Down syndrome cell adhesion molecule and its functions in neural development

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Abstract: The nervous system is a complex network with many types of neurons and numerous synaptic connections. The present knowledge on how neurons recognize specific targets and form such an intricate network is still limited. The Down syndrome cell adhesion molecule (DSCAM) belongs to the immunoglobulin superfamily and contributes to defects in the central nervous system in Down syndrome patients. DSCAM plays important roles in neural development, including dendritic patterning and self-avoidance, axon guidance and branching, axon target recognition and synaptic formation. However, the functional mechanisms and the underlying signaling pathways are still largely unknown. Here the functions of DSCAM in neural development were reviewed. Future research for better understanding DSCAM function and the relevance of DSCAM to human diseases was also discussed.

Keywords: Down syndrome cell adhesion molecule; neural development; Down syndrome

1 Introduction

The nervous system is one of the most complicated systems in both vertebrates and invertebrates. In the human brain, there are approximately 1×10^{12} neurons, weaving an intricate and precise neural network. These neurons communicate with each other via over 1×10^{15} synapses. The mechanisms underlying the formation of this system, including neuronal identity specification, axon guidance, dendritic patterning, and synaptic formation, are still largely unknown. Many membrane proteins, especially cell ad-

hesion molecules such as Deleted in Colorectal Cancer (DCC), roundabout (Robo), and neuroligins, participate in various steps of neural development. These molecules exhibit adhesive, attractive or repellent properties by binding to their specific ligands or components in the extracellular matrix, and affect many aspects of neural development including cell migration, axon guidance and dendritic patterning. In 1998, Yamakawa *et al.* isolated Down syndrome cell adhesion molecule (*DSCAM*) gene from the human chromosome band 21q22.2-22.3, which is a critical region for many neurological phenotypes of Down syndrome (DS)^[1]. *DSCAM* encodes a type I transmembrane protein that belongs to the immunoglobulin (Ig) superfamily and represents a new class of neural cell adhesion molecules. The extracellular domain of DSCAM contains 10 Ig domains and 6 fibronectin type III (FN) repeats, and the tenth

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Article ID: 1673-7067(2011)01-0045-08

Received date: 2010-11-19; Accepted date: 2010-12-31

Ig domain is located between the fourth and the fifth FN repeats (Fig. 1). DSCAM also contains a small intracellular domain^[1-3], the function of which is largely unknown. Human and mouse DSCAMs share 90% and 98% identities in the nucleotide and the amino acid levels, respectively^[4]. The number and organization of the extracellular domains of the fly Dscam are identical to those of human DSCAM^[3]. DSCAM is expressed at a high level in the developing nervous systems in human, mouse and drosophila, implying a crucial role of DSCAM in the development of the nervous system. The present review was focused on the role of DSCAM in neural development and the remaining questions on the function and signaling mechanisms of DSCAM were also discussed.

2 The *Drosophila* Dscam gene

Drosophila genome contains 4 genes encoding Dscam family members, *Dscam1-4*^[5]. *Dscam1* is often referred to as *Dscam*. The most fascinating property of *Drosophila* Dscam is that thousands of Dscam protein isoforms can be generated from a single gene through alternative splicing^[6]. Although the other 3 *Dscam* genes encode proteins with similar extracellular domains as *Dscam1*, they do not undergo extensive alternative splicing^[5].

2.1 Alternative splicing of *Dscam* Alternative splicing is one of the most powerful mechanisms of proteomic diversity. *Drosophila* Dscam gene is an extreme case that increases the coding efficiency via alternative splicing in 4 variable exon clusters, exons 4, 6, 9 and 17, which contain 12, 48, 33 and 2 alternatives, respectively^[3,7]. Only one exon is chosen during each mRNA splicing (Fig. 1). Assuming that all exon combinations are possible, *Dscam* gene would generate 38 061 distinct isoforms through alternative splicing^[3,8]. The resulting isoforms have the same domain structure but diverse amino acid sequences located in the extracellular domains Ig2, Ig3 and Ig7, and in the transmembrane segment (Fig. 1)^[3,8,9]. All these 3 variable Ig domains are important for Dscam isoform-specific homophilic binding and contribute to Dscam function. Besides alternative splicing of exons in the ectodomain and the transmembrane domain, splicing of exons 19 and 23

encoding parts of the endodomains is regulated at different developmental stages, and the resulting Dscam proteins govern different stage-specific neuronal morphogenetic processes (Fig.1)^[10].

How does alternative splicing of the 4 exon clusters take place? Graveley's work on the alternative splicing of the *Dscam* exon cluster 6 has provided a clue^[11]. Two important elements are involved in this splicing process: a docking site located in the intron downstream of constitutive exon 5 and the selector sequences located upstream of each exon 6 variant. The interaction of a single pair of these 2 elements in mRNA splicing guarantees mutually exclusive splicing of exon 6 within the cluster^[11]. However, whether the similar alternative splicing mechanism also applies to other *Dscam* exon clusters is still unknown and needs further investigation.

For the precise neural circuitry formation and function, neurons migrate to their final positions and form their axons and dendrites, recognizing each other and finally forming synapses. A large number of molecules are required for the precise recognition of individual neurons. *Drosophila* Dscam offers a unique strategy to generate numerous molecules for neural recognition via alternative splicing. Interestingly, the molecular diversity of Dscam transcripts is also utilized in the *Drosophila* immune system for phagocytic uptake of bacteria, a system that requires an extensive diversity of recognition at the molecular level^[12].

2.2 Homophilic binding of Dscam isoforms and the structural basis Another unique property of *Drosophila* Dscam that endows its function in neuronal recognition is its isoform-specific homophilic binding. Initially, a cell aggregation assay showed that Dscam protein exhibited homophilic binding^[2]. Further analysis showed that despite the diversity of *Drosophila* Dscam isoforms, only the same isoforms whose 3 variable domains (Ig 2, Ig 3 and Ig 7) match perfectly can bind to each other. If there is difference in any of these domains, there will be no or at most a very low binding affinity^[2,8,13-15].

The isoform-specific binding property of Dscam can be attributed to its specific structure. Strong homophilic

Fig. 1 Generation of diverse isoforms via alternative splicing (adopted from Hattori D *et al.*, 2008)^[46]. There are 4 alternative-spliced exon clusters in the *Drosophila Dscam* gene: the exon 4 contains 12 alternatives, the exon 6 contains 48 alternatives, the exon 9 contains 33 alternatives and the exon 17 contains 2 alternatives. Each transcript contains one alternative exon from each exon cluster. The full-length of endodomain is largely restricted in embryogenesis stage, while most Dscams have no exon 19 and exon 23 in postembryonic stages. The extracellular domain of Dscam contains 10 immunoglobulin (Ig) domains (ellipse), 6 fibronectin type III repeats (hexagons) and a short transmembrane domain (TM). Alternative splicing generates diversity in the Ig2, Ig3, Ig7 and TM domains.

binding of Dscam requires not only the 7 Ig domains at the N-terminus of the protein (Ig1-7), but also direct Ig2-Ig2, Ig3-Ig3 and Ig7-Ig7 bindings^[8]. This is also supported by the crystal structure of specific Dscam isoforms. Ig2-Ig2, Ig3-Ig3, Ig7-Ig7 interactions are observed in a Dscam Ig1-8 homophilic dimer, and each of the 3 variable Ig domains binds to its identical counterpart in an antiparallel mode^[16]. Dscam Ig1-8 monomers fold into an S shape, and

the double-S homophilic dimer is formed by pairing of the 2 S-shaped monomers through homophilic binding^[16]. At the top half of the S curve, Ig1-4 domains fold into a horseshoe structure which is accommodated by a long linker region between Ig2 and Ig3, and the bottom half of S curve is formed by another long linker region between Ig5 and Ig6 (Fig. 2)^[9,15,17]. Thus, differences in amino acid sequences between variants, even small ones, can result in

Fig. 2 Conformation of Dscam Ig domains (adopted from Hattori D *et al.*, 2008)^[46]. Binding of Dscam monomers on opposing membrane surface depends on specific domain topology, and all Ig2, Ig3 and Ig7 domains in the 2 monomers need to match perfectly. Dscam extracellular domains are highly flexible. The first 4 Ig domains form a stable horseshoe structure through intramolecular interactions, thus leading to a juxtaposition of Ig2 and Ig3. Strong bend between Ig5-Ig6 domains enable each monomer to appear as an S shape. This configuration is essential for homo-dimer formation.

changes in the entire variable domain interface and lead to loss of binding.

2.3 Function of *Drosophila* Dscam in neural development *Drosophila* Dscam plays important roles in many aspects of neural development. Dscam participates in path-finding of Bolwig's nerve to an intermediate target in the embryo, through interaction with Dock and Pak proteins^[3]. Dscam also regulates axon targeting specificity of olfactory receptor neurons (ORNs) in the antenna, ensuring that specific ORN classes form synapses in the correct glomeruli. In *Dscam* mutants, ORNs frequently terminate in ectopic sites both within and outside the antennal lobe^[17]. Moreover, Dscam is involved in growth and extension of axon branches of mechanosensory neurons^[18].

Among various functions in neural development, the role of Dscam in self-avoidance, a process in which axonal or dendritic branches of the same neuron recognize and avoid each other, has been extensively studied. In the development of mushroom body (MB), each axon of MB neurons bifurcates and the resulting 2 sister branches segregate into different pathways. In the *Dscam* mutant flies, axons of these neurons can bifurcate but the 2 sister branches fail to segregate. Thus the sister branches frequently grow in parallel along the same pathway^[19]. The innervated fields of neurons belonging to the same class do

not overlap and the dendrites from the same neuron do not self-cross, a phenomenon known as dendritic tiling (Fig. 3)^[20-22]. In the fly visual system, neurites from L1 cells in adjacent columns interact through Dscam2 homophilic interactions, which results in repulsion and subsequent retraction of neurites to their column of origin^[5].

Enormous molecular diversity generated by alternative splicing of *Dscam* gene is essential for self-avoidance. For different isoforms, only identical ones can bind to each other and this binding promotes repulsion (Fig. 3). To ensure that the homophilic repulsion is restricted to self-branches, different neurons express different sets of Dscam isoforms in a stochastic fashion. When the number of total available Dscam isoforms is reduced to less than 4 752, deficits in the branching of 3 classes of neurons (dendritic arborization neurons, MB neurons and posterior scutellar neurons) will appear. However, when the potential number of isoforms gradually increases, the defects will be improved, indicating that thousands of Dscam isoforms are necessary for neurons to distinguish between self and non-self and to avoid itself during development^[23].

In addition to its function in axon and dendrite development, *Drosophila* Dscam also regulates postsynaptic specificity at multiple-contact synapses. Millard *et al.* have found that *Drosophila* Dscam1 and Dscam2 promote in-

Fig. 3 Self-avoidance and tiling. Repulsion mediated by homophilic binding of Dscam keeps axons or dendrites of neurons in the same class repelling each other in fly and mouse visual systems, a process also known as self-avoidance. In *Dscam* mutant neurons, dendrites can not separate, resulting in self-cross and overlapping innervation fields.

variable postsynaptic partnership between lamina interneuron L1 and L2 through homophilic repulsion. In *Dscam1* and *Dscam2* double-mutant flies, this strict pairing is lost. Therefore, *Drosophila* Dscam may play a key role in regulating the composition of tetrad synapses^[24].

3 The vertebrate DSCAM genes

There are 2 DSCAM homologs, DSCAM and DSCAML1, in the human genome. DSCAML1 is located on chromosome 11q23. The deduced DSCAML1 protein also contains 10 Ig domains, 6 FN repeats and one intracellular domain. All of them are structurally similar to DSCAM^[3]. Despite the many studies on invertebrate DSCAM, functions of the vertebrate DSCAM are still largely unknown. However, in recent years, researchers have paid more and more attention to the vertebrate DSCAM and its function in neural development.

3.1 DSCAM mediates homophilic repulsion or adhesion in vertebrates *Drosophila* Dscam mediates homophilic repulsion via a large number of isoforms resulting from alternative splicing. Unlike their invertebrate homologs, vertebrate DSCAM and DSCAML1 do not undergo extensive alternative splicing, but whether the vertebrate DSCAM can play a similar role in neural development is an intriguing question. Fuerst *et al.* have found that in the *Dscam* mutant mice, 2 subsets of retinal amacrine cells (dopaminergic amacrine cells and bNOS-positive cells) that would normally express DSCAM have hyperfasciculated dendrites, and their cell bodies exhibit defects in mosaic spacing^[25]. Their findings indicate that although mouse *Dscam* gene is not extensively alternative spliced, DSCAM protein still undergoes homophilic binding and mediates neuronal self-avoidance for dendritic arborization and heteroneuronal self-avoidance within the same cell types. More recently, Fuerst *et al.* have found that DSCAM is also expressed in all retinal ganglion cells (RGCs) during embryonic development. In the *Dscam* mutant mice, each type of RGCs exhibits profound defects in soma spacing and dendrite arborization^[26]. Therefore, DSCAM plays a role in preventing self-adhesion between neurons of the same subset. However, many questions still exist and

need to be answered, such as the mechanism of vertebrate DSCAM-mediated homophilic repulsion, and whether vertebrate DSCAM mediates homophilic repulsion in all species. For the mechanism of vertebrate DSCAM-mediated homophilic repulsion, one hypothesis is that DSCAM masks adhesive codes that are shared by cells of a given type, and in the absence of DSCAM, these adhesive cues are unmasked. Therefore, DSCAM effectively mediates self-avoidance and does so in the absence of molecular diversity. For the question of whether vertebrate DSCAM mediates homophilic repulsion in all species, the study on the function of chicken DSCAM gave a negative answer^[27].

Yamagata *et al.* have found that DSCAM, DSCAML1, Sidekick-1 and Sidekick-2 are expressed in different subsets of interneurons and RGCs in the chicken retina. Sidekick-1 and Sidekick-2 are large transmembrane adhesion molecules of the Ig superfamily, and are the closest relatives of DSCAMs. Knocking down DSCAMs resulted in the disruption of the layer-specific targeting of DSCAM-expressing neurons, while ectopic expression of DSCAMs in other layers redirected dendrites to those layers expressing the same DSCAM protein. This suggests that DSCAMs mediate synaptic formation through homophilic adhesion in the chicken retina^[27].

The findings that DSCAM plays divergent roles in different vertebrate species are puzzling and the mechanisms remain elusive. One possible explanation is that different signaling pathways mediate DSCAM functions in different species, just like the case of the axon guidance molecule netrin which acts as attractant in some cases and repellent in others, depending on which receptor it binds and the levels of the intracellular signaling molecules^[28,29].

3.2 Involvement of DSCAM in neuronal guidance Besides mediating homophilic repulsion or adhesion in vertebrates, DSCAM is also involved in axon guidance. In neural development, axon pathfinding is regulated by attractive and repulsive guidance cues^[30]. Netrins are a family of axon guidance cues that can promote neurite outgrowth and guide growth cone navigation in species ranging from *C. elegans* to mammals^[30-34]. In *C. elegans*, the

receptors for netrin have been identified, including UNC-40 and UNC-5^[31,35,36]. In mammals, the homologs of UNC-40 are identified to be DCC and neogenin^[37,38]. Recently DSCAM has been identified as another receptor for netrin-1^[39,40]. The study by Liu *et al.* indicates that DSCAM is expressed in the commissural axons and interacts with netrin-1. They have also found defects in commissural axon projection and pathfinding when DSCAM is knocked down using siRNA^[40]. Ly *et al.* have reported the same findings, but their work further suggests that DSCAM and DCC can form a complex receptor in the absence of netrin-1, and when netrin is present, this complex begins to dissociate. Thus, DSCAM and DCC may collaborate in mediating turning response to netrin-1, although they can also signal independently^[39].

Although DSCAM has been found to be a netrin receptor, the downstream signaling pathways of netrin-DSCAM are still unknown. Some *Drosophila* Dscam-interacting molecules, such as Dock and Pak, have been identified^[3]. However, it is still unknown whether these molecules are involved in the netrin-Dscam pathways. Further studies are required to reveal the signaling mechanism of netrin-DSCAM in axon guidance.

3.3 DSCAM and neuronal function Kenji *et al.* have found that DSCAM plays a critical role in central respiratory regulation, and is implicated in synchronous activation of pre-inspiratory (Pre-I) neurons. The synchrony of Pre-I neuron firing is reduced in *Dscam*^{+/-} mice, and is totally lost in *Dscam*^{-/-} mice that die of abnormal central respiratory regulation within 24 h after birth^[41]. This work suggests that DSCAM may regulate neuronal function *in vivo*. Also, it would be interesting to examine whether DSCAM is a susceptible gene in human diseases with respiratory dysfunction.

3.4 The role of DSCAM in DS DSCAM is mapped to human chromosome 21^[1], and DS is caused by trisomy of this chromosome^[42,43]. Therefore, DSCAM may be implicated in the pathology of DS, and recent studies have provided some evidence supporting this hypothesis. Alves-Sampaio *et al.*^[44] found that the dendritic level of DSCAM was increased in the hippocampal neurons of Ts1Cje mice

(a mouse model of DS), and overexpression of DSCAM in hippocampal neurons inhibited dendritic branching. These results are consistent with the dendritic phenotype observed in DS patients^[45]. Moreover, they also found that dendritic level of DSCAM protein was regulated by NMDA receptor-mediated synaptic activity, and this regulation was lost in the Ts1Cje mice^[44]. In sum, these findings suggest a mechanistic association of DSCAM with DS. However, the exact role of DSCAM in the pathology of DS may far beyond the current realization, and requires more studies.

4 Perspectives

Since the first identification of DSCAM as a novel member of the Ig superfamily related to DS in 1998, DSCAM has raised more and more attention in the recent 10 years. *Drosophila* Dscam has attracted much attention because of its unique properties of alternative splicing and isoform-specific homophilic binding. Its crucial role in neural development has been repeatedly reported in *Drosophila* and later in the vertebrate. Some similar functions of Dscam have been demonstrated in both invertebrates and vertebrates, such as its role in dendritic self-avoidance and tiling mediated by homophilic repulsion. However, vertebrate DSCAM also mediates homophilic attraction in neuronal layer-targeting in the chicken retina. Moreover, vertebrate DSCAM is not restricted to homophilic binding. It also functions as a receptor for netrin in mediating axon guidance. Many questions about the functions of DSCAM in neural development still remain to be addressed. What are the signaling mechanisms that mediate homophilic repulsion or attraction? Is DSCAM involved in other signaling pathways besides netrin-mediated axon guidance? What DS-related developmental deficits would be produced from DSCAM mutation? In-depth studies of DSCAM at molecular, cellular and functional levels may provide new insights into the mechanism of neural development and the pathogenesis of human diseases such as DS.

Acknowledgements: This work was supported by the grants from the Ministry of Science and Technology, China

(No. 2009CB825402, 2010CB529603) and National Natural Science Foundation of China (No. 30900845).

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唐氏综合征细胞黏附分子及其神经发育功能

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摘要: 神经系统是一个包含有多种类型神经元和无数个突触连接的复杂网络。关于神经元如何识别特定的目标和形成这样一个错综复杂的网络的认识目前仍然很有限。唐氏综合征细胞黏附分子(Down syndrome cell adhesion molecule, DSCAM)是免疫球蛋白超家族的成员, 与唐氏综合征患者的中枢神经系统病变有密切的关系。DSCAM在神经发育过程中起着重要的作用, 包括树突形成、自我回避、轴突导向和分支、轴突目标识别和突触形成等。然而, DSCAM在神经系统中作用的机制和相关信号通路仍不清楚。本文综述了DSCAM在神经发育中的作用, 并对未来的研究进行探讨, 以期更好地理解DSCAM的功能及其与人类疾病的关系。

关键词: 唐氏综合征细胞黏附分子; 神经发育; 唐氏综合征