Nature Reviews Neuroscience | AOP, published online 13 May 2015; doi:10.1038/nrn3968

GENE EXPRESSION

Converging pathways

> LRP8 processing by γ-secretase is a common step in the NMDA receptor and reelin signaling pathways

The reelin signalling pathway modulates synaptic plasticity, but it is not known whether it does so by regulating a specific pattern of transcription in neurons. Telese *et al.* now characterize enhancer regions of the mouse genome that are activated by reelin signalling, and show that proteolytic cleavage of the reelin receptor by γ-secretase is an essential step in conveying the reelin signal from the synapse to the nucleus.

The authors treated cultured mouse cortical neurons with reelin for 1 hour and found expression changes in many genes that have been associated with synaptic plasticity. Approximately one-third of the reelin target genes were also induced by NMDA receptor activation, and blocking the NMDA receptor in cultured cortical neurons prevented reelin-induced upregulation of some of these shared target genes, including that encoding brain-derived neurotrophic factor (*Bdnf*). These observations fit with previous findings that the reelin receptor — low-density lipoprotein receptor-related protein 8 (LRP8) — forms a complex with the NMDA receptor, and that reelin can modulate NMDA receptor activity.

Next, the authors used epigenetics and sequencing techniques to identify enhancer regions (DNA sequences that regulate transcription of target genes) that were activated by reelin signalling. Through genome editing, they silenced some of these enhancer regions, which resulted in decreased expression of target genes in response to NMDA receptor activation. This confirmed that these reelin-responsive enhancer regions have a direct role in the NMDA receptor-mediated transcriptional response.

Reelin stimulation also increased the formation of an intracellular domain fragment of LRP8 in neurons, which translocated to the nucleus and interacted with reelin enhancer regions. LRP8 is cleaved by γ-secretase, and the authors found that formation of this nuclear-targeted LRP8 fragment in response to reelin required the activity of this enzyme. NMDA receptor activation also increased levels of the LRP8 intracellular domain fragment, and γ-secretase inhibition prevented both reelin- and NMDA receptor-induced gene expression. This suggests that LRP8 processing by γ-secretase is a common step in the NMDA receptor and reelin signalling pathways, which results in downstream transcriptional changes.

To determine the role of these molecular pathways *in vivo*, the authors showed that mice with one mutant allele of reelin and mice lacking the gene encoding LRP8 had impaired fear conditioning responses. Furthermore, mice with one mutant reelin allele did not show the gene expression changes that typically occur in the hippocampus after fear conditioning. This suggests that reelin signalling is required for associative learning and the accompanying molecular changes that occur in the hippocampus.

Together, these findings reveal the epigenetic and transcriptional targets of reelin signalling via the NMDA receptor, and identify a γ-secretase-dependent mechanism by which the extracellular reelin signal is conveyed from the synapse to the nucleus. This molecular pathway may guide future studies on reelin function in healthy brains and in neurodevelopmental disorders in which this pathway is disrupted.

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ORIGINAL RESEARCH PAPER Telese, F. *et al.* LRP8-reelin-regulated neuronal enhancer signature underlying learning and memory formation. *Neuron* http://dx.doi.org/10.1016/j.neuron.2015.03.033 (2015)