Molecules and Cells

Editorial

# A decade of discovery: Deciphering the synaptic adhesion code

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The brain's ability to process information, store memories, and execute complex behaviors relies on the exquisite precision of its neural circuitry. At the core of this precision is the synapse—a specialized junction where neurons communicate. For decades, the molecular glue that holds these junctions together was viewed as a static structural component. However, the field of neuroscience has witnessed a paradigm shift over the last 2 decades. We now understand that synaptic cell-adhesion molecules (CAMs) are not merely structural anchors but rather act as dynamic computational hubs that dictate the specificity, maturation, and functional plasticity of neural connections (Kim et al., 2021; Lim et al., 2022). The "Synaptic Adhesion Code" hypothesis suggests that the staggering diversity of neural circuits is programmed by specific combinations of multifarious trans-synaptic adhesion complexes. As we celebrate a decade of unprecedented progress in this field, this special mini-review series, entitled "Evolving Landscape of Synaptic CAMs," showcases 5 forward-thinking perspectives. These reviews span the hierarchy of neuroscience from the atomic-scale organization of proteins to the clinical manifestations of molecular deficiency and the broad systems-level regulation of brain states.

Our journey into the synaptic code begins with a look at the fundamental scaffolding proteins that organize the molecular machinery of the synapse. In their review, Tabuchi et al examine the critical role of calcium/calmodulin-dependent serine protein kinase (CASK) in brain development and pathology (Tabuchi et al., 2026). CASK was originally identified as an intracellular binding partner for neurexins (Nrxns), the quintessential presynaptic CAMs. As an X-linked multidomain protein, CASK acts as a bridge between the cell membrane and the cytoskeleton. However, its significance transcends simple scaffolding. Clinical evidence shows that loss-of-function mutations in CASK lead to microcephaly with pontine and cerebellar hypoplasia, a devastating neurodevelopmental disorder. The authors highlight a critical shift in our understanding of CASK: While it was long thought to be essential for initial synapse formation, recent evidence from genetically engineered mouse models suggests it is actually indispensable for neuronal survival. In the absence of CASK, cerebellar granule cells undergo massive apoptosis during postnatal development, driven by overactivation of the c-Jun N-terminal kinase signaling pathway. The Nrxn-CASK-liprin-α2 complex emerges as a vital sensor that integrates synaptic adhesion with pro-survival signaling. This review reminds us that the synaptic code is not just about connectivity; it is a prerequisite for the very survival of the circuit-forming neurons.

Moving from the broad survival of neurons to the precise architecture of the synaptic cleft, Zhang and colleagues provide a comprehensive analysis of how neuroligins (Nlgns) organize synapses at the nanoscale (Han et al., 2026). The advent of super-resolution microscopy techniques, such as stochastic optical reconstruction microscopy and photoactivated localization microscopy, has revealed that synapses are not uniform disks of proteins but rather are organized into nanoclusters (Damenti et al., 2026). Nlgns are central to this organization. By interacting with presynaptic Nrxns, Nlgns ensure that the neurotransmitter release machinery (i.e., the presynaptic active zone) is perfectly aligned with postsynaptic receptor clusters. The authors detail how different Nlgn isoforms dictate specific synaptic properties. Nlgn1 is found predominantly at excitatory synapses, Nlgn2 at inhibitory and modulatory synapses, and Nlgn3/4 at all of the above. A groundbreaking concept discussed is the role of liquid-liquid phase separation (Hayashi et al., 2021). The interactions between the C-terminal tails of Nlgns and scaffolding proteins, like PSD-95 and Shank3, create a condensed protein phase that stabilizes the postsynaptic density. This nanoscale precision allows the brain to fine-tune synaptic strength with extraordinary fidelity, and its disruption is a hallmark of synaptopathies, including autism spectrum disorders.

The complexity of the synaptic code is further enriched by the adhesion G protein-coupled receptors (aGPCRs). Watson and Sando explore the dual nature of these molecules, which act as both high-affinity adhesion molecules and potent signaling receptors (Watson and Sando, 2026). This review focuses on three key subfamilies: latrophilins (Lphns), cadherin EGF LAG seven-pass G-type receptors, and brain-specific angiogenesis inhibitors. Lphns, in particular, have emerged as master regulators of synaptic specificity. In the hippocampus, Lphn3 employs a coincidence detection mechanism, binding simultaneously to presynaptic teneurins and fibronectin leucine-rich repeat transmembrane proteins to specify where and when a synapse should form. Unlike traditional CAMs, aGPCRs possess a unique GPCR autoproteolysis inducing (GAIN) domain that allows for autoproteolysis, exposing a "tethered

agonist" that triggers intracellular G-protein signaling upon ligand binding. This link between physical adhesion and biochemical signaling allows aGPCRs to translate extracellular cues into structural changes in the synapse. The authors emphasize that understanding these receptors is crucial for tackling neuropsychiatric conditions, including attention deficit hyperactivity disorder and substance use disorders, where aGPCR signaling is often compromised.

The last 10 years have witnessed leucine-rich repeat (LRR) transmembrane proteins (LRRTMs) and Slit-and Trk-like proteins (Slitrks) rise to prominence as central pillars of the synaptic adhesion code. Ko and colleagues synthesize a decade of progress regarding these LRR-containing transmembrane proteins (Kim et al., 2026). LRRTM family proteins are primarily known for their roles in excitatory synapse development. They compete with Nlgns for binding to Nrxns, particularly those lacking the insert at splice site 4. This competition provides a regulatory layer to balance synaptic inputs. Meanwhile, the Slitrk family proteins display remarkable diversity. While Slitrk1, Slitrk2, and Slitrk5 organize excitatory synapses, Slitrk3 acts as a dedicated organizer of inhibitory synapses through its interaction with the LAR-type receptor protein tyrosine phosphatases. The review highlights how these molecules are distributed in a cell-type-specific manner across brain regions like the hippocampus. The "decade of progress" has moved the field from identifying these molecules to understanding their "non-canonical" roles in axon guidance and their profound impact on the excitation/inhibition (E/I) balance, a fundamental metric of healthy brain function.

Finally, the series extends the synaptic adhesion code to the realm of neuromodulation. Futai and colleagues challenge the traditional view that dopamine and serotonin systems operate purely through volume transmission (diffuse signaling) (Li et al., 2026). Recent single-cell ribonucleic acid sequencing data reveal that neuromodulatory neurons express a vast array of synaptic CAMs, including Nrxns, Nlgns, and cadherins. These molecules are not just present; they are functional organizers of discrete modulatory synapses. For instance, Nlgn2 is essential for the efficiency of dopamine release in the striatum. This review opens a new frontier in neuroscience, suggesting that the same molecular logic used to build fast-acting glutamatergic circuits is also applied to slower, state-dependent modulatory systems. This integration of CAMs into neuromodulation offers a new lens through which we can view reward-seeking behavior, mood regulation, and the treatment of addiction.

## CONCLUSION: TOWARD A MULTISCALE SYNTHESIS OF THE SYNAPTIC CODE

Collectively, the 5 reviews in this special issue provide a multiscale overview of the current state of synaptic adhesion research. We have moved from identifying the "parts list" of the synapse to understanding the dynamic, nanoscale, and circuit-wide principle that governs neural connectivity. The challenges for the next decade are clear: We must integrate these molecular findings with systems-level behavioral data, leverage artificial intelligence to model complex protein-protein interaction networks, and develop targeted therapies for the synaptopathies discussed throughout this series. I thank the authors for their invaluable contributions and hope this series serves as motivation for the next generation of discoveries in molecular and cellular neuroscience. The deciphering of the synaptic adhesion code is far from over, but the landscape has never looked more promising.

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The author declares that he has no known competing interest or personal relationship that could have appeared to influence the work reported in this paper.

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