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The semaphorins and their receptors as modulators of tumor progression

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ABSTRACT

The semaphorins were initially characterized as repulsive axon guidance factors. However, they are currently also recognized as important regulators of diverse biological processes which include regulation of immune responses, angiogenesis, organogenesis, and a variety of additional physiological and developmental functions. The semaphorin family consists of more than 20 genes divided into seven subfamilies, all of which contain the sema domain signature. They usually transduce signals by activation of receptors belonging to the plexin family, either directly, or indirectly following the binding of some semaphorins to receptors of the neuropilin family which subsequently associate with plexins. Additional receptors which form complexes with these primary semaphorin receptors are also frequently involved in semaphorin signalling, and can strongly influence the nature of the biological responses of cells to semaphorins. Recent evidence suggests that semaphorins play important roles in the etiology of multiple forms of cancer. Some semaphorins such as some semaphorins belonging to the class-3 semaphorin subfamily, have been found to function as bona fide tumor suppressors and to inhibit tumor progression by various mechanisms. Because these class-3 semaphorins are secreted proteins, these semaphorins may potentially be used as anti-tumorigenic drugs. Other semaphorins, such as semaphorin-4D, function as inducers of tumor progression and represent targets for the development of novel anti-tumorigenic drugs. The mechanisms by which semaphorins affect tumor progression are diverse, ranging from direct effects on tumor cells to modulation of accessory processes such as modulation of immune responses and inhibition or promotion of tumor angiogenesis and tumor lymphangiogenesis. This review focuses on the diverse mechanisms by which semaphorins affect tumor progression.

1. The semaphorins and their receptors

1.1. The semaphorins

Members of the semaphorin family are divided into 8 subclasses of which subclasses 1 and 2 contain invertebrate semaphorins, whereas subclasses 3-7 contain the 22 vertebrate semaphorins and subclass 8 contains viral semaphorins. In early publications, semaphorins were assigned confusing names. This situation was rectified by the adoption of a unified semaphorin nomenclature in which sema is followed by the subclass number and by alphabetic designation within the subclass (Goodman et al., 1999). The semaphorins as well as their plexin receptors are characterized by a ~500 amino acids-long sema domain located close to their N-termini, and by a plexin-semaphorin-integrin (PSI) domain located downstream to the sema domain. The sema domain has a β propeller topology (Love et al., 2003; Antipenko et al., 2003; Liu et al., 2010), is essential for semaphorin activity, and determines to some extent, the receptor binding specificity (Feiner et al., 1997). Different semaphorin subclasses can be distinguished by class-specific structural motifs. Thus, vertebrate semaphorins belonging to classes 4 and 7 contain immunoglobulin-like domains, class-5 semaphorins contain thrombospondin repeats and class-3 semaphorins contain a basic domain. Class-3 semaphorins are the only vertebrate semaphorins produced as secreted proteins while other vertebrate semaphorins are membrane anchored. Some membrane-anchored semaphorins can be further processed into soluble forms by proteolytic cleavage (Fig. 1). Some membrane anchored semaphorins may also be able to function as signal transducing proteins (Toyofuku et al., 2012; Segarra et al., 2012). The active forms of several class-3 and class-6 semaphorins are homodimers (Klostermann et al., 1998; Liu et al., 2010; Janssen et al.,

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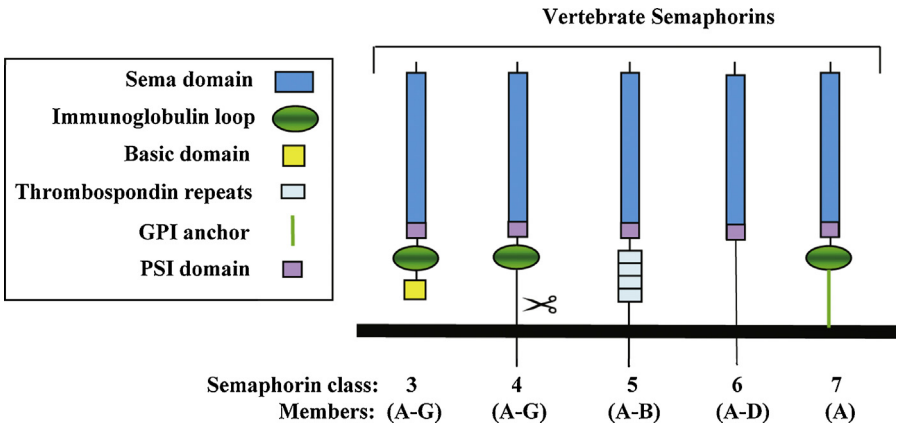

Fig. 1. The vertebrate semaphorins: (A) The structural elements of vertebrate semaphorin subclasses are shown. All semaphorins feature the signature N-terminal sema domain. A conserved stretch of amino-acid residues near the C-terminal of the sema domain bears homology to the N-terminal of β-integrins and is designated as the PSI domain. Class-3 semaphorins are the only secreted semaphorins and are distinguished by a conserved basic domain at their C-termini. Class 4-7 semaphorins are membrane-anchored. Class 5 semaphorins are distinguished by thrombospondin repeats. All the vertebrate semaphorins except for the class-5 and 6 semaphorins also contain an immunoglobulin-like domain. The extracellular domains of class-4 semaphorins can be cleaved with metalloproteases generating active soluble extracellular domains.

2010; Nogi et al., 2010), suggesting that the active forms of all the semaphorins are dimeric.

1.2. Plexin family receptors

The receptors of the plexin family are segregated into four groups consisting of four Type-A plexins, three Type-B plexins, and single C and D plexins (Negishi et al., 2005a; Gutmann-Raviv et al., 2006). Most semaphorins bind to one or to several plexins (Hota and Buck, 2012). For example, plexin-B1 is a receptor for sema4D (Tamagnone et al., 1999), plexin-A2 and plexin-A4 function as sema6A and sema6B receptors (Suto et al., 2007; Suto et al., 2005) and plexin-D1 is a receptor for sema3E and sema4A (Gu et al., 2005; Toyofuku et al., 2007) (Fig. 2). The sema domain found in the extracellular domain of the plexins serves as an auto-inhibitory domain in the basal, non-activated state of the receptor and the inhibition is removed following a conformational change induced by the binding of a semaphorin (Takahashi and Strittmatter, 2001). The intracellular domains of plexins are characterized by the presence of a conserved GTPase activating (GAP) domain (Oinuma et al., 2004; He et al., 2009; Sakurai et al., 2010). Most of the developmental effects of plexin-D1 and plexin-B1 are lost when the GAP domain is mutated suggesting that it plays an essential role in plexin mediated semaphorin signal transduction (Worzfeld et al., 2014). Type-A plexins associate spontaneously to form homodimers (Janssen et al., 2010; Nogi et al., 2010) or heterodimers (Kigel et al., 2011). Recent data indicates that activation of plexin signaling by semaphorins that bind directly to plexins such as sema6A is associated with a conformational change that shifts the conformation of the dimer from the inactive to the active conformation (Liu et al., 2010; Nogi et al., 2010).

Activation of plexin signaling by semaphorins activates the GAP domain leading to the inactivation of R-ras, resulting in the subsequent inactivation of beta1-integrin, and finally reduced adhesion (Negishi et al., 2005b; Toyofuku et al., 2005; Sakurai et al., 2010; Sakurai et al., 2011). Activation of type-A plexins was also found to induce the activation of enzymes of the Mical family. These enzymes perform reduction-oxidation (redox) enzymatic reactions and oxidize actin subunits leading to the disassembly of actin fibers and to the localized collapse of the actin cytoskeleton of axonal growth cones, thereby contributing to growth cone guidance (Terman et al., 2002; Hung et al., 2010; Hung et al., 2011; Hung et al., 2013). Activation of plexin signaling by semaphorins also results in the activation of various intracellular tyrosine-kinases (Franco and Tamagnone, 2008) and to the inactivation of small GTPases that control the polymerization of the actin cytoskeleton such as Rho as a result of the activation of regulators of Rho activity including the p190 Rho-GTPase and Rho guanine nucleotide exchange factors (Puschel, 2007; Worzfeld et al., 2014). However, semaphorin induced signal transduction is far from being completely understood and its thorough description is beyond the scope of the present review.

1.3. Neuropilins

Six of the seven class-3 semaphorins are unable to bind to plexins directly but instead bind to one or to both receptors of the neuropilin family (Gu et al., 2005; Neufeld and Kessler, 2008). Because of their short intracellular domains, neuropilins are not able to transduce semaphorin signals independently, and associate with type-A plexins or with plexin-D1 after binding a class-3 semaphorin to transduce semaphorin signals (Tamagnone et al., 1999; Takahashi et al., 1999; Gitler et al., 2004). Recent structural studies indicate that functional class-3 semaphorin receptors consist of a tetramer containing a neuropilin homodimer and a plexin homodimer that are linked together by the binding of a class-3 semaphorin homodimer (Janssen et al., 2012). However, there is evidence indicating that functional class-3 semaphorin receptors can also contain plexin heterodimers since inhibition of the expression of either neuropilin-1 or plexin-A1 or plexin-A4 in endothelial cells was found to be sufficient to completely abrogate sema3A signal transduction suggesting that the receptor complex in these cells contains plexin-A4 as well as plexin-A1 in addition to neuropilin-1 (Kigel et al., 2011). Similarly, both plexin-A2 and plexin-A4 are required for sema3B induced signal transduction suggesting that functional sema3B receptors also contain more than one type of plexin (Sabag et al., 2014).

The neuropilins can perhaps be best described as “scaffold receptors” since they seem to bind to and modulate the activities of diverse types of receptors and ligands but do not appear to transduce signals independently. In addition to class-3 semaphorins, the neuropilins also function as receptors for several types of growth factors including several members of the vascular endothelial growth factor (VEGF) family (Gitay-Goren et al., 1996; Soker et al., 1998; Makinen et al., 1999; Karpanen et al., 2006; Migdal et al., 1998), hepatocyte growth factor (HGF) (Sulpice et al., 2007) and TGF-β (Glinka and Prud’homme, 2008) to name but a few. The VEGF-A binding domain of neuropilin-1 seems to be