE DISORDERS

Another piece of the prion puzzle



The prion hypothesis — that spongiform encephalopathies are caused and transmitted by a misfolded prion protein — has been accepted for some time, but has not yet been proved. Now, research published in *Science* takes us a step closer to proving the infectivity of prion protein. Legname *et al.* report that synthetic mammalian prions cause disease when they are transferred to transgenic mice.

Legname *et al.* used *Escherichia coli* to produce recombinant mouse prion protein (recMoPrP), which they polymerized into amyloid fibrils, creating the synthetic prions. Intracerebral injection was used to administer these synthetic prions to transgenic mice that expressed very high levels of cellular prion protein (PrP^C). The mice subsequently

developed neurological disease, although with a long incubation period of between 380 and 660 days. Control mice, inoculated with phosphate-buffered saline, did not develop symptoms of neurological dysfunction after 620 days.

The authors then took prions from the brains of mice infected with the synthetic prion and transferred them to transgenic and wild-type mice. This resulted in disease in both types of mice, and, although the incubation period was longer in wild-type mice, the incubation period in all the mice was considerably shorter than that of the mice that received the original synthetic prions.

Legname *et al.* point out that as the amino-acid sequence used in creating the synthetic prion did not contain the asparagine-linked

SYNAPTOGENESIS

New players in presynaptic organization

One of the most intriguing questions in developmental neuroscience is: how are growth cones transformed into presynaptic terminals? Retrograde signals from the postsynaptic cell are believed to be instrumental in this process, and a new study from the laboratory of Joshua Sanes has uncovered an important role for members of the fibroblast growth factor (FGF) family in presynaptic organization.

Umemori *et al.* prepared an extract from postnatal day 7 mouse forebrains, and screened this extract for molecules that could induce clustering of synaptic vesicles in the neurites of cultured chick motor neurons. They purified one of the main components of the extract that promoted vesicle clustering, and identified this component as FGF22. The FGF22-induced vesicle clusters underwent recycling in response to neuronal depolarization, implying that FGF22 was promoting the development of functional presynaptic structures.

The authors then went on to investigate whether FGF22 promotes presynaptic

differentiation *in vivo*, and they obtained several lines of evidence to indicate that this is indeed the case. FGF22 is expressed in cerebellar granule cells at the same time that they are being innervated by mossy fibres from vestibular and pontine neurons, and, in turn, the vestibular and pontine neurons express the *FGFR2* gene, which codes for the main FGF22 receptor FGFR2b. Mossy-fibre presynaptic differentiation was impaired both *in vivo* and *in vitro* when FGF22 activity was neutralized with a soluble recombinant form of FGFR2b (FGFR2bAP), and conditional deletion of the *FGFR2* gene in newborn mice produced a similar result.

FGF22 belongs to an FGF subfamily that also includes FGF7 and FGF10. All three molecules were shown to promote vesicle clustering *in vitro*, and all three bind to FGFR2b and are neutralized by FGFR2bAP. Therefore, the authors could not rule out the possibility that FGF7 and FGF10 were responsible for the effects that they observed *in vivo*. However, FGF22 is expressed at a much higher level in the cerebellum than

either FGF7 or FGF10, so it seems likely that it is the main presynaptic organizing molecule, at least in this part of the brain.

Through this work, Umemori *et al.* have not only defined a new role for postsynaptically derived FGFs in presynaptic assembly, but they have also assigned a developmental function to the FGF7/10/22 subfamily, which has not previously been implicated in neural development. The next step will be to show by more direct means that FGF22 induces presynaptic differentiation *in vivo*, and mice with mutations in the *FGF22* gene are already being generated to test this hypothesis. It will also be interesting to find out whether FGF7 and FGF10 have similar roles at other types of synapse.

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 **References and links**

ORIGINAL RESEARCH PAPER Umemori, H. *et al.* FGF22 and its close relatives are presynaptic organizing molecules in the mammalian brain. *Cell* **118**, 257–270 (2004)

FURTHER READING Ziv, N. E. & Garner, C. G. Cellular and molecular mechanisms of presynaptic assembly. *Nature Rev. Neurosci.* **5**, 385–399 (2004)