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PATHOLOGIES OF AXONAL TRANSPORT IN NEURODEGENERATIVE DISEASES

Xin-An Liu,
Valerio Rizzo,
Sathyanarayanan V. Puthanveettil*

Department of Neuroscience,
The Scripps Research Institute,
Scripps Florida, 130 Scripps Way. Jupiter,
Fl-33458, United States of America

Abstract

Gene products such as organelles, proteins and RNAs are actively transported to synaptic terminals for the remodeling of pre-existing neuronal connections and formation of new ones. Proteins described as molecular motors mediate this transport and utilize specialized cytoskeletal proteins that function as molecular tracks for the motor based transport of cargos. Molecular motors such as kinesins and dynein's move along microtubule tracks formed by tubulins whereas myosin motors utilize tracks formed by actin. Deficits in active transport of gene products have been implicated in a number of neurological disorders. We describe such disorders collectively as "transportopathies". Here we review current knowledge of critical components of active transport and their relevance to neurodegenerative diseases.

Keywords

• Axonal transport • Neurodegenerative diseases

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Introduction

Neurons are highly polarized cells characterized by their unique morphology and compartmental specialization. Compartments such as cell body, axons, dendrites and synapses possess a unique stoichiometry of various gene products for carrying out specific biochemical functions. Synapses that connect two neurons are dynamic and mediate intercellular communication between neurons in the circuitry. Gene products such as RNA, proteins and organelles fundamental for neuronal survival, morphogenesis, function and plasticity are synthesized in the cell body and are transported through axons and delivered to synapses. For example, organelles such as mitochondria and synaptic vesicles, proteins such as ion channels and neurotropic factor receptors, and RNAs such as CaMKII and Arc are actively transported to synaptic terminals [1]. Most of the proteins necessary for the axon and synaptic terminals must be synthesized in the cell body and then transported down the axon [1]. An active transport mechanism is necessary not only to supply newly synthesized materials from soma; but also to transport of damaged organelles from the axon terminal to the cell body [2-4].

Active transport of gene products is a complex process and requires three critical components such as cytoskeletal tracks (formed by microtubules, MTs, and actin), molecular motors (kinesin, dynein, and myosin), and various cargos transported in neurons (Figure 1). Microtubules and neurofilaments are the fundamental longitudinal cytoskeletal filament in the axon and dendrites of neurons, while actin filaments are generally considered to form the major cytoskeletal architecture in the synaptic regions, such as presynaptic terminals and postsynaptic spines. Apart from motors, tracks and cargos, active transport also requires several scaffolding proteins as adaptors which facilitate transport of specific cargos [5-9].

1. Molecular motors in neuronal tracks

Microtubules (MT) are key determinants of neuronal polarity [10-13] and form the transport highways for cargo trafficking in axons and dendrites in neurons [6]. MT are formed from the association of dimers of α-tubulin and β-tubulin into protofilaments. The head to tail association of α- β heterodimers imparts polarity, β monomer pointing towards the plus end (faster growing end), α monomers are pointing towards minus (or slow growing end). Protein such as γ tubulin binds to the minus ends [14] whereas end binding proteins (EB) bind to the plus end of MT [15,16] and stabilize the ends. Several proteins such as microtubule associated proteins (MAP) binding to MT regulate their stability and interaction with motors [17-21].

A. Kinesin- and dynein-driven transports on microtubules

Active transport of gene products is mediated by three classes of molecular motor proteins: kinesin, dynein and myosin. Anterograde axonal transport (from cell body to synaptic terminals) of cargos is mediated by kinesin proteins, whereas retrograde transport (from synaptic terminals to cell body) use the dynein-dynactin system. Both kinesins and dyneins move along microtubules and require ATP for motility [22]. Kinesins were originally identified by Brady [23] and Vale et al., [24], and were found to be composed of two heavy chains (KHC) and two light chains (KLC). To date, more than 45 kinesins, which are classified into 14 classes, have been identified in mammals [1,25,26]. Kinesins mediate a number of important processes such as cell division,

*E-mail: sputhanv@scripps.edu

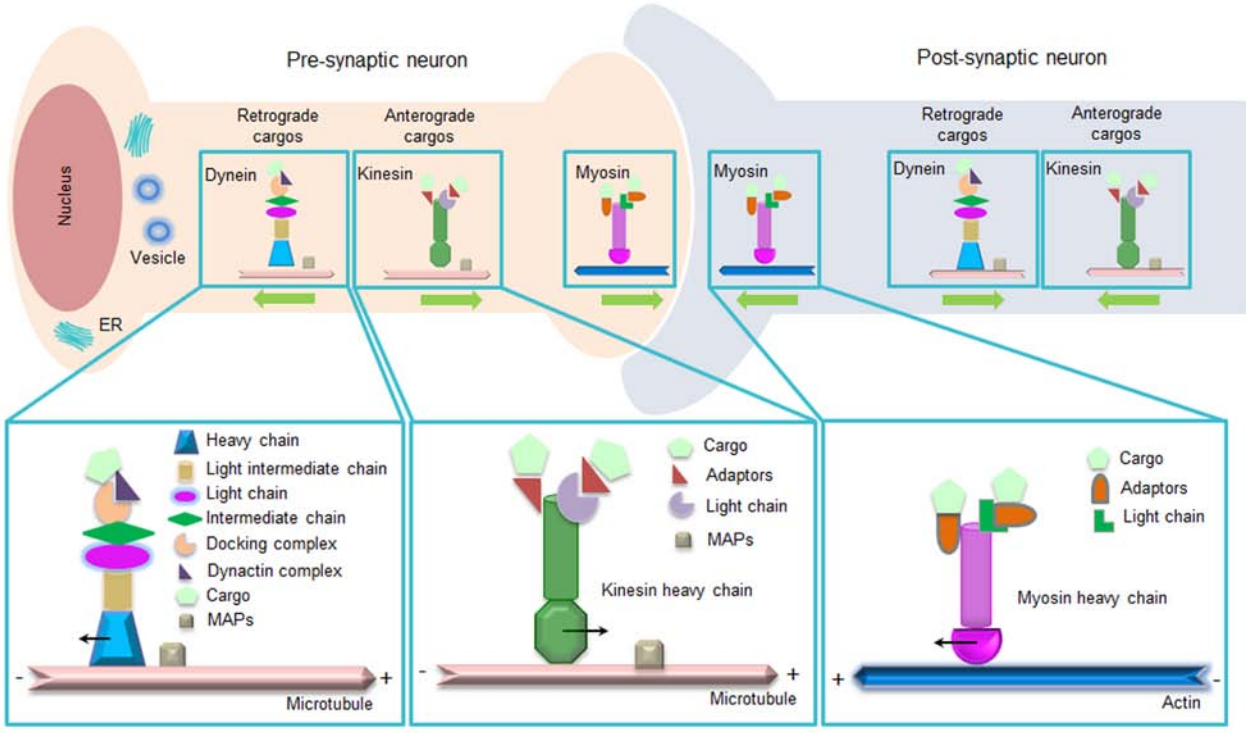

Figure 1. Components of the active transport machinery. Microtubule and actin forms the tracks for active transport. Kinesin, dynein and myosin are the ATP dependent molecular motors that transport various cargos. Pre and postsynaptic neurons and direction of transport and components of the transport machinery are shown.

differentiation and development of the nervous system by transporting different gene products such as proteins, organelles and RNA (reviewed in [1,27-32]). Kinesin heavy chain, ApKHC1 and light chain ApKLC2 are upregulated during the formation of long-term memory in marine snail Aplysia. The coordinated regulation of axonal transport in pre and post-synaptic neurons has been identified to play a critical mediator of long-term learning-related plasticity [33].

Dynein protein was originally identified from cilia by Gibbons and Rowe [34] and from the nervous system by Burns and Pollard [35]. Dynein is a large complex and consists of two dynein heavy chains (DHC), two dynein intermediate chains (DIC), four dynein light intermediate chains (DLIC), and various dynein light chains (DLC) and move towards the minus end of MTs (reviewed in [22,29,30,36,37]). Dynein requires dynactin, which increases the motor efficiency of dynein and cross-links dynein for retrograde transport [38,39]. Like kinesins, dyneins are also involved in a number of functions such as cell division, retrograde transport of organelles and vesicles, and are important in the development of the nervous system (reviewed in [22,28,36,40,41]).

B. Myosin-driven transport on actin

Actin exists as globular monomer called G-actin and filamentous polymer called F-actin. In the presence of Mg^{2+}, K^{+} or Na^{+} ions G-actin assembles into long, helical F-actin polymers. Actin filaments are generally considered to function as mediators of synapse dynamics and plasticity, and the predominant cytoskeletal element in dendritic spines [42]. Like microtubule tracks, actin filaments also have a polarity: the barbed end (the growing end) points to the plasma membrane in the presynaptic and postsynaptic regions. Actin organization and dynamics is important for neuronal morphology and function (reviewed in [43,44]). As in the case of microtubule binding proteins regulating MT, several actin binding proteins are known and regulate actin cytoskeleton [45].

The presence of myosin in the brain was discovered in the late 1960s [46,47]. Myosin superfamily motor proteins are classified into 18 classes and use the energy of ATP hydrolysis to generate force for movement along actin (reviewed in [48-52]. Myosins function as monomers [53], dimers [54] or oligomers [55] for cargo transport in different organs or cell types based on their different kinetic properties, structural adaptations and functional properties. In general, myosins are composed of three domains: motor domain or head, which is the most conserved, usually located at the amino terminus and which binds ATP and actin [56]; the head is mechanically connected to a second domain consisting of an extended α-helical 'neck', which contains numerous IQ motifs that bind light chains of calmodulin family. The C-terminal tail of unconventional myosins can include coiled-coil motifs for dimerization and a terminal globular cargo-binding domain, as well as domains that bind to membranes or to cargo receptors mediating specific interactions

with vesicular or non-vesicular cargo [57]. The general myosin head-coiled coil-cargo binding domain architecture of many unconventional myosins facilitate the walking motions of the dimer along the actin filaments that result from vesicles or organelles attached at the cargo binding domain of the dimer and the ATPase hydrolysis [58].

Myosins contribute to three types of transport processes in neurons: recycling of receptors or other membrane components; dynamic tethering of vesicular components; and transport or tethering of protein translational machinery including mRNA. Myosin Vb transports recycling endosomes into the dendritic spines of hippocampal neurons in response to strong spine stimulation. These endosomes then serve as a source of AMPA receptors for insertion into the postsynaptic membrane to drive LTP [59]. Myosin Va serves as a point-to-point transporter to move tubules of ER into the dendritic spines of cerebellar Purkinje neurons, which is required for the local Ca^{2+} transients that drive LTD [60]. Myosin VI is the only known retrograde myosin, which walks toward the minus end of the actin filament and the dimerization of which appears to occur upon cargo binding [61]. Myosin Vb (MyoVb), a Ca^{2+}-sensitive motor, conducts spine trafficking during long-term potentiation (LTP) of synaptic strength [59]. Myosin II, which is present presynaptically, is important for synaptic vesicle mobility at the Drosophila neuromuscular junction [62] and for memory storage in mouse [63,64].

C. Regulation of microtubule (MT) and actin dependent transport

Synaptic activity could play an important role in regulation of MT. It has been suggested that raising global electrical activity increases the number of MT invading dendritic spines in hippocampal cultures [65]. MT are generally considered to be the main tracks for transporting synaptic materials to and from synapses. Increased synaptic activity might reorganize microtubule to redirect the transport of synaptic proteins and organelles into spines [66]. Local regulation of microtubule stability and subsequent microtubule modifications might be the primary regulators of activity-induced synaptic changes [67,68]. Several post-translational modifications of microtubules that regulate its properties are known [69-75]. For example, Kinesin-1, which is abundant in axons, moves preferentially on acetylated microtubules [76], a post-translational modification of microtubules [77], instead of tyrosinated microtubules [78]. Microtubule modifications can be regulated by synaptic activity, including reduced motor protein mobility and cargo delivery into neurites [66].

Mammalian plus-end-tracking proteins (+TIP) localize to the ends of growing microtubules and regulate both the dynamic behavior of microtubules as well as the interactions of microtubules with other cellular components [16]. Mutations in the MT-associated protein Futsch, the fly homolog of microtubule-associated protein 1B (MAP1B), has been proved to disrupt the architecture and network of axonal MT that induce defects in axonal transport, causing progressive degeneration of neurons in the fly brain [79].

Actin cytoskeleton is also highly responsive to changes in electrical activity, which can be dynamically rearranged by depolarization [80]. In addition, actin polymerization is required for the maintenance of prolonged periods of synaptic activity during LTP [81]. Rho family proteins of GTPases have been shown to act as molecular switches that increase/decrease actin polymerization rates, crosslinking activities, or branch formation [82], which could be a cellular basis for impaired cognitive functions.

Apart from MT and actin cytoskeleton being covalently modified to regulate transport, molecular motors are also post-translationally modified. For example, kinesins are modified by phosphorylation and regulate its interaction with microtubules and cargos [83-85]. Active c-Jun N-terminal kinase (JNK) phosphorylates kinesin-1 heavy chains and inhibits kinesin-1 microtubule-binding activity [86]. The inflammatory cytokine tumor necrosis factor-alpha (TNF) stimulates phosphorylation of JNK and induces dissociation of KIF5B from tubulin in axons, it accordingly inhibits axonal transport of mitochondria and synaptophysin by reducing the mobile fraction [87]. JNK interacting proteins (JIP), which are scaffolding molecules for JNK signaling pathways, are illustrated to regulate Kinesin-1 mediated transport [88]: they activate Kinesin-1 in concert with FEZ1/UNC-76 [89]; release JIP-dependent cargo through activation of the JNK cascade, in turn inactivating Kinesin-1 [90]; and regulate the dynamics of neuronal microtubules by modulating phosphorylation's of MT-associated proteins (MAP) [91,92] and microtubule-destabilizing protein SCG10 [93]. The regulation of kinesin/cargo association through adaptor proteins is another major control point for regulating cargo-specific transport. Phosphorylation of huntingtin at S421 promotes recruitment of kinesin-1 to the dynactin complex on vesicles and MT and the following anterograde transport, which suggests that huntingtin phosphorylation can act as a molecular switch for anterograde/retrograde transport in neurons [94]. Actin and MT cytoskeleton also interact [95,96] and such interactions are important for axon guidance and specification [97,98].

2. Neuronal cargos

A wide variety of cargos such as organelles, cytoskeletal components, growth factors, trophic factors [99], synaptic vesicle precursors, neurotransmitter, signaling molecules, and mRNA etc., are actively transported from their sites of synthesis in the cell body through the axoplasm to intracellular target sites. Transported cargos can be mainly classified into three groups: proteins, RNA, and organelles. Specific sets of cargos are packaged and transported along axons to specific destinations for the establishment of neuronal connections and for the modifications of these connections during memory storage. Recognition, binding and unloading of cargos are important regulation mechanisms for neuronal traffic.

Proteins are transported in various membranous organelles and protein complexes, and mRNA are carried in large protein complexes [100]. RNA transport is an important and fundamental event for local protein synthesis, especially in neurons, while local protein synthesis is believed to contribute to synaptic plasticity that requires a rapid supply of new proteins to specific synaptic sites

in response to appropriate stimuli and may also participate in long-lasting changes in synaptic strength [101-108]. A number of transported protein components including synaptic proteins have been identified [28,33,109]. Kinesin 1 family KIF5 motors can directly bind to and transport large RNase-sensitive granules, known as messenger ribonucleoprotein (mRNP) complexes, which contain mRNA and at least 40 RNA binding proteins [110]. However it remains to be determined how, when, and what mRNA and proteins are assembled into these complexes and transported down to the dendrites.

3. Pathologies of axonal transport in neurodegenerative diseases - "transportopathies"

As illustrated above, molecular motors regulate several vital processes in neurons. Disruption of axonal transport is a hallmark and precipitating factor of a wide variety of neurodegenerative diseases. Table 1 lists the involvement of active transport machinery in these disorders. They involve different components of the transport machinery and affect different regions of the brain.

Here we discuss three different causes of axonal transport defects: gene mutation, oxidative stress and post-translational modifications of the transport machinery. We specifically focus on Alzheimer's disease (AD), frontotemporal dementia (FTD) and amyotrophic lateral sclerosis (ALS) and briefly describe transport defects in other nervous system diseases with axonal pathologies.

3a. Gene mutations and axonal transport defects

Mutations in motor proteins and other defects in intracellular transport have been described to cause neuropathologies [111]. Gene mutations that disrupt axonal transport are gaining attention as a cause of neuronal dysfunction in a variety of neurodegenerative motor neuron diseases in humans. Mutations in motor proteins, such as kinesins or dyneins, cause acute organelle jams in axons, preventing transport and recycling of synaptic metabolites. The *immaculate connections (imac)*, a *Drosophila* Kinesin-3, are selectively required in motoneurons for transport of many synaptogenic cargos. In *imac* embryos, motoneuron axons extend properly and are guided to and arrest on the appropriate muscle fibers, but synapses cannot form. Loss of *imac* leads to a severe reduction of synaptic vesicles (SV) at terminals and an increase of SV stranded in the cell body [32]. Active zone proteins are greatly reduced, synaptic vesicles are absent, and the nerve endings do not mature into rounded boutons [112], which also illustrates that axonal transport is critically required for forming synapses. In addition, Kinesin-1 mutants or mutations in proteins associated with Kinesin-1 motors including kinesin light chain (KLC), the JNK scaffolding adaptor [88,113] and its associated MAPKKK/MAPKK/JNK signaling complex, Liprin-alpha [114] and Unc-76 [115] develop an SV transport phenotype. Mutations in Kinesin-3 prevent synapse formation at the *Drosophila* neuromuscular junction although axon outgrowth and guidance are normal. The phenotype illustrates the selectivity of this Kinesin-3 motor for synaptogenesis [112].

In mammalian cells, KIF5B (Kinesin-1 family) and KIF1B (Kinesin-3 family) are reported to mediate transport of mitochondria. Proteins milton and miro form an essential protein complex that links kinesin to mitochondria for light chain-independent, anterograde transport to synapses. The amino-terminus variant of *Drosophila* milton, milton-C, inhibits kinesin binding to milton and thereby prevents kinesin recruitment to mitochondria [116].

In 2003, it was reported that missense point mutations in the cytoplasmic dynein heavy chain result in late onset and progressive motor neuron degeneration (MND) in two lines of mice called Legs at odd angles (Loa/+) and Cramping 1 (Cra1/+) [117], which was also proved by Vallee et al. [118], while some other studies provide evidence that the primary pathology in Cra1/+ animals may be an early onset, non-progressive synaptic dysfunction that affects the neuromuscular junction [119] without motor neuron involvement [120]. A point mutation in dynein heavy chain gene leads to striatal function deficit and striatal atrophy, which supports a role for dynein dysfunction in the pathogenesis of neurodegenerative disorders of the basal ganglia, such as Perry syndrome and Huntington's disease (HD) [121].

Dynactin-1 mRNA is indicated to be down regulated in degenerating spinal motor neurons of autopsied patients with sporadic ALS [122]; KIF1A, was reported to be mutated in hereditary sensory and autonomic neuropathy type 2 (HSANII), which is a rare autosomal-recessive disorder characterized by peripheral nerve degeneration resulting in a severe distal sensory loss [123], the causative mutation in the motor domain of KIF1A is also implicated in hereditary spastic paraplegias (HSP) patients [124]. Mutations in the KIF5A gene can also be associated with adult onset of autosomal dominant hereditary spastic paraplegia (AD HSP) [125]. Mutations in the KIF7 gene were identified to cause modified microtubule stability and growth direction, which is an underlying disease mechanism contributing to *Joubert syndrome* (JBTS) [126]. De novo truncating mutation in Kinesin17 is associated with schizophrenia [127] and KIF21A mutation is involved in congenital fibrosis of the extra-ocular muscles type 1 and 3 [128,129]. Charcot-Marie-Tooth disease type 2A (CMT2A) patients contain a loss-of-function mutation in the motor domain of the KIF1B gene [130].

3b. Mitochondrial oxidative stress and axonal transport defects

Oxidative stress is regulated by the levels of reactive oxygen species (ROS) that includes superoxides, hydroxyl radical, and hydrogen peroxide. Oxidative stress, which induce mitochondrial injury, impairs axonal transport rates in mice [131,132] and would result in an accumulation of axonal constituents delivered by fast and slow axonal transport [133,134], disorders of synaptic transmission and synapse degeneration. Oxidative stress may also disrupt the MAP:tubulin ratio and thus result in disruption of neuronal intracellular transport [135]. Hirai et al. suggested that mitochondrial abnormalities might be part of the spectrum of chronic oxidative stress of AD [136]. Accumulation of mitochondrial DNA was found in the neurons vulnerable to death in AD and attributed it to a possible reduction in the number of microtubules,

Table 1. The neurodegenerative disorders and the involvement of active transport machineries.

Neurodegenerative diseases	Component of the transport machinery involved	References
Alzheimer (AD)	Tau and Aβ facilitate cargo release and disturbed neuronal trafficking	[176,189]
	PS1 Mutations increase KLC phosphorylation and cargo release	[190]
	Mitochondrial abnormalities lead to reduction in the number of microtubules	[136]
Huntington's disease (HD)	Mutant Htt causes defective anterograde mitochondrial movement	[259]
Amyotrophic lateral sclerosis (ALS)	Kinesin-associated protein 3 (KAP3) is sequestrated by misfolded SOD1 and results in axonal transport inhibition of ChAT	[210]
	Dynactin mutation in the p150 subunit	[154,216-219]
	Mutations in dynein-dynactin retrograde system protein genes	[222-224]
	KHC gene mutation	[262]
	Mislocalization and disruption of dynein function	[214]
Frontotemporal dementia (FTD)	Hyperphosphorylated tau deposition decrease binding of motor proteins to MT tracks	[167,168,176]
	Mutation of FUS, which is a DNA/RNA-binding protein involved in transport of mRNA molecules	[263]
Hereditary spastic paraplegias (HSP)	Mutations in the KIF5A in families with SPG10 reduce microtubule binding affinity	[240]
	SPG7 models exhibit impaired mitochondrial axonal transport	[241]
HSAN II	*FAM134B* mutations lead to KIF1A mutations	[123]
Charcot-Marie-Tooth (CMT2)	*DYNC1H1* mutation impairs dynein heavy chain 1 involved retrograde axonal transport	[264]
	Mfn2 mutation produces a severe mitochondrial transport disorder	[257]
	Mutation in kinesin 5A	[249]
	KIF1Bβ mutation	[130]
axonal CMT	Expression of mutant HSPB1 decreased acetylated α-tubulin abundance and induced axonal transport deficits	[251]
	Mutations in GDAP1 alter the interaction between mitochondria and the microtubule cytoskeleton and affect mitochondrial axonal transport	[252,253,255]
X-linked spinal and bulbar muscular atrophy (SBMA)	Androgen receptor gene mutations with enlargement of the CAG repeat form aggregates that alter axonal trafficking	[265-267]
Parkinson's disease (PD)	Mutation and phosphorylation of α-synuclein reduces its axonal transport	[268]
	Mutations of parkin, PINK1, and DJ-1 lead to damage to mitochondria and perturb transport of mitochondria through axons	[269,270]
	Inhibition of complex I of the electron transport chain decreases anterograde and increases retrograde axonal transport of membranous vesicles	[271]
Multiple sclerosis (MS)	Ca^{2+}, free radical production and mitochondrial dysfunction impair axonal transport	[272]
Spinal muscular atrophy (SMA)	*SMN1* mutation leads to reduced transport of specific mRNAs within motor neurons	[273,274]
polyglutamine disorder (polyQ)	Polyglutamine proteins interrupt axonal transport and affect enzymatic activities involved in FAT regulation	[275-277]
Prion diseases	Intracerebral prion lead to axonal transport impairments which involves Rab7-mediated cargo attachment to the dynein-dynactin pathway	[278]
Glaucoma	Mitochondrial dysfunction and axonal transport failure induce retinal ganglion cell death	[279]
Spinocerebellar ataxia type 5 (SCA5)	SCA5 mutant spectrin impair axonal transport and induce neurodegeneration	[280]
Traumatic brain injury (TBI)	Extensive axonal injury result in the interruption of axonal transport and long-term accumulation of proteins	[281]
Dystonia musculorum (dt)	Microtubule network perturbation lead to axonal transport defects	[282]
Tuberous sclerosis (TSC1) disease	kinesin-related gene *ATSV* is characterized as candidate genes for TSC1 disease locus on chromosome 9q34	[283]

which would result in diminished vesicular transport and mitochondrial turnover [136]. Reduction of mitochondrial superoxide significantly prevented the deficits in axonal transport rates in Tg2576 mice, indicating that ROS of mitochondrial origin are a key factor in transducing the impact of Aβ on neuronal physiology in AD mice model [137]. Axonal transport deficits and accumulation of depolarized mitochondria could be concurrent with axonal neuropathy and without increased reactive oxygen species production [138]. Mitochondrial dysfunction, such as altered Ca^{2+} homeostasis and increase in reactive oxygen species [139], have been reported in both in vitro and in vivo models of ALS [140]. Mitochondria accumulation was also shown in the axons of spinal motor neurons in sporadic ALS (SALS) patients, suggesting the deficit in mitochondria metabolism due to impaired axonal transport in ALS [141,142].

The autophagosomes are membraneous cargos that move bidirectionally along microtubules and are transported by kinesin and dynein/dynactin complex, which accumulate in motor neurons with altered axonal transport [143-144]. The dysfunction of autophagy-lysosome pathway that is responsible for recycling of intracellular contents, have been described to cause neurodegeneration [145,146]. Abnormal intraneuronal accumulation of autophagosomes occurs in AD [147,148], Parkinson's disease (PD) [149], HD [150,151], and in ALS patients [152] as well as the mutant dynein model (Loa mouse) [153] and the mutant dynactin-1 mouse model [154].

3c. Post translational changes of the transport machinery

3C1. Alzheimer's disease (AD)

Widespread synaptic and neuronal loss and the pathological accumulation of amyloid-beta peptide (Aβ) in senile plaques, as well as hyperphosphorylated tau in neurofibrillary tangles (NFT) are the pathological hallmarks of AD, the leading cause of dementia among the elderly [155]. Axonal transport deficits may represent an early step in AD pathogenesis because the reduced axonal transport was observed before the apparent AD hallmarks.

Tau, axonal transport and AD

Tau, a major microtubule-associated protein that plays an important role in the outgrowth of neuronal processes and the development of neuronal polarity, promotes microtubule assembly, stabilizes microtubules, and affects the dynamics of microtubules in neurons [156,157]. Tau is hyperphosphorylated, which loses its capability to bind with microtubules, accumulates in neurons, and forms paired helical filaments in AD [158]. It has been reported that Aβ, which is produced by putative intramembranous processing of β-amyloid precursor protein (APP) at the proposed active site of the γ-secretase/PS1 aspartyl protease, is a critical factor for hyperphosphorylation of tau in AD neurons [159], while increasing evidence suggests that hyperphosphorylated tau is critically involved in AD pathogenesis, particularly in impairing axonal transport of APP and subcellular organelles including mitochondria in neurons affected by AD [160-162]. Various intronic and exonic pathogenic mutations of *TAU* gene provided unequivocal proof that tau abnormalities alone are sufficient to cause neurodegeneration [163].

As kinesin and dynein motor proteins transport cellular cargoes toward opposite ends of microtubule tracks, which are abundantly decorated with microtubule-associated proteins (MAP) such as tau in neurons, long-distance trafficking uses mainly the axonal microtubule highway and tau does (de)stabilize this network. Therefore, it is no surprise that a deregulation of its expression and/or phosphorylation level can lead to defects in axonal transport such as found in the early stages of AD [164] or even at the later stages of the disease [165]. Tau expression in stably transfected CHO cells and differentiated neuroblastoma N2a cells dramatically alters the distribution of various organelles, including mitochondria and endoplasmic reticulum, known to be transported via microtubule-dependent motor proteins. These effects were caused by tau's binding to microtubules and slowing down intracellular transport by preferential impairment of plus-end–directed transport mediated by kinesin motor proteins [166]. Axonal transport defects have also been reproduced in wild-type tau transgenic mice [167] and in K369I mutant tau K3 mice [168]. Mice transgenic for human four-repeat tau [169,170] and neurofilament [171,172] have been suggested to indicate disturbed axonal transport. Transgenic (Tg) mice expressing the longest human tau isoform (T40) with R406W mutation developed retarded axonal transport, which indicate that R406W mutation causes reduced binding of the mutant tau to microtubules, resulting in slower axonal transport [173]. Tg mice expressing the FTDP-17 human P301L mutant tau cause neurodegeneration by disrupting axonal transport since impairments in axonal transport occurred earlier, whereas motor deficits subsequently developed [174]. Reduced axonal transport and increased excitotoxic retinal ganglion cell degeneration were also revealed in mice transgenic for human mutant P301S tau [175]. Dixit et al. suggested that kinesin was inhibited at about a tenth of the tau concentration that inhibited dynein; higher tau concentration at the synapse would facilitate cargo release, and the microtubule-binding domain of tau was sufficient to inhibit motor activity, which suggests tau can spatially regulate the balance of microtubule-dependent axonal transport in the neuron by locally modulating motor function [176]. On the other hand, kinesin-1 deficient mice ($KLC1^{-/-}$) revealed that axonal transport defects could initiate biochemical changes that induce activation of axonal c-jun N-terminal stress kinase pathways leading to abnormal tau hyperphosphorylation [177].

Several studies have suggested a critical role for tau in axonal transport and in AD [160,178-180]. In drosophila and mouse models of tauopathies reductions in axonal transport can exacerbate human tau protein hyperphosphorylation, formation of insoluble aggregates and tau-dependent neurodegeneration [181]. However, Yuan et al. showed that global axonal transport rates of slow and fast transport cargoes in axons are not significantly impaired when tau expression is eliminated or increased, which suggest that tau is not essential for axonal transport [182].

Although tau did not affect axonal transport under baseline untreated conditions, partial tau reduction can prevent Aβ-induced axonal transport defects in hAPP mice [160]. Thus, whether and how tau affects axonal transport and its physiological functions are still poorly understood.

Aβ, axonal transport and AD

APP is axonally transported by binding to the motor protein kinesin-1 on microtubules [183]. Reductions in microtubule-dependent transport may stimulate proteolytic processing of beta-amyloid precursor protein, resulting in the development of senile plaques and AD [184]. The axonal swellings and varicosities were found to contain abnormal accumulations of transport cargos, APP, and Aβ, and such transport deficits appear to enhance APP processing and local Aβ production. Additionally, it was reported that impairing axonal transport by reducing the dosage of a kinesin molecular motor protein enhanced the frequency of axonal defects and increased amyloid-beta peptide levels and amyloid deposition. In aged *APP/PS1* mice, axonal swellings as well as amyloid plaques, were found in dorsal funiculus, a region with strong *APP* expression in axonal processes. The observations that spheroids, the most prominent evidence for axonopathy, were immunoreactive with axonal markers such as APP, neurofilament subunits and ubiquitin, instead of tau or phosphorylated tau, add significant evidence to the assumption that toxic Aβ peptides play a role in the mediation of disturbed neuronal trafficking [185]. Early axonopathy and transport deficits in *APP*-transgenic mice, could be fostered by a reduction in the amount of the kinesin light-chain (KLC1) by crossing *APP*-transgenic with *KLC-1* knockout mice [184]. Hiruma has found that Aβ exerts its inhibitory effect on axonal transport via actin polymerization and aggregation in cultured rat hippocampal neurons [186]. Furthermore, Aβ could likely act through GSK3 to impair mitochondrial transport, and the impairment can be alleviated by PKA activation, without affecting actin polymerization and mitochondria membrane polarization [187].

Soluble oligomers of the amyloid-β peptide (AβO), recognized as the proximal neurotoxins in AD pathology, can induce disruption of organelle transport in primary hippocampal neurons by a mechanism that is initiated by NMDAR and mediated by GSK-3β leading to microtubule destabilization [188]. Real-time analysis of vesicle mobility in isolated axoplasms perfused with AβO, instead of unaggregated Aβ or fibrillar Aβ, showed bidirectional axonal transport inhibition as a consequence of endogenous casein kinase 2 (CK2) activation. Both AβO and CK2 treatment of axoplasm led to increased phosphorylation of kinesin-1 light chains and subsequent release of kinesin from its cargoes, which cause deficiencies in fast axonal transport in AD [189].

Other factors involved in transport defects observed in AD

Mutations in presenilin 1 (*PS1*), which is associated with early-onset familial Alzheimer's disease (FAD), have been implicated to be involved in kinesin-based axonal transport due to an interaction with glycogen synthase kinase 3β (GSK3β). The relative levels of GSK3β activity were increased either in the presence of mutant *PS1* or in the absence of *PS1*, leading to increased kinesin light chain phosphorylation, the release of kinesin-1 from membrane-bound organelles (MBO) and reduced fast anterograde axonal transport [190]. It is also reported that defects in anterograde fast axonal transport and motor neuron deficits underlie *PS-1*-mediated neurodegeneration in transgenic mice expressing familial AD linked mutant *PS-1* through a mechanism involving impairments in neurotrophin signaling and synaptic dysfunction [190-192].

The epsilon 4 allele (e4) of the human apolipoprotein E gene (*ApoE4*) constitutes an important genetic risk factor for AD. Transgenic mice expressing human *ApoE4* in neurons developed axonopathy and impairment of axonal transport. In *ApoE4* transgenic mice, axonal dilatations with accumulation of synaptophysin, neurofilaments, mitochondria, and vesicles were observed, suggesting impairment of axonal transport [193].

3C2. Frontotemporal dementia (FTD)

Frontotemporal dementia (FTD) is the clinical syndrome caused by degeneration of the frontal lobe of the brain and is the second most common pre-senile dementia after AD among people under the age of 65 [194]. About 50% of FTD patients have an associated family history. Several genes such as microtubule-associated protein tau (*MAPT*), progranulin (*PGRN*), chromatin modifying protein 2B (*CHMP2B*), and fused in sarcoma (*FUS*), have been described to be associated with FTD. Both *MAPT* and *PGRN* are pathogenic genes located on chromosome 17 associated with FTDP phenotype [195]. FTD frequently presents with tau-containing lesions histopathologically, which result from mutations in the *MAPT* gene. The identification of early and progressive axonal swellings [196] and impaired Rab7 recruitment to endosomes [197] in $CHMP2B^{intron\ 5}$ mice suggested a potential mechanism for impaired axonal transport.

The transgenic mouse model (K3) which expresses human tau carrying the FTD mutation K369I showed early-onset memory impairment, amyotrophy in the absence of overt neurodegeneration, which may result from impaired transport in sciatic nerves, and particularly revealed an early-onset motor phenotype that reproduces parkinsonism with tremor, bradykinesia, abnormal gait, and postural instability. The functional impairment of K3 mice is accompanied by progressive morphological changes including axonal swellings and spheroids that are histopathological correlates of disrupted axonal transport [184]. The deposition of hyperphosphorylated tau in K3 mice selectively impaired kinesin-driven anterograde transport of identified cargos such as TH-containing vesicles and mitochondria [168] by decreasing binding of motor proteins to MT tracks [167,176]. The kinesin motor complex formation is also disturbed by tau in K3 mice with the mechanism that hyperphosphorylated tau interacts with c-Jun N-terminal kinase-interacting protein 1 (JIP1), which is associated with the kinesin motor protein complex. Because JIP1 is involved in regulating cargo binding to kinesin motors, these findings partly explain how hyperphosphorylated tau

mediates impaired axonal transport in FTD [198]. Moreover, it has been identified that N-terminal projection domain of tau binds to the C-terminus of the p150 subunit of the dynactin complex and the attachment of the dynactin complex to microtubules is enhanced by tau. Mutations of the N-terminus arginine residue of tau, found in patients with FTDP-17, wreck its binding to dynactin, which is abnormally distributed in the retinal ganglion cell axons of transgenic mice expressing human tau with a mutation in the microtubule-binding domain [199,200].

The increased ratio of 4 repeat over 3 repeat tau isoforms is associated with neurodegeneration in inherited forms of FTD. Tau overexpression that diminishes axonal transport in several models has been well studied. Furthermore, Hyman et al. found that both 3 repeat and 4 repeat tau change normal mitochondrial distribution within the cell body and reduce mitochondrial localization to axons; 4 repeat tau has a greater effect than 3 repeat tau, while 3 repeat tau has a slightly stronger effect on retrograde and anterograde axon transport dynamics [201]. The effect of tau/PTL-1 (protein with tau-like repeats) on the transport characteristics of the major axonal transporter kinesin-3 KIF1A/UNC-104 was also proved in the nervous system of *Caenorhabditis elegans* [202].

Recently, Coleman et al. have generated a novel knock-in mouse model of an inherited tauopathy, FTD with parkinsonism linked to *TAU* mutations on chromosome 17 (FTDP-17T). The engineered mice with a mutation in the endogenous *MAPT* gene that is homologous with the common P301L *MAPT* mutation found in patients with FTDP-17T, mimicking the human disease situation, revealed reduced tau phosphorylation and reduced MT association of tau, intriguing age-dependent changes in axonal transport of mitochondria, and increased spontaneous locomotor activity in old age [203].

3C3. Motor neuron diseases: Amyotrophic lateral sclerosis (ALS)

Amyotrophic lateral sclerosis (ALS) is a fatal and progressive neurodegenerative disease with the selective death of motor neurons in the brain, spinal cord and brainstem as a main pathological feature which leads to muscle weakness and paralysis [204]. ALS leads specifically to muscle weakness and atrophy of limb and respiratory muscles. The molecular basis of this disease is still poorly understood and several hypotheses for its etiology is under debate [205]. Axonal transport derangement is advocated as the early molecular event and a key event of pathogenic mechanisms leading to neurodegeneration in ALS.

Five Mendalian gene defects have been reported to cause ALS, in which copper-zinc superoxide dismutase type 1 (*SOD1*) gene mutations [206,207] have been demonstrated to be the most prevalent. Transgenic mice with mutant *SOD1* show slowing of axonal transport early in the disease course [208], Cu/Zn *SOD1*(G93A and G37R) transgenic mice develop phenotypical hallmarks of ALS and therefore serve as an established model to study the molecular mechanisms underlying this disease. Both slow and fast anterograde transport are slowed in transgenic G93A and G37R ALS mice prior to disease onset and is exacerbated as the disease progresses [208,209]. Kinesin-associated protein 3 (KAP3) sequestration by misfolded SOD1 species and the resultant inhibition of the axonal transport of choline acetyltransferase (ChAT) play a role in the dysfunction of ALS [210], and the reduction in the levels of KAP3 has been linked to increased survival in ALS patients [211], While an early upregulation of the kinesin superfamily motor protein KIF1A was detected in spinal motor neurons in SOD mutant mice [212]. Retrograde transport is also disrupted in ALS mice [213]. The decreased retrograde transport was described in G93A SOD1 mice at an early stage of disease, coincident with neuromuscular junction degeneration and muscle weakness [140,214,215].

Reduction of retrograde transport in ALS mice has been attributed to the mislocalization and disruption of dynein function [214]. Mutations in the p150 subunit of dynactin is involved in ALS [154,216-219] and a dynein mutation which attenuates motor neuron degeneration in SOD1(G93A) mice has also been described [220,221]. Mutations in dynein-dynactin retrograde system protein genes has been demonstrated to be linked to neuronal degenerations in ALS mouse model [222,223] and *Drosophila melanogaster* [224], as well as distal spinal and bulbar muscular atrophy (dSBMA) [225]. Studies using autopsy material and spinal cord tissue from ALS animal models suggest that damage to the axonal cytoskeleton due to alterations of neurofilament [226] and of molecular motor proteins such as dynein and kinesin contribute to spheroid formation.

Densely accumulated neurofilaments can be seen in axons in close proximity with vacuoles and at many other proximal axon sites without vacuoles in human SOD1 transgenic mice, suggesting that axonal transport begins to fail before the onset of rapid declining (RD) stage [215,227]. In SOD (G93A) model of ALS, transport deficits are detected soon after birth, months before the onset of axon degeneration, suggesting axons can survive despite long-lasting transport deficits. On the other hand, in SOD (G85R) model of ALS motor axons degenerate, but transport is unaffected. This finding suggests that transport deficits are not necessary for axon degeneration. Additionally, axons show chronic transport deficits, but survive in mice that overexpress wild-type *SOD1*, indicating that axon transport deficits are not sufficient to cause immediate degeneration in this ALS model [228]. Cytoskeletal abnormalities with accumulation of ubiquinated inclusions in the anterior horn cells are a pathological hallmark of both familial and sporadic ALS and of mouse models for ALS. Further, it was reported that p38 mitogen-activated protein kinase (p38MAPK) is activated in ALS patients and mutant *SOD1* transgenic mice [229,230], and biochemical studies revealed that KHC are phosphorylated by p38, which inhibited conventional kinesin-based motility, indicating that mutant *SOD1* impairs anterograde fast axonal transport by activation of p38 MAPK [231].

High levels of intracellular calcium observed in ALS model neurons may interfere with mitochondria movement toward the extremities of long axons causing retrograde degeneration because microtubule transported mitochondria can be stopped at high calcium concentration sites such as the neuromuscular junction [232]. Ca^{2+}-mediated

glutamate excitotoxicity has been put forward as one of the potential mechanisms for the motor neuron-selective death in ALS [233]. It was also reported that mutant *SOD1* increase the formation of damaging hydroxyl radicals and peroxynitrite derivatives [234], which inhibit the mitochondrial electron-transport chain [235]. Intracellular free radical species inhibit the activities of specific mitochondria enzymes. The mitochondria accumulate in proximal axons of the anterior horn neurons in ALS patients because of blocking of axonal trafficking into proximal neurons [141].

Hereditary spastic paraplegias (HSP)

HSP comprise a heterogeneous group of genetic neurodegenerative disorders characterized by progressive spasticity and weakness of lower limbs due to retrograde degeneration of the corticospinal tracts and posterior columns, which is often accompanied by brisk reflexes, extensor plantar reflexes, and urinary urgency [236,237]. Genetic loci for HSP are designated SPG for "spastic gait" followed consecutively by the locus number, which is assigned in order of its discovery. The identification of genes that are implicated in HSP has shown that the largest group of HSP proteins are either known or thought to be involved in the intracellular trafficking, including KHC gene, *KIF5A*, directly implicating axonal transport impairments to HSP pathogenesis in SPG10 [238,239]. SPG10, which causes dominant forms and originates in point mutations in the neuronal *KINESIN-1* gene (*KIF5A*), reduces microtubule binding affinity of KIF5A that acts in a dominant negative manner by competing with wild-type motors for cargo binding, impairs motor-based transport underlying HSP [240]. Mouse models of SPG7 [241], which is associated with mutations in the mitochondrial ATPase paraplegin, and SPG4 [242-244], which results from mutations in microtubule severing protein spastin, provide *in vivo* evidence for axonal transport impairment in HSP. Mutations in REEP1 were recently associated with a pure dominant Hereditary spastic paraplegias (HSP), SPG31 [245] and direct evidence for axonal transport defects in a novel mouse model of mutant spastin-induced HSP and human HSP patients have also been produced [246,247].

Charcot-Marie-Tooth (CMT) disease

Charcot-Marie-Tooth (CMT) disease is the most common inherited disorder of the peripheral nervous system. Two classes of CMT have been differentiated until now: demyelinating forms of CMT (CMT1), in which nerve conduction velocities are decreased, and the axonal CMT2 forms, in which nerve conduction velocities are preserved [248]. Mutation in *Kif5A* causes hereditary spastic paraparesis type 10 [125] and axonal Charcot-Marie-Tooth type 2 disease (CMT2) [249]. An autosomal dominant mutation in *DYNC1H1* was identified in a family with CMT2 which was also proved to cause severe intellectual disability with neuronal migration defects [250]. Mutations in the 27-kDa small heat-shock protein gene (*HSPB1*) cause axonal CMT or distal hereditary motor neuropathy (distal HMN). Expression of mutant *HSPB1* decreased acetylated α-tubulin abundance induced severe axonal transport deficits [251].

Mutations in *GDAP1* (ganglioside-induced differentiation-associated protein-1), which alter the interaction between mitochondria and the microtubule cytoskeleton and affect mitochondrial axonal transport and movement [252,253], are described as the cause of the inherited human neuropathy CMT [254,255] disease: autosomal recessive demyelinating CMT4A [256], autosomal recessive axonal CMT2K or dominant axonal CMT2K. Defects in axonal transport due to a mutation in the motor protein KIF1Bβ, has been described to be responsible for axonopathy in the CMT type 2A [130].

Mitofusins (Mfn1 and Mfn2) are outer mitochondrial membrane proteins involved in regulating mitochondrial dynamics. Mutations in *MFN2* alone cause CMT type 2A for the reason that Mfn2 is a key component of the linker/adaptor complex between mitochondria and kinesin/microtubules, the deficit of which produce a severe mitochondrial transport disorder in dorsal root ganglion neurons [257].

Other motor neuron diseases

Dysfunction of dynactin-mediated transport is also documented to lead human motor neuron disease [219]. Mutations in anterograde axonal transport proteins, including KIF1B, lead to slow progressive motor neuronopathy [130]. These studies indicate the potential generality of the link between retrograde and anterograde axonal transport deficits and motor neuron degeneration [117].

Huntington's disease (HD)

Huntington's disease (HD) is one of an increasing number of human neurodegenerative disorders caused by a CAG/polyglutamine-repeat expansion. Mice models of HD (transgenic for exon 1 of the human HD gene carrying (CAG)115 to (CAG)156 repeat expansions), develop characteristic morphological changes within neurons, which are strikingly similar to abnormalities observed in biopsy material from HD patients [258]. Mutant huntingtin (Htt) interacts with mitochondrial protein Drp1, leading to impairment of mitochondrial biogenesis, defective axonal transport and synaptic degeneration in HD [259]. Htt activates axonal c-Jun N-terminal kinase (JNK3) that phosphorylate kinesin 1. Phosphorylated kinesin 1 has reduced affinity for MT leading to impaired transport [260]. Disruption of axonal transport is also described in *Drosophila* model for HD [261].

4. Conclusion

Studies described in this review establish a major role of axonal transport defects in several neurodegenerative diseases. These defects are caused by genetic mutations, oxidative stress and post-translational modifications of the transport machinery. However, detailed experiments are necessary to elucidate the causality of these defects as underlying mechanisms for neurodegeneration. Though we understand aspects of the major players of active transport and their physiological functions, details of the spatial and temporal regulation of transport and various cargos transported in the normal or pathological state of neuron are poorly defined. Thus, dissecting the molecular mechanisms of axonal transport and its regulation in different parts of the brain during development and maturation of the nervous system and their role in neurodegenerative diseases is required to understand cell biology and biochemistry of active transport process. A systems level

understanding of the axonal transport is critical in identifying novel molecular targets for therapeutic development in treating these disorders.

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