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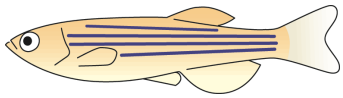

An attractive Reelin gradient establishes synaptic lamination in the vertebrate visual system

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The specificity of connections between neurons ensures proper neural circuit function and thus constitutes the basis for perception and behavior initiation. Axon-dendrite connections are often anatomically segregated into synaptic laminae, frequently devoted to specific sensory information processing. Although synaptic lamination represents a conserved organizational and functional principle of neural networks, at present a comprehensive model for their establishment remains lacking. We show that the secreted protein Reelin is critical for the cytochemical pre-patterning of synaptic laminae in the vertebrate visual system. In particular, we unveil a previously unidentified role of Reelin as a wiring molecule that coordinates targeting of growing retinal afferents via the receptor VLDLR and the intracellular transducer Dab1a. Furthermore, we find that Reelin is distributed in a concentration gradient within the target tissue and that this gradient is stabilized by heparan sulfate proteoglycans (HSPGs) in the extracellular matrix (ECM). Finally, we demonstrate that target-derived Reelin exerts an attractive effect on retinal ganglion cell (RGC) axons, enabling them to identify their specific target lamina. Almost 30 years ago, theoretical studies established that axons are steered to their correct target zone by at least two counteracting molecular forces per target axis such that axons stop along the axis where the two forces are exactly balanced. Although a recent study proposed that retinal axon lamination is influenced by repulsive Slit1 signaling, this molecular force alone cannot account for the steering of ingrowing axons toward their proper target laminae. By identifying attractive Reelin signaling as a force that counter-balances the repulsive activity of Slit1, our work provides the first experimental evidence for a comprehensive model of lamina formation in which these signals direct RGC axons toward their synaptic lamina. Notably, this mechanism may represent a general principle for neural network assembly in other species and brain areas.

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