

Volume 11, Issues 5-6, 2017
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To cite this article: Tomoyuki Masuda (2017) Contactin-2/TAG-1, active on the front line for three decades, Cell Adhesion & Migration, 11:5-6, 524-531, DOI: [10.1080/19336918.2016.1269998](https://doi.org/10.1080/19336918.2016.1269998)

To link to this article: <https://doi.org/10.1080/19336918.2016.1269998>



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Published online: 31 Jan 2017.



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REVIEW



Contactin-2/TAG-1, active on the front line for three decades

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ABSTRACT

Contactin-2/transiently expressed axonal surface glycoprotein-1 (TAG-1) is a cell adhesion molecule belonging to the immunoglobulin superfamily (IgSF). It has six immunoglobulin-like extracellular domains and four fibronectin III-like ones, with anchoring to the cell membrane through glycosylphosphatidylinositol. Contactin-2/TAG-1 is expressed in specific neurons transiently on the axonal surface during the fetal period. In postnatal stages, Contactin-2/TAG-1 is expressed in cerebellar granule cells, hippocampal pyramidal cells, and the juxtaparanodal regions of myelinated nerve fibers. In the embryonic nervous system, Contactin-2/TAG-1 plays important roles in axonal elongation, axonal guidance, and cellular migration. In the postnatal nervous system, it also plays an essential role in the formation of myelinated nerve fibers. Moreover, Contactin-2/TAG-1 has been linked to autoimmune diseases of the human nervous system. Taken together, Contactin-2/TAG-1 plays a central role in a variety of functions from development to disease.

ARTICLE HISTORY

Received 6 September 2016
Revised 14 November 2016
Accepted 2 December 2016

KEYWORDS

axonin-1/SC2; cerebral cortex; commissural neuron; dorsal root ganglion; floor plate; juxtaparanode; L1; NrCAM; TAX-1

Introduction

Contactin-2/transiently expressed axonal surface glycoprotein-1 (TAG-1) is a cell-surface molecule belonging to the immunoglobulin superfamily (IgSF). This molecule was originally found to be recognized by the monoclonal antibody 4D7, which was raised against an antigen of the fetal rat brain; therefore, it was termed stage-specific neurite-associated protein (SNAP).¹ Subsequently, this antigenic molecule was identified in the fetal rat brain/spinal cord and renamed TAG-1.² Later, the cDNA for rat TAG-1 was generated and sequenced.³

Independent of the above reports, axonin-1/SC2 was identified in the chick.⁴ It was subsequently revealed that axonin-1/SC2 was a chick homolog of rat TAG-1 and human TAG-1/axonin-1 (TAX-1).⁵ Although the name “TAG-1” refers to the molecule found in rodents, in actuality, it is widely used for its human and chick homologues. Recently, while the unified name “Contactin-2” has come into use, familiarity with this name is weak, and this review will not use it on its own. Instead, the term Contactin-2/TAG-1 will be used when referring to the molecule found in all animal types, TAG-1 when referring to the rodent homolog, and TAX-1 and axonin-1/SC2 when referring to human and chick homologues,

respectively. This distinction has been applied so that the animal type that applies to the research results can be discerned at a glance. As described later (see Fig. 2), chicken axonin-1/SC2 and rodent TAG-1 have different expression patterns in commissural axons and show some different functions. There is a possibility that they are not closely related to each other evolutionarily. Currently, the gene for all homologues has been universally named *CNTN2* or *Cntn2*.

Molecular structure

Domain structure and subfamily

Contactin-2/TAG-1 is a glycoprotein with a molecular weight of 135 kDa, and it is 1040 aa long in humans, rats, and mice, and 1035 aa long in the chick. Contactin-2/TAG-1 belongs to group II of the IgSF. Molecules of this group comprise multiple extracellular immunoglobulin-like domains and multiple fibronectin III-like domains and are expressed in the nervous system. Group II is further divided into subgroups, with Contactin-2/TAG-1 belonging to the Contactin subgroup. The Contactin subgroup comprises six different molecules named Contactin-1–6.

All six molecules of the Contactin subgroup, which includes Contactin-2/TAG-1, have six extracellular immunoglobulin-like domains and four fibronectin III-like domains, are anchored to the lipid bilayer of the cell membrane via glycosylphosphatidyl inositol, and are found on the membrane surface (Fig. 1A).

Contactin-2/TAG-1 also includes a secreted form, and large amounts of soluble TAG-1 have been detected in the rat fetal brain.³ The β -site amyloid β precursor protein (APP)-cleaving enzyme 1 (BACE1) cleaves TAG-1 near its GPI anchor site and generates soluble TAG-1.^{6,7} The inhibition of BACE1 activity increases the levels of TAG-1 on the cell surface *in vitro*.⁸ As described later, TAG-1 is present on the cell surface and plays an important role in axonal growth and guidance of a variety of neurons and formation and maintenance of myelinated fibers. The surface level of TAG-1 is reduced by BACE1, which results in defects in these functions, while soluble TAG-1 may bind to cell surface molecules on other axons and in turn contribute to another axonal event. Hence, the cleavage of TAG-1 is thought to play a role in modifying the function of TAG-1 *in vivo*.

Structural arrangement

The crystalline structures of the N-terminus of axonin-1/SC2 and TAX-1 have been investigated (<http://pdj.org/mine/summary/1cs6>, and <http://pdj.org/mine/summary/2om5>, respectively).^{9,10} As for the mode of

Contactin-2/TAG-1 in cell-to-cell interactions, the following two models have been proposed.⁹ The model proposed for axonin-1/SC2 is called “zipper mode,” which shows trans interactions between the second and third immunoglobulin-like domains (Fig. 1B). In contrast, the model proposed for TAX-1 is called “four molecule mode,” which shows not only trans interactions between the immunoglobulin-like domains, but also cis interactions of the fibronectin III-like domains (Fig. 1C). Additionally, Tzimourakas et al. assumed the possibility of trans interactions between fibronectin III-like domains; however, it has not been validated.¹¹ Various binding patterns may be considered depending on the species (TAX-1, TAG-1, and axonin-1/SC2), sites (axon-axon and axon-glia), and periods.

Expression patterns in the nervous system

Expression patterns obtained by *in situ* hybridization staining for TAG-1 in the mouse brain (sagittal section) during the fetal periods (E11.5, E13.5, E15.5, E18.5) and postnatal periods (P4, P14, P28, P56) have been published in Allen Brain Atlas (<http://www.brain-map.org/>).

Contactin-2/TAG-1 is expressed in specific neurons. In particular, it has been reported to be transiently expressed on the surface of elongating axons and the nerve fibers of spinal commissural interneurons and embryonic spinal motor neurons.¹ In the fetal rodent nervous system, TAG-1 expression has been observed in

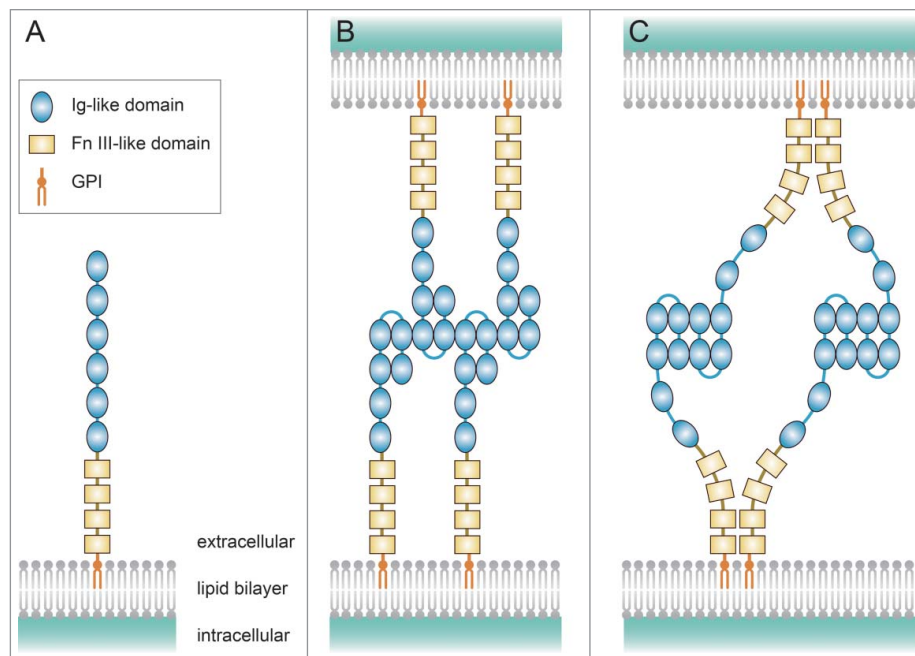


Figure 1. The domain structure and structural arrangements of Contactin-2/TAG-1. (A) Contactin-2/TAG-1 consists of six extracellular immunoglobulin (Ig)-like domains, four fibronectin (Fn) III-like domains, and glycosylphosphatidyl inositol (GPI) and is anchored to the lipid bilayer via GPI. (B) The zipper mode model proposed for axonin-1/SC2 in cell-to-cell interactions. (C) The four molecule mode model proposed for TAX-1 in cell-to-cell interactions.

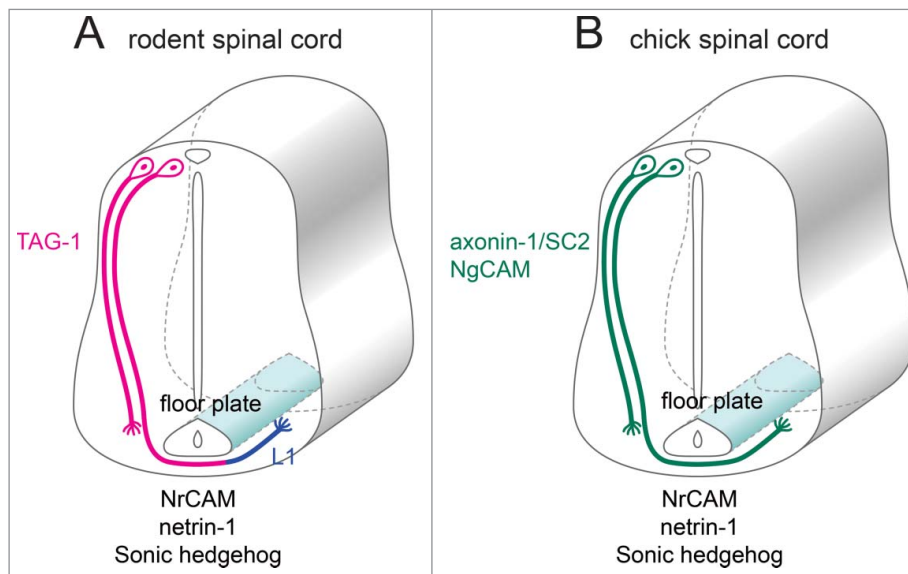


Figure 2. Molecules expressed in the spinal floor plate and commissural interneurons during the fetal period. (A) Molecules expressed in commissural axons and the floor plate of fetal rodents. (B) Molecules expressed in commissural axons and the floor plate of chick embryos.

such locations as the cell bodies and nerve fibers of dorsal root ganglion cells (DRG), the lateral olfactory tract, the anterior commissure, the corpus callosum, and the molecular layer of the cerebellar cortex.^{1,12} Moreover, during the postnatal period, transient TAG-1 expression has been observed within the premigratory cells of the external granular layer in the cerebellum.³ Additionally, axonin-1/SC2 is expressed in the retinotectal projection system of chick embryos.^{13,14}

In the nervous system of adult rodents, TAG-1 is expressed in cerebellar granule cells, olfactory bulb mitral cells, and the pyramidal cells of hippocampal Cornu Ammonis areas 1 and 3.^{15,16} Its expression has also been observed in the juxtaparanode of myelinated nerve fibers.¹⁷

Physiological functions

Binding proteins

TAG-1 and axonin-1/SC2 undergo homophilic binding.¹⁸⁻²⁰ Moreover, studies have shown that TAX-1 binds to the IgSF member L1²¹ and that axonin-1/SC2 binds to the neuron-glia cell adhesion molecule (NgCAM, an L1 chicken homolog).^{20,22,23} Furthermore, TAX-1 binds to the IgSF member Contactin-1/F3 and to the NgCAM-related cell-adhesion molecule (NrCAM);²¹ whereas axonin-1/SC2 also binds to NrCAM.^{24,25} Additionally, axonin-1/SC2 binds to the IgSF member neural cell adhesion molecule (NCAM), to neurocan and phosphacan known as the members of chondroitin sulfate proteoglycans, and to tenascin-C, a constituent of the extracellular matrix (ECM).²⁶ One study also has shown that TAG-1/TAX-1 binds to the APP.²⁷

The adhesion to the ECM is essential for neurons to extend their axons, which is called anchorage dependence. TAG-1 on the cell surface mediates the adhesion of axons to the ECM by binding to ECM molecules as described above. Thus, it is considered that the binding of TAG-1 and ECM molecules plays a central role in axonal growth and guidance.

Signaling cascade

Although Contactin-2/TAG-1 does not possess a transmembrane domain, it is associated with intracellular signaling cascades. Analyses of neurons from the cerebral cortex of mouse embryos have shown that TAG-1 controls neuron polarization via Lyn, a Src family tyrosine kinase.²⁸ Similarly, in cerebellar granule cells of rat embryos, Lyn mediates the transmission of TAG-1 signals into cells.²⁹ Furthermore, it is reported that Fyn, another Src family tyrosine kinase, mediates the transmission of axonin-1/SC2 signals into cells in the chick embryo.³⁰ A recent report has shown that the receptor for activated C kinase 1 (RACK1) interacts with TAG-1.³¹ This study indicates that TAG-1 may mediate the effect of RACK1 on the growth and differentiation of glioma cells. Future research on signal cascades of TAG-1 is required.

Function in the fetal nervous system

The floor plate of the spinal cord secretes axonal guidance factors such as netrin-1 and sonic hedgehog to attract the axonal projections of spinal commissural interneurons. Their axons approach the ventral midline of the spinal floor plate, then pass through it to project toward the

contralateral side.³² In fetal rodents, the axons of commissural neurons strongly express TAG-1 on their surface when approaching the floor plate. Once the commissural axons pass through the floor plate, however, TAG-1 expression fades out and L1 is expressed instead (Fig. 2A).² In contrast, the axons of spinal commissural neurons in chick embryos express axonin-1/SC2 and NgCAM even after passing through the floor plate, exhibiting a slightly different expression pattern from that of rodents (Fig. 2B). Yet, although axonin-1/SC2 is involved in the fasciculation and guidance of commissural axons, it is not involved in axonal elongation.^{25,33} Moreover, to allow commissural axons to pass through the floor plate, axonin-1/SC2 on the surface of these axons is required to interact with NrCAM on the surface of the floor plate cells (Fig. 2B).^{25,34,35}

Contactin-2/TAG-1, which is expressed on DRG axonal surfaces during the fetal period, is known to be involved in the elongation,^{3,36} fasciculation,^{36,37} and guidance³⁷⁻⁴¹ of DRG axons. Additionally, the elongation of DRG axons is promoted by the homophilic binding of TAG-1 on the axonal surface not only to TAG-1 in the ECM but also to L1/NgCAM and $\beta 1$ integrin.^{18,19,22} Contact-mediated interactions between axonin-1/SC2 expressed on the surface of DRG axons (afferent fibers) and other members of the IgSF molecules expressed in the spinal cord (NgCAM, NrCAM, and F11) are essential for guiding DRG axons to innervate specific target layers in the spinal cord.³⁸ Furthermore, Contactin-2/TAG-1 on the DRG axonal surface is involved in the reception of chemorepellents secreted by the notochord or ventral spinal cord.^{37,39-41} Moreover, TAG-1 regulates the responsiveness of DRG axons to the axon repellent semaphorin 3A through endocytosis of its receptor complex (L1/Neuropilin-1).^{41,42}

In the cerebral cortex of mouse embryos, TAG-1 mediates interactions between mature axons (pioneer axons) and immature neurons, and plays an important role in the axonal formation of the latter.²⁸

TAG-1 is also important for the migration of various nerve cells. In the cerebral cortex of mouse embryos, neural stem cells are long and narrow; however, in *TAG-1*-deficient mouse embryos, these cells are shorter and their nuclei become immobile.⁴³ Accordingly, the formation of the cerebral cortex layer is disorganized.⁴³ Moreover, analysis of *TAG-1*-deficient fetal mice has shown that *TAG-1* deficiency causes apoptosis of cells migrating to the surface layer and shrinkage of the lateral reticular nuclei in the caudal medulla.⁴⁴ However, it has been suggested that TAG-1 is *not* involved in the migration of GABAergic interneurons from ganglionic eminences to the cerebral cortex.⁴⁴

In the cerebellum of mouse embryos, TAG-1 is expressed on the surface of cerebellar granule precursor cells, and prevents their premature differentiation.⁴⁵ In addition, axonin-1/SC2 is essential for guiding

the parallel fibers of cerebellar granule cells in chicks, but is not necessary for their elongation.⁴⁶

Function in the adult nervous system

In the adult rodent nervous system, TAG-1 is expressed in both axons and the myelin sheath. TAG-1 is known to interact with both the contactin-associated protein-like 2 (Caspr2) and K^+ channel via its immunoglobulin-like domains (Fig. 3).¹¹ In the juxtaparanode region, TAG-1 forms cis-bonds with Caspr2 to create heterodimers on the axonal side, which in turn complex with TAG-1 on the myelin side (Fig. 3).^{17,47-49} These complexes are necessary for K^+ channel clustering at the juxtaparanode.^{48,49} TAG-1 thus plays an essential role in the formation and maintenance of myelinated nerve fibers. Besides its role at the juxtaparanode, TAG-1 also co-localizes with Caspr2 at synapses.⁵⁰

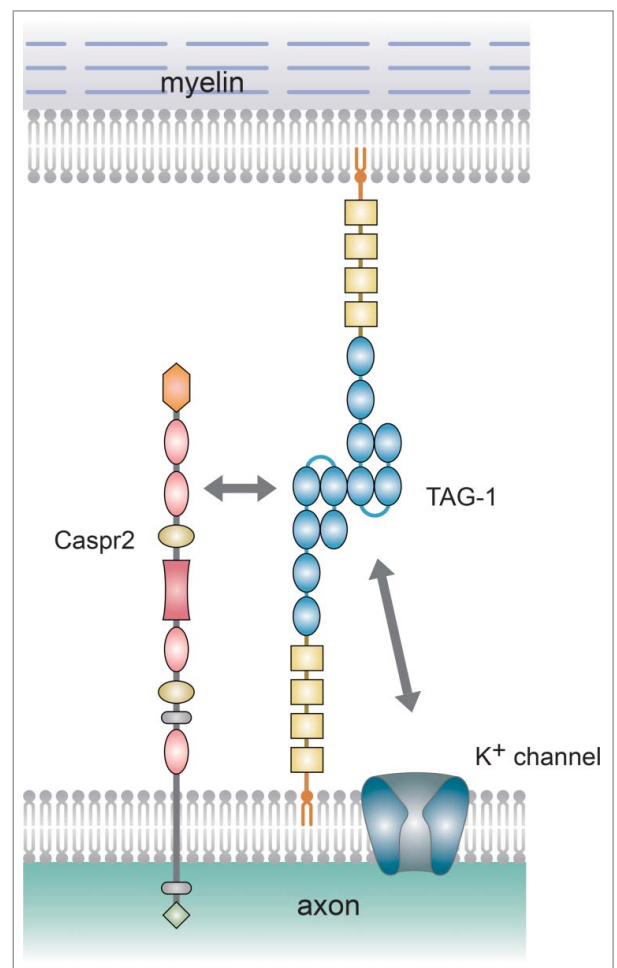


Figure 3. Molecular interactions at the juxtaparanode. At the juxtaparanode, TAG-1 is present both on the axonal and myelin sides, and forms a complex by binding to Caspr2 (Trans binding between TAG-1 molecules has been shown with the zipper mode model.).

Association with pathologies

Meinl's group has searched for targets of the autoimmune response in patients with multiple sclerosis (MS), an autoimmune disease of the central nervous system (CNS), and identified that TAX-1 is a target protein of autoantibodies in patients with MS.⁵¹

As described above, TAG-1/TAX-1 is a ligand for APP. The binding of TAG-1 and APP triggers the γ -secretase-dependent release of APP intracellular domain (AICD), resulting in the suppression of mouse neurogenesis.²⁷ More recently, *in vitro* experiments have revealed that TAG-1 inhibits TGF β 2-induced cell death of neurons by reducing the binding between TGF β 2 and APP.⁵² Based on the common understanding that AICD leads to amyloid β formation and that the neuronal cell death could result in progression of Alzheimer's disease (AD), it may be inferred that TAG-1/TAX-1 affects the pathogenesis of AD.

TAX-1 is reported to be overexpressed in malignant gliomas.⁵³ More recently, comprehensive bioinformatics analyses have shown that TAX-1 is linked to the oligodendroglioma to the highest degree.⁵⁴ As described above, *in vitro* experiments have further shown that TAX-1 is involved in the growth and differentiation of glioma cells.³¹ Thus, the determination of Contactin-2/TAG-1 signal cascades may be essential for therapeutic approaches that target these diseases.

Genetic mutations

Genetic mutations in humans

TAX-1 has been mapped to chromosome 1 (1q32).⁵⁵ SNP analysis of genes linked to chronic inflammatory demyelinating polyneuropathy (CIDP), an autoimmune disease of the peripheral nervous system, has shown that the TAX-1 gene affects CIDP's refractoriness and resistance to treatment.^{56,57} Furthermore, The TAX-1 gene has also been reported to be a gene responsible for cortical tremors and epilepsy.⁵⁸

TAG-1-deficient mouse established in 2001 (C57/BL/6)

A Japanese research group has engineered a TAG-1-deficient mouse by deleting exons 2 through 5 of the TAG-1 gene.⁵⁹ Compared to wild-type mice, these mice show no major abnormalities in appearance or brain tissue structure. However, an increased number of adenosine receptors in the hippocampus, susceptibility to events such as convulsive seizures, and other functional abnormalities of the nervous system are observed.⁵⁹

Moreover, K⁺ channels and Caspr2 expression levels are reduced in the sciatic nerve fibers, and behavioral experiments revealed impairments in learning and memory, of these deficient mice.⁶⁰ Furthermore, incomplete myelin formation is observed in the retinal ganglion cell axons of these deficient mice.⁶¹ Additionally, in these deficient mice the number of olfactory bulb mitral cells is reduced and abnormalities in olfactory behavior are clearly observed.⁶²

TAG-1-deficient mouse established in 2003 (C57/BL/6J)

A British research group has engineered a TAG-1-deficient mouse by deleting exons 2 through 6 of the TAG-1 gene.⁴⁸ These deficient mice are born at the Mendelian rate and show no obvious differences from wild-type mice. Morphological abnormalities similar to those in the TAG-1-deficient mice established by the Japanese group have been observed upon analysis of CNS tissues.⁴⁸ Moreover, these mice have lower metabolic function than wild-type mice.⁶³

Conclusions

Contactin-2/TAG-1 has been one of the best-known cell adhesion molecules for three decades in our field. Despite its importance, the comprehensive review that covers a wide range of its role in the nervous system has not yet been written. In this review, I first presented an overview of the role of Contactin-2/TAG-1 in the nervous system. In comparison to Contactin-1/F3, the signal cascade of Contactin-2/TAG-1 has not yet been elucidated in detail. I hope it will be revealed in future research. As mentioned in this review, Contactin-2/TAG-1 has been reported to be involved in various diseases such as gliomas, AD, MS, CIDP, and epilepsy. Future findings on the signal cascade of Contactin-2/TAG-1 may provide a potential target for therapeutic intervention of these diseases.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

Funding

This work was supported by JSPS KAKENHI Grant Nos. JP15K08148 and JP15H02765 from the program Grants-in-Aid for Scientific Research of the MEXT, Japan to T.M.

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