RA might act through a classical receptor to facilitate spontaneous neurotransmitter release by means of a non-classical mechanism.

RA has recently been implicated in long-term synaptic plasticity in the brain, and these new findings indicate that it also regulates synaptic efficacy in the developing peripheral nervous system. Neuronal activity is important for synaptic competition and maturation at the neuromuscular junction, and for the assembly of postsynaptic structures, so RA might have an important role in regulating these processes.

Heather Wood

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DEVELOPMENT

Hoxb1's double act

The hindbrain is organized in segmental units called rhombomeres that give rise to cranial sensory ganglia and motor nuclei. Loss-of-function mutants show that *Hoxb1* is required for the development of both central and peripheral components of the developing nervous system at the level of rhombomere 4, but its precise role is still unclear. Reporting in *Genes and Development*, Arenkiel and colleagues show that *Hoxb1* is important in establishing and maintaining the VII cranial nerve circuitry between the rhombomere-born motor nuclei and the neural crest-derived branchial arch tissues.

They first conducted a genetic chimaera analysis by forming blastomere aggregates comprised of cells from both wild-type and *Hoxb1*^{-/-} embryos. The authors found that animals with high numbers of *Hoxb1*^{-/-} cells had very few of the neuronal progenitors that would normally give rise to facial branchiomotor neurons (FBMs). Interestingly, the few remaining wild-type cells that express *Hoxb1* maintain a normal developmental program. These findings indicate that *Hoxb1* is required cell autonomously for early neuronal specification.

Arenkiel *et al.* then studied the role of *Hoxb1* in peripheral tissues by using Cre/loxP-mediated conditional mutagenesis to remove the conditional allele of *Hoxb1* (*Hoxb1*^o) from specific tissues. They used two constructs, *Wnt1-Cre* and *AP2-Cre*, which targeted pre- and post-migratory neural crest cells, respectively, for Cre expression and concomitant deletion of *Hoxb1*. By removing *Hoxb1* in the pre-migratory neural crest cells, the authors reproduced null mutant phenotypes such as the failure to blink or to move whiskers, which were consistent with defects in FBM development. By contrast, there was no behavioural deficit in conditional mutants in which expression of *Hoxb1* in post-migratory neural crest cells was removed.

By comparing the number of motor neurons in *Hoxb1*^o/*Wnt1-Cre*^{+/-} mutants at different stages of embryogenesis, the authors were able to pinpoint a time when the loss of *Hoxb1* in the neural crest affected FBM development. They found that the neuron numbers in the mutants began to decrease at embryonic day (E) 14.5, when normal neuronal pruning, through apoptosis, is initiated during development. By E16.5, when cell loss is almost complete, the mutants had only a third as many motor neurons as wild-type animals. Therefore, expression of *Hoxb1* in the pre-migratory neural crest cells is important for the survival of motor neurons at a stage when neuronal elimination occurs.

The authors next investigated the developmental fates of *Hoxb1*-expressing neural crest cells. Genetic lineage analysis shows that, in adult animals, peripheral *Hoxb1* derivatives involved in FBM circuits give rise primarily to glia and that a large percentage of these glial cells are associated with the VII nerve. Interestingly, more than 95% of the FBM axons are myelinated by glia that express the same set of *Hox* genes, which is the molecular signature of cells derived from a particular rhombomere segment. This indicates that there is a correlation between motor neurons born in rhombomere 4 and the subsequent ensheathment by glia derived from the same segment.

This elegant study reveals novel functions for *Hoxb1* in FBM development and delineates the temporal and physical element of its action. The study also sheds light on how complex developmental programmes are coordinated through dynamic regulation of gene expression in multiple cell and tissue types at a given axial level. It opens doors for future research to identify downstream targets involved in this process.

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