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Axonal transport deficits in the pathogenesis of diabetic peripheral neuropathy

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Diabetic peripheral neuropathy (DPN) is a chronic and prevalent metabolic disease that gravely endangers human health and seriously affects the quality of life of hyperglycemic patients. More seriously, it can lead to amputation and neuropathic pain, imposing a severe financial burden on patients and the healthcare system. Even with strict glycemic control or pancreas transplantation, peripheral nerve damage is difficult to reverse. Most current treatment options for DPN can only treat the symptoms but not the underlying mechanism. Patients with long-term diabetes mellitus (DM) develop axonal transport dysfunction, which could be an important factor in causing or exacerbating DPN. This review explores the underlying mechanisms that may be related to axonal transport impairment and cytoskeletal changes caused by DM, and the relevance of the latter with the occurrence and progression of DPN, including nerve fiber loss, diminished nerve conduction velocity, and impaired nerve regeneration, and also predicts possible therapeutic strategies. Understanding the mechanisms of diabetic neuronal injury is essential to prevent the deterioration of DPN and to develop new therapeutic strategies. Timely and effective improvement of axonal transport impairment is particularly critical for the treatment of peripheral neuropathies.

KEYWORDS

axonal transport, diabetic peripheral neuropathy, diabetes, microtubules, molecular motors, cytoskeleton

1 Introduction

Diabetes mellitus (DM) has become a serious global public health problem. According to the International Diabetes Federation (IDF), more than 460 million people worldwide suffer from diabetes mellitus. By 2045, the number of people with diabetes worldwide is expected to reach 628 million (1) The incidence of diabetic complications is also on the rise, with diabetic peripheral neuropathy (DPN) being the most widespread complication of

diabetes and a major cause of disability, foot ulcers and even amputation (2–4).The pathogenesis of DPN involves oxidative stress, excessive activation of polyol pathway, neuroinflammation, diacylglycerol protein kinase C (PKC) pathway activation, accumulation of advanced glycosylation end products (AGEs), and poly ADP-ribose polymerase (PARP) activity increased, Nacetyl glucosamine through homocysteine pathway enhanced protein modification and neurotrophin reduction (3, 5, 6). Many of these mechanisms are intrinsically linked. Despite various preclinical trials targeting pathological features of DPN including accumulation of AGEs, PARP, activation of PKC, activation of polyol pathway and hexosamine pathway, oxidative stress and inflammation have produced some beneficial effects in animal models, all clinical trials for modifying DPN progression have failed (6–9). DPN typically manifests as numbness at the ends of the extremities in a stocking-glove pattern, with the feet in particular being affected ealier and more severely (10). In addition the symptoms of DPN are pain, autonomic and motor neuropathy (11).

Axonal transport plays an instrumental role in neuronal development, the ability to perform normal function and post-injury regeneration. Over the past decade, the significance of axonal transport in neurological disorders has become increasingly clear. Impaired axonal transport, as an influential cause of DPN caused by or exacerbated by diabetes, is strongly linked to the onset and progression of DPN. This seems to be a common thread in most DPNs. Strengthening axonal transport is favorable to the outcome of neurological disorders (12–14). Axonal transport disorders appear early in diabetes, and abnormalities in axonal transport further promotes the pathological progression of DPN. Under normal conditions Axons receive a supply of lipids, proteins, and organelles from the soma (via retrograde transport), while components requiring degradation or recycling are transported back to the cell body (via retrograde transport). Thus structural integrity is critical for neuronal microtubules to serve as stable tracks for long-distance transport of neurofilament (NF), proteins, vesicles containing multiple neurotransmitters, organelles, and Nerve growth factor (NGF) (15, 16).Rapid retrograde axonal transport includes distal nutritional signals (such as autophagy) from the axon to somatic cell transport distal, as well as protein misfolding and aggregation (17).What this process does is return fragmented organelles and membrane constituents to the lysosome for processing and digestion, and possibly transmit information about the status of axons and nerve endings to the cell body (15, 18). In addition, mitochondria, some endosomal groups, lysosomes, and mRNAs undergo bidirectional transport (17). Axonal transport maintains a stable balance between the motor and quiescent states, thereby maintaining neuronal development, function, and survival and protecting the integrity of the entire neuron (19). Diminished anterograde transport, inability of proteins and lipids to reach distal synapses, and inability of mitochondria to meet local energy demands, lead to progressive abnormalities in peripheral sensory nerves, manifesting as hypoesthesia in a sock and glove pattern and eventually sensory loss (13, 20, 21). When axonal transport is damaged, excessive retention and accumulation will lead to mitochondrial metabolic dysfunction, diminished membrane potential, enhanced reactive oxygen species, and calcium overload, thereby damaging mitochondrial function and causing serious toxic effects on cells (22–28). Increasing the transport rate of mitochondria in damaged proximal axons can promote neural regeneration (29, 30), and retrograde transport the injured mitochondria to the cell body for repair or degradation. In streptozocin-induced diabetic rats, impairment of axonal slow transport caused by altered proximal and distal characterization of axonal caliber caused by NF. Specifically, large microtubule cytoskeletal proteins accumulate in the proximal axon region, causing axons to rise and cytoskeletal proteins reaching the distal axons cytoskeleton protein to shrink their size. This results in hypertrophy of the proximal axon area of hypertrophy and thinning of the distal part of the motor neuron dysfunction, with impaired axonal transport (31). In addition, axonal transport allows neurons to respond adequately to distal nutritional and stress signals (32). Failure of rapid axonal transport results in degeneration of nerve fibers, and the damaged nerve fibers aim to regenerate. Although they are vigorous, they are shortlived and a large number of regenerated buds cannot survive. Consequently, neuropathy steadily deteriorates (33).

Hence, any defect involving this hub could contribute to cellular dysfunction and degeneration. This article reviews the mechanisms of axonal transport and their relationship to DPN and provides an outlook on potential future therapeutic targets to enhance the understanding of DPN pathogenesis as well as to provide future research directions and possibilities.

2 Axonal transport

2.1 Axonal transport mechanism

2.1.1 Cytoskeleton

Cargo is transported along the cytoskeleton, which includes actin filament (AF), NF, and microtubule (MT). While all cytoskeletal components are critical for the morphology and function of neurons, axonal transport is almost exclusively determined by MT and its related molecular motors: kinesin, dynein, and myosin (34, 35). MT, the primary track for intra-axonal cargo transport, is a hollow cylindrical structure composed of microtubule proteins (MTs) and microtubule-associated proteins (MAPs). Among them, the aggregation of α-microtubulin heterodimers and β-microtubulin heterodimers is the foundation for the correct orientation of axonal transport. The negative end of α-microtubulin generally is directed towards the cytosol, while the positive end of β-microtubulin faces the axon terminal (34, 35). The positive end of the MT is arranged radially toward the periphery (+ end, positive end). Katanin, a protein associated with microtubules with ATPase activity, is able to sever the central MT and release small viable MTs of varying sizes that can be delivered to axons or synapses (34, 35). Kinesin or Dynein then drives MTs located at the same polarity

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(negative or positive end) for transport along axons. MTs undergo both polymerization (growth) and depolymerization (shrinkage) cycles during transport, which is described as the dynamic instability of MT (36–38). The activity of intrinsic GTPases in MTs and MAPs intervenes in the transformation of MTs from growth to contraction (mutation) or from contraction to growth (rescue) (39). MAPs binds to MT full length, altering its structure, stability and kinetics. Changes in axonal cytoskeletal integrity in DPN support reduced axonal diameter, impaired axonal transport and reduced neural regeneration (39, 40) (Figure 1).

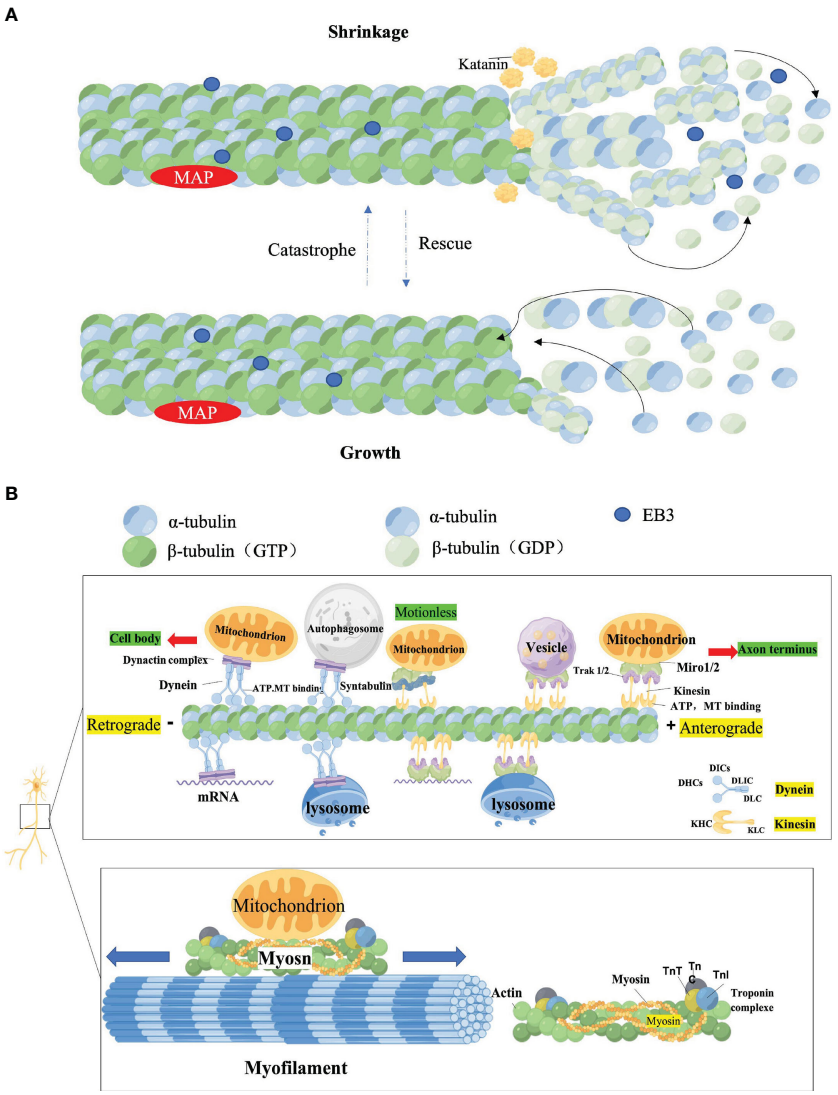

FIGURE 1
(A) Assembly of microtubules (MT). MTs are heterodimers of α-microtubulin and β-microtubulin, arranged radially with positive ends (positive end) facing the periphery and negative ends (−end, negative-end) facing the cytosol. The microtubule-associated protein Katanin cuts off the centrosomal MTs, releasing small and dynamic MTs of different sizes that can be delivered to axons or exons. MTs can proceed concurrent cycles of convergence (growth) and depreciation (contraction) at their plus ends. Microtubule Associated Proteins (MAPs) EB protein, a microtubule-associated protein belonging to the MT plus end tracking protein (+TIPs), binds to EB3 and accumulates at the apex when MTs grow, and dissociates when growth stops or switches from growth to contraction (MTs become smaller). EB3 is also known to regulate microtubule dynamics during axonal outgrowth. **(B)** Axonal transport. Molecular motors, dependent MT and ATP, driven the long-distance transport Microtubules bind to motor proteins, which then link cargo through adaptor proteins to form a cargo transport complex, and the motor proteolysis of ATP provides energy to ensure a smooth process. The major components of molecular motors are Kinesin, Dynein, and Myosin. Kinesin directs the plus end, and Kinesin coordinates the anterograde transport of cargo (such as Vesicle) from the cell body to the axon end along microtubules. Kinesin includes two heavy (KHC) and two light (KLC) chains. The motor domain of KHC, with ATPase activity can bind directly to MTs, whereas its C-terminal domain Interact with KLC or interact with cargo. Dynein coordinates the retrograde transport of cargo such as autophagosomes from axon terminals to the cell body along microtubules. Dynein consists of two Dynein heavy chains (DHCs) and distinct intermediates (DICs), mild intermediates (DLIC), and light chains (DLC). It is mainly required to bind Dynactin (dynein-activating protein) to form the dynein-dynactin complex to bind cargo for axonal transport. In addition, mRNA, Lysosome, and mitochondrial were transported along the axon in both directions. Mitochondria can also use myosin motors for bidirectional transport over short distances along actin filaments. Syntaphilin (SNPH) is a static anchoring protein of axon mitochondria. The MiRO1-TraK2 adaptor complex acts as an important regulator of neuronal cargo transport and increases mitochondrial motility by anchoring mitochondria to MTs.

2.1.2 Molecular motor

In the cytoplasm of neurons, cargo is attached *via* adapters to the corresponding motor proteins, which in turn are attached to the MTs. This process requires the hydrolysis of ATP by motor proteins to provide the driving force for the smooth transport of cargo along the track (41). Various major molecular motors interact to maintain normal axonal transport and are involved in different mechanisms and regulation of cargo axonal transport. In general, kinesins drive the cis-transport of cargo, i.e. the cis-transport from the cell body to the axon terminal is actuated by the motor protein superfamily of kinesins, a process that delivers RNA, proteins and organelles to the growth cones and synapses (42). In contrast, retrograde transport is Dynein-dependent, which is critical for neurotrophic factor signaling, autophagylysosome decay, and response to neural damage (42). In addition, Myosin regulates the short-distance transport of cargo-directed actin filaments (42) (Figure 1).

2.2 Impaired axonal transport promotes DPN progression

2.2.1 Axonal degeneration

Axonal atrophy is the most common pathological feature in type 1 diabetic peripheral neuropathy, manifesting as persistent peripheral nerve fiber loss (43–45). The size of fibers is regulated by the axonal cytoskeleton, and the reduction in axon diameter is associated with a decrease in slow transport proteins (structural proteins) delivered to the axon. In particular, NF, which is the main determinant of axon size (45), directly affects the caliber of the axon, and the number of axons is closely related to the cross-sectional size of the axon with medulla (46–48). In STZ-induced the sciatic nerve (SCN) in DM rats, delayed axonal transport of proteins such as NFs and MTs is not compensated for by delayed protein synthesis, delayed half-lives, or delayed transport volume (31, 49). Furthermore, abnormally phosphorylated NFs are unable to align and interact with other cytoskeletal components, resulting in impaired axonal function and eventual atrophy and loss. This is first manifested by the loss of sensory epidermal fibers (50–53). As this death process proceeds, it causes peripheral nerve stem fibers loss, which begins with the distal nerves and progress to more proximal nerves. Axon diameter in turn affects the fundamental biological characteristics of neurofibers, such as conduction velocity (The increases conduction velocity in proportion to the square root of the interior diameter (54)), excitability and degree of myelination. Another potential pathological feature associated with DPN IENFD deficiency is axonal swelling (55–57). These axonal swellings may be associated with symptoms of sensory enhancement in patients with probable microfibrillary neuropathy (58, 59). Microstructural studies by Ebenezer and colleagues targeting the microstructure of axonal swellings in sensory neuropathies have shown that axonal swelling contains an accumulation of mitochondria, vesicular organelles and NF (60). When axonal transport is disrupted, cargo accumulates abnormally, leading to axonal swelling (58, 61). This is followed by secondary axonal detachment and Wallerian degeneration induced by the damaged axonal transport (62). Axonal degeneration is a predominant pathological change in many peripheral neuropathies, including DPN (63–67) (Figure 2).

2.2.2 Action potential drop

Myelin, the multilaminar sheath on axons,greatly speeds neurotransmission by fundamentally changing the way action potentials are propagated.The myelin sheath that insulates the axon allows action potential to be conducted in a skipping fashion, which conducts faster and consumes less energy than unmyelinated axons. Myelinated axons of nerve cells are organized into a series of polarized fields centered on the Ranvier's node. These structural domains are multimeric protein complexes composed of different cell adhesive molecules, as well as ion channels and scaffold domains of different diameters, that are

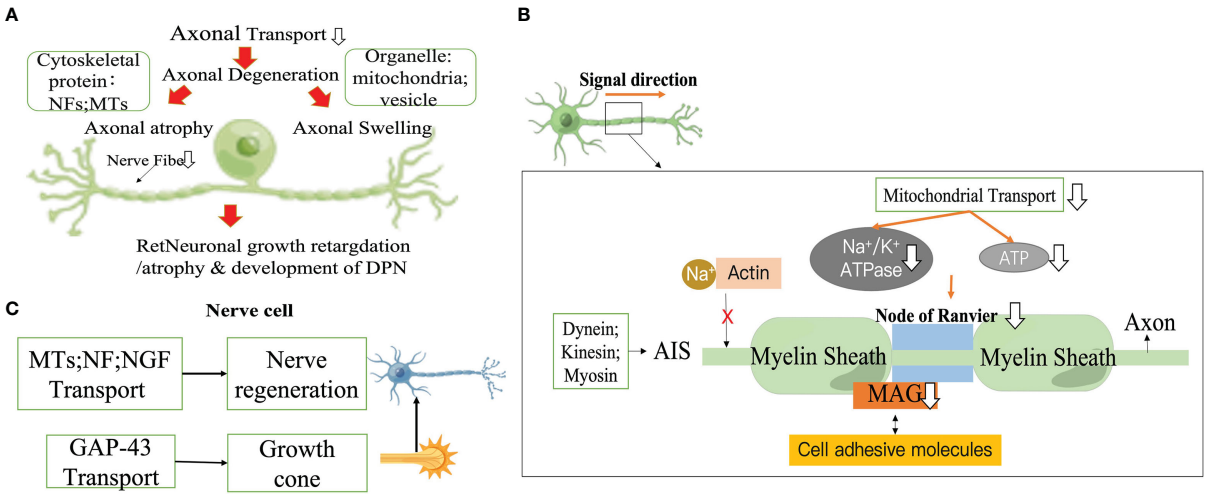

FIGURE 2
Impaired axonal transport promotes DPN progression. **(A)** Axonal degeneration. **(B)** Action potential drop. **(C)** Impaired nerve regeneration. NF, neurofilament; MT, Microtubule; MAG, Myelin associated glycoprotein; AIS, Axon initiation segment; NGF, Neurotrophic factors.

essential for normal jump conduction, axonal transport rates, organelle and skeletal component distribution (68–70). The extracellular matrix (ECM) receptors of the PNS are located in the outer membrane of axon, which is composed of dense myelin, and in the endosome of axon (especially myelin-associated glycoprotein (MAG)) that mediate interactions with axons (71, 72). A several studies have reported significant differences in the intracellular transport of freshly synthesized MAG at Ranvier's node (69). In an early experimental model of diabetes, MAG showed retrograde transport abnormalities (73), exacerbating the reduced nerve conduction velocity as well as the reduced diameter of myelinated fibers in diabetic rats (73–77). Ndel1 is a modulator of kinesin which can be stably anchored to the axon initiation segment (AIS) by interacting with Gankyrin-G and initiates the vesicular cycle through kinesin transport in the AIS (78). Structural maintenance of AIS is closely related to actin-related proteins, casein kinase2 (CK2), myosin ring-associated proteins (actin ring-associated protein, actin ring-associated protein), myosin light chain (MLC) and tropomyosin (Tpm) 3.1 (79–81). Na+ is prevented from entering the AIS after Na+ channels is tightly bound to the actin cytoskeleton (82). ATP at sites of high energy demand (e.g., active growth cones, synapses, axonal branches, or Ranffian nodes) is reduced if mitochondrial transport in axons is impaired (83–86). In the Ranvier's node, impaired mitochondrial transport impairs Na+/K+ ATPase activity, which in return promotes the reversal of axonal membrane Na+/Ca2+ transport proteins and induces an increase in cytoplasmic Ca2+ levels, thereby initiating a number of degenerative pathological processes (87, 88). Because action potentials propagate along axons, it takes a lot of energy to get neurons to transmit action potentials along the identical length of axons. In demyelinating neuropathies, enhanced transport of cargoes (e.g., mitochondria) by axons contributes to their redistribution along axons to areas where demyelination leads to increased ATP demand, which may be a useful therapeutic strategy (Figure 2).

2.2.3 Impaired nerve regeneration

There are various potential mechanisms for the adverse effects of hyperglycemia on peripheral nervous system (PNS). Progressive neuropathy deteriorates not only by nerve fiber degeneration, but also by damaged nerve fibers attempting to regenerate, but but are short-lived despite their vigor and fail to survive even when they produce a large number of regenerative shoots. Failure of fast axonal transport causes this deterioration occurring in a distalto-proximal order (33). Regulation of MTs and NF expression and reduced synthesis/transport of neurotrophic factor have been shown to be linked to defective axonal regeneration in diabetic animals (89–91). Furthermore, aberrations in the growth cone which is the first step in neuronal regeneration can depress the success of regeneration. Growth-associated protein 43 (GAP-43) can be translocated from the cell body to the distal axon *via* rapid axonal transport within the vesicle. Basic experiments have confirmed that GAP-43 deficiency can contribute to abnormal growth cones. In ligation and extrusion experiments in STZ-induced DM rats, it was concluded that immunostaining for GAP-43 was reduced on neuronal proximal peduncles (92). Changes in axonal transport rates in diabetic patients may involve presynaptic calmodulin supply and mechanisms associated with GAP-43 disruption (93). *In vitro*, GAP -43 binds to calmodulin at moderate Ca2+ concentrations and dissociates from calmodulin at higher Ca2+ concentrations, while hyperglycemia-induced phosphorylation of protein kinase eliminates this calcium dependence (94–96) (Figure 2).

3 Mechanisms of axonal transport injury

3.1 Glycosylation

Excessive glycosylation is present in the neural tissue of diabetic patients with elevated blood glucose levels, resulting in the deposition of AGEs in various sites of diabetic peripheral nerve tissue (97). Amadori compounds appearto be the main pathway responsible for the formation of AGE products. Accumulation of Amadori glycosylation products has been demonstrated in the spinal cord of patients with amyotrophic lateral sclerosis and spinal medullary amyotrophy, possibly associated with the glycosylation of cytoskeletal proteins. Increased glycosylation of AGEs and MTs in diabetic rats can lead to abnormal axonal transport and impaired nerve growth and regeneration after 2 weeks (46, 98–100). Amino acid analysis has shown that the lysine residue was the major glycosylation site (101). This suppresses the GTP-dependent aggregation of MTs and stiffens axonal structures, thus disrupting axonal transport. However, the extent to which increased glycosylation of MTs interferes with peripheral axonal transport remains unclear. In diabetic nerves, NF protein glycosylation, NF impairment and active transport are often accompanied by histological and electrophysiological alterations, leading to long-term neurodegenerative changes (31, 46, 49, 102, 103). Binding of a receptor for advanced glycosylation end products (RAGE) with cell surface receptors and its cytoplasmic structural domain interacts with Diaphanous Related Formin 1(DIAPH1) on the cytoskeleton, whose dysfunction may lead to neuropathy. The cumulative effect of hyperglycemia on RAGE- DIAPH1-mediated signaling pathways may disrupt the organization and transport of axonal cytoskeleton (104). Axonal transport of mDia1, RAGE-interacting protein and actin binding protein was affected in RAGE knockout mice compared to wild-type mice at 3 h and 6 h after diabetic sciatic nerve injury (102). The loss of RAGE showed a positive correlated with the decrease of AGE level. The mDia1 axonal transport correlates better to diabetes-induced glycosylation of actin induced by diabetes. Glycosylated actin has been reported to be found in brain homogenates derived from diabetic animals and in platelets from early diabetic patients (102, 105). Alterations in the structure of actin may affect mDia1 actin interactions, leading to impaired translocation between the two. In addition, research on extracellular matrix proteins found in diabetic nerve endosomes suggests that premature glycosylation of these proteins affects axon growth (102, 106). Osonoi et al. reported that high glucose induced the activation of AGE/RAGE signaling

pathway, which could further promote the progress of DPN by reducing insulin signaling pathway and inducing macrophage activation. Phosphorylation of TNF-α directly stimulates JNK, thereby disrupting retrograde axonal transport. On the other hand, TNF-α stimulation attenuates insulin signaling in neuronal cells. GSK3β is located downstream of insulin and JNK signaling, which phosphorylates components of the dynein complex and decreases retrograde vesicle transport (107) (Figure 3).

Current evidence suggests that the fast axonal transport rates may not be affected by RAGE (102). This is because glycosylation of proteins associated with diabetes is a relatively long process and the rapid transport of axons is so fast that hyperglycemia does not to mediate this change. STZ-induced DM rats have highly increased microtubule protein glycosylation in peripheral nerves, but brain microtubule protein glycosylation in controls did not show any increased changes (102), suggesting that inhibition of microtubule assembly in the brain is independent of the the level of glycosylation (106). The mechanisms of impaired axonal transport are very complex in nature and are not limited to a single cause (108).

3.2 Post-translational modification

The main modality of MT regulation is *via* post-translational modifications (PTMs), involving acetylation, phosphorylation and glutamylation (109–111). Microtubule protein PTMs abnormalities in sensory neurons have been related to axonal regeneration damage (112, 113).

Acetylation modifications of microtubule protein can promote self-healing and stabilization of MT (114–117). The α/β heterodimeric a-subunit of Lys40 in MTs is the site of acetylation modification of microtubulin (114), which can determine MT motor processivity (118–121). Kinesin-1 reacts preferentially with acetylated and demethylated MT (120, 122, 123). In fact, acetylation-modified MTs is the preferred pathway for driving protein 1-independent mitochondrial translocation, and the ER/mitochondrial contact and mitochondrial fusion/division also selectively take place on acetylated MTs (117, 124–126). Histone acetyltransferases (HATs) and histone deacetylases (HDACs) are involved in the acetylation modification of microtubulin, as well as their regulation of the acetylation and deacetylation loops of lys40 on MTs in -microtubulin, respectively (117). Histone deacetylase 6 (HDAC 6) is a cytoplasmic class II histone deacetylase that targets acetyl groups on posttranslationally modified non-histone proteins (e.g., microtubules) to with significant alteration the target protein (127). Microtubule stability is affected by the balance between HDAC6 and HAT1, and once this balance is disrupted, cellular damage is induced. In particular, increased HDAC6 activity is specifically detrimental to neurons (128, 129), and its dysregulation is closely interlinked with the occurrence of peripheral neuropathy, neuronal microtubule instability, and reduced mitochondrial axonal transport (130–132).

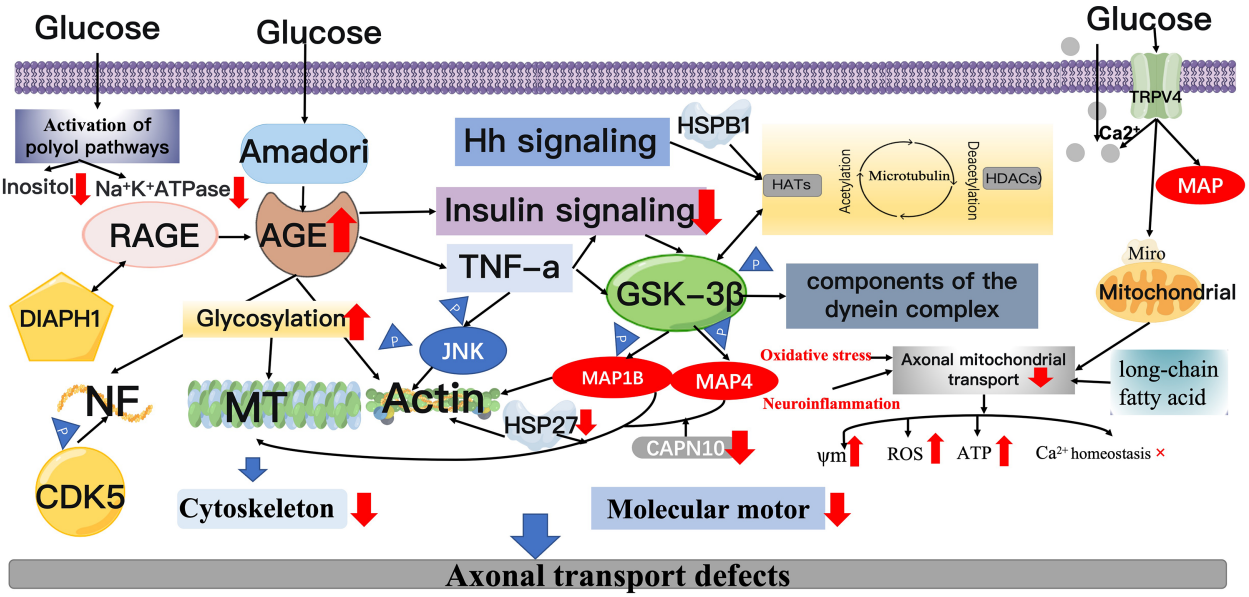

FIGURE 3
Mechanisms of axonal transport injury. AGEs: Hyperglycemia induces the production of Amadori compounds, which undergo a series of changes to form AGEs, which are deposited on the cytoskeleton of peripheral nerve cells. AGEs bind to its receptor, RAGE. On the one hand, the RAGE cytoplasmic structural domain can inhibit GTP-dependent MT aggregation by associating with DIAPH1 on the cytoskeleton, and on the other hand, it can impair axonal transport by interacting with the actin-binding protein mDia1.Espectively, regulate the acetylation and deacetylation cycle of microtubulin in MTs *via* lys40; GSK-3β can inhibit the phosphorylation of MAP1B, MAP4, and dynein, affecting MT assembly and stability and actin filament remodeling. GSK-3β can also directly phosphorylate dynein intermediate chains. The NDEL1 bound region that promotes dynein export. CDK5 can be modified by posttranslational modifications and phosphorylation of NF. JNK3 phosphorylates the motor structural domain of KIF5 and suppresses binding to MT. Heat shock proteins: Maintain the stability of actin cytoskeleton. TRPV4: TRPV4 promotes extracellular Ca^{2+} influx, and elevated Ca^{2+} levels may directly inhibit mitochondrial axonal transport by binding to the mitochondrial surface protein Miro. TRPV4 also contributes to MT demolition through direct binding to microtubule proteins. In combination with the direct glycosylation damage of hyperglycemia, prolonged exposure to high glucose levels induces oxidative stress, activation of polyol pathways and inflammation.

Serine protein kinase 3β (GSK-3β), cyclin-dependent kinase 5 (CDK5), and c-jun NH2 -terminal kinase 3 (JNK3)have affinity for cytoskeletal elements (133–135). GSK-3β is a potent protein phosphorylation stress kinase. A whole transcriptomic study of SCN in experimental models of T1DM and T2DM found that downregulation of microtubule-associated protein 1B (MAP1B) and microtubuleassociated protein 4 (MAP4) was associated with common alterations in the structure of SCNs (136, 137). It is hypothesized that this is associated with impaired insulin and IGF-1 signaling pathways, leading to reduced GSK-3β, which inhibits phosphorylation of MAP1B. MAP1B coordinates the remodeling of MT and actin filaments within neuronal cells, regulates MT assembly and stability (138, 139), provides the basis for axonal transport and polarity, and plays an essential part in the evolution and sustenance of the PNS network (140). GSK-3β directly phosphorylates MAP and kinesin in neurons, and the binding of MAP and MT is enhanced, further regulating MT kinetics (141). Furthermore, MAP1B is the first candidate susceptibility gene for type 2 diabetes (138). Calpain-10 (CAPN10) is a part of the calpain family of enzymes, which coordinates its binding activity to MT and actin filaments by processing microtubule-associated protein 1 (MAP1) family proteins to form heavy and light chains (142). Impaired MT-F actin integration and abnormal actin dynamics are associated with deletion of CAPN10 and MAP1B. It was found that insulin and glucagon secretion was significantly increased in CAPN10 knockout mice (142) (Figure 3).

In addition, GSK-3β negatively modulates the kinesin engagement with NDEL1. GSK -3β directly phosphorylates the intermediate chain of kinesin, which is a key site in the binding region of the protein to NDEL1, and can facilitate kinesin output. Enhancement of insulin signal or direct GSK-3β suppression can activate kinesin movement (143). The reduction of GSK-3β activity enhances transport capacity and leads to retrograde migration of organelles compared to quiescent organelles, such as eosinophilic organelles, but this has little effect on anterograde transport. In most cases, phosphorylation coordinates their binding to MTS, which may involve the movement of dynamic proteins in many ways. TRAK1 is the key protein that connects the MOM protein Miro to the motor kinesin and kinetic protein of the molecule (144). GSK-3β has been described to be essential for the function of kinesin and dynein proteins (145). GSK-3β forms a complex by physically binding to TRAK1, DISC1 and NDE1, though GSK-3β does not alter mitochondrial motility speed or mitochondrial excursion length (146). The Hedgehog (Hh) signaling pathway can affect the level of MT acetylation in mammalian cells. Activity of the Hh pathway induces an increase in the level of MT-associated DYRKiB kinase, inhibits GSK3 β *via* phosphorylation of serine 9 and subsequently inhibits HDAC6 enzyme activity, which in turn promotes acetylation levels of MT. The Hh signaling pathway can promote MT non-independent processing by activating of DRKiB, such as intracellular mitochondrial transport, polarization of mesenchymal cells and directed cell migration (Figure 3).

Phosphorylation of NFs is influenced by CDK5 expression (46, 147), and abnormalities in this process are present in peripheral nerve injury (49, 98, 148, 149). Aberrant phosphorylation of neurofilament proteins (NFs) and abnormal MTs caused by NF-related protein kinases were found in dorsal root ganglion cells (DRGs) of DPN rats, a result that led to reduced axonal transport of NFs and progressive defects in axonal function (147, 150, 151). NF mRNA is not elevated during development and radial growth, therefore post-transcriptional regulation of NF appears to be more important. The stability of NF transcript is mediated by various neurotrophic molecules like nerve growth factor (NGF), NT-3, IGF-1, insulin and c-peptide.

Studies have revealed that in the SCN of experimental DPN rats, retrograde transport of NGF is impaired and abnormal phosphorylation of NF disrupts its arrangement and interaction with other cytoskeletal components, leading to compromised axonal functions and eventual atrophy and loss (152). In addition to MT changes, insufficient or incorrect NF protein synthesis can also severely damage the axonal cytoskeleton, and abnormal NF expression, processing, and structure can lead to DPN progression (153) (Figure 3).

JNK3 phosphorylates the KIF5 locomotor region and suppresses its binding to MT (154, 155). JNK, p38, and ERK are activated in DRG and in the sural nerve with the potential to mediate neurodegenerative diseases (156, 157). This may be connected to the fact that activation of JNK and ERK mediates abnormal phosphorylation of NF in DM sensory neurons, leading to axon diameter loss and nerve terminal death (157). However, the enhanced DM-induced activation of JNK and p38 is limited to the anterograde portion of axonal transport (157).

3.3 Heat shock proteins

Heat shock proteins (HSPs) are a class of highly conserved proteins discovered in 1962. HSPs, have been demonstrated to be upregulated in many neurological diseases as a mechanism to counteract the aggregation or formation of abnormal proteins identified in disease conditions (158, 159). Minor heat shock protein B1(HSPB1, also referred to as HSP27) is broadly expressed *in vivo* (160). HSP27 is associated with neuronal survival and hereditary neuropathy, which is reported to be essential for the recovery of both sensory and motor neurons (159, 161–163). Overexpression of HSP27 occurs in some target tissues of diabetes complications (163–166). In mice, knockdown or overexpression of HSP27 correlates with diminished or enhanced regenerative properties after nerve injury (167–169). The neuroprotective mechanism may be related to the stabilization of the actin cytoskeleton (170). Overexpression of transgene HSP27 in T1DM mice displays protective effects against loss of thermal sensation, mechanical nociceptive sensitization, epidermal innervation loss and delayed sensory transmission (171). Serum levels of HSP27 (sHSP27) might thus be a novel biomarker of DPN (172): sHSP27 expression levels in T1DM are independently associated with distal symmetric polyneuropathy, and low serum levels of HSP27 are linked to extensive nerve fiber dysfunction (173). In the peripheral nerve samples from asymptomatic mutant

HSPB1 transgenic mice, it was discovered that it did not modify the level of acetylated α-tubulin, so its stabilizing effect on microtubules was enhanced (174). Interestingly, in symptomatic mutant HSPB1 transgenic mice, acetylated α-tubulin levels were decreased and microtubule instability was raised, possibly due to enhanced HDAC6 recruitment (174). Defective axonal transport is related to the downregulation of acetylated α-microtubulin, and this instability can result in defective axonal transport (175). This transport defect can be remedied by the use of the optional HDAC6 inhibitor Tubastatin A or the class I and class II HDAC inhibitors trigonelline A (176). Similarly, Kim et al. recently found defective mitochondrial axonal transport in motor interneurons extracted in patients carrying the HSPB1 synapse, and this could also be repaired by using specific HDAC6 inhibitors (177). HSPB1 protects well against diabetic distal polyneuropathy in DM mice, as overexpression of HSPB1 in neurons of DM mice can protect against a range of neuropathies, including mechanical hyperalgesia, loss of footpad thermal sensation, reduced sensory conduction velocity, and loss of epidermal innervation (178). The function of P150 provides the link between various cellular cargoes and the reverse molecule kinesin, as well as governing kinesin movement (179) Mutant HSPB1 colocalizes with P150, causing mislocalization of P150 in the cell, impeding retrograde transport necessary for cell function and survival, specifically for motor neurons. Nonetheless, mitochondrial transport defects were not involved, possibly because the HSPB1 mutation has no effect on anterograde axonal transport, or perhaps only some anterograde transport substances are disrupted (180) (Figure 3).

3.4 Molecular motor

Forty-five kinesin motor genes have been identified, among which the kinesin-1 family (KIF5) is the core motor gene responsible for driving neuronal cargo transport (155, 181). KIF5A, KIF5B and KIF5C in mammalian KIF5 genes are all expressed in neurons, but at different levels in different cell types (182, 183). In STZ-induced DM rats, KIF5B levels are elevated in the SCN and KIF5B mRNA expression was increased in the spinal sensory and motor neurons (184). Recently, various studies have indicated that expression is low in the dorsal root ganglion (DRG) neurons of diabetic male rats (185). Upregulation of KIF5B expression may be a compensatory mechanism associated with the re-establishment of axonal motor levels. KIF5A is involved in both fast axonal transport in mitochondria and slow axonal transport in NFs. NFs are involved from the early stages of the disease and the accumulation of these NFs in somatic cells leads to the depletion, loss and degeneration of large diameter axons (186–190). KIF5A translocation plays an essential role in PI3Kmediated cell survival and sensitization of supporting neurons (191). KIF1A participates in the trafficking of synaptic vesicles, NGF receptors, and TrkA (192), and any changes in this kinesin may promote the progression of diabetic neuropathy (191). Children with KIF1A mutations exhibit global developmental delay, mental retardation, bilateral lower extremity weakness, and diabetes mellitus (193).

Interestingly, there are gender differences in the expression of axonal motor proteins in DM (194), and Pesares et al. observed in early DM that the the mRNA level protein content of kinesin family members KIF1A, KIF5B, KIF5A and Myosin was altered only in male rats (185). Both the time to onset, incidence and severity of neuropathy are higher in males than in females (195–197). The decline in IENFD is more pronounced in males presenting with neuropath, such as high contraction thresholds in the foot and paw (198, 199). It is speculated that it may be related to neuroactive steroid activity. Neuroactive steroids are able to regulate mitochondrial function, which plays an essential part in axonal transport through the production of ATP (the energy source for movement). The gender-specific alterations in this motor protein identified in animal models of diabetes may eventually explain the gender differences in pain and analgesia observed in DPN (197, 198). Furthermore, expression of activated dynamin-1-like protein (DRP1) is significantly enhanced in the DRG of male DM patients, with rapid mitosis ultimately leading to unhealthy mitochondria (20). It promotes mitochondrial fragmentation and may impair mitochondrial function. Reduced transit ATP content further exacerbates axonal transit damage.

3.5 TRPV4 ion channel

Transient receptor potential cation channel subfamily V member 4 (TRPV4) is located in the cell membrane of sensory cell neurons derived from the PNS and other cell types throughout the body. Upon activation, TRPV4 promotes extracellular Ca2+ influx. In the adipose tissue of prediabetic mice fed with high-fat diet, high expression of TRPV4 leads to an injurious hypersensitivity response (200). Ca2+ coordinates the start of fast axonal transport as well as the stable transport of intraaxonal cargo (201, 202). Ca2+ fluctuations gravely alter mitochondrial function and movement (203–205). For example, rising Ca2+ levels can inhibit mitochondrial axonal transport directly through Ca2+ association with the Miro, a mitochondrial surfactant protein involved in docking with the motor domain of kinesin-1 (206). Moreover, the interaction of TRPV4 with MAP Ensconsin is an essential requirement for kinesin-1 (207–209).

Treatment of STZ-induced DM mice with the selective TRPV4 channel antagonist HC067047 markedly inhibited mechanical hyperalgesia (210, 211). Ca2+ influx in neurons occurs in the presynaptic-post-synaptic membrane, where a large amount of energy is required to maintain ionic gradients and mitochondrial abundance. In addition, when local ATP levels are relatively low, the ability of Ca2+ to pump across the cytoplasmic membrane is compromised, resulting in a sustained rise in Ca2+ in the cytoplasm. Therefore, locally elevated Ca2+ can be anchored to high energy demand and low supply by blocking the passing mitochondria. Conversely, where ATP is high with excess mitochondria, Ca2+ will be low and mitochondria will migrate freely.TRPV4 can also bind directly to microtubule proteins, leading to MT disassembly (212) (Figure 3).

3.6 Other

In parallel to direct glycosylation damage caused by hyperglycemia, chronic exposure to high levels of glucose can induce oxidative stress, activation of polyol pathways, and inflammation. All types of damage may interfere with axonal transport. The state of oxidative stress raises the amount of the retrograde mitochondria, while neuroinflammation increases the quantity of resting mitochondria and inhibits retrograde mitochondrial transport. Slowness of mitochondrial transport promotes an increase in ROS related to mitochondrial dysfunction, and the accumulation of mitochondrial mutations (213). In contrast, it has been indicated that anterograde transport of nerve cells exposed to ROS is more likely to be inhibited than retrograde transport (214). Increased glucose levels in neuronal cells lead to saturation of the normal glucose metabolic pathway, with excess glucose being shunted to polyol pathway and converted to sorbitol and fructose *via* the enzymes aldose reductase and sorbitol dehydrogenase (215). The accumulation of these substances causes a decrease in inositol, diminished membrane Na+/K+ ATPase activity, impaired axonal transport and disruption of neural structures, which induces the propagation of abnormal potentials (216). Treatment with an aldose reductase inhibitor reduces susceptibility to rapid axonal transport after STZ-induced nerve entrapment in diabetic rats (217, 218), and reduces the inhibition of fast axonal transport. Cis-axonal transport of choline acetyltransferase has been reported to be restored following treatment (219, 220) (Figure 3).

Plasma free saturated fatty acid (SFA) levels are generally higher in patients with T2DM and may be involved in the occurrence and progress of peripheral neuropathy (221). It was found that DRG neurons exposed to elevated SFAs have reduced numbers of mitochondria in their axons (222, 223). long-chain fatty acids (e.g. palmitic and stearic acids) in SFA can damage DRG neurons, and their elevated concentrations disrupt mitochondrial transport, alter mitochondrial bioenergetics (224, 225) (222), reduce the amount and speed of mitochondrial motility, and depolarize mitochondria (223). Increased levels of complex lipids such as palmitic and stearic acids in the SCN of HFD and HFD- STZ mice have been shown to impede mitochondrial function and its transport, inducing apoptosis in DRG neurons (226, 227). Increased intake of a diet rich in monounsaturated fatty acid (MUFA) reversed neuropathy and restored nerve transmission velocity and nerve fiber density within the epidermis (228), which may be related to the prevention of impaired mitochondrial transport in SFA palmitate-treated sensory neurons cultured *in vitro* by MUFA oleic acid (Figure 3).

In addition, axons may be affected by microvascular alterations in the vascular plexus of peripheral nerves (229) in advanced cases of diabetes. Alterations in microvascular structure, together with neurological and biochemical disorders, may lead to a decline in internal blood flow and partial oxygen pressure. Regional compression of normal peripheral nerves by 30 mmHg can cause changes in internal circulation and increased internal vascular permeability (230, 231), which may be more pronounced in DM patients. As a result of such changes, axonal transport induced by compression may be remarkably inhibited (232) (Figure 3).

4 Conclusions and future directions

Treatment for reversing impaired axonal transport is still largely in experimental animal models of DPN without effective methods to detect axonal transport in the clinic. For example, in diabetic rats, impaired cis-axonal transport can be improved by aldose reductase inhibitors or oral inositol. The addition of an aldose reductase inhibitor 3 weeks after induction of diabetes reversed defects in choline acetyltransferase axonal transport and motor nerve conduction velocity (220, 233–235), which may be related to the promotion of actin slow component B (SCb) and βtubulin (SCb) in DM rats (236). Ginkgo biloba extract (GBe), increasing the mean axonal diameter, slowed down the slow axonal transport block induced by high glucose (234). Exercise, as a non-drug pathway, exerts a beneficial effect in the treatment of DPN axonal transport defects. Endurance exercise inhibits the increase of KIF5, KIF1B, Dynein and other molecular motor protein contents in SCN of DPN rats (237), promotes axonal transport, and ameliorates nerve damage (238, 239). Diabetic rats treated with gangliosides have been proven to prevent the progression of MNCV deficiency (240–243), and another study showed that gangliosides protect against impaired axonal transport of different molecular versions of acetylcholinesterase in diabetic animals (242). In *in vitro* cultured SFA palmitatetreated sensory neurons, increased intake of a diet rich in monounsaturated fatty acid (MUFA) prevented impaired mitochondrial transport and reversed neuropathy (228). Aminoguanidine protects the cytoskeleton of DPN rats by inhibiting the accumulation of AGEs and glycosylation of structural proteins (49, 74, 149, 244–247). In cultured adult DRG neurons, Hsp27 expression promotes axonal growth (248), which may be related to its ability to promote actin polymerization (249, 250), a key component of axonal extension (251). Recent work has shown that HDAC6 inhibitors, such as Ricolinostat, an inhibitor of histone deacetylase 6, have been effective in improving DPN (252), chemotherapy-induced peripheral neuropathy (CIPN) (253, 254), and peroneal muscular dystrophy (CMT) type 2 disease (255) in animal models with good safety and tolerability. The mechanism is to inhibit HDAC6 to improve acetylation of microtubulin, promote mitochondrial translocate to the outer end of neurons, provide and maintain necessary energy and nutrition for nerve fibers, stimulate regeneration of intraepidermal nerve fibers (IENFs), restore nerve fiber function, and essentially alleviate and heal peripheral nerve injury (Table 1).

In experimental models and animal nerve samples from DPN patients, neuroanatomical and electrophysiological aberrations linked to axonal transport include reduced fiber diameter, reduced motoneuron conduction velocity, segmental demyelination and axonal lost, ultimately leading to impaired neuronal degeneration and regeneration. The metabolic mechanism of hyperglycaemia are well studied and have been

TABLE 1 Potential therapeutic approaches to improve axonal transport mechanisms in diabetic peripheral neuropathy.

Treatment	Pathological Changes	Mechanism	Evidence-based
Essential fatty acid (228)	Nerve conduction velocities	Mitochondrial transport Intraepidermal nerve fiber density	Animal studies Cell culture experiments
Aldose reductase inhibitors (220, 233–236); Inositol (233)	Nervous conduction velocity; Axonal transport of choline acetyltransferase	Promotion of actin slow component B (SCb) and βtubulin (SCb)	Animal studies
Ginkgo biloba extract (GBe) (234)	Disturbed slow axonal transport	Increased the mean diameter of axons	Animal studies
Exercise (237–239)	Retrograde axonal transport is impaired	Inhibit the increase in the content of molecular motor proteins	Animal studies
Gangliosides (240–243)	Prevents defects in the accumulation of systolic PFK activity; reverses damaged transport of different forms of the molecule acetylcholinesterase by axons.	Inhibit the structural breakdown of the axonal endoskeleton	Animal studies
Aminoguanidine (49, 74, 149, 244–246)	Nervous conduction velocity; Improved myelin fiber size reduced axonal atrophy	Inhibition of structural protein glycosylation, thereby preserving cytoskeletal organization.	Animal studies
Microtubule stabilizer (HDAC6 inhibitors) (252–255)	Stimulate the regeneration of intraepidermal nerve fibers, recover nerve fiber function	Increasing the acetylation of tubulin by inhibiting HDAC6	Animal studies Cell culture experiments
Hsp27 (248–251)	Enhances neurite growth	Promoting actin polymerization	Cell culture experiments

recognised as impairing axonal transport and promoting the occurrence and development of DPN by activating glycosylation, polyols, oxidative stress, and inflammation. Hyperlipidemia is more extreme, and light loss due to excess saturated fatty acids contributes to the pathogenic mechanism. The insulin signaling pathway aggravates the progression of DPN through protein phosphorylation kinases and kinase phosphorylation modifying microtubules and molecular motors. In the future, the heat shock protein sHSP27 may be a novel biomarker for diabetic neuropathy by promoting microtubule stabilization to enhance axonal transport disorders and successfully restore nerve regeneration.

Even with strict glycemic control or pancreatic transplantation, established neuropathy is difficult to reverse. Hence, targeted approaches that use axonal regeneration to reverse the abnormalities are imperative. Reconstructing the axonal transport function of nerve cells is promising as a potential therapeutic target for DPN.

Author contributions

CY conceived and wrote the article. FL proofread the data and provided guidance for writing and submission. XZ revised the grammar of the text. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher’s note

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