This Week in The Journal

A New Protein in Synapse Assembly

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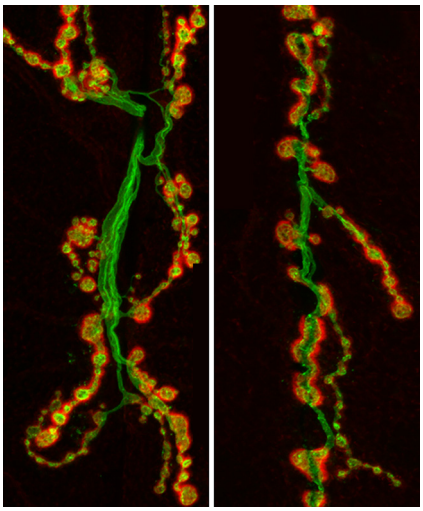
(see pages 7016–7030)

Carpenter syndrome is a rare condition characterized by abnormal development of the heart, appendages, and/or skull, sometimes accompanied by intellectual disability. Variations in two genes have been linked to different varieties of Carpenter syndrome. One gene, *Multiple Epidermal Growth Factor-Like Domains 8* (*MEGF8*), encodes a transmembrane protein that, in mice, participates in signaling via the bone morphogenetic protein (BMP) pathway and is involved in axon guidance. Chen et al. report that the *Drosophila* homolog *dMegf8* helps regulate the development of glutamatergic synapses at the neuromuscular junction (NMJ).

dMegf8 was present at NMJs in *Drosophila* larvae, and deletion of *dMegf8* reduced the number of boutons; but it also increased the number of active zones per bouton. The active zones were appropriately apposed to postsynaptic clusters of glutamate receptors, but three presynaptic proteins—the scaffolding protein Discs large (Dlg), the BMP receptor wishful thinking (wit), and the synaptic adhesion molecule neurexin (Dnrx)—were abnormally dispersed within mutant boutons. Notably, deleting either *Dnrx* or *wit* led to the dispersion of dMegf8 in presynaptic boutons. And although heterozygous deletion of *dMegf8*, *wit*, or *Dnrx* did not alter synaptic growth, heterozygous deletion of both *dMegf8* and *Dnrx* or both *dMegf8* and *wit* produced phenotypes similar to those of homozygous deletion of *dMegf8*.

In addition to changes in presynaptic structure in *dMegf8*-null animals, the amplitude of excitatory junction potentials was reduced, and both larvae and adult flies exhibited locomotor deficits. Furthermore, the postsynaptic density was longer than normal, and the structure of the subsynaptic reticulum was disrupted in muscles. Most of these deficits were rescued by expressing wild-type *dMegf8* selectively in motor neurons, but not by expressing it solely in postsynaptic muscle. In contrast, the rescue of subsynaptic reticulum structure required the expression of *dMegf8* in muscle.

These data suggest that dMegf8, wit, and Dnrx function together in *Drosophila* motor axons to regulate formation of the NMJ. dMegf8 also appears to have a role in the formation of postsynaptic structures. If dMegf8 has similar roles in the formation of glutamatergic synapses in the mammalian brain, its dysfunction might contribute to intellectual disability in people with Carpenter syndrome.



In *Drosophila* lacking dMegf8 (right), larval NMJs have fewer boutons, and expression of Dlg (red) is more dispersed than normal (left). See Chen et al., for details.

Interaction between Tau and α-Synuclein

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(see pages 7031–7046)

Many neurodegenerative diseases are characterized by aggregation of specific proteins in intracellular inclusions. Such diseases are often grouped by which protein predominates in these inclusions. For example, synucleinopathies, such as Parkinson's disease, are marked by aggregation of α-synuclein, while tauopathies, such as Pick's disease, feature aggregation of tau. These groups are not mutually exclusive, however: both tau and α-synuclein aggregate in several diseases. Moreover, mutation or overexpression of either tau or α-synuclein can lead to accumulation of the other protein in animal models. The extent to which these proteins interact in nonpathologic conditions is unclear, but Wang et al., suggest they interact to regulate cortical development.

Consistent with previous work, knocking out either tau or α-synuclein had no obvious effect on brain development. Yet when both proteins were knocked out, brains of 6-week-old mice were smaller than normal, and the cortex was thinner. Nevertheless, the number of neurons per layer was unchanged in mutant mice. Moreover, at embryonic day 14, the brains of mice lacking α-synuclein and tau were larger than those of wild-type mice. This was attributable partly to an increase in the number of postmitotic cortical neurons as a result of accelerated neurogenesis. This, in turn, led to premature depletion of the progenitor pool, which—because the progenitor pool that gives rise to neurons later generates astrocytes—was associated with a shortage of astrocytes in the postnatal cortex. This, together with a decrease in oligodendrocyte numbers, explained the reduced brain size in adult mice.

Both tau and α-synuclein can influence microtubule dynamics. Consistent with this, knocking out both proteins slowed microtubule elongation in fibroblasts. It also accelerated interkinetic nuclear migration, a microtubule-dependent process that influences neural progenitor proliferation and differentiation. Notch signaling, which promotes proliferation over differentiation of neural progenitors, was also reduced in double-knock-out mice.

These results suggest that tau and α-synuclein have complementary functions in regulating microtubule dynamics during cortical neurogenesis. Although knocking out either protein alone is insufficient to disrupt this process, knocking out both leads to precocious generation of neurons, premature depletion of the progenitor pool, and reduced numbers of glia in the adult brain. Future work should investigate how reduced Notch signaling relates to these effects.

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