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Mini Review

The Role of SAM`s as Key Player in Synapse Formation and Dysfunction: Make a Synapse, Shape a Synapse

Stefan Bittmann[1,2]*, Elisabeth Luchter[1] and Elena Moschüring Alieva[1]

[1]*Department of Pediatrics, Ped Mind Institute (PMI), Hindenburgring 4, Germany*

[2]*Professor (Honorary Prof.), Shangluo Vocational and Technical College, China*

***Corresponding author:** Prof. Stefan Bittmann MA, Honorary (Hon.Prof.) and Visiting Professor (Visit. Prof.) in Pediatrics, School of Medicine, Shangluo Vocational and Technical College, Shangluo, China and Ped Mind Institute (PMI) Department of Pediatrics, Medical and Finance Center Epe, Gronau, Germany..

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Abstract

Neurexins and neuroligins are the most impactful SAMs on synaptic formation, with other key molecules including EphB/ephrin-B, immunoglobulin (Ig)-containing SAMs, cadherins, and SynCAMs. These molecules facilitate synaptogenesis by linking pre- and postsynaptic terminals and organizing the components within them, with specific subtypes dictating whether they are involved in excitatory or inhibitory synapses. Neurexins and Neuroligins are a central pair of SAMs where neurexins are presynaptic and neuroligins are postsynaptic, forming a trans-synaptic complex that is crucial for both excitatory and inhibitory synapse formation. EphB and Ephrin-B are a pair of SAMs controls synaptic development by regulating glutamate receptor localization and function. Immunoglobulin (Ig)-Containing SAMs are a family of molecules includes SynCAMs and plays a role in shaping synapses and modulating synaptic plasticity, influencing activity-dependent remodeling of synapses. Like neurexins and neuroligins, cadherins contribute to both the general formation of synaptic contacts and the determination of specific synaptic partners. As members of the Ig-domain SAM family, SynCAMs contribute to synaptic plasticity by shaping synapses and promoting activity-dependent remodeling. SAMs act as "bridges" to connect pre- and postsynaptic neurons, forming the foundation for stable synaptic connections. They recruit and organize specific sets of proteins to the pre- and postsynaptic terminals, ensuring the proper assembly of synaptic machinery. Different SAM subtypes can specify different types of synapses, ensuring that excitatory and inhibitory synapses are formed at the correct locations. Specialized motifs within SAMs can induce downstream signaling pathways that control aspects of synaptic development and plasticity.

Keywords: Synapse-Transmission-Formation-SAM

Introduction

Synaptic Adhesion Molecules (SAMs) organize and stabilize synapses, mediating protein-protein interactions across the synaptic cleft to facilitate formation and function of neural circuits [1,2]. Prominent examples include neurexins and neuroligins, which interact to organize presynaptic and postsynaptic components and establish specific excitatory or inhibitory connections. SAMs are essential for synaptic plasticity, with their expression and localization regulated by synaptic activity, and they play roles in both synapse formation and long-term function. SAMs are crucial for the initial establishment and proper development of synapses by coordinating molecular components. They form trans-synaptic bridges and complexes that align pre- and postsynaptic machinery, ensuring the proper positioning of neurotransmitters and receptors. SAMs enable bi-directional signaling between presynaptic and postsynaptic neurons, mediating interactions that drive synaptic differentiation and plasticity. SAM function can be modified by synaptic activity,

influencing protein levels, interactions, and localization, which contributes to the dynamic nature of synaptic strength. A well-studied pair of SAMs that form a bridge between the presynaptic (neurexin) and postsynaptic (neuroligin) membranes, playing critical roles in synapse formation and function. Cadherins are a class of SAMs that contribute to synaptic adhesion and organization within neural networks. Immunoglobulin superfamily (IgSF) members include various SAMs like neuroligins, which are involved in synaptic assembly and stability. Amyloid Precursor Protein (APP) family are proteins like APP, APLP1, and APLP2 are also considered SAMs due to their roles in synapse formation and plasticity. SAMs typically form complexes with different partner molecules on the opposing neuron, creating specific binding interactions. Different subtypes and variations of SAMs allow for fine-tuning of synaptic connections, ensuring that specific types of excitatory or inhibitory synapses are formed. Neuronal transmission relies on signals transmitted through excitatory and inhibitory synaptic connections. Contact between axons and dendrites leads to synapse formation, with axonal and dendritic filopodia playing key roles. Changes in morphology and molecular content result in the formation of mature synapses, characterized by the accumulation of synaptic vesicles and receptors at the synaptic junction. Especially in pediatric diseases like autism and epilepsy, recent research focus on the relation to synaptic dysfunction in these pediatric patients and in other neurodevelopmental disorders.

Key Feature of SAM`s

Synaptic Adhesion Molecules (SAMs) are cell-surface proteins that facilitate connections between neurons at synapses, mediating key functions like synapse development, stabilization, and signaling. They bridge the pre-synaptic and post-synaptic membranes, directly participating in structural adhesion and also transmitting signals that regulate synapse formation, function, and plasticity. Examples include immunoglobulin superfamily members like SynCAMs and SALMs/Lrfn proteins, which have diverse roles in organizing synaptic architecture and influencing neural activity. Key functions SAMs are recognizing specific neuronal targets, stabilizing initial contacts between neurons, and guiding the formation of new synapses. They are crucial for the long-term stability and organization of mature synapses. Beyond physical adhesion, SAMs act as receptors, relaying signals to the cytoplasm that control cellular events like the formation of dendritic spines and the modulation of synaptic strength. SAMs can interact with other synaptic proteins and receptors, influencing the dynamic changes in synaptic strength associated with learning and memory. SAMs can form complexes with other molecules on neighboring cells, creating a bridge across the synaptic cleft. They can also bind to intracellular partners, such as the scaffolding protein PSD-95, which then recruits other proteins to the synapse or triggers intracellular signaling pathways. This interaction allows SAMs to regulate the recruitment and activity of synaptic components, thereby modulating synaptic function.

Examples of Synaptic Adhesion Molecules

Neurexin: It is a family of cell adhesion molecules that play a crucial role in the formation and function of synapses in the nervous system [1,3]. There are two main types, α-neurexin and β-neurexin, and through alternative splicing, many different variants are generated that differ in their function. Neurexins bind to postsynaptic proteins such as Neuroligin and are associated with neurological disorders such as autism and schizophrenia. Neurexins are presynaptic cell adhesion molecules that bind to postsynaptic proteins such as Neuroligin. They play a role in coupling calcium channels and vesicle exocytosis to ensure the release of neurotransmitters. They influence synaptic strength and plasticity, such as Long-Term Potentiation (LTP).

Synaptic Cell Adhesion Molecules (SynCAMs): These are members of the immunoglobulin-like protein family that form transsynaptic adhesion complexes, contributing to synaptic structure and function.

Synaptic Adhesion-like Molecules (SALMs/Lrfn proteins): A family of proteins containing leucine-rich repeat (LRR) and fibronectin III domains, SALMs are involved in synapse development and function and are linked to certain brain disorders.

Neural Cell Adhesion Molecule (NCAM): A prominent member of the immunoglobulin superfamily that plays a role in various aspects of synaptic development and function.

Discussion

Understanding the molecular signals that guide neurons to form synaptic junctions is a key challenge in cellular neuroscience. Many proteins that promote synaptic junction formation share a common feature-they create strong bonds across the synapse through adhesive interactions [1-4]. Adhesive interactions play a crucial role in synaptic junction organization, engineered adhesion molecules rely on intracellular signaling to facilitate synapse organization [5-7]. These innovative adhesion molecules serve as valuable tools for manipulating synaptic organization patterns and adhesion in various systems [1-7]. Synaptic cell adhesion molecules play a crucial role in synapse formation. Among these molecules, synaptic adhesion-like molecules have been identified as key regulators of neurite outgrowth and synapse maturation. In particular, SALM3 and SALM5 have been found to induce both excitatory and inhibitory presynaptic differentiation in axons. These proteins are enriched in synaptic fractions and interact with Postsynaptic Density-95 (PSD-95), a scaffolding protein at excitatory synapses. SALM3 induces clustering of PSD-95 on dendritic surfaces, while SALM5 is involved in the formation and function of excitatory and inhibitory synapses. This suggests that SALM3 and SALM5 play distinct roles in promoting synapse formation through different mechanisms. Cell-adhesion molecules in multicellular organisms connect cells into tissues and mediate intercellular signaling [8-10].

In vertebrate brains, synaptic cell-adhesion molecules play a crucial role in synapse formation, specification, and plasticity [11,12]. While some SAMs promote synaptic specialization, genetic deletion of SAMs often impairs synaptic transmission without affecting synapse numbers. Recently, novel SAMs from bacterial proteins, named 'Barnoligin' and 'Starexin', which drive synapse formation in a specific and directional manner in cultured neurons, were found. These engineered adhesion proteins require both extracellular and intracellular domains for synapse formation, supporting a model where SAMs drive synapse organization through adhesive interactions and signaling cascades. Synapses in neural circuits rapidly transfer and transform information between neurons. The computational properties of synapses are influenced by interactions between pre- and postsynaptic neurons. The mechanisms behind synapse assembly and specificity remain largely unknown. Various SAMs work together to achieve the specificity and plasticity of synapses, each contributing unique functions. SAMs likely function as signal transduction devices in orchestrating synapse assembly. While many SAM candidates exist, only a few have a significant impact on synapse formation. It is possible that a limited set of collaborating SAMs are responsible for synapse formation. Notably, several SAMs are associated with neuropsychiatric disorders, suggesting that disruptions in synapse assembly may contribute to these conditions.

Multicellular organisms rely on cell-adhesion molecules for tissue integrity and intercellular communication. In the vertebrate Central Nervous System (CNS), Synaptic Adhesion Molecules (SAMs) play a crucial role in organizing synaptic junctions and facilitating synaptic transmission. However, the function of SAMs in synapse formation has been a subject of debate. Studies have shown that overexpression of SAMs like Neuroligin and Neurexin in non-neuronal cells can induce the formation of synaptic specializations in co-cultured neurons. This led to the hypothesis that SAMs stimulate synaptic assembly. However, genetic deletion of these SAMs in mice did not result in a significant deficit in synapse numbers, challenging this view. Further research has revealed that while some SAMs drive synapse organization when overexpressed in non-neuronal cells, they are not essential for synapse formation in vivo. In contrast, adhesion-GPCRs like BAIs and latrophilins, and their ligands, have been found to be crucial for synapse formation In-vivo. These findings suggest that SAMs can be classified into two groups: those that "make" a synapse, like latrophilins and BAIs, and those that "shape" a synapse, like Neuroligin and Neurexin. This distinction highlights the complex role of SAMs in synaptic development and function. Understanding the mechanisms that drive synapse organization is a fundamental challenge in cellular neuroscience. Evidence suggests that synaptic adhesion molecules play a crucial role in aligning synaptic machinery, but testing their role as physical forces in synapse formation is challenging. While mouse genetics have enabled the inactivation of SAM gene families, eliminating all synaptic adhesion would require identifying all SAMs in the CNS and disabling them simultaneously. Our approach of creating novel adhesion molecules demonstrates that adhesion between neuronal membranes is likely necessary for synaptic machinery organization. The diversity among SAMs capable of inducing synaptic organization in cultured neurons suggests that their extracellular domains need only form a functional adhesion complex to induce synapse organization. Some synapses may require multiple SAMs for sufficient adhesion, while others may rely on a subset. Genetic deletion of SAMs reduces synapse formation in specific cell types, indicating the collective role of SAMs in securing adhesive interactions for synapse organization. High-affinity adhesion is essential for synapse formation, but our engineered adhesion molecules also require intracellular sequences from SAMs for full effectiveness in organizing synapses. This suggests that adhesion alone is not sufficient and requires intracellular signaling once the adhesion complex is formed. Future studies could explore how different SAM intracellular domains drive synapse formation and their contribution to excitatory versus inhibitory synaptic organization.

In conclusion, Synaptic Adhesion Molecules (SAMs) like MDGAs play a crucial role in forming and maturing synaptic connections in neural networks. This discovery sheds light on how SAMs regulate synaptic organization and function. Further research is necessary to further evaluate the role of SAM in neurological disorders like autism, epilepsy and other neurodevelopmental disorders in childhood.

Ethics Approval and Consent to Participate

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Conflict of Interest

The authors declare no conflict of interest.

References

1. Boyd R, Jaqaman K, Wang W (2024) Weaker neuroligin 2-neurexin 1β interaction tethers membranes and signal synaptogenesis through clustering. bioRxiv [Preprint] 10.16.618688.
2. Zhang H, Lei M, Zhang Y, Li H, He Z, et al. (2024) Phosphorylation of Doc2 by EphB2 modulates Munc13-mediated SNARE complex assembly and neurotransmitter release. Sci Adv 10(20): eadi7024.
3. Sclip A, Südhof TC (2023) Combinatorial expression of neurexins and LAR-type phosphotyrosine phosphatase receptors instructs assembly of a cerebellar circuit. Nat Commun 14(1): 4976.
4. Yokokawa T, Kido K, Sato K, Hayashi T, Fujita S (2023) Altered expression of synaptic proteins and adhesion molecules in the hippocampus and cortex following the onset of diabetes in nonobese diabetic mice. Physiol Rep 11(8): e15673.

5. Zhou Q (2023) Organizing the synaptic junctions. J Biol Chem 299(5): 104716.

6. Hale WD, Südhof TC, Huganir RL (2023) Engineered adhesion molecules drive synapse organization. Proc Natl Acad Sci USA 120(3): e2215905120.

7. Südhof TC (2021) The cell biology of synapse formation. J Cell Biol 220(7): e202103052.

8. Onodera W, Asahi T, Sawamura N (2021) Rapid evolution of mammalian APLP1 as a synaptic adhesion molecule. Sci Rep 11(1): 11305.

9. Wakita M, Yamagata A, Shiroshima T, Izumi H, Maeda A, et al. (2020) Structural insights into selective interaction between type IIa receptor protein tyrosine phosphatases and Liprin-α. Nat Commun 11(1): 649.

10. Schilling S, Mehr A, Ludewig S, Stephan J, Zimmermann M, et al. APLP1 Is a Synaptic Cell Adhesion Molecule, Supporting Maintenance of Dendritic Spines and Basal Synaptic Transmission. J Neurosci 37(21): 5345-5365.

11. Rudenko G (2017) Dynamic Control of Synaptic Adhesion and Organizing Molecules in Synaptic Plasticity. Neural Plast 2017: 6526151.

12. O'Callaghan EK, Ballester Roig MN, Mongrain V (2017) Cell adhesion molecules and sleep. Neurosci Res 116: 29-38.