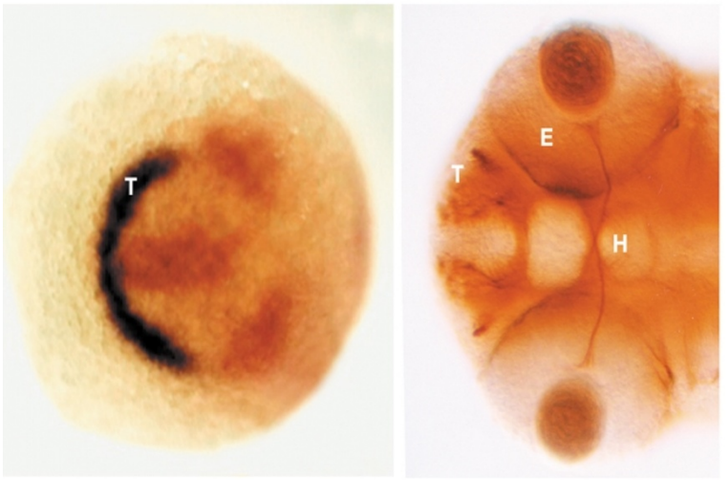
DEVELOPMENT

Tlc for the telencephalon



Left: the neural plate of a zebrafish embryo. Dark staining indicates the telencephalic territory. Right: brain of a three-day-old zebrafish stained with an antibody to show axonal pathways in the telencephalon (T), eyes (E) and hypothalamus (H). Courtesy of Corinne Houart, MRC Centre for Developmental Neurobiology, King's College London, UK.

The telencephalon is the most anterior structure to arise from the neural tube, and its development — from a simple neuroepithelium to a highly complex structure consisting of cerebral cortex and basal ganglia — has been the subject of many studies. However, an even more fundamental question still remains to be answered: how is the telencephalon induced in the first place? In a new paper in *Neuron*, Houart *et al.* provide us with some answers.

In the zebrafish, induction of the telencephalon requires signals from the anterior boundary of the neural plate (ANB). If this tissue is ablated, telencephalon-specific genetic markers fail to be activated. Conversely, transplanting the ANB to more posterior regions of the neural tube causes upregulation of telencephalic markers.

The authors identified a new gene called *tlc*, which encodes an antagonist of the Wnt signalling pathway and is expressed in the ANB at the time of telencephalic induction. They found that Tlc-expressing cells could restore telencephalic gene expression after ablation of the ANB, and that these cells could also activate these genes in more posterior regions. By contrast, overexpression of Wnt proteins inhibited telencephalic cell fates.

These results indicate that Wnt antagonism is required for induction of the telencephalon, and that Tlc can act as the antagonist. But is Tlc actually the endogenous signal that initiates telencephalic development in the zebrafish? To test this, Houart *et al.* inactivated Tlc in wild-type embryos using an antisense oligonucleotide. They found that, like ablation of the ANB, this manipulation led to a loss of early telencephalic marker-gene expression, making Tlc a strong candidate for being an important component of this endogenous signal.

CELL BIOLOGY OF THE NEURON

Recoil and retract

Axonal elongation requires the polymerization of tubulin to form microtubules. Axonal retraction is just as important as elongation in the wiring of the nervous system, but its underlying mechanisms remain obscure. A commonly held belief is that retraction involves a global depolymerization of microtubules, although the experimental evidence is not uniform in this regard. Now He *et al.* have taken a closer look at axonal retraction in culture, and have found that, instead of depolymerizing, microtubules form coiling and sinusoidal bundles as the axon shortens.

The authors used chick sensory neurons and exposed them to nitric oxide donors to elicit retraction. Morphologically, this type of axonal retraction closely resembles what is seen *in vivo*: an enlarged distal region, a thin remnant and sinusoidal bends along the axon are observed. He *et al.* used quantitative immunofluorescence methods to determine whether there was a significant decrease in the amount of microtubule polymer during this form of retraction, and found that there was no difference between control axons and those exposed to the nitric oxide donor. Instead, they found that the microtubules formed coils that seemed to follow the contours of the sinusoidal bends of the shortening axon. Furthermore, they compared this observation with the retraction that is seen in response to the microtubule-depolymerizing agent nocodazole. Morphologically, nocodazole-treated axons differed from those treated with nitric oxide: the axonal shaft withered, and abnormal 'beads' and lateral extensions formed along its length. But more importantly, microtubules were not detected, indicating that the wholesale depolymerization of tubulin is accompanied by a totally different axonal response. Last, He *et al.* tested whether axons treated with the microtubule-stabilizing agent taxol would retract in response to nitric oxide. Indeed, the axons retracted, and they showed the same coiling and sinusoidal bundles that the authors had described previously.

He *et al.* propose that the coiling of microtubules depends on alterations in the activity of axonal motor proteins, the identities of which remain to be established. In more general terms, it is interesting to compare retraction with elongation in the light of this study. Like axonal retraction, elongation was first proposed to depend strictly on tubulin polymerization, but subsequent studies showed that tubulin polymers can be transported, 'ready made', down the axon by molecular motors. It would not be surprising if, similarly, retraction involves both depolymerization and the reconfiguration of microtubules to achieve the precise wiring of the developing brain.

Juan Carlos López

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The next step will be to find out whether Tlc has functional homologues in other vertebrate species. Although it is similar in sequence to members of the mammalian sFRP family of Wnt antagonists, none of these has yet been shown to be expressed in the mammalian equivalent of the ANB. However, mutations in other Wnt antagonists, such as the mouse dickkopf gene, can cause loss of telencephalic structures. Taken together with the latest discovery, this indicates that studying the role of Wnt antagonism puts us on track for elucidating the molecular basis of telencephalic induction.

Heather Wood

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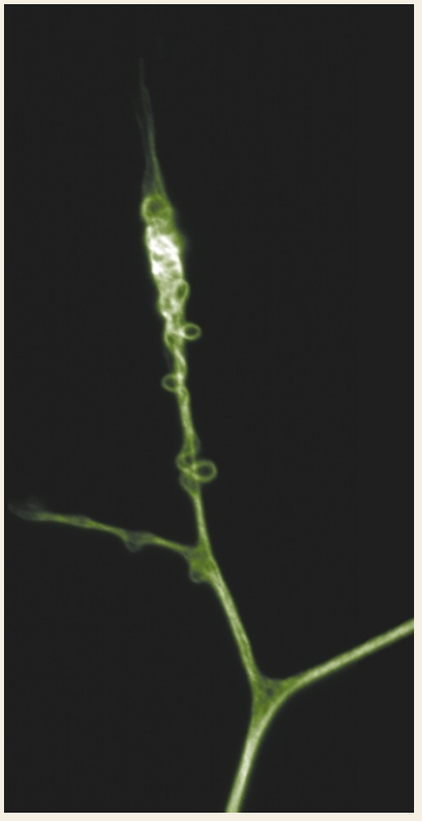
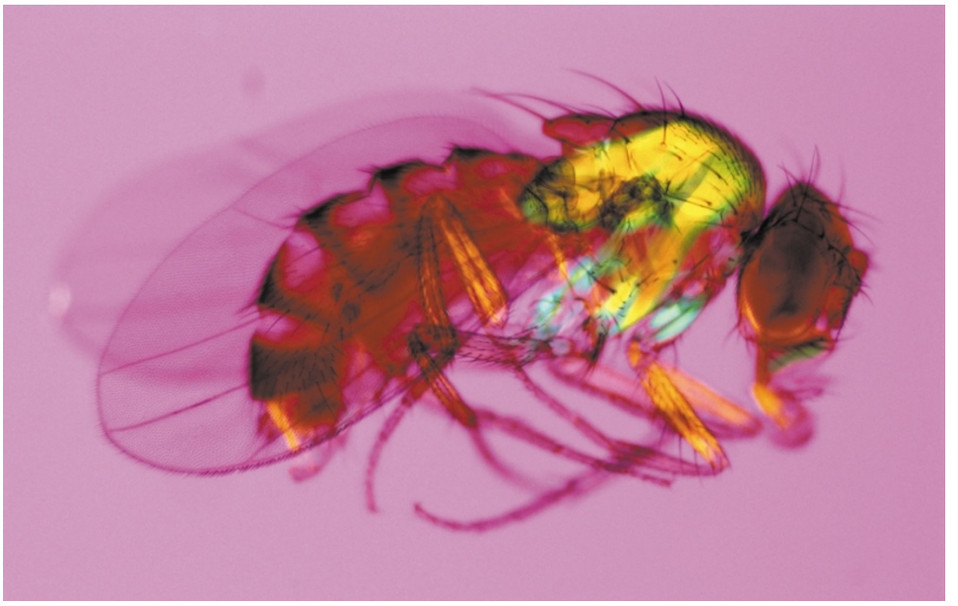


Coiling of microtubule bundles in a retracted axon. Courtesy of Peter Baas, Drexel University College of Medicine, Philadelphia, Pennsylvania, USA.



DEVELOPMENT

Sox, flies and neurogenesis

The Sox genes encode a family of DNA-binding proteins, and they are divided into several subgroups on the basis of sequence homology. The vertebrate group B genes, *Sox1*, *Sox2* and *Sox3*, are all expressed in the neural tube from the early stages of its development, but their roles in early neural development remain unclear. Now, Buescher *et al.* and Overton *et al.* report in *Development* that the fruitfly *Drosophila melanogaster* could provide some clues.

In the *Drosophila* neuroectoderm, the neuronal precursor cells, or neuroblasts, arise from proneural clusters, which are arrayed along three longitudinal stripes on each side of the embryo. From each cluster, one cell is singled out to become a neuroblast, and lateral inhibition prevents the rest from adopting a neuronal fate. The clusters are specified by proneural genes, including *achaete* (*ac*). The dorsoventral patterning genes *ventral nerve cord defective* (*vnd*), *intermediate neuroblasts defective* (*ind*) and *muscle segment homeobox* (*msh*) confer spatial identity on the ventral, intermediate and lateral clusters, respectively.

In *Drosophila*, there are two group B Sox genes — *SoxNeuro* (*SoxN*) and *Dichaete*. *Dichaete* is expressed only in the ventral and intermediate neuroectodermal stripes, and *SoxN* is expressed throughout the neuroectoderm. Mutations in *Dichaete* cause a reduction in the numbers of ventral and intermediate neuroblasts, and in these new studies, both groups showed that mutations in *SoxN* cause specific neuroblasts to be lost from the lateral and intermediate regions. Mutating the *SoxN* gene in a *Dichaete*-negative background generated a more severe phenotype in the intermediate and ventral clusters, indicating that *Dichaete* and *SoxN* act in a partially redundant manner to control the development of neuroblasts in these domains.

To investigate the precise function of *SoxN* during neurogenesis, Buescher *et al.* asked whether it is required for the formation of proneural clusters. They found that although *ac* expression was reduced in *SoxN* mutant embryos, the initial establishment of proneural clusters was largely normal. However, in many clusters, no cells were singled out to become neuroblasts, so SoxN seems to be crucial for this step.

Buescher *et al.* also examined the interactions of *SoxN* with the patterning genes *vnd* or *ind*. In a mutant strain in which *SoxN* function was only partially lost, the additional loss of one copy of *vnd* or *ind* increased the severity of the *SoxN* mutant phenotype in the ventral and intermediate clusters, respectively. However, mutations in *SoxN* did not affect the expression of either gene. The authors concluded that SoxN might interact with Vnd and Ind to modulate their activities, but not by controlling their expression.

Much of the molecular machinery that regulates the processes of neural induction and neuronal specification has been conserved throughout evolution, so it is likely that at least some aspects of Sox gene function have been conserved too. Homologues of the proneural genes and *vnd* and *ind* have been found in vertebrates, and these genes should provide a good starting point for further investigations into the roles of the group B Sox genes in neural development.

Heather Wood

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