Jeong, J Alzheimers Dis Parkinsonism 2016, 6:7
DOI: 10.4172/2161-0460.1000293

Journal of
Alzheimer's Disease & Parkinsonism

Commentary OMICS International

Diversification of Plexin Signaling: How to Regulate Complex Neural Circuits with a Limited Number of Axon Guidance Molecules

Sangyun Jeong*

Department of Molecular Biology, Chonbuk National University, Jeonju, Jeollabukdo 54896, Republic of Korea

Keywords: Plexin; Semaphorin; Co-receptor; Ligand regulation; Axon guidance; Forward signaling; Reverse signaling

Introduction

Plexins are a large family of phylogenetically conserved guidance receptors that play diverse roles in shaping neural circuits [1]. Plexin signaling through semaphorins (Semas), another large family of guidance molecules, was identified to mediate repulsive axon guidance function during neural development [2]. Plexins are grouped into four subfamilies (plexinA-plexinD), comprising two members in flies (PlexA and PlexB) and nine members in vertebrates (PlxnA1-PlxnA4, PlxnB1-PlxnB3, PlxnC1 and PlxnD1) [3]. Semas are grouped into seven classes and include five members (classes 1, 2 and 5) in flies and twenty members (classes 3, 4, 5, 6 and 7) in vertebrates [4]. One common characteristic of plexins and Semas is the presence of a semaphorin (Sema) domain in the extracellular region [5-7]. These Sema domains are responsible for most plexin-semaphorin interactions, mediating signal transduction pathways downstream of the plexin receptors [5-7]. A large number of members found in the plexin and semaphorin families themselves can provide diverse guidance functions during neural development. However, this number does not seem to be sufficient to account for an overwhelming number of cellular processes required for the development of complex patterns of neuronal wiring. Therefore, one intriguing question is how a limited number of guidance cue molecules regulate a much larger number of cellular events. A growing body of evidence demonstrates several mechanisms, including differential ligand regulation, combinatorial receptor codes, and forward and reverse signaling, to explain how regulation of complex neural circuits can occur with a limited number of guidance cue molecules. Overlapping but distinct patterns of diversified plexin signaling are also observed in the regulation of tumor growth and metastasis [8-10]. However, this topic is beyond the scope of the present commentary.

Differential Ligand Regulation

A single guidance cue receptor can be utilized to control distinct axon pathfinding events of different neuronal types. One example is the differential ligand regulation of PlexB signaling during the Drosophila embryonic neural development [11]. PlexB functions as a receptor for the secreted semaphorins Sema-2a and Sema-2b in both the embryonic central nervous system (CNS) and the peripheral nervous system [11-13]. Sema-2a and Sema-2b induce repulsive and attractive axon guidance through the same receptor PlexB [11-13]. These opposing guidance functions could be explained by differences in the amino acid sequences of Sema-2a and Sema-2b (68% identity), leading to differential interactions with PlexB [12]. Sema-2a and Sema-2b exert opposite and mutually independent functions in the CNS, since Sema-2a responsive axons appear to be different from Sema-2b-responsive ones [12]. However, in the peripheral intersegmental nerve b (ISNb) pathway, PlexB integrates opposing Sema-2a and Sema-2b guidance cues in a mutually dependent manner, suggesting that the same ISNb axons appear to respond to opposing guidance cues in a competitive manner [11]. Furthermore, a different type of ligand regulation of PlexB signaling is found in the peripheral segmental nerve a (SNa) pathway [11]. Although Sema-2a and Sema-2b guidance functions contribute to motor axon pathfinding in the SNa, PlexB-mediated target recognition function observed in the SNa pathway appear to be independent of Sema-2a and Sema-2b and requires the action of an unknown ligand [11]. Taken together, these results illustrate that PlexB can expand receptor signaling capacities through differential interactions with multiple ligands, including Sema-2a and Sema-2b.

Combinatorial Receptor Codes

Single guidance receptor signaling can be diversified by differential interactions with co-receptors. One well-known example is the gating of the plexin response by neurophilin (Nrp) during the assembly of vertebrate forebrain neuronal circuits [14]. The vertebrate class 3 secreted semaphorins (Sema3A to Sema3G) generally bind to a receptor complex consisting of Nrps as ligand-binding components and plexins as signal-transducing components [15,16]. Interestingly, in a subset of coticofugal and striatonigral neurons, Sema3E directly interacts with PlxnD1 rather than Nrp1, resulting in repulsive guidance [14,17]. This is consistent with the fact that coticofugal and striatonigral neurons express PlxnD1 but not Nrp1. However, in subiculo-mammillary neurons, the formation of a specific PlxnD1 receptor complex with co-receptors Nrp1 and VEGFR2 switches from a repulsive to an attractive response upon binding to Sema3E [14,18]. Recently some other receptor tyrosine kinases were shown to be implicated in plexin signaling. For example, the vertebrate PlxnB1 activation, which results in axonal growth cone collapse, requires the receptor tyrosine kinase, ErbB-2 [16,19,20]. Transmembrane Sema4D directly binds to PlxnB1 but not via Nrp, thereby stimulating the ErbB-2 tyrosine kinase activity that subsequently leads to phosphorylation of both PlxnB1 and ErbB-2 [16]. This finding is reminiscent of a previous observation that the association between the Drosophila PlexA and the receptor tyrosine kinase, Off-track, mediates repulsive guidance function in embryonic PNS axon path finding [21]. This co-receptor-based diversification of single guidance receptor signaling is frequently observed in other guidance cue molecules [22-25]. In addition, semaphorin-independent plexin signaling and plexin-independent semaphorin signaling further diversify their functions. For example, homophilic interaction of PlxnB3 *in trans* through the Sema domains stimulates neurite outgrowth of cerebellar neurons [26]. In contrast, integrins were shown to mediate Sema7A-induced axon outgrowth in a PlxnC1-independent manner

***Corresponding author:** Sangyun Jeong, Department of Molecular Biology, Chonbuk National University, Jeonju, Jeollabukdo 54896, Republic of Korea, Tel: +82632703355; E-mail: sjeong4@jbnu.ac.kr

Received November 15, 2016; **Accepted** December 23, 2016; **Published** December 30, 2016

Citation: Jeong S (2016) Diversification of Plexin Signaling: How to Regulate Complex Neural Circuits with a Limited Number of Axon Guidance Molecules. J Alzheimers Dis Parkinsonism 6: 293. doi: 10.4172/2161-0460.1000293

[27]. Heparan and chondroitin sulfate proteoglycans also appear to function as receptors for guidance cue molecules Sema5A and Sema3A [28,29]. In conclusion, increasing the number of receptors and co-receptors, and their combinations for a single ligand is a simple way of diversifying single guidance receptor signaling.

Forward and Reverse Signaling

Plexins function not only as receptors for Semas (forward signaling in plexin-bearing cells), but also as ligands for some transmembrane Semas (reverse signaling in Sema-bearing cells). The Drosophila PlexA appears to act as a ligand for the class 1 transmembrane semaphorin Sema-1a in order to regulate the axon guidance of photoreceptor (R cell) axons in the developing visual system [30]. However, it is not clear whether PlexA-mediated forward signaling is also involved in the regulation of R-cell axon guidance [30]. On the other hand, the receptor function of PlexA via Sema-1a plays an important role in shaping Drosophila neuromuscular connectivity, whereas embryonic CNS axon guidance does require the PlexA receptor function but not Sema-1a as a ligand for PlexA [31]. These results indicate that, instead of PlexA bidirectional signaling, either forward or reverse signaling is utilized to control distinct cellular processes in different types of neurons during neural development. In contrast, the vertebrate plexins PlxnA1, PlxnA2 and PlxnA4 were shown to mediate forward and/or reverse signaling [32-35]. Some vertebrate class 6 semaphorins including Sema6A, Sema6B and Sema6D, which are structurally and phylogenetically related to the transmembrane Sema-1a [36], function as both ligands and receptors for their cognate partners in this bidirectional signaling. PlxnA1/Sema6D-mediated bidirectional signaling was first identified in cardiac chamber formation [35]. This bidirectional signaling contributes to the circumferential migration of myocardial cells, while forward and reverse signaling is required for perpendicular migration of myocardial cells and inhibition of endocardium migration, respectively [35].

Recent studies also showed that PlxnA2/A4/Sema6A-mediated bidirectional signaling plays an essential role in the vertebrate visual circuit assembly [34,37]. PlxnA2/Sema6A forward signaling acts as a repulsive guidance cue to regulate dendritic arborizations and stratification of starburst amacrine cell in the mouse retina [37]. In contrast, PlxnA2/A4/Sema6A reverse signaling functions as an attractive guidance cue to control the functional assembly of accessory optical system circuits [34]. In a separate study using primary neurons, PlxnA2/Sema6A reverse signaling was also shown to regulate neuronal morphology *in vitro* [33]. Another study in chick spinal cord commissural neurons demonstrates that PlxnA2/Sema6B reverse signaling is required for post-crossing commissural axon guidance [32]. The functional roles of Plexin/Sema-mediated bidirectional signaling during neural development appear to be independent, in most cases, except for PlxnA1/Sema6D bidirectional signaling in cardiac development. This indicates non-overlapping expression patterns of plexins and semaphorin proteins. Frequent gain and loss of gene expression occur through evolutionary changes in *cis*-regulatory elements [38]. Therefore, the seemingly independent mode of regulation for plexin forward and reverse signaling may provide another simple way to expand guidance cue signaling capacities in different neuronal types.

Conclusion

Babies are born with approximately 20 billion neocortical neurons [39]. Precise neuronal connections through axons and dendrites are responsible for the functional assembly of complex neural circuits and normal nervous system functions. Axon guidance molecules are key players in the establishment of neuronal circuits. However, the number of axon guidance molecules present in our genome is much smaller than the number of axon guidance requirements to regulate complex neural circuits. Here I outline three main mechanisms underlying the diversification of plexin signaling to account for how a limited number of guidance cue molecules generate a much larger number of axon guidance events. Further studies on differential ligand regulation, combinatorial receptor codes, and bidirectional signaling will be helpful for a better understanding of molecular mechanisms that regulate neuronal connections. Furthermore, knowledge of diversified plexin signaling, which relies on specific protein interactions between semaphorins, plexins and their co-receptors, can be applied to drug development for the treatment of various diseases including central nervous system injury and cancer [9]. Indeed, the administration of small-molecule drugs that interfere with semaphorin/plexin signaling shows preventive or therapeutic effects in preclinical experimental models of disease [9].

Acknowledgement

This work was supported by NRF-2013R1A1A4A01011329 (S.J.).

References

1. Pasterkamp RJ, Kolodkin AL (2003) Semaphorin junction: Making tracks toward neural connectivity. Curr Opin Neurobiol 13: 79-89.
2. Kolodkin AL, Tessier-Lavigne M (2011) Mechanisms and molecules of neuronal wiring: A primer. Cold Spring Harb Perspect Biol 3.
3. Zhou Y, Gunput RA, Pasterkamp RJ (2008) Semaphorin signaling: Progress made and promises ahead. Trends Biochem Sci 33: 161-170.
4. Pasterkamp RJ (2012) Getting neural circuits into shape with semaphorins. Nat Rev Neurosci 13: 605-618.
5. Janssen BJ, Robinson RA, Perez-Branguli F, Bell CH, Mitchell KJ, et al. (2010) Structural basis of semaphorin-plexin signalling. Nature 467: 1118-1122.
6. Liu H, Juo ZS, Shim AH, Focia PJ, Chen X, et al. (2010) Structural basis of semaphorin-plexin recognition and viral mimicry from Sema7A and A39R complexes with PlexinC1. Cell 142: 749-761.
7. Nogi T, Yasui N, Mihara E, Matsunaga Y, Noda M, et al. (2010) Structural basis for semaphorin signalling through the plexin receptor. Nature 467: 1123-1127.
8. Cagnoni G, Tamagnone L (2014) Semaphorin receptors meet receptor tyrosine kinases on the way of tumor progression. Oncogene 33: 4795-4802.
9. Worzfeld T, Offermanns S2 (2014) Semaphorins and plexins as therapeutic targets. Nat Rev Drug Discov 13: 603-621.
10. Neufeld G, Mumblat Y, Smolkin T, Toledano S, Nir-Zvi I, et al. (2016) The semaphorins and their receptors as modulators of tumor progression. Drug Resist Updat 29: 1-12.
11. Roh S, Yang DS, Jeong S (2016) Differential ligand regulation of PlexB signaling in motor neuron axon guidance in Drosophila. Int J Dev Neurosci 55: 34-40.
12. Wu Z, Sweeney LB, Ayoob JC, Chak K, Andreone BJ, et al. (2011) A combinatorial semaphorin code instructs the initial steps of sensory circuit assembly in the Drosophila CNS. Neuron 70: 281-298.
13. Zlatic M, Li F, Strigini M, Grueber W, Bate M (2009) Positional cues in the Drosophila nerve cord: Semaphorins pattern the dorso-ventral axis. PLoS Biol 7: e1000135.
14. Chauvet S, Cohen S, Yoshida Y, Fekrane L, Livet J, et al. (2007) Gating of Sema3E/PlexinD1 signaling by neuropilin-1 switches axonal repulsion to attraction during brain development. Neuron 56: 807-822.
15. Bagri A, Tessier-Lavigne M (2002) Neuropilins as Semaphorin receptors: *In vivo* functions in neuronal cell migration and axon guidance. Adv Exp Med Biol 515: 13-31.
16. Tamagnone L, Artigiani S, Chen H, He Z, Ming GI, et al. (1999) Plexins are a large family of receptors for transmembrane, secreted, and GPI-anchored semaphorins in vertebrates. Cell 99: 71-80.
17. Gu C, Yoshida Y, Livet J, Reimert DV, Mann F, et al. (2005) Semaphorin 3E

and plexin-D1 control vascular pattern independently of neuropilins. Science 307: 265-268.

18. Bellon A, Luchino J, Haigh K, Rougon G, Haigh J, et al. (2010) VEGFR2 (KDR/Flk1) signaling mediates axon growth in response to semaphorin 3E in the developing brain. Neuron 66: 205-219.
19. Takahashi T, Fournier A, Nakamura F, Wang LH, Murakami Y, et al. (1999) Plexin-neuropilin-1 complexes form functional semaphorin-3A receptors. Cell 99: 59-69.
20. Swiercz JM, Kuner R, Offermanns S (2004) Plexin-B1/RhoGEF-mediated RhoA activation involves the receptor tyrosine kinase ErbB-2. J Cell Biol 165: 869-880.
21. Winberg ML, Tamagnone L, Bai J, Comoglio PM, Montell D, et al. (2001) The transmembrane protein Off-track associates with Plexins and functions downstream of Semaphorin signaling during axon guidance. Neuron 32: 53-62.
22. Castellani V, Chédotal A, Schachner M, Faivre-Sarrailh C, Rougon G (2000) Analysis of the L1-deficient mouse phenotype reveals cross-talk between Sema3A and L1 signaling pathways in axonal guidance. Neuron 27: 237-249.
23. Falk J, Bechara A, Fiore R, Nawabi H, Zhou H, et al. (2005) Dual functional activity of semaphorin 3B is required for positioning the anterior commissure. Neuron 48: 63-75.
24. Hong K, Hinck L, Nishiyama M, Poo MM, Tessier-Lavigne M, et al. (1999) A ligand-gated association between cytoplasmic domains of UNC5 and DCC family receptors converts netrin-induced growth cone attraction to repulsion. Cell 97: 927-941.
25. Kantor DB, Chivatakarn O, Peer KL, Oster SF, Inatani M, et al. (2004) Semaphorin 5A is a bifunctional axon guidance cue regulated by heparan and chondroitin sulfate proteoglycans. Neuron 44: 961-975.
26. Hartwig C, Veske A, Krejcova S, Rosenberger G, Finckh U (2005) Plexin B3 promotes neurite outgrowth, interacts homophilically, and interacts with Rin. BMC Neurosci 6: 53.
27. Pasterkamp RJ, Peschon JJ, Spriggs MK, Kolodkin AL (2003) Semaphorin 7A promotes axon outgrowth through integrins and MAPKs. Nature 424: 398-405.
28. Kantor DB, Chivatakarn O, Peer KL, Oster SF, Inatani M, et al. (2004) Semaphorin 5A is a bifunctional axon guidance cue regulated by heparan and chondroitin sulfate proteoglycans. Neuron 44: 961-975.
29. Dick G, Tan CL, Alves JN, Ehlert EM, Miller GM, et al. (2013) Semaphorin 3A binds to the perineuronal nets via chondroitin sulfate type E motifs in rodent brains. J Biol Chem 288: 27384-27395.
30. Yu L, Zhou Y, Cheng S, Rao Y (2010) Plexin a-semaphorin-1a reverse signaling regulates photoreceptor axon guidance in Drosophila. J Neurosci 30: 12151-12156.
31. Jeong S, Juhaszova K, Kolodkin AL (2012) The Control of semaphorin-1a-mediated reverse signaling by opposing pebble and RhoGAPp190 functions in Drosophila. Neuron 76: 721-734.
32. Andermatt I, Wilson NH, Bergmann T, Mauti O, Gesemann M, et al. (2014) Semaphorin 6B acts as a receptor in post-crossing commissural axon guidance. Development 141: 3709-3720.
33. Perez-Branguli F, Zagar Y, Shanley DK, Graef IA, Chédotal A, et al. (2016) Reverse signaling by Semaphorin-6A regulates cellular aggregation and neuronal morphology. PLoS One 11: e0158686.
34. Sun LO, Brady CM, Cahill H, Al-Khindi T, Sakuta H, et al. (2015) Functional assembly of accessory optic system circuitry critical for compensatory eye movements. Neuron 86: 971-984.
35. Toyofuku T, Zhang H, Kumanogoh A, Takegahara N, Yabuki M, et al. (2004) Guidance of myocardial patterning in cardiac development by Sema6D reverse signalling. Nat Cell Biol 6: 1204-1211.
36. Yazdani U, Terman JR (2006) The semaphorins. Genome Biol 7: 211.
37. Sun LO, Jiang Z, Rivlin-Etzion M, Hand R, Brady CM, et al. (2013) On and off retinal circuit assembly by divergent molecular mechanisms. Science 342: 1241974.
38. Carroll SB (2008) Evo-devo and an expanding evolutionary synthesis: A genetic theory of morphological evolution. Cell 134: 25-36.
39. Larsen CC, Bonde Larsen K, Bogdanovic N, Laursen H, Graem N, et al. (2006) Total number of cells in the human new-born telencephalic wall. Neuroscience 139: 999-1003.