SYNAPTOGENESIS

A new partner for neurexins

Synapse formation is driven by a host of different cell adhesion molecules. One of the most recent to be identified is leucine-rich repeat transmembrane neuronal protein 2 (LRRTM2). Two papers now provide details of the mechanisms by which LRRTM2 affects synaptogenesis, revealing that it acts as a ligand for neurexin 1, a receptor that is widely known for its binding to the neuroligins.

In the new studies, Ghosh and colleagues and Südhof and colleagues first confirmed and extended previous findings, showing that LRRTM2 overexpression specifically induces excitatory synapse formation in cultured hippocampal neurons, and then turned their attention to the mechanisms by which LRRTM2 promotes synaptogenesis.

LRRTM2 is localized postsynaptically, and Ghosh and colleagues discovered that it interacts with the synaptic scaffolding protein PSD95 (also known as DLG4), implicating it in the organization of the postsynaptic region. Indeed, they showed that LRRTM2 recruits glutamate receptors to the postsynaptic cell membrane: knocking down LRRTM2 using short hairpin RNA technology decreased the surface density of AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid) and NMDA (*N*-methyl-D-aspartate) receptor subunits. Consistent with this role, loss of LRRTM2 reduced the strength of AMPA and NMDA receptor-mediated postsynaptic currents in granule cells recorded from mouse hippocampal slices.

LRRTM2 also induces presynaptic differentiation in co-culture experiments: hippocampal neurons cultured with LRRTM2-expressing cells form synapses onto these cells. However, the presynaptic receptor to which the protein binds to mediate these effects was unknown. Both groups carried out affinity chromatography screens that revealed the neurexin family members to be strong candidates for LRRTM2 binding. Südhof and colleagues found that LRRTM2 bound all neurexin isoforms, and both studies highlighted particularly strong binding to neurexin 1α and neurexin 1β. Furthermore, Südhof and colleagues showed that the binding of these two neurexin isoforms to LRRTM2 was regulated by alternative splicing: the proteins bound LRRTM2 only when they lacked a particular insert at splice site 4 (variants NRX1α^{SS4-} and NRX1β^{SS4-}).

The authors examined the importance of the neurexin 1–LRRTM2 interaction for cell adhesion and presynaptic differentiation. Südhof and colleagues revealed that cell surface expression of LRRTM2 in HEK293T cells promoted their adhesion to cells expressing NRX1α^{SS4-} or NRX1β^{SS4-}. Furthermore, Ghosh and colleagues showed that knocking down the neurexin 1 gene inhibited the ability of LRRTM2 to induce presynaptic differentiation in hippocampal neurons, and Südhof and colleagues showed that recombinant soluble NRX1β^{SS4-} blocked the ability of LRRTM2 to promote synapse formation in co-culture experiments.

These studies show that LRRTM2 promotes postsynaptic and — by binding to specific splice variants of neurexin 1 — presynaptic synapse assembly. Although core details remain to be uncovered, such as which aspects of the synaptogenic process LRRTM2 contributes to, and whether there are differences in the activation and function of neurexin binding by LRRTM2 and by neuroligins, these findings provide new molecular insights into a process that is linked to several developmental disorders, including autism and schizophrenia.

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ORIGINAL RESEARCH PAPERS de Wit, J. *et al.* LRRTM2 interacts with neurexin1 and regulates excitatory synapse formation. *Neuron* **64**, 799–806 (2009) | Ko, J. *et al.* LRRTM2 functions as a neurexin ligand in promoting excitatory synapse formation. *Neuron* **64**, 791–798 (2009)
FURTHER READING Dalva, M. B., McClelland, A. C. & Kayser, M. S. Cell adhesion molecules: signalling functions at the synapse. *Nature Rev. Neurosci.* **8**, 206–220 (2007) | Linhoff, M. W. *et al.* An unbiased expression screen for synaptogenic proteins identifies the LRRTM protein family as synaptic organizers. *Neuron* **61**, 734–749 (2009).