DEVELOPMENT

Charting neural induction

Fibroblast growth factor (FGF) signalling has been implicated in neurulation and in the induction of mesodermal cell types. How can a single signalling pathway bring about such dissimilar effects? Two recent reports in *Cell* dissect out the downstream signals that mediate the dual responses to FGF in two different species, shedding light on this fundamental embryological problem.

In the first study, Sheng *et al.* carried out a genetic screen in chick embryos, looking for genes that were differentially expressed five hours after the initiation of neural induction by FGF. This interval is needed to sensitize cells to the action of bone morphogenetic protein (BMP) antagonists, which allow ectodermal cells to adopt a neural fate by interfering with BMP signalling. The authors identified the gene *Churchill* (*Chch*), which encodes a transcription factor that is expressed with a slow time course by neural tissue in response to FGF. The functional characterization of *Chch* disclosed that it is required for the expression of the transcriptional repressor *Sip1* (*Smad-interacting protein 1*), which inhibits the expression of the mesodermal gene *brachyury*. In addition, *Chch* expression arrests the movement of epiblast cells that would otherwise migrate through the primitive streak to form mesoderm. These results indicate that the decision to adopt a neural or mesodermal fate in response to FGF is regulated in time and space by *Chch*. As this transcription factor appears rather late after the tissue is exposed to FGF, it will be of interest to identify the factors that act upstream of *Chch* to control its expression.

Bertrand *et al.*, the authors of the second paper, charted the FGF signalling pathway in the ascidian *Ciona intestinalis*, and discovered a different way in which FGF exerts its dual action. In the embryo of this organism, FGF induces animal cells to form neural tissue and vegetal cells to form mesoderm. Trying to understand the mechanism that governs this choice, the authors first mapped the regulatory elements of the *Otx* gene, the earliest known marker of ascidian neural tissue, and subsequently identified the molecules that interact with such sequences to control *Otx* expression. The authors found that expression of the endogenous gene *Fgf9/16/20* activates an enhancer of *Otx* expression through the action of the transcription factors Ets1/2 and GATAa, which can directly bind this regulatory sequence. Overexpression and knockdown experiments led Bertrand *et al.* to conclude that, whereas Ets1/2 activity regulates the expression of *Otx* in both animal and vegetal cells, the regulatory role of GATAa is limited to animal cells. So, GATAa seems to be the key factor that restricts the manifestation of the neural programme in a specific cell population. But how is GATAa targeted to the right cells in the first place? Further experiments will be required to answer this intriguing question.

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References and links

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IN THE NEWS

Going up!

We all know that drugs can get you high, and new findings presented at the Society for Neuroscience meeting indicate that this is literally true in the case of D-cycloserine. A team from the Emory University School of Medicine revealed that this antibacterial drug, which is used to treat tuberculosis, has an intriguing side effect — it helps people to overcome their fear of heights.

The researchers, led by Michael Davis, subjected people with a fear of heights to a virtual reality experience that simulated a ride in a glass elevator. At the start of the experiment, most of the patients would only go up one or two floors. Both the treated and the control patients dared to go higher after repeated exposure to the task, but D-cycloserine seemed to accelerate their progress. Davis had previously tested the drug in rats, and he concluded that it "does not dissolve fear. But … it helped them to unlearn fears faster" (*Associated Press*, 10 November 2003).

The patients' newly acquired courage translated into the real world too: "those who had taken the drug were twice as likely as those on the placebo to be going up in elevators, driving over high bridges and doing other things that fear of panic attacks had kept them from doing before the therapy" (*Associated Press*).

However, cognitive behavioural therapist David Kupfer believes that drugs are not necessarily the answer. He said "people [who go through therapy without medication] learn … that they are the powerful agent of change, not the medication" (*Associated Press*). However, he conceded that the drug might benefit those who find behavioural therapy too unpleasant, and fear researcher Mark Barad agreed that "it's likely to make people more compliant" (*Nature Science Update*, 11 November 2003).

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