Eph/ephrin signaling in morphogenesis, neural development and plasticity
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Ephrins are cell-surface-tethered ligands for Eph receptors, the largest family of receptor tyrosine kinases. During development, the Eph/ephrin cell communication system appears to influence cell behavior such as attraction/repulsion, adhesion/de-adhesion and migration, thereby influencing cell fate, morphogenesis and organogenesis. During adulthood, the Eph/ephrin system continues to play roles in tissue plasticity, for example in shaping dendritic spines during neuronal plasticity. Mechanistically, Eph–ephrin repulsive behavior appears to require ligand–receptor internalization and signaling to Rho GTPases.

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Abbreviations
A–P anterior–posterior
CPG central pattern generator
D–V dorsal–ventral
fss fused somites
GEF guanine nucleotide exchange factor
GPI glycosyl phosphatidylinositol
L–M lateral–medial
LMC lateral motor column
MMC medial motor column
NMDA N-methyl-D-aspartate
OR olfactory receptor
PDZ postsynaptic density protein, discs large, zona occludens
RGCs retinal ganglion cells
RTK receptor tyrosine kinase
Vte ventral telencephalon

Introduction
The coordinated behavior of cells during development is regulated as a result of stimuli from the cells’ changing environment. Receptor tyrosine kinases (RTKs) are transmembrane proteins with an extracellular domain that recognizes such stimuli and an intracellular kinase domain that transmits signals to the inside of the cell. Many RTKs directly influence the division, fate, growth and survival of cells by regulating intracellular programs, including transcription. The Eph-receptor family, the largest family of RTKs, appears to do so only indirectly, by modulating the cell’s affinity towards its neighboring cells and/or a given substrate and by promoting cell migration. Processes mediated by Eph receptors include the formation and guidance of cellular appendages such as extending growth cones from differentiating neurons and the induction and maturation of neuronal spines, small thorn-like structures on the surface of dendrites [1]. Molecularly, the signaling pathways downstream of Eph receptors converge to regulate the cytoskeleton and appear to have little influence on nuclear events [2,3].

The Eph/ephrin system has additional unique features that distinguish it from other RTKs. While most RTKs become activated by dimerization, the ephrin–Eph system additionally requires the formation of higher-order signaling clusters ([4] and references within). In contrast to other subfamilies of RTKs, Eph receptor functions are often redundant as a result of the receptors’ overlapping expression patterns and promiscuous binding affinities towards the ephrins, a fact that makes the genetic analysis of this system challenging. The receptors are termed EphA (EphA1–8, only including those found in mammals) or EphB (EphB1–4, EphB6) on the basis of sequence homologies and depending on the subgroup of ligands that they bind. A-type receptors typically bind to most or all A-type ephrins (ephrinA1–5), which are tethered to the cell membrane by a glycosyl phosphatidylinositol (GPI) anchor. B-type receptors bind to most or all B-type ephrins (ephrinB1–B3), which have a transmembrane domain that is followed by a short cytoplasmic region. Exceptions to this rule are EphA4, which can bind both A-type and most B-type ligands [5], and ephrinA5, which was recently shown to bind and signal through EphB2 (besides EphA receptors), but not other EphBs [6,7].

Another unique feature is that an Eph receptor can also act as a ligand in the same way that an ephrin ligand can act as a receptor (Figure 1). Ephrin ligand binding induces Eph receptor ‘forward’ signaling, which usually requires a catalytically active kinase domain. But ephrins can also signal into their host cell — a process referred to as ‘reverse’ signaling. Here, the ephrin cytoplasmic tail is subject to modifications and recruits signaling effectors. In this review article, I will summarize work on ephrins published over the course of the past year in those fields in which progress was highest, including morphogenesis, neuronal development and plasticity. I will also review...
progress in our understanding of the underlying cellular and molecular mechanisms. Due to space constraints, I will not extensively discuss those fields in which Eph/ephrin progress was more modest, such as vascular development, tumor angiogenesis and tumorigenesis (for recent reviews see [1,8]).

**Ephrins and Ephs in early segmentation and morphogenesis**

Cell migration during morphogenesis is influenced by short-range and long-range cues from the environment. Ephrins represent short-range repulsive cues for migration of epithelial cells of the Caenorhabditis elegans epidermis and the mammalian intestine, of neural stem cells and progenitors such as neural crest cells, and of differentiated neurons, for example cerebellar granule cells (for recent reviews see [1,5,9,10].) The Eph/ephrin system is also crucially involved in segmentation processes operating in vertebrates; examples include the vertebrate hindbrain, where the ephrins and Ephs function in rhombomere-specific cell sorting [11], and the somites, where the Eph/ephrin system appears to contribute to the segmentation of the paraxial mesoderm and to the division of the somites into anterior (EphA4-positive) and posterior (ephrinB2-positive) halves [12,13]. Recent work from the Wilson lab has now elucidated the events for which Eph/ephrin signaling is required by investigating the zebrafish mutant fused somites (fss) [14]. fss encodes Tbx24, a T box transcription factor involved in maturation of the presomitic mesoderm. In fss mutants, loss of Eph/ephrin expression is accompanied by a failure of paraxial cells to undergo mesenchymal-to-epithelial transition, a process involving changes in cell shape, cell adhesive interactions, and subcellular polarization of organelles and proteins. Restoration of Eph/ephrin signaling interfaces in fss mutants rescued the formation and subsequent maturation of different segment boundaries. Unidirectional ephrinB reverse signaling appeared to be sufficient to induce the formation of a physical furrow at the intersomitic interface as was previously observed at rhombomere boundaries [15]. Eph/ephrin signaling therefore appears to mediate the final step of somitogenesis, downstream of the acquisition of anterior or posterior cell identity. Several Ephs and ephrins may be functionally redundant in this system, since no single mouse mutant has so far been reported to display defects in early segmentation.

Somitogenesis is intimately linked to skeletal patterning. For example, the most anterior somites form the occipital bones, which surround the opening in the base of the skull, and the sklerotome portions of the somites will form parts of the vertebrae. Recent data indicates that eph/ephrin signaling is critically required for normal development of the vertebrate skeleton [16]. Ralf Adams and co-workers studied the phenotypes of mice carrying deletions of the X-linked ephrinB1 gene or of the genes encoding EphB2/EphB3 receptors and found a range of malformations in the axial and appendicular skeleton, such as asymmetric attachment of ribs and lack of joints.
in sternum and limbs (Figure 2). The initial steps of bone formation (i.e. the condensation of mesenchymal cells and their differentiation into cartilage and bone) were not affected in these mutants. Rather, the expression patterns and phenotypes suggested a model in which interactions between opposing cells expressing either ephrinB1 or EphB receptors generated local signals that shape mesenchymal condensations (i.e. promote fusion or division). An independently generated ephrinB1 knockout confirmed the bone formation phenotype of ephrinB1 heterozygotes [17]. Through the use of a neural-crest-specific Cre (‘causes recombination’) mouse, Phil Soriano and co-workers further showed that ephrinB1 is required in neural crest cells for development of the secondary palate. The formation of the secondary palate involves the fusion of palatal shelves during embryonic development and absence of the secondary palate results in perinatal lethality, as it does not allow uptake of milk. A significant fraction (50%) of EphB2/EphB3 knockouts had previously been shown to suffer from cleft palate [18]. Now, loss of ephrinB1 or the inability of ephrinB1 to interact with PDZ-containing effector proteins affected the fusion of palatal shelves, suggesting that regulation at both ephrinB and EphB cytoplasmic domains is required for correct cell behavior during palatal shelf fusion [17].

Consistent with the findings in mutant mice, mutations in the human ephrinB1 gene (EFNB1) were recently shown to cause craniofrontonasal syndrome, an X-linked craniofacial disorder that mostly affects heterozygous females [19,20].

**Nervous system development**

In the nervous system, repulsive interactions between ephrins and Ephs regulate the guidance of neuronal growth cones [1], and the selective bundling (fasciculation) and dispersal (defasciculation) of axons [21]. Repulsive guidance is particularly important at intermediate targets where pathfinding axons are confronted with ephrins. The central nervous system midline is one such target and is the source of long- and short-range guidance molecules [22]. In the visual system, retinal ganglion cells (RGCs) send their axons across the midline to the appropriate area in the midbrain (in mammals called the superior colliculus). In species with binocular vision, a fraction of RGC axons are prevented from crossing the midline and instead project ipsilaterally by repellent guidance cues expressed by the critical midline choice point, the optic chiasm [23]. Previous work had demonstrated that overexpression of ephrinB in the embryonic chiasm of developing frogs was sufficient to redirect EphB-expressing retinal axons to project ipsilaterally [24]. This suggested a physiological role for ephrinB repellents in preventing subsets of retinal axons from crossing the midline. Recent work by Carol Mason and coworkers has shown that a fraction of RGC axons express and use EphB1 receptors to sense ephrinB2 at the chiasm and turn ipsilaterally [25] (Figure 3). Loss of EphB1, but not of EphB2 or EphB3, in mutant mice specifically reduced ipsilateral projections. Blocking ephrinB2 by a soluble form of the EphB4 receptor (EphB4-Fc) in eye-chiasm explant culture systems eliminated the ipsilateral projections, indicating that EphB1 and ephrinB2 are the key molecules controlling midline crossing at the mouse chiasm.

Retinal axon connections with the superior colliculus are topographically organized such that neighborhood relationships are preserved from the RGCs to their target cells. Ephrins and Ephs are critical components that help to set up topographic maps in all directions. A-type
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Figure 3

Midline guidance in the visual system. In animals with binocular vision, most retinal axons (red) cross to the contralateral side of the brain, while a smaller subset of retinal axons (blue) project to the ipsilateral side. Retinal axons expressing EphB1 are repelled from the optic chiasm by ephrinB2 and directed to an ipsilateral pathway. Contralaterally projecting axons do not express EphB receptors and therefore are not repelled by ephrinB2.

Ephs and EphA receptors are required for anterior–posterior (A–P) topographic mapping [26,27], whereas B-type ephrins and EphB receptors are required for dorsal–ventral (D–V) mapping along the lateral–medial (L–M) axis of the midbrain target area [28]. Mechanistically, A–P mapping appears to involve repulsive interactions, including reverse signaling by ephrinAs [29]. Novel findings from the Flanagan lab [30] suggest a model in which ephrinA ligands are both growth promoting and inhibitory. Their model says that low, unclustered ephrinA densities in the anterior midbrain trigger EphA forward signaling that promotes axon growth, possibly via adhesive forces. In posterior regions, however, ephrinAs are instead present at high densities and are clustered, and trigger repulsive signaling. Retinal axons terminate in the target at the neutral position between these positive and negative effects [30]. A somewhat similar situation had previously been suggested for D–V mapping involving ephrinB and EphB proteins. According to a study by Dennis O’Leary and coworkers, ephrinB1 in the midbrain controls the direction that retinal axon branches take along the L–M axis. Depending on the position of RGC axons within the ephrinB1 gradient, ephrinB1 can act both as a repellent and as an attractant to direct branch extension along the L–M axis [31].

The mammalian olfactory system recognizes a range of odorants, which are detected by a large family of olfactory receptors (ORs). Peripheral olfactory neurons expressing the same OR are randomly dispersed within the nasal epithelium, yet their axons converge on two precise positions, the so-called glomeruli, in the olfactory bulb, generating a topographic map [32]. Previous work indicated that the OR not only recognizes odors in the environment, but, when expressed on axon termini, also participates in guiding the axon to its precise glomerular position. A recent study by Richard Axel and coworkers demonstrated that ephrinA–EphA interactions participate in olfactory topographic mapping [33]. EphrinAs are expressed on olfactory sensory axons, while corresponding EphA receptors are expressed in the olfactory bulb. Levels of ephrinAs differ among neurons expressing different ORs, suggesting that protein levels are coordinately controlled. Gene targeting experiments revealed that alterations in the levels of ephrinAs change the glomerular map. Interestingly, GPI-anchored ephrinAs on sensory axons appear to transduce a ‘reverse’ signal similar to what has been proposed for other topographic maps [29].

Eph/ephrin signaling has previously been implicated in the formation of discontinuous, segregated maps, such as the connections between the thalamus and the neocortex and those between spinal motor neurons and limb muscles. Understanding the cues that guide topographic connections between the dorsal thalamus and the neocortex is important because of their prominent functional role in processing sensory and motor information.
Cell-to-cell communication via Eph/ephrin signaling regulates thalamocortical projections at two different levels. First, EphA/ephrinA signaling helps to establish the topographic organization of specific thalamic projections to distinct cortical regions (inter-areal topography). For example, this ensures correct connection of the parts of the thalamus that relay visual and motor information with the visual and motor cortices, respectively (Figure 4). Importantly, the topographic organization of these projections takes place at an intermediate target, the ventral telencephalon, rather than within the cortex itself [34*]. Second, the projections of each thalamic nucleus (e.g. the somatosensory thalamus) to a specific cortical area (the somatosensory cortex) are also topographic and are regulated by EphA/ephrinA signaling (Figure 4) (for a recent review see [35]).

Motor neuron innervation of muscle targets is also positionally selective and in part regulated by repulsive EphA/ephrinA interactions. Those motor neurons that innervate limb muscles are positioned within the lateral motor column (LMC), whereas motor neurons that project to axial (trunk) muscles have their cell bodies in the medial motor column (MMC). LMC is further divided into a lateral LMC and a medial LMC, which project to dorsal and ventral limb muscles, respectively. Previous work had shown that ephrinA expression in ventral limb repels EphA4-expressing lateral LMC neurons ([36] for review see [1]). Recent work from Tom Jessell’s laboratory has shown that LIM (lin-11, isl-1, mec-3) homeodomain transcription factors regulate LMC axonal trajectories by defining the pattern of EphA4 expression by motor neurons and of ephrinA expression by the limb mesenchyme [37]. A recent report from Cathy Krull and coworkers [38] has extended Eph/ephrin signaling to MMC neurons. Their data indicates that MMC axons are constrained to specific parts of the sklerotome by an attractive activity that probably represents ephrinA5. For example, ectopic expression of ephrinA5 in chick embryos caused EphA4-positive MMC axons to extend into novel, ephrinA5-positive territories [38]. This is in contrast to the repulsive action of ephrinA5 on EphA4-expressing LMC axons and may reflect a different subcellular localization of phosphorylated EphA4. Because EphA4 forward signaling appears to be required for both MMC and LMC projections, the authors speculated that the downstream signaling pathways are different in both cell populations.

Recent evidence indicates that EphA4 is also part of a spinal cord neuronal circuit that controls rhythmic walking of rodents ([39**], for review see [40]). Such local circuits that have the ability to produce rhythmic firing patterns in the absence of sensory feedback are called central pattern generators (CPGs). Spinal cords from mice lacking either EphA4 or its ligand ephrinB3 fail to display the normal left-right alternating firing pattern in response to a novel stimulus [41]. This is consistent with the idea that EphA4/ephrinA signaling is required for the generation of the locomotor rhythm in the spinal cord [41].

Figure 4

(a) Area specificity and topography of thalamocortical projections. (a) Intra-areal topographic mapping. EphA4 and its repulsive ligand ephrinA5 are expressed in medial to lateral gradients in the thalamus and presumptive somatosensory cortex, respectively. In wild-type mice, axons expressing high levels of EphA4 project to cortical regions with low levels of ephrinA5. In mice lacking ephrinA5 and EphA4, axons from the medial thalamus send ectopic projections (dashed line) to medial regions of the cortex. Since topography is only partially defective, other ephrinA/EphA genes were postulated to compensate the loss of ephrinA5/EphA4. (b) Inter-areal topographic mapping. A gradient of ephrinA5 in an intermediate target of thalamic projections, the ventral telencephalon (VTc), is largely responsible for imposing the inter-areal topography on thalamocortical projections. In wild-type mice, axons of the rostromedial thalamus expressing high levels of EphA4 navigate through regions of the VTc expressing low levels of ephrinA5. Lack of ephrinA5/EphA4 caused those axons normally projecting to the motor cortex to instead target the somatosensory cortex.
that underlies walking behavior. Instead these mice display synchronous rhythm caused by aberrant midline crossings of excitatory EphA4-positive neurons. This study identified EphA4 neurons as an excitatory component of the locomotor CPG. Those neurons normally form connections with other neurons on the ipsilateral side. Identification of additional molecular components and cellular subtypes will eventually allow understanding of the circuitry of the locomotor CPG.

Dendritic spine formation and neuronal plasticity

Dendritic spines are small thorn-like structures that receive excitatory input. Spine formation is thought to underlie synaptic plasticity and perhaps long-term memory. The molecular mechanisms controlling changes in spine morphology are poorly understood. Using mainly cultured neurons, several reports have implicated EphB receptor forward signaling as a positive signal in spine formation (see [1] and references within). Using mouse genetics, Iryna Ethell and coworkers have now demonstrated a highly redundant requirement of three EphB receptors (EphB1–3) for dendritic spine morphogenesis in the hippocampus [41]. Defective spine formation in the triple knockouts was associated with a drastic reduction of excitatory synapses and of glutamate receptor clustering. The authors noticed that in vivo few spines still formed in triple mutants, whereas mutant cultured neurons completely lacked spines. This could be explained by the presence in vivo of glial cells which stabilize spines by enwrapping the synapses. While axodendritic spine formation may be regulated by ephrinB–EphB interactions, glial–dendritic control of spine formation may involve ephrinA–EphA4 signaling (Figure 5) ([42], reviewed in [43]).

While control of spine formation by Eph/ephrin appears to be highly redundant, the signaling events leading to activity-dependent synaptic plasticity require the presence of the EphB2 receptor. Until recently, the unifying view had been that EphB2 acts postsynaptically whereas ephrinBs act on the presynaptic side (for recent reviews see [1,44,45]). EphB2 regulates NMDA (N-methyl-D-aspartate) receptors to promote NMDA-dependent plasticity, or is clustered via PDZ interactions to activate reverse signaling by presynaptic ephrinBs, thus promoting NMDA-independent forms of plasticity. Recent evidence indicates that in certain circumstances, depending on the type of synapse, the Eph/ephrin system is used in an inverted manner: in the CA1 region of the hippocampus, where synaptic plasticity correlates best with learning and memory, ephrinBs are predominantly localized in postsynaptic neurons, whereas EphBs and EphA4 are expressed both pre- and postsynaptically [46]. Because conditional mutants of ephrinB2 and ephrinB3-null mutants display drastically reduced long-term plasticity, we suggested that postsynaptic signaling is modulated by ephrinBs via an as-yet unknown pathways (Figure 6).

Cellular mechanisms and signaling

Although most Eph/ephrin functions can be explained by repulsive mechanisms, in some contexts Eph/ephrin signaling appears to increase cellular adhesion. This is true for both ligands and receptors. For example, Eph forward signaling mediates repulsion at the central nervous system midline [25,47] and during vascular remodeling [48], but is likely to positively direct MMC axons to ephrinA target cells [38]. EphrinB reverse signaling can collapse growth cones [49] and helps to restrict cell intermingling [50], but axonal ephrinA signaling appears to mediate attraction in the olfactory system [29,33]. While downstream signaling pathways may determine the cellular response, recent reports provided evidence for ligand-receptor internalization as a mechanism for turning attraction into repulsion (for reviews see [51,52]). Zimmer et al. [53] confronted two different cell populations that expressed either EphB2 or ephrinB1 (fibroblasts and neurons) with each other, and showed that internalization of the Eph–ephrin complex was bi-directional and involved full-length proteins. Blockage of internalization
Differential expression of ephrinB proteins at hippocampal synapses. In situ hybridization showing ephrinB3 expression (blue color) in adult mouse hippocampus overlaid with parts of its neuronal circuit. (a) An ephrinB-negative, presynaptic CA3 neuron (white) forms a synapse with an ephrinB-positive, postsynaptic neuron (pink). (b) EphrinB-negative CA3 neurons (white) are postsynaptic for neurons whose cell bodies reside in the dentate gyrus and which are intensely ephrinB3 positive.

(achieved by removing the cytoplasmic domains of both proteins) converted repulsion into adhesion of the cells. Marston et al. [54**] performed similar experiments with microinjected fibroblasts and endothelial cells and demonstrated trans-internalization of ephrinB2 into EphB4-expressing cells concomitantly with cell retraction. Both events were dependent on actin polymerization, which in turn was dependent on Rac signaling within the receptor-expressing cells. These studies introduced a novel mechanism operating during cell-contact-dependent repulsion. It will be interesting to see how internalization is regulated in different cell types. For example, in young cultured hippocampal and retinal neurons ephrinB-mediated endocytosis is more vigorous than Eph-mediated endocytosis [49,53**]. Moreover, endocytosis may influence downstream signaling events, which in turn may modulate the kinetics of internalization. It also remains to be demonstrated that (trans-)endocytosis plays a role in vivo, and whether this mechanism is critical for cell-to-cell signaling at neuronal synapses.

Among the signaling pathways activated by Eph receptors, those that regulate the activity of the Rho family of GTPases appear to be important for Eph-mediated repulsion and morphogenesis [3]. The Rho family members RhoA, Rac1, and Cdc42 are key regulators of actin cytoskeleton dynamics in a variety of different cell types, including neurons. They act as molecular switches, cycling between an active GTP-bound state and an inactive GDP-bound state. Guanine nucleotide exchange factors (GEFs) for Rho GTPases have been implicated downstream of Ephs in neurite outgrowth/collapse and spine formation (reviewed in [3]). Different Ephs appear to bind different Rho-GEFs, suggesting a certain degree of specificity and that their activity undergoes fine-tuned modulation. EphA receptors bind and activate ephexin, a member of the Dbl family of exchange factors that activate RhoA and, to a lesser extent, Cdc42. Expression of a mutant form of ephexin in primary neurons interfered with ephrinA-induced growth cone collapse, suggesting that ephexin is required for EphA-receptor-mediated repulsive guidance [55]. Ephexin is a member of a closely related group of five exchange factors [56]. It will be interesting to see the phenotypes of ephexin and ephexin-related loss-of-function mutants and how they compare to known EphA gene knockouts. EphB receptors appear to associate with other GEFs, including kalirin and intersectin, with exchange activity towards Rac1 and Cdc42, respectively [57,58]. Spine morphogenesis
in cultured neurons was shown to depend on EphB2 signaling via kalirin/Rac1 and intersectin/Cdc42/N-WASP to promote filamentous actin formation. The most recent addition to this scenario is Tiam1, a Rac1-GEF that appears to regulate aspects of EphA2 forward signaling and ephrinB1 reverse signaling [59].

Rho GTPases may also be involved in the crosstalk between Ephs and other RTKs. Hepatocyte growth factor/scatter factor (HGF) induces branching morphogenesis of epithelial cells via its RTK Met. Met activation of Rho GTPases appears critical in this process, since Eph signaling suppressed the formation of cell protrusions by inhibiting Rac1 and the downstream p21-activated kinase PAK [60]. Not only Eph receptor signaling, but also ephrinB reverse signaling, appears to crosstalk with RTKs (reviewed in [5]). Recent work by Moore et al. [61] showed that ephrinB1 reverse signaling counteracts cell movements mediated by fibroblast growth factor receptor in the developing eye field of Xenopus embryos. Other pathways downstream of ephrin–Eph signaling include the Jak/Stat proteins in muscle [62] and the Ras/Mapk and c-Jun N-terminal kinase (JNK) [63–65].

Conclusions and perspectives

During the past year we have seen interesting novel concepts in ephrin/Eph biology and signaling. In the nervous system, ephrins represent important midline choice points for pathfinding axons and regulate topographic mapping in various systems, including the olfactory and thalamocortical systems. Dendritic spine formation depends on Eph receptor forward signaling, while ephrin–Eph signaling in long-term plasticity appears to be bi-directional. Outside the nervous system, bone morphogenesis was shown to depend on ephrinB1. Mechanistically, dynamic internalization of the ephrin–Eph complex determines the outcome of the cellular response and signaling to Rho GTPases appears to be a critical pathway for implementing cell shape changes. Many important questions remain to be addressed. In some cases, the phenotypic changes observed in null mutant mice have not been dissected down to the cellular level. For example, to what extent does ephrin–EphB signaling regulate spine formation through neuron–neuron and neuron–glia interactions? Likewise, is muscle innervation by motor neurons dependent on EphA4 signaling in neurons and mesenchyme? Moreover, the direction of signaling (uni-directional forward or reverse or bi-directional) remains to be established genetically for certain biological processes, in particular those that involve ephrinA reverse signaling (which include topographic mapping, spine formation and synaptic plasticity). Finally, to get at the critical downstream signaling events, we will need to characterize and manipulate molecular components in animal models using genetics and to study the crosstalk with other signaling systems.

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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

• of special interest
•• of outstanding interest


This paper, together with [17–18], reports on the identification of ephrinB1–EphB interactions as positional cues required for normal morphogenesis of skeletal elements. The underlying mechanism appears to be differential cell adhesion and restricted cell movements.


See annotation to [16*].


This careful study reveals two distinct functions of ephrinA/EphA signaling in thalamocortical topography. Ephrin-As not only represent cues within the cortex that provide targeting information for thalamic axons, but are also part of the intermediate target that is used by navigating thalamic axons to find their correct cortical area.


This study identifies EphA4-positive neurons as an excitatory component of local circuits in the spinal cord that generate locomotion termed CPGs. Genetic miswiring is corrected by chemical reinforcement of inhibitory components of this circuit.


Using mouse genetics, the authors show that EphB receptors are required for the formation of dendritic spines, structures in neurons that are connected to synaptic plasticity and long-term memory. Cultured hippocampal neurons from EphB1/EphB2/EphB3 triple knockout mice fail to form mature spines.


This paper shows that interaction between ephrinA3 and the EphA4 receptor regulates the morphology of dendritic spines, motile protrusions on neurons that are the sites of innervation by other neurons. Interestingly, signaling occurs between ephrinA3 in astrocytic processes and EphA4 in the postsynaptic membrane.


This study provides further evidence that ephrinB/Eph signaling regulates long-term hippocampal plasticity. Depending on the type of synapse, ephrinBs appear on either the pre- or postsynaptic side, suggesting that the Eph/epphin system is used bi-directionally and in an inverted manner.


