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DEVELOPMENT

A *COUP* for regionalization

There are two schools of thought on how regional identity is established in the cerebral cortex. The protomap hypothesis proposes that neurons are specified by intrinsic factors as they emerge from the ventricular zone, whereas the protocortex hypothesis favours a requirement for neuronal activity, in particular from the thalamus. Happily, we do not have to choose between these two models, as both seem to hold true for specific stages of development. Regionalization apparently occurs in two phases; the first is controlled intrinsically and occurs before thalamic innervation of the cortex. A later, activity-dependent phase refines and maintains the initial pattern. *Pax6* and *Emx2* have already been identified as intrinsic patterning factors and, as reported in *Genes and Development*, Zhou *et al.* have now implicated a third gene, *COUP-TFI*, in this process.

COUP-TFI, which encodes a nuclear receptor, is expressed in a graded (high caudolateral, low rostromedial) pattern in the neocortex from the onset of corticogenesis. By knocking out *COUP-TFI* in mice, the authors showed that this gene regulates the expression patterns of several region-specific markers in the cortex, including *Id2*, *ROR β* and cadherin 8. The expression of the other intrinsic patterning genes, *Pax6* and *Emx2*, was unaffected in the mutant brains, indicating that *COUP-TFI* acts in a separate pathway from these factors. Region-specific expression of *COUP-TFI* is maintained after birth, so it



could be involved in the maintenance as well as the establishment of regional identity.

The patterns of thalamocortical connectivity were also changed in the *COUP-TFI* mutant brain. The lateral geniculate nucleus (LGN) usually projects to the visual cortex and the ventrobasal thalamus (VB) projects to the somatosensory cortex. But axonal labelling revealed projections from the VB to the visual cortex in the *COUP-TFI* mutants. On the basis of marker gene expression, the patterning of the thalamus seemed to be unaffected, indicating that the defect lay in the axon target; that is, the cortex. One possibility is that *COUP-TFI* activates guidance cues in the cortex that direct the migration of thalamic

axons. However, Zhou *et al.* showed that the axons seem to be misdirected from the moment that they exit the internal capsule, and they consider it unlikely that diffusible molecules from the cortex could act over such a long distance.

So, Zhou *et al.* have provided a tantalizing glimpse of the role of *COUP-TFI* in cortical regionalization, but it is clear that there are many aspects of its function that are still to be discovered.

Heather Wood

References and links

ORIGINAL RESEARCH PAPER Zhou, C. *et al.* *COUP-TFI*: an intrinsic factor for early regionalization of the neocortex. *Genes Dev.* **15**, 2054–2059 (2001)

FURTHER READING Ragsdale, C. W. & Grove, E. A. Patterning the mammalian cerebral cortex. *Curr. Opin. Neurobiol.* **11**, 50–58 (2001)