The authors found that both the SH2-binding and PDZ-binding domains are required for restricting dendritic growth, but only the PDZ-binding domain is required for the regulation of dendritic spine and synapse number (**Fig. 1**). The fact that different mutations lead to different phenotypes indicates that the decreases in dendritic spine and synapse number in CA1 neurons of ephrinB3 knockout mice are not just an outcome of perturbed dendritic development, but are in fact a result of independent signaling pathways.

The authors next asked how these different signaling modules on ephrinB3 could lead to different biological outputs. In selecting from the many potential downstream signaling components for further study, rather than simply pick one or grab four they settled on three: syntenin and Pick1, which bind ephrinB3 via their PDZ domains, and Grb4, whose SH2 domain docks at phosphotyrosine residues along ephrinB3. In an attempt to determine which features of dendritic growth and synapse development are mediated by each of these proteins, the authors created protein chimeras in which ephrinB3 was fused to each of the effector proteins. They then assessed which of the phenotypes observed in the ephrinB3 knockout neurons were rescued by the chimeras. EphrinB-Pick1 was found to exclusively rescue the decrease in spine and synapse number observed in ephrinB3 knockout neurons, whereas the ephrin-Grb4 chimera reversed the increase in primary dendrite number. Notably, the ephrin-syntenin chimera was capable of rescuing both the dendritic and the synaptic defects observed in ephrinB3 mutant mice, suggesting that syntenin signaling is involved in both functions. A limitation of these overexpression experiments using chimeric molecules is that they cannot recapitulate the dynamic nature of ephrinB reverse signaling. However, these experiments nevertheless provide support for the conclusion that, through effector proteins including Pick1, Grb4 and syntenin, ephrinB3 can produce divergent biological outcomes.

Although they fill in gaps in the ephrinB signaling puzzle, these new findings still point to major unresolved questions in the field of reverse signaling. For example, what initially engages reverse signaling? If it is clustering of EphBs, then what initiates this? Can the phosphorylation and PDZ signaling pathways be activated independently? Given that ephrinBs are often expressed presynaptically, is the pathway described here specific to the CA3-CA1 synapse or does it also operate at other synapses at which ephrinB3 is expressed presynaptically? And perhaps most interestingly, how do the present findings fit together with previous observations demonstrating that presynaptic ephrinB3 can function as a mediator of axon pruning[9]? The ability of ephrinB3 to serve this function from both sides of the synapse suggests either some shared common mechanism pre- and postsynaptically or that there are more pieces to the puzzle.

Despite these unresolved issues, the experiments described here represent an important advance in understanding ephrinB-EphB signaling. Similar approaches to those used by Xu *et al.*[2] should help to clarify ephrinB signaling in the adult and may even be applied to the EphB receptors where signaling mechanisms remain an enigma.

COMPETING FINANCIAL INTERESTS
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Same players, different game: AMPA receptor regulation in oligodendrocyte progenitors

Lindsay M De Biase & Dwight E Bergles

Neurons form synapses with oligodendrocyte precursor cells (OPCs) that may control their maturation and myelination. Key signaling molecules regulating glutamate receptors at neuronal synapses also act in OPCs, but to opposite effect.

Imagine learning that birds can talk to trees. Such a surprising find would raise a host of pressing questions. How does such communication work and what do birds and trees get from this exchange? We face a similar conundrum with the discovery that neurons form synapses with OPCs, also referred to as NG2-positive cells. As their name suggests, these glial progenitors give rise to oligodendrocytes, and glutamate can influence their differentiation *in vitro*. The revelation that OPCs form synapses with glutamatergic neurons[1] led to fervent speculation that neural activity instructs these progenitors *in vivo* and provided a potential explanation for the observation that neuronal activity influences CNS myelination[2]. Nonetheless, synaptic currents do not substantially depolarize OPCs[3], raising mechanistic questions about how synaptic signaling could be linked to changes in gene expression and cell behavior. Unlike most mature neurons, OPCs express calcium-permeable AMPA receptors (CP-AMPARs), which may provide a conduit for neuronal activity to engage calcium-dependent signaling pathways in these progenitors. In this issue of *Nature Neuroscience*, Zonouzi *et al.*[4] find that activation of group 1 metabotropic glutamate receptors (mGluRs) in OPCs can increase their surface expression of CP-AMPARs by tapping into signaling components similar to those used to regulate AMPARs in neurons. Ultimately, this plasticity depends on the association of AMPARs with transmembrane AMPAR regulatory proteins (TARPs), providing an important step forward in our understanding of how AMPAR trafficking and function are regulated in these progenitors.

OPCs are a distinct class of glial cell with a track record of breeding controversy. Although essential for generation of oligodendrocytes during development, they persist at a high density in the mature CNS and continue to divide. It is unclear whether this sustained OPC proliferation supports lifelong myelin turnover, and disagreement remains about whether these progenitors serve

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additional functions during adulthood. Synapses between neurons and OPCs emerge in parallel with neuronal synaptogenesis[5], are present in all of the brain regions studied thus far, including white-matter tracts[3,6], and appear to persist throughout life. Individual axons form synapses with both neurons and neighboring OPCs, and electron microscopic analysis reveals that neuron-OPC synapses show key ultrastructural features found in neuronal synapses[7]. Evidence indicates that unmyelinated axons make contact with these progenitors[3] and synaptic input is rapidly lost as OPCs differentiate into oligodendrocytes[5], suggesting that synaptic signaling may shape progenitor maturation. Nonetheless, the function of neuron-OPC synapses has not been clearly demonstrated and substantial gaps remain in our knowledge of how signaling at these junctions is regulated. With the work of Zonouzi *et al.*[4], several pieces of this puzzle begin to fall into place.

In a series of *in vitro* experiments, Zonouzi *et al.*[4] show that pharmacological activation of mGluRs leads to an increase in the proportion of CP-AMPARs expressed on the surface of OPCs, which could be detected during electrophysiological recordings and through surface biotinylation experiments. As is the case for most types of plasticity in neurons, this phenomenon requires an increase in intracellular calcium. It also requires the activity of PICK-1, which mediates aspects of AMPAR trafficking in neurons, and the activity of two kinases, Jun N-terminal kinase and phosphatidylinositol-3-OH kinase, which participate in mGluR-mediated plasticity in neurons. Although these experiments were performed in an oligodendrocyte progenitor cell line, the mGluR-induced increase in CP-AMPAR surface expression was also observed in OPCs cultured from optic nerve. Previous studies involving cultured OPCs isolated from brain tissue noted that these cells possess physiological characteristics of both neurons and glia. Consistent with this theme, the experiments performed by Zonouzi *et al.*[4] reveal that OPCs use the same molecular machinery as neurons to modulate AMPAR surface expression. However, they co-opt these mechanisms for a glial-specific outcome; mGluR stimulation reduces CP-AMPAR surface expression in cerebellar stellate cells[8], whereas mGluR stimulation increases CP-AMPAR surface expression in OPCs (**Fig. 1**). At present, the functional implications of this finding for OPC behavior *in vivo* are unknown.

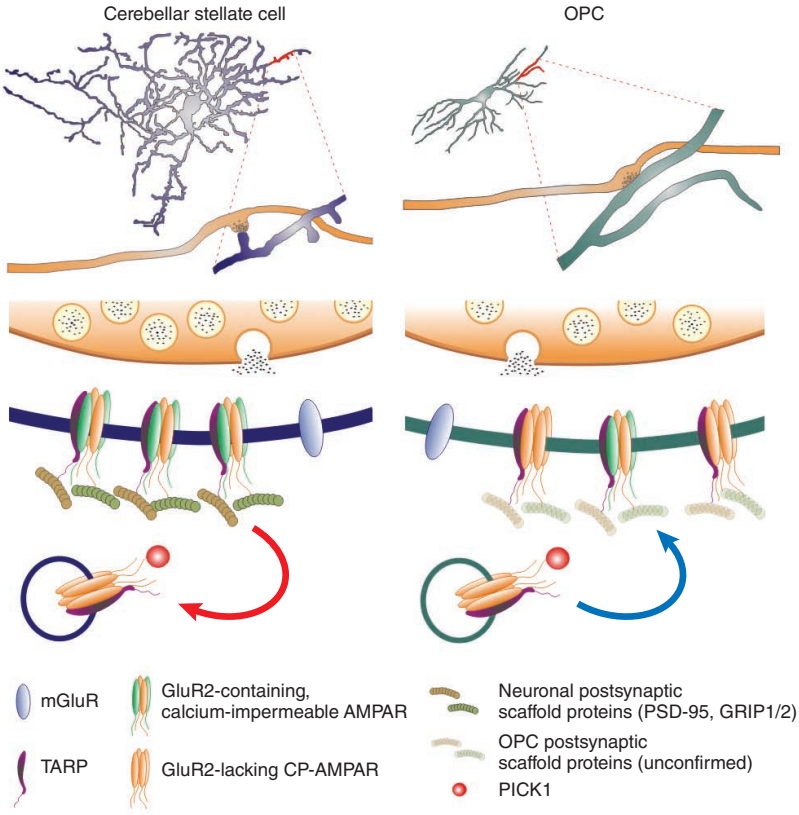

Figure 1 Dynamic regulation of CP-AMPA receptors in neurons and oligodendrocyte precursor cells. Top, both cerebellar stellate cells and OPCs in the cerebellum receive glutamatergic synaptic input, but the mechanisms governing surface expression of AMPARs in OPCs have not been clarified. Bottom left, in cerebellar stellate cells, activation of mGluRs (blue) leads to internalization of CP-AMPARs (orange). Similar forms of AMPAR plasticity in neurons often depend on the activity of PICK-1 (red) and the association of AMPARs with TARPs (purple), which mediate interactions with scaffolding proteins (tan and green circles) in the postsynaptic domain. Bottom right, Zonouzi *et al.*[4] show that mGluR activation in OPCs activates similar intracellular signaling pathways, but, unexpectedly, this stimulus results in an increase in surface expression of CP-AMPARs. This plasticity depends on the activity of PICK-1 and the association of AMPARs with TARPs, demonstrating that these auxiliary proteins are also involved in regulation of AMPARs in OPCs.

The study of AMPARs was revolutionized in recent years by the discovery that the TARP family of auxiliary proteins associate with AMPARs and alter receptor trafficking and function[9]. Individual cell types can express distinct complements of TARPs, and the effects of combinatorial TARP expression on AMPAR function are still being mapped. Furthermore, little is known about whether TARP expression is regulated by development or particular patterns of neuronal activity. Gene expression profiling has suggested that TARPs are present in OPCs[10], and Zonouzi *et al.*[4] add to this evidence by performing reverse-transcription PCR in optic nerve, a white-matter tract composed exclusively of glial cells and the axons of retinal ganglion cells. These experiments revealed that transcripts for a cornucopia of TARPs (γ-2, γ-3, γ-4, γ-5, γ-6) are present in optic nerve, suggesting that these auxiliary proteins are not solely relevant for neurons.

TARPs were initially discovered through the study of stargazer mice, which show dyskinesia, severe ataxia and characteristic head-tossing behavior, phenotypes that were eventually linked to a spontaneous mutation in the gene encoding TARP γ-2, Stargazin (*Cacng2*). Subsequent studies revealed that γ-2 is critical for surface AMPAR expression in cerebellar granule cells[9]. In neurons that express more than one TARP, knockout of individual TARPs often results in only mild abnormalities, indicating that TARP family members possess a substantial capacity to compensate for one another. To determine whether TARPs function in receptor trafficking in OPCs, Zonouzi *et al.*[4] focused on a critical TTPV motif that is present in the C terminus of γ-2. In neurons, this motif allows γ-2 to interact with scaffolding proteins in the postsynaptic density, such as PSD-95, and anchor AMPARs at synapses[9]. When OPCs were transfected *in vitro* with a truncated γ-2 lacking this motif, surface expression of CP-AMPARs was minimal. Furthermore, expression of truncated γ-2 prevented the mGluR-dependent increase in CP-AMPAR surface expression.

These data suggest that TARPs are important for regulating AMPAR trafficking in OPCs and provide tantalizing hints that the scaffolding proteins responsible for anchoring receptors in the postsynaptic compartment may be similar between neurons and OPCs. Because the truncated γ-2 is likely to act in a dominant-negative fashion for the TARP family, these experiments do not necessarily indicate that γ-2 is the sole or even the predominant TARP that modulates AMPAR trafficking in these cells. Indeed, although OPCs and myelination have not been directly investigated in TARP knockout mice, it is unlikely that marked deficits in myelination are present, as failure to myelinate leads to early postnatal death. This may indicate that TARPs and AMPAR signaling are not critical for OPC differentiation or that OPCs express multiple TARP subtypes and compensate successfully for the loss of one or more TARPs. These results also argue for caution in interpreting the effects of global pharmacological or genetic TARP manipulation, as glutamate signaling in OPCs could also be perturbed.

In a final experiment, Zonouzi *et al.*[4] recorded from OPCs in acute cerebellar slices and examined their responses to climbing fiber stimulation. At synapses between climbing fibers and OPCs, a substantial proportion of postsynaptic AMPARs are calcium permeable[7], making this an attractive region for the study of AMPAR trafficking in OPCs. In these slices, mGluR activation led to a postsynaptic increase in CP-AMPARs, suggesting that the signaling mechanisms observed *in vitro* are likely to mediate this plasticity *in situ* and be relevant to AMPAR trafficking at neuron-OPC synapses. As the experiments described here rely on pharmacological activation of mGluRs, a critical future direction will be to determine whether physiological patterns of activity can engage these signaling pathways to alter CP-AMPARs on OPCs. Experiments in the hippocampus hint that this may be the case, as theta burst stimulation can lead to the potentiation of AMPAR-mediated currents at CA1 pyramidal neuron–OPC synapses[11].

These observations suggest that precise tuning of AMPAR signaling in OPCs is possible, and perhaps required, for the proper function of these cells. Indeed, Zonouzi *et al.*[4] observe that ATP can decrease CP-AMPARs in OPCs, and activation of NMDA-type glutamate receptors (NMDARs) in OPCs seems to negatively regulate CP-AMPAR surface expression[12], indicating that several regulatory pathways may influence these receptors. The recently discovered cornichon proteins[9], which bind to and modify AMPARs, may also contribute an extra layer of complexity to AMPAR regulation in OPCs.

An enhanced understanding of AMPAR signaling in OPCs is likely to advance our knowledge of their behavior in disease and injury contexts. OPCs can give rise to oligodendrocytes after chemically induced myelin loss, and progenitors in demyelinated lesions receive synaptic input before maturing[13], suggesting that this communication with neurons may represent an important stage of OPC differentiation. However, OPCs are present in chronic multiple sclerosis lesions[14], and the reasons for their failure to mature are unclear. In addition to their role as progenitors, OPCs react to many forms of tissue injury and may contribute to formation of glial scars and promote tissue repair. However, the signaling mechanisms that regulate their response to injury are largely unknown. OPCs are particularly susceptible to damage during perinatal hypoxia and ischemia, a leading cause of cerebral palsy. Although activation of both AMPARs and NMDARs has been implicated in this vulnerability[15], cell-specific *in vivo* manipulation of these receptors will be necessary to clarify whether the protective effects of glutamate receptor antagonists result from inhibition of neuronal or glial receptors. With more information about the signaling proteins involved in AMPAR regulation in OPCs, Cre lines specific for these progenitors can be used to address whether AMPAR signaling contributes to remyelination failure in multiple sclerosis lesions, whether AMPAR signaling guides OPC reactivity after brain injury, and whether AMPAR expression renders OPCs susceptible to glutamate excitotoxicity.

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An axis of good and awful in odor reception

Marion E Frank & Thomas P Hettinger

Patchy variation in odor-evoked electrical activity in the human olfactory epithelium is found to correlate with stimulus pleasantness. This finding depends on a new technique for recording directly from awake humans.

One of the most enduring mysteries in neuroscience is how our senses interpret the external world. The spectral and spatial features involved in coding in the visual and auditory systems are fairly well understood at both the receptor and perception level, and the relationships between stimuli and perception are easily defined. In the chemical senses, things are not so simple because there are many receptor subtypes, an enormous diversity of chemical stimuli and no spectral stimulus continuum. Studying coding in human olfaction is difficult because it is generally impossible to study both receptor activity and perception at the same time.

Previously, Sobel and colleagues[1] presented evidence for a correlation between olfactory stimulus (odorant) pleasantness and chemical structure. In this issue of *Nature Neuroscience*, Lapid *et al.*[2] extend this concept to ask whether recorded neural activity in the olfactory epithelium of humans can be correlated with perception. By means of electro-olfactogram (EOG) recordings from the nasal olfactory epithelium in humans, they were able to study

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