This Week in The Journal

The Axonal Partner of Schwann Cell CADM4

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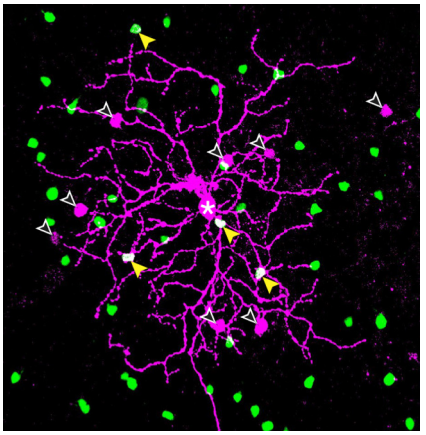
(see pages 1393–1400)

Neurite growth, synapse formation, and myelination depend on interactions between neurons and adjacent cells mediated by a variety of transmembrane proteins called cell adhesion molecules. These molecules bind to specific partners on adjacent cells and not only hold the cells together, but also recruit scaffolding, cytoskeletal, and other proteins to form specialized structures. For example, binding between two members of the CADM family, dendritic CADM1 and axonal CADM2, initiates synapse formation by inducing postsynaptic clustering of neurotransmitter receptors and presynaptic assembly of release machinery (Frei and Stoeckli, 2014, Eur J Neurosci 39:1752).

Another member of the CADM family, CADM4, is expressed in myelinating Schwann cells in the PNS. Knocking out this protein impairs myelination and the formation of specialized domains in the underlying axon, as evidenced by dispersion of Caspr (a protein involved in creating paranodal tight junctions between axons and myelin) and Kv1.2 potassium channels, which normally cluster near nodes of Ranvier. CADM4 likely interacts with one or more of the three CADM family members (CADM1–3) that are expressed in peripheral axons, but which of these is most important for organizing axonal domains has been unclear. To find out, Sukhanov et al. knocked out CADM1–3 individually and in various combinations to determine which manipulations mimicked the effect of CADM4 knockout.

Knocking out CADM1, CADM2, or CADM3 individually had no effect on the distribution of Caspr or Kv1.2 channels; knocking out all three CADMs disrupted the localization of these proteins, however. In fact, Caspr was nearly absent along the interface between axons and the inner layer of myelin in triple-knockout mice. Similar phenotypes occurred in double-knockout mice lacking CADM3 and CADM2 or CADM3 and CADM1, whereas mice lacking CADM1 and CADM2 appeared normal.

These results suggest that axonal CADM3 is the main partner of Schwann-cell CADM4, but that CADM1 and CADM2 together can compensate for the loss of CADM3 to direct formation of paranodal junctions and potassium channel clusters. Future work should determine whether *cis* interactions between CADM3 and CADM1 and/or CADM2 within the axonal membrane are required for proper myelination and should identify other interaction partners that help them create specialized paranodal domains.



When biotin was injected into an M5 ipRGC (magenta), it spread to cells coupled by gap junctions (arrowheads), including several CRH^+ amacrine cells (green). See Pottackal et al. for details.

Coupling between Photosensitive RGCs and Amacrine Cells

Joseph Pottackal, Hannah L. Walsh, Pouyan Rahmani, Kathy Zhang, Nicholas J. Justice, et al.

(see pages 1489–1504)

The retina is a remarkably complex structure. Photoreceptor output is shaped by horizontal, bipolar, and >60 types of amacrine cells before reaching retinal ganglion cells (RGCs), which transmit information about light patterns to the brain. In addition, some ganglion cells are directly activated by light, because they express melanopsin. These intrinsically photosensitive RGCs (ipRGCs) regulate the circadian clock, the pupillary light reflex, arousal, and mood, as well as contributing to image formation. Notably, ipRGCs not only transmit information to the brain, but also shape processing within the retina via chemical and electrical synapses with amacrine cells. Little is known about which specific types of amacrine cells form synapses with different types of ipRGCs, however. Mapping these connections is an important step toward understanding the role of ipRGCs in visual function.

Pottackal et al. hypothesized that ipRGCs may form electrical synapses with a type of amacrine cell that produces corticotropin-releasing hormone (CRH), because these cells extend neurites that overlap with ipRGC dendrites. Consistent with their hypothesis, CRH^+ amacrine cells were depolarized by light even when glutamate receptors were blocked. Importantly, the time course of these responses matched those of ipRGCs, and the responses were eliminated or significantly reduced by knocking out melanopsin or blocking gap junctions, respectively. Additional experiments indicated that CRH^+ amacrine cells were coupled primarily to M5-type ipRGCs, although some subtypes of CRH^+ amacrine cells were coupled with M2-type ipRGCs.

CRH^+ amacrine cells are nonspiking cells that release GABA, as well as CRH. Pottackal et al. found that stimulation of CRH^+ amacrine cells evoked inhibitory currents in M2, M4, and M5 ipRGCs. The currents in M2 cells appeared to be indirect and likely mediated by wide-field amacrine cells, which were previously shown to be inhibited by CRH^+ cells. Previous work has also shown that CRH^+ amacrine cells inhibit suppressed-by-contrast retinal ganglion cells, which are not intrinsically photosensitive. Altogether, these results suggest that electrical coupling with CRH^+ amacrine cells may allow M5 ipRGCs to exert broad influence on retinal output. The ultimate effects of this signaling remain to be determined, but one possibility is that it helps retinal circuits adapt to changes in irradiance.

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