DEVELOPMENT

Head start

To be or not to be, that is the question faced by cells in an early developing *Xenopus* embryo. Whether a cell's fate is to become ectoderm, mesoderm or endoderm, is determined by the end of gastrulation. Several zygotically expressed genes are known to have roles in mesoderm and endoderm induction. But so far, the only maternally expressed genes that have been identified show mesoderm-inducing properties. Research has led to the prediction that there might be a gene that prevents the ectodermal cells — fated to become neural or epidermal — from becoming mesoderm. In other words, there seems to be an early acting (maternally expressed) mesoderm inhibitor in the embryo. Until now, there have been no strong candidates. Mesoderm-inhibiting factors, such as Cereberus have only been found to be expressed zygotically at later stages in development. In the journal *Development*, Bell *et al.* describe the biological and biochemical characterization of the secreted factor Coco and propose that Coco fulfils the properties of a maternally expressed mesoderm inhibitor.

In a developing embryo, cell-fate specification occurs both directly, as expression of genes instructs induction of a cell type, and indirectly, whereby one factor causes inhibition of another factor, thereby preventing the action of the second factor on the induction of specific cell types. Examples include the *Nodal* gene *Vg1*, which induce cells to become mesoderm, and *Cerberus*, which induces neural tissue and ectoderm by blocking Nodal signals and by inhibiting the expression of mesodermal markers (such as *Xnr1*) and bone morphogenetic proteins (BMPs).

Bell *et al.* identified *Coco* in a screen for genes regulated by the TGFβ-inhibitor Smad7, and found that it shows homology to the Cerberus/Dan/Gremlin superfamily of BMP inhibitors. *In situ* hybridization and RT-PCR analysis showed that Coco is a unique member of this family of proteins as it is maternally expressed and is present in an animal–vegetal gradient in the egg. Complementary to this, the mesoderm-inducers, such as *Vg1* and *Xnr1*, are expressed in a vegetal–animal gradient. As the embryo develops, *Coco* expression becomes restricted to the animal pole, whereas Vg1 remains in the vegetal pole to induce genes such as *brachyury* that go on to characterize general mesoderm. So, the expression pattern of *Coco* has been determined, but what is its function?

In vivo and animal-cap explant injections of *Coco* mRNA in two-cell stage embryos prevents expression of mesoderm markers *brachyury* and *Fgf8* at the beginning of gastrulation, even when co-injected with BMPs, TGFβs and Wnts. The authors propose that Coco represses these mesoderm inducers by blocking BMP and TGFβ signals in the ectoderm. To elucidate the mechanism behind this effect, they injected *Coco* mRNA with the Wnt8 and the Bmp4 responsive promoters; co-injected embryos showed complete inhibition of transcriptional activation of both *Wnt8* and *Bmp4*. Coco immunoprecipitated with Bmp4 and Xnr1, further implying that Coco can directly interact with BMP/TGFβ proteins. To test the specificity of this interaction, when *Coco* was injected in the presence of another signalling molecule, fibroblast growth factor (FGF), it did not prevent mesoderm formation. So, the effect of *Coco* is not global, but is specific for selected signalling molecules.

The phenotypes of the *Xenopus* embryos that result from the overexpression of *Coco* show that it also acts as an ectodermal inducer. Embryos that were injected with *Coco* mRNA in the animal pole showed extended anterior structures and ectopic cement glands at the tadpole stage. After injection in the vegetal pole, 75% of embryos had extra head-like structures containing forebrain and midbrain tissue, with some even containing a single eye.

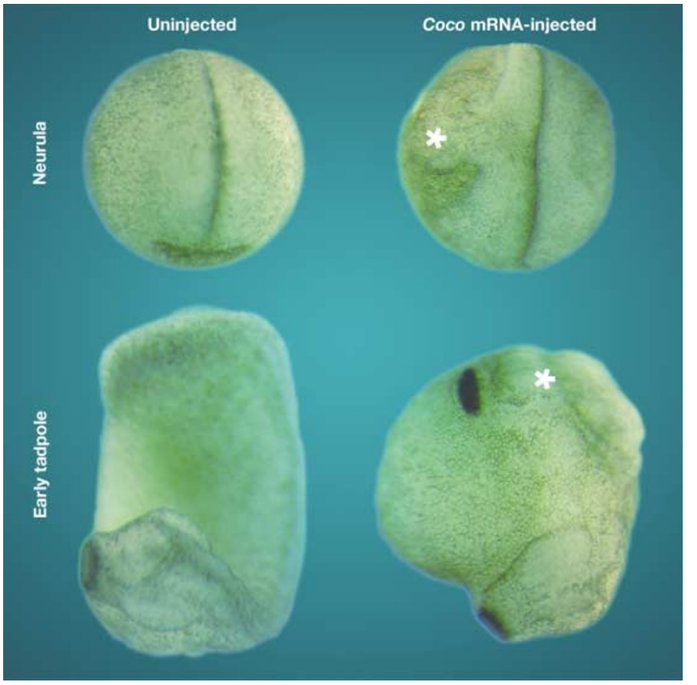
Bell *et al.* have described the biological actions of *Coco*, together with the mechanisms that might lie behind them. The next step will be to confirm these findings through loss-of-function experiments.

Emma Green

References and links

ORIGINAL RESEARCH PAPER Bell, E. *et al.* Cell fate specification and competence by Coco, a maternal BMP, TGFβ and Wnt inhibitor. *Development* **130**, 1381–1389 (2003)

FURTHER READING Muñoz-Sanjuán, I. & Brivanlou, A. H. Neural induction, the default model and embryonic stem cells. *Nature Rev. Neurosci.* **3**, 271–280 (2002)



Xenopus embryos injected with *Coco* mRNA in one cell of the four-cell stage embryo. The asterisk shows an ectopic head. Courtesy of E. Bell, Rockefeller University, New York, USA.

IN THE NEWS

Smoke signals

It is well known that a high proportion of people with schizophrenia are heavy smokers, but why should this be so? According to researchers from Toronto, the answer might be straightforward — they derive more pleasure from nicotine than the average individual.

The key is not in the schizophrenia itself, but in the dopamine-blocking drugs that are often used to treat the condition. It was previously thought that dopamine enhanced the rewarding effects of nicotine, by stimulating the ventral tegmental area (VTA). However, team leader Steve Laviolette found that the VTA is also responsible for aversion to nicotine, and that "blocking dopamine blocked the adverse effects of nicotine, but ramped up the rewarding sensations induced by the drug" (*Canadian Press*, 13 February 2003).

Investigations into α7 nicotinic receptor function, by a team in Colorado, provide evidence that smoking might even help to relieve some of the distressing symptoms of schizophrenia: "When most people hear a clock tick or a bird chirp, their brains can filter out the sounds after the first few ticks or chirps. But schizophrenics hear each of those ticks and chirps as equally loud and intrusive. Smoking heavily appears to lower these sounds a bit" (*Rocky Mountain News*, USA, 14 February).

But do the costs outweigh the benefits? Laviolette says "It's a two-edged sword. The drug is removing the psychosis but at the same time making them addicted to … extremely dangerous drugs" (*Canadian Press*). However, the Colorado team leader Cathy Adams points out that "understanding the delicate balance between the nicotinic receptor and other chemicals in the brain could lead to a medication far more effective and healthy than tobacco" (*Rocky Mountain News*).

Heather Wood