Phase transition at the synaptic ribbon

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In a recent study published in *Vita*, Liu *et al.* reveal that RIBEYE forms supramolecular assemblies involving liquid–liquid phase separation, which may explain its ability to form synaptic ribbons in sensory neuron synapses.

To transmit external stimuli to the central nervous system, some sensory neurons, such as photoreceptors and auditory hair cells, as well as electroreceptors of fish, evolved a specialized structure, the synaptic ribbon. In the 1950s, electron microscopic analyses found that synaptic ribbons tether hundreds of synaptic vesicles and line up these vesicles at the active zones, seemingly to enable continuous recruitment of synaptic vesicles to neurotransmitter release sites. This presynaptic architecture differs from that of conventional synapses in which vesicles are only tethered to the active zones (Fig. 1a, b). Strikingly, synaptic ribbons are composed largely of a single protein, RIBEYE, the only protein currently known to be essential for synaptic ribbons[1,2]. RIBEYE is composed of a largely unstructured A domain including a SAM domain and a structured B domain identical with CtBP2 that was evolutionarily 'stolen' from the regulatory machinery of transcription (Fig. 1c)[1]. Synaptic ribbons are anchored at the active zone where RIBEYE interacts with Bassoon[3], a peripheral component of the presynaptic active zone scaffold. How RIBEYE assembles into synaptic ribbons, however, and how synaptic ribbon assembly is dynamically regulated by the diurnal light–dark cycle[4], remains unknown.

In the present paper[5], Liu *et al.* provide stunning new mechanistic insights into how RIBEYE assembles into synaptic ribbons. Using cryo-electron microscopy and cryo-electron tomography, Liu *et al.* reveal that RIBEYE forms filamentous structures which coalesce into a ribbon-like architecture via a phase transition process (Fig. 1d). In the authors' experiments, the filamentous structures were modulated by Piccolino and CtBP1, suggesting a potential mechanism of how the synaptic ribbon is regulated physiologically. This interplay of order and stochasticity allows the synaptic ribbon to maintain a delicate balance whereby it serves both as a rigid structural anchor for vesicles and as a dynamic sensor ready to respond to environmental stimuli.

Several important observations of this study are worth pointing out. First, both the SAM domain and B domain of RIBEYE can independently form double-helical filaments. In a test tube and in non-neuronal cells, these two different filaments crosslink to form large ribbon-like structures, which resemble the filamentous structures of the synaptic ribbon in sensory neurons. This result suggests that RIBEYE alone is sufficient to establish the basic framework of synaptic ribbon, as postulated when RIBEYE was discovered[1].

Second, RIBEYE's filamentous structure can be modulated by Piccolino and CtBP1. Piccolino, a short splice variant of the presynaptic active zone protein Piccolo[6], promotes the side-by-side stacking of RIBEYE filaments consistent with the previous observation that Piccolino contributes to synaptic ribbon assembly. CtBP1 disrupts the RIBEYE filaments by competing with the B domain of RIBEYE that is identical with CtBP2. Although these data suggest that CtBP1 may regulate the formation of synaptic ribbons in the dark–light cycle, synaptic ribbons are not changed by the CtBP1 deletion[7]. The effect of Piccolino and CtBP1 show that the RIBEYE-produced ribbon is dynamic, with its diurnal regulation likely controlled by phosphorylation events since kinases are known to be associated with synaptic ribbons.

Third, the RIBEYE filaments assemble into distinctive forms: spherical and ribbon-shaped condensates. The spherical-shaped condensates reflect typical liquid–liquid phase separation due to multivalent interactions. These structures may correspond to the disrupted form of synaptic ribbon. On the other hand, the ribbon-shaped condensates may correspond to the established form of the synaptic ribbon, where RIBEYE filaments stack together with increased order. This spherical to ribbon transition of RIBEYE is reminiscent of the liquid to fibrous aggregate transition of other proteins, including FUS, hnRNPA2, and amyloid fibers[8]. Thus, biomolecular condensates exhibit distinctive mesoscopic forms. The controlled transition between these forms is the key to assembling physiological structures and to preventing pathological aggregations.

As with every important study, the present paper also raises new questions. What controls the assembly of synaptic ribbon *in vivo*? The synaptic ribbon in photoreceptors is a highly organized filamentous structure whereas in hair cells it has a rounder shape. These unique morphologies make one wonder how the shape of these ribbons is determined and how excessive filament formation is prevented. Another key question is how synaptic ribbons are anchored to presynaptic release sites. The long synaptic ribbons of photoreceptors are perpendicular to the presynaptic release site, suggesting that an adaptor protein such as Bassoon may link the synaptic ribbon to the presynaptic site. Moreover, trans-synaptic interactions, such as the teneurin–latrophilin[9,10] or ELFN1–mGluR6 adhesion complexes[11], may provide the nucleation sites for the synaptic ribbon.

It is fascinating that the B domain of RIBEYE that is identical with CtBP2 binds to NADH and less so to NAD^+ (Fig. 1c). Via such binding, RIBEYE may serve as a redox sensor which could contribute to the diurnal regulation of synaptic ribbons. However, the precise functions of NADH binding to RIBEYE (and to the parental CtBP2) are unknown, except that NADH binding

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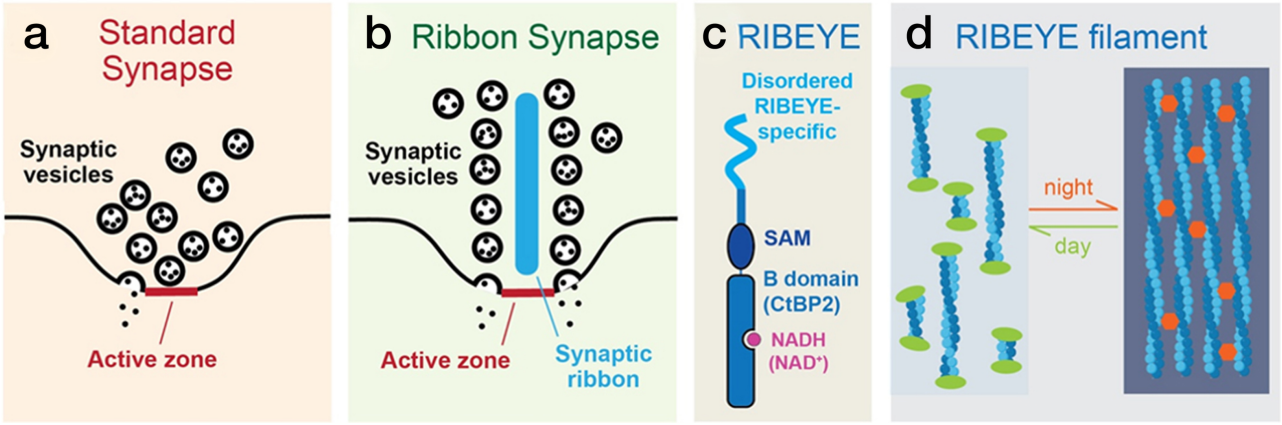

Fig. 1 Synaptic ribbon assembly by RIBEYE. a At conventional synapses, synaptic vesicles are tethered directly to active zones. **b** At ribbon synapses, conversely, synaptic vesicles are tethered to synaptic ribbons composed primarily of RIBEYE[1]. **c** RIBEYE is composed of a largely disordered A domain containing a SAM domain and a structured B domain identical with the transcription factor CtBP2. **d** As now shown by Liu *et al.*, RIBEYE forms filamentous structure that can coalesce into ribbon-shaped condensates which depend on both the RIBEYE disordered region and its SAM and B domains. Their formation is dynamically regulated by circadian cycles[4].

appears to be functionally important. Thus, one of the most pressing questions in understanding RIBEYE's assembly and dynamics is how NADH binding contributes to RIBEYE's function.

Finally, the current study prompts the question of whether dysregulation of RIBEYE's phase transition might contribute to sensory neurodegeneration. Aging, metabolic stress, or perturbations in the NAD^+/NADH redox balance could shift the balance of phase transition, favoring aberrant material states that are less dynamic and more aggregation prone. Such a shift may impair vesicle tethering and release kinetics in photoreceptors and hair cells, thereby contributing to retinal degeneration and age-related hearing loss[12]. In this view, the synaptic ribbon represents a physiological system for studying how cells tune the boundary between functional phase transitions and pathological aggregation.

By demonstrating that RIBEYE forms both liquid–liquid phase-separated condensates and filaments, the present paper provides a first physicochemical framework for synaptic ribbon assembly and regulation. Understanding how the RIBEYE filaments assemble into synaptic ribbon *in vivo*, and how synaptic ribbon components relate to circadian clock will likely constitute the central research agenda for the ribbon synapse field in the years ahead. The synaptic ribbon is emerging as a dynamically regulated protein complex poised at the interface of phase transition, synaptic transmission, energy metabolism, and circadian biology.

COMPETING INTERESTS

The authors declare no competing interests.

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ADDITIONAL INFORMATION

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