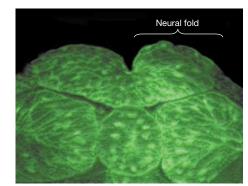
NEURULATION

The long and the short of it

In vertebrate embryos, the process of neurulation, which transforms a flat neural plate into a three-dimensionally patterned tube, relies on a sequence of morphogenetic events that are tightly coordinated with cell proliferation. Changes in cell shape cause the neuroepithelium to thicken, and the neural folds to elevate and acquire a concave profile. Continued cell shape changes and expansion of the flanking epidermis help to push the lateral edges of the neural plate together to allow fusion to occur. Writing in Development, Wallingford and Harland now highlight the importance of another process convergent extension — in neural tube closure.

Convergent extension is a twodimensional cellular rearrangement, in which a tissue elongates along one axis while simultaneously narrowing at right angles to that axis (imagine a crowd of marathon runners converging into a narrow column as they cross the starting line). The authors previously showed that in *Xenopus*, the signal transduction molecule Dishevelled (Xdsh) is required for both convergent extension and neural tube closure, but the relationship between these two events remained unclear.

Wallingford and Harland inactivated Xdsh by injecting a mutant form of the *Xdsh* gene into *Xenopus* embryos. Using histological techniques and time-lapse photography they examined the effects on neurulation.



Transverse section of a normal *Xenopus* embryo, showing elevated neural folds. Courtesy of J. Wallingford, Department of Molecular and Cell Biology, University of California, Berkeley, USA.

They found that most of the mechanisms that are involved in neurulation, including elevation and medial movement of the neural folds, still occurred normally, but in many embryos the neural tube failed to close. Interestingly, however, Xdsh function at the lateral edges of the neural folds was not necessary for neural tube closure. Rather, it seemed to function within the medial portion of the neural plate.

Evidence that convergent extension was contributing to neural tube closure came from the observation that the closure defect was associated with reduced elongation of the neural tube, and that the elevated neural folds remained further apart than in control embryos. In normal embryos, the midline marker netrin is initially expressed in a broad medial band along the anteroposterior axis of the neural plate, and this band becomes longer and narrower as neurulation proceeds. When Xdsh function was blocked, the netrin expression domain failed to undergo this change. Taken together, these findings indicate that the shaping of the midline through convergent extension is an integral part of the neural tube closure mechanism.

So, changes in neuroepithelial cell morphology and medial movements of the neural folds are insufficient to bring about neural tube closure on their own, and convergent extension can provide the additional force that is required to draw the lateral edges of the neural folds together. In humans, neural tube defects are among the most common birth defects — by increasing our understanding of the mechanisms that underlie neurulation, it should be possible to develop more effective treatments and preventive measures.

Heather Wood Performance and links ORIGINAL RESEARCH PAPER Wallingford, J. B. & Harland, R. M. Neural tube closure requires Dishevelled-dependent convergent extension of the midline. Development 129, 5815–5825 (2002) FURTHER READING Smith, J. L. & Schoenwolf, G. C. Neurulation: coming to closure. Trends Neurosci. 20, 510–517 (1997)



NEUROLOGICAL DISORDERS

A shortcut to mental retardation

New data published in *Science* points to a new mechanism to account for some cases of non-syndromic mental retardation: a mutation in the presynaptic protease neurotrypsin.

In non-syndromic mental retardation, there are no obvious neuroanatomical defects and no additional clinical features that could account for the abnormal phenotype. As the condition is so heterogeneous and there are no large pedigrees for its genetic analysis, we have limited information on the mechanisms that underlie this form of mental retardation. In the recent report, Molinari et al. studied a family in which four out of eight siblings have mental retardation, and carried out a genome-wide scan to identify any chromosomal regions of shared homozygosity in the affected children. They found a single region of chromosome 4q and homed in on the PRSS12 gene, which codes for neurotrypsin. After analysing this gene in the affected siblings, Molinari et al. discovered that they were homozygous for a 4-base-pair deletion that resulted in the production of a truncated protein. Moreover, the authors showed that a seemingly unrelated child, with a similar form of mental retardation, carried the same mutation.

Molinari *et al.* went on to investigate the pattern of neurotrypsin expression in the developing human brain. They found that the protein appears as early as 44 days of gestation, and is present in brainstem motor nuclei, cerebral cortex and hippocampus. Last, the authors analysed the subcellular distribution of neurotrypsin in the adult human brain and observed that, by contrast to most brain proteases, which are secreted and act extracellularly, neurotrypsin is located inside the presynaptic terminal.

Neurotrypsin is a poorly understood protease, the substrates and functions of which remain largely unknown. The data of Molinari *et al.* invite us to take a closer look at this enigmatic protein, not only in relation to non-syndromic mental retardation, but also regarding its role at the synapse. Their results also remind us that we need to reappraise the general involvement of proteolysis at the synapse on processes such as transmitter release and synaptic plasticity.

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(3) References and links

ORIGINAL RESEARCH PAPER Molinari, F. et al. Truncating neurotrypsin mutation in autosomal recesive nonsyndromic mental retardation. *Science* **298**, 1779–1781 (2002) FURTHER READING Wolfer, D. P. et al. Multiple roles of neurotrypsin in tissue morphogenesis and nervous system development suggested by the mRNA expression pattern. *Mol. Cell. Neurosci.* **18**, 407–433 (2001)