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Axonal transport defects: a common theme in neurodegenerative diseases

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Abstract A core pathology central to most neurodegenerative diseases is the misfolding, fibrillization and aggregation of disease proteins to form the hallmark lesions of specific disorders. The mechanisms underlying these brain-specific neurodegenerative amyloidoses are the focus of intense investigation and defective axonal transport has been hypothesized to play a mechanistic role in several neurodegenerative disorders; however, this hypothesis has not been extensively examined. Discoveries of mutations in human genes encoding motor proteins responsible for axonal transport do provide direct evidence for the involvement of axonal transport in neurodegenerative diseases, and this evidence is supported by studies of animal models of neurodegeneration. In this review, we summarize recent findings related to axonal transport and neurodegeneration. Focusing on specific neurodegenerative diseases from a neuropathologic perspective, we highlight discoveries of human motor protein mutations in some of these diseases, as well as illustrate new insights from animal models of neurodegenerative disorders. We also review the current understanding of the biology of axonal transport including major recent findings related to slow axonal transport.

Keywords Axonal transport · Alzheimer's disease · Frontotemporal dementias · Parkinson's disease · Polyglutamine diseases

Introduction

The misfolding and aggregation of brain proteins leading to the relentless accumulation of abnormal intra- and extracellular filamentous deposits in diverse central nervous system (CNS) cell types, including neurons and glia, are pathological hallmarks of many neurodegenerative diseases (Table 1). Indeed, neurofibrillary tangles (NFTs) and senile plaques (SPs) were recognized as significant lesions of Alzheimer's disease (AD) nearly 100 years ago [9, 17, 43], followed shortly thereafter by the discovery of Lewy bodies (LBs) in the brains of patients with Parkinson's disease (PD) [9, 34, 43]. Although many of these fibrillary lesions are considered to be diagnostic hallmarks of specific disorders, a key unanswered question is whether these filamentous protein aggregates contribute to the onset and progression of neurodegeneration, are mere bystanders in the degenerating process, or even play a neuroprotective role. An abundance of data, including several disease-specific mutations in the aggregated proteins suggests that protein aggregates have a central role in neurodegenerative diseases [9, 43, 44]. However, even in disorders characterized by filamentous inclusions formed by specific mutated proteins, it has been argued that it is not straightforward to determine if these lesions are actually neurotoxic or are merely a part of a neuroprotective response.

Regardless of uncertainties about the biological consequences of protein aggregates, progressive intracellular accumulations of disease proteins can result from one or more of the following pathological processes: (1) abnormal synthesis and folding of disease proteins; (2) aberrant interactions of disease proteins with other proteins; (3) impaired degradation and turnover of disease proteins; (4) impaired intracellular transport of disease proteins, especially those targeted for axonal transport over long distances. While the first three mechanisms have been the subject of intense investigation especially over the last 5 years, far less

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Table 1 Abnormal protein aggregates in diverse hereditary and sporadic neurodegenerative disorders. Most lesions are in nuclei, cell bodies and processes of neurons and/or glia, but some are extracellular (i.e., SPs) (*Aβ* amyloid- β peptides, *AD* Alzheimer's disease, *ALS* amyotrophic lateral sclerosis, *DLB* dementia with LBs, *DS* Down's syndrome, *GCI*s glial cytoplasmic inclusions, *LB*s

Lewy bodies, *LBVAD* Lewy body variant of AD, *MSA* multiple system atrophy, *NBIA 1* neurodegeneration with brain iron accumulation type 1, *NF* neurofilaments, *NFT*s neurofibrillary tangles, *NIID* neuronal intranuclear inclusion disease, *PD* Parkinson's disease, *PHFtau* paired helical filament tau, *SOD1* superoxide dismutase 1, *SP*s senile plaques)

Disease	Lesion/components	Location
AD ^{a,b,c}	SPs/A β NFTs/PHFtau LBs/ α -synuclein	Extracellular Intracytoplasmic Intracytoplasmic
ALS ^a	Spheroids/NF subunits, SOD1	Intracytoplasmic
DLB ^c	LBs/ α -synuclein	Intracytoplasmic
DS ^{a,b,c}	SPs/A β NFTs/PHFtau LBs/ α -synuclein	Extracellular Intracytoplasmic Intracytoplasmic
NBIA 1 ^c	LBs/ α -synuclein GCI/s/ α -synuclein	Intracytoplasmic Intracytoplasmic
LBVAD (AD + DLB) ^c	SPs/A β NFTs/PHFtau LBs/ α -synuclein	Extracellular Intracytoplasmic Intracytoplasmic
MSA ^c	GCI/s/ α -synuclein	Intracytoplasmic
NIID	Inclusions/expanded polyglutamine tracts	Intranuclear
Prion diseases ^a	Amyloid plaques/Prions	Extracellular
Tauopathies ^{a,b}	Tangles/abnormal tau	Intracytoplasmic
Tri-nucleotide repeat diseases	Inclusions/expanded polyglutamine tracts	Intranuclear and Intradendritic

^aBoth hereditary and sporadic forms of these disorders occur

^bNeurodegenerative diseases with prominent tau pathology are tauopathies

^cNeurodegenerative diseases with prominent synuclein pathology are synucleinopathies

attention has been focused on the role of axonal transport in the aggregation of proteins and in mechanisms underlying neurodegenerative diseases.

In this review, we focus on the role of axonal transport in neurodegenerative diseases, briefly summarizing classical and recent studies on the biology of axonal transport, and highlighting major recent findings including pathogenic mutations in human genes that encode proteins involved in axonal transport and studies of animal models of disease related to impairments of axonal transport.

The biology of axonal transport

Neurons are the most polarized cells known. In humans, neurons typically have a cell body measuring ~6–120 μ m in diameter, but they may have an axonal process that can run up to a meter or more. In a more extreme example like the blue whale (the largest mammals with a recorded length of over 30 m), axons can run more than 10 m in length. Despite their extreme length, axons are generally devoid of the machinery for biosynthesis of proteins and other molecules, and all axonal components are synthesized in the cell body, translocated from the cell body into the axonal process and then transported to its destination within the axon (anterograde transport; for a review, see [5] and the accompanying video). At the same time, a complementary mechanism translocates “cargo” (effete or internalized proteins, organelles, etc.) in the opposite direction, i.e., away from the axon, into the cell body

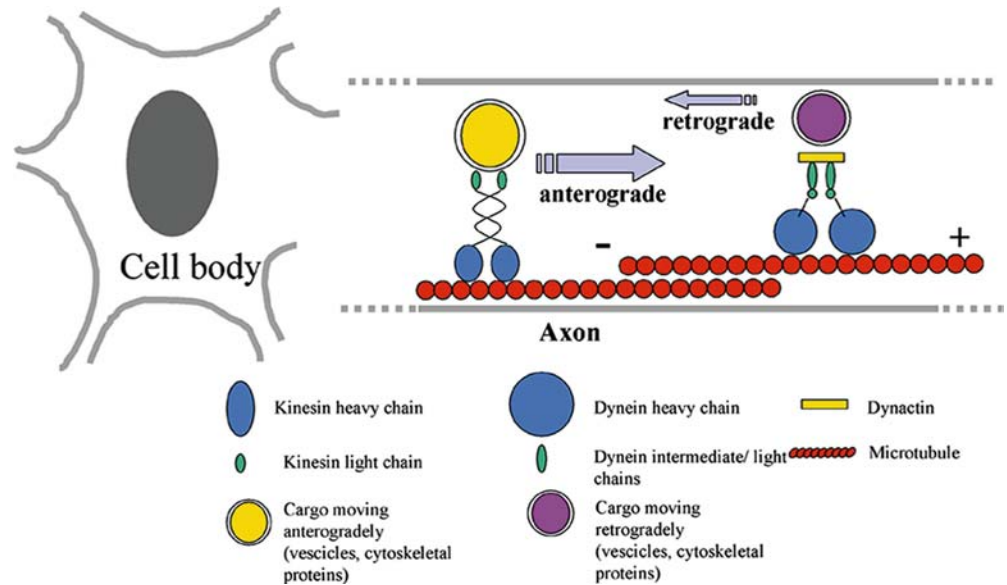
(retrograde transport). This mechanism of axonal transport is not exclusive to neurons, but is a rather exaggerated version of transport seen in other cell types. Such transport mechanisms also exist in the dendrites, but little is known about mechanisms of dendritic transport and for the purposes of this review, we will focus on axonal transport.

Generally speaking, to move any cargo, two components are required: “motors” to move the cargo, and “rails” to transport them. For the rails, the neurons use the complex network of cytoskeleton, mainly the microtubules and also actin polymers (see [5] and the accompanying video). For the motors, the neurons have an abundance of small molecular machines, known as kinesins and dyneins, moving the cargo mainly in the anterograde or retrograde direction, respectively (Fig. 1).

Historical perspective of axonal transport

In sharp contrast to most other fields of neurobiology, the history of axonal transport study is a relatively short one [5]. While nerve ligation experiments in the 1940s defined that active axonal transport existed, it was not until the 1960s that ingenious experiments designed by Lasek and co-workers used pulse injections of radiolabeled amino acids into the dorsal root ganglia of live animals as a model system to study axonal transport [26]. The injected radiolabeled amino acids entered the cell bodies of dorsal root ganglia cells, were incorporated into the newly synthesized proteins in the cell

Fig. 1 Anterograde and retrograde axonal transport by motors kinesins and dyneins, respectively. Kinesins and dyneins move on microtubules and transport Golgi-derived vesicles, cytosolic protein complexes, cytoskeletal polymers, and other cargos like ribosomes and messenger RNAs



body, and the pulse of newly synthesized radiolabeled proteins were then transported into the axon. As the wave peak of radiolabeled proteins moved through the axon, the protein composition at any given point varied according to time and distance from the cell body, and by studying the protein composition at various points along the axon, serial snapshots of transported proteins could be obtained (Fig. 2A). While some of the proteins were very rapidly transported, at rates of 100–400 mm/day (1–5 $\mu\text{m/s}$), quickly reaching up to the tip of the axon, another wave of proteins were found to move significantly slower, at about 0.2–5 mm/day (0.0002–0.05 $\mu\text{m/s}$). These two components were called fast axonal transport and slow axonal transport, respectively, but it is clear that this simplistic view of rates of cargo movement in axons is no longer tenable as originally proposed; see below and [5, 26]. While fast transport mainly consisted of vesicular cargo, slow axonal transport was mainly composed of cytoskeletal proteins, mainly microtubules, neurofilaments and actin, along with many additional cytosolic proteins (for detailed reviews, see [1, 5]).

After these remarkable experiments that defined the nature of axonal transport, the next spurt of activity came in the 1980s and the 1990s when a tremendous amount of scientific activity defined the biochemical nature and the mechanisms of the specific motors (kinesins and dyneins) that were involved in the transport (for a comprehensive review, see [31]).

While the discovery of molecular motors greatly increased our understanding of fast axonal transport, one puzzling aspect was that all the motor proteins discovered were found to move fast, in line with the speeds seen in fast axonal transport; however, it was difficult to reconcile the significantly slower transport rates seen in slow axonal transport. It was generally felt that visualization of axonal transport in real time would lead to more insights into axonal transport in general, and slow

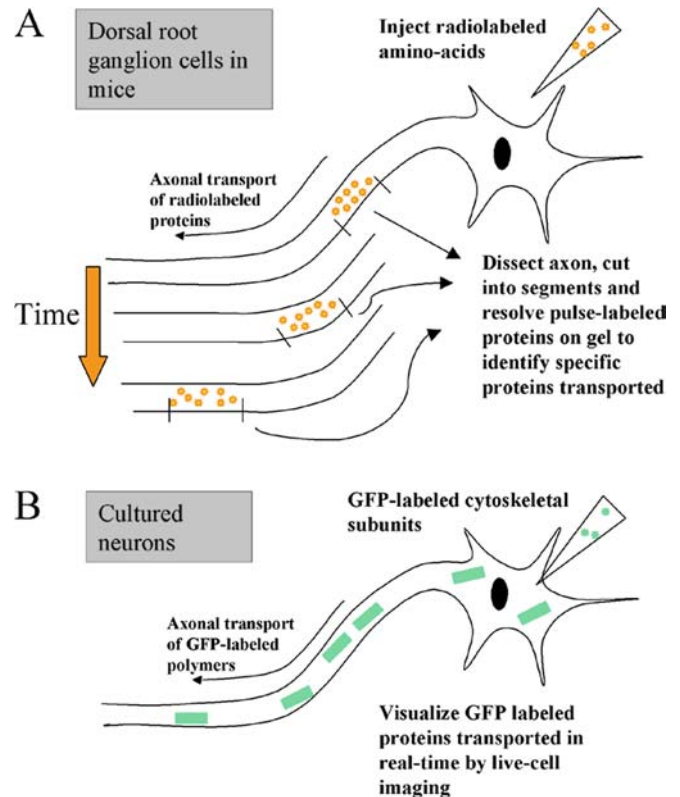


Fig. 2 Two techniques commonly used in studying axonal transport. **A** shows a technique pioneered by Lasek and co-workers, where a pulse of radiolabeled amino acids is injected into dorsal root ganglia in animals. The radiolabeled amino acids are incorporated into newly synthesized proteins in the cell bodies, and the labeled proteins are subsequently transported along the axon as a wave of radiolabeled proteins. By looking at the protein composition of the radiolabeled proteins at progressively distal segments along the axon, serial snapshots of transported radiolabeled proteins can be obtained. Another technique is shown in **B**, where axonal transport can be visualized in real time. In this method, fluorescently labeled proteins are introduced into the cell body, and then the transport of the labeled proteins is studied by using epifluorescence microscopy

axonal transport in particular [2]. In 2000, two studies using cultured cells and labeled neurofilaments protein showed transport of neurofilaments, a component of slow axonal transport, in real time [39, 47] (Fig. 2). Surprisingly, neurofilaments were found to move rapidly, with rates up to 3 $\mu\text{m/s}$, in line with the rates reported for known motors (kinesins and dyneins); however, unlike fast axonal transport cargo that moved rapidly down the axon, without much pause, neurofilaments were found to undergo prolonged pauses in their transit, often up to several minutes [39]. Also, at any given time, only a small fraction of the cargo was actually moving, making the overall transport much slower than fast axonal transport. These studies support a unified model where both fast and slow axonal transport, although qualitatively different, are moved by known “fast” motors like kinesins and dyneins [5].

Axonal transport defects in neurodegenerative diseases

Axonal transport can be fundamentally thought to comprise three basic components: the cargo, the motor proteins that move the cargo, and the rails on which the cargo moves. In reality, of course, the system is much more complicated, with various adaptor/linker and regulatory proteins involved in the process, along with possible modulation at the gene/RNA level. In principle, defects in any of the three components can lead to transport functional and/or pathological changes, and potentially neurodegeneration. From the very early days of research on neurodegenerative diseases, it has been postulated that defects in axonal transport may be responsible for these human disorders [10]. Although various mutant and transgenic animal models gave indirect support for the hypothesis, three recent developments have dramatically highlighted the role and significance of axonal transport in human neurodegenerative diseases. They are (1) discovery of human motor protein mutations in neurodegenerative diseases; (2) axonal transport defects in animal and in vitro cellular models harboring human mutations; and (3) newly discovered roles for pathogenic proteins like amyloid precursor protein (APP), tau, presenilins and synucleins in modulation and regulation axonal transport.

Kinesin mutation in hereditary spastic paraplegia

Hereditary spastic paraplegias (HSP), also known as familial spastic paraplegias, represents a heterogeneous inherited group of neurodegenerative diseases characterized by progressive lower limb spasticity and weakness. It can be transmitted in an autosomal dominant fashion, with patients presenting in their thirties or forties with spasticity in the lower limbs, with gradual proximal spread of symptoms. Neuropathologically, a distal axonal neuropathy is seen, with severe degeneration and gliosis of the distal corticospinal tracts, and

relative sparing of the tracts in the brain stem and proximal cord. In more complex forms of the disease, sensory symptoms, mental retardation and optic atrophy are also seen [31]. Many different loci for HSP have been identified, and the commonest gene involved in about 40% of the cases, is spastin, an ATPase with unclear functions [15]. Due to the peculiar slow “dying back” neuropathy observed in this disease, it has been hypothesized that dysfunctions in axonal transport, leading to selective damage of the distant portions of the axons may be responsible for the pathogenesis of HSP.

Indeed, a missense mutation in one of the genes encoding a major kinesin protein (i.e., the gene for kinesin heavy chain Kif 5a) was recently found in a family with HSP [38]. The same missense mutation is found in all affected members of the family, as well as in some presymptomatic members. This mutation occurs within a functional motor domain of the kinesin protein and a homologous mutation in yeast has been found to decouple kinesin binding to microtubules, underlining the functional role of the kinesin mutation in the pathology of HSP.

Dynein mutations in a family with motor neuron disease

Dynein is one of the major motor proteins responsible for retrograde axonal transport, i.e., transport of cargo from the axons towards the cell bodies. Dynein is a large motor protein consisting of at least three different classes of subunits [45]. Dynein binds to a multiprotein complex called dynactin. Dynactin acts as a platform for binding dynein to its cargo, and is also thought to play a role in modulation of dynein [22, 48]. Recently, dynactin was also shown to bind to the anterograde motor kinesin, and may act as a molecular switch between anterograde and retrograde transport [6]. Animal models disrupting the dynein/dynactin complex develop a late onset motor neuron degeneration [25], and missense mutations in a dynein subunit causes Lewy body-like inclusions and progressive motor neuron degeneration in mice [14]. Due to the central role of the dynein/dynactin complex in axonal transport, and due to evidence from animal studies, it was hypothesized that dynein mutations could play a role in neurodegeneration. Indeed, a search for dynein mutations in neurodegenerative diseases led to the discovery of mutations in the gene encoding an important subunit (p150) of the dynactin complex in a family with motor neuron disease [37]. In this family, the disease is transmitted in an autosomal dominant fashion, and is a primary lower motor type neuropathy with patients presenting in their 30s, often with breathing difficulty due to vocal fold paralysis. The mutation is a single base pair change (substitution of serine for glycine at position 59), and it has been found in all affected family members. However, it has not been detected in unaffected family members or unaffected controls. Further, the mutation reduces the binding affinity of dynactin to microtubules [37]. These findings provide

convincing evidence that dynein mutations are involved in a small subset of motor neuron diseases.

Kinesin mutations in Charcot-Marie-Tooth disease

Charcot-Marie-Tooth (CMT) disease comprises a heterogeneous group of inherited peripheral neuropathies characterized by motor and sensory deficits, often presenting in young adults as tingling, numbness and loss of deep reflexes. The progression of the disease varies among individuals, with symptoms ranging from mild neuropathy to complete disability. Two basic forms can be recognized, with primary demyelinating (CMT1), or axonal (CMT2) types of degeneration predominating [4]. Various genes have been implicated in CMT syndromes, including several genes known to play a role in myelination (PMP22, MPZ) and genes for gap junctional proteins (Connexin 32) [4]. However, in a remarkable series of studies, it was shown that mutations in a kinesin subunit protein (Kif 1B beta) can lead to an axonal type of CMT (CMT type 2A).

While studying animal models of kinesin knockout mice, Hirokawa and co-workers [53] found that heterozygous knockout mice for one of the kinesins, Kif 1B, developed progressive muscle weakness with normal motor nerve conduction velocities, symptoms closely resembling axonal type CMT, CMT type 2. Incidentally, the gene for CMT type 2A was mapped to the same interval as the gene for Kif 1B [3, 33], and genomic analysis of pedigrees with CMT type 2A revealed that these patients had a mutation in the Kif 1B gene [53]. It was further shown that the mutant motor protein may not tightly bind to microtubules [53], thus suggesting a loss of function of the Kif 1B protein in patients with CMT type 2A.

Axonal transport in AD and tauopathies

The story of the role of axonal transport in AD is a rapidly developing one [17, 27]. Neuropathologically, the two hallmarks of AD are (1) deposits of fibrillar A β into diffuse and neuritic plaques in the extracellular space, and (2) filamentous accumulations of tau proteins as NFTs and neuropil threads within neurons and their processes. Tau is also involved in a group of disorders known as tauopathies, in which the hallmark lesions are AD-like filamentous tau inclusions only [17, 27]. While amyloidogenic A β peptides are generated by proteolytic processing of APP, tau is a microtubule binding protein. The normal functions of neither A β nor APP are clear at this time, although many activities have been ascribed to both, as described below.

Recent studies have implicated APP in axonal transport by suggesting it might act as a receptor for the anterograde motor kinesin [21]. Further, it has also been proposed that defects in APP can translate into major axonal transport defects, leading to neuronal damage or

neurodegeneration. While this proposed role of APP in axonal transport needs to be validated and confirmed by other laboratories, this work draws further attention to the possibility that impairments in axonal transport may underlie neurodegenerative disease mechanisms in AD. On the other hand, tau is a microtubule binding protein with well-defined functions, such as binding to and stabilizing microtubules in vivo and promoting their assembly from tubulin monomers [17]. Indeed, since tau is sequestered into tangles where it is hyperphosphorylated and unable to bind microtubules, it was proposed as long ago as 1994 that functional defects in pathological tau observed in AD brains would destabilize microtubules, thereby disrupting axonal transport [27]. Below, we summarize known features of axonal transport of APP, review possible roles of APP and tau in impairment of axonal transport in AD, and highlight the recently discovered link between presenilins and kinesin regulation.

It is well established that APP is transported in axons via fast axonal transport [23]. Further, there is convincing evidence that APP transport is dependent on the major kinesin protein, kinesin-I [8, 21], and it has also been proposed that APP may be transported in a vesicular complex containing presenilins and BACE that play critical roles in the processing of APP into amyloidogenic A β peptides [11, 21]. These findings suggest that misregulation of APP, either directly from known APP mutations (as in familial AD), or indirectly via proteins associating/interacting with APP can lead to misregulation of fast axonal transport in general, leading to axonal depletion of critical components, and neurodegeneration [12].

Another interesting line of evidence highlighting the role of presenilins in regulation of fast axonal transport in AD came from a recent study of presenilin mutant mice. Presenilins are proteins responsible for regulated proteolysis of APP, and mutations in presenilins are seen in most cases of early familial AD. Several studies indicate that presenilins interact with glycogen synthase kinase 3 β (GSK3 β) [41]. GSK3 β is a kinase with many different roles, including the phosphorylation of kinesin light chains, and it has been shown that GSK3 β -mediated phosphorylation of kinesin light chains leads to detachment of the kinesin motor from the cargo, thus preventing further transport of cargo (Fig. 3) [30]. Using transgenic presenilin mutant mice, Pigino et al. [35] showed that mutant or absent presenilin increased GSK3 β levels, thereby phosphorylating kinesin light chains, detaching the kinesins from their cargo, and impairing axonal transport. While preliminary, these studies are significant for opening up new lines of investigation into how abnormalities in APP or presenilins might perturb neuronal functions by disrupting axonal transport, and lead to neurodegeneration in AD.

With respect to tau pathologies and mechanisms of neurodegeneration in AD, the first experimental evidence supporting the hypothesis that tau pathologies could impair axonal transport came from the work of

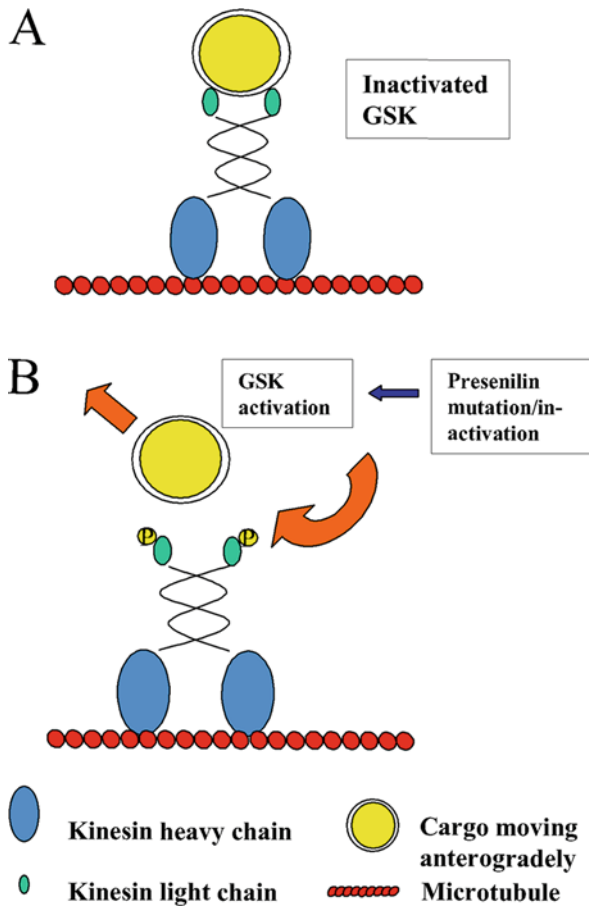


Fig. 3 Model illustrating the role of presenilins in the regulation of axonal transport. Presenilin mutation/inactivation leads to GSK3 β activation that in turn phosphorylates kinesin light chains. Phosphorylation of kinesin light chains releases vesicles destined to undergo fast axonal transport, thereby clogging the axons with vesicles and inducing/facilitating neurodegeneration (*GSK3 β* glycogen synthase kinase 3 β)

Ishihara et al. [18], showing that sequestration of human tau into filamentous inclusions in tau transgenic mice leads to a neurodegenerative phenotype in mice, similar to neurodegeneration seen in motor neuron disease of Guam [44]. Further, by studying tau transport in mice expressing the human tau mutation (R406W), which is pathogenic for the tauopathy familial frontotemporal dementia with parkinsonism linked to chromosome 17 (FTDP-17), Zhang et al. [51] showed that the transport of mutated human tau (but not normal human tau) is retarded in the axons of these transgenic mice. It has also been shown that the R406W mutation impairs the ability of tau to bind to and stabilize microtubules [16]. Given these findings, the study by Zhang et al. provides experimental evidence for a mechanism of tau accumulation (Fig. 4). In this model, the mutated tau in FTDP-17 fails to bind to microtubules cannot be transported into the axon and in turn aggregates in the cell body, leading to a depletion of tau in the axons. The lack of normal tau binding to microtubules in axons leads to destabilization of microtubules, subsequently causing

neurodegeneration by impairment of axonal transport on the unstable microtubules. As described above, many of the predictions of the mechanism whereby tau pathologies might cause neurodegeneration by impairing axonal transport have been directly demonstrated in experimental model systems.

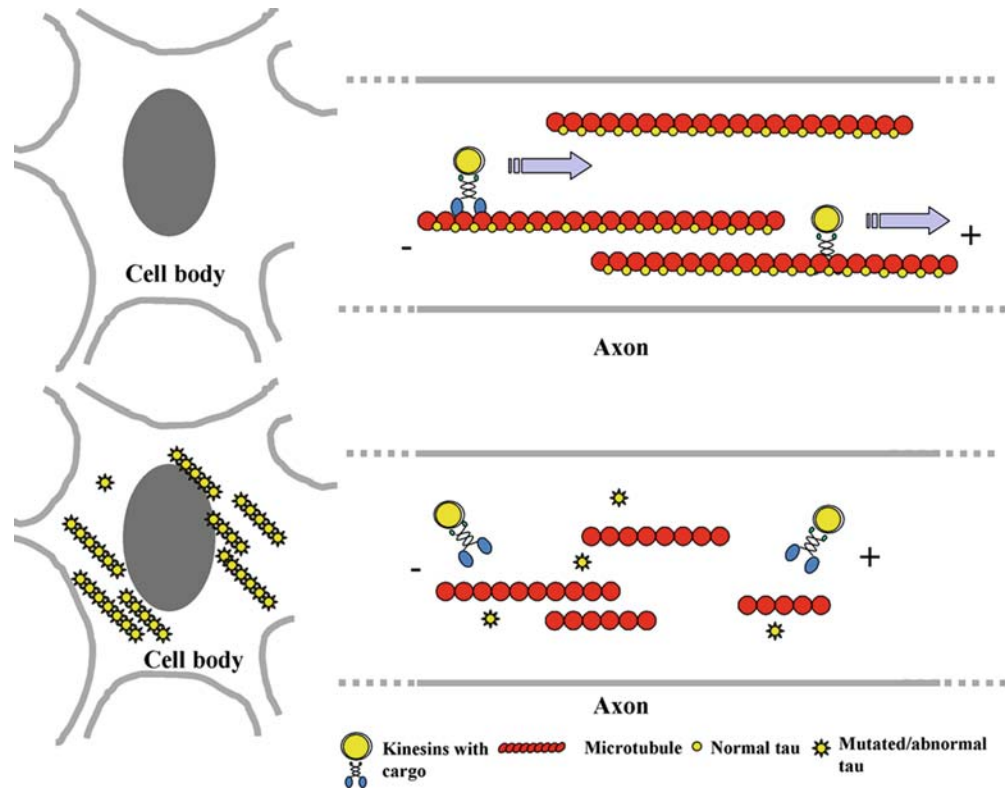
A final line of evidence suggesting a role of axonal transport defects in AD comes from studies of ApoE4, a gene whose allelic state is associated with an increased risk for AD. Mice expressing human ApoE4 exhibit defects in axonal transport [42], and the receptor for ApoE4, ApoER2 binds to JIP1/2, a protein that appears to mediate the binding of APP to kinesin I [46]. Thus, it can be postulated that overexpression of ApoE4 protein can lead to misregulation of JIP1/2-mediated binding of kinesin to APP, leading to defects in fast axonal transport.

Although many of the above findings need to be rigorously investigated by more direct experiments, the findings summarized above provide support for the hypothesis that impairments in fast axonal transport by abnormalities in APP, presenilins and tau play a role in mechanisms of brain degeneration in AD. Whether misregulation of axonal transport has a direct role in the pathogenesis of the disease or is a secondary phenomenon leading to axonal degeneration remains to be seen. However, these uncertainties notwithstanding, therapeutic intervention in AD by modulation/correction of axonal transport defects remains a viable hypothesis. In this regard, a recent study showed that a microtubule-stabilizing drug, Paxceed (paclitaxel family), could ameliorate the neurodegenerative phenotype in transgenic tau mice by offsetting the loss of tau function by stabilizing the microtubules and correcting the fast axonal transport defects in these mice [52].

Axonal transport and Huntington's disease

Neuropathologically, Huntington's disease is characterized by atrophy and degeneration of striatal neurons, with aggregates of the pathological polyglutamine-containing protein, Huntingtin. Huntingtin is a predominantly cytoplasmic protein that associates with vesicles and moves in the fast axonal transport component. Although it has been known for several years that polyglutamine repeats within the Huntingtin protein cause a gain of deleterious function leading to neurodegeneration, the exact pathogenic role of the repeats is unclear. Recently, by infusing pathological polyglutamine repeats into a model for studies of fast axonal transport, Szebenyi et al. [40] demonstrated that fast axonal transport was specifically inhibited by pathologically expanded polyglutamine repeats (but not normal proteins), along with inhibition of neurite extension in cultured cells. Further, disruption of the *Drosophila* huntingtin gene also caused axonal transport defects [11]. In combination with the findings that a Huntingtin binding protein HAP1 interacts with a major protein of

Fig. 4 Model illustrating mechanism of axonal transport disruption by mutant/abnormal tau. Under physiological circumstances, tau is transported into the axon, where it binds to and stabilizes microtubules. However, mutant/abnormal tau fails to be transported and/or fails to bind to microtubules, leading to sequestration of tau in the neuronal cell bodies, and offsetting tau-induced microtubule stabilization. Unstable microtubules lead to disruption of microtubule-dependent axonal transport, inducing/facilitating neurodegeneration



the dynactin complex, important for dynein- and possibly kinesin-based movements, as well as the neuropathological findings of accumulated vesicles and organelles in dystrophic axons from patients with the disease, these studies lend support to a model in which aggregates of polyglutamine repeats disrupt fast axonal transport. Whether the disruption of axonal transport is a direct effect of the polyglutamine repeats, or a secondary phenomenon remains to be established.

Axonal transport and amyotrophic lateral sclerosis

The histopathologic observation of prominent neurofilament-rich inclusions in the axons of spinal motor neurons of patients with amyotrophic lateral sclerosis (ALS) led to the hypothesis that disrupted axonal transport of proteins may play a role in the pathogenesis of the disease. However, the first direct evidence showing that axonal transport is disrupted in ALS awaited the development of transgenic mouse models of familial ALS based on expression of mutant SOD-1 proteins in mice [13] that replicate several key aspects of ALS. Studies on these SOD-1 transgenic mouse models of ALS showed that the transport of neurofilament proteins was retarded in these animals [50], even before the mice were symptomatic [49], thereby implicating impaired axonal transport as an early deficit in the onset and progression of neurodegeneration in ALS. To date, no motor protein gene mutations have been reported in ALS, but this notwithstanding, there are persuasive data

to suggest that impairments in axonal transport contribute to neurodegeneration in ALS.

Axonal transport and synucleinopathies

Synucleinopathies, also known as α -synucleinopathies, are a group of neurodegenerative disorders in which the primary pathology is the intracytoplasmic accumulation of α -synuclein (α -syn) primarily in neurons and also in glial cells. These disorders include PD, dementia with LB (DLB), the LB variant of AD (LBVAD), multiple system atrophy (MSA), and neurodegeneration with brain iron accumulation [7, 9, 34]. In familial forms of PD, missense mutations in genes encoding for α -syn are seen, suggesting a role of α -syn in the pathogenesis of these disorders. α -syn is a highly conserved protein belonging to a multigene family that includes β -synuclein and γ -synuclein; α -syn is strongly expressed in neurons and is highly enriched in presynaptic terminals [34]. α -syn is transported predominantly in the slow component, but a fraction (about 10–15%) is also reported to move in fast transport [20]. Axonal transport abnormalities of α -syn have been proposed in synucleinopathies, based on observations that axonal synuclein pathology is pronounced in the disease, and also experimental evidence suggesting that α -syn may play a role in transport of presynaptic vesicles [7, 19]. For example, cell culture studies have shown that the presynaptic vesicular pool is depleted in cultured neurons in which α -syn is suppressed [32], and biochemical studies have shown that

mutant α -syn fails to bind adequately to synaptic vesicles [19], suggesting that α -syn may play a role in vesicular transport. A recent study also showed that, although there was no difference in the axonal transport of mutant α -syn when compared to normal α -syn, there was significant age-related retardation in the normal transport of α -syn [28]. This study proposes a model in which age-related retardation of synuclein transport leads to accumulations of synuclein over time and predisposes synuclein pathology in axons. Although these findings are interesting, many questions remain unanswered. The physiological role of synuclein is far from clear, and much work needs to be done to uncover the role of synuclein in neurodegenerative disorders.

Conclusions and future directions for research

An increasing body of evidence implicates axonal transport defects in the etiology of neurodegenerative diseases. While human mutations in genes encoding motor proteins are very compelling and direct evidence for this, studies of transgenic mice also provide evidence that axonal transport impairments contribute to neurodegeneration. Although finding motor protein defects in neurodegenerative diseases points directly to defects in transport, it is probable that many other disease proteins are directly or indirectly linked to the complicated machinery of axonal transport. Thus, it is imperative that studies into the molecular mechanisms of transport must go hand in hand with the discovery of additional human mutations in familial neurodegenerative diseases linked to the axonal transport machinery. Another exciting but largely neglected avenue is drug discovery efforts to counteract axonal transport impairments as therapeutic interventions for neurodegenerative diseases. Indeed, if axonal transport defects are shown to be part of a common mechanism of disease in many neurodegenerative disorders, the discovery of drugs that modulate axonal transport could become important therapeutic interventions for the treatment of these disorders.

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