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Isoform-specific interactions between presynaptic neurexins (NRXNs) and postsynaptic neuroligins (NLGNs) have key roles in synapse formation and function. Expanding the complexity of NRXN–NLGN interactions, Singh *et al.* now show that hevin (also known as SPARC-like protein 1), a synaptogenic protein released by astrocytes, acts as a 'bridge' between a NRXN and a NLGN that do not interact directly, and that this bridging is crucial for the formation and function of thalamocortical synapses.

Previous studies showed that hevin is required for synaptogenesis in the developing cortex and in retinal ganglion cells (RGCs), and that, in RGCs, it has both pre- and postsynaptic effects. However, its precise mechanism of action was unknown.

Singh *et al.* examined whether hevin organizes pre- and postsynaptic structures by first co-culturing rat RGCs with HEK293 cells expressing a membrane-tethered version of hevin. Synapsin 1 puncta clustered at the HEK293 cells, indicating the presence of RGC presynaptic structures. Then, the authors co-cultured RGCs with hevin-coated beads and found that these beads could bind to neuronal processes and induce the clustering of homer 1, a postsynaptic protein. Together, these data indicate that hevin organizes both pre- and postsynaptic structures.

The authors next examined whether hevin interacted with NRXNs and NLGNs, which are known to have roles in organizing presynaptic and postsynaptic compartments, respectively. Hevin co-immunoprecipitated with NLGN1, NLGN2 and NLGN3 but not NLGN4 expressed in HEK293 cells, and knockdown of *Nlgn1*, *Nlgn2* or *Nlgn3* in cultured RGCs prevented hevin-induced synaptogenesis. Moreover, hevin co-precipitated with HEK293-expressed NRXN1α but not NRXN1β, and application of an NRXN1α-specific antibody prevented hevin's synaptogenic effects on RGCs. These findings suggest that the presynaptic target of hevin is NRXN1α and that its postsynaptic targets are NLGN1, NLGN2 and NLGN3.

NLGNs can be further subdivided according to the absence or presence of a short B-splice insertion (for example, NLGN1A and NLGN1B, respectively), and this insertion can affect the ability of a NLGN to bind NRXNs. Interestingly, RGCs and their target neurons in the superior colliculus predominantly express NRXN1α and NLGN1B, respectively, but these proteins weakly bind each other, so the authors examined whether hevin acts as bridge between them. Indeed, hevin bound NLGN1B and the level of NRXN1α–NLGN1B co-immunoprecipitation increased with increasing hevin concentration. Hevin also promoted clustering of NRXN1α-expressing COS7 cells with NLGN1B-expressing RGCs, supporting hevin's role as a synaptic bridge.

The authors next examined hevin's role at thalamocortical synapses, as a previous study had found that hevin-knockout mice showed a loss of such structures. Co-culturing experiments revealed that NRXN1α expressed in thalamic neurons and NLGN1B expressed in cortical neurons were required for hevin-induced thalamocortical synaptogenesis. Moreover, *Nrxn1a*- and *Nlgn1*-knockout mice showed a loss of thalamocortical synapses, and injection of purified hevin rescued thalamocortical synapse formation in hevin-knockout animals but not in *Nlgn1*-knockout mice, suggesting that hevin bridges NRXN1α and NLGN1 *in vivo*.

Monocular deprivation during a developmental critical period can induce changes in function and anatomy in the primary visual cortex, and can lead to loss of contralateral ocular dominance. This plasticity depends on NMDA receptors (NMDARs) in thalamocortical synapses. Here, hevin-knockout mice showed a decrease in NMDAR NR1 subunit expression, and after monocular deprivation, these animals did not exhibit ocular dominance plasticity. Virally expressed hevin in visual cortex astrocytes rescued this effect, suggesting that astrocyte-produced hevin is necessary for such plasticity.

Together, these findings indicate that hevin acts as bridge between a NRXN isoform and a NLGN isoform to enable formation of certain types of synapses, and that astrocyte-derived hevin has an important role in thalamocortical synapse plasticity during neurodevelopment.

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ORIGINAL ARTICLE Singh, S. K. *et al.* Astrocytes assemble thalamocortical synapses by bridging NRX1α and NL1 via hevin. *Cell* **164**, 183–196 (2016)