



REVIEW

Presynaptic perspective: Axonal transport defects in neurodevelopmental disorders

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Disruption of synapse assembly and maturation leads to a broad spectrum of neurodevelopmental disorders. Presynaptic proteins are largely synthesized in the soma, where they are packaged into precursor vesicles and transported into distal axons to ensure precise assembly and maintenance of presynapses. Due to their morphological features, neurons face challenges in the delivery of presynaptic cargos to nascent boutons. Thus, targeted axonal transport is vital to build functional synapses. A growing number of mutations in genes encoding the transport machinery have been linked to neurodevelopmental disorders. Emerging lines of evidence have started to uncover presynaptic mechanisms underlying axonal transport defects, thus broadening the view of neurodevelopmental disorders beyond postsynaptic mechanisms. In this review, we discuss presynaptic perspectives of neurodevelopmental disorders by focusing on impaired axonal transport and disturbed assembly and maintenance of presynapses. We also discuss potential strategies for restoring axonal transport as an early therapeutic intervention.

Introduction

The human central nervous system (CNS) consists of hundreds of thousands of interconnected neuronal circuits that give rise to perception, cognition, and behavior. These circuits are wired together through the formation of $\sim 10^{15}$ synapses between $\sim 10^{12}$ neurons (Herculano-Houzel, 2012). Intense synaptogenesis occurs during embryonic and early postnatal stages, persisting throughout adolescence and even into the third decade of human life (Petanjek et al., 2011). Any disruption of synapse assembly, maturation, or remodeling leads to a broad spectrum of neurodevelopmental disorders (NDDs) characterized by an inability to reach cognitive, emotional, and motor developmental milestones, including autism spectrum disorders (ASDs), attention-deficit/hyperactivity disorder, intellectual disability (ID), disorders in communication, learning, and motor function, developmental epilepsies, and schizophrenia (SZ) (Sydnor et al., 2021; Thapar et al., 2017). NDD prevalence has progressively increased over the past decades; an estimated one in six children aged 3–17 years old in the United States have one form of NDD (Zablotsky et al., 2019). Despite the broad genetic heterogeneity of NDDs, genetic studies have revealed many human NDD-linked variants in genes associated with synapse formation and function, leading to a central hypothesis that synaptic pathology is one of the major causative mechanisms underlying the etiology of NDDs (Grant, 2012).

Synapse formation (or synaptogenesis) is a multistage process in the assembly of specialized synaptic structures, including

(1) axon and dendrite contacts through dynamic filopodia, (2) synaptic cargo transport from the soma to nascent synapses, (3) recruitment and assembly of these synaptic components at newly forming synapses, and (4) maintenance and remodeling of synapses (Chia et al., 2013; Jin and Garner, 2008; Südhof, 2021). Deleterious variants in genes encoding cell-adhesion molecules (CAMs) and scaffolding proteins located at the post-synaptic density significantly alter the course of brain development, and therefore it is not surprising that they have been repeatedly associated with NDDs (Bourgeron, 2015; Exposito-Alonso and Rico, 2022; Michetti et al., 2022; Parenti et al., 2020). In contrast, little is known about the impact of axonal transport of presynaptic components on the etiology of NDDs, largely due to challenges in characterizing transient and dynamic transport events in live neurons. Recent studies have started to decipher genetic variants in the axonal transport machinery that may contribute to presynaptic mechanisms underlying NDDs (Rizalar et al., 2021).

Presynaptic proteins are largely synthesized in the soma where they are packaged into precursor vesicles and then anterogradely transported into nascent synapses along axonal microtubules (MTs) by kinesin motors. Defective presynaptic organelles and proteins are retrogradely transported toward the soma by dynein motors for degradation or turnover (Fig. 1 A). Amazingly, human motor neuron axons can extend up to 1 m long with extensive terminal branching, and thus presynaptic

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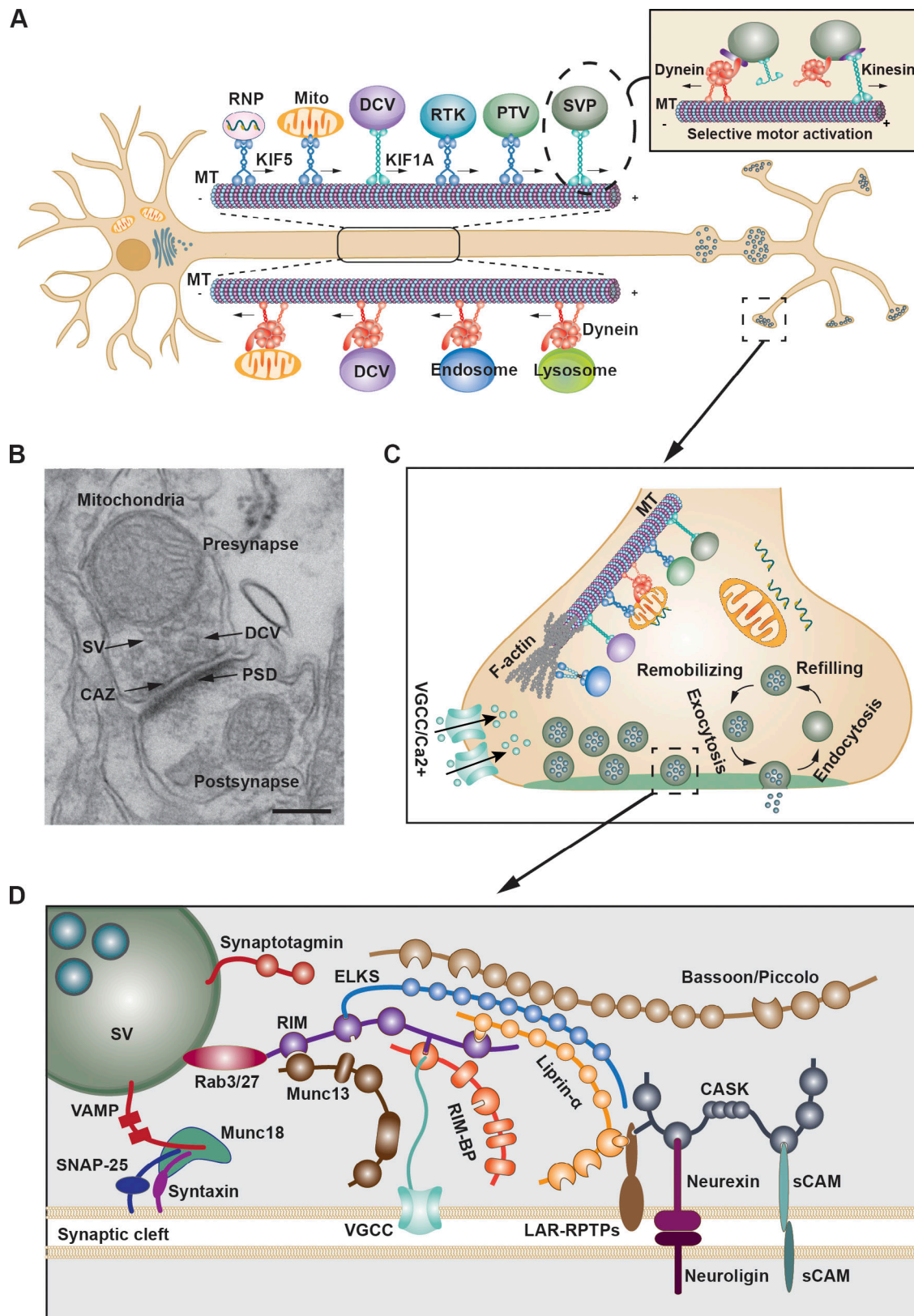


Figure 1. Axonal transport in presynaptic assembly and maintenance. (A) Schematic of the bidirectional axonal transport essential for presynapse assembly and maintenance. Major presynaptic proteins are synthesized in the cell body and transit the Golgi apparatus where they are sorted into presynaptic cargos, including SVPs, PTVs, DCVs, and RTK-carrying vesicles. These cargos are delivered along axonal MT tracks by kinesin motors to presynaptic terminals. SEs, mitochondria, and endo-lysosomes carrying defective proteins undergo dynein-driven retrograde transport toward the soma for retrograde signaling, degradation, or turnover. The insert indicates that both kinesin and dynein motors can be recruited to presynaptic cargos and their net favored transport

direction is determined by the differentially activated motor state. **(B)** Electron micrograph showing pre- and postsynaptic specializations from mouse hippocampal slices in CA1 regions. Scale bar: 200 nm. **(C)** Transported cargos are released to build a presynapse where SVs give rise to mature SVs and proteins are assembled into CAZ. Mitochondria are recruited to provide ATP and modulate Ca^{2+} signals. mRNAs serve as a platform to replenish presynaptic proteins locally. The presynaptic F-actin networks are required for SV docking and mobilization. **(D)** Schematic of presynaptic components, including sCAMs (neurexin, neuroligin, and LRPTP), CAZ proteins (ELKS, CASK, RIM, RIM-RBP, liprin- α , Munc13, Piccolo, and Bassoon), VGCCs, and SV fusion machinery (VAMP, SNAP25, Syntaxin, Synaptotagmin, Munc18, and Rab3). (Note that not all interactions are displayed. Sizes of molecules and cargoes are only for illustrative purposes and are not drawn to scale).

terminals are positioned far away from the cell body. Due to these morphological features, neurons face exceptional challenges for the targeted delivery of presynaptic components along such long axons. Several adaptors and scaffolding proteins assist motor proteins in driving the bidirectional transport of synaptic cargos to ensure precise assembly, maintenance, and remodeling of presynapses (Cai et al., 2007; Guedes-Dias and Holzbaaur, 2019). A growing number of mutations in genes encoding the transport machinery have been associated with NDDs (Hirokawa et al., 2010; Sleight et al., 2019; Xiong et al., 2021). These findings have broadened our view beyond the scope of postsynaptic mechanisms. Thus, elucidating presynaptic mechanisms of NDDs is an important emerging frontier. In this review, we limit our discussion to presynaptic perspectives of NDDs by focusing on impaired axonal transport of presynaptic cargos. First, we provide an overview of axonal transport machineries and mechanisms driving targeted axonal transport of various presynaptic cargos to ensure the stoichiometric assembly and maintenance of presynaptic active zones (AZs). Second, we examine current literature emerging from human and mouse studies revealing genetic mutations in genes encoding transport machineries that associate with a wide range of NDDs. Finally, we discuss perspectives on the potential strategies for restoring axonal transport as an early therapeutic intervention for NDDs.

Presynaptic assembly and maintenance

Synapses are highly asymmetric intercellular junctions composed of a presynaptic terminal and a juxtaposed postsynaptic density, separated by the synaptic cleft, where trans-synaptic CAMs provide connections between pre- and postsynaptic membranes (Fig. 1 B). Presynaptic terminals (or boutons) are established from the axonal growth cone and along axonal segments, which allow one axon to form enormous *en passant* synaptic connections with many dendrites along its route. A single rat hippocampal CA3 mossy/pyramidal neuron makes ~40,000 synapses over ~0.2 m length of axon (Buckmaster et al., 1996; Ishizuka et al., 1990; Li et al., 1994). The presynaptic compartment contains hundreds of neurotransmitter-filled synaptic vesicles (SVs) and a network of scaffolding proteins known as the cytomatrix of active zones (CAZs), a patterned structure with multiple protein complexes that (1) serves as the platform for recruiting and anchoring SVs at AZ release sites, (2) enables the physical coupling of voltage-gated calcium channels (VGCCs) to SV fusion sites, and (3) renders SV fusion competent by facilitating SNARE complex formation (Fig. 1, C and D). With this sophisticated protein machinery, SV exocytosis is executed within less than 1 ms upon VGCC opening in response to action potential firing (Südhof, 2012).

These presynaptic components are mainly synthesized in the soma and anterogradely transported along lengthy axonal MTs

into distal presynaptic sites. While membranous presynaptic components (such as CAMs, VGCCs, and SV proteins) are synthesized by the rough endoplasmic reticulum in the soma and exported to the trans-Golgi network, non-membrane CAZ proteins are mainly synthesized on cytoplasmic ribosomes in the soma before undergoing axonal transport (Maas et al., 2012; Shapira et al., 2003; Zhai et al., 2001). Upon arrival at nascent synapses, these transported cargos are unloaded from motors and captured for assembly of AZ structures through multiple protein interactions (Fig. 1 D). AZ-like condensates may form by phase separation through multiple low-affinity interactions (Wu et al., 2019), although these condensates have not been validated at synapses *in vivo*.

Once a synapse is established, its structure and function are highly plastic with neuronal development and undergo activity-dependent remodeling. Existing synaptic connections can be strengthened, weakened, or eliminated, allowing the brain to adjust and optimize synaptic responses throughout life (Südhof, 2021). In response to appropriate signals, large (75–100 nm) dense-core vesicles (DCVs) and signaling endosomes (SEs) containing neuropeptides and neurotrophins, respectively, are transported anterogradely or retrogradely along the axon to regulate synapse maturation and synaptic strength (Harrington and Ginty, 2013; Wong et al., 2012). Studies combining *in vivo* metabolic labeling and mass spectrometry suggest that turnover rates of presynaptic proteins can range from 5 h or less to more than 50 days (Cohen et al., 2013; Fornasiero et al., 2018; Truckenbrodt et al., 2018). Thus, the maintenance of presynapses requires continual anterograde transport and replenishment of new presynaptic components and retrograde transport of defective or aged presynaptic components toward the soma for turnover through the autophagy and endolysosomal systems (Di Giovanni and Sheng, 2015; Farfel-Becker et al., 2019; Jin et al., 2018; Roney et al., 2022). Therefore, presynaptic assembly and maintenance require seamless integration of biogenesis, bidirectional transport, and degradation of synaptic components.

Mature presynaptic terminals also contain a local protein synthesis system that transcribes a heterogeneous population of mRNAs supplied by axonal mRNA transport in the form of ribonucleoprotein granules (RNPGs) (Dalla Costa et al., 2021; Hafner et al., 2019). Synaptic mRNA translation has been recognized as a dynamic platform to replenish synapses with new proteins that transduce intrinsic and extrinsic cues into structural and functional presynapse remodeling (Akins et al., 2009). It is less clear whether CAZ proteins can be synthesized locally at nascent presynapses.

The formation and maturation of nascent presynaptic terminals and the remodeling of mature presynapses require tight

coordination of the axonal transport of at least seven major cargos and organelles with distinct transport mechanisms: (1) SV-like precursors (SVPs); (2) Piccolo-Bassoon Transport Vesicles (PTVs) containing CAZ scaffolding and membrane proteins; (3) DCVs delivering neuropeptides, (4) receptor tyrosine kinase (RTK)-carrying vesicles and SEs propagating retrograde neurotrophic signaling, (5) mRNAs in the form of RNPGs, (6) mitochondria, and (7) the autophagy and endolysosomal systems (Fig. 1 A). In the next two sections, we provide an overview of axonal transport machineries and mechanisms for targeted delivery of five “primary” presynaptic cargos to ensure the assembly and maintenance of functional presynapses. For axonal transport of mitochondria and autophagy and endolysosomal systems, we refer the readers to recent reviews (Cason and Holzbaaur, 2022; Devine and Kittler, 2018; Li and Sheng, 2022; Misgeld and Schwarz, 2017; Roney et al., 2022).

Axonal transport machineries

Long-distance axonal transport relies on the coordination of three key components of the transport machinery: MTs as trafficking tracks, molecular motors driving cargo transport, and motor adaptors and effectors that selectively connect cargo and motors and/or activate motor processivity.

MTs

MTs are polarized tubulin polymers with fast-growing plus ends and more stable minus ends. In the axon, parallel MTs form a unipolar array with the plus ends pointing toward the axon terminals. Axonal MTs serve as the major commute tracks for various cargo binding and movement. They are stabilized by MT-associated proteins (MAPs), which can affect motor protein recruitment (Monroy et al., 2018). Various plus-end tracking proteins (+TIPs), such as EBI, accumulate at the growing MT plus end to regulate axonal MT dynamics and facilitate their interactions with motors and cargos (Akhmanova and Steinmetz, 2008; Miryala et al., 2022). Posttranslational MT modifications, including acetylation, detyrosination, and tyrosination, affect cargo trafficking efficiency by regulating motor activity (Kapitein et al., 2010; Sirajuddin et al., 2014; Tas et al., 2017). Tyrosinated tubulin is enriched at the plus ends of growing MTs (near growth cones), while acetylation and detyrosination are more likely to be seen in the middle or minus end of MTs to maintain MT stabilization (Song and Brady, 2015). Kinesin-1 binds preferentially to MTs that are acetylated or detyrosinated to transport cargos along the axon (Hammond et al., 2009; Konishi and Setou, 2009; Nakata et al., 2011), while kinesin-3 and dynein motors prefer to bind to tyrosinated MTs exhibiting non-selective cargo delivery to both axons and dendrites (Nirschl et al., 2016; Tas et al., 2017). However, the mechanisms for these modifications in selectively guiding motor-MT engagement within axons versus dendrites remain largely unknown.

Motor proteins

Kinesin and dynein are two major classes of MT-based and ATP-driven molecular motors that move cargos in the anterograde (from the soma to distal axons) and retrograde (from axonal

terminals to the soma) directions, respectively. The kinesin superfamily (KIF) constitutes at least 45 genes in the human genome, 38 of which are expressed in brain, and is classified into 15 subfamilies, designated as kinesin-1 to kinesin-14B (Hirokawa et al., 2010). Motors from four of these subfamilies—kinesin-1 (KIF5A, KIF5B, and KIF5C), kinesin-2 (KIF3 and KIF17), kinesin-3 (KIF1A, KIF1B, KIF13, and KIF16B), and kinesin-4 (KIF21A)—drive long-distance trafficking of diverse cargos and organelles from the soma into the axon (Gicking et al., 2022). Kinesin-1 motors are formed from two heavy chains (KHCs) and two light chains (KLCs); each KHC contains a catalytic motor domain that binds to MTs and generates movement via ATP hydrolysis, a neck linker, a coiled-coil stalk domain that mediates dimerization, and an inter-head to a tail domain that associates with a KLC. Kinesin-1 mediates axonal transport of AZ precursors PTVs, mitochondria, and RNA granules (Fukuda et al., 2021; Pilling et al., 2006; Su et al., 2004). Kinesin-2 motors drive the anterograde motility of vesicles containing presynaptic sCAM proteins, including N-cadherin and β -catenin (Teng et al., 2005). Kinesin-3 motors drive the motility of SVPs, DCVs, SEs, and RNA granules (Bentley et al., 2015; Lo et al., 2011; Okada et al., 1995; Pichon et al., 2021).

In contrast to such diversity in kinesin motor subfamilies, retrograde axonal transport is mediated by a single cytoplasmic dynein motor, which is a large complex consisting of two heavy chains (DHCs) with ATPase activity, two intermediate chains (DICs), two light intermediate chains (DLICs), and several light chains (DLCs) (Reck-Peterson et al., 2018). In addition, the dynein complex interacts with dynein and is required for motor-cargo association and motor processivity (Gill et al., 1991; King and Schroer, 2000). The actin-based myosin motors, including myosins V and VI, drive short-range cargo trafficking along actin filaments (F-actin). At presynaptic terminals, F-actin is highly enriched and serves as a platform for CAZ assembly, SV recruitment and recycling, and the anchor of presynaptic mitochondria, thus controlling presynaptic cargo switch from MT-based trafficking to actin-based anchoring (Cingolani and Goda, 2008; Gutnick et al., 2019; Li et al., 2020; Schroeder et al., 2010).

Motor adaptors and effectors

A diverse array of adaptors and effectors have been identified to serve as a linker recruiting motor proteins to specific cargos/organelles or act as effectors activating the motility of kinesin or dynein motors. These include the kinesin adaptors liprin- α , Arl8, syntabulin, JIP1, JIP3, and Huntingtin (HTT). All of these link either the kinesin KHC tail or KLC to its trafficking cargo and/or activate the motility of anterograde axonal transport (Colin et al., 2008; Klassen et al., 2010; Miller et al., 2005; Su et al., 2004; Verhey et al., 2001). For dynein motors, adaptors/effectors include HTT, Huntingtin-associated protein-1 (HAP1), BICD1 and 2 (N-terminal domain of protein bicaudal D homolog 1 and 2), Hook1 and 3, Snapin, and JIP3. These proteins connect specific cargos with dynein motors, enhance dynein-dynein interaction, or activate retrograde processivity (Caviston et al., 2007; Celestino et al., 2022; Engelender et al., 1997; Olenick et al., 2016; Schlager et al., 2014; Zhou et al., 2012).

Presynaptic cargos and their transport mechanisms SVPs

Mature SVs consist of >130 proteins involved in SV exocytosis and endocytosis, trafficking, and refilling of neurotransmitters (Blondeau et al., 2004; Morciano et al., 2005; Takamori et al., 2006; Taoufiq et al., 2020). These SV components are transported separately in distinct SVP forms and then assembled through a recycling endosome trafficking route. An immuno-EM study in developing rat hippocampal neurons revealed pleiomorphic vesicles (50–300 nm in size) carrying SV integral membrane proteins, while SV-associated proteins synapsin and α -synuclein proceed through different routes of biosynthesis and axon transport and are sorted into the same SV clusters when they are in axons (Tao-Cheng, 2020). Upon transport into nascent presynapses, SVPs are thought to form mature SVs by undergoing constitutive exo-endocytic cycling locally or by directly budding from SVPs (Rizalar et al., 2021).

Anterograde SVP transport is driven by kinesin-3 motors (Fig. 2 A), including UNC-104 in *C. elegans*, Imac in *Drosophila*, and KIF1A and KIF1B β in mammals and humans (Hall and Hedgecock, 1991; Pack-Chung et al., 2007; Okada et al., 1995; Zhao et al., 2001). Kinesin-3 is a monomeric motor that is autoinhibited by the binding of its stalk coiled-coil domain to its motor heads. Relief from autoinhibition is achieved by cargo-mediated motor dimerization, which promotes the fast anterograde transport of SVPs (>3 μ m/sec) with a few pauses along GDP-rich MT lattices (Hammond et al., 2009; Tomishige et al., 2002). However, at MT plus ends at presynaptic terminals, where GTP-tubulin is enriched, KIF1A shows weak MT-binding affinity, thus favoring SVP release upon arrival at *en passant* synapses (Guedes-Dias et al., 2019) (Fig. 2 A). In *C. elegans*, null mutants of *unc-104* lead to impaired axonal transport of SVPs, reduced number of SVs at presynapses, and deficits in locomotion (Hall and Hedgecock, 1991). Reduced UNC-104 levels in *unc-104*^{+/−} cause SVP pausing at branch points, impeding their entry into synaptic terminals (Vasudevan et al., 2024). In *Drosophila*, *Imac* knockout impairs the axonal transport of SVPs and formation of presynaptic boutons (Pack-Chung et al., 2007). In mice, a *KIF1A* loss-of-function mutation leads to decreased axonal transport of SVPs and their accumulation in the soma, along with a dramatic reduction of mature SVs at synapses, which are associated with sensorimotor deficits and early postnatal death (Yonekawa et al., 1998). Conversely, *KIF1A* overexpression promotes presynaptic bouton formation (Kondo et al., 2012). In humans, a set of mutations in *KIF1A* and *KIF1B β* have been linked to abnormal axonal transport of SVPs and synapse phenotypes observed in NDDs (Chiba et al., 2023).

Kinesin-3 motors possess a C-terminal pleckstrin homology (PH) domain and a conserved stalk domain. The PH domain binds phosphatidylinositol-4,5-bisphosphate on the cargo membrane, which is critical for SVP loading onto motors (Klopfenstein and Vale, 2004). Cargo specificity is achieved by adaptors, which bind to the stalk domain (Fig. 2 A). For example, liprin- α interacts directly with KIF1A through its coiled-coil domain (Shin et al., 2003); liprin- α mutations decrease anterograde SVP transport (Miller et al., 2005). Similarly, HTT acts as a scaffolding protein that colocalizes with KIF1A on VAMP2-

positive SVPs. HTT phosphorylation at S421 recruits KIF1A to SVPs and thus enhances SVP transport (Vitet et al., 2023). The death domain of DENN/MADD (differentially expressed in normal and neoplastic cells/MAP kinase activating death domain), a guanine nucleotide exchange factor, binds to the stalk region of KIF1A and KIF1B β , while the MADD domain interacts with the GTPase-Rab3 on SVP membranes (Niwa et al., 2008). Thus, DENN/MADD connects kinesin-3 with SVPs carrying GTP-bound Rab3. RAB3A phosphorylation disrupts its binding to MADD, thus preventing SVP loading onto KIF1A/KIF1B β motors for anterograde transport (Dou et al., 2024). In *DENN/MADD* knockout mice, SV numbers are reduced (Tanaka et al., 2001). In *C. elegans*, the GTPase *Arl8* activates *unc-104/KIF1A* by relieving autoinhibition in a GTP-dependent manner (Niwa et al., 2016). *ARL8* loss-of-function results in SV accumulation at proximal axons and a loss of distal boutons due to insufficient *unc-104/KIF1A* activation (Klassen et al., 2010). Therefore, this GTPase switch may regulate SVP transport into presynaptic terminals. Fasciculation and elongation protein zeta-1 (FEZ1) acts as an adaptor that activates kinesin-1 and thus drives the axonal transport of Synaptotagmin-1 (Syt-1)-carrying SVPs (Blasius et al., 2007). The cargo-motor coupling is controlled by the phosphorylation state of FEZ1 via the kinase UNC-51 (Toda et al., 2008). Interestingly, Disrupted in Schizophrenia-1 (DISC1), a genetic risk factor for SZ, regulates Syt-1-carrying SVP transport by binding both kinesin-1 and FEZ1; *DISC1* mutation causes defective transport by disrupting motor-cargo assembly (Flores et al., 2011).

PTVs

The CAZ is organized by a set of multidomain proteins, including two large scaffolding proteins Piccolo and Bassoon, ELKS/CAST, Munc13s, Rab3-interacting molecules (RIMs), RIM-binding proteins (RIM-BPs), and liprin- α (Südhof, 2012). After being synthesized in the soma, the CAZ components are sorted and assembled into distinct sets of Golgi-derived transport cargos termed PTVs (Ackermann et al., 2015; Garner et al., 2000). PTVs are 80-nm dense core vesicles containing CAZ scaffolds, CAMs N-cadherin, and presynaptic plasma membrane proteins Syntaxin and SNAP-25. PTVs also gather Munc13-1 and RIM1 α in a post-Golgi step forming a “mature” PTV (Maas et al., 2012). The CAZ functions to dock and prime SVs for exocytosis, recruit VGCCs to release sites, and tether synaptic adhesion molecules. Individual CAZ scaffold size and composition can scale synaptic strength by affecting SV release probability (Holderith et al., 2012). As few as five PTVs could provide sufficient scaffold proteins to form a functional CAZ in developing neurons. PTVs have been suggested to appear prior to SVP arrival at nascent boutons (Ahmari et al., 2000; Friedman et al., 2000; Zhai et al., 2000) or are cotransported with SVPs during development (Tao-Cheng, 2020; Vukoja et al., 2018). The SNARE proteins syntaxin 1 and SNAP-25 are also cotransported with Piccolo and Bassoon, indicating that the SV fusion machinery is packaged with the CAZ to lay the structural foundation for recruiting other presynaptic components and SVs (Zhai et al., 2001). Similarly, VGCCs are thought to be assembled in the soma and cotransported to presynapses (Macabuag and Dolphin, 2015).

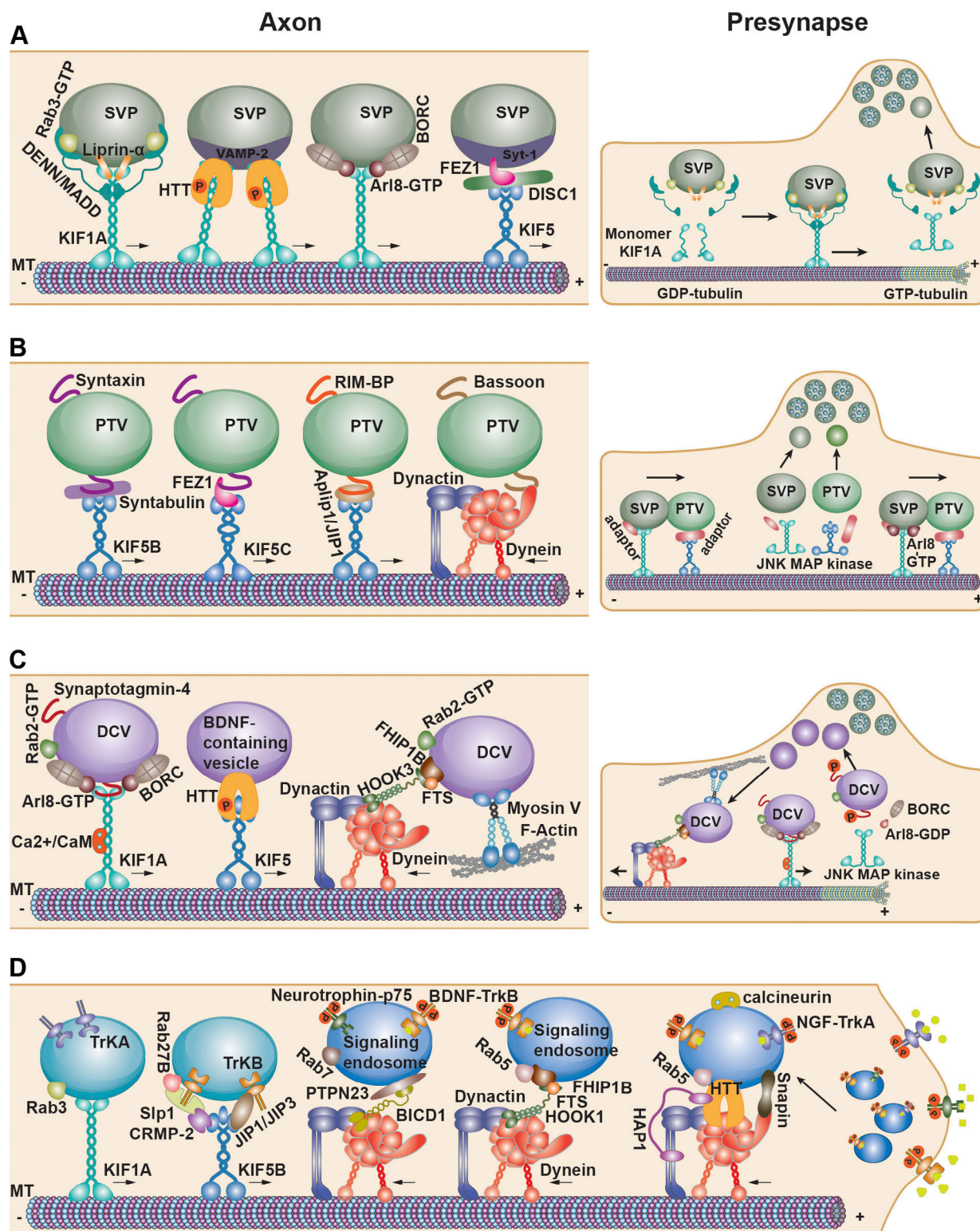


Figure 2. Mechanisms driving presynaptic cargo transport. (A) The SVP transport machinery. Anterograde SVP transport is driven by the kinesin motor KIF1A, which is autoinhibited by the binding of its stalk coiled-coil domain to its motor heads. Cargo specificity is achieved by adaptor/effector proteins which bind to the stalk domain to relieve motor autoinhibition. DENN/MADD binds to the KIF1A stalk region and recruits the motor to SVP membranes through cooperation with Rab3-GTP. Liprin- α and HTT serve as adaptors to recruit KIF1A to SVPs. KIF1A is also relieved from its autoinhibition status by cargo-mediated dimerization, resulting in increased binding and processivity on MTs compared with its monomeric state. The BORC-Arl8-KIF1A complex also drives SVP transport into axons. In addition, KIF5 motors drive axonal transport of Syt-1-carrying SVPs through interactions with FEZ1-DISC1. Upon arrival at *en passant* presynaptic boutons, SVPs are unloaded by detaching motors from the GTP-tubulin bound MT plus ends. **(B)** The PTV transport machinery. PTVs are distinct 80-nm dense core vesicles containing the CAZ scaffolds (Piccolo and Bassoon), CAZ proteins (Munc13-1, RIM1 α , and ELKS2), sCAM N-cadherin, and presynaptic

plasma membrane proteins Syntaxin-1 and SNAP-25. Syntabulin functions as a KIF5 adaptor driving PTV transport via an interaction with syntaxin. Syntabulin loss-of-function leads to impaired axonal transport of PTVs from the soma toward distal axons. FEZ1 binds syntaxin, thus loading KIF5C onto PTVs. In addition, Aplip1/JIP1 act as a kinesin-1 adaptor to mediate RIM-BP-carrying PTV transport into presynapses. Dynein motors drive retrograde PTV transport by binding to Bassoon. PTVs are cotransported with SVPs facilitated by Arl8-GTP bound to SVP membrane. The JNK-MAP kinase pathway suppresses anterograde transport and promotes SV and AZ protein clustering for presynaptic assembly. **(C)** The DCV transport machinery. DCVs convey neuropeptides and neurotrophins along axons to modulate synapse function. Both KIF1A and KIF5 drive anterograde DCV transport into axon terminals, while dynein/dynactin mediates DCV retrograde transport. Rab2 is recruited to DCVs and assists the BORC-Arl8-KIF1A complex in mediating axonal transport, which is also regulated by Ca^{2+} /calmodulin upon increased neuronal activity. Phosphorylated HTT promotes anterograde transport of BDNF-containing DCVs by increasing kinesin-1 recruitment. Rab2 also helps recruit dynein to DCVs, and HOOK3 activates dynein–dynactin motility. Myosin Va binds to DCVs via its tail domain and facilitates retrograde transport of DCVs. Phosphorylation of Syt-4 (S135) on DCV membranes by JNK MAP kinase destabilizes Syt4-KIF1A coupling and thus unloads DCVs at *en passant* presynaptic boutons. **(D)** The SE transport machinery. KIF1A is the motor driving anterograde transport of TrkA in Rab3-positive secretory vesicles to axon terminals. Anterograde transport of TrkB is driven by the Slp1–CRMP-2–KIF5B complex in a Rab27B-dependent manner. JIP3 also binds TrkB and mediates TrkB anterograde transport by linking TrkB and KLC. At presynaptic terminals, Rab5-positive SEs are formed following neurotrophin binding to its receptors and undergo retrograde transport toward the soma. Dephosphorylated HTT by calcineurin in response to elevated Ca^{2+} leads to kinesin-1 detachment and facilitates retrograde transport of SEs carrying BDNF–TrkB by dynein motors. HAP1 acts as a dynein activator. Hook1 acts as a dynein effector to drive retrograde transport via forming the FTS–Hook–FHPIB–Rab5 complex. Other adaptor proteins, such as BICD1, PTPN23, and Snapin, also recruit dynein motors to SEs to drive their retrograde signaling.

Therefore, multiple presynaptic proteins are cotransported by the same precursor organelle or by clusters of “distinct” carriers through a coordinated transport that ensures the delivery of stoichiometric amounts of AZ and SV contents for efficient presynaptic assembly in developing neurons (Bury and Sabo, 2011; Wu et al., 2013). However, the current concept of a “distinct” presynaptic carrier model requires further validation concerning their molecular identity, biogenesis sorting, and transport mechanisms.

Kinesin-1 motors KIF5B and KIF5C drive anterograde PTV transport (Fig. 2 B). Syntabulin functions as a kinesin-1 adaptor driving PTV transport via an interaction with PTV-carrying cargo syntaxin 1 (Su et al., 2004). Syntabulin loss-of-function leads to impaired transport of PTVs from the soma toward distal axons and reduced density of presynapses and AZs in developing neurons and mature CNS in mice (Cai et al., 2007; Xiong et al., 2021). The second adaptor-like protein for driving PTVs is FEZ1, which binds syntaxin 1 and Munc-18 and thus loads KIF5C onto the syntaxin-containing PTVs (Chua et al., 2012). APP-like protein-interacting protein 1 (Aplip1), a homolog of JIP1 functioning as a kinesin-1 adaptor, interacts with RIM-BP through its proline-rich (PxxP) motif. The mutation in the motif leads to ectopic accumulation of RIM-BP-enriched PTVs due to defective anterograde transport (Siebert et al., 2015). PTVs have been reported to cotransport with SVPs, promoting SVP clustering and capture (Bury and Sabo, 2011; Lipton et al., 2018; Vukoja et al., 2018). As a motor adaptor, Arl8 facilitates kinesin-cargo coupling and promotes anterograde cotrafficking of PTVs and SVPs (Wu et al., 2013). The JNK-MAP kinase signaling pathway promotes SV and AZ protein clustering for presynaptic assembly. Interestingly, Bassoon itself functions as an adaptor binding DLC for retrograde PTV transport. Disruption of Bassoon–DLC interactions impairs trafficking and distribution of Piccolo and Bassoon along axons (Fejtova et al., 2009), providing insights as to how bidirectional PTV transport is critical for precise targeting of presynaptic scaffolds at *en passant* synaptic sites.

DCVs

DCVs convey neuropeptides and neurotrophins along axons to modulate synaptic maturation and plasticity in a neuron-type-

dependent manner (Altar et al., 1997; van den Pol, 2012). Axonal DCV transport displays a complex motility pattern: long-range circulation and sporadic capture (Bharat et al., 2017; Wong et al., 2012). The small GTPase Rab2 mediates DCV biogenesis and maturation in the cell body (Ailion et al., 2014; Edwards et al., 2009). Either kinesin-3 alone or kinesin-3 and kinesin-1 work in concert to drive anterograde transport of DCVs from the soma into axons (Lim et al., 2017; Lo et al., 2011), while the dynein/dynactin complex mediates DCV retrograde transport (Kwinter et al., 2009) (Fig. 2 C). The BORC subunit Blos1 activates Arl8 to a GTP-bound state to promote its binding and activation of KIF1A, thus driving DCV transport into axons. Rab2 is recruited to DCVs by Ema, thus assisting the BORC–Arl8–kinesin complex in driving the axonal transport of DCVs (Lund et al., 2021). Anterograde transport of DCVs slows down and frequently pauses at and near presynapses (Guedes-Dias et al., 2019; Nassal et al., 2022), where DCVs are preferentially captured in an activity-dependent manner. The calcium-binding protein calmodulin (CaM) binds to KIF1A in response to Ca^{2+} signaling and thus facilitates DCV trafficking upon increased neuronal activity (Cavolo et al., 2016; Stucchi et al., 2018). KIF1B β contains a conserved CaM binding site and likely undergoes a similar Ca^{2+} /CaM-dependent regulation of DCV transport. In addition, HTT phosphorylation by AKT promotes anterograde transport of brain-derived growth factor (BDNF)-containing DCVs by increasing kinesin-1 recruitment (Colin et al., 2008).

Syt-4 binds KIF1A and is cotransported with DCVs. Phosphorylation of Syt-4 (S135) by JNK kinase, which is upregulated upon neuronal activity, destabilizes Syt4-KIF1A coupling, leading to a transition from MT-based DCV trafficking to F-actin-based capture at *en passant* presynaptic boutons (Bharat et al., 2017). The Syt4-KIF1A coupling is also modulated by Ca^{2+} /CaM binding to KIF1A (Stucchi et al., 2018). DCV capture at synapses may also rely on liprin- α , which captures KIF1A-bound DCVs upon their synapse entry by interacting with KIF1A (Goodwin and Juo, 2013). At presynaptic boutons, uncaptured DCVs can be converted to a retrograde transport mode and return to the proximal axon, where they again switch to the anterograde transport route (Wong et al., 2012). Rab2 recruits dynein to DCVs with the help of HOOK3 to activate dynein–dynactin

motility (Lund et al., 2021; Olenick et al., 2016). Myosin Va binds to DCVs via its tail domain and facilitates retrograde DCV axonal transport (Bittins et al., 2010). Therefore, fine-tuned coordination of anterograde versus retrograde DCV motility contributes to presynaptic targeting of neuropeptides and neurotrophins.

SEs

Propagation of retrograde neurotrophic signaling conveyed by SEs is essential for axon growth, synaptogenesis, and plasticity. At presynapses, neurotrophins, including nerve growth factor, BDNF, neurotrophin-3 or -4/5, bind RTKs of the Trk family or the p75 neurotrophin receptor (p75^{NTR}) to trigger the internalization of ligand-bound receptors into Rab5-positive SEs (Chao, 2003). Trk-harboring SEs can function locally by promoting axonal growth and synapse formation, or distally by transporting to the soma to activate transcriptional signaling necessary for synapse maturation and plasticity (Harrington and Ginty, 2013). To trigger retrograde neurotrophic signaling, the prerequisite is the trafficking of newly synthesized RTKs (TrkA/TrkB) from the soma to axon tips. Kinesin-1 (KIF5B) and kinesin-3 (KIF1A) motors drive anterograde transport of RTKs in Rab3- or Rab27B-positive secretory vesicles (Fig. 2 D) (Scott-Solomon and Kuruvilla, 2018). In mouse sensory neurons, anterograde transport of TrkA-carrying cargos is driven by KIF1A with the help of GTP-bound Rab3. Dorsal root ganglia from *Kifla*^{+/-} mice exhibit progressive sensory neuron loss and sensory neuropathy (Tanaka et al., 2016). TrkB-carrying cargos are loaded onto KIF5B by a complex of CRMP-2, Slp1, and Rab27B. The cytoplasmic tail of TrkB binds to Slp1 in a Rab27B-dependent manner, and CRMP-2 connects Slp1 to KIF5B (Arimura et al., 2009). JIP3 also mediates TrkB anterograde transport by linking TrkB and KLC in mouse hippocampal neurons (Huang et al., 2011). JIP1 and JIP3 form a complex that functions to relieve kinesin-1 autoinhibition (Sun et al., 2017); overexpressing JIP1 or JIP3 enhances TrkB-KLC interaction and promotes TrkB transport, while knocking down JIP1 or JIP3 diminishes TrkB anterograde transport. It was also reported that Rab6-positive TrkB carriers are driven by KIF1A for anterograde transport in hippocampal neurons (Zahavi et al., 2021).

After internalization at presynaptic terminals, Trk and its ligands—neurotrophins—are sorted into Rab5-positive early endosomes and then trafficked to Rab7-positive late endosomes targeted for dynein-driven retrograde transport toward the soma (Fig. 2 D) (Deinhardt et al., 2006; Heerssen et al., 2004). In hippocampal neurons, BDNF-TrkB signaling activates PI3K that promotes anterograde transport of TrkB cargos into the nascent axon and further enhances surface insertion of TrkB, creating a self-amplifying feed-forward loop to promote axon growth (Cheng et al., 2011). HTT, as a BDNF scaffold, can be dephosphorylated by calcineurin in response to Ca²⁺ transients in synapses (Scaramuzzino et al., 2022). Dephosphorylation of HTT (S421) leads to kinesin-1 detachment and thus promotes retrograde transport of SEs carrying BDNF-TrkB by binding to dynein (Colin et al., 2008).

Neurotrophin signaling mediated by SEs conveys synapse-to-nucleus communication, helping neurons respond to presynaptic signaling with transcriptional changes (Terenzio et al.,

2017; Yamashita, 2019). Multiple motor adaptors/effectors and sorting pathways are involved in the retrograde transport of SEs. HAP1 is required for TrkB internalization upon BDNF binding and activation of dynein motility through its interaction with the p150^{Glued} dynactin subunit (Lim et al., 2018). Hook1 acts as a dynein effector to drive retrograde transport of both Rab5- and Rab7-positive SEs carrying BDNF-TrkB (Olenick et al., 2019), likely by forming an FTS-Hook-FHIP1B-Rab5 complex (Christensen et al., 2021) (Fig. 2 D). BICD1, a dynein adaptor, is also necessary for retrograde transport of TrkB- and p75-containing SEs (Terenzio et al., 2014). PTPN23, a member of the endosomal sorting complex, binds BICD1 and contributes to dynein recruitment to SEs (Budzinska et al., 2020). Snapin, an adaptor binding to dynein DIC, helps recruit dynein motors to BDNF-TrkB-carrying SEs for retrograde axonal transport (Zhou et al., 2012). *Snapin* knockout mice exhibit embryonic and neonatal death accompanied by abnormal brain development manifested as reduced cortical plates and cell density (Zhou et al., 2011). Some activated BDNF-TrkB complexes are colocalized with LC3b-II-positive autophagic organelles that undergo retrograde transport to confer long-range signaling capabilities (Kononenko et al., 2017; Andres-Alonso et al., 2019). Upon reaching the soma, SEs exhibit extended periods of signal up to 25 h via Coronin-1-mediated local recycling and reinternalization of RTKs into Rab11-positive recycling endosomes that escape lysosomal targeting and degradation (Moya-Alvarado et al., 2022; Suo et al., 2014). Rab11-positive endosomes can further traffic recycled RTKs outward to the axon for a feedback loop of neurotrophic signaling amplification (Ascaño et al., 2009). BICD1 also plays a role in maintaining the balance between RTK receptor degradation and recycling (Terenzio et al., 2014). Such persistent singling may help activate transcriptional programs necessary for neurite growth and synapse formation. SEs originating from distal axons can also be transported all the way to dendrite arbors to regulate synaptic connectivity (Sharma et al., 2010).

mRNA transport via RNA granules

One mechanism of presynaptic protein replenishment involves the axonal transport of mRNAs in RNA granules to presynaptic sites for local translation (Batista et al., 2017; Turner-Bridger et al., 2018). RNA profiling studies have revealed more than 1,000 different mRNAs enriched in axons and presynaptic terminals, thus providing a platform for local protein synthesis for structural and functional maintenance and remodeling of presynapses (Cajigas et al., 2012; Dalla Costa et al., 2021; Hafner et al., 2019). In neurons, mRNAs transcribed in the nucleus are packaged into large protein complexes called ribonucleoproteins (RNPs) through association with RNA-binding proteins (RBPs). After nuclear export, RNPs undergo long-distance axonal transport driven directly by motors (Kanai et al., 2004; Sladewski et al., 2013). mRNA transport in axons may also occur via hitchhiking of RNA granules on moving organelles, such as endosomes, lysosomes, or mitochondria (Cioni et al., 2019; Gershoni-Emek et al., 2018; Liao et al., 2019). Synaptic mRNA arrest and anchoring are thought to rely on F-actin as well as deactivation of driving motors (Sladewski et al., 2013).

The 3' and 5' untranslated regions of mRNAs play key roles in transport and localization selectivity (Andreassi and Riccio, 2009; Merianda et al., 2013; Tushev et al., 2018). Multiple motifs or *cis*-acting elements are necessary and sufficient for mRNA localization into axons, including the “zip code” motif, MAIL (mail for axonal importin localization) motif, and AU-rich sequences bearing AUUUA element; many RBPs can also bind to a single RNA element, suggesting that different mRNAs may be cotransported by the same RBP in a single RNA granule (Lee et al., 2018). The number of localization motifs on a single mRNA is linearly correlated with the number of motors loaded, thus affecting its processivity or run length (Sladewski et al., 2013). However, how different RBPs recruit motor proteins to form a transport granule in axons and whether this process requires additional adaptors remains unclear. Future studies are needed to reveal mechanisms underlying localization and translation of mRNA for the maintenance of synaptic remodeling and plasticity.

NDD-linked mutations in the axonal transport machinery

During nervous system development, any perturbation in axonal transport will cause a mistargeted distribution of presynaptic proteins/cargos, leading to impaired presynaptic formation and maintenance. Missense mutations and small genomic deletions or rearrangements in genes encoding the transport machinery are increasingly revealed via disease-related genome screening. Growing lines of evidence indicate that axonal transport disruption contributes to a broad spectrum of NDDs. Presynaptic assembly and maturation are regulated at multiple levels and through redundant mechanisms that integrate biosynthesis, transport, and assembly of presynaptic building blocks (Emperador-Melero and Kaeser, 2020). It is thus challenging to determine whether defective axonal transport alone has a major pathogenic role or is just an epiphenomenon that may occur in a short time window. In this section, we summarize NDD-associated mutations in genes encoding transport machineries that result in a wide range of NDD phenotypes, including lissencephaly, ASD, mental retardation, ID, cognitive and motor impairment, complex cortical malformations, and infant-onset epilepsy (Table 1). Although some of these mutations impair MT stability, motor activity, or motor-cargo coupling, presynaptic assembly and maintenance have not been examined *in vitro* or *in vivo* nerve systems. One of the well-characterized models with identifiable phenotypes of defective axonal transport and presynaptic assembly is the ASD-linked mutation of KIF5 adaptor syntabulin for PTV transport (Xiong et al., 2021). These observations may direct future studies by testing the emerging hypothesis that defective axonal transport is one of the mechanisms contributing to synaptic pathology in NDDs (Badal and Puthanveetil, 2022; Lasser et al., 2018; Sleight et al., 2019).

Microtubules

MTs are composed of α - and β -tubulin heterodimers, which undergo a dynamic process of polymerization (growing state) and depolymerization (shrinking state). After neurite extension during early neurodevelopment, MT stabilization is essential for

axon specification and the polarity of developing neurons (Conde and Cáceres, 2009; Hoogenraad and Bradke, 2009). MTs control fundamental processes occurring during neurodevelopment, including intracellular transport, axon guidance, and synapse formation. Stabilized MTs can recruit kinesin-1 motors to initiate polarized trafficking of various organelles and cargos that are necessary for the formation of axons and synapses. Mutations in tubulin genes disturb MT stability leading to abnormalities in brain development commonly referred to as tubulinopathies, including lissencephaly (“smooth brain”), polymicrogyria (“excessive cerebral cortex folding and malformations of cortical layering”), and malformations of cortical development. Strikingly, ~300 mutations have been described in the genes encoding α - and β -tubulins, including *TUBA1A*, *TUBA1C*, *TUBA4A*, *TUBB1*, *TUBB2A*, *TUBB2B*, *TUBB3*, *TUBB4A*, *TUBB4B*, and *TUBB8*, from patients displaying severe brain malformations associated with ID and refractory childhood epilepsy (Fourel and Boscheron, 2020; Pham and Morrisette, 2019). These mutations are thought to disrupt MT dynamics by switching from growth to shrinkage (depolymerization), which disrupts axon growth, presynaptic cargo transport, and synaptogenesis (Fig. 3). Mutations in tubulin genes, such as *TUBB3*, not only affect MT stability but also reduce kinesin localization to MTs, thus disrupting axonal transport (Minoura et al., 2016; Niwa et al., 2013). Future studies using neurons differentiated from patient-derived induced pluripotent stem cells (iPSCs) will provide direct evidence of how these tubulin mutations affect presynaptic assembly.

MT modification

MAPs, +TIPs, and signaling proteins involved in posttranslational modifications play critical roles in MT nucleation, assembly, or stability. Mutations in these proteins were reported in patients with lissencephaly, ID, and ASD, resulting in MT destabilization and impaired axonal transport (Fig. 3). For example, *LIS1* is one of the first identified MT-related genes in type-I lissencephaly patients (Reiner et al., 1993). *LIS1* increases the MT-binding of dynein and activates dynein by relieving its autoinhibited form, thus facilitating retrograde transport (Htet et al., 2020; Karasmanis et al., 2023). *Lis1*-null mice die prenatally and *Lis1*^{+/-} mice display deficits in motor coordination and cognition, as well as severe brain abnormalities (Hirosune et al., 1998; Youn et al., 2009), while increased *LIS1* expression causes severe brain malformation (Bi et al., 2009). CAP-Gly domain-containing linker protein 1 (CLIP1) is localized at +TIP of growing MTs and regulates MT-based axonal transport in developing neurons by recruiting dynein to MTs through its interaction with *LIS1* (Coquelle et al., 2002). A mutation deleting *CLIP1* was identified in families of ID patients (Larti et al., 2015).

Kinesin motors

The kinesin-3 motor KIF1A mediates axonal transport of a large population of presynaptic cargos, including SVPs, matured SVs, DCVs, as well as some PTVs (Fig. 4 A). Whole-genome sequencing identified more than 100-point mutations in *KIF1A* with dominant and recessive inheritance from patients suffering from a broad spectrum of KIF1A-associated neurological

Table 1. **NDD-linked mutations in genes encoding axonal transport machineries**

Protein	Gene with mutation	Inheritance	Disease: Phenotypes	References
Microtubules				
α 1A-tubulin	<i>TUBA1A</i>	AD: Missense/insertion/deletion mutations	LIS3: Congenital microcephaly, mental retardation, no language development	Fallet-Bianco et al., 2014; Poirier et al., 2013
β 2A-tubulin Class IIa	<i>TUBB2A</i>	AD: Missense mutations	CDCBM5: Intellectual disability, hypotonia, developmental delay, epilepsy	Cushion et al., 2014; Rodan et al., 2017; Schmidt et al., 2021
β -tubulin Class I	<i>TUBB</i>	AD: Missense mutations	CDCBM6: Delayed psychomotor development and microcephaly	Breuss et al., 2012
β 2B-tubulin Class IIb	<i>TUBB2B</i>	AD: Missense mutations	CDCBM7: Microcephaly, mental retardation, severe neuromotor impairment, no visual contact, infantile seizures	Cederquist et al., 2012; Laquerriere et al., 2016
β 3-tubulin Class III	<i>TUBB3</i>	AD: Missense mutations	CDCBM1: Mental retardation, strabismus, axial hypotonia, and spasticity	Fallet-Bianco et al., 2014; Poirier et al., 2010
β 6-tubulin Class V	<i>TUBB6</i>	AD: Missense mutations	FPVEPD: Bilateral ptosis and facial palsy, severe rhinophonia aperta with speech articulation defects	Fazeli et al., 2017
γ 1-tubulin	<i>TUBG1</i>	AD: Missense mutations	CDCBM4: Complex cortical malformations, intellectual disability	Poirier et al., 2013
Motor proteins				
Kinesin-1	<i>KIF5A</i>	AD: Missense mutations in tail domain	NEIMY: Myoclonic seizures, lack of developmental progress	Duis et al., 2016; Rydzanicz et al., 2017
		AD: Missense mutations in motor/stalk/tail domain	SPG 10: Limb spasticity and weakness, sensorimotor polyneuropathy, cognitive impairment	de Boer et al., 2021; de Souza et al., 2017; Méreaux et al., 2022
		AD: Missense mutations in stalk domain	CMT2: Chronic axonal motor and sensory polyneuropathy	de Boer et al., 2021
	<i>KIF5B</i>	AR: Missense mutations	Developmental and speech delay	Chang et al., 2016
	<i>KIF5C</i>	AD: Missense mutations in motor domain	CDCBM2: Microcephaly, developed clonic seizures, severe intellectual disability	de Ligt et al., 2012; Poirier et al., 2013
Kinesin-2	<i>KIF3B</i>	AD: Missense mutations in motor domain	SZ: Cognitive impairment, delusions, hallucinations, disorganized speech and movements	Alsabban et al., 2020
Kinesin-3	<i>KIF1A</i>	AD: Missense mutations in motor domain	NESCAVS: Global developmental delay, intellectual disabilities, seizures	Lee et al., 2015; Ohba et al., 2015
		AD: Missense mutations in motor domain	HSES: Severe brain edema and atrophy, developmental delay, peripheral neuropathy, autonomic dysfunction	Isobe et al., 2022
		AR: Truncating mutation	HSN2C: Early onset of hereditary sensory neuropathy, distal muscle weakness, slowed speech development	Rivière et al., 2011
		AD/AR: Missense mutations in motor domain	SPG30: Early childhood onset unsteady spastic gait, hyperreflexia of the lower limbs, learning disabilities	Citterio et al., 2015; Klebe et al., 2012; Nemani et al., 2020; Pennings et al., 2020
	<i>KIF1Bβ</i>	AD: Missense mutations in motor domain	CMT2A: Chronic axonal motor and sensory polyneuropathy	Xu et al., 2018; Zhao et al., 2001
Dynein	<i>DYNC1H1</i>	AD: Missense mutations in motor/tail domain	CDCBM13: Global developmental delay, intellectual disability, seizures	Poirier et al., 2013; Vissers et al., 2010; Willemssen et al., 2012
		AD: Missense mutations in tail domain	SMALED1: Early childhood onset of muscle weakness and atrophy	Harms et al., 2012; Tsurusaki et al., 2012
Myosin V	<i>MYO5A</i>	AR: Nonsense or truncating mutation	Hindbrain malformation and developmental delay	Chang et al., 2016

Table 1. NDD-linked mutations in genes encoding axonal transport machineries (Continued)

Protein	Gene with mutation	Inheritance	Disease: Phenotypes	References
Motor adaptors and regulatory proteins				
Kinesin-binding protein	<i>KIF1BP/KBP</i>	AR: Nonsense mutation	GOSHS: Intellectual disability, microcephaly	Brooks et al., 2005; Drévilion et al., 2013
		AR: Truncating mutations	Polymicrogyria: Microcephaly	Valence et al., 2013
Bicaudal D2	<i>BICD2</i>	AD: Missense mutations	SMALED2A: Early childhood onset of muscle weakness and atrophy	Neveling et al., 2013; Peeters et al., 2013
		AD: Missense mutations	SMALED2B: Decreased fetal movements, severe hypotonia, muscle atrophy, and respiratory insufficiency after birth	Koboldt et al., 2018; Ravenscroft et al., 2016; Storbeck et al., 2017
Lissencephaly 1	<i>PAFAH1B1</i>	AD: Missense or truncating mutations	LIS: Developmental delay, early onset of seizures	Reiner et al., 1993; Saillour et al., 2009
NudE neurodevelopment protein 1	<i>NDE1</i>	AR: Truncating or nonsense mutations	LIS4: Severe microcephaly, mental retardation, early-onset epilepsy	Abdel-Hamid et al., 2019; Alkuraya et al., 2011
		AR: Nonsense mutation or intragenic deletion	MHAC: Microcephaly, motor and mental retardation	Abdel-Hamid et al., 2019; Guven et al., 2012
Syntabulin	<i>SYBU</i>	N/A: Missense mutation	Autism: Delayed or absent language development, learning disability, repetitive speech or motor behaviors, social deficits, seizure	Herman et al., 2016; Xiong et al., 2021
Disrupted in schizophrenia 1	<i>DISC1</i>	N/A: Missense mutation	SZ9: Cognitive impairment, delusions, hallucinations, disorganized speech and movements	Schumacher et al., 2009; Song et al., 2008
FMRP	<i>FMR1</i>	XLD: Missense and truncating mutations, unstable expanded CCG repeat	FXS: Impaired intellectual development, autistic traits, distinct facial features, and seizures	De Boule et al., 1993; Grønskov et al., 2011; Kremer et al., 1991
CLIPs	<i>CLIP1</i>	AR	ARID: Intellectual disability	Larti et al., 2015

NDD-linked genetic mutations in genes encoding the axonal transport machinery, along with their inheritance patterns and disease phenotypes. Inheritance: AD, autosomal dominant; AR, autosomal recessive; N/A, not applicable; XLD, X-linked dominant; ARID, autosomal recessive intellectual disability; CDCBM1-13, complex cortical dysplasia with other brain malformations-1-13; CMT2, Charcot-Marie-Tooth disease 2; FPVEPD, facial palsy with ptosis and velopharyngeal dysfunction; FXS, fragile X syndrome; GOSHS, Goldberg-Shprintzen syndrome; HSES, hemorrhagic shock and encephalopathy syndrome; HSN2C, hereditary sensory neuropathy type IIC; IAHS, infantile-onset ascending hereditary spastic paralysis; LIS, lissencephaly; LIS3, lissencephaly 3; LIS4, lissencephaly 4; MHAC, microhydranencephaly; NEIMY, neonatal intractable myoclonus; NESCAVS, neurodegeneration and spasticity with or without cerebellar atrophy or cortical visual impairment syndrome; SCZD, schizophrenia; SMALED1, lower extremity-predominant spinal muscular atrophy-1; SMALED2A, childhood-onset lower extremity-predominant spinal muscular atrophy-2A; SMALED2B, prenatal-onset lower extremity-predominant spinal muscular atrophy-2B; SPG10, spastic paraplegia type 10; SPG30, spastic paraplegia type 30.

disorder (KAND) (see <https://Kifla.org>) (Boyle et al., 2021). *KIFIA* autosomal dominant mutations cause moderate to severe developmental delay with ID and cerebellar atrophy, while recessive mutations lead to progressive spastic paraplegia and hereditary sensory neuropathy. Most variants in *KIFIA* locate in the motor domain with loss-of-function mutations and a few gain-of-function mutations (Chiba et al., 2023; Nair et al., 2023). Some *KIFIA* variants (Thr99Met, Glu239Lys, and Pro305Leu) disrupt motor activity in a dominant-negative manner, impeding axonal transport and accumulating SVs in the somadendrites with reduction in presynapses (Fig. 4 B) (Anazawa et al., 2022; Morikawa et al., 2022). Other *KIFIA* mutations (Ala255Val, Val8Met, and Arg350Gly) disrupt its autoinhibition, leading to abnormally hyperactive motors and overtransport of SVs to axon tips but disturb the proper distribution of SVs to *en passant* synapses in *C. elegans* (Fig. 4 C) (Chiba et al., 2019). Patients carrying Arg13His and Asn222His *KIFIA* mutations are at a high

risk of ASD, characterized by moderate to severe deficits in social interaction and communication (Huang et al., 2021; Kurihara et al., 2020). Two heterozygous mutations in *KIF1B* (Gln98Leu and Tyr1087Cys) were identified in patients with Charcot-Marie-Tooth disease type 2A1 (CMT2A1) presenting with childhood-onset motor retardation (Zhao et al., 2001). The Gln98Leu variant resides in the conserved ATP-binding site and significantly reduces ATPase activity, resulting in perinuclear accumulation of mutant *KIF1B*. The Tyr1087Cys variant decreases *KIF1B* cargo binding capacity and impairs the axonal transport of insulin-like growth factor 1 receptor, which is critical for neuronal survival and axonal development (Xu et al., 2018).

For the kinesin-1 family, numerous missense *KIF5A* mutations located in the motor and stalk domains have been linked to spastic paraplegia type 10 (SPG10), a genetic neurodevelopmental disorder (Carosi et al., 2015; Crimella et al., 2012;

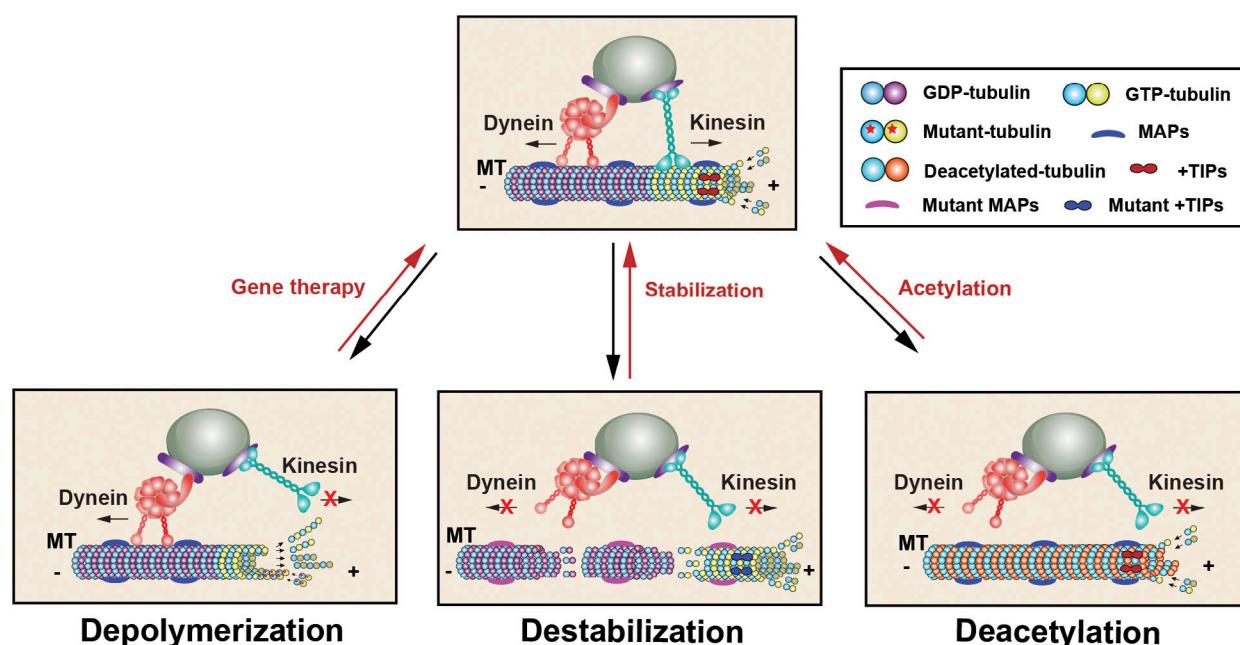


Figure 3. NDD-linked mutations in MTs. MTs are hollow tubes that are composed of α - and β -tubulin heterodimers, which undergo dynamic cycles of growth (polymerization) and shrinkage (depolymerization). Newly incorporated tubulin is bound to guanosine triphosphate (GTP) that gets rapidly hydrolyzed upon polymerization, generating guanosine diphosphate (GDP)-bound tubulin along the MT lattice. Hundreds of mutations in genes encoding tubulin were reported in patients presenting with NDDs. These mutations were thought to disrupt MT dynamics via switching from growth to shrinkage (depolymerization), which disrupts axon growth, presynaptic cargo transport, and synaptogenesis. MT dynamics are also regulated by MAPs and +TIPs. Mutations in these proteins were reported in patients with NDDs, resulting in MT destabilization and impaired axonal transport. MT-stabilizing agents have shown some beneficial effects in ameliorating neurological and behavioral deficits in some models of NDDs. The C-terminal tail of α -tubulin undergoes posttranslational modifications such as acetylation, which facilitates the recruitment of motor proteins to MTs. Decreased α -tubulin acetylation and increased levels of tubulin-specific histone deacetylase 6 were observed in certain NDD-linked models. Treatment with HDAC6 inhibitor Tubastatin A is thought to counteract MT defects and restore MT-based cargo trafficking.

Méreaux et al., 2022). These KIF5A mutants show abnormal motor ATPase activity and perturbed axonal transport. Three *KIF5A* *de novo* stop-loss frameshift variants were reported in patients suffering from severe infantile-onset myoclonic seizures and early developmental arrest (Duis et al., 2016; Rydzanicz et al., 2017). These mutations either cause truncation (921delC) or abnormal elongation (2854delC and 2934delG) of the *KIF5A* C-terminus. A whole exome sequencing study revealed a homozygous *KIF5B* variant (His751Arg) in a family with brain malformation and ID (Charng et al., 2016). A heterozygous variant in the *KIF5C* motor domain (Glu237Lys) was reported in patients with severe ID (de Ligt et al., 2012; Poirier et al., 2013).

The kinesin-2 motor KIF3 is one of the most abundantly expressed KIFs in the nervous system (Kondo et al., 1994). KIF3 is a heterotrimer containing two distinct heavy chains, KIF3A and KIF3B, and one light chain, KAP3. KIF3 plays a role in neurite elongation and branching by transporting a variety of organelles, including fodrin-associated vesicles and collapsin response mediator protein 2 (CRMP2)-containing vesicles (Takeda et al., 2000; Yoshihara et al., 2021). A *KIF3B* nonsense mutation (Arg654Ter) was found in SZ patients (Alsabban et al., 2020). Neurite hyperbranching resulting from impaired transport of CRMP2-containing vesicles is a causative mechanism of KIF3B-related SZ pathogenesis. KIF3 expression is reduced in brains of patients with SZ. *Kif3b*^{+/-} mutant mice display a range of

behavioral characteristics of SZ, and KIF3B (Arg654Ter) mutant protein fails to rescue the cellular phenotypes observed in *Kif3b*^{+/-} neurons (Yoshihara et al., 2021).

Dynein motors

Over 100 *de novo* heterozygous mutations in the *DYNC1H1* gene have been identified in patients with malformations of cortical development and/or developmental delay and ID (Ge et al., 2023; Poirier et al., 2013; Willemsen et al., 2012), as well as early childhood-onset motor retardation (Jamuar et al., 2014; Weedon et al., 2011), or a combination of these phenotypes. These variants are scattered throughout the dynein motor stem, motor, and neck domains and have a dominant-negative or gain-of-function effect (Amabile et al., 2020; Hoang et al., 2017). Functional analysis of 14 *DYNC1H1* patient mutations showed that most mutations result in impaired motility due to reduced dynein expression/stability (Lys671Glu) or compromised processivity (Arg1962Cys and His3822Pro) (Fig. 4 B). A combination of clinical, molecular, and cellular investigations will provide mechanistic insights into the relationships between axonal transport defects in *DYNC1H1* mutations and presynaptic assembly/maturation in NDDs.

Motor adaptors and effectors

Kinesin-binding protein (KBP, KIF1BP) directly binds to the motor domain of KIF1A and KIF1B. This binding inhibits motor-

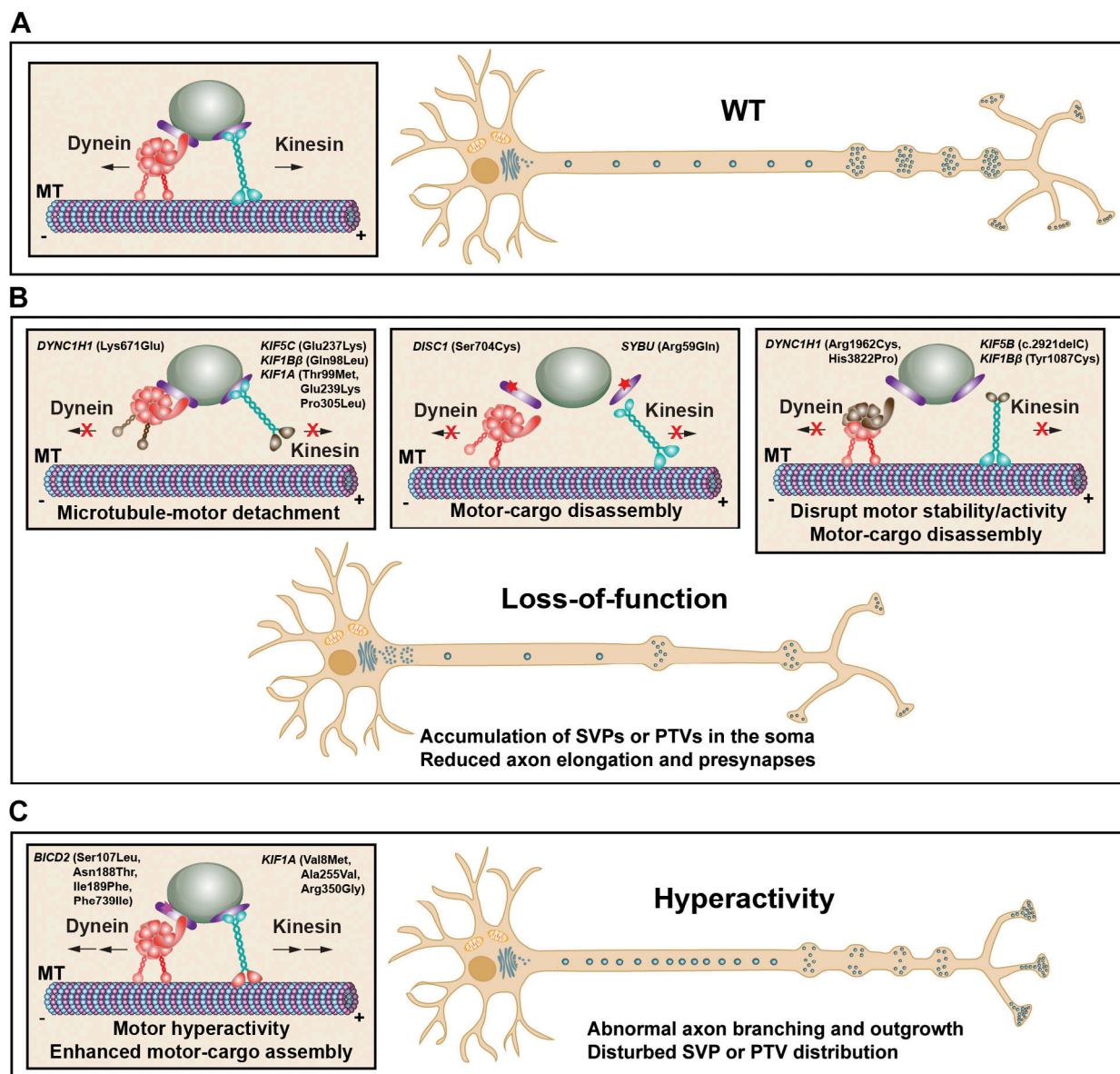


Figure 4. **NDD-linked mutations in motors and adaptors.** (A) Kinesin and dynein are MT-based and ATP-driven molecular motors that move cargos in the anterograde and retrograde directions, respectively. Proper axonal transport is essential for presynaptic assembly. (B) Loss-of-function mutations: growing numbers of NDD-linked variants in genes encoding motors and adaptors are loss-of-function mutations that lead to MT-motor detachment, motor-cargo disassembly, or disruption of motor stability and activity, therefore impairing axonal transport of presynaptic cargos, inducing the accumulation of presynaptic components in the somadendritic regions and reduction in axon elongation and presynaptic formation. (C) Hyperactive mutations: certain NDD-linked variants in dynein regulatory proteins BICD2 display hyperactive motor activity by enhancing formation of the dynein-dynactin motor complex. Some KIF1A variants disrupt its autoinhibition leading to abnormally hyperactive motors and over-transport of SVPs to axon tips, disturbing axon branching and outgrowth as well as the targeted distribution of presynaptic cargos along axons.

MT attachment and thus interferes with cargo transport (Atherton et al., 2020). While overexpressing KBP inhibits axonal transport of SVPs in cultured hippocampal neurons and in *C. elegans* sensory neurons (Kevenaar et al., 2016), depleting KBP results in abnormal KIF1A and SV accumulation in axonal growth cones. Mice lacking KBP die shortly after birth with smaller brains. In addition, KBP can alter MT dynamics by inhibiting MT-depolymerizing kinesins, such as KIF18A. Human genetic data shows that homozygous mutations in KBP are linked to Goldberg-Shprintzen syndrome (GOSHS) distinguished by ID,

microcephaly, and axonal neuropathy (Brooks et al., 2005; Valence et al., 2013; Salehpour et al., 2017).

Our previous studies provided direct evidence supporting an axonal transport mechanism underlying autism-like synaptic dysfunction and social behavioral traits. Syntabulin functions as a kinesin-1 adaptor driving PTV transport for synapse assembly and maintenance (Cai et al., 2007; Su et al., 2004). Syntabulin expression in mouse brains peaks during the first 2 wk after birth and then progressively declines with brain maturation (Xiong et al., 2021). The syntabulin gene (SYBU) is located within

the autism susceptibility loci 8q22–24 (Chen et al., 2017; Sánchez Delgado et al., 2014). A recent whole exome sequencing study identified an autism-linked *de novo* missense variant (Arg59Gln) in the human *SYBU* gene (Herman et al., 2016). These findings raise a fundamental question of a mechanistic link between defects in syntabulin-mediated PTV transport and autism-like phenotypes. We recently demonstrated striking phenotypes in *Sybu* conditional knockout (cKO) mice: (1) impaired transport of PTVs from the soma towards distal axons, (2) reduced density of presynapses and AZs in mouse brains, and (3) altered synaptic transmission and plasticity (Fig. 4 B). Intriguingly, *Sybu* cKO mice also exhibit core autism-like traits, including defective social recognition and communication, increased stereotypic behavior, and impaired spatial learning and memory (Xiong et al., 2021). Functional studies confirmed that the autism-linked missense variant (Arg59Gln) loses its adapter capacity for binding kinesin-1 motors and thus impairs anterograde axonal transport of PTVs. These phenotypes establish for the first time that human autism-linked deficits in axonal PTV transport contribute to autism-like behavioral abnormalities.

Disease-linked mutations in dynein regulatory proteins, including BICD2 and nuclear distribution protein E1 (NDE1), are also associated with a broad phenotypic spectrum from early-onset peripheral neuropathies to malformations of cortical development (Lipka et al., 2013). BICD2 binds to the dynein-dynactin motor complex through its coiled-coil domains and thus modulates dynein-driven cargo transport, such as mRNA and Rab6-positive secretory vesicles (Grigoriev et al., 2007; Sladewski et al., 2018). Dominant missense mutations in *BICD2* were linked to prenatal/childhood-onset spinal muscular atrophy (SMALED), a developmental disease of motor neurons affecting the lower limbs (Neveling et al., 2013; Rossor et al., 2015; Storbeck et al., 2017; Trimouille et al., 2018). Certain *BICD2* mutants (Ser107Leu, Asn188Thr, Ile189Phe, and Phe739Ile) display hyper-activated motors by enhancing dynein-dynactin motor complex formation (Fig. 4 C). However, increased retrograde transport blocks neurite outgrowth in rat hippocampal neurons (Huynh and Vale, 2017). These studies suggest that an imbalanced anterograde versus retrograde axonal transport may underlie NDDs.

The fragile X mental retardation protein (FMRP) is an mRNA-binding protein involved in the transport, localization, and translational regulation of a subset of dendritic mRNAs (Grossman et al., 2006); its loss is associated with ID and ASD (O'Donnell and Warren, 2002). FMRP and its homologs, FXRIP and FXR2P, are highly expressed in the developing brain and observed in the form of discrete granules (fragile X granules) localized in axons and presynaptic terminals in a set of mouse brain regions (Christie et al., 2009). FMRP loss leads to cell-autonomous defects in presynaptic terminal formation in organotypic mouse hippocampal slices (Hanson and Madison, 2007). Interestingly, BICD2 colocalizes with FMRP transport particles and facilitates their bidirectional trafficking (Bianco et al., 2010), which may also involve kinesin-1 and dynein motors (Splinter et al., 2010). FMRP protein levels are reduced in neurons over-expressing disease variant *BICD2* (Lys730Met), which displays reduced FMRP puncta trafficking into processes leading to abnormal neuron morphogenesis (Bianco et al., 2010).

NDE1 and its ortholog NDEL1 work together with LIS1 to promote dynein motor activity (Garrott et al., 2022). Truncating mutations in *NDE1* were reported in patients with lissencephaly-4 (Alkuraya et al., 2011; Bakircioglu et al., 2011). As a DISC1 binding partner, NED1/NDEL1 may also play a role in the etiology of SZ (Burdick et al., 2008). Rare *NED1* mutations within exon 7 contribute to SZ susceptibility by affecting axonal outgrowth (Kimura et al., 2015). NDEL1, FEZ1, and LIS1 expression levels are significantly reduced in the hippocampus of SZ patients carrying *DISC1* polymorphisms (Ser704Cys) (Lipska et al., 2006). These genetic studies support the emerging concept that disruptions in presynaptic cargo transport are the earliest contributors to the pathogenesis of a broad spectrum of NDDs; therefore, restoration of these transport defects is an attractive therapeutic strategy.

Therapeutic restoration of defective axonal transport in NDDs

At present, significant attention is focused on three promising themes: (1) stabilizing MTs to restore trafficking tracks; (2) targeting signaling pathways to modify transport machinery; and (3) gene-based editing to correct mutations in tubulin, motors, and adaptors.

MT stabilizers

A well-stabilized MT network constitutes a base for efficient axonal transport. Alterations in MT dynamics are one of the major causative mechanisms for many NDDs. MT-stabilizing agents have shown some beneficial effects on ameliorating neurological and behavioral deficits in various models of NDDs, including ID, ASD, SZ, and epilepsy (Fig. 3) (Bonini et al., 2017; Gambino et al., 2022; Liaci et al., 2021). For example, Epothilone D (EpoD), a taxol-related compound that interacts with tubulin to stabilize MTs, ameliorates synaptic function and behavior in mouse models of neuropathy and SZ (Andrieux et al., 2006; Brunden et al., 2010). At nanomolar concentrations, EpoD improves MT density and axonal transport, reduces axonal dystrophy, and enhances cognitive performance (Zhang et al., 2012). MT stabilization can also be achieved by targeting MT-regulating proteins. Calpain inhibitors that protect LIS1 from proteolysis can recover retrograde transport and improve behavioral performance in *LIS1*^{+/−} mice (Toba et al., 2013; Yamada et al., 2009). Alterations in tubulin posttranslational modifications have been reported in certain forms of NDDs (Moutin et al., 2021). For example, Rett Syndrome (RTT), a severe NDD with ID, autistic features, and motor dysfunction, is caused by loss-of-function mutations in the X-linked methyl-CpG-binding protein 2 (MECP2). Decreased acetylated α -tubulin levels, but increased tubulin-specific histone deacetylase 6 (HDAC6) levels, were observed in *Mecp2*-deficient cells (Gold et al., 2015). Treatment with the HDAC6 inhibitor Tubastatin A can counteract MT defects and thus restore the recruitment of kinesin-1 and dynein motors to promote MT-based cargo trafficking. As promising results are emerging in animal models and clinical trials, MT-targeted interventions represent an attractive therapeutic opportunity.

Targeting signaling pathways

NDD-linked mutations in genes encoding motors and adaptors also contribute to altered axonal transport. Therefore, the

signaling modulation of these motors or adaptors is another therapeutic approach to restore axonal transport. Several protein kinases that directly phosphorylate motors and adaptors are suggested as potential targets. For example, GSK3 β , involved in regulation of both kinesin-1 and dynein-driven axonal transport (Du et al., 2010; Gao et al., 2015), was reported to be upregulated in a subset of NDDs. Increased GSK3 β activity appeared to disrupt axonal transport through the dissociation of motors and their cargos via phosphorylating KLC and DIC, respectively (Banerjee et al., 2021; Dolma et al., 2014). In addition, treatment with lithium or GSK3 β inhibitors suppress GSK3 β activity and thus corrects behavioral phenotypes in animal models of NDDs, including ID, ASD, SZ, and epilepsy (Fuchs et al., 2015; Guo et al., 2012; Mao et al., 2009). In RTT, BDNF signaling is disrupted through an HTT-mediated transport mechanism. Surprisingly, promoting HTT-Ser421 phosphorylation by FK506, a calcineurin inhibitor, restores axonal transport of BDNF-carrying SEs and thus improves behavioral phenotypes and survival of *Mecp2* knockout mice (Ehinger et al., 2020). These studies suggest that restoring axonal transport by targeting signaling pathways is an alternative approach, although off-target effects and crosstalk of signaling cascades need to be considered.

Gene therapy

Thousands of genetic mutations have been associated with distinct types of NDDs. Given that the exact mechanism, timing, and progression of the molecular pathology are largely unknown, 90% of rare NDDs do not currently have an approved treatment. Gene-based editing opens a new avenue for the treatment of NDDs through expression of exogenous or suppression of endogenous genes. Gene therapy has been recently shown to be effective in various animal models of NDDs, such as ASD and epilepsy (Megagiannis et al., 2022; Ozlu et al., 2021; Turner et al., 2021), with several strategies moving toward clinical trials. We previously showed that axonal retrograde transport could be rescued via AAV9-based gene delivery of dynein adaptor Snapin, which reduces disease progression in Amyotrophic Lateral Sclerosis (ALS) mice model (Xie et al., 2015). Recent technological innovations, including improved therapeutic delivery of genetic material and the development of *in vivo* CRISPR-based gene editing, will further improve the feasibility of personalized gene therapy that corrects causative gene mutations to reverse defective axonal transport in NDDs.

Conclusions and perspectives

NDDs are recognized as one class of “synaptic disorders” where alterations in synaptic structures and functions impair both local and global brain connectivity and information processing. Proper synaptic transmission requires seamless integration of biogenesis, sorting, transport, and assembly of presynaptic components, and maintenance and remodeling of synaptic structures. While synapse development is regulated in multiple steps, the targeted delivery of presynaptic cargos is vital to building and maintaining functional synapses, which requires intricate mechanisms to orchestrate bidirectional transport of

various cargos between cell bodies and axon terminals. Recent studies have started to uncover presynaptic mechanisms underlying NDD-linked axonal transport defects. Mutations in genes encoding the axonal transport machinery disturb axonal trafficking in early developmental stages contributing to “synaptopathies,” one of the predominant mechanisms underlying NDDs. A particular area of future investigations will be the molecular compositions and identity of various presynaptic cargos: specifically, (1) how a unique presynaptic cargo can be sorted and packaged in the soma and loaded by a specific set of transport motors and adaptors, (2) how motors initiate and terminate their transport, (3) how motor activity is controlled by local cues within the axon and how motors unload cargos with high precision at thousands of *en passant* boutons and terminal presynapses, (4) whether multiple CAZ and SV proteins package into one transport cargo or cluster together for cotransport, and (5) whether all CAZ components arrive at nascent synapses simultaneously or sequentially. Addressing these fundamental questions will continue to build a more coherent view of mechanisms that maintain synaptic assembly, maturation, and remodeling during brain development and throughout life. Although genetic screenings have identified a growing list of NDD-linked mutations in genes encoding the transport machinery, pathological mechanisms related to these disease variants are rarely studied. As we learn more about the specific interactions among MTs, motors, adaptors, and cargos being transported, the pathobiology induced by these NDD-linked mutations may become clearer. Future studies using advanced single-molecule live imaging and *in vivo* approaches, combined with high-throughput genomics and proteomics, will provide new insights into NDD-linked causative mechanisms underlying axon transport defects of presynaptic cargos during neurodevelopment. Knowledge from human iPSC-derived models, along with gene-editing approaches, could have significant impact on the development of potential therapeutic restoration of defective axonal transport for currently incurable NDDs.

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