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Review

Semaphorin 5A mediated cellular navigation: Connecting nervous system and cancer

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ABSTRACT

The ultraprecise wiring of neurons banks on the instructions provided by guidance cue proteins that steer them to their appropriate target tissue during neuronal development. Semaphorins are one such family of proteins. Semaphorins are known to play major physiological roles during the development of various organs including the nervous, cardiovascular, and immune systems. Their role in different pathologies including cancer remains an intense area of investigation. This review focuses on a novel member of this family of proteins, semaphorin 5A, which is much less explored in comparison to its other affiliates. Recent reports suggest that semaphorins play important roles in the pathology of cancer by affecting angiogenesis, tumor growth and metastasis. We will firstly give a general overview of the semaphorin family and its receptors. Next, we discuss their roles in cellular movements and how that makes them a connecting link between the nervous system and cancer. Finally, we focus our discussion on semaphorin 5A to summarize the prevailing knowledge for this molecule in developmental biology and carcinogenesis.

Contents

Abbreviations: aa, Amino acid(s); CRD, Cysteine rich domain; CSPG, Chondroitin sulfate proteoglycan; ECD, Extracellular domain; ECM, Extracellular matrix; GPI, Glycophosphatidylinositol; HSPGs, Heparan sulfate proteoglycans; IL-8, Interleukin-8; RT-PCR, Reverse transcriptase polymerase chain reaction; Sema5A, Mouse semaphorin 5A; SEMA5A, Human semaphorin 5A; TGF, Transforming growth factor; TSP-1, Thrombospondin repeats; PSI, Plexins, semaphorins and integrin; IPT, Immunoglobulin like plexin transcription factor domain

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1. Introduction

The term semaphorin originates from the word *semaphore*, which is a system of sending signals visually using flags [1]. Semaphorins are a large family of phylogenetically conserved proteins, initially identified as guidance cue ligands that with their cognate receptors regulate axonal and dendritic growth during the development of embryonic nervous system. Later, the expression of semaphorin receptors on various cells including immune cells, endothelial cells and vascular smooth muscle cells suggested their roles in non-neuronal processes. Semaphorins regulate cardiovascular development, vasculogenesis and also the functioning of immune system [2–4]. Recent reports suggest that semaphorins play important roles in the pathology of cancer by affecting angiogenesis, tumor growth and metastasis.

2. Classification and nomenclature

The first identified semaphorin was fasciclin IV in grasshoppers [5]. Since then the family has expanded to thirty proteins having 21 vertebrate and 8 invertebrate members [6]. They were originally named "collapsins" for their roles in the collapse of neuronal growth cones [7]. Later, the term "semaphorin" was introduced. The general rule for naming any member of semaphorin family is "sema" followed by the class number and then an alphabet which represents the member of the class, for *e.g.* sema5A (lower case in mice) and SEMA5A (upper case in humans) [1].

The sub-classification of semaphorins into eight classes is based on their structural similarities, species of origin and presence of class specific carboxy-terminal domains. The members of semaphorin family show a complex multi-domain structure [8]. They are characterized by a conserved sema domain of ~500 amino acids present in the N-terminal region, which is necessary for their binding to the cognate receptors (Fig. 1) [9]. The characteristic structure of sema domain is a seven blade beta propeller topology with similarity to alpha integrins [8]. The sema domain is also shared by plexin (semaphorin interacting protein), Met and Ron receptor tyrosine kinases [1]. A cysteine rich domain (CRD) that is also referred to as the MET related sequence (MRS as they have homology with Met subfamily of tyrosine-kinase receptor) or PSI domain (as it is found common in plexins, semaphorins and integrins) occurs immediately next to the sema domain at its terminal end in almost all of the semaphorin family members. However, the viral semaphorins (except fowlpox virus) lack the CRD domain (Fig. 1) [10]. Though the semaphorin family of proteins, in general, shares sema and PSI domains, they have unique features representing each class. In class 2–5 and class 7 semaphorins, the CRD domain is followed by one immunoglobulin domain that is absent in class 6 semaphorin proteins. More relevant to this review, class 5 semaphorins are unique in having thrombospondin repeats (TSP-1) [11,12]. It is suggested that this domain aids in ligand receptor binding leading to the effective functioning of the molecule [11,12]. Based on the mode of expression, semaphorins can also be classified as secreted (classes 2, 3, 5 and V) or membrane bound (classes 1, 4–7). Fig. 1 describes the structures of various classes of the semaphorin family. The membrane bound semaphorins can be transmembrane having a membrane spanning domain (classes 1, 4–6) or membrane anchored (class 7) *via* Glycophosphatidylinositol (GPI) sequences [13]. The diversity in the domain structures of semaphorins accounts for the distinct roles played by these molecules.

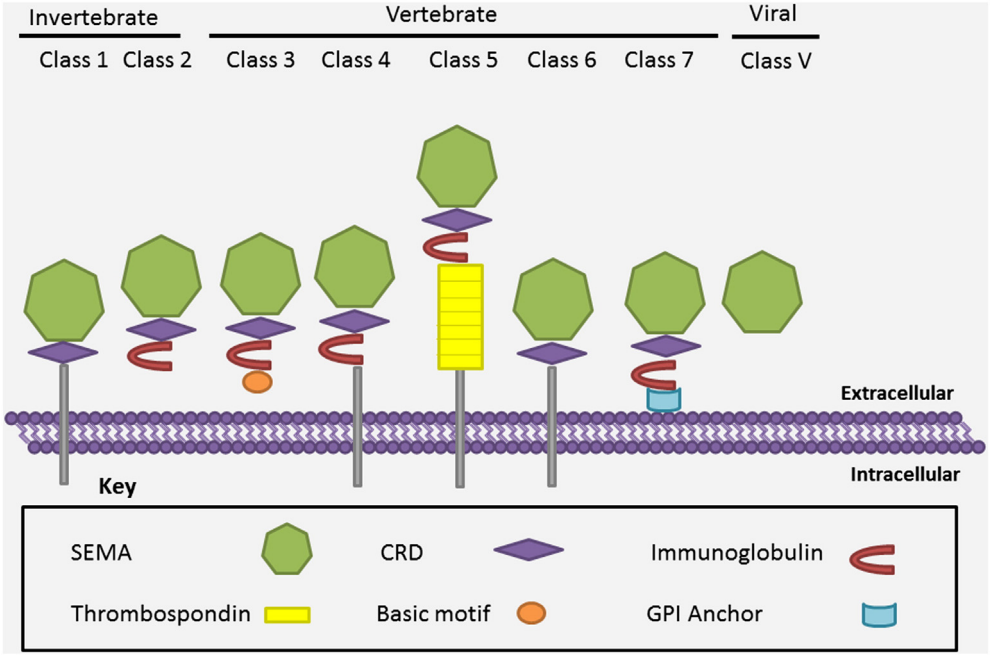

Fig. 1. The members of semaphorin family. This classification is based on the similarity in domain architecture and the species in which it is expressed. All the members of this family share the characteristic Sema domain, which is known to have a seven blade beta propeller topology (represented here as a heptagon). Semaphorins can also be classified based on their property of being trans-membrane, membrane anchored or secreted. Abbreviations, CRD: Cystine rich domain, GPI: Glycophosphatidylinositol.