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Review

The role and mechanism-of-action of Sema3E and Plexin-D1 in vascular and neural development

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ABSTRACT

Class 3 secreted semaphorins (Sema3A–3G) participate in many aspects of axon guidance through holoreceptor complexes that include Neuropilin-1 (Npn-1) or Neuropilin-2 and one of the four class A plexin proteins. However, unlike other Sema3 family proteins, Sema3E directly binds to Plexin-D1 without neuropilins. Its biological function was first explored in intersomitic vessel formation and since its initial discovery, Sema3E–Plexin-D1 signaling has been found to participate in the many biological systems in addition to vascular development, via seemingly different mode of actions. For example, temporal and spatial control of ligand vs. receptor results in two different mechanisms governing vascular patterning. Interactions with other transmembrane proteins such as neuropilin and VEGFR2 result in different axonal behaviors. Ligand receptor localization on pre- vs. post-synaptic neurons is used to control different types of synapse formation. Perhaps different downstream effectors will also result in different functional outcomes. Given the limited number of ligands and receptors in the genome and their multifunctional nature, we expect that more modes of action will be discovered in the future. In this review, we highlight current advances on the mechanisms of how Sema3E–Plexin-D1 interaction shapes the networks of multiple biological systems, in particular the vascular and nervous systems.

Contents

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1. Introduction

The semaphorins are a large family of axon guidance cues that consists of both secreted and membrane-bound proteins. There are seven class 3 secreted semaphorins (Sema3A–3G) [1–3]. In contrast to their membrane-associated semaphorin cousins, most vertebrate class 3 semaphorins are known to bind neuropilins and form holoreceptor complex with plexins. The exception to this rule is Sema3E, which binds its receptor Plexin-D1 directly and independently of the neuropilins [4].

Like other Sema3s, Sema3E contains Sema, PSI (plexin–semaphorin–integrin), and Ig (immunoglobulin) domains and a basic C terminus tail [5]. Plexin-D1 is a relatively new member of the Plexin family, which is made up of A, B, C and D subfamilies [6]. Like all plexin family members, Plexin-D1 contains a sema-domain, three Met-related sequences (MRS), three glycine/proline-rich motifs, a single transmembrane domain, and two highly conserved intracellular domains known together as the SEX-plexin domain. Plexin-D1 differs from other plexins in the third MRS motif, which contains only six of the eight conserved cysteines normally encountered in a MRS. Semaphorins and plexins can interact via their sema domains [6,7]. Recent structural work has revealed that binding of each homodimer arrangement of semaphorins and plexins forms a heterodimer complex that then elicits conformational change in the complex. This structural alteration transmits signals to the intracellular domain of Plexins [8]. Semaphorin signaling has largely been studied in vitro in the context of axon guidance, and proteins found to be downstream of the ligand–receptor interaction include small GTPases, cyclic nucleotides, and kinases [3,9]. Several recent in vivo studies have elegantly demonstrated that specific downstream effectors mediate specific aspect of semaphorin-mediated neuronal function, suggesting that unique pathways exist to control different semaphorin mediated effects [10]. As a relative novel ligand–receptor pair, so far little is known about Sema3E–Plexin-D1, signaling especially in in vivo settings.

2. The mechanisms of Sema3E and Plexin-D1 in shaping vascular topology

2.1. Mechanism-of-action I: the tightly controlled spatial and temporal distribution of guidance cue (Sema3E gradient in the somite) determines the intersomitic vascular topology via its repulsive interaction with its receptor (Plexin-D1)

Plexin-D1 is dynamically expressed in endothelial cells of the entire body during early development, indicating an important role in vascular network formation. Plexin-D1 mRNA can be detected as early as E9.5 in the blood vessels of developing mouse embryos and continues to be expressed in endothelial cells during embryogenesis until it is down-regulated shortly before birth [7]. Both Plexin-D1 morphant zebrafish and Plexin-D1 knockout mice exhibit severe intersomitic vessel defects [4,11,12]. In addition, Plexin-D1 is expressed in the endocardium and Plexin-D1 knockout mice have failed septation of the cardiac outflow tracts, leading mice to be born with defects of the aortic arch arteries. The ligands that mediate Plexin-D1's effect on cardiac function are Sema3A and Sema3 C, which act through Plexin-D1/neuropilin complexes [12]. However, the ligand that mediates Plexin-D1 function in endothelial cells is Sema3E and, surprisingly, Sema3E binds directly to Plexin-D1 independently of neuropilins [4]. It was first studied in the context of intersomitic vessel formation, where Sema3E is expressed in the caudal region of each developing somite, whereas Plexin-D1 is expressed in the intersomitic blood vessels adjacent to the somite boundary on the rostral region of each somite (Fig. 1A). Sema3E acts as a repulsive cue to restrict vessel growth and branching in the intersomitic space, as ectopic Sema3E overexpression in chick embryos inhibits vessel growth [4]. Conversely, in both Sema3E and Plexin-D1 knockout mice, the intersomitic vessels are

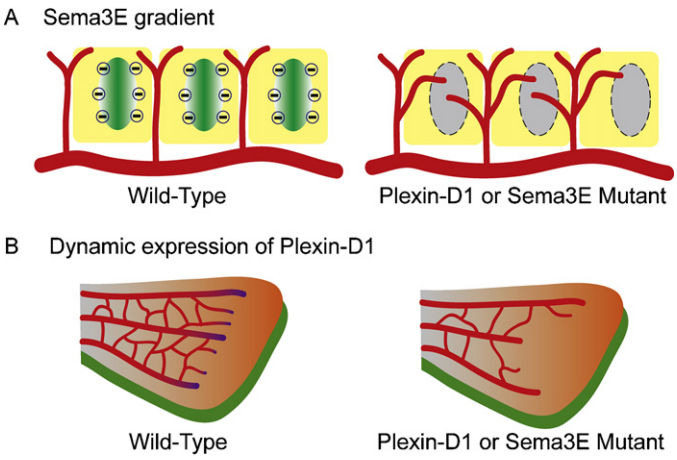

Fig. 1. Temporal and spatial control of ligand vs. receptor results in two different mechanisms governing vascular patterning.
(A) The repulsive gradient generated by Sema3E in the mouse somite determines the proper patterning of Plexin-D1-expressing intersomitic vessels [4]. During intersomitic vessel (red) development in the mouse embryo, Sema3E (gradient in green) is expressed in the caudal region of each somite (yellow), whereas Plexin-D1 is expressed in the adjacent intersomitic vessels (red) on the rostral region of each somite. The repulsive cues generated by the Sema3E gradient restrict vessel growth and branching in the intersomitic space. Mice lacking Sema3E or Plexin-D1 lose the repulsive gradient signals (gray oval), thereby allowing blood vessels to encroach on somites and display exuberant blood vessel growth in the entire somite and a loss of the normal segmented pattern.
(B) In the retina, dynamic regulation of Plexin-D1 level instead of a Sema3E gradient is crucial to establish properly patterned retinal vasculature [15,16]. In contrast to Sema3E gradient in the intersomitic vessels, in the retinal vasculature (red), Plexin-D1 is selectively expressed in endothelial cells (purple gradient) at the front of sprouting blood vessels in response to the VEGF gradient (orange), whereas Sema3E (green) is evenly expressed in RGCs underneath the retinal vasculature. The dynamic regulation of Plexin-D1 by VEGF in the sprouting front cells modulates the ratio between tip and stalk cells via VEGF-induced feedback mechanism to ensure balanced vascular network formation. Therefore, loss of dynamic Plexin-D1 regulation in the Plexin-D1 or Sema3E mutant shows less-branched and uneven front vasculature (right side of B).