

*The Regulatory Function of Netrin-4 and Interactions with Netrin-1 Receptors*

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Netrins, a family of laminin-related molecules, have been proposed to act as guidance cues either during nervous system development or the establishment of the vascular system. This was clearly demonstrated for netrin-1 via its interaction with the receptors DCC and UNC5. Due to shared homologies with netrin-1, netrin-4 was also proposed to play a role in neuronal outgrowth and developmental/pathological angiogenesis via interactions with netrin-1 receptors. Here we present a 3.1 Å structure of netrin-4[1], which possesses unique features in comparison to previously crystallized netrin-1[2][3], and demonstrate that netrin-4 lacks the epitopes required to bind netrin-1 receptors. We show that netrin-4 disrupts laminin networks and basement membranes through high-affinity binding to the laminin  $\gamma$ 1 chain, and hypothesize that this laminin-related function is essential for the previously described effects on axon growth promotion and angiogenesis.

[1]McDougall, M. et al. (2016). Nature Communications, 7, 13515, 1-17

[2]Grandina, M. et al. (2016). Cancer Cell, 29, 175-185

[3]Finci, L.I. et al. (2014). Neuron, 83, 839-849

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