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REVIEW

Eph-ephrin signaling in nervous system development [version 1; referees: 2 approved]

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Abstract

Ephrins and Eph receptors enable contact-mediated interactions between cells at every stage of nervous system development. In spite of their broad binding affinities, Eph proteins facilitate specificity in neuronal migration and axon targeting. This review focuses on recent studies that demonstrate how these proteins interact with each other, and with other signaling pathways, to guide specificity in a diverse set of developmental processes.



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Introduction

The complexity of nervous system function reflects a vast underlying diversity of neuronal cells and their integration in precise circuitry. During development, newly born neurons migrate to their final destination, become the right type of cell, and form precise connections with their synaptic partners. Given the relatively small number of genes in our genome, how is this complexity generated? A major contributor to the formation of neural circuitry is the Eph family of proteins, which comprises Eph receptors and their ephrin binding partners. These membrane-associated proteins participate throughout neuronal development, during which they display promiscuous binding properties yet specify uniquely targeted events from proliferation to synaptogenesis.

In this large family of signaling molecules, such event specificity does not generally arise from binding selectivity between Eph receptors and ephrins. Instead, multiple modes of Eph-ephrin signaling provide combinatorial codes that differentiate between groups of cells and coordinate multiple aspects of neural development, including cell migration and axon targeting.

Recent studies have demonstrated that differential responses depending on ephrin expression levels and expression of ephrin-associated molecules allow cells born in one place at the same time to adopt distinct migratory routes. In addition, studies have shown how multiple signaling pathways enable distinct axons that grow through a common pathway to terminate in distinct locations.

Specification of neural circuits arises from multiple interacting signaling molecules. The large family of Eph proteins uses both redundancy in expression and multiple modes of signaling to direct this specificity, causing neurons to migrate to their final locations and make synaptic connections there that are appropriate for their function. How can a large family of molecules with broad binding capabilities and redundant expression confer this precision? Here, we discuss recent work focused on factors that determine specificity during cell migration, axon guidance, and midline specializations.

Eph-ephrin signaling

Eph receptors and ephrins display broad spatial and temporal expression throughout nervous system development. During early development, they contribute to neurogenesis (reviewed in 1) and differentiation². Some interesting new perspectives that take into account the unique features of Eph-ephrin signaling have emerged.

Binding within and among cell classes

The Eph receptors are the largest known class of receptor tyrosine kinase. Together with the ephrins, they are divided into the A and B classes on the basis of sequence homology and binding affinities³. The EphA receptors (EphA1-10 in mammals) bind to all ephrin-A molecules (ephrin-A1-6), and the EphB receptors (1-6) bind to all ephrin-Bs (1-3); some variability has been reported in the binding affinities of individual pairs within a class⁴. There is some crosstalk between classes in that EphB2 can bind to ephrin-A5 and EphA4 can bind to ephrin-B2^{3,5,6}.

Forward and reverse signaling

Unlike most ligands for receptor tyrosine kinases, the ephrins are associated with cell membranes. Ephrin-B proteins contain a transmembrane domain, and ephrin-A proteins are associated with cell membranes through a glycosylphosphatidylinositol linkage. A major consequence of this membrane association is that Eph-ephrin signaling mediates short-range cell-cell communication, although in some cases soluble forms of ephrin molecules can provide longer-range cues⁷⁻⁹. The communication between receptors and membrane ligands operates in both directions upon the binding of an Eph receptor in one cell with an ephrin on another cell. Forward signaling refers to signal transduction in a cell expressing the Eph receptor, which upon ligand binding initiates tyrosine phosphorylation. In reverse signaling, signal transduction events are initiated in a cell expressing an ephrin upon its binding with an Eph receptor. Both ephrin-A and ephrin-B proteins can mediate reverse signaling¹⁰⁻¹².

Attractive and repulsive interactions

In cell migration and axon guidance, movement ultimately relies on the integration of signals that influence the cytoskeleton. Eph-ephrin signaling influences the functions of Rho GTPase proteins, which in turn regulate the actin cytoskeleton (reviewed in 4,13). Although Eph-ephrin signaling was initially thought to mediate chemorepulsive interactions, later evidence showed that both attractive and repulsive interactions occur. Recent studies have begun to illuminate the factors that determine how Eph-ephrin interactions influence cell migration, adhesion, and axon guidance.

Combinations and clustering

One potential switch for determining attractive versus repulsive interactions relates to the assembly of higher-order clusters upon ephrin binding to Eph receptors, a prominent feature unique to Eph receptors among the receptor tyrosine kinases^{14,15}. Cluster formation relies on the ligand-binding domains as well as on interactions between adjacent receptors^{16,17}. These clusters, needed for initiation of signal transduction pathways, can be expansive and can include more than one type of Eph receptor within a cluster¹⁸. Large clusters can include inactive receptors that can be phosphorylated within the cluster; consequently, a single ligand can result in phosphorylation of multiple receptors of both classes^{4,14,15}.

Several new studies have shed light on the role of clustering in the unique responses of Eph-ephrin signaling. EphA4 and EphA2 have similar affinities to ephrin-A5 but have opposing responses in cell assays, whereby EphA4 promotes repulsion while EphA2 promotes adhesion. Seiradake and colleagues¹⁹ studied the crystal structure and clustering properties and determined that EphA4 forms small clusters while EphA2 forms large arrays and that these clusters largely determine the cellular response. Along these lines, Klein and colleagues²⁰ prepared clusters of EphB2 of varying sizes and compared effects on phosphorylation, cell collapse, and growth cone collapse. They determined that whilst dimers were associated with a lack of response, trimers and tetramers produced a functional response and that the relative abundance of multimers correlated with the degree of the response. These studies suggest that

factors influencing the clustering of Eph receptors are critical for determining how cells will respond to ephrin binding.

Other interactions in *cis*

Receptor clustering represents a *cis* interaction; that is, two Eph receptor molecules signaling within a single cell. Another type of *cis* interaction observed is the interaction of ephrins and Eph receptors within the same cell, where they are often co-expressed. These interactions have been shown to decrease forward signaling^{21–23} and may play an important role in topographic mapping^{24,25} as well as axon guidance for spinal motor neurons²¹.

Differential control of cortical cell migration

Eph-ephrin interactions regulate cell migration throughout development and are important for establishing boundaries and regulating intermixing of cells^{26,27}. Several new studies highlight the complexity in the regulation of cell movement by Eph-ephrin signaling. Cell sorting is accomplished by using both repulsive and attractive interactions, both forward and reverse signaling, and a range of selective downstream targets of Eph-ephrin signaling.

Cerebral cortex development

The diverse and coordinated functions of Eph-ephrin signaling in cell migration are demonstrated by recent studies of cerebral cortex formation. Early in neural tube development, adhesion of neural progenitors to the apical surface is associated with symmetric cell division. A study of null mutations in ephrin-B1 found that these mice exhibited abnormal neuroepithelia and exencephaly²⁸ and that the mutation further disrupted the apical localization of integrin β 1. The authors used biochemical assays and culture approaches to show that ephrin-B1 negatively regulates the GTPase Arf6, which is essential for maintaining appropriate integrin β 1 localization and adhesion of apical progenitors. In cortical development, some of the first cells to populate the nascent cortical surface are the Cajal-Retzius (CR) cells. This transient population of cells plays a critical role in cortical layering through its release of reelin, which is essential for the characteristic “inside-out” formation of layers. Although apical progenitors require ephrin-B1-mediated adhesion, a recent study used *in vivo* time-lapse imaging together with modeling of cell movement to show that tangential dispersion of CR cells relies on contact-mediated repulsion²⁹. Pharmacological and genetic disruption of Eph signaling showed that both EphA and EphB signaling contribute critically to this repulsion²⁹. Interestingly, the function of reelin in establishing the cortical layers depends extensively on ephrin-B-EphB signaling. Reelin enhances clustering of ephrin-Bs and EphBs, in addition to binding to its receptors. Mutant mice lacking ephrin-B-EphB signaling display severe migration phenotypes with inverted lamination, similar to those seen in *reeler* mice, and activation of ephrin-B-EphB signaling can rescue migration phenotypes in *reeler* mice^{30,31}.

Another influence of Eph proteins occurs during radial migration. During cortical development, electrical synapses form preferentially between radial glial cells and their sister neurons, forming networks of lineage-related cells in radial columns. When inside-out radial migration is genetically disrupted, the preferential coupling between sister cells is lost³². The tangential dispersion of a subpopulation of these developing cortical neurons promotes

crosstalk between clonal columnar units and is significantly reduced in mutant mice lacking ephrin-A signaling³³.

Tangential migration of interneurons

In addition to regulating radial migration and cell dispersion, Eph-ephrin signaling is critical for the tangential migration of interneurons. Excitatory cortical neurons are born at the ventricular zone and migrate radially. In contrast, inhibitory interneurons are generated in the basal telencephalon and migrate extensively along a tangential route. Cortical interneurons born in the medial ganglionic eminence (MGE) migrate along a deep route, whereas preoptic area (POA)-derived interneurons migrate along a superficial route. These routes exhibit complementary expression of EphA4 and ephrin-B3, respectively. A study using organotypic cultures and stripe assays together with gene knockdown and pharmacological approaches showed that forward signaling through EphA4 and reverse signaling through ephrin-B3 induce repulsion of MGE and POA interneurons in the inappropriate routes³⁴. MGE interneurons also express ephrin-As, and reverse signaling induced in ephrin-As by EphA4 enhances motility in these migrating MGE interneurons³⁵.

The POA also generates striatal neurons, which are generated at a similar time and also express ephrin-B3. However, striatal neurons traverse an intermediate route and terminate in the striatum, which expresses EphB1. Reverse signaling through ephrin-B3 elicited by striatal EphB1 is repulsive for migrating cortical interneurons but is an attractive stop signal for migrating striatal cells³⁶. What accounts for these divergent effects? In cortical interneurons, EphB1-ephrin-B3 reverse signaling leads to enhanced phosphorylation of Src tyrosine kinase and of focal adhesion kinase (FAK), leading to enhanced repulsion. For striatal neurons, this same signaling leads to a dephosphorylation of Src and FAK, which leads to attraction³⁶. These divergent effects might arise from endogenously high levels of phosphorylated Src and FAK in striatal cells and/or to distinct combinations of transcription factors in these two cell populations that can influence elements of signal transduction pathways.

Striatal interneurons are generated in the MGE along with cortical interneurons. They are attracted to the striatum through Nrg1/ErbB4 signaling and are simultaneously repelled from the adjacent cortex through EphB forward signaling³⁷. These authors used chromatin immunoprecipitation and luciferase assays to show that the expression of EphB1 and EphB3 is enhanced by Nkx2-1, which is expressed in striatal but not in cortical interneurons born in the MGE.

Eph-ephrin signaling thus provides both repulsive and attractive cues for tangentially migrating neurons. The determination of migratory route depends on the ensemble of Eph receptors expressed along with the molecular context within cells destined for different routes.

Axon guidance

Topographic mapping

The function of Eph-ephrin signaling in axon guidance was originally discovered in the context of topographic mapping. Graded expression of ephrin-As in the optic tectum and opposing gradients

of EphA receptors were found to be necessary for forming the high degree of topography seen in this pathway^{38–40}. Since then, further evidence has shown that Eph-ephrin signaling is critical for establishing topographic projections in the auditory system^{10,41,42}, somatosensory system⁴³, olfactory system⁴⁴, and others^{45–47}. Both forward and reverse signaling play a role, as do attractive and repulsive interactions and interactions in *cis*.

Formation of topography thus uses graded, or continuous, targeting signals. However, Eph-ephrin signaling also contributes significantly to selection of discrete, or discontinuous, synaptic targets, and these modes of targeting often occur together in a single neural pathway. Interestingly, the function of individual Eph or ephrin family members is specialized within a structure, so that family members regulating topography are distinct from those regulating modular⁴⁸, laminar⁴⁹, or ipsilateral versus contralateral⁵⁰ axon targeting decisions.

Choice points

Eph-ephrin signaling plays an important role in axon targeting at choice points, where axons select between two alternative routes. For example, null mutations in EphB1 result in reduced numbers of retinal ganglion cells that project ipsilaterally through the optic chiasm to the ipsilateral region of the lateral geniculate nucleus⁵¹. This phenotype is recapitulated when the cytoplasmic domain of EphB1 is deleted, suggesting that reverse signaling is not necessary for this targeting choice. Conversely, overexpression of EphB1 in mouse embryos is sufficient to direct retinal ganglion cell axons to the ipsilateral trajectory⁵². Interestingly, loss or gain of EphB1 reduces or increases ipsilateral targeting, respectively, whereas changes in EphB2 and EphB3 are relatively ineffective, even though these receptors are co-expressed to varying degrees in retinal ganglion cell axons^{51,52}. Analysis of the effectiveness of overexpressed chimeric receptors suggests that unique sequences in both the juxtamembrane and the extracellular domains of EphB1 work together to direct axons ipsilaterally. The selective role for EphB1 might result from differences in its ability to engage downstream signaling pathways. Additionally, crossing axons might express additional proteins that normally overcome this ipsilateral cue. In this study, the authors overexpressed the zinc finger transcription factor *Zic2*, which is expressed in retinal ganglion cells and which activates EphB1 and regulates numerous other genes as well. They found that early exogenous expression of *Zic2* was significantly more effective at inducing ipsilateral projections than EphB1, consistent with the view that a network of genes is needed to balance responses to ipsilateral versus contralateral cues. The identification of these genes and the integration of their roles in target selection, which may require a computational modeling approach, will greatly facilitate our understanding of how Eph-ephrin signaling leads to precision in axon targeting.

Several other studies highlight the broad significance for Eph-ephrin signaling in determining whether axons cross the midline^{53–56}. Eph family molecules play key roles in establishing the crossed projections of the central nervous system^{54,57}. Repulsion from

ephrins expressed at the midline may serve to limit crossing projections spatially⁵⁸ or temporally⁵³. Eph-ephrin signaling is a significant factor in determining whether axons make ipsilateral or contralateral synaptic target selections. This role has been demonstrated in the auditory brainstem pathway from the cochlear nucleus to the medial nucleus of the trapezoid body, a strictly contralateral projection in the normal brain. Mutations that reduce reverse signaling through ephrin-B proteins⁵⁹ and null mutations in ephrin-A2 or ephrin-A5 (or both) similarly reduce the specificity of this pathway, resulting in a significant ipsilateral projection⁵⁰. The similarity in these phenotypes suggests crosstalk between the classes and redundancy in cues for generating the crossed projection. Unlike the optic chiasm, in which a subset of axons is selectively targeted ipsilaterally by EphB1, this auditory projection uses multiple Eph-ephrin signaling molecules to prevent the formation of *any* ipsilateral projections. In this case, downstream signaling molecules might be similarly engaged by both classes of Eph proteins.

Recent studies of motor neuron axon guidance have shed new light on the molecular mechanisms by which Eph-ephrin signaling coordinates distinct choices. Two groups of motor neurons of the lateral motor column (LMC) in the spinal cord innervate the limb. The medial LMC (LMC_M) motor neurons innervate ventral limb muscles, whereas the lateral LMC (LMC_L) motor neurons innervate the dorsal limb muscles⁶⁰. The axons of the LMC motor neurons grow out of the spinal cord together in one fascicle and make a dorsal versus ventral choice as they enter the limb. Another group of motor neurons in the medial portion of the medial motor column (MMC_M) at the level of the hindlimb initially project axons together with the LMC axons but abruptly change course toward dorsal axial muscle targets. Both LMC_L and MMC_M axons express EphA4 and encounter ephrin-A5 along their trajectories. *In ovo* electroporation studies in chick embryos revealed that the two populations have opposite responses to ephrin-A5: LMC_L axons avoid ephrin-A5 in the limb, whereas MMC_M axons grow through ephrin-A5-positive somite regions⁶¹.

The distinct responses of these EphA4-positive axons are further complicated by the fact that these axons also express ephrin-A proteins. EphAs and ephrin-As in LMC_L motor axons are maintained in separate membrane compartments⁶², so that *trans* interactions are favored, whereas in LMC_M motor axons, EphAs and ephrin-As can reside in the same membrane compartments and interact in *cis*²¹. LMC_M motor neurons are also guided by EphB signaling⁶³.

In the *trans* signaling guiding LMC_L motor neurons, the effects of forward signaling through EphA receptors are repulsive, whereas reverse ephrin-A signaling is attractive^{62,64}. Both forward and reverse signaling are necessary to target LMC_L axons to the dorsal limb. Using co-immunoprecipitation assays to identify novel ephrin-A co-receptors, Bonanomi and colleagues⁶⁴ found that the selective attraction of LMC_L axons through ephrin-A reverse signaling is mediated by Ret, a tyrosine kinase. Ret also interacts with GFR α 1, a GPI-linked receptor for glial-derived neurotrophic factor, which

is secreted in the limb. Ret thus integrates signals from these two sources and generates a synergistic interaction that promotes axon attraction. This study highlights the significance of combinatorial codes in establishing diversity and precision in neuronal contacts.

Midline specializations

Corpus callosum

Eph proteins play a key role in establishing midline structures. In humans, mutations in *EFNB1*, the gene coding for ephrin-B1, leads to craniofrontonasal syndrome (CFNS). This syndrome is characterized by abnormally large distance between the eyes, a central nasal groove, cleft palate, and skeletal/sternum abnormalities, along with other midline distortions in the body. CFNS is also associated with agenesis of the corpus callosum, a large neural tract that interconnects the cerebral hemispheres^{65,66}.

The mouse model for CFNS parallels many of the cranial deformities and also exhibits incomplete formation of the corpus callosum⁶⁵, which depends on ephrin-B1 reverse signaling⁶⁷. Deeper examination of corpus callosum formation in several Eph family mutant mice revealed axon outgrowth defects near the midline, after axons have progressed out of cortical layers and traveled medially toward their contralateral journey. These axons coalesce and turn to project longitudinally, not medially via the commissure, similar to the human CFNS phenotype⁵⁴. Axon guidance across the midline is largely dependent on ephrin-Bs and EphBs, which are expressed in growing callosal fibers. Furthermore, abnormal glial proliferation at the midline in mutant mice brains suggested that Eph family proteins regulate this population through growth suppression⁵⁴. These studies suggest that agenesis of the corpus callosum in CFNS results from defects in axon guidance regulated by Eph-ephrin signaling.

Neural crest

Owing to the large morphological impact of the *EFNB1* mutation in CFNS, investigations into the mechanisms have focused on earlier developmental stages. Indeed, *in vivo* manipulation of ephrin-B1 expression in the developing mouse results in perturbations of cephalic neural crest cell precursors⁶⁸, which give rise to the bone and cartilage of the head. Whereas neural crest cell migration is known to be regulated by Eph proteins⁶⁹, craniofacial defects in ephrin-B1 mutants largely arise from impaired cell proliferation in the developing palate⁶⁸ as well as from impaired cell survival⁷⁰. Craniofacial development relies on ephrin-B1 reverse signaling⁶⁷. Interestingly, loss of ephrin-B1 in the developing palate leads to increased expression of EphB3, as forward signaling normally modifies EphB3 so as to promote endocytosis and degradation⁶⁸. Together, these studies show that loss of ephrin-B1 affects several aspects of central and peripheral development through multiple molecular interactions.

New research directions

Apart from CFNS, an understanding of the impact of mutations affecting Eph-ephrin signaling on human brain conditions is in its very early stages. Genetic studies have linked these mutations with neurodevelopmental disorders, including autism spectrum disorder (ASD)⁷¹, characterized by dysfunction in social interactions, repetitive behaviors, and sensory abnormalities. Some of these behaviors can be identified in simplified form in mouse models of ASD. To explore the potential link with Eph proteins, Wurzman and colleagues⁷² performed a comprehensive series of behavioral tests on ephrin-A2/A3 double-knockout mice. In a three-chamber social interaction test, the knockout mice spent significantly less time than wild-types did in a chamber exposed to a novel mouse, indicating social aversion. Compared with wild-type mice, the ephrin-A2/A3 mice exhibited significantly greater repetitive and self-injurious grooming behavior. They also showed decreased acoustic startle response and increased prepulse inhibition of the startle reflex. These behavioral phenotypes are similar to those in other mouse models of ASD. This work, though still in its early stages, expands the relevance of developmental Eph-ephrin signaling in establishing normal sensory function and behavior.

Summary

A large body of work on the roles of Eph proteins and the mechanisms underlying their versatility has emerged. Recent work demonstrates the breadth of roles throughout development and the significance for assembly of sensory, motor, and cognitive neural systems. Determining how these multiple functions are coordinated remains a significant challenge. The recent studies highlighted here have begun to shed light on this complex issue, showing that specificity arises from differential clustering, forward and reverse signaling, and unique combinations of protein family members that engage distinct signaling pathways.

Abbreviations

ASD, autism spectrum disorder; CFNS, craniofrontonasal syndrome; CR, Cajal-Retzius; FAK, focal adhesion kinase; LMC, lateral motor column; LMC_L, lateral lateral motor column; LMC_M, medial lateral motor column; MGE, medial ganglionic eminence; MMC_M, medial motor column; POA, preoptic area.

Competing interests

The authors declare that they have no disclosures.

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References



1. Laussu J, Khuong A, Gautrais J, *et al.*: **Beyond boundaries--Eph:ephrin signaling in neurogenesis.** *Cell Adh Migr.* 2014; **8**(4): 349–359.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
2. Wilkinson DG: **Regulation of cell differentiation by Eph receptor and ephrin signaling.** *Cell Adh Migr.* 2014; **8**(4): 339–348.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
3. Gale NW, Holland SJ, Valenzuela DM, *et al.*: **Eph receptors and ligands comprise two major specificity subclasses and are reciprocally compartmentalized during embryogenesis.** *Neuron.* 1996; **17**(1): 9–19.
[PubMed Abstract](#) | [Publisher Full Text](#)
4. Lisabeth EM, Falivelli G, Pasquale EB: **Eph receptor signaling and ephrins.** *Cold Spring Harb Perspect Biol.* 2013; **5**(9): pii: a009159.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
5. Himanen JP: **Ectodomain structures of Eph receptors.** *Semin Cell Dev Biol.* 2012; **23**(1): 35–42.
[PubMed Abstract](#) | [Publisher Full Text](#)
6. **F** Himanen JP, Chumley MJ, Lackmann M, *et al.*: **Repelling class discrimination: ephrin-A5 binds to and activates EphB2 receptor signaling.** *Nat Neurosci.* 2004; **7**(5): 501–509.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
7. **F** Lema Tomé CM, Palma E, Ferluga S, *et al.*: **Structural and functional characterization of monomeric EphrinA1 binding site to EphA2 receptor.** *J Biol Chem.* 2012; **287**(17): 14012–14022.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
8. Wykosy J, Palma E, Gibo DM, *et al.*: **Soluble monomeric EphrinA1 is released from tumor cells and is a functional ligand for the EphA2 receptor.** *Oncogene.* 2008; **27**(58): 7260–7273.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
9. **F** Ieguchi K, Tomita T, Omori T, *et al.*: **ADAM12-cleaved ephrin-A1 contributes to lung metastasis.** *Oncogene.* 2014; **33**(17): 2179–2190.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
10. Cramer KS, Gabriele ML: **Axon guidance in the auditory system: multiple functions of Eph receptors.** *Neuroscience.* 2014; **277**: 152–162.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
11. Cowan CA, Henkemeyer M: **Ephrins in reverse, park and drive.** *Trends Cell Biol.* 2002; **12**(7): 339–346.
[PubMed Abstract](#) | [Publisher Full Text](#)
12. Kullander K, Klein R: **Mechanisms and functions of Eph and ephrin signalling.** *Nat Rev Mol Cell Biol.* 2002; **3**(7): 475–486.
[PubMed Abstract](#) | [Publisher Full Text](#)
13. Pasquale EB: **Eph-ephrin bidirectional signaling in physiology and disease.** *Cell.* 2008; **133**(1): 38–52.
[PubMed Abstract](#) | [Publisher Full Text](#)
14. Nikolov DB, Xu K, Himanen JP: **Eph/ephrin recognition and the role of Eph/ephrin clusters in signaling initiation.** *Biochim Biophys Acta.* 2013; **1834**(10): 2160–2165.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
15. Janes PW, Nievergall E, Lackmann M: **Concepts and consequences of Eph receptor clustering.** *Semin Cell Dev Biol.* 2012; **23**(1): 43–50.
[PubMed Abstract](#) | [Publisher Full Text](#)
16. **F** Himanen JP, Yermekbayeva L, Janes PW, *et al.*: **Architecture of Eph receptor clusters.** *Proc Natl Acad Sci U S A.* 2010; **107**(24): 10860–10865.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
17. **F** Seiradake E, Harlos K, Sutton G, *et al.*: **An extracellular steric seeding mechanism for Eph-ephrin signaling platform assembly.** *Nat Struct Mol Biol.* 2010; **17**(4): 398–402.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
18. **F** Janes PW, Griesshaber B, Atapattu L, *et al.*: **Eph receptor function is modulated by heterooligomerization of A and B type Eph receptors.** *J Cell Biol.* 2011; **195**(6): 1033–1045.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
19. **F** Seiradake E, Schaupp A, del Toro Ruiz D, *et al.*: **Structurally encoded intraclass differences in EphA clusters drive distinct cell responses.** *Nat Struct Mol Biol.* 2013; **20**(8): 958–964.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
20. **F** Schaupp A, Sabet O, Dudanova I, *et al.*: **The composition of EphB2 clusters determines the strength in the cellular repulsion response.** *J Cell Biol.* 2014; **204**(3): 409–422.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
21. **F** Kao TJ, Kania A: **Ephrin-mediated cis-attenuation of Eph receptor signaling is essential for spinal motor axon guidance.** *Neuron.* 2011; **71**(1): 76–91.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
22. **F** Falivelli G, Lisabeth EM, Rubio de la Torre E, *et al.*: **Attenuation of eph receptor kinase activation in cancer cells by coexpressed ephrin ligands.** *PLoS One.* 2013; **8**(11): e81445.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
23. Yin Y, Yamashita Y, Noda H, *et al.*: **EphA receptor tyrosine kinases interact with co-expressed ephrin-A ligands in cis.** *Neurosci Res.* 2004; **48**(3): 285–296.
[PubMed Abstract](#) | [Publisher Full Text](#)
24. Hornberger MR, Dütting D, Ciossek T, *et al.*: **Modulation of EphA receptor function by coexpressed ephrinA ligands on retinal ganglion cell axons.** *Neuron.* 1999; **22**(4): 731–742.
[PubMed Abstract](#) | [Publisher Full Text](#)
25. **F** Carvalho RF, Beutler M, Marler KJ, *et al.*: **Silencing of EphA3 through a cis interaction with ephrinA5.** *Nat Neurosci.* 2006; **9**(3): 322–330.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
26. Klein R: **Eph/ephrin signalling during development.** *Development.* 2012; **139**(22): 4105–4109.
[PubMed Abstract](#) | [Publisher Full Text](#)
27. Terriente J, Pujades C: **Cell segregation in the vertebrate hindbrain: a matter of boundaries.** *Cell Mol Life Sci.* 2015; **72**(19): 3721–3730.
[PubMed Abstract](#) | [Publisher Full Text](#)
28. **F** Arvanitis DN, Béhar A, Tryoen-Tóth P, *et al.*: **Ephrin B1 maintains apical adhesion of neural progenitors.** *Development.* 2013; **140**(10): 2082–2092.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
29. **F** Villar-Cerviño V, Molano-Mazón M, Catchpole T, *et al.*: **Contact repulsion controls the dispersion and final distribution of Cajal-Retzius cells.** *Neuron.* 2013; **77**(3): 457–471.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
30. **F** Bouché E, Romero-Ortega MI, Henkemeyer M, *et al.*: **Reelin induces EphB activation.** *Cell Res.* 2013; **23**(4): 473–490.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
31. **F** Sentürk A, Pfennig S, Weiss A, *et al.*: **Ephrin Bs are essential components of the Reelin pathway to regulate neuronal migration.** *Nature.* 2011; **472**(7343): 356–360.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
32. **F** He S, Li Z, Ge S, *et al.*: **Inside-Out Radial Migration Facilitates Lineage-Dependent Neocortical Microcircuit Assembly.** *Neuron.* 2015; **86**(5): 1159–1166.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
33. **F** Torii M, Hashimoto-Torii K, Levitt P, *et al.*: **Integration of neuronal clones in the radial cortical columns by EphA and ephrin-A signalling.** *Nature.* 2009; **461**(7263): 524–528.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
34. **F** Zimmer G, Rudolph J, Landmann J, *et al.*: **Bidirectional ephrinB3/EphA4 signaling mediates the segregation of medial ganglionic eminence- and preoptic area-derived interneurons in the deep and superficial migratory stream.** *J Neurosci.* 2011; **31**(50): 18364–18380.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
35. **F** Steinecke A, Gampe C, Zimmer G, *et al.*: **EphA/ephrin A reverse signaling promotes the migration of cortical interneurons from the medial ganglionic eminence.** *Development.* 2014; **141**(2): 460–471.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
36. **F** Rudolph J, Gerstmann K, Zimmer G, *et al.*: **A dual role of EphB1/ephrin-B3 reverse signaling on migrating striatal and cortical neurons originating in the preoptic area: should I stay or go away?** *Front Cell Neurosci.* 2014; **8**: 185.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
37. **F** Villar-Cerviño V, Kappeler C, Nóbrega-Pereira S, *et al.*: **Molecular mechanisms controlling the migration of striatal interneurons.** *J Neurosci.* 2015; **35**(23): 8718–8729.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
38. Cheng HJ, Nakamoto M, Bergemann AD, *et al.*: **Complementary gradients in expression and binding of ELF-1 and Mek4 in development of the topographic retinotectal projection map.** *Cell.* 1995; **82**(3): 371–381.
[PubMed Abstract](#) | [Publisher Full Text](#)
39. Drescher U, Kremoser C, Handwerker C, *et al.*: **In vitro guidance of retinal ganglion cell axons by RAGS, a 25 kDa tectal protein related to ligands for Eph receptor tyrosine kinases.** *Cell.* 1995; **82**(3): 359–370.
[PubMed Abstract](#) | [Publisher Full Text](#)
40. Feldheim DA, Kim YI, Bergemann AD, *et al.*: **Genetic analysis of ephrin-A2 and ephrin-A5 shows their requirement in multiple aspects of retinocollicular mapping.** *Neuron.* 2000; **25**(3): 563–574.
[PubMed Abstract](#) | [Publisher Full Text](#)
41. Huffman KJ, Cramer KS: **EphA4 regulates tonotopic ordering of projections in the chick auditory brainstem.** *Soc Neurosci Abstr.* 2006.
[Reference Source](#)
42. Miko IJ, Nakamura PA, Henkemeyer M, *et al.*: **Auditory brainstem neural activation patterns are altered in EphA4- and ephrin-B2-deficient mice.** *J Comp Neurol.* 2007; **505**(6): 669–681.
[PubMed Abstract](#) | [Publisher Full Text](#)
43. Prakash N, Vanderhaeghen P, Cohen-Cory S, *et al.*: **Malformation of the functional organization of somatosensory cortex in adult ephrin-A5 knock-out mice revealed by in vivo functional imaging.** *J Neurosci.* 2000; **20**(15): 5841–5847.
[PubMed Abstract](#)

44. **F** Serizawa S, Miyamichi K, Takeuchi H, *et al.*: **A neuronal identity code for the odorant receptor-specific and activity-dependent axon sorting.** *Cell*. 2006; **127**(5): 1057–1069.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
45. **F** Wilks TA, Rodger J, Harvey AR: **A role for ephrin-As in maintaining topographic organization in register across interconnected central visual pathways.** *Eur J Neurosci*. 2010; **31**(4): 613–622.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
46. Cang J, Niell CM, Liu X, *et al.*: **Selective disruption of one Cartesian axis of cortical maps and receptive fields by deficiency in ephrin-As and structured activity.** *Neuron*. 2008; **57**(4): 511–523.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
47. Dufour A, Seibt J, Passante L, *et al.*: **Area specificity and topography of thalamocortical projections are controlled by ephrin/Eph genes.** *Neuron*. 2003; **39**(3): 453–465.
[PubMed Abstract](#) | [Publisher Full Text](#)
48. **F** Wallace MM, Kavianpour SM, Gabriele ML: **Ephrin-B2 reverse signaling is required for topography but not pattern formation of lateral superior olivary inputs to the inferior colliculus.** *J Comp Neurol*. 2013; **521**(7): 1585–1597.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
49. **F** Sweeney NT, James KN, Sales EC, *et al.*: **Ephrin-As are required for the topographic mapping but not laminar choice of physiologically distinct RGC types.** *Dev Neurobiol*. 2015; **75**(6): 584–593.
[PubMed Abstract](#) | [Free Full Text](#) | [F1000 Recommendation](#)
50. Abdul-Latif ML, Salazar JA, Marshak S, *et al.*: **Ephrin-A2 and ephrin-A5 guide contralateral targeting but not topographic mapping of ventral cochlear nucleus axons.** *Neural Dev*. 2015; **10**: 27.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
51. **F** Chenaux G, Henkemeyer M: **Forward signaling by EphB1/EphB2 interacting with ephrin-B ligands at the optic chiasm is required to form the ipsilateral projection.** *Eur J Neurosci*. 2011; **34**(10): 1620–1633.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
52. **F** Petros TJ, Shrestha BR, Mason C: **Specificity and sufficiency of EphB1 in driving the ipsilateral retinal projection.** *J Neurosci*. 2009; **29**(11): 3463–3474.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
53. Cramer KS, Cerretti DP, Siddiqui SA: **EphB2 regulates axonal growth at the midline in the developing auditory brainstem.** *Dev Biol*. 2006; **295**(1): 76–89.
[PubMed Abstract](#) | [Publisher Full Text](#)
54. Mendes SW, Henkemeyer M, Liebl DJ: **Multiple Eph receptors and B-class ephrins regulate midline crossing of corpus callosum fibers in the developing mouse forebrain.** *J Neurosci*. 2006; **26**(3): 882–892.
[PubMed Abstract](#) | [Publisher Full Text](#)
55. **F** Imondi R, Kaprielian Z: **Commissural axon pathfinding on the contralateral side of the floor plate: a role for B-class ephrins in specifying the dorsoventral position of longitudinally projecting commissural axons.** *Development*. 2001; **128**(23): 4859–4871.
[PubMed Abstract](#) | [F1000 Recommendation](#)
56. Kaprielian Z, Runko E, Imondi R: **Axon guidance at the midline choice point.** *Dev Dyn*. 2001; **221**(2): 154–181.
[PubMed Abstract](#) | [Publisher Full Text](#)
57. **F** Robichaux MA, Chenaux G, Ho HY, *et al.*: **EphB1 and EphB2 intracellular domains regulate the formation of the corpus callosum and anterior commissure.** *Dev Neurobiol*. 2016; **76**(4): 405–20.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
58. Kadison SR, Mäkinen T, Klein R, *et al.*: **EphB receptors and ephrin-B3 regulate axon guidance at the ventral midline of the embryonic mouse spinal cord.** *J Neurosci*. 2006; **26**(35): 8909–8914.
[PubMed Abstract](#) | [Publisher Full Text](#)
59. Hsieh CY, Nakamura PA, Luk SO, *et al.*: **Ephrin-B reverse signaling is required for formation of strictly contralateral auditory brainstem pathways.** *J Neurosci*. 2010; **30**(29): 9840–9849.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
60. Tosney KW, Landmesser LT: **Growth cone morphology and trajectory in the lumbo-sacral region of the chick embryo.** *J Neurosci*. 1985; **5**(9): 2345–2358.
[PubMed Abstract](#)
61. **F** Eberhart J, Barr J, O'Connell S, *et al.*: **Ephrin-A5 exerts positive or inhibitory effects on distinct subsets of EphA4-positive motor neurons.** *J Neurosci*. 2004; **24**(5): 1070–1078.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
62. **F** Marquardt T, Shirasaki R, Ghosh S, *et al.*: **Coexpressed EphA receptors and ephrin-A ligands mediate opposing actions on growth cone navigation from distinct membrane domains.** *Cell*. 2005; **121**(1): 127–139.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
63. Luria V, Krawchuk D, Jessell TM, *et al.*: **Specification of motor axon trajectory by ephrin-B:EphB signaling: symmetrical control of axonal patterning in the developing limb.** *Neuron*. 2008; **60**(6): 1039–1053.
[PubMed Abstract](#) | [Publisher Full Text](#)
64. **F** Bonanomi D, Chivatakarn O, Bai G, *et al.*: **Ret is a multifunctional coreceptor that integrates diffusible- and contact-axon guidance signals.** *Cell*. 2012; **148**(3): 568–582.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
65. Twigg SR, Kan R, Babbs C, *et al.*: **Mutations of ephrin-B1 (EFNB1), a marker of tissue boundary formation, cause craniofrontonasal syndrome.** *Proc Natl Acad Sci U S A*. 2004; **101**(23): 8652–8657.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
66. Compagni A, Logan M, Klein R, *et al.*: **Control of skeletal patterning by ephrinB1-EphB interactions.** *Dev Cell*. 2003; **5**(2): 217–230.
[PubMed Abstract](#) | [Publisher Full Text](#)
67. **F** Bush JO, Soriano P: **Ephrin-B1 regulates axon guidance by reverse signaling through a PDZ-dependent mechanism.** *Genes Dev*. 2009; **23**(13): 1586–1599.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
68. **F** Bush JO, Soriano P: **Ephrin-B1 forward signaling regulates craniofacial morphogenesis by controlling cell proliferation across Eph-ephrin boundaries.** *Genes Dev*. 2010; **24**(18): 2068–2080.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
69. Krull CE: **Neural crest cells and motor axons in avians: Common and distinct migratory molecules.** *Cell Adh Migr*. 2010; **4**(4): 631–634.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
70. **F** Noh H, Park E, Park S: **In vivo expression of ephrinA5-Fc in mice results in cephalic neural crest agenesis and craniofacial abnormalities.** *Mol Cells*. 2014; **37**(1): 59–65.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
71. Casey JP, Magalhaes T, Conroy JM, *et al.*: **A novel approach of homozygous haplotype sharing identifies candidate genes in autism spectrum disorder.** *Hum Genet*. 2012; **131**(4): 565–579.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
72. **F** Wurzman R, Forcelli PA, Griffey CJ, *et al.*: **Repetitive grooming and sensorimotor abnormalities in an ephrin-A knockout model for Autism Spectrum Disorders.** *Behav Brain Res*. 2015; **278**: 115–128.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)

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