Molecular Vision 2026; 32:131-141 <http://www.molvis.org/molvis/v32/131>
Received 15 July 2025 | Accepted 22 February 2026 | Published 25 February 2026

Retinal ribbon synapses and the potential functional role of TIAM1: A structural and molecular perspective

Martha Emil Adly

Human Anatomy and Embryology Department, Faculty of Medicine, Assiut University, Assiut, Egypt

Purpose: Retinal and inner ear ribbon synapses are specialized sensory synapses characterized by synaptic ribbons, electron-dense and protein-rich structures that enable rapid and sustained neurotransmitter release. This review aims to examine the molecular architecture of ribbon synapses with a particular focus on the potential involvement of Tiam1, a guanine nucleotide exchange factor implicated in neuronal development and synaptic plasticity.
Methods: A comprehensive review of the available literature was conducted to summarize current knowledge on the structural organization and molecular components of ribbon synapses. Particular attention was given to studies investigating Tiam1 expression, function, and its possible role in cytoskeletal remodeling and synaptic regulation.
Results: Evidence supports the central role of RIBEYE as the primary structural component of ribbon synapses; however, the regulatory mechanisms governing ribbon formation and function remain incompletely understood. Recent studies suggest a potential contribution of Tiam1 in modulating synaptic organization and function through Rac1 activation and cytoskeletal regulation, although direct experimental evidence in ribbon synapses is still limited.
Conclusions: Ribbon synapses are critical for sustained neurotransmission in sensory systems, yet their molecular regulation remains incompletely defined. Tiam1 emerges as a promising candidate molecule that may influence ribbon synapse function. Future experimental studies are needed to clarify its localization, molecular interactions, and contribution to synaptic organization and plasticity.

Sensory receptor cells are highly specialized to detect changes in our external environment. When these cells encounter a stimulus, such as light, sound, or pressure, they convert this energy into an electrical signal through a process known as sensory transduction. The strength of this electrical signal, referred to as a graded potential, varies in proportion to the intensity of the stimulus. If the stimulus is strong enough, this graded potential can trigger an action potential, which then transmits the information to the central nervous system for processing. In sensory systems such as vision, balance, and hearing, the synapses from receptor cells exhibit unique structural and functional attributes. They operate in a tonic manner, transmitting graded signals with remarkable precision across a wide spectrum of stimulus intensities and over extended durations, which demands tight control over their mechanisms of neurotransmitter release [1–4].

DISCUSSION

Structural and functional features of ribbon synapses: Sensory cells, which utilize ribbon synapses, are specialized to continuously and precisely process information from the environment. To achieve this, these cells have developed a unique structure called the synaptic ribbon at their active zones, the sites where neurotransmitters are released. This ribbon acts as a scaffold, holding numerous synaptic vesicles close to the membrane, ready for rapid and sustained release. Such an arrangement is essential for functions such as vision and hearing, where signals vary in intensity and require fine-tuned, ongoing neurotransmitter release. The presence of synaptic ribbons is characteristic of systems that depend on graded modulation of vesicle exocytosis [4–7].

While the precise functions of these protein-rich organelles remain unclear, synaptic ribbons provide a structural scaffold for holding synaptic vesicles and play an active role in their release at the active zone [8–11].

Although synaptic ribbons differ widely in their dimensions, configurations, and quantity across cell types, they all consistently feature numerous glutamate-packed synaptic vesicles attached to their surface via fine, filament-like connectors. On an ultrastructural scale, ribbon synapses are distinct from traditional central synapses. At conventional synapses, 10 to 100 synaptic vesicles are bunched near the plasma membrane at the active zone. In contrast, at ribbon synapses, a large number of small clear-core synaptic vesicles are anchored by protein filaments to an electron-dense, pentalaminar structure, the synaptic ribbon, which is located between two active zones situated on either side of the ribbon and just adjacent to it [1,6,12–14].

Correspondence to: Martha Emil Adly, Human Anatomy and Embryology Department, Faculty of Medicine, Assiut University, Assiut, Egypt; email: marthaemil@aun.edu.eg

Table 1. Structural and functional differences between traditional and ribbon synapses.

Feature	Traditional synapses	Ribbon synapses
Type of release	Phasic (brief bursts)	Tonic (sustained)
Active zone	Single or few	Broad with ribbon
Vesicle priming	Follows docking	May precede docking
Calcium channels	N-, P/Q-type	L-type (sustained)
Key proteins	Synaptotagmin, SNARE	RIBEYE, Bassoon, RIM

This table compares key features of traditional versus ribbon synapses, highlighting differences in neurotransmitter release, active zone structure, vesicle handling, calcium channel type, and associated molecular components.

In traditional synapses, vesicle release follows a strict sequence: vesicles move to the active zone, dock via protein interactions, and undergo priming. Once calcium rises, fusion happens almost immediately. In contrast, at ribbon synapses, studies indicate that vesicles tethered to the ribbon are held in a prerelease, "primed" state and ready to fuse rapidly in a calcium-dependent manner even if they are not docked at the membrane. This implies that priming at ribbon synapses may precede docking. A summary of structural and functional differences between traditional and ribbon synapses is presented in Table 1 [1,9,15–18].

Anatomical and physiological evidence suggests that ribbon synapse terminals contain at least three distinct pools of synaptic vesicles: the cytoplasmic pool, the ribbon-associated pool, and the docked pool. Cytoplasmic vesicles arrive at the ribbon via passive diffusion or active transport pathways. These vesicles appear to contain glutamate and incorporate the necessary docking proteins at the active zone, making them capable of fusion. Docking is mediated by protein–protein interactions involving vesicle-integral proteins, proteins concentrated in the active zone membrane, and cytosolic proteins [1,19–21].

Given that synaptic ribbons are predominantly found in synapses where graded depolarization facilitates continuous neurotransmitter release, they are widely believed to enhance the availability of vesicles for ongoing transmission. This is achieved by acting as a reservoir for vesicles primed for release and potentially functioning as a mechanism for transporting and/or timing the delivery of these vesicles to the plasma membrane. Supporting this perspective, vesicles associated with ribbons remain distinct from cytoplasmic vesicle pools in resting synapses but undergo rapid turnover upon the opening of calcium channels. Additionally, ribbons may serve another, possibly primary, function in certain contexts: coordinating the simultaneous release of multiple vesicles right at the start of a stimulus [6,13,22–26].

Vesicles situated at the base of the ribbon constitute the immediately releasable pool, also known as the readily releasable pool. These vesicles are primed for rapid neurotransmitter release, making them ideal for signaling the swift onset of stimuli. In contrast, vesicles positioned higher up on the ribbon, often referred to as "tethered vesicles," are part of a pool that releases neurotransmitters with slower kinetics, termed the slowly releasable pool. This arrangement supports continuous or sustained neurotransmission, effectively conveying information about both the magnitude and the temporal span of a stimulus [27–35].

Ribbon synapses serve as a hallmark of primary sensory neurons, found in light-detecting photoreceptors of both the vertebrate retina and pineal gland, and in mechanosensitive hair cells located in the cochlea, vestibular apparatus, and the fish lateral line [4,6,31,36,37].

The retinal ribbon synapses: In the retina, ribbon synapses are formed by rod and cone photoreceptors, as well as bipolar cells, where they play a crucial role in fine-tuning neurotransmitter release [10,38,39]. Retinal ribbon synapses share many molecular components with conventional chemical synapses, such as the v-SNARE synaptobrevin 2, the SM-protein Munc18-1, and active-zone constituents like RIM and bassoon, but differ in key ways: they use slowly inactivating L-type calcium channels (instead of N-, P/Q-, or R-type) to trigger release, employ the t-SNARE syntaxin 3 rather than syntaxin 1, and often lack rabphilin and synapsins, although this absence varies between species. These and other key proteins associated with ribbon synapses are summarized in Table 2 [8,13,40–43]. Another feature distinguishing ribbon synapses from classical synapses is the presence of multiprotein complexes, called Ribeye proteins, as its unique and principal component [8].

Photoreceptor ribbons: Rod and cone photoreceptors are organized into two distinct regions, the inner segment and the outer segment, linked by a slender, immotile cilium [44,45]. A

Table 2. Key proteins at ribbon synapses and their structural or functional roles.

Protein	Function	Localization
RIBEYE	Structural scaffold	Synaptic ribbon
Bassoon	Anchoring ribbon to membrane	Arciform density
VGCC (Cav1.4)	Calcium influx	Near base of ribbon
Tiam1	Rac1 activation, cytoskeletal regulation	Putative (needs validation)

This table summarizes major proteins associated with ribbon synapses, highlighting their specific localization and functional contributions. The localization of Tiam1 remains putative and requires further experimental validation

photoreceptor neuron has two distinct extensions: one outer, one inner. The outer segment, a specialized structure, is where phototransduction occurs: light-sensitive pigments absorb photons and induce alterations in the cell's electrical potential across its membrane. From the inner side of the photoreceptor cell body, an inner process extends and terminates in a unique presynaptic terminal. This terminal houses synaptic ribbons within its active zones. Through these ribbon synapses, the graded electrical signals triggered by photon absorption in the outer segment are constantly relayed to neurons in the inner retina [29,44–47].

The inner segment of photoreceptor cells houses ion channels that modulate the response to light, alongside the cellular components responsible for energy production and synaptic transmission. A cluster of many mitochondria sits in the outer region of the inner segment just beneath the connecting cilium. In darkness, cGMP-gated ion channels in the outer segment stay open, allowing a constant influx of Na^+. The mitochondria generate ATP to fuel the Na^+/K^+-ATPase pumps, which use this energy to pump sodium out and maintain the ionic balance [47–51]. Mitochondrial sequestration of Ca^{2+} helps isolate calcium fluctuations occurring in the inner segment from those in the outer segment [52–55].

In photoreceptors, synaptic ribbons are flat, planar structures. When viewed in cross-section using electron microscopy, they appear as electron-dense bars approximately 30 nm thick, projecting perpendicular to the plasma membrane, extending inward into the cytoplasm, perpendicular to the active zone. When ideally sectioned, they display a multilayered structure, typically three layers, with a central electron-lucent band flanked by two electron-dense, osmiophilic layers. Three-dimensional reconstructions have confirmed that these ribbons are plate-shaped, providing a large surface area, for instance, about 0.77 μm^2 in mammalian rod cells. Although they appear long and narrow in single cross-sectional images (which inspired the term "ribbon"), this can be misleading regarding their actual three-dimensional form. In spatial reconstructions, they are shown to be broad plates running parallel to the plasma membrane for several microns, bending into a horseshoe shape around an invaginated portion of the presynaptic membrane, where dendrites from horizontal and bipolar cells make contact. These horseshoe-shaped ribbons can extend up to 1 µm deep. They are anchored to the presynaptic membrane at their base by an electron-dense structure called the arciform density, which acts like a tether, keeping the ribbon suspended just above the membrane. The cytomatrix protein Bassoon is believed to play a key role in this tethering, and in its absence, ribbons detach and float freely within the cytoplasm of the photoreceptor terminal [4,6,8,29,39,56–58].

In mammals, rod photoreceptor synaptic terminals typically feature a single active zone accompanied by one large, flat synaptic ribbon. This ribbon binds approximately 770 synaptic vesicles, with about 130 vesicles located in a basal row at the membrane-anchored end, considered "docked" and ready for immediate release. The remaining 640 vesicles are "tethered" in more distal rows along the ribbon [29,39]. Conversely, cone photoreceptor terminals possess multiple active zones and several, usually smaller, synaptic ribbons—typically 10 to 12 per terminal, although some species have up to 50. Individual ribbons in cones are slightly shorter (~1 µm long, 0.2 µm high) compared to those in rods (~2 µm long, 0.4 µm high). However, the total ribbon surface area and the number of ribbon-tethered vesicles are significantly greater in cones (~2 μm^2). For instance, in the cat retina, cone synaptic ribbons can bind approximately 3,600 vesicles in total, with about 600 docked and 3,000 tethered at more distal positions. This indicates that the pool of ribbon-associated synaptic vesicles in cone synapses is substantially larger than in rod synapses, likely reflecting the higher synaptic demands of cones [29,39].

At ribbon synapses, the fusion of synaptic vesicles with the presynaptic plasma membrane is initiated by the inflow of calcium ions (Ca^{2+}) via voltage-gated calcium channels. These channels are predominantly of the L-type variety, known for

their minimal inactivation and ability to remain open during extended periods of depolarization. This characteristic is crucial for sustaining continuous neurotransmitter release. The voltage-gated calcium channels are strategically positioned linearly along the ribbon's long axis, adjacent to the arciform density, and are located near the end of the synaptic ribbon, anchored to the plasma membrane [6,29,39,59–63].

Ribbon synapses rely on calcium channels that stay active during prolonged depolarizations and rapidly respond to voltage changes. As a result, the calcium currents at these synapses exhibit minimal inactivation, with swift activation upon depolarization and rapid deactivation once the membrane potential changes [6,26,64].

The postsynaptic structure of photoreceptor ribbon synapses is notably intricate, as a single photoreceptor must distribute its output across multiple parallel pathways that concurrently process various types of visual information [6,65]. To facilitate this process, glutamate is released at the active zones of ribbon synapses. Synaptic vesicles containing glutamate are arranged in a hexagonal pattern on the ribbon's surface, each secured by three to five slender filaments that tether them to the ribbon [1,34,66].

Glutamate released at ribbon synapses reaches various postsynaptic sites, including the dendrites of horizontal cells and multiple classes of bipolar neurons. These targets are situated at increasing distances from the ribbon and possess either ionotropic or metabotropic glutamate receptors, each characterized by specific kinetics and affinity suited to their function [1,6,67].

Bipolar cell ribbons: Retinal bipolar neurons possess synaptic ribbons that are considerably smaller than the elongated ribbons found in rod photoreceptors. Despite their diminutive size, each bipolar cell contains numerous ribbons, ranging from 30 to over 100, depending on the species and specific bipolar cell subtype. Due to their compactness, individual bipolar cell ribbons can tether approximately 100 synaptic vesicles, with around 20 docked at the active zone. This limited vesicle pool contributes to the transient nature of synaptic output in bipolar neurons, enhancing the detection of rapid changes in light intensity. Similarly, cone photoreceptor ribbons are smaller than those in rods and may function to deliver brief bursts of neurotransmitter release when illumination decreases. Typically, each bipolar cell ribbon forms synapses with a pair of postsynaptic processes, symmetrically positioned near the active zone. These dyadic arrangements can involve two amacrine cell processes, a combination of an amacrine cell process and a ganglion cell dendrite or, less commonly, two ganglion cell dendrites. Although this dyadic configuration is simpler than the complex synaptic architecture of photoreceptors, it effectively allows a single ribbon to transmit signals to multiple postsynaptic targets [1,4,6,68].

Synaptic ribbons attach to specialized presynaptic sites, active zones, which are loaded with Cav calcium channels, RIM family proteins, and scaffolding molecules such as CASK. CASK itself forms complexes with multiple partners, including the guanine nucleotide exchange factor TIAM1 [69,70,71].

To date, no direct immunolocalization studies have demonstrated Tiam1 at ribbon synapses. However, its interaction with CASK, an essential scaffolding protein at these synapses, suggests a potential presynaptic localization near the active zone [70,72].

Given the critical role of actin cytoskeleton remodeling in maintaining vesicle dynamics at ribbon synapses, Rho family GTPases, particularly their upstream activators such as Tiam1, represent key candidates for regulating these processes. These considerations highlight the importance of exploring cytoskeletal regulation and its upstream molecular regulators at synapses [73–75].

Cytoskeletal regulation and Rho GTPase signaling at synapses: The structural and functional integrity of synapses depends critically on the dynamic regulation of the actin cytoskeleton. At conventional glutamatergic synapses, actin remodeling shapes the presynaptic active zone, vesicle trafficking, and postsynaptic density organization. These processes are tightly controlled by members of the Rho family of small GTPases, mainly Rac1, RhoA, and Cdc42, which act as molecular switches orchestrating cytoskeletal rearrangements in response to synaptic activity [21,76–78].

Guanine nucleotide exchange factors (GEFs) serve as upstream activators of Rho GTPases by promoting the exchange of GDP for GTP. Several Rho family GEFs, including Kalirin, βPIX, and Tiam1, have been implicated in synaptic development and plasticity, particularly at excitatory synapses, where they regulate dendritic spine morphology and synaptic strength. Given that ribbon synapses share certain presynaptic specializations but lack classical postsynaptic densities, it is plausible that similar GEF-mediated signaling cascades modulate their cytoskeletal organization and vesicle dynamics [79–81].

Among these GEFs, Tiam1 is of particular interest because of its well-established role in Rac1 activation and actin cytoskeleton remodeling at excitatory synapses. This raises the intriguing possibility that Tiam1 may play a comparable role in regulating the structural and functional plasticity of ribbon synapses [82,95].

Tiam1 protein: T-cell lymphoma invasion and metastasis 1 (Tiam1) was initially characterized in 1994, identified in murine T-lymphoma cell lines, where researchers observed not only elevated expression of full-length TIAM1 but also various truncated versions [83].

Tiam1 is a Rac1-specific guanine nucleotide exchange factor that promotes the exchange of GDP for GTP to selectively activate Rac1. This Rac1 activation orchestrates actin cytoskeleton remodeling, which is vital for shaping neuronal structure, especially dendritic spine formation during hippocampal development, while also affecting cell–cell adhesion, directional cell migration, and front–rear polarity. In cancer, Tiam1–Rac1 signaling plays a dual role: it can enhance invasive and metastatic behavior through cytoskeletal reorganization but, in some contexts, promote adhesion and potentially suppress migration. Beyond the cytoskeleton, Tiam1 localizes to centrosomes in S-phase cells, maintaining centriole duplication fidelity by regulating PLK4 degradation via βTRCP—thus preventing chromosome segregation errors. Finally, Tiam1-associated Rac1 activation also supports microtubule stability, centrosome positioning, receptor-mediated endocytosis, and general intracellular trafficking processes essential for cell division, growth, and survival [84–93].

In retinal bipolar cells, Tiam1 likely plays a key role in shaping and sustaining their intricate dendritic arbors, thereby affecting how these cells process and relay visual information [94,95]. By activating Rac1, TIAM1 triggers multiple downstream signaling cascades, such as the PAK–LIMK–cofilin and WAVE–Arp2/3 pathways, that regulate synaptic plasticity and flexibility, which are essential for processing changing visual inputs [96–99].

Tiam1 has been shown to function as the Rac1-specific GEF that facilitates NT3-driven migration of Schwann cells via TrkC signaling. In this pathway, Tiam1 operates upstream of Rac1; however, it is not the only Rac1-specific GEF present in primary Schwann cells. Ras-GRF2 and mSos1/2 are also expressed in these cells and likely contribute to Rac1 activation [100].

The Rho family of small GTPases now encompasses around 20 distinct proteins, which are categorized into seven subfamilies: Rho, Rac, Cdc42, Rnd, RhoD, RhoBTB, and RhoH. Most members cycle between an active GTP-bound state and an inactive GDP-bound state, with this guanine nucleotide exchange tightly controlled by regulatory proteins. GEFs activate Rho GTPases by promoting GDP-to-GTP exchange, while GTPase-activating proteins inactivate them by accelerating GTP hydrolysis. Adding further complexity, guanine nucleotide dissociation inhibitors bind the inactive GTPases and sequester them in the cytosol [101–105].

Beyond Tiam1, several other Rho GTPase regulatory proteins have been implicated in excitatory synapse development and plasticity. Kalirin and Trio, two paralogous multidomain Dbl-family GEFs, are key postsynaptic organizers that couple synaptic activity to Rac1-mediated actin remodeling. Kalirin 7, the predominant neuronal isoform, localizes to the postsynaptic density, where it regulates dendritic spine morphogenesis and long-term potentiation, while Trio contributes to both dendritic and presynaptic organization through interactions with active zone proteins [106,107]. βPIX (also known as ARHGEF7) represents another critical GEF enriched at excitatory synapses; it activates Rac1/Cdc42 in response to glutamatergic signaling and promotes spine maturation and synaptic stability via complexes with GIT1/2 and Shank proteins [108–110]. In addition, Dock family GEFs, such as Dock180 and Dock7, provide an alternative Rac/Cdc42 activation pathway, operating in concert with ELMO proteins to regulate dendritic spine morphology and synaptic connectivity [111,112].

These diverse GEFs share several mechanistic features with Tiam1 that may be relevant to ribbon synapse regulation. All converge on Rac1 and, to a lesser extent, Cdc42, promoting actin cytoskeletal remodeling at postsynaptic sites [106,113]. Like Tiam1, Kalirin and Trio integrate upstream synaptic signals, including NMDA receptor activation and Ca^{2+} influx, to couple neuronal activity with structural plasticity [106]. βPIX and Dock family GEFs function in multiprotein scaffolding complexes (Shank, GIT, ELMO), reminiscent of the interactions proposed for Tiam1 [112,113]. These shared pathways suggest that Tiam1, together with other Rho GEFs, participates in a conserved signaling network fine-tuning actin organization, vesicle cycling, and synaptic stability, raising the possibility of analogous mechanisms at ribbon synapses [6,37].

While Tiam1 shares these mechanistic features with other excitatory synapse GEFs, direct evidence for its role at ribbon synapses remains limited. Nevertheless, the conservation of Rac1/Cdc42-mediated cytoskeletal regulation suggests that Tiam1 may similarly contribute to actin remodeling and vesicle dynamics in these specialized synapses, warranting further investigation.

Throughout development, Tiam1 is abundantly present in the central nervous system, with its expression persisting into postnatal stages. It plays a well-documented role in guiding neuronal migration and promoting axon growth both in vitro and in living organisms. Within cells, Tiam1 is found in dendrites and dendritic spines, concentrating particularly at the postsynaptic density [95,114–116].

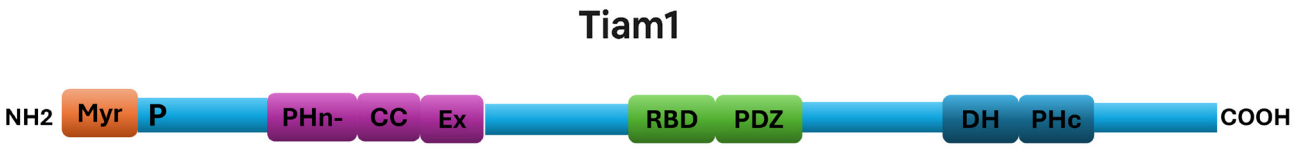

Figure 1. Tiam1 protein domain structure. This figure shows a schematic representation of the Tiam1 protein domains, including the myristylation sequence (Myr), PEST sequence, Ras-binding domain (RBD), Dbl-homology domain (DH), C-terminal pleckstrin homology domain (PHc), N-terminal PH-CC-Ex domain (PHn-CC-Ex), and PDZ domain.

Tiam1 plays a pivotal role in tumor biology by shielding cancer cells from apoptosis and facilitating tumor angiogenesis. Its expression is upregulated in various cancers, including lymphoma and pancreatic, breast, bladder, and lung cancers. Furthermore, Tiam1 overexpression contributes to multiple tumor progression mechanisms such as evasion of apoptosis, promotion of lymphangiogenesis, and enhanced cellular migration processes that are linked to the metastasis of cancers such as breast cancer and nasopharyngeal carcinoma. These findings highlight Tiam1 as a promising therapeutic target in oncology [117–120].

Tiam1 is upregulated in retinoblastoma and plays a key role in its invasive behavior. Researchers knocked down Tiam1 in retinoblastoma cell lines (Y79 and Weri-Rb1) using pooled small interfering RNAs targeting different segments of its messenger RNA. Microarray analysis revealed that Tiam1 depletion mainly affected genes involved in actin cytoskeleton dynamics, apoptotic signaling, and tumorigenic pathways. Functionally, cells lacking Tiam1 exhibited slower proliferation, had heightened apoptosis, and displayed a noninvasive phenotype [121,122].

The human TIAM1 gene, a member of the guanine nucleotide dissociation stimulator family that regulates Rho-type GTPases, is located on YAC 760H5 between markers D21S298 and D21S404 at chromosomal band 21q22.1, and it may play a significant role in the development or spread of malignancies linked to chromosome 21 abnormalities, such as the leukemias commonly seen in trisomy 21 [123].

Tiam1 is a large, multidomain protein (Figure 1) that begins with a myristoylation site at its N-terminus, followed by two PEST motifs. Next comes a composite PH-CC-Ex region (including a pleckstrin homology domain, a likely coiled-coil segment, and a conserved extra portion), a Ras-binding domain, and a PDZ domain. These precede the catalytic Dbl-homology (DH) domain, which is immediately succeeded by another pleckstrin homology (PH) domain and a PDZ (PSD-95, Dlg, ZO-1) domain at the C-terminus that mediates protein–protein interactions at specific cellular sites [115,124].

Tiam1 harbors its essential activity in a tandem DH-PH domain at the C-terminus. DH domains, initially discovered in the oncogenic diffuse B-cell lymphoma (Dbl) protein and yeast Cdc24, roughly span ~250 amino acids and facilitate activation of Rho-family GTPases by acting as selective GEFs. These DH domains were first recognized due to sequence similarity between the transforming gene from Dbl and *Saccharomyces cerevisiae*'s Cdc24. Subsequent studies confirmed that both Dbl and Cdc24 serve as specific GEFs for the Rho-family GTPase Cdc42 [125,126].

All DH domains are directly followed at their C-terminal end by a PH domain, which plays key roles in localization and regulation. PH domains are approximately 100–amino acid modules commonly found in proteins involved in cell signaling and cytoskeletal reorganization. It is now well established that PH domains primarily guide their host proteins to the plasma membrane by binding specific phospholipids, such as phosphoinositides [125,127,128].

The Tiam1 PDZ domain is a class II protein-interaction module that recognizes C-terminal –X–Φ–X–Φ sequences in synthetic peptides, which can act as inhibitors or model ligands. PDZ domains are compact (~90 amino acids), structurally comprising six β-strands and two α-helices, and are evolutionarily conserved from bacteria to vertebrates. The human genome features over 250 PDZ-containing proteins, many of which play key roles in cell migration, invasion, proliferation, and polarity [92,129,130].

The N-terminal PH domain of Tiam1 directs its association with the plasma membrane and drives invasion, unlike the C-terminal PH domain; disrupting the N-terminal PH domain impairs both cell migration and invasive behavior [122].

Conclusions and outlook: Ribbon synapses are highly specialized structures that sustain continuous neurotransmitter

release through rapid vesicle cycling and precise cytoskeletal regulation. Insights from conventional synapses highlight the central roles of Rho GTPases and their regulators, including multiple GEFs and GTPase-activating proteins, in coordinating actin dynamics, synaptic architecture, and vesicle trafficking. Within this broader framework, Tiam1, a Rac1-specific GEF, emerges as a particularly compelling candidate due to its well-established functions in dendritic spine morphogenesis, excitatory synapse development, and neuronal polarity. Although direct evidence of Tiam1's role at ribbon synapses remains limited, positioning it within the wider context of Rho GTPase signaling provides a more balanced and evidence-based perspective.

Future studies should clarify whether Tiam1 is localized at ribbon synapse complexes and whether it modulates actin-dependent processes underlying vesicle tethering, release, and recycling. Such investigations, using localization and functional approaches, could establish Tiam1's contribution to the fidelity of sensory neurotransmission in the retina and inner ear. Elucidating these mechanisms would not only broaden our understanding of ribbon synapse biology but may also identify new molecular targets for therapeutic intervention in synaptopathies of the eye and ear.

Collectively, these considerations lead to the hypothesis that Tiam1, through its interaction with CASK and activation of Rac1, may regulate actin-dependent vesicle tethering and release at the ribbon's active zone, paralleling its role in excitatory synapses of the hippocampus.

ACKNOWLEDGMENTS

The author declares that this work received no financial support from any funding agency in the public, commercial, or not-for-profit sectors. The author also declares no commercial or financial conflicts of interest related to the content of this manuscript. This manuscript has not been previously presented at any scientific meeting or conference.

REFERENCES

1. Heidelberger R, Thoreson WB, Witkovsky P. Synaptic transmission at retinal ribbon synapses. Prog Retin Eye Res 2005; 24:682-720. [PMID: 16027025].
2. Wicher D. Design principles of sensory receptors. Front Cell Neurosci 2010; 4:25-[PMID: 20725512].
3. Tsay AJ, Giummarra MJ, Allen TJ, Proske U. The sensory origins of human position sense. J Physiol 2016; 594:1037-49. [PMID: 26537335].
4. Moser T, Grabner CP, Schmitz F. Sensory processing at ribbon synapses in the retina and the cochlea. Physiol Rev 2020; 100:103-44. [PMID: 31373863].
5. Morgans CW. Presynaptic proteins of ribbon synapses in the retina. Microsc Res Tech 2000; 50:141-50. 3.0.CO[PMID: 10891878].
6. Matthews G, Fuchs P. The diverse roles of ribbon synapses in sensory neurotransmission. Nat Rev Neurosci 2010; 11:812-22. [PMID: 21045860].
7. Becker L, Schnee ME, Niwa M, Sun W, Maxeiner S, Talaei S, Kachar B, Rutherford MA, Ricci AJ. The presynaptic ribbon maintains vesicle populations at the hair cell afferent fiber synapse. Elife 2018; 7:e30241[PMID: 29328021].
8. Schmitz F, Königstorfer A, Südhof TC. RIBEYE, a component of synaptic ribbons: a protein's journey through evolution provides insight into synaptic ribbon function. Neuron 2000; 28:857-72. [PMID: 11163272].
9. Zenisek D, Steyer JA, Almers W. Transport, capture and exocytosis of single synaptic vesicles at active zones. Nature 2000; 406:849-54. [PMID: 10972279].
10. Sterling P, Matthews G. Structure and function of ribbon synapses. Trends Neurosci 2005; 28:20-9. [PMID: 15626493].
11. Mesnard CS, Barta CL, Sladek AL, Zenisek D, Thoreson WB. Eliminating Synaptic Ribbons from Rods and Cones Halves the Releasable Vesicle Pool and Slows Down Replenishment. Int J Mol Sci 2022; 23:6429-Erratum in: Int J Mol Sci. 2023 Jan 13;24 2 :1561. doi: 10.3390/ijms24021561[PMID: 35742873].
12. LoGiudice L, Matthews G. The role of ribbons at sensory synapses. Neuroscientist 2009; 15:380-91. [PMID: 19264728].
13. Maxeiner S, Luo F, Tan A, Schmitz F, Südhof TC. How to make a synaptic ribbon: RIBEYE deletion abolishes ribbons in retinal synapses and disrupts neurotransmitter release. EMBO J 2016; 35:1098-114. [PMID: 26929012].
14. Reiner A, Levitz J. Glutamatergic Signaling in the Central Nervous System: Ionotropic and Metabotropic Receptors in Concert. Neuron 2018; 98:1080-98. [PMID: 29953871].
15. Lenzi D, von Gersdorff H. Structure suggests function: the case for synaptic ribbons as exocytotic nanomachines. Bioessays 2001; 23:831-40. [PMID: 11536295].
16. Südhof TC. The molecular machinery of neurotransmitter release (Nobel lecture). Angew Chem Int Ed Engl 2014; 53:12696-717. [PMID: 25339369].
17. Grabner CP, Moser T. The mammalian rod synaptic ribbon is essential for Ca_v channel facilitation and ultrafast synaptic vesicle fusion. Elife 2021; 10:e63844[PMID: 34617508].
18. Radecke J, Seeger R, Kádková A, Laugks U, Khosrozadeh A, Goldie KN, Lučić V, Sørensen JB, Zuber B. Morphofunctional changes at the active zone during synaptic vesicle exocytosis. EMBO Rep 2023; 24:e55719[PMID: 36876590].
19. Cadetti L, Bartoletti TM, Thoreson WB. Quantal mEPSCs and residual glutamate: how horizontal cell responses are shaped at the photoreceptor ribbon synapse. Eur J Neurosci 2008; 27:2575-86. [PMID: 18547244].

20. Bartoletti TM, Babai N, Thoreson WB. Vesicle pool size at the salamander cone ribbon synapse. J Neurophysiol 2010; 103:419-23. [PMID: 19923246].

21. Hanke-Gogokhia C, Zapadka TE, Finkelstein S, Klingeborn M, Maugel TK, Singer JH, Arshavsky VY, Demb JB. The Structural and Functional Integrity of Rod Photoreceptor Ribbon Synapses Depends on Redundant Actions of Dynamins 1 and 3. J Neurosci 2024; 44:e1379232024[PMID: 38641407].

22. Jackman SL, Choi SY, Thoreson WB, Rabl K, Bartoletti TM, Kramer RH. Role of the synaptic ribbon in transmitting the cone light response. Nat Neurosci 2009; 12:303-10. [PMID: 19219039].

23. Frank T, Rutherford MA, Strenzke N, Neef A, Pangršič T, Khimich D, Fejtova A, Gundelfinger ED, Liberman MC, Harke B, Bryan KE, Lee A, Egner A, Riedel D, Moser T. Bassoon and the synaptic ribbon organize Ca^{2}+ channels and vesicles to add release sites and promote refilling. Neuron 2010; 68:724-38. Erratum in: Neuron. 2010 Dec 22;68 6 :1202. Fetjova, Anna corrected to Fejtova, Anna[PMID: 21092861].

24. Baden T, Euler T, Weckström M, Lagnado L. Spikes and ribbon synapses in early vision. Trends Neurosci 2013; 36:480-8. [PMID: 23706152].

25. Vaithianathan T, Henry D, Akmentin W, Matthews G. Nanoscale dynamics of synaptic vesicle trafficking and fusion at the presynaptic active zone. Elife 2016; 5:e13245[PMID: 26880547].

26. Williams B, Maddox JW, Lee A. Calcium Channels in Retinal Function and Disease. Annu Rev Vis Sci 2022; 8:53-77. [PMID: 35650675].

27. Stevens CF, Sullivan JM. Regulation of the readily releasable vesicle pool by protein kinase C. Neuron 1998; 21:885-93. [PMID: 9808473].

28. Denker A, Rizzoli SO. Synaptic vesicle pools: an update. Front Synaptic Neurosci 2010; 2:135-[PMID: 21423521].

29. Schmitz F. Presynaptic [Ca(2+)] and GCAPs: aspects on the structure and function of photoreceptor ribbon synapses. Front Mol Neurosci 2014; 7:3-[PMID: 24567702].

30. Kaeser PS, Regehr WG. The readily releasable pool of synaptic vesicles. Curr Opin Neurobiol 2017; 43:63-70. [PMID: 28103533].

31. Okawa H, Yu WQ, Matti U, Schwarz K, Odermatt B, Zhong H, Tsukamoto Y, Lagnado L, Rieke F, Schmitz F, Wong ROL. Dynamic assembly of ribbon synapses and circuit maintenance in a vertebrate sensory system. Nat Commun 2019; 10:2167-[PMID: 31092821].

32. Vaden JH, Banumurthy G, Gusarevich ES, Overstreet-Wadiche L, Wadiche JI. The readily-releasable pool dynamically regulates multivesicular release. Elife 2019; 8:e47434[PMID: 31364987].

33. Wesseling JF. Considerations for Measuring Activity-Dependence of Recruitment of Synaptic Vesicles to the Readily Releasable Pool. Front Synaptic Neurosci 2019; 11:32-[PMID: 31824292].

34. Thoreson WB. Transmission at rod and cone ribbon synapses in the retina. Pflugers Arch 2021; 473:1469-91. [PMID: 33779813].

35. Parsons TD, Sterling P. Synaptic ribbon. Conveyor belt or safety belt? Neuron 2003; 37:379-82. [PMID: 12575947].

36. Suli A, Pujol R, Cunningham DE, Hailey DW, Prendergast A, Rubel EW, Raible DW. Innervation regulates synaptic ribbons in lateral line mechanosensory hair cells. J Cell Sci 2016; 129:2250-60. [PMID: 27103160].

37. Lagnado L, Schmitz F. Ribbon Synapses and Visual Processing in the Retina. Annu Rev Vis Sci 2015; 1:235-62. [PMID: 28532378].

38. Prescott ED, Zenisek D. Recent progress towards understanding the synaptic ribbon. Curr Opin Neurobiol 2005; 15:431-6. [PMID: 16023852].

39. Schmitz F. The making of synaptic ribbons: how they are built and what they do. Neuroscientist 2009; 15:611-24. [PMID: 19700740].

40. Curtis L, Datta P, Liu X, Bogdanova N, Heidelberger R, Janz R. Syntaxin 3B is essential for the exocytosis of synaptic vesicles in ribbon synapses of the retina. Neuroscience 2010; 166:832-41. [PMID: 20060037].

41. Wahl S, Katiyar R, Schmitz F. A local, periactive zone endocytic machinery at photoreceptor synapses in close vicinity to synaptic ribbons. J Neurosci 2013; 33:10278-300. [PMID: 23785143].

42. Liu X, Heidelberger R, Janz R. Phosphorylation of syntaxin 3B by CaMKII regulates the formation of t-SNARE complexes. Mol Cell Neurosci 2014; 60:53-62. [PMID: 24680688].

43. Hays CL, Grassmeyer JJ, Wen X, Janz R, Heidelberger R, Thoreson WB. Simultaneous Release of Multiple Vesicles from Rods Involves Synaptic Ribbons and Syntaxin 3B. Biophys J 2020; 118:967-79. [PMID: 31653448].

44. Burns ME, Baylor DA. Activation, deactivation, and adaptation in vertebrate photoreceptor cells. Annu Rev Neurosci 2001; 24:779-805. [PMID: 11520918].

45. Fain GL, Hardie R, Laughlin SB. Phototransduction and the evolution of photoreceptors. Curr Biol 2010; 20:R114-24. [PMID: 20144772].

46. Arshavsky VY, Burns ME. Photoreceptor signaling: supporting vision across a wide range of light intensities. J Biol Chem 2012; 287:1620-6. [PMID: 22074925].

47. Ingram NT, Fain GL, Sampath AP. Elevated energy requirement of cone photoreceptors. Proc Natl Acad Sci U S A 2020; 117:19599-603. [PMID: 32719136].

48. Zhang X, Cote RH. cGMP signaling in vertebrate retinal photoreceptor cells. Front Biosci 2005; 10:1191-204. [PMID: 15769618].

49. Okawa H, Sampath AP, Laughlin SB, Fain GL. ATP consumption by mammalian rod photoreceptors in darkness and in light. Curr Biol 2008; 18:1917-21. [PMID: 19084410].

50. Kühlbrandt W. Structure and function of mitochondrial membrane protein complexes. BMC Biol 2015; 13:89-[PMID: 26515107].

51. Tejero A, León-Navarro DA, Martín M. Membrane ATPases and Mitochondrial Proteins in Fetal Cerebellum After Exposure to L-Glutamate During Gestation. Membranes (Basel) 2025; 15:152-[PMID: 40422762].

52. Thoreson WB, Nitzan R, Miller RF. Reducing extracellular Cl- suppresses dihydropyridine-sensitive Ca2+ currents and synaptic transmission in amphibian photoreceptors. J Neurophysiol 1997; 77:2175-90. [PMID: 9114264].

53. Krizaj D, Copenhagen DR. Compartmentalization of calcium extrusion mechanisms in the outer and inner segments of photoreceptors. Neuron 1998; 21:249-56. [PMID: 9697868].

54. Szikra T, Krizaj D. Intracellular organelles and calcium homeostasis in rods and cones. Vis Neurosci 2007; 24:733-43. [PMID: 17986362].

55. Giarmarco MM, Cleghorn WM, Sloat SR, Hurley JB, Brockerhoff SE. Mitochondria Maintain Distinct Ca^{2+} Pools in Cone Photoreceptors. J Neurosci 2017; 37:2061-72. [PMID: 28115482].

56. Chakrabarti R, Wichmann C. Nanomachinery Organizing Release at Neuronal and Ribbon Synapses. Int J Mol Sci 2019; 20:2147-[PMID: 31052288].

57. Vaithianathan T, Wollmuth LP, Henry D, Zenisek D, Matthews G. Tracking Newly Released Synaptic Vesicle Proteins at Ribbon Active Zones. iScience 2019; 17:10-23. [PMID: 31247447].

58. Joselevitch C, Zenisek D. Direct Observation of Vesicle Transport on the Synaptic Ribbon Provides Evidence That Vesicles Are Mobilized and Prepared Rapidly for Release. J Neurosci 2020; 40:7390-404. [PMID: 32847965].

59. Catterall WA. Voltage-gated calcium channels. Cold Spring Harb Perspect Biol 2011; 3:a003947[PMID: 21746798].

60. Cho S, von Gersdorff H. Ca(2+) influx and neurotransmitter release at ribbon synapses. Cell Calcium 2012; 52:208-16. Epub2012Jul8[PMID: 22776680].

61. Ackermann F, Waites CL, Garner CC. Presynaptic active zones in invertebrates and vertebrates. EMBO Rep 2015; 16:923-38. [PMID: 26160654].

62. Li YC, Kavalali ET. How Do RIM-BPs Link Voltage-Gated Ca(2+) Channels to Evoked Neurotransmitter Release? Neuron 2015; 87:1119-21. [PMID: 26402594].

63. He R, Zhang J, Yu Y, Jizi L, Wang W, Li M. New Insights Into Interactions of Presynaptic Calcium Channel Subtypes and SNARE Proteins in Neurotransmitter Release. Front Mol Neurosci 2018; 11:213-[PMID: 30061813].

64. Magistretti J, Spaiardi P, Johnson SL, Masetto S. Elementary properties of Ca(2+) channels and their influence on multivesicular release and phase-locking at auditory hair cell ribbon synapses. Front Cell Neurosci 2015; 9:123-[PMID: 25904847].

65. Thoreson WB. Kinetics of synaptic transmission at ribbon synapses of rods and cones. Mol Neurobiol 2007; 36:205-23. [PMID: 17955196].

66. Usukura J, Yamada E. Ultrastructure of the synaptic ribbons in photoreceptor cells of Rana catesbeiana revealed by freeze-etching and freeze-substitution. Cell Tissue Res 1987; 247:483-8. [PMID: 3494517].

67. Oyetayo B, Mendoza-Silva Y, Subair T, Hernández-Kelly LC, Felder-Schmittbuhl M-P, Olivares-Bañuelos TN, Ortega A. Glutamate Receptor Signaling in Retina Müller Cells: Plausible Role in Neurodegeneration. Receptors (Basel) 2025; 4:4-.

68. Yu WQ, Swanstrom R, Sigulinsky CL, Ahlquist RM, Knecht S, Jones BW, Berson DM, Wong RO. Distinctive synaptic structural motifs link excitatory retinal interneurons to diverse postsynaptic partner types. Cell Rep 2023; 42:112006[PMID: 36680773].

69. Stafford RL, Ear J, Knight MJ, Bowie JU. The molecular basis of the Caskin1 and Mint1 interaction with CASK. J Mol Biol 2011; 412:3-13. [PMID: 21763699].

70. Dembla E, Dembla M, Maxeiner S, Schmitz F. Synaptic ribbons foster active zone stability and illumination-dependent active zone enrichment of RIM2 and Cav1.4 in photoreceptor synapses. Sci Rep 2020; 10:5957-[PMID: 32249787].

71. Ohtsuka T. CAST: functional scaffold for the integrity of the presynaptic active zone. Neurosci Res 2013; 76:10-5. [PMID: 23517713].

72. Anjum R, Ayoubian H, Schmitz F. Differential synaptic distribution of the scaffold proteins Cask and Caskin1 in the bovine retina. Mol Cell Neurosci 2014; 62:19-29. [PMID: 25123431].

73. Sit ST, Manser E. Rho GTPases and their role in organizing the actin cytoskeleton. J Cell Sci 2011; 124:679-83. [PMID: 21321325].

74. Spiering D, Hodgson L. Dynamics of the Rho-family small GTPases in actin regulation and motility. Cell Adh Migr 2011; 5:170-80. [PMID: 21178402].

75. Filić V, Mijanović L, Putar D, Talajić A, Ćetković H, Weber I. Regulation of the Actin Cytoskeleton via Rho GTPase Signalling in *Dictyostelium* and Mammalian Cells: A Parallel Slalom. Cells 2021; 10:1592-[PMID: 34202767].

76. Dillon C, Goda Y. The actin cytoskeleton: integrating form and function at the synapse. Annu Rev Neurosci 2005; 28:25-55. [PMID: 16029114].

77. Dutta P, Bharti P, Kumar J, Maiti S. Role of actin cytoskeleton in the organization and function of ionotropic glutamate receptors. Curr Res Struct Biol 2021; 3:277-89. [PMID: 34766008].

78. Gentile JE, Carrizales MG, Koleske AJ. Control of Synapse Structure and Function by Actin and Its Regulators. Cells 2022; 11:603-[PMID: 35203254].

79. Govek EE, Newey SE, Van Aelst L. The role of the Rho GTPases in neuronal development. Genes Dev 2005; 19:1-49. [PMID: 15630019].

80. Rossman KL, Der CJ, Sondek J. GEF means go: turning on RHO GTPases with guanine nucleotide-exchange factors. Nat Rev Mol Cell Biol 2005; 6:167-80. [PMID: 15688002].

81. Cook DR, Rossman KL, Der CJ. Rho guanine nucleotide exchange factors: regulators of Rho GTPase activity in development and disease. Oncogene 2014; 33:4021-35. [PMID: 24037532].

82. Tang LT, Diaz-Balzac CA, Rahman M, Ramirez-Suarez NJ, Salzberg Y, Lázaro-Peña MI, Bülow HE. TIAM-1/GEF can shape somatosensory dendrites independently of its GEF activity by regulating F-actin localization. Elife 2019; 8:e38949[PMID: 30694177].

83. Habets GG, Scholtes EH, Zuydgeest D, van der Kammen RA, Stam JC, Berns A, Collard JG. Identification of an invasion-inducing gene, Tiam-1, that encodes a protein with homology to GDP-GTP exchangers for Rho-like proteins. Cell 1994; 77:537-49. [PMID: 7999144].

84. Michiels F, Habets GG, Stam JC, van der Kammen RA, Collard JG. A role for Rac in Tiam1-induced membrane ruffling and invasion. Nature 1995; 375:338-40. [PMID: 7753201].

85. Hordijk PL, ten Klooster JP, van der Kammen RA, Michiels F, Oomen LC, Collard JG. Inhibition of invasion of epithelial cells by Tiam1-Rac signaling. Science 1997; 278:1464-6. [PMID: 9367959].

86. Mertens AE, Roovers RC, Collard JG. Regulation of Tiam1-Rac signalling. FEBS Lett 2003; 546:11-6. [PMID: 12829230].

87. Adams HC 3rd, Chen R, Liu Z, Whitehead IP. Regulation of breast cancer cell motility by T-cell lymphoma invasion and metastasis-inducing protein. Breast Cancer Res 2010; 12:R69-[PMID: 20819206].

88. Xu K, Rajagopal S, Klebba I, Dong S, Ji Y, Liu J, Kuperwasser C, Garlick JA, Naber SP, Buchsbaum RJ. The role of fibroblast Tiam1 in tumor cell invasion and metastasis. Oncogene 2010; 29:6533-42. [PMID: 20802514].

89. Sherry DM, Blackburn BA. P-Rex2, a Rac-guanine nucleotide exchange factor, is expressed selectively in ribbon synaptic terminals of the mouse retina. BMC Neurosci 2013; 14:70-[PMID: 23844743].

90. Boissier P, Huynh-Do U. The guanine nucleotide exchange factor Tiam1: a Janus-faced molecule in cellular signaling. Cell Signal 2014; 26:483-91. [PMID: 24308970].

91. Genau HM, Huber J, Baschieri F, Akutsu M, Dötsch V, Farhan H, Rogov V, Behrends C. CUL3-KBTBD6/KBTBD7 ubiquitin ligase cooperates with GABARAP proteins to spatially restrict TIAM1-RAC1 signaling. Mol Cell 2015; 57:995-1010. [PMID: 25684205].

92. Panel N, Sun YJ, Fuentes EJ, Simonson T. A Simple PB/LIE Free Energy Function Accurately Predicts the Peptide Binding Specificity of the Tiam1 PDZ Domain. Front Mol Biosci 2017; 4:65-[PMID: 29018806].

93. Porter AP, Reed H, White GRM, Ogg EL, Whalley HJ, Malliri A. The RAC1 activator Tiam1 regulates centriole duplication through controlling PLK4 levels. J Cell Sci 2021; 134:jcs252502[PMID: 33758078].

94. Tolias KF, Bikoff JB, Burette A, Paradis S, Harrar D, Tavazoie S, Weinberg RJ, Greenberg ME. The Rac1-GEF Tiam1 couples the NMDA receptor to the activity-dependent development of dendritic arbors and spines. Neuron 2005; 45:525-38. [PMID: 15721239].

95. Cheng J, Scala F, Blanco FA, Niu S, Firozi K, Keehan L, Mulherkar S, Froudarakis E, Li L, Duman JG, Jiang X, Tolias KF. The Rac-GEF Tiam1 Promotes Dendrite and Synapse Stabilization of Dentate Granule Cells and Restricts Hippocampal-Dependent Memory Functions. J Neurosci 2021; 41:1191-206. [PMID: 33328293].

96. Lai KO, Wong AS, Cheung MC, Xu P, Liang Z, Lok KC, Xie H, Palko ME, Yung WH, Tessarollo L, Cheung ZH, Ip NY. TrkB phosphorylation by Cdk5 is required for activity-dependent structural plasticity and spatial memory. Nat Neurosci 2012; 15:1506-15. [PMID: 23064382].

97. Duman JG, Tzeng CP, Tu YK, Munjal T, Schwechter B, Ho TS, Tolias KF. The adhesion-GPCR BAI1 regulates synaptogenesis by controlling the recruitment of the Par3/Tiam1 polarity complex to synaptic sites. J Neurosci 2013; 33:6964-78. [PMID: 23595754].

98. Um K, Niu S, Duman JG, Cheng JX, Tu YK, Schwechter B, Liu F, Hiles L, Narayanan AS, Ash RT, Mulherkar S, Alpadi K, Smirnakis SM, Tolias KF. Dynamic control of excitatory synapse development by a Rac1 GEF/GAP regulatory complex. Dev Cell 2014; 29:701-15. [PMID: 24960694].

99. Zhang H, Ben Zablah Y, Zhang H, Liu A, Gugustea R, Lee D, Luo X, Meng Y, Li S, Zhou C, Xin T, Jia Z. Inhibition of Rac1 in ventral hippocampal excitatory neurons improves social recognition memory and synaptic plasticity. Front Aging Neurosci 2022; 14:914491[PMID: 35936771].

100. Yamauchi J, Miyamoto Y, Tanoue A, Shooter EM, Chan JR. Ras activation of a Rac1 exchange factor, Tiam1, mediates neurotrophin-3-induced Schwann cell migration. Proc Natl Acad Sci U S A 2005; 102:14889-94. [PMID: 16203995].

101. Vega FM, Ridley AJ. Rho GTPases in cancer cell biology. FEBS Lett 2008; 582:2093-101. [PMID: 18460342].

102. Haga RB, Ridley AJ. Rho GTPases: Regulation and roles in cancer cell biology. Small GTPases 2016; 7:207-21. [PMID: 27628050].

103. Phuyal S, Farhan H. Multifaceted Rho GTPase Signaling at the Endomembranes. Front Cell Dev Biol 2019; 7:127-[PMID: 31380367].

104. Voena C, Chiarle R. RHO Family GTPases in the Biology of Lymphoma. Cells 2019; 8:646-[PMID: 31248017].

105. Clayton NS, Ridley AJ. Targeting Rho GTPase Signaling Networks in Cancer. Front Cell Dev Biol 2020; 8:222-[PMID: 32309283].

106. Penzes P, Johnson RC, Sattler R, Zhang X, Huganir RL, Kambampati V, Mains RE, Eipper BA. The neuronal Rho-GEF Kalirin-7 interacts with PDZ domain-containing proteins and

regulates dendritic morphogenesis. Neuron 2001; 29:229-42. [PMID: 11182094].

107. Ma XM, Wang Y, Ferraro F, Mains RE, Eipper BA. Kalirin-7 is an essential component of both shaft and spine excitatory synapses in hippocampal interneurons. J Neurosci 2008; 28:711-24. [PMID: 18199770].

108. Zhou W, Li X, Premont RT. Expanding functions of GIT Arf GTPase-activating proteins, PIX Rho guanine nucleotide exchange factors and GIT-PIX complexes. J Cell Sci 2016; 129:1963-74. [PMID: 27182061].

109. Martin-Vilchez S, Whitmore L, Asmussen H, Zareno J, Horwitz R, Newell-Litwa K. RhoGTPase Regulators Orchestrate Distinct Stages of Synaptic Development. PLoS One 2017; 12:e0170464[PMID: 28114311].

110. Kwon Y, Lee SJ, Shin YK, Choi JS, Park D, Shin JE. Loss of neuronal βPix isoforms impairs neuronal morphology in the hippocampus and causes behavioral defects. Anim Cells Syst (Seoul) 2025; 29:57-71. [PMID: 39802101].

111. Kim JY, Oh MH, Bernard LP, Macara IG, Zhang H. The RhoG/ELMO1/Dock180 signaling module is required for spine morphogenesis in hippocampal neurons. J Biol Chem 2011; 286:37615-24. [PMID: 21900250].

112. Shi L. Dock protein family in brain development and neurological disease. Commun Integr Biol 2013; 6:e26839[PMID: 24563715].

113. Zhou Q, Homma KJ, Poo MM. Shrinkage of dendritic spines associated with long-term depression of hippocampal synapses. Neuron 2004; 44:749-57. [PMID: 15572107].

114. Ehler E, van Leeuwen F, Collard JG, Salinas PC. Expression of Tiam-1 in the developing brain suggests a role for the Tiam-1-Rac signaling pathway in cell migration and neurite outgrowth. Mol Cell Neurosci 1997; 9:1-12. [PMID: 9204476].

115. Miller MB, Yan Y, Eipper BA, Mains RE. Neuronal Rho GEFs in synaptic physiology and behavior. Neuroscientist 2013; 19:255-73. [PMID: 23401188].

116. Zhu G, Zhang Y, Wang Q, Che S, Yang Y, Chen L, Lin Z. The prognostic value of Tiam1 correlates with its roles in epithelial-mesenchymal transition progression and angiogenesis in lung adenocarcinoma. Cancer Manag Res 2019; 11:1741-52. [PMID: 30863182].

117. Minard ME, Ellis LM, Gallick GE. Tiam1 regulates cell adhesion, migration and apoptosis in colon tumor cells. Clin Exp Metastasis 2006; 23:301-13. [PMID: 17086355].

118. Li Z, Liu Q, Piao J, Hua F, Wang J, Jin G, Lin Z, Zhang Y. Clinicopathological implications of Tiam1 overexpression in invasive ductal carcinoma of the breast. BMC Cancer 2016; 16:681-[PMID: 27562113].

119. Ikram M, Lim Y, Baek SY, Jin S, Jeong YH, Kwak JY, Yoon S. Co-targeting of Tiam1/Rac1 and Notch ameliorates chemoresistance against doxorubicin in a biomimetic 3D lymphoma model. Oncotarget 2017; 9:2058-75. [PMID: 29416753].

120. Yang Y, Wu Q, Li N, Che S, Jin T, Nan Y, Lin Z, Chen L. Upregulation of Tiam1 contributes to cervical cancer disease progression and indicates poor survival outcome. Hum Pathol 2018; 75:179-88. [PMID: 29452216].

121. Adithi M, Venkatesan N, Kandalam M, Biswas J, Krishnakumar S. Expressions of Rac1, Tiam1 and Cdc42 in retinoblastoma. Exp Eye Res 2006; 83:1446-52. [PMID: 17027002].

122. Subramanian N, Navaneethakrishnan S, Biswas J, Kanwar RK, Kanwar JR, Krishnakumar S. RNAi mediated Tiam1 gene knockdown inhibits invasion of retinoblastoma. PLoS One 2013; 8:e70422[PMID: 23950931].

123. Chen H, Antonarakis SE. Localization of a human homolog of the mouse Tiam-1 gene to chromosome 21q22.1. Genomics 1995; 30:123-7. [PMID: 8595894].

124. Terawaki S, Kitano K, Mori T, Zhai Y, Higuchi Y, Itoh N, Watanabe T, Kaibuchi K, Hakoshima T. The PHCCEx domain of Tiam1/2 is a novel protein- and membrane-binding module. EMBO J 2010; 29:236-50. [PMID: 19893486].

125. Soisson SM, Nimnual AS, Uy M, Bar-Sagi D, Kuriyan J. Crystal structure of the Dbl and pleckstrin homology domains from the human Son of sevenless protein. Cell 1998; 95:259-68. [PMID: 9790532].

126. Matsuzawa K, Akita H, Watanabe T, Kakeno M, Matsui T, Wang S, Kaibuchi K. PAR3-aPKC regulates Tiam1 by modulating suppressive internal interactions. Mol Biol Cell 2016; 27:1511-23. [PMID: 26941335].

127. Jackson SG, Zhang Y, Haslam RJ, Junop MS. Structural analysis of the carboxy terminal PH domain of pleckstrin bound to D-myo-inositol 1,2,3,5,6-pentakisphosphate. BMC Struct Biol 2007; 7:80-[PMID: 18034889].

128. Powis G, Meuillet EJ, Indarte M, Booher G, Kirkpatrick L. Pleckstrin Homology [PH] domain, structure, mechanism, and contribution to human disease. Biomed Pharmacother 2023; 165:115024[PMID: 37399719].

129. Shepherd TR, Hard RL, Murray AM, Pei D, Fuentes EJ. Distinct ligand specificity of the Tiam1 and Tiam2 PDZ domains. Biochemistry 2011; 50:1296-308. [PMID: 21192692].

130. Liu X, Fuentes EJ. Emerging Themes in PDZ Domain Signaling: Structure, Function, and Inhibition. Int Rev Cell Mol Biol 2019; 343:129-218. [PMID: 30712672].

Articles are provided courtesy of Emory University and The Abraham J. & Phyllis Katz Foundation. The print version of this article was created on 25 February 2026. This reflects all typographical corrections and errata to the article through that date. Details of any changes may be found in the online version of the article.