Class 3 semaphorins in cardiovascular development

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ABSTRACT
Secreted class 3 semaphorins (Sema3), which signal through holoreceptor complexes that are formed by different subunits, such as neuropilins (Nfps), proteoglycans, and plexins, were initially characterized as fundamental regulators of axon guidance during embryogenesis. Subsequently, Sema3A, Sema3C, Sema3D, and Sema3E were discovered to play crucial roles in cardiovascular development, mainly acting through Nrp1 and Plexin D1, which funnels the signal of multiple Sema3 in vascular endothelial cells. Mechanistically, Sema3 proteins control cardiovascular patterning through the enzymatic GTPase-activating-protein activity of the cytodomain of Plexin D1, which negatively regulates the function of Rap1, a small GTPase that is well-known for its ability to drive vascular morphogenesis and to elicit the conformational activation of integrin adhesion receptors.

The complex morphogenetic events that lead to the development of cardiovascular system, which have been extensively described\textsuperscript{1} and/or reviewed\textsuperscript{2,3} elsewhere, rely on the property of cells to differentiate, adhere to each other as well as to the surrounding extracellular matrix and migrate in response to guidance cues.\textsuperscript{2,3} Among the different molecules capable of regulating the directionality of cell motility, semaphorins (Semas) represent a large family of secreted or membrane-associated glycoproteins, conserved both structurally and functionally from viruses to mammalians and able to provide repulsive or attractive signals to migrating cells.

Semas were originally identified as axon guidance molecules in the developing nervous system.\textsuperscript{4,5} Afterward, these molecules have been shown to regulate other physiological and pathological processes outside of the nervous system, such as vascular endothelial cell motility, cardiovascular development, lymphocyte activation, bone and lung morphogenesis, cancer angiogenesis and metastatic dissemination.\textsuperscript{3,6,7,8} The Sema family is divided into 8 classes accordingly to structural characteristics and organisms of origin: class 1 and 2 are encoded by invertebrates, classes 3–7 are from vertebrates, and class V Sema are found in viruses. The overall molecular architecture is quite different for the various Semas, being characterized by class-specific structural domains. The only exception is the conserved 500 amino acid-long 7-blade \(\beta\)-propeller folded “sema” domain, located close to the N-terminus of the proteins and present in all family members.\textsuperscript{9} In vertebrates, class 3 Sema (Sema3) consists of 7 soluble molecules of \(\sim\)100 kDa (designated by letters from A to G), which are produced as secreted proteins by cells of multiple lineages, including endothelial and epithelial cells, neurons, and specific tumor cells. In Sema3, the N-terminal sema domain is followed by a plexin-sema-phorin-integrin (PSI) domain, an immunoglobulin (ig)-like domain, and a C-terminal basic domain (Fig. 1).

The core components of the Sema3 holoreceptor complexes (Fig. 1) belong to the families of plexins and neuropilins (Nfps) (Table 1). Plexins are a wide family of transmembrane proteins categorized into 4 (A to D) classes on the basis of structural similarities. The extracellular portion of plexins consists of several different moieties, among which a central role is played by a divergent sema domain; their intracellular region contains instead a functionally crucial triphosphate (GTPase)–activating protein (GAP) domain\textsuperscript{10–13}.
Different Sema crystals have been analyzed so far, indicating how all Semas are homodimers, in which, differently from sema domain containing plexins, a ‘face-to-face’ interaction between the top surfaces of the sema domains occurs. If compared to membrane associated Semas, secreted Sema3 proteins display a less hydrophobic dimer interface that crucially need to be stabilized by disulphide bonds between Ig domains, which are negatively regulated by the proteolytic activity of furins. Crystal structures of several membrane associated Semas in complex with their cognate plexin receptors unveiled that electrostatic interactions mediate an head-to-head interaction between each sema domain of a Sema dimer and the sema domain of a monomeric plexin, giving rise to a 2:2 Sema-plexin heterotrimer. Functional studies provided evidence that the same head-to-head interface is likely employed by Sema3 to bind to and signal through plexin receptors, nevertheless, since so far no physiological high affinity binding has been revealed between the sema domains of Sema3 and plexins, such a canonical binding between Sema3 and plexins must be extremely weak and need the essential involvement of co-receptors such as Nrp1 or proteoglycans.

In vertebrates 2 Nrps are present (Nrp1 and Nrp2) that act as Sema3 co-receptors. The extracellular domains of both Nrps contain 2 complement binding domains (a1/a2), 2 coagulation factor V/VIII homology domains (b1/b2), and a MAM domain (c), while the short cytoplasmic domain is about 40 amino acids long, and contains a C-terminal 3 amino acid-long (S-E-A) sequence that represents a PDZ-binding motif. In addition to Sema3, Nrp1 and Nrp2 also bind to vascular endothelial growth factor-A (VEGF-A) and -C (VEGF-C) family members respectively and function as their co-receptors. The b1 domain mediates the high affinity binding of Nrp1 to the basic domain of Sema3 proteins and VEGF-A. While VEGF-A naturally displays a C-terminal arginine, a furin-dependent proteolytic processing of Sema3 must occur to allow the exposure of the Nrp1-binding C-terminal basic sequence.
Accordingly, the C-terminal basic stretch peptides of furin-processed Sema3A or Sema3F inhibit effectively and dose-dependently the binding of VEGF-A to the b1 domain of Nrp1. 9,30,33 Furthermore, 3 independent studies proved that VEGF-A and Sema3A compete for binding Nrp1 on the cell surface and how this competition encompasses a binding site within Nrp1 b1 domain. 24-36 A surface plasmon resonance-based study did not detect any competition between Sema3A and VEGF-A for binding to immobilized Nrp1-Fc, 37 the reason(s) for discrepancies among the work by Appleton et al. 37 and the other 3 studies 34-36 are presently unclear, but they could be due, for example, to differences in furin-cleavage patterning of Sema3A C-terminal basic stretch. 9,33 Indeed, an-N-terminal disulphide-bonded helical region precedes the C-terminal basic stretch of Sema3 proteins and, while the C-terminal basic stretch of Sema3F has only one furin consensus site, Sema3A displays instead 3 furin cleavage sites whose processing is central for Sema3A regulation. 9,33 In particular, shortening the distance between the helical region and the C-terminal motif results in a concomitant reduction of Sema3A affinity for Nrp1 b1 domain 33 and biological activity. 19 The recent finding that proteolytic processing is needed to expose the C-terminal arginine of VEGF-C that directly binds the Nrp2 b1 domain 25 suggests how the binding of Nrp ligands other than Sema3 proteins might also be regulated by the protease-driven strategy. The a1 domain of Nrp1 does not directly bind with high affinity the sema domain of Sema3A, 18 but rather favors the coordination of the latter with the sema domain of type A plexins, such as Plexin A2 9,18 All together, these data suggest a model in which, while the b1 domain of Nrp1 binds with high affinity to the basic domain of Sema3A, the a1 domain of Nrp1 help the sema domain of Sema3A to coordinate with sema domain of type A plexins and likely activate the signaling of the latter. 9,18,38

In this review, we summarize the current advances on the involvement of Sema3 in cardiovascular development (Table 2).

**Sema3A**

In the developing zebrafish embryo, Sema3A is required for the proper patterning of trunk intersegmental blood vessels. 39,40 Gene and/or genome duplication are mechanisms for functional improvement during evolution. 41 Compared to other vertebrate species, the zebrafish teleost ancestor underwent an additional round of whole-genome duplication. 41 As a consequence, the zebrafish displays 2 Sema3a ortholog genes, sema3a1 and sema3a2 that are expressed in the developing somites. 39 Somite-derived Sema3A1 and Sema3A2 proteins restrain within the intersomitic boundaries the vascular sprouts that bud from trunk large blood vessels. Indeed, sema3a1/ sema3a2 and plxnd1 morphants, as well as the genetic plxnd1 mutant out-of-bounds (obd) display inter-segmental blood vessel patterning defects characterized by angiogenic sprouts invading the central region of somites. In addition, Sema3A/PlexinD1 signaling in quiescent aortic ECs adjacent to somites was found to promote the autocrine secretion of a soluble VEGFR1 splice variant capable of sequestering VEGF and restricting blood vessel sprouting to somite boundaries. 39

Immunohistochemical analysis of the spatial distribution of Sema3A protein in the developing quail embryo was consistent with a negative regulation of vascular patterning. 42 Fittingly, implantation of Sema3A antibody-soaked beads in the developing forelimb of vascular pattern; capillaries surrounding the Sema3A antibody-soaked bead were dilated, disorganized, and converged toward the bead. 42 Similarly, retrovirus-mediated delivery of dominant negative constructs of Sema3A holoreceptor components in vascular ECs of the developing chick embryo impaired blood vessel remodeling. 43

The very few Sema3a null mice that survive and go beyond weaning, live longer, and display an altered sympathetic cardiac innervation pattern that results in sinus bradycardia. 44 Cardiac-specific overexpression of Sema3a induces a reduction of sympathetic innervation and transgenic animals display susceptibility to ventricular tachycardia. 44 Accordingly, it has been reported that myocardial overexpression of Sema3a 45 or intravenous administration of recombinant Sema3A protein 46 after infarction in rats can reduce the probability of ventricular tachycardia that frequently is an associated response to injury, as a result of attenuated sympathetic reinervation. Moreover, a nonsynonymous polymorphism (I334V, rs138694505A>G) in exon 10 of the human SEMA3A gene was associated with unexplained cardiac arrest and ventricular fibrillation; the axon repelling activity SEMA3A 334V appears significantly weaker of that of its wild type counterpart and in the hearts of patients sympathetic nerves invade the subepicardial layer. 47

The angiogenic remodeling of both cephalic plexus and dorsal longitudinal anastomotical vessel into mature hierarchically organized vascular trees is severely defective in Sema3a knockout embryos. 43 In addition, Sem3a−/− pups that survive until the adulthood present an excessive number of glomerular ECs associated with renal vascular defects. 48 The reported lack of vascular abnormalities in one study on Sema3a null mice 49 could be due to the use of an age-and-stage matching strategy to compare wild type and Sema3a null embryos; indeed,
Table 2. Sema3 and Sema3 receptor mutants with cardiovascular phenotype.

| Protein  | Animal model | Experimental strategy | Cardiovascular phenotype                                                                 | References |
|----------|--------------|-----------------------|------------------------------------------------------------------------------------------|------------|
| Sema3A   | Mouse        | General ko            | Atrial defects, sinus bradycardia, angiogenic remodeling defect of cephalic and dorsal longitudinal vessels, excessive number of glomerular ECs. | 43,44,48   |
|          |              | EC specific ko        | No obvious cardiovascular phenotype                                                        | 49         |
|          |              | Zebrafish Morphants   | Increased number and length of filopodia in retinal tip endothelial cells                 | 52         |
|          |              | Blocking antibodies,  | Inter-segmental blood vessel patterning defects                                            | 39,40      |
|          |              | dominant-negative     | Vascular patterning alterations, vascular remodeling impairment.                           | 42,43      |
|          |              | receptor constructs   |                                                                                            |            |
| Sema3B   | Mouse        | General ko            | Cardiovascular phenotype not analyzed                                                    | 79         |
| Sema3C   | Mouse        | General ko            | Improper septation of the cardiac outflow tract, ventricular septal defects, aortic arch defects | 82         |
| Sema3D   | Mouse        | General ko            | Anomalous pulmonary venous connection, atrial septal defects, improper patterning of the coronary veins | 88,89      |
| Sema3E   | Mouse        | General ko            | Initially severe vascular defects (e.g., in dorsal aorta patterning) that normalize during development | 64,65,68   |
| Sema3F   | Mouse        | General ko            | Cardiovascular phenotype not analyzed                                                    | 105        |
| Sema3G   | Mouse        | General ko            | No obvious cardiovascular phenotype                                                        | 91         |
| Nrp1     | Mouse        | General ko            | Angiogenic remodeling defects of major head and trunk blood vessels, improper septation of the cardiac outflow tract | 56         |
| Nrp1     | Mouse        | EC specific ko        | Cardiac defects, lung vascular abnormalities                                               | 53-55      |
| Nrp1     | Mouse        | General ko            | Brain vasculature abnormalities, reduced branching and vessels interconnections           | 106        |
| Nrp2     | Mouse        | General ko            | No obvious cardiovascular phenotype                                                        | 107,108    |
| Nrp1 and Nrp2 | General ko | Vascular anomalies in embryos and placenta.                                               | 109        |
| Nrp1     | Mouse        | General ko            | Bilateral atrial enlargement, abnormal origin of the coronary arteries, ventricular septal defect, improper septation of the cardiac outflow tract, no obvious vascular defects | 53         |
| Nrp1     | Mouse        | General ko            | No obvious cardiovascular phenotype                                                        | 110,111    |
| Nrp1     | Mouse        | General ko            | Persistent truncus arteriosus and lack of aortic and pulmonary channel septation with incomplete penetrance. | 112,113    |
| Plexin A1| Mouse        | General ko            | No obvious cardiovascular phenotype                                                        | 113        |
| Plexin A2| Mouse        | General ko            | Inter-segmental blood vessel patterning defects                                            | 39         |
| Plexin A2 and A4| General ko | Inter-segmental blood vessel patterning defects | 39 |
| Plexin A2 and A4| Mouse | General ko | Inter-segmental blood vessel patterning defects | 39 |
| Plexin A2 and A4| Mouse | General ko | Inter-segmental blood vessel patterning defects | 39 |
| Plexin D1| Zebrafish    | Morphants and obd     | Cyanotic after birth, vascular invasion in somite                                         | 63         |
|          |              | genetic mutant        | Myocardial defects, reduction of bone microvasculature                                    | 62         |

age-and-stage matching inherently overlooks the growth retardation phenotype that, as previously described, usually characterize knockout embryos that display vascular remodeling defects, such as Sema3a null mice. Of note, endothelial tip cells of murine retinal vascular sprouts were found to express much more Sema3a mRNA than stalk ECs, and EC-specific Sema3a knockout mice were recently described to exhibit a significantly increased number and length of endothelial tip cell filopodia in retinal vascular sprouts. The latter finding emphasize how paracrine Sema3A secreted by non-vascular cells of adjacent tissues does not rescue the specific function(s) that autocrine EC-derived Sema3A exerts during sprouting angiogenesis.

The role of Nrp1 in Sema3A signaling in ECs appears to be controversial. A Nrp1 null mouse showed that in mutant Nrp1Sema−− mouse was originally reported to survive until P7 and to exhibit cardiac, but not vascular abnormalities. However, more recently 2 independent studies reported how only 18% of Nrp1Sema−− mouse survive until P4 and present lung vascular abnormalities phenocopying the so-called alveolar capillary dysplasia, i.e. severely reduced capillary density, centrally located and dilated alveolar capillaries, hypertensive changes in arteriolar walls, anomalous and misaligned pulmonary veins. However, the lack angiogenic remodeling defects of major head and trunk blood vessels in Nrp1Sema−− mice and the fact that the vascular phenotype in both Sema3A and Nrp1 knockout mice is, on the contrary, highly severe raises the possibility that in mutant Nrp1Sema−− the responsibility of ECs to Sema3A, albeit reduced, could be, at least in part, maintained due to the existence of additional Sema3A co-receptors other than Nrp1, such as proteoglycans.

Along this line, it is remarkable that some misprojected axon bundles are present in Plexaa4 null, but neither in Nrp1Sema−− or in
Sema3E

Sema3E binds with high affinity to Plexin D1 in a Nrp1-independent manner (Table 1). Both in Sema3e and Plxnd1 knockout embryos blood vessels expand ectopically throughout somites causing the loss of the typical stereotyped intersomitic vascular pattern. However, while Plxnd1 knockout pups become cyanotic sudden after birth and succumb within 24 hours, Sema3e−/− mice are viable, fertile and survive throughout adulthood although displaying initially severe vascular defects, thus implying that in the developing embryo Plexin D1 transduces not only the signals of Sema3E, but also those elicited by other Sema3 proteins, such as Nrp1 or proteoglycans, and signal through manifold low-affinity receptors, e.g. Plexin A1, Plexin A2, Plexin A4 and Plexin D1 (Table 1).

Other Sema3 proteins

Sema3B is as an angiogenesis inhibitor and exerts its effect through the binding to Nrp1 (Table 1). Sema3B knockout mice are viable and fertile. An unbiased

NrplSema−53 mutant mice, implying that Plexin A4 may deliver Nrp1-independent Sema3A signals in some neuronal populations. Such a scenario would also be compatible with the hypothesis that, similarly to membrane associated Semas, Sema3A would directly bind, albeit at very low affinity, and signal via plexins.17 Sema3A has been reported to signal through Plexin A1,59 Plexin A2,18,60 Plexin A4,58,61 and Plexin D162 (Table 1). In turn, Plexin D1 was shown to be significantly more efficient than type A plexins in forming high affinity Nrp-dependent holoreceptor complexes for Sema3A and Sema3C.65 Both Plexin A1 and Plexin A4 were found to be required for Sema3A-elicited collapse of cultured ECs.61 In addition, aortic ring sprouting assays and Boyden chamber assays revealed how Sema3A inhibits less efficiently the sprouting of aortic blood vessels or the migration of primary ECs isolated from Plxnd1−/− than from wild type animals.62 Therefore, Sema3A may control in vivo vascular morphogenesis by binding with high affinity to coreceptors, such as Nrp1 or proteoglycans, and signal through manifold low-affinity receptors, e.g. Plexin A1, Plexin A2, Plexin A4 and Plexin D1 (Table 1).
transcriptomic analysis revealed that in severe forms of human preeclampsia SEMA3B is upregulated in and inhibits the differentiation of placental cytotrophoblasts; furthermore, cytotrophoblasts-derived SEMA3B may act in a paracrine way to impair uterine microvascular ECs functions.80

Sema3C protein binds with high affinity to Nrp1-Plexin D1 and, albeit with lower affinity, to Nrp2-Plexin D1 complexes63 (Table 1). Accordingly, Sema3C was recently reported to inhibit angiogenesis by signaling via Nrp1 and Plexin D1.81 Deletion of either Sema3c62 or Nrp156 or PlxnD163 gene causes postnatal lethality due to cardiovascular defects among which the improper septation of the cardiac outflow tract (OFT), resembling the persistent truncus arteriosus observed in humans.85 OFT septation depends on the formation, expansion, and fusion of endocardial cushions, finally resulting into a septal bridge; subsequently second heart field-derived smooth muscle cells invade to myocardialize the septum.84 A recent study proposed that neural crest cell-derived Sema3C elicits the Nrp1-dependent endothelial-to-mesenchymal transition that is needed to give rise to the cell population that form the endocardial cushions; in addition, Sema3C-Nrp1 signaling would also drive septum myocardialization.85

Sema3D inhibits EC spreading and migration through a Nrp1 and phosphatidylinositol 3 kinase/Akt dependent pathway86 (Table 1). Fate mapping studies both in mouse and chick established that Sema3D is expressed in a subpopulation of proepicardial cells that give rise to sinus venosus, a tissue that, at later stages, contributes to the development of the coronary endothelium.87 Moreover, Sema3D is expressed in the mesocardial reflections that are located between the splanchnic mesoderm and the venous pole of the heart.88 In the developing embryo, Sema3D would exert a repulsive guidance effect to constrain and to direct pulmonary venous ECs toward the left atrium.88 Consistently, Sema3d null mice exhibit anomalous pulmonary venous connection (APVC) and a c.1806T>G missense mutation that results in the F602L substitution was present in a partial APVC patient.88 Sema3D F602L binding to Nrp1 and ability to repel the migration of cultured ECs is significantly reduced.88 Sema3D was recently reported to be expressed in the left anterior atrioventricular groove to repel venous ECs from aberrantly connecting with the left atrium.89 It appears that in venous ECs the inhibitory Sema3D signals are conveyed through a Nrp1-ErbB2 holoreceptor complex.89

Sema3F binds with high affinity to Nrp2 and, with lower affinity, to Nrp190 (Table 1). Although it is well known that Sema3F is an effective inhibitor of cancer angiogenesis (for review see ref. 5), so far no defects in cardiovascular development were reported in Sema3f null mice.

Sema3G binds with high affinity to Nrp2 and, with lower affinity, to Nrp191 (Table 1). Sema3g<sup>−/−</sup> mice were reported to be viable and to do not display any obvious vascular phenotype.91 Sema3G displayed preferential arterial expression in all organs during embryonic development (from E9.5) and postnatally throughout adolescence, while it was downregulated in the adult. Sema3G is produced by ECs and acts as a positive regulator of angiogenic functions both in an autocrine and paracrine way, by promoting smooth muscle cell migration.91

Disclosure of potential conflicts of interest
No potential conflicts of interest were disclosed.

Funding
This work was supported by grants from: Italian Association for Cancer Research (AIRC-IG grant # 15645 to E.G.; # 13016 and # 16702 to G.S.); FPRC-ONLUS Grant "MIUR 2010 Vaschetto - 5 per mille 2010 MIUR" (to E.G. and G.S.); Swiss National Science Foundation (SNSF), Sinergia Grant (# CRSII3 160742/1), (to E.G.); Telethon Italy (GGP09175) (to G.S.); Associazione ‘Augusto per la Vita’ (to G.S.). D.R. was supported by FPRC-ONLUS Grant "MIUR 2010 Vaschetto-Chiodo Fellowship."

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