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NEURAL DEVELOPMENT

# Relaying control of neuronal identity

Neuronal identity is established through transcriptional programmes that are initiated by 'programming' transcription factors. Despite the transient expression of these programming factors, the effector genes that they regulate are often stably expressed throughout neuronal maturation. Rhee *et al.* provide new insight into the mechanisms that underlie this process, showing that stage-specific regulation of a series of DNA enhancers by islet 1 (ISL1) contributes to the maintenance of stable effector gene expression in mouse spinal motor neurons differentiating *in vitro*.

The transcriptional programme that drives the differentiation of embryonic stem cells into spinal motor neurons is well characterized. The programming transcription factors ISL1 and LHX3 are initially co-expressed in nascent postmitotic motor neurons (after 5 days of differentiation), but LHX3 is downregulated as the neurons mature (after 6 days of differentiation). This system therefore provided an opportunity for Rhee *et al.* to investigate how stable effector gene expression can be maintained in the face of changes in the expression of programming factors.

It is known that ISL1 and LHX3 form a heterodimer that binds to the enhancers of effector genes in nascent postmitotic motor neurons to regulate their transcription. Here, the authors carried out genome-wide analysis of transcription factor binding in nascent and maturing postmitotic motor neurons. They found that downregulation of LHX3 in maturing postmitotic motor neurons correlates with displacement of ISL1 from the enhancers to which it had bound in nascent postmitotic neurons. ISL1 is subsequently recruited to an alternative set of enhancers that are occupied by clusters of the transcription factor one cut homeobox 1 (OC1). Further analysis indicated that protein–protein interactions between ISL1 and LHX3 or OC1 are responsible for the efficient recruitment of ISL1 to stage-specific subsets of enhancers. This relocation of ISL1 resulted in concomitant shifts in enhancer activation: enhancers previously bound by ISL1 in nascent postmitotic neurons exhibited a decrease in histone H3 lysine 27 acetylation (H3K27ac), whereas newly occupied enhancers in maturing motor neurons exhibited a corresponding increase in H3K27ac.

These results suggest that binding of transcription factors to and activation of particular sets of enhancers during development may be both transient and stage specific. Indeed, the authors showed that many effector genes that are associated with neuronal development were preferentially associated with enhancers showing transient patterns of transcription factor binding and activation. Reporter assays in developing chick embryos and specific deletion of enhancers that are active during either nascent or maturing stages of motor neuron differentiation showed that these 'transient' enhancers regulate gene expression in a stage-specific manner and that activation of both types of enhancer is required to maintain the expression of effector genes.

These findings support a new model for postmitotic neuronal maturation in which the control of gene expression underlying neuronal identity is passed from one set of stage-specific transcription factor-bound enhancers to another as neuronal maturation proceeds.

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“binding of transcription factors to and activation of particular sets of enhancers during development may be both transient and stage specific”

**ORIGINAL ARTICLE** Rhee, H. S. *et al.* Expression of terminal effector genes in mammalian neurons is maintained by a dynamic relay of transient enhancers. *Neuron* http://dx.doi.org/10.1016/j.neuron.2016.11.037 (2016)

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