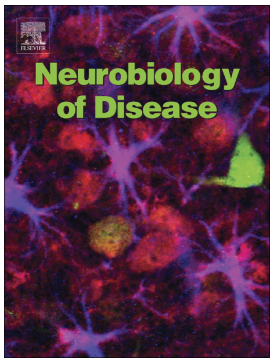

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Defective Axonal Transport: A Common Pathological Mechanism in Inherited and Acquired Peripheral Neuropathies

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Abstract:

Peripheral neuropathies are characterized by a progressive and length-dependent loss of peripheral nerve function. This can be caused either by genetic defects, classified as 'inherited peripheral neuropathies', or they can be acquired throughout life. In that case, the disease is caused by various insults such as toxins and mechanical injuries, or it can arise secondary to medical conditions such as metabolic disorders, nutritional deficiencies, inflammation and infections. Peripheral neuropathies are not only very heterogeneous in etiology, but also in their pathology and clinical presentation. A commonality amongst all peripheral neuropathies is that no pharmacological disease-modifying therapies currently exist that can reverse or cure these diseases. Moreover, the length-dependent nature of the disease, affecting the longest nerves at the most distal sites, suggest an important role for disturbances in axonal transport, directly or indirectly linked to alterations in the cytoskeleton. In this review, we will give a systematic overview of the main arguments for the involvement of axonal transport defects in both inherited and acquired peripheral neuropathies. In addition, we will discuss the possible therapeutic strategies that can potentially counteract these disturbances, as this particular pathway might be a promising strategy to find a cure. Since counteracting axonal transport defects could limit the axonal degeneration and could be a driving force for neuronal regeneration, the benefits might be twofold.

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Introduction

Peripheral nerves connect the central nervous system with peripheral tissues in the body and are therefore crucial for all living animals to communicate with their environment. The visceral peripheral nervous system (PNS) innervates the internal organs, blood vessels and glands, while the somatic PNS connects the central nervous system (CNS) to the skin, joints and muscles through both sensory and motor nerve axons (reviewed in (Benoy et al., 2015b)). The motor neuron perikaryon is localized in the spinal cord, while the cell body from a sensory neuron resides in the dorsal root ganglia (DRG).

Unlike the CNS, which is protected by the bone of the spine and skull, the peripheral nerves are only surrounded by an incomplete blood-nerve barrier. Additionally, the extensive length is an important factor contributing to the vulnerability of peripheral nerve axons. Peripheral neuropathies are characterized by the progressive length-dependent loss of peripheral nerve function and are heterogeneous in etiology, pathology and clinical presentation. The current classification is based on medical observations, although the typical clinical and genetic heterogeneity hampers epidemiologic and clinical studies (Weis et al., 2016). Peripheral neuropathies can arise as a consequence of various insults such as toxins (e.g. chemotherapeutics) and mechanical injuries. In addition, they can also occur secondary to medical conditions such as metabolic disorders (e.g. diabetes), nutritional deficiencies (e.g. alcohol-abuse), inflammation and infectious diseases (Benoy et al., 2015a; England and Asbury, 2004). These cases are referred to as the 'acquired peripheral neuropathies' (APNs). A second group of peripheral neuropathies is distinguished based on evidence for a genetic origin, the 'inherited peripheral neuropathies' (IPNs) (Baets et al., 2014; Weis et al., 2016). Further classification of IPNs is based on clinical observations of which nerve fiber type is affected. Patients are diagnosed with 'Hereditary Motor and Sensory Neuropathy' (HMSN) or 'Charcot-Marie-Tooth disease' (CMT) when both motor and sensory nerve axons are involved. Based on electrophysiological analysis, patients with CMT are further categorized in type 1 (CMT1), type 2 (CMT2) or an intermediate type. Generally, CMT1 is associated with reduced nerve conduction velocities, correlated to decreased myelination of the peripheral nerves, while CMT2 patients show reduced action potentials, related to a reduced number of active axons within a nerve fiber. Patients with both signs of demyelination and axonal degeneration are diagnosed with intermediate CMT (Bassam, 2014). 'Hereditary Motor Neuropathy' (HMN) arises when predominantly degeneration of motor nerve axons occurs while 'Hereditary Sensory and Autonomic Neuropathy' (HSAN) involves dysfunction of both sensory and autonomic nerve axons.

At present, alterations in more than 70 genes are associated with IPN (for a detailed overview: http://neuromuscular.wustl.edu/ and http://www.molgen.ua.ac.be/CMTMutations) (Baets et al., 2014). Currently, there is no pharmacological therapy available to treat or cure peripheral neuropathies. Identification of underlying genetic defects contributes to a better understanding of the pathogenic

mechanisms leading to IPN and the development of potential therapeutic strategies to treat peripheral neuropathies. However, recently interesting advances have been made that can lead to the identification of new potential therapeutic targets (d'Ydewalle et al., 2012).

Peripheral neuropathies are often associated with disturbances in axonal transport or alterations in the cytoskeleton (Pareyson et al., 2015). Neurons are terminally differentiated cells, requiring the cytoskeleton for their typical architecture consisting of one long extending axon and multiple dendrites (Baas et al., 2016). The cytoskeleton not only ensures this characteristic structure, but also supports several functional processes within a neuron such as axonal transport dynamics. Three distinct, interacting structural complexes form the cytoskeleton: the microfilaments (actin), the intermediate filaments (neurofilaments) and the microtubules. Microtubules are cylindrical polymers composed of α- and β-tubulin heterodimers (Fig. 1a) (Chakraborti et al., 2016; Garnham and Roll-Mecak, 2012). These α-/β-tubulin building blocks form a protofilament and, in general, 13 protofilaments are laterally positioned to construct a microtubule with a lumen of about 25 nm diameter. Built by heterodimers, the microtubule obtains a specific orientation with a stable minus and a dynamic plus end, favored for addition and subtraction of subunits (Fig. 1a). Moreover, the microtubules are uniformly distributed with their plus end away from the soma in the axon of a neuron, while a more mixed but preferred distal-minus-end orientation is observed within the dendrites (Baas et al., 2016; Chakraborti et al., 2016).

Microtubules are used as molecular tracks to guide delivery of cargoes (such as newly synthesized proteins, lipids, RNA, and organelles) to different parts of the cell. An intact microtubule network is also required for the clearance of damaged organelles by cellular degradation mechanism (Gibbs et al., 2015). This cellular transport is essential in neurons as this also ensures the crosstalk between soma and synapse through the axon. Axonal transport can be classified according to the speed of transport. Vesicles, RNA and organelles are part of fast axonal transport which is conducted at a speed of 0.5–3 mm/s. Slow axonal transport (0.1–3 mm/day) is used by some soluble proteins and cytoskeletal components such as neurofilaments and tubulin itself (Gibbs et al., 2015). Apart from the microtubules, several other components can be distinguished (Gibbs et al., 2015). The molecular motors driving this transport are two ATP-dependent protein families (Fig. 1a). The kinesin family members are required for the microtubule plus end directed transport which is indicated as anterograde transport. The cytoplasmic dynein carries cargoes in the retrograde direction, towards the minus end of microtubules. Kinesin and dynein are assisted by adapter proteins that couple these motor proteins to the different cargoes and regulate the activity of the motors (De Vos et al., 2008; Gibbs et al., 2015). Over the past decade, the histone deacetylase 6 enzyme (HDAC6) has emerged as an important regulator of axonal transport through its deacetylating modification of α-tubulin (Simões-Pires et al., 2013a), which inhibits motor proteins binding to the microtubules and interferes with transportation of

different cargoes. Moreover, HDAC6 also bind $p150^{glued}$, a subunit of the dynactin-dynein complex, and interacts directly with kinesin-1 (reviewed in (Van Helleputte et al., 2014)).

Defects in axonal transport dynamics, but also in the cytoskeleton architecture, often contribute to peripheral neuropathies (Pareyson et al., 2015). The importance of axonal transport in neurodegeneration has also become evident over the last decade (De Vos et al., 2008; Millecamps and Julien, 2013). Multiple studies report that improving axonal transport has beneficial effects on the outcome of neurodegenerative disorders (reviewed in (Hinckelmann et al., 2013; Van Helleputte et al., 2014)). Moreover, improvements in axonal trafficking has been shown to facilitate regeneration of damaged axons (Yogev et al., 2016; Zhou et al., 2016), making it an interesting pathway to study in the context of developing an effective therapy for the treatment of peripheral neuropathies. Therefore, we will discuss in this review the current understanding of the potential role of axonal transport dysfunction and alterations in the cytoskeleton in the pathology of the acquired, as well as of inherited peripheral neuropathies. Furthermore, we will highlight potential new therapeutic strategies to treat peripheral neuropathies targeting axonal transport dynamics as well as the cytoskeleton.

Figure 1a| Schematic overview of the cytoskeleton and the axonal transport machinery. (1) Axonal transport cargoes, such as lysosomes and mitochondria, anchored to the motor proteins kinesin and dynein. (2) The molecular motors kinesin and dynein travel along the microtubules with their bound cargoes in an anterograde and retrograde fashion, respectively. (3) Heat shock protein B1 (HSPB1) has putative roles in cytoskeleton stabilization and roles in neurofilament assembly. (4) Histone deacetylase 6 (HDAC6) is an important regulator of axonal transport. (5) Stabilized microtubules with the minus end facing the soma and dynamic plus end facing the synaptic terminals.

The genetic code: indications for axonal transport dysfunction

The most common inherited peripheral neuropathy is CMT with a prevalence of approximately 1 in 2,500 individuals (van Paassen et al., 2014). CMT is a heterogeneous disease which is reflected in both its phenotype and genotype. However, the general pathology is caused by a breakdown in signalling from the nerves to their connected muscles in the distal regions of the body, which ultimately causes the disability. Axonal transport defects are one of the main suspected pathogenic mechanisms, as they appear to be a common denominator in several neurodegenerative diseases (Millecamps and Julien, 2013). A number of gene products of CMT-causing genes seem to be directly involved in axonal transport, while others could have a more ambiguous role. For instances, the proteins encoded by *DYNC1H1* and *KILF1B* genes are molecular motors with a direct role in axonal transport of cargoes. Others gene products of disease-related genes could indirectly influence axonal transport. One example are mutations in the gene encoding the TRPV4 ion channel that could influence the intracellular Ca^{2+} concentration which can inhibit mitochondrial transport. Other examples are mutations in proteins related to systems that heavily rely on axonal transport, such as mitochondria (e.g. MFN2 protein associates with the Miro-Milton complex for the transport of

mitochondria), or in proteins that have putative roles in axonal transport dynamics (e.g. HSPB1 by influencing microtubule dynamics). However, for other proteins encoded by CMT-causing genes, such as those that belong to the aminoacyl-tRNA synthetases, it is currently unclear how they cause pathology only in the longest nerves in the body, as these proteins are ubiquitously expressed. In the following sections, we will discuss the mutations in genes that have a direct and indirect link to axonal transport and will be summarized in table 1.

Molecular motors: KIF1β & DYNC1H1

Kinesins are a large superfamily of microtubule-dependent molecular motors which are mainly responsible for the axonal transport of cargoes in the anterograde direction and are powered by the hydrolysis of ATP. Thus far, there are 45 genes identified that give rise to the kinesin superfamily proteins (KIFs) in mammals. However, much more variants may exist due to alternative mRNA splicing (Hirokawa et al., 2009). KIFs can be grouped into 15 subgroups of kinesin families (kinesin 1-14b) based on phylogenetic clustering (Shen et al., 2012). These kinesin families can be further subdivided into three major groups on the basis of the position of their motor domain within either the amino-terminal region, middle, or carboxyl-terminal region (N-KIFs, M-KIFs, and C-KIFS, respectively). KIF1B is a member of the monomeric family of kinesin 3 family and has two major splice forms, KIF1Bα and KIF1β. Both isoforms are involved in axonal transport of synaptic vesicles in an anterograde fashion, with some of the synaptic vesicles containing proteins such as synaptotagmin, synaptophysin, and Rab3A (Okada et al., 1995). KIF1Bα and KIF1β are identical in their primary amino-terminal sequence. However, they differ in their carboxyl-terminal region, which dictates their binding specificity to different client proteins. A point mutation causing a loss of function in the ATPase domain of KIF1β has been reported to cause CMT2A1 (Zhao et al., 2001). Although, there is some controversy over this discovery, as it is the only case reported of KIF1β mutations causing CMT.

The other major molecular motor superfamily in eukaryotes is the dynein and dynactin superfamily of proteins comprising of cytoplasmic dyneins and axonemal dyneins. These proteins are primarily responsible for axonal retrograde transport (Hirokawa et al., 2010). Cytoplasmic dynein is an enormous protein complex of approximately 15.5 megadaltons and is used for intracellular transport. This protein complex is composed of multiple polypeptide subunits: two heavy chains, two intermediate chains, four intermediate light chains, and several light chains. Dyneins are mechanoenzymes that move along microtubules by hydrolyzing ATP through their two heavy chain domains (Hirokawa et al., 2010). Importantly, cytoplasmic dynein interacts with its cargoes through an associated dynactin complex composed of $p150^{Glued}$, dynamitin, actin-related protein 1, p27, p24, p62, CAPZa and CAPZb (Hirokawa et al., 2010). Mutations in the *DYNC1H1* gene, which codes for 'dynein, cytoplasmic 1, heavy chain 1' (DYNCH1), lead to axonal CMT (CMT2O) (Rossor et al., 2012; Weedon et al., 2011). Furthermore, these mutations have been shown to reduce axonal

retrograde transport (Zhao et al., 2016), but also impair mitochondrial morphology and function with age (Eschbach et al., 2013). Interestingly, it was shown that mutations in *DYNC1H1* impair Schwann cell myelination in a zebrafish model (Langworthy and Appel, 2012). These results give insight into how proper Schwann cell-neuronal interactions are required for Schwann cell myelination, but also axonal transport, which will be discussed further in the section on Schwann cell myelination related proteins Additionally, mutations in the *DYNC1H1* gene are also known to cause a number of other neurodegenerative conditions, such as dominant spinal muscular atrophy with lower extremity predominance, and intellectual disabilities, (reviewed in (Eschbach et al., 2013; Hoffman and Talbot, 2012; Schiavo et al., 2013; Wee et al., 2010)).

Structural intermediate filaments: NEFL & LMNA

Neurofilaments (NFs) are a complex class of intermediate filament proteins and constitute the most abundant cytoskeleton component in large myelinated axons (Laser-Azogui et al., 2015). They are formed from three different subunits in the PNS, NF light chain (NFL), NF medium chain (NFM), and NF heavy chain (NFH). Peripherin intermediate filament proteins also associate with NF proteins in the PNS and α-internexin has also been shown to form dimers with NF proteins, but this is mainly restricted to neurodevelopmental stages or in the CNS (Laser-Azogui et al., 2015). The three NF proteins are structurally distinct proteins that share a common basic ternary domain and can form intricate hetero-polymeric complexes between themselves (Yuan and Nixon, 2016). This basic ternary domain consists of a conserved central α-helical rod domain flanked by a variable head and tail domain located in the amino- and carboxyl-terminal regions, respectively. The head domain is rich in serine and threonine residues, and the highly variable tail region is composed of lysine- and glutamine-rich repeats of varying lengths, thus being one of the main factors that establishes the size range of the four subunits (Yuan and Nixon, 2016). Furthermore, it has long been known that NFs have an intrinsic role in forming and maintaining the axonal architecture, axon calibre, and intracellular transport of cargoes within the dendrites of neurons (de Waegh et al., 1992; Hoffman et al., 1987). In addition, post-transcriptional modifications of NF head and tail domains have a prominent influence on NF assembly and the axon calibre of large myelinating neurons (Fig. 1b) (de Waegh et al., 1992; Laser-Azogui et al., 2015; R. L. Friede and T. Samorajski, 1970). Axoplasm regions encased by Schwann cell compact myelin are predominately composed of NFs with their tail regions phosphorylated. This renders the surface area more negative, repelling other NF tail regions which increases the overall diameter in that segment of axon (Fig. 1b) (de Waegh et al., 1992; Pant, 1994). In contrast, nodal regions, which are indicated as the nodes of Ranvier, have a significantly lower amount of NF phosphorylation, which is accompanied with a reduction in axon calibre and a higher density of NFs (Fig.1b) (de Waegh et al., 1992). As a consequence, clusters high in densities of voltage-gated Na^+ and K^+ ion channels, and Na^+/K^+ ATPase ion pumps are located at these nodes of Ranvier (Fig. 1b). Interestingly, during the progression of demyelination in disorders such as multiple sclerosis, there is a

significant decrease of Na^+/K^+ ATPase ion pumps (Young et al., 2008) and upregulation of voltage-gated Na^+ ion channels (Craner et al., 2004) at these regions of highly phosphorylated NFs (Craner et al., 2004; de Waegh et al., 1992). The consequence of a progressive ion disequilibrium and energy demanding redistribution will be discussed further in the next section on demyelinating CMT forms.

Additionally, NFs have been shown to have a fundamental role in maintaining Schwann cell-axon interactions, as *NEFL*-null mice show reduced maturation and regeneration of myelination (Zhu et al., 1997). Moreover, alternative roles for NFs at the synapses have been highlighted in recent years (Yuan and Nixon, 2016). As indicated in the previous paragraphs, NFs have a role in maintaining both the axonal architecture as well as axon-Schwann cell interactions. Thus, mutations in NFs can lead to a neuropathy with a predominant axonal (Mersiyanova et al., 2000) or a demyelinating phenotype (Jordanova et al., 2003). An affirmation of this is the fact that mutations in the NF light polypeptide gene (*NEFL*) can cause autosomal dominant demyelinating CMT phenotype (CMT1F) or axonal CMT (CMT2E) (Tazir et al., 2013). In addition, mutations in *NEFL* have been shown to cause autosomal recessive (AR) forms of CMT (ARCMT2/CMT2B5), where there are no NFs or intermediate filaments in the axons, resulting in a loss of large-diameter fibers (Yum et al., 2009). These patients typically have an early onset and a severe CMT2 phenotype. In line with this, missense mutations in the *NEFL* gene have been shown to cause NF accumulation in the cell body and proximal axon, and disrupt NF assembly, as well as impair axonal transport of mitochondria (Brownlees et al., 2002). Phosphorylation of the NFL head domain was shown to be an essential regulator of NF axonal transport (Yates et al., 2009). More recently, $NEFL^{N98S}$ patient derived induced pluripotent stem cells (iPSCs) were differentiated into spinal motor neurons (iPSC-MNs) (Saporta et al., 2015). These iPSC-MNs had significant abnormalities in mitochondrial trafficking and electrophysiological characteristics, such as a reduced action potential threshold and abnormal channel current properties (Saporta et al., 2015). This may be due to altered K^+ and Ca^{2+} channel kinetics.

Mutations in the lamin A/C gene (*LMNA*) have been shown to cause autosomal recessive axonal forms of CMT (CMT2B1) and these mutations have only been found to date in families originating from North Western Africa (Hamadouche et al., 2008; Lassuthová et al., 2009). Lamin A and C proteins are structural components of the nuclear lamina at the nucleoplasmic side of the nuclear envelope and have roles in normal functioning of chromatin (Dechat et al., 2008). They have ternary structures composed of a head-domain, a central α-helical rod-domain, and an immunoglobulin-like tail domain (Dittmer et al., 2011). Mutations in the *LMNA* gene have previously been shown to cause premature aging, cardiac, neuromuscular, and lypodystrophy disorders. More recently, a CMT2B1 patient carrying a $LMNA^{M348I}$ mutation was shown to also have arrhythmogenic right ventricular cardiomyopathy (Liang et al., 2016). Using *Xenopus* retinal ganglion cell axons, Yoon and colleagues demonstrated that inhibiting lamin B2 causes axonal degeneration, mitochondrial dysfunction, and deficits in axonal transport (Yoon et al., 2012). Their work suggests that axonally synthesised lamin B

mRNA plays a crucial role in axon maintenance by promoting mitochondrial functioning (Yoon et al., 2012). One could speculate that dysfunction of this extranuclear function of lamin forms may be a possible underlying cause of the axonal CMT2B1 phenotype (discussed in the review (Gentil and Cooper, 2012)).

Figure 1b| Schematic representation of the node of Ranvier and the internodal interface. (1) Abundance of Na^+, K^+ and Na^+/K^+ ATPase pumps positioned at the nodal regions. (2) Dense neurofilament network positioned at the nodal regions. (3) Schwann cell myelination over the axon. (4) PMP22 and P0 are located in the compact myelin regions, while Cx32 is located in non-compact myelin regions. (5) Phosphorylation of the neurofilament tail and head domains render them to have a negative surface charge repelling them from one another. (6) Increase in axon caliber at myelinated axon regions

Ion channels: TRPV4

Mutations in the transient receptor potential cation channel, subfamily V, member 4 (TRPV4) cause axonal CMT2C and scapuloperoneal spinal muscular atrophy (Auer-Grumbach et al., 2010; Deng et al., 2010; Landouré et al., 2009). TRPV4 is a cation channel that is also Ca^{2+}-permeable and which has multiple functions. Mutations in the *TRPV4* gene have shown to cause cytotoxic hypercalcemia (Klein et al., 2011) which can cause axonal degeneration. Moreover, mitochondrial function and motility are sensitive to Ca^{2+} fluctuations (Del Arco et al., 2016; Jeyaraju et al., 2009; Mironov et al., 2005). Specifically, increased levels of Ca^{2+} can directly inhibit mitochondrial axonal transport by Ca^{2+} binding to the mitochondrial surface protein Miro, which is responsible for the docking to the motor domain of kinesin-1 (Wang and Schwarz, 2009). In addition, TRPV4 also interacts with the microtubule-associated protein, ensconsin (Suzuki et al., 2003), which is required for the recruitment of kinesin-1 (Barlan et al., 2013; Sung et al., 2008). Thus, although no direct evidence is currently available to link *TRPV4* gene mutations to axonal transport deficits, it is a possible pathogenic mechanism in TRPV4-related diseases. Although, it is worth noting that axonal transport deficits could be secondary symptoms to the primary cause of disease, hypercalcemia.

Schwann cell myelination related proteins: MPZ, PMP22 and Cx32

The "demyelinating" form of CMT, CMT1, accounts for the largest majority of CMT patients, with, depending of the demographics, between 38 to 84% of patients being diagnosed with CMT1 (Barreto et al., 2016). Some of the first studies linking mutations in myelin specific proteins to defects in axonal transport were conducted by de Waegh and colleagues, (de Waegh et al., 1992; de Waegh and Brady, 1990). Using the Trembler mouse, which carries point mutation in the gene coding for peripheral myelin protein 22 (PMP22), the authors demonstrated that disruption of normal myelination caused a reduction in slow axonal transport, abnormal cytoskeletal organization and NF phosphorylation. PMP22 is an integral membrane glycoprotein in compact myelin that is needed for normal myelin formation. Point mutations in *PMP22* cause CMT1E, while the most common form of CMT, CMT1A, is caused by duplications in the segment of chromosome 17p11.2 harbouring the

coding region for the *PMP22* gene (Raeymaekers et al., 1992, 1991; Timmerman et al., 1992). Interestingly, haploinsufficiency of the *PMP22* gene causes hereditary neuropathy with liability to pressure palsies (van Paassen et al., 2014). Furthermore, it was shown that point mutations in *PMP22* lead to a destabilized microtubule network, which may be the direct cause of the observed axonal transport deficits (Kirkpatrick et al., 1994) (see table 1). For CMT1A, it was also shown that overexpression of PMP22 protein leads to formation of PMP22 aggregates which impairs the autophagosome-lysosomal pathways (Fortun et al., 2007, 2006; Ryan et al., 2002). These autophagosome-lysosomal pathway and myelin homeostasis disruptions ultimately leads to the breakdown of the Schwann cell-neuronal interactions. This could impair axonal transport due to neuronal abnormalities in the cytoskeleton organization and NF phosphorylation.

In a *Gjb1-null* mouse model, which replicates the X-linked form of CMT in patients (CMT1X), axonal pathology was shown to precede demyelination (Vavlitou et al., 2010). The *GJB1* gene codes for the connexin 32 protein (Cx32), which is essential for forming gap junctions between myelinating Schwann cell's layers of cytoplasm. These gap junctions are required for an efficient transport of ions and small molecules between the adaxonal and abaxonal layers of cytoplasm. Interestingly, Vavlitou *et al.* demonstrated that the lack of expression of Cx32 can cause axonal retrograde transport defects, NF abnormalities, such as reduced NF spacing and phosphorylation, and a reduction in axon calibre (Vavlitou et al., 2010). In CMT1X patients, hundreds of mutations in the *GJB1* gene were reported that all appear to lead to a loss-of-function, as mutations and complete deletions give rise to the same disease manifestations (Kleopa et al., 2013). How these axonal cytoskeletal abnormalities are the result of impaired gap-junction formations in Schwann cells at the paranodal regions remains unclear. However, these results illustrate the close link between normal Schwann cell myelin homeostasis and axonal cytoskeleton integrity.

Another transmembrane glycoprotein protein is P0 encoded by the myelin protein zero gene *(MPZ)*. P0 is a major structural component of myelin and is specific to the PNS. Mutations in the *MPZ* gene cause a variety of neuropathies including congential hypomyelinating neuropathy and Déjèrin-Sottas syndrome, as well as both a demyelinating and axonal forms of CMT (CMT1B and CMT2I/J, respectively) (Auer-Grumbach et al., 2003; Bird, 1998). Under normal conditions, P0 interacts with PMP22 (D'Urso et al., 1999) which may be essential for the maintenance of myelin sheath in the PNS. Mutations in the cytoplasmic domain of the P0 protein impair its cytoplasmic cellular trafficking (Konde et al., 2006). Moreover, the fact that mutations in the *MPZ* gene can also cause axonal forms of CMT suggests that there are pathological modifications to the cytoskeleton network. One possibility could be that the NF status is affected, as is seen in patients with *GJB1* or *PMP22* point mutations, which could impair axonal transport. Similarly, mutations in the *MPZ* gene that lead to a demyelinating phenotype may induce a neuropathology through structural reorganization of voltage-operated Na^+ channels, Na^+/Ca^{2+} exchangers, and Na^+/K^+ ATPase pumps to counteracting the loss of

the axon's conductor, myelin (Fig. 2a). In fact, a severe transgenic mouse model for neuropathies, which is completely deficient in P0, showed an improved motor performance and compound muscle action potentials after oral treatment with a $Na_V1.8$ blocker (Rosberg et al., 2016).

Interestingly, Kiryu-Seo *et al.* revealed a significant increase in mitochondrial transport and mitochondrial size in the demyelinated neurons through comparison of myelinated and lysolecithin-induced demyelinated rat dorsal root ganglion cultures (Kiryu-Seo et al., 2012). Axonal transport levels returned to normal after neurons were remyelinated. These results give insight into how neuronal cells may try to cope with the increased oxidative stress and energy demands bestowed on the demyelinated neurons, possible due to remodelling of voltage-gated Na^+ channels, Na^+/Ca^{2+} exchanger, and Na^+/K^+ ATPase pumps (Craner et al., 2004; Stys et al., 1993, 1992). Action potentials are conducted in a diffuse manner requiring the influx of Na^+ ions followed by an efflux of K^+ ions. Moreover, during demyelination, voltage-operated Na^+ channels are redistributed along the axolemma in order to compensate for the loss of myelin (Fig. 2a), which acted as a conductor for the action potential at internodal regions. Furthermore, increased colocalization of the Na^+/Ca^{2+} exchanger was altered in demyelinating pathologies and represents a possible pathological mechanism (Craner et al., 2004). The increased demand of Na^+ channels results in an increase of Ca^{2+} being exchanged, which can be toxic for the axons (Stys et al., 1993, 1992). Na^+/K^+ ATPase pumps are required to restore the resting membrane potential of the axolemma after action potentials, but this requires energy in the form of ATP. Thus, in demyelinating pathologies, there is a redistribution of Na^+/K^+ ATPase pumps along the axon to regions that are no longer myelinated. In doing so, the action potential is conducted in a "continuous conduction", rather than a "saltatory conduction". As action potentials are propagated along the axon in a diffuse manner, there is a higher energy demand on the neuron to conduct the action potentials along the same length of axon. Possible therapeutic strategies for demyelinating neuropathies would benefit from increasing axonal transport of cargoes, such as mitochondria, to help redistribute them along the axon to regions where there is an increased ATP production needed, due to the demyelination.

Mitochondrial proteins: MFN2

Mitochondria have a fundamental role in cellular bioenergetics by producing the cell's energy source, ATP, by oxidative phosphorylation. In addition, mitochondrial dynamics are an essential element in how mitochondria can respond to cellular stress and still maintain their functionality (Silva Ramos et al., 2016). Mitochondrial fission and fusion are dynamic events which allow mitochondria to respond to increased cellular energy demands, for example during cell growth (Chada and Hollenbeck, 2003). Fusion of dysfunctional mitochondria to healthy mitochondria enables the healthy mitochondria to compensate for the dysfunctional ones (Youle and Bliek, 2012). Alternatively, fusion events may also occur between healthy mitochondria in order to respond to the increased cellular demand of oxidative phosphorylation. Thus, the correct functioning and the position of mitochondria along the

axon is essential to provide the energy required and to ensure the proper functioning of neurons (Fang et al., 2016; Silva Ramos et al., 2016). The key proteins that enable these agile organelles to carry out the fusion events are mitofusin proteins 1 and 2 (MFN1 and MFN2, respectively) (Youle and Bliek, 2012). These mitochondrial outer membrane proteins are not only involved in fusion events, but are also required for mitochondria morphology (Santel and Fuller, 2001), endoplasmic tethering (Naon et al., 2016), synaptic formation (Fang et al., 2016), and mitochondrial motility (Baloh et al., 2007; Misko et al., 2010). Mutations in the *MFN2* gene cause CMT2A2 and account for approximately 4% of all CMT patients (Verhoeven et al., 2006). *MFN2* mutations predominately cause an axonal form of CMT. However, in some patients these mutations can also cause an intermediate form of CMT with demyelinating features (Verhoeven et al., 2006). Baloh *et al.* demonstrated that there was altered axonal transport of mitochondria in rat DRG neurons expressing disease-associated human MFN2 protein (Baloh et al., 2007). Furthermore, there was abnormal clustering of mitochondria at the cell body and proximal regions of the axons (Baloh et al., 2007). In a follow-up study, Misko and colleagues demonstrated that the MFN2 protein was required for axonal transport of mitochondria and that MFN2 interacts with the Miro/Milton complex (Misko et al., 2010). In a separate study, Chapman *et al.*, demonstrated mitochondrial axonal transport deficits in a loss-of-function zebrafish model, which had a N-ethyl-N-nitrosourea (ENU)-induced nonsense mutation in the zebrafish *Mfn2* gene (Chapman et al., 2013). Strickland *et al.* showed in a *Mfn2* knock-in mouse model expressing $Mfn2^{R94W}$, a mutation previously reported in humans, that homozygous pups died at P1, while heterozygous mice demonstrated decreased open-field activity. However, neither exhibited deficits in axonal mitochondrial motility. Similarly, Saporta *et al.* used CMT2A2 patient derived iPSCs, differentiated into spinal cord motor neurons. These cells only demonstrated mild axonal transport abnormalities, while changes in the action potential threshold and channel current properties were more pronounced (Saporta et al., 2015).

Figure 2a| Schematic overview of various pathogenic mechanisms that indirectly impair axonal transport. (1) Enhanced influx of Ca^{2+} into the cell can cause axonal degeneration and impair mitochondrial transport. Also, redistribution of Na^+, K^+, and Na^+/K^+ ATPase pumps along regions previously covered in myelin. (2) Increased neurofilament densities in areas previously myelinated. (3) Repeated Schwann cell myelination causes "onion bulb" formations and causes the Schwann cell to lose its contact with the axon. (4) Mutations in myelin specific proteins, such as PMP22, P0, and Cx32 cause abnormal myelination. (5) Alterations to neurofilament phosphorylation, assembly, and accumulation are common pathological events that are associated with axonal transport defects. (6) A reduction in axon calibre due the loss of contact with the associated Schwann cell and neurofilament phosphorylation.

Heat-shock proteins: HSPB1, HSPB3, and HSPB8

Mutations in the small heat-shock protein B1 (HSPB1, also known as HSP27) cause CMT2F and distal HMN2B (Evgrafov et al., 2004; Rossor et al., 2012). HSPB1 is a member of the small heat-shock protein (small HSP) family which are ubiquitously expressed. It has putative functions as

molecular chaperone proteins preventing misfolded or non-native proteins from aggregating (Horwitz, 1992). Small HSPs have an evolutionary conserved α-crystallin domain which confers chaperone activity, and N-terminal and C-terminal domains that vary between different members and are essential for forming oligomeric structures (Haslbeck et al., 2005). Additionally, HSPB1 is involved in a myriad of functions ranging from cytoskeleton stabilization (Almeida-Souza et al., 2011) and neuronal protection against apoptosis-inducing factors (Kalwy et al., 2003; Lewis et al., 1999) to roles in NF assembly (Evgrafov et al., 2004) (Fig. 2a) and autophagy (Matsumoto et al., 2015; Tang et al., 2011). Mutations in these small HSPs alter the binding affinity to their client proteins, rather than acting as loss-of-function mutations (Almeida-Souza et al., 2011). This was demonstrated by mutant *HspB1* transgenic mice having an increased stabilizing effect on microtubules without altering the acetylation α-tubulin levels in peripheral nerve samples from presymptomatic *HspB1* transgenic mice (Almeida-Souza et al., 2011). Interestingly, the acetylated α-tubulin level was reduced in symptomatic mutant *HspB1* transgenic mice, which could be due to the enhanced recruitment of HDAC6. This could have a net destabilizing effect on the microtubules (d'Ydewalle et al., 2011). This destabilizing effect could lead to deficits in axonal transport, which correlated with a reduction of acetylated α-tubulin levels. Moreover, this axonal transport deficits could subsequently be rescued with the treatment of a selective HDAC6 inhibitor, tubastatin A, or a class I and class II HDAC inhibitor, trichostatin A (d'Ydewalle et al., 2011). More recently, we confirmed that the axonal transport deficit in DRG neurons isolated from mutant *HspB1* mice can be rescued by different new HDAC6 inhibitors (Shen et al., 2016). A library of selective HDAC6 inhibitors was tested on increasing acetylated α-tubulin levels in comparison to tubastatin A (Shen et al., 2016). In line with this, Kim *et al*. recently demonstrated mitochondrial axonal transport deficits in motor neurons differentiated from iPSCs obtained from patients with *HSPB1* mutations (Kim et al., 2016). Moreover, these axonal transport deficits could also be rescued using different HDAC6 inhibitors. Collectively, this data suggest that post-translational modifications, and more specifically acetylation of α-tubulin, allows for rapid and precise regulation of microtubule dynamics.

Also other members of the small HSP family, such as HSPB3 and HSPB8, are known to cause CMT2 and distal HMN (Irobi et al., 2004; Kolb et al., 2010). HSPB3 and HSPB8 (also known as HSPL27 and HSP22, respectively) have roles in autophagy and in preventing formation of protein aggregates in cells (Rossor et al., 2012). There was a reduction in membrane potential and aggregates containing mutant HSPB8 proteins were formed in fibroblasts isolated from distal HMN patients harbouring mutations in *HSPB8* (Irobi et al., 2012). Moreover, these proteins are also known to have an essential role in autophagy, as overexpression of the wild type HSPB8 protein in motor neuron-like NSC34 cells resulted in autophagosomes co-localized with protein aggregates that failed to fuse with lysosomes (Kwok et al., 2011). In the same study, the authors demonstrated that similar results were seen in peripheral blood mononuclear cells from two distal HMNII patients with the *HSPB8*^{K141E}

mutation (Kwok et al., 2011). HSPB8 mutations could also induce the CMT2 phenotype through their direct interactions with HSPB1 (Sun et al., 2004) or, like HSPB1, through their indirect or direct interactions with the cytoskeletal network (Holmgren et al., 2013), although evidence for this is currently lacking.

Mutations in the *HSPB3* gene cause distal HMN2C and spinal muscular atrophy (SMA) (Wee et al., 2010). Nothing is known about the mechanisms that underlie the distal HMN phenotype caused by mutations in *HSPB3*. One possibility is that mutant HSPB3 has similar detrimental effects on axonal transport as mutant HSPB1 mutations.

Aminoacyl-tRNA-synthetases: YARS, KARS, AARS, MARS, HARS, & GARS

Aminoacyl-tRNA-synthetases (ARS) are ubiquitously expressed enzymes that catalyse tRNA molecules to bind to their cognate amino acids, an essential step in protein translation. There are six genes encoding ARS proteins that are known to cause axonal CMT. These CMT-causing genes are encoding for tyrosyl-tRNA synthetase (YARS) (Jordanova et al., 2006), lysine-tRNA synthetase (KARS) (McLaughlin et al., 2010), alanine-tRNA synthetase (AARS) (Latour et al., 2010), methionyl-tRNA synthetase (MARS) (Gonzalez et al., 2013), histidyl-tRNA synthetase (HARS) (Vester et al., 2013), and glycyl-tRNA synthetase (GARS) (Antonellis et al., 2003). How these ubiquitously expressed proteins cause axonal CMT remains unclear, but it indicates that there is a non-canonical function of the ARS proteins in the peripheral nerves (He et al., 2015). Some mutations in the *GARS* gene alter the ability of the enzyme to link tRNA to glycine, while other pathogenic mutations do not (Motley et al., 2010). Whether mutations in the *GARS* gene cause the disease through a 'loss-of-function' or a 'gain-of-function' is not yet clear. Some recent work favours a toxic 'gain-of-function' mechanism (Grice et al., 2015; Malissovas et al., 2016; Motley et al., 2011; Niehues et al., 2015). Recently, we observed that wild type GARS protein interacts with HDAC6 in co-immunoprecipitation experiments as well as in a mouse model carrying an endogenous $Gars^{C201R}$ mutation. The mutated GARS protein has an enhanced binding capacity for HDAC6 (Benoy et al., 2015a). Moreover, axonal transport defects were observed in DRG neurons cultured from these $Gars^{C201R}$ mice and these axonal transport deficits could be rescued by treatment with a HDAC6 inhibitor (Benoy et al., 2015a).

Whether mutations in the other AARS proteins increase their affinity to the HDAC6 enzyme or whether axonal transport defects in the neurons of these patients are present remains unknown. It is tempting to speculate that similar pathogenic mechanisms (i.e. gain-of-function toxicity and axonal transport defects) could be at play for each of these analogous proteins.

Small GTPase: RAB7

There are more than 60 Rab GTPase proteins in humans, which show approximately 50% homology (Srikanth et al., 2016). The ubiquitously expressed Rab GTPase family of proteins belong to the Ras GTPase superfamily. These are master regulators of vesicle formation and intracellular

membrane transport through vesicular targeting, tethering, and fusion with targeted compartments (Saraste, 2016). Furthermore, they are involved in the recruitment of molecular motors for vesicular transport and trafficking of ion channels (Amaya et al., 2016; Bucci et al., 2014; Saraste, 2016). Rab GTPase proteins exhibit an active state when bound GDP is catalysed by guanine-nucleotide exchange factor to GTP. Conversely, these proteins are in an inactive state when bound GTP is hydrolysed to GDP (McCray et al., 2010). Mutations in the *RAB7* gene cause axonal CMT2B which has a prominent sensory phenotype and distal muscular atrophy (Verhoeven et al., 2003). Due to prominent sensory loss, CMT2B patients can present with ulcerations, osteomyelitis, which can lead to amputations (Auer-Grumbach et al., 2000). This particular small Rab GTPase functions in late endosomal/lysosomal pathways. Moreover, mutations in *Rab7* have been demonstrated to cause axonal transport deficits and axonal degeneration in rat DRG neurons (Zhang et al., 2013). Additionally, a novel interaction between Rab7 and the intermediate filament protein, peripherin was demonstrated using a yeast two-hybrid system. The mutated Rab7 protein demonstrated enhanced binding to peripherin (Cogli et al., 2013). This interaction could also play a role in destabilizing the axonal NF network, which could be a possible mechanism explaining how *RAB7* mutations impair axonal transport.

Giant axonal neuropathy/CMT2

Giant axonal neuropathy (GAN) is an extremely rare, yet devastating, lethal autosomal recessive inherited neuropathy, in which there is a mutation in the *Gigaxonin* gene (Boizot et al., 2014). The *Gigaxonin* gene encodes for the ubiquitously expressed gigaxonin protein, which is thought to be a E3 ubiquitin ligase adaptor protein (Bomont, 2016). The disruption of gigaxonin's function causes the aggregation of intermediate filament proteins leading to the formation of giant axons that are thinly myelinated (Bomont and Koenig, 2003). Although, GAN has classically been described to have a CNS involvement, milder forms have being reported in which no CNS involvement was detected (Aharoni et al., 2016; Koichihara et al., 2016). Recently, the gigaxonin protein has been demonstrated to be involved in the ubiquitin–proteasomal degradation of neuronal intermediate filaments. Moreover, the accumulation of these intermediate filaments impaired mitochondrial axonal transport and caused metabolic and oxidative stress (Fig. 2b) (Israeli et al., 2016; Lowery et al., 2016).

Figure 2b| Schematic overview of the various pathogenic mechanisms directly affecting axonal transport. (1) Mutations or alterations that impair the docking of motor proteins kinesin and the dynein and dynactin complex from assembling or interacting with their cargo. (2) Mutations in mitochondrial proteins or proteins involved in lysosomal trafficking, such as MFN2 and RAB7, respectively. (3) Improper degradation of neurofilaments can impair axonal transport. (4) Mutations in the heat shock protein B1 (HSPB1) protein can impair its putative roles in neurofilament assembly. (5) Over recruitment of HDAC6 can have a destabilizing effect on the microtubule network.

Table 1. Summary of the mutated genes associated with IPNs with their direct and indirect links to axonal transport dysfunction.

Acquired peripheral neuropathies

The majority of patients develop a peripheral neuropathy unrelated to their genetics. These acquired peripheral neuropathies (APNs) are the major neurological complication worldwide and coincide with a variety of diseases or treatments such as diabetes, metabolic syndromes, infectious or auto-immune disorders, alcohol abuse and malnutrition, anti-viral or anti-cancer therapies and industrial toxins (England and Asbury, 2004; Baron, 2006). In the majority of patients with APNs, the large sensory neurons are primarily affected, resulting in a painful neuropathy with symptoms that include dysesthesia, paresthesia and hypersensitivity. Depending on the noxious insult motor symptoms can also arise, although these are usually less pronounced. Symptoms of APNs arise in a length-dependent, stocking-glove distribution. Moreover, many forms of APNs persist even when the underlying cause has been treated or when the neurotoxic stimulus has been withdrawn, a phenomenon known as coasting (England and Asbury, 2004). Despite the heterogenic etiology of APNs, the symptoms are very alike and resemble those of patients with a hereditary form of peripheral neuropathy, suggesting that similar pathophysiological mechanisms could be involved. Indeed, Cashman and Höke proposed that unrelated to the causal neurotoxic insult, six major downstream pathways are disturbed in peripheral neuropathies, each affecting the nerves in a negative way. These insults include abnormalities in the metabolism, the formation of reactive oxygen species, defective ion channel dynamics, covalent modification of axonal proteins, inflammation and, last but not least, axonal transport defects (Cashman and Höke, 2015). In the next part, we summarize the current knowledge of axonal transport defects in a number of APNs.

Peripheral neuropathies associated with physical injury

The severity of physical injuries can range from minor neurapraxia to complete axotomy of the peripheral nerves. In the case of complete nerve transection, the pathophysiology is not mediated by a length-dependent dying-back neuropathy, which typically characterizes APNs. On the other hand, entrapment, compression and neurapraxia of a nerve causes a distal mononeuropathy, with carpal tunnel syndrome being the most frequent (Waldman and Waldman, 2009). Interestingly, the incidence of compression neuropathies increases significantly in patients with increased susceptibility for APNs, for example diabetic patients (Rota and Morelli, 2016). Therefore, similar processes could be involved in the development of a peripheral neuropathy, and managing these pathways could promote regeneration after nerve injury.

In general, focus lies on improving nerve regeneration while reducing the degeneration of the distal part (Höke, 2006). Interestingly, regeneration of the nerve progresses at a rate similar to slow axonal transport, suggesting that axonal transport is a key determinant of the regeneration process (Forman et al., 1980). In contrast to the CNS, where retraction bulbs form at the tip of the cut axon, the microtubules of severed peripheral nerves maintain their initial organization (plus end towards the synapse/growth cone) and continue to serve as tracks for motor proteins that provide support for the

growing axon (Ertürk et al., 2007). As such, traumatic nerve injury is associated with accumulation of cargoes at the plus end of microtubules (e.g. Golgi-derived vesicles) and subsequent axonal swelling at the site of injury (Tang-Schomer et al., 2012). These cargoes can then supply the regenerating nerve with lipids and proteins for growth cone formation (Bradke et al., 2012). The regenerative capacity of an axon depends on the localization of the injury. When an axon is cut in the proximity of the cell body, one or more neurites can mediate the outgrowth response, while more distal damage result in axonal regrowth (Bradke et al., 2012). Regardless of the nature of regeneration, the trophic dependency in the growing axon is significant (Zhou et al., 2016). This emphasizes the importance of proper axonal transport, not only to supply lipids and proteins, but also to answer the high energetic demand at the site of injury and in the regenerating axon. As such, improving axonal transport could be a valid therapeutic strategy to promote neuronal regeneration (Zhou et al., 2016; Kleele et al., 2014).

Diabetic-induced peripheral neuropathies

Over the last decade, diabetic-induced peripheral neuropathies have become the lead cause of chronic polyneuropathy in affluent cultures (Said, 2007; Tesfaye et al., 2010). Due to the multifactorial underlying mechanisms, a lot of controversy on the cause of diabetic-induced neuropathies remains. Chronic hyperglycemia appears to be a central contributing factor, deregulating the metabolic pathways which results in neurotoxic intermediates (Luo et al., 2016). When glucose levels are chronically elevated, the glucose-6-phosphate dehydrogenase (GP6D) is inhibited, diverting glucose to the polyol pathway. This results in the production of sorbitol which can reduce lipogenesis, myelination, neuronal membrane stability and nerve conduction (Tomlinson and Gardiner, 2008; Cashman and Höke, 2015). In addition, the processing of glucose via the polyol pathway depletes NADH, the major intracellular antioxidant. Together with the reduced flux through the pentose phosphate pathway, this results in severely impaired antioxidant capacity and increased radical damage to the neuron (Zhang et al., 2010). The increase in reactive oxygen species (ROS) during diabetes is considered to originate not only from the metabolic shift in neurons, but it could also be due to binding of advanced glycosylated end products (AGEs) to endothelial cells. This activates the nuclear factor-κB (NF-κB), leading to a pro-inflammatory response that could contribute to microvascular deficits, worsening the ROS production (reviewed in (R. Singh et al., 2014). Furthermore, increased ROS production has been associated with activation of the p38-mitogen-activated protein kinase (MAPK) pathway, impaired nerve conduction velocities and axonal transport (summarized in table 2) (Sharma et al., 2010; Price et al., 2004).

The pathophysiology of diabetic-induced neuropathies reaches far beyond the neurotoxic effects of hyperglycemia alone. Defects in axonal transport are clearly present both at early and advanced stages of the disease. While reduced fast axonal transport of neurotransmitters and trophic factors was observed already at early disease stages (Lee et al., 2002; Lee et al., 2001; Mizisin et al.,

1999), transport of structural proteins associated with neuronal regeneration was impeded in diabetic animal models (Jakobsen and Sidenius, 1980). Structural proteins, including neurofilaments and tubulin, can also be influenced by the presence of AGEs and their receptors (RAGE) (Singh et al., 2014; Williams et al., 1982), which in turn can be detrimental for axonal transport. Indeed, uncontrolled glycation of either α- or β-tubulin can alter microtubule dynamics and consequently axonal transport (Wloga and Gaertig, 2010). Furthermore, AGEs also amend the myelinating properties of protein P0, which could contribute to the demyelination of peripheral nerves (Vlassara et al., 1981). Where most studies don't make the distinction between fast- and slow-axonal transport or retro- and anterograde axonal transport, a recent study by Juranek *et al*. reported on differential transport deficiencies after nerve crush in diabetic rodents (Juranek et al., 2013). In this study, hyperglycemia-related glycation of proteins only affected slow axonal transport, consistent with previous reports studying the advanced-phase axonal degeneration (Medori et al., 1988).

Taken together, cellular changes associated with diabetes can damage the nerve in multiple ways, including vascular changes, membrane damage by reactive metabolic intermediates, increased ROS and organelle damage, non-enzymatic covalent modification of cytoskeletal proteins and DNA, and reduced axonal transport (summarized in table 2) (Das Evcimen and King, 2007; Murphy, 2009; Singh et al., 2014; Juranek et al., 2013). Besides direct damaging effects on the neuron, these cellular changes can also influence axonal transport, further adding to axonal degeneration and limiting the regenerative capacity (Sharma et al., 2010; Hoffman and Lasek, 1980). As a consequence, improving axonal transport could not only slow down progression, it could also improve the regeneration of nerves.

Inflammatory peripheral neuropathies

Inflammatory peripheral neuropathies can be triggered by auto-immune diseases or infectious agents that either directly damage the nerves, or cause an excessive immunological response. Lyme disease, human immunodeficiency virus (HIV), Herpes zoster virus, and hepatitis B and C are the most predominant infectious diseases associated with a high incidence of peripheral neuropathy. Guillain-Barré syndrome, rheumatoid arthritis, sarcoidosis, chronic inflammatory demyelinating polyneuropathy and peripheral neuropathies associated with protein abnormalities are examples of a dysregulated immune response that results in axonal damage of the nerves with a principal role for macrophages (reviewed in (Cashman and Höke, 2015)). While macrophages initially promote axon regrowth by removing myelin debris during Wallerian degeneration (Dubový, 2011), chronic inflammation contributes to distal axonal degeneration and to the development of neuropathic pain (Pardo et al., 2001; Ristoiu, 2013; Woolf, 2004). Macrophage-associated cytokines and chemokines such as tumor necrosis factor-α (TNF-α), interleukins IL-1β, IL-6 and macrophage inflammatory protein-1α (MIP-1α) have been suggested to mediate hypersensitivity in inflammatory peripheral neuropathies through caspase-dependent injury and degeneration (Sommer and Kress, 2004; Melli et

al., 2006). As for infectious neuropathies such as HIV and HVC-related neuropathies, aberrant inflammatory signaling is the primary pathogenic mechanism leading to the neuropathy (Keswani et al., 2002; Zheng et al., 2011). Neurotoxicity has also been partly allocated to the infected macrophages which shed viral particles, and produce neurotoxic excitatory amino acids and cytokines (Kaul et al., 2005; Laast et al., 2011).

In addition to the chronic inflammation following infection, the viral proteins themselves can also damage the peripheral nerves in multiple manners. For example, the glycoprotein-120 (gp-120), exposed on the envelope of an HIV particle was shown to activate the mitochondrial caspase pathway in the axon, which caused local damage to the nerve. Furthermore, gp-120 was shown to induce neuronal apoptosis in a Schwann cell-dependent manner (Melli et al., 2006), suggesting an important role for non-neuronal cells. The induction of focal swellings along the axons following macrophage activation is an early sign of neuronal dysfunction which could be mediated by mitochondrial dysfunction and inhibition of axonal transport (Takeuchi et al., 2005; Avdoshina et al., 2016).

Furthermore, certain viruses have the ability to capture the axonal transport machinery of peripheral nerves (Berth et al., 2009). A recent study by Berth and colleagues demonstrated that peripheral DRG neurons internalize viral proteins via lipid rafts and pinocytosis, after which they are transported in the retrograde direction via the fast axonal transport system (Berth et al., 2015). It is still unclear whether internal viral particles cause direct neurotoxicity. However, it has been suggested that viral particles affect signaling pathways involved in axonal transport and mediate apoptosis in distal neurons (Berth et al., 2015; Bachis et al., 2006). In addition to viral transport, the neuro-immune communication is also highly dependent on axonal transport. In fact, axonal transport of TNF-α in DRG neurons has been put forward as a critical mechanism in neuropathic pain. Myers and Shubayev suggest that TNF-α neuroinflammation, instigated at the site of the injury by activated Schwann cells, and the retrograde transport to neuronal and glial structures in the pain pathway coincide and contribute to the development of a painful peripheral neuropathy (Myers and Shubayev, 2011).

Besides the neuroinflammation and direct neurotoxicity of infectious agents, anti-viral medication can also be noxious to peripheral neurons. The nucleoside reverse transcriptase inhibitor (NRTI) class of antiretroviral drugs are well known to induce a peripheral neuropathy on their own. Indeed, the treatment with the antiretroviral drug ddC induced a peripheral neuropathy in the absence of viral particles. Interestingly, the addition of gp-120 to this model exacerbated the symptoms (Wallace et al., 2007). An study by Huang *et al.* demonstrated that intravenous treatment with NRTI stavudine induced damage to the peripheral nerves and to the central terminals of L5 DRG neurons, even in the absence of inflammation (Huang et al., 2013). How antiretroviral drugs induce a peripheral neuropathy needs to be further elucidated, but the inhibition of γ-DNA polymerases and subsequent

mitochondrial DNA depletion, mitochondrial dysfunction and axonal transport defects have been proposed (Niescier et al., 2013; Avdoshina et al., 2016).

Taken together, more and more evidence points towards the contribution of mitochondrial dysfunction and alteration in axonal transport in the pathophysiology of inflammatory peripheral neuropathies, although the primary mechanism is undoubtedly mediated by aberrant neuroinflammation. The hypothesis is supported by the fact that genetic risk factors include mutations in genes affecting mitochondrial functions or genes involved in inflammatory responses (Kamerman et al., 2012; Kallianpur and Levine, 2014).

Chemotherapy-induced peripheral neuropathies

Chemotherapy-induced peripheral neuropathies (CIPN) are present in up to 80% of patients that receive certain anti-cancer drugs such as platinum compounds (e.g. cisplatin, carboplatin, oxaliplatin), taxanes (e.g. paclitaxel, docetaxel), vinca alkaloids (e.g. vincristine, vinblastine), thalidomide and proteasome inhibitors (bortezomib). Similar to most forms of APNs, patients principally present with sensory symptoms, while motor and autonomic involvement is usually only present in more severe forms or with selected chemotherapeutics (Kannarkat et al., 2008). The symptoms are dose dependent and arise in a stocking-glove distribution, typical for peripheral neuropathies. CIPN is often the dose-limiting side effect of an anti-cancer regimen and can even persist after drug-withdrawal (Grisold et al., 2012). Even though the clinical presentation of different subsets of CIPN is largely overlapping, the noxious mechanisms and location of neuronal damage varies among the different classes of chemotherapeutics.

Platinum drugs accumulate in the cell body of DRG neurons where they bind to DNA and induce apoptosis, which can result in a reversible painful neuropathy (Ta et al., 2006; Grisold et al., 2012). Thalidomide, bortezomib, and microtubule-interfering agents (such as the taxanes and vinca alkaloids) are assumed to cause an axonal neuropathy. How exactly thalidomide causes a peripheral neuropathy is poorly understood but could include immunomodulatory and anti-angiogenic effects (Richardson et al., 2002). In practice, thalidomide is usually combined with bortezomib, a synthetic proteasome inhibitor that also induces a reversible peripheral neuropathy in up to 80% of treated patients (San Miguel et al., 2008; Chaudhry et al., 2008). Bortezomib-associated neurotoxicity most likely has multifactorial causes resulting in a dying-back degeneration of nerves. Evaluation of animal models indicated that tubulin stabilization associated with a dose-dependent reduction in sensory nerve conduction velocities and a mechanical hypersensitivity could be possible mechanisms (Poruchynsky et al., 2008; Meregalli et al., 2010). Furthermore, inhibition of the proteasome results in the accumulation of cytoplasmic aggregates, a common hallmark of neurodegenerative disorders, as well as nuclear retention of polyadenylated RNAs in nuclear bodies (reviewed in (Meregalli, 2015)). Recent studies suggest that mitochondrial dysfunction and mitotoxicity proceed bortezomib-induced

neuropathic pain. Bortezomib treatment in rats induced dysfunction of the Complex-I and Complex-II mediated respiration and ATP production. This could be completely prevented by prophylaxis with acetyl-L-carnitine, a substrate used in mitochondrial β-oxidation and known to improve mitochondrial function (Zheng et al., 2012; Kathirvel et al., 2013). Not only intrinsic mitochondrial dysfunction and microtubule polymerization, but also axonal transport is disrupted after treatment with bortezomib (Staff et al., 2013). This block in axonal transport is associated with increased tubulin polymerization and stabilization (Poruchynsky et al., 2008; Staff et al., 2013).

Alterations of microtubule dynamics are also considered to underlie the neuropathy induced by microtubule-interfering agents (e.g. paclitaxel and vincristine). Paclitaxel binds to β-tubulin in polymerized microtubules which causes a conformational change acting against depolymerization, thus rendering microtubules more stabilized and less dynamic (Andreu et al., 1992; Xiao et al., 2006). On the other hand, vincristine binds the αβ-tubulin heterodimers, rendering them unable to be incorporated into growing microtubules (Risinger et al., 2009). Disturbing microtubule dynamics results in mitotic arrest, inhibiting proliferation of tumor cells. Despite being extremely effective against neoplastic tumors, microtubule-interfering agents also interfere with the highly dynamic neuronal microtubules, resulting in structural alterations and axonal transport defects (Grisold et al., 2012; Nicolini et al., 2015; LaPointe et al., 2013; Shemesh and Spira, 2010).

In summary, axonal transport defects are observed in multiple forms of CIPN. Microtubule-interfering agents have a direct effect on microtubule dynamics and axonal transport (Silva et al., 2006; Xiao et al., 2006). Other agents primarily target other cellular components or mechanisms, including the proteasome, DNA replication and mRNA translation, but have also been shown to influence axonal transport via ion channel expression and adduct formation of motor proteins (reviewed in (Nicolini et al., 2015)), emphasizing the importance of axonal transport problems in the pathophysiology of CIPN.

Toxin-induced peripheral neuropathies

Post-mitotic neurons are explicitly susceptible to specific toxins, including heavy metals, certain insecticides or pesticides and alcohol (Wright and Baccarelli, 2007; Grandjean and Landrigan, 2006; Chopra and Tiwari, 2012). Although the incidence of industrial-related neurotoxicity has decreased over the last decades, mainly due to increased biosafety measures, the occurrence of alcohol-induced peripheral neuropathies is still increasing.

Alcohol is the most consumed toxin worldwide which distributes throughout the body and rapidly penetrates the blood-brain-barrier after digestion. Therefore, alcohol-associated toxicity appears in a variety of tissues including the liver, pancreas, skeletal and cardiac muscles, but also in the CNS and PNS (Risks and Consumption, 2000). The underlying mechanism of alcohol neuropathy is not fully understood but involves microglial activation in the spinal cord, cytokine production,

caspase-3 activation, stimulation of the metabotropic glutamate subtype-5 receptor (mGlu5R) and the hypothalamic-pituitary-adrenal (HPA) axis, oxidative stress of free radical damage to the nerves, neuroinflammation and nutritional deficiencies (Alfonso-Loeches et al., 2013; Canton Santos et al., 2013; Hama, 2003; Gianoulakis et al., 2003; Albano, 2006; Dina et al., 2000). Neuronal damage can arise via direct toxicity of ethanol, or via its toxic metabolite acetaldehyde, which damages cytoplasmic proteins (Chopra and Tiwari, 2012). This results in ROS production and activation of the MAPK pathway (Tong et al., 2011), which is also assumed to be involved in diabetic neuropathies (Price et al., 2004). Indeed, ethanol has an inhibitory effect on insulin and increases the presence of AGEs (Tong et al., 2011), suggesting that the pathophysiology of alcohol- and diabetic-induced peripheral neuropathies are intertwined.

The presence of defects in fast axonal transports as a consequence of ethanol or acetaldehyde is known since the late eighties (McLane, 1987). This was confirmed *in vivo* as ethanol induced impairment of retrograde axonal transport of cholinergic enzymes in the rat sciatic nerve (Malatová and Cízková, 2002). Indeed, post translational modifications of cytoskeletal proteins such as NFs and microtubules are influenced by ethanol (Kannarkat et al., 2006). Therefore, defects in axonal integrity and transport is considered to play a major role in the development of alcohol-induced peripheral neuropathies.

Table 2. Summary of the diseases associated with APNs with their direct and indirect links to axonal transport dysfunction.

Therapeutic interventions

To date, treatment of peripheral neuropathies only consists of supportive measures and is in most cases insufficient to ease all the symptoms. For instance, CMT patients can only rely on rehabilitation, orthotics, symptomatic drug therapy for pain, and the surgical corrections of foot and hand deformities (Kenis-Coskun and Matthews, 2016). Similarly, therapeutic strategies to treat APNs are limited to supportive care, focused on pain relief with anti-convulsants, anti-depressants, corticoids and opioids. However, these drugs have a variety of adverse effects and could lead to drug-dependence (Majithia et al., 2016; Marmiroli and Cavaletti, 2016). No pharmacological disease-modifying therapies currently exist that can reverse these debilitating symptoms in either case. However, a number of preclinical and clinical trials have shown some encouraging results.

Therapeutic interventions for inherited peripheral neuropathies

Several therapeutic approaches assessed the efficacy of progesterone, neurotrophins and ascorbic acid in the context of CMT1 (reviewed in (d'Ydewalle et al., 2012)). Furthermore, as genetic alterations of the *PMP22* gene are the most common cause of CMT, many studies focused on identifying therapeutic strategies for CMT1A. Currently, the PXT3003 trial is one of the ongoing phase III clinical trials targeting multiple disease-relevant pathways using a combination of drugs, previously approved for other unrelated diseases (Chumakov et al., 2014). This polytherapy, consisting of (RS)-baclofen, naltrexone hydrochloride and D-sorbitol, targets PMP22 expression and pathways important for myelination and axonal integrity. PXT3003 synergistically reduced PMP22 expression and improved myelination both *in vitro*, in a co-culture of DRG neurons and Schwann cells, and *in vivo* in a CMT1A rat model (Chumakov et al., 2014). Moreover, the clinical phenotype of the CMT1A rat model improved upon treatment with PXT3003 (Chumakov et al., 2014). A Phase II clinical trial showed safety and tolerance of PXT3003, as well as evidence for clinical improvement in CMT1A patients (Attarian et al., 2014). Interestingly, PXT3003 treatment could enhance the nerve conduction and remyelination in a nerve crush model, indicating therapeutic efficacy beyond CMT1A-related pathology.

As several genetic causes of CMT2 are associated with alterations in the cytoskeleton and/or aberrant axonal transport, targeting these processes could be an alternative therapeutic approach for CMT2. HDAC6 is an α-tubulin deacetylase implicated in axonal transport (Chen et al., 2010) and HDAC6 inhibition has been shown to improve axonal transport deficits in several neurodegenerative disorders such as Parkinson's disease and Huntington's disease (Dompierre et al., 2007; Godena et al., 2014). HDAC6 belongs to the class II HDACs and is unique amongst all the HDACs, as it has two catalytic deacetylating domains in its N-terminus and an ubiquitin-binding domain in its C-terminus (Simões-Pires et al., 2013b). It is also unique in that it has a specific tetradecapeptide domain coupled with two leucine rich nuclear export sequences which enables cytosolic retention, and therefore, enabling it to modify non-histone substrates (for a review: (Van Helleputte et al., 2014)). Selective

inhibition of the deacetylating function of HDAC6 using small drug-like molecules restored the mitochondrial axonal transport defects in cultured DRG neurons from mutant *HspB1*^{S135F} mice (Benoy et al., 2016; d'Ydewalle et al., 2011; Shen et al., 2016), as well as in motor neurons differentiated from iPSCs obtained from patients with HSPB1 mutations (Kim et al., 2016). Furthermore, HDAC6 inhibition induced a significant improvement of the motor and sensory CMT2 phenotype in these mice (d'Ydewalle et al., 2011).

Literature suggests a broader involvement of HDAC6 in CMT2-related pathogenesis. Mutations in aminoacyl-tRNA synthetases cause CMT and several proteins have been demonstrated to be interactors of small heat shock proteins (Mymrikov et al., 2016; Wan et al., 2015). Interestingly, pulldown experiments showed that HDAC6 can co-immunoprecipitate with HSPB1 (CMT2E) (Zhang et al., 2007), but also with GlyRS (CMT2D) (Hutchins et al., 2010). The biological significance of these interactions remains an intriguing question. Mutations in *MFN2* are the most common genetic cause of CMT2, accounting for 20% of all diagnosed cases and are associated with mitochondrial abnormalities and axonal transport deficits (Stuppia et al., 2015). Interestingly, HDAC6 is also a regulator of the degradation of MFN2 through MARC5 and protects MFN2 from hypoxia-induced degradation (Kim et al., 2015). As a consequence, it would be of interest to study whether alterations in axonal transport and the cytoskeleton are common hallmarks of CMT and related peripheral neuropathies and whether HDAC6 can be used as a therapeutic target.

However, as axonal transport defects have been demonstrated to be a common pathological mechanism in the discussed IPNs, it is worth noting that a number of these mutations will have a separate underlying pathological mechanism that will require a direct intervention. An example of this would be mutations in the *TRPV4* gene. An ideal therapeutic strategy for TRPV4-related diseases would be to target the hypercalcemia, as this is most likely the cytotoxic effect. Thus, targeting axonal transport as the main pathological mechanism and not addressing the hypercalcemia could not be the best therapeutic strategy for such diseases. In cases like this, one needs to focus on the primary pathological mechanism as the therapeutic target. Alternatively, a possible synergistic approach could be favourable, where, in the case of TRPV4-related diseases, the primary therapeutic target would be the reduction of Ca^{2+}, with the axonal transport defects being a secondary therapeutic target. As a consequence, the patient might experience enhanced benefits from a combination therapy, comparable to the strategy used in the PXT3003 trial.

Therapeutic interventions for acquired peripheral neuropathies

Despite the fundamentals of acquired peripheral neuropathies being tremendously pleiotropic, similar pathophysiological mechanisms seem to be involved. As already indicated, six main pathways were suggested as the most important players in the development of a peripheral neuropathy, regardless of the noxious insult (Cashman and Höke, 2015). Indeed, multiple forms of APNs, if not

all, show alterations in a number of these suggested pathways; cellular metabolism, covalent changes of cytoplasmic proteins, dysfunction of organelles such as mitochondria, the production of ROS and reduced anti-oxidant capacity, activation of intracellular and inflammatory pathways and axonal transport defects. Interestingly, many of these processes have downstream effects that eventually can result in reduction of axonal transport. While for hereditary peripheral neuropathies, the dysfunctional gene stays present, the noxious incent causing an APN can usually be cured or withdrawn. Unfortunately, resolving the causative disease or neurotoxic insult is sometimes insufficient to cure the peripheral neuropathy as coasting is observed (England and Asbury, 2004).

Therefore, therapies focused on neuronal regeneration, in addition to treatment of the causative malignancies, could improve success. Since multiple acquired but also hereditary peripheral neuropathies show evidence for disrupted axonal transport, targeting this particular pathway might be a promising therapeutic strategy. Since counteracting axonal transport defects could limit axonal degeneration and could also be a driving force for neuronal regeneration, benefits might be twofold.

Conclusions

It is clear that more basic research is needed to get a better insight into the molecular mechanisms underlying both IPNs and APNs. Especially the development of reliable *in vitro* and *in vivo* models for these different diseases is crucial. Our current knowledge strongly indicates that there are a number of direct and indirect links both in the genetic and acquired neuropathies that intersect at the axonal transport highway and its machinery. Neurons with very long axons in the PNS heavily rely on efficient axonal transport of a variety of factors, such as vesicles, organelles, mRNA, lysosomes, and protein aggregates for clearance. An imbalance of this system or on the cargoes being transported will have detrimental effects on neurons with the longest axons and their distal connecting muscles and sensory receptors, thus resulting in peripheral neuropathies. Moreover, it has become increasingly clear that axonal transport defects are not limited to primarily axonal neuropathies, such as CMT2. Also the supporting glial cells play a crucial role in maintaining the neuronal cytoskeleton architecture, and hence these cells can have a role in regulating axonal transport. Whether through a singleor a combination of toxic insults, or through genetic inheritance, peripheral neuropathies can arise from a myriad of causes, yet impairments to the axonal transport system seems to be a common pathological mechanism. As a consequence, it seems a good therapeutic strategy for the treatment of peripheral neuropathies. Furthermore, improvements in axonal transport could not only reduce axonal degeneration, but also improve neuronal regeneration.

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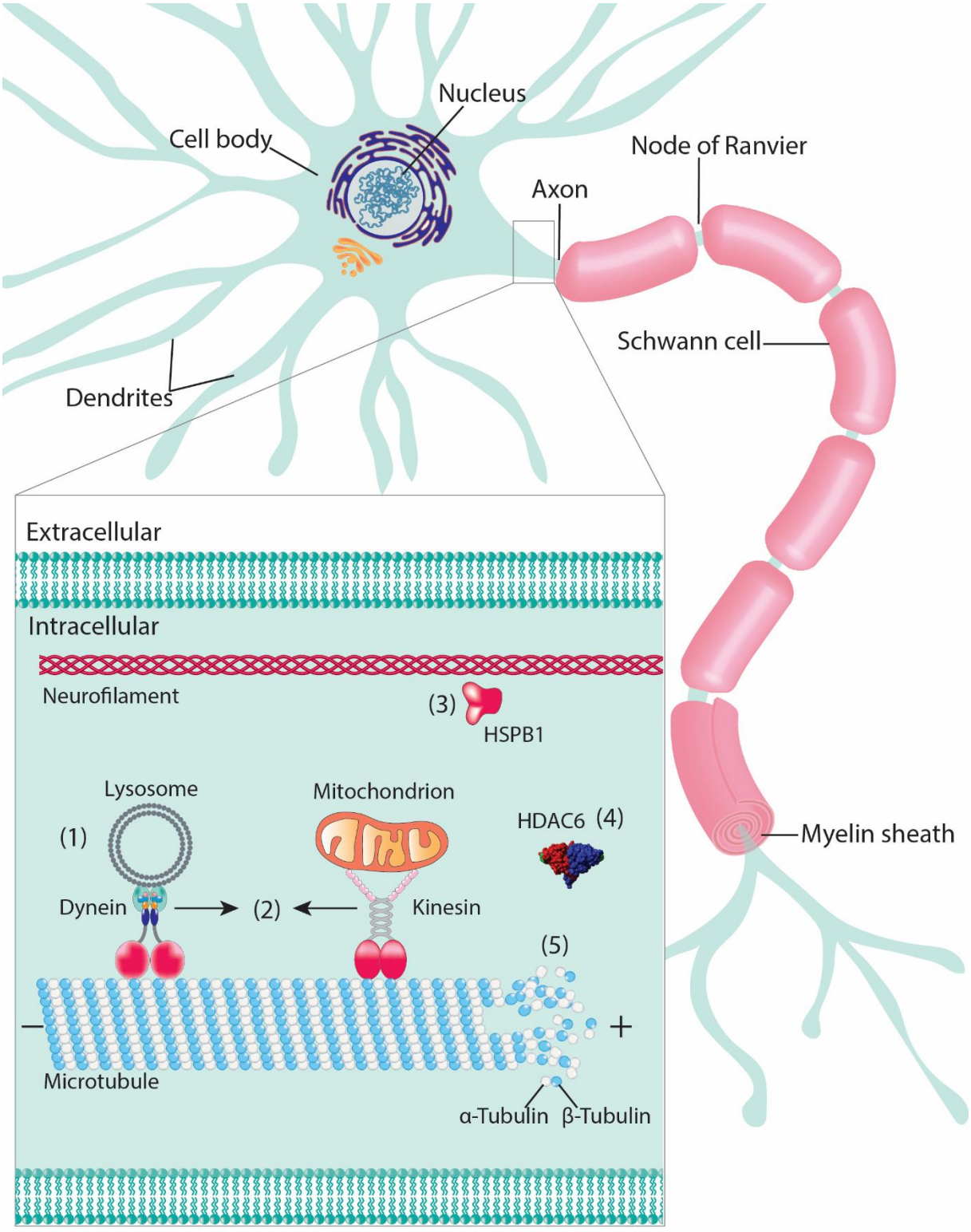
A



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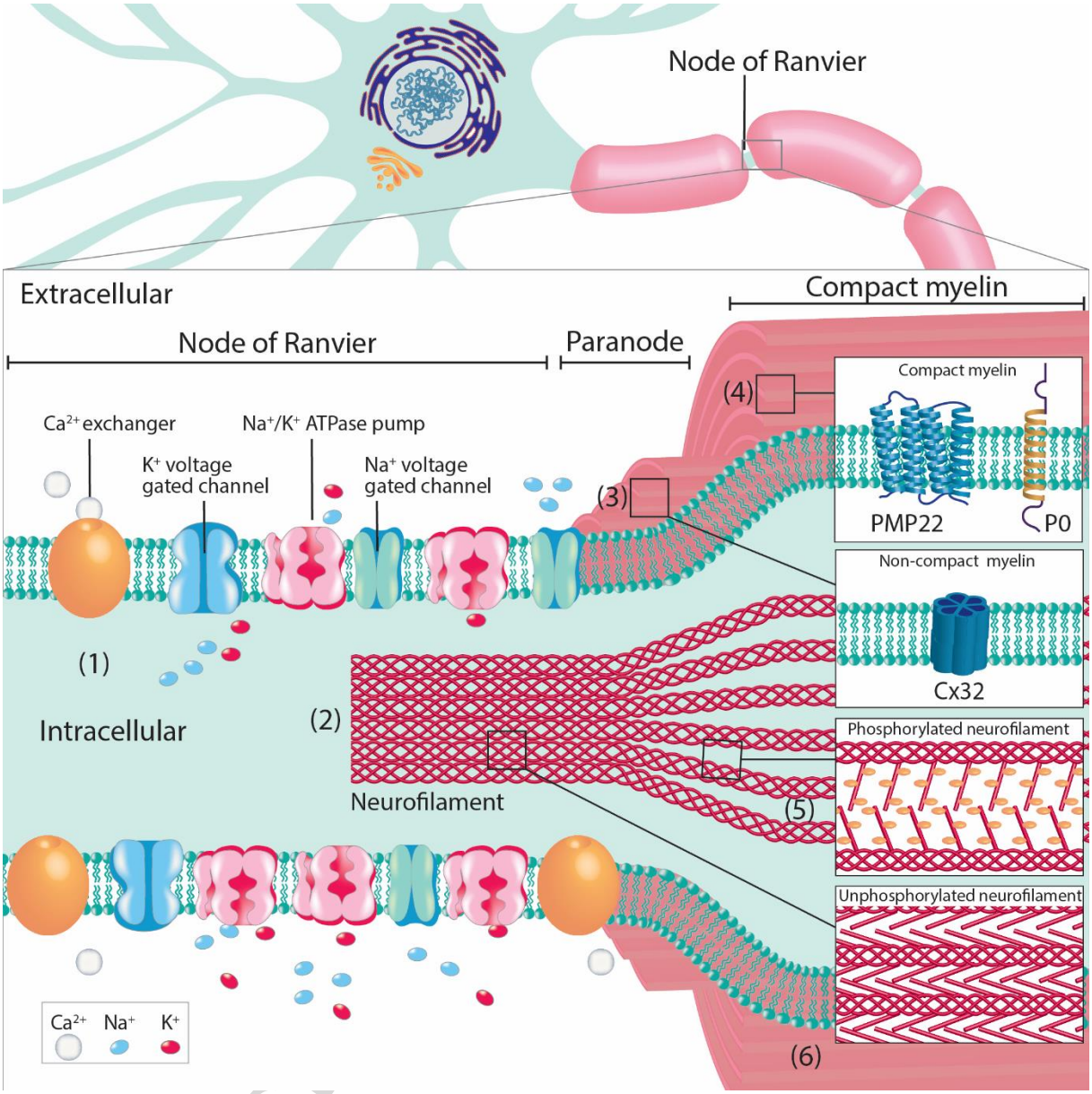

Figure 1

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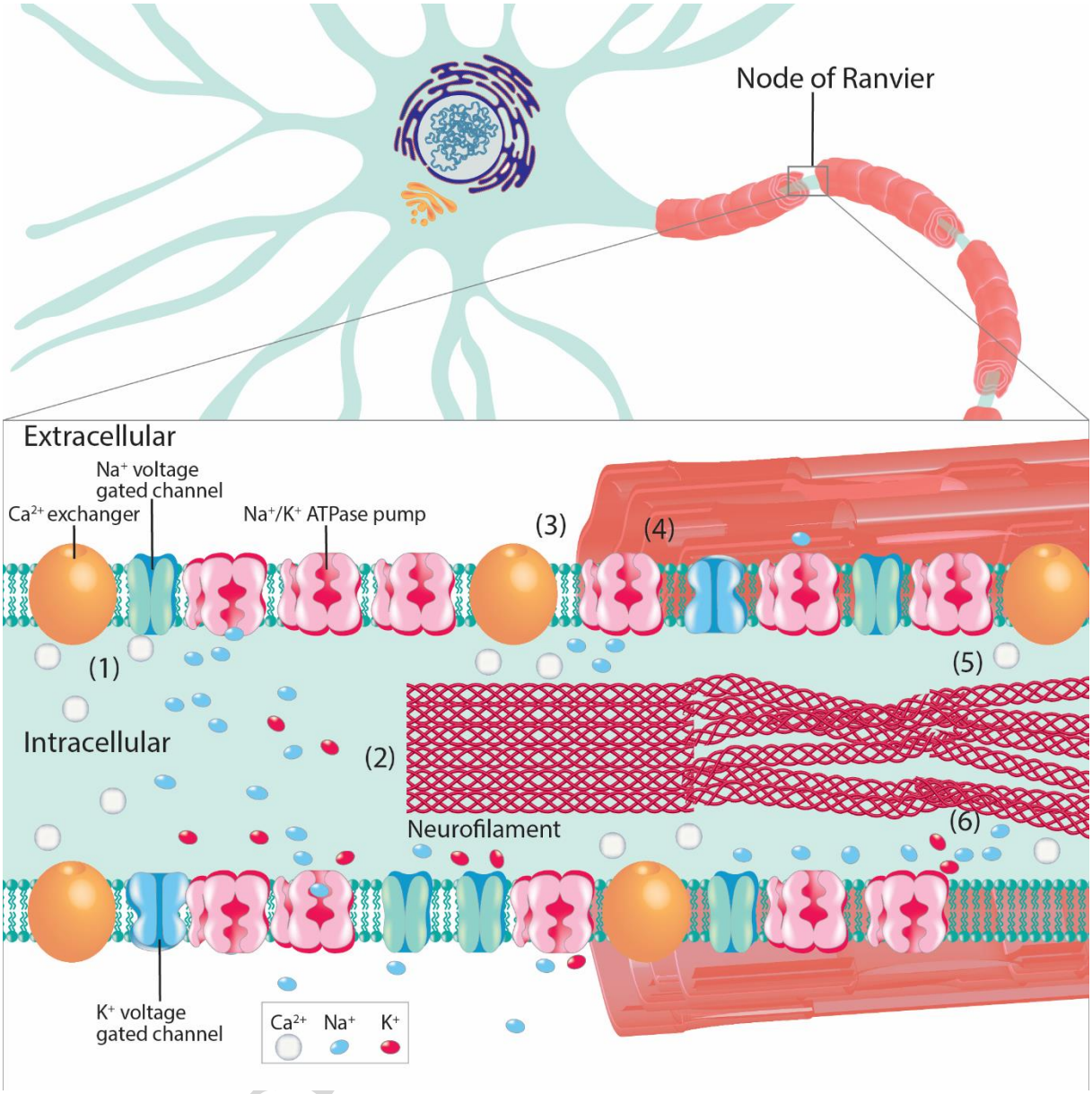

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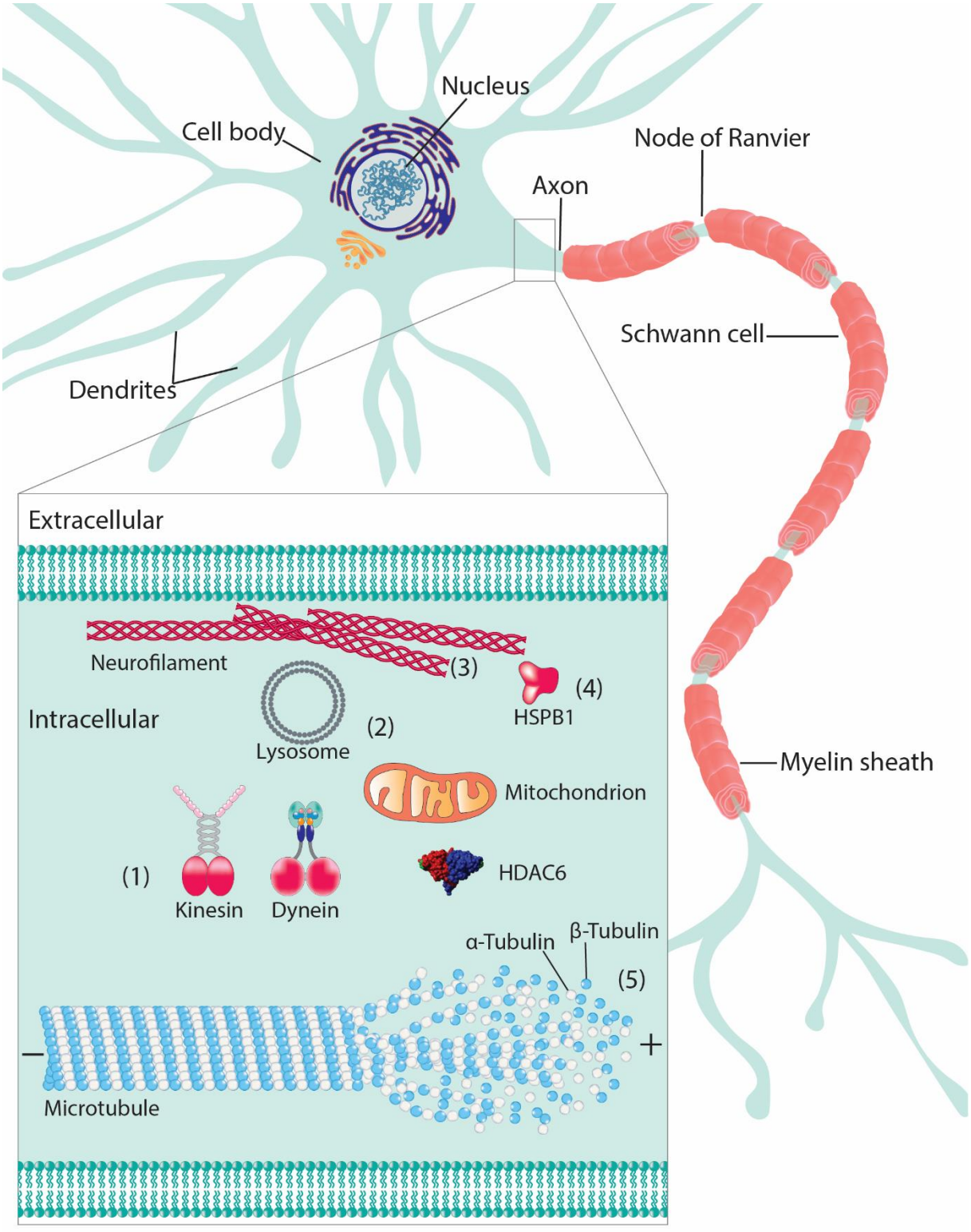

Figure 2

Table 1

Mutated gene (linked IPNs)	Contributing Mechanism(s)	Links to Axonal Transport		References
KIF1β **(CMT2A1)**	- Impairs the molecular motor kinesin	Direct Indirect	- Impairs the anterograde axonal transport* - Impairs axonal transport of synaptic vesicles that rely on KIF1β*	(Zhao et al., 2001) (Okada et al., 1995)
DYNC1H1 **(CMT2O)**	- Impairs the molecular motor dynein - Impair mitochondrial morphology and function with age - Impair Schwann cell myelination	Direct Indirect	- Directly impairs the retrograde axonal transport - Impairs Schwann cell myelination which can alter the neurofiliment network & axon diameter	(Zhao et al., 2016) (Langworthy and Appel, 2012)
NEFL **(CMT1F, CMT2E, & ARCMT2/CMT2B5)**	- NF accumulation in the cell body and proximal axon - Disrupt NF assembly - Impair axonal transport of mitochondria	Direct Indirect	- Impair NF & mitochondrial axonal transport - Structural alterations of cytoskeletal proteins - Myelination abnormalities	(Brownlees et al., 2002; Saporta et al., 2015; Yates et al., 2009) (Fabrizi et al., 2007)
LMNA **(CMT2B1)**	- Malfunctioning of extranuclear function** - Axonal degeneration** - Mitochondrial dysfunction** - Deficits in axonal transport**	Direct Indirect	- Impairments of axonal transport has been linked to lamin B mutations → mutations in lamin A/C may have a similar pathogenesis** - Axonal degeneration has been linked to lamin B mutations → mutations in lamin A/C may have a similar pathogenesis**	(Yoon et al., 2012) (Yoon et al., 2012)
TRPV4 **(CMT2C)**	- Hypercalcemia - Interaction with microtubule associated proteins	Direct Indirect	- Increased levels of Ca2+ inhibit the mitochondrial protein, Miro, which impairs mitochondrial transport* - Interacts with the	(Klein et al., 2011; Wang and Schwarz, 2009) (Barlan et al., 2013; Sung et al., 2008; Suzuki et al., 2003)

			microtubule associated protein, ensconsin which is required for the recruitment of the kinesin-1	
PMP22 **(CMT1A, CMT1E, & HNPP)**	- Disruption of normal myelination - Reduction in slow axonal transport - Reduced cytoskeleton organization and NF phosphorylation	Direct Indirect	- Microtubule destabilization - Myelination abnormalities - Structural reorganization of ion channels - Structural alterations of cytoskeletal proteins - Formation of aggregates that rely on axonal transport for clearance	(Kirkpatrick et al., 1994) (de Waegh et al., 1992; de Waegh and Brady, 1990; Fortun et al., 2006; Notterpek et al., 1999)

Mutated gene (linked IPNs)	**Contributing Mechanism(s)**	**Links to Axonal Transport**		**References**
GJB1 **(CMT1X)**	- Axonal degeneration - Deficit in axonal transport - Myelination abnormalities	Direct Indirect	- Impairment of retrograde transport - Structural alterations of cytoskeletal proteins - Myelination abnormalities - NF abnormalities - Structural reorganization of ion channels[¥]	(Sargiannidou et al., 2009; Vavlitou et al., 2010) (Kiryu-Seo et al., 2012; Vavlitou et al., 2010)
MPZ **(CMT1B, CMT2I/J, congential hypomyelinating neuropathy and Déjèrin-Sottas syndrome)**	- Cytoplasmic cellular trafficking - Reduced cytoskeleton organization and NF phosphorylation[¥] - Axonal degeneration	Direct Indirect	- Assumed to have similar pathogenic mechanisms as mutations in PMP22 and Cx32[¥] - Structural alterations of cytoskeletal proteins[¥] - Structural reorganization of ion channels	(Konde et al., 2006; Vavlitou et al., 2010) (Rosberg et al., 2016)

MFN2 **(CMT2A2)**	- Abnormal clustering of mitochondria - Electrophysiological abnormalities - Altered action potential threshold and channel current properties	Direct Indirect	- Impaired mitochondrial axonal transport - Impaired interaction with the Miro/Milton complex - Selective mitochondrial depletion, apoptosis resistance, and increased mitophagy	(Baloh et al., 2007; Chapman et al., 2013; Misko et al., 2010; Saporta et al., 2015) (Rizzo et al., 2016)
HSPB1 **(CMT2F and distal HMN2B)**	- Impaired chaperone activity - Impaired cytoskeleton stabilization - Impaired NF assembly - Impaired autophagy	Direct Indirect	- Impaired mitochondrial axonal transport - Reduced acetylated α-tubulin level - Structural alterations of cytoskeletal proteins - NF abnormalities	(Benoy et al., 2016; d'Ydewalle et al., 2011; Kim et al., 2016; Shen et al., 2016) (Almeida-Souza et al., 2011)
HSPB3 & HSPB8 **(HMN2C & CMT2L, respectively)**	- Assumed to have similar pathogenic mechanisms as HSPB1 as these proteins interact with HSPB1**	Direct Indirect	- Assumed to have similar pathogenic mechanisms as mutations in HSPB1** - Structural alterations of cytoskeletal proteins** - Interacts with HSPB1	(Sun et al., 2004) (Evgrafov et al., 2004)
GARS **(CMT2D)**	- Toxic-gain of function interaction with HDAC6 - Impairs axonal transport	Direct Indirect	- Impairs mitochondrial transport - Mutated GARS protein interacts with HDAC6 which may enhance HDAC6's deacetylating activity	(Benoy et al., 2015) (Benoy et al., 2015; Motley et al., 2011)

Mutated gene (linked IPNs)	Contributing Mechanism(s)	Links to Axonal Transport		References
***YARS, KARS, MARS, AARS* & *HARS* (CMTDIC, CMTRIB, CMT2U, CMT2N & CMT2W, respectively)**	- Assumed to have similar pathogenic mechanisms as GARS - Proteins interact with GARS**	Direct Indirect	- Assumed to have similar pathogenic mechanisms as mutations in GARS** - Assumed to have similar pathogenic mechanisms as mutations in GARS**	(Gonzalez et al., 2013; Jordanova et al., 2006; Latour et al., 2010; McLaughlin et al., 2010; Vester et al., 2013)
***RAB7* (CMT2B)**	- Axonal transport defects - Axonal degeneration - Destabilization of NF network	Direct Indirect	- Axonal transport defects - NF abnormalities	(Zhang et al., 2013) (Cogli et al., 2013)
***Gigaxonin* (Giant axonal neuropathy/CMT2)**	- Aggregation of intermediate filaments - Abnormal myelination - Axonal transport defects - Metabolic and oxidative stress	Direct Indirect	- Impaired mitochondrial axonal transport - NF aggregation - Impaired ubiquitin–proteasomal degradation of NFs	(Israeli et al., 2016; Lowery et al., 2016) (Bomont, 2016; Lowery et al., 2016)

* Circumstantial evidence, ** deduced due to functional similarities between related proteins, ¥ deduced due to functional similarities between myelin related proteins.

Abbreviations: ARCMT2 (autosomal recessive Charcot-Marie-Tooth disease type 2), CMT1B (Charcot-Marie-Tooth disease type 1B), CMT2I/J (Charcot-Marie-Tooth disease type 2I/J), CMT1F (Charcot-Marie-Tooth disease type 1F), CMT2B1 (Charcot-Marie-Tooth disease type 2B1), CMT2E (Charcot-Marie-Tooth disease type 2E), CMT2B5 (Charcot-Marie-Tooth disease type 2B5), CMT2 (Charcot-Marie-Tooth disease type 2), CMT2A1 (Charcot-Marie-Tooth disease type 2A1), CMT2O (Charcot-Marie-Tooth disease type 2O), CMT2B (Charcot-Marie-Tooth disease type 2B), CMT2D (Charcot-Marie-Tooth disease type 2D), CMTDIC (Charcot-Marie-Tooth disease-dominant intermediate C), CMT2L (Charcot-Marie-Tooth disease type 2L), CMTRIB (Charcot-Marie-Tooth disease recessive intermediate B), CMT2C (Charcot-Marie-Tooth disease type 2C), CMT2U (Charcot-Marie-Tooth disease type 2U), CMT2N (Charcot-Marie-Tooth disease type 2N), CMT2W (Charcot-Marie-Tooth disease type 2W), IPNs (inherited peripheral neuropathies), HDAC6 (histone deacetylase 6), HMN2B (Hereditary Motor Neuropathy type 2B), HMN2C (Hereditary Motor Neuropathy type 2C), HNPP (hereditary neuropathy with liability to pressure palsies) and NF (neurofilament).

Table 2

Disease	Contributing Mechanism(s)	Links to Axonal Transport		References
Trauma/injury induced peripheral neuropathies	- Physical compression on nerves - Complete transection of nerves - Microvascular changes	Direct Indirect	- Fiber deformation and block of axonal transport - Vascular changes (ischemia) and edema - Oxidative stress and ROS production	(Bradke et al., 2012; Höke, 2006; Zhou et al., 2016) (Gao et al., 2013; Menorca et al., n.d.) (Cashman and Höke, 2015; Gao et al., 2013)
DIPN	- Hyperglycemia and metabolic shift - Microvascular changes - Oxidative stress and ROS production - Organelle damage - Non-enzymatic covalent protein changes	Direct Indirect	- Structural alterations of cytoskeletal proteins -> e.g.: glycation α- and β-tubulin - Activation MAPK pathway and phosphorylation of motor proteins - Oxidative stress and ROS production - Metabolic shift, nutrient and energy insufficiency - Non-cell autonomous nutrient deficiency	(Luo et al., 2016; Singh et al., 2014; Williams et al., 1982; Wloga et al., 2011)(Du et al., 2010; Price et al., 2004) (Cashman and Höke, 2015; Juranek et al., 2013; Sharma et al., 2010; Singh et al., 2014; Vlassara et al., 1981; Zhang et al., 2010)
Inflammatory peripheral neuropathies	- Chronic, aberrant inflammation - Neurotoxic excitatory amino acids - Viral proteins - Neurotoxicity of anti-viral medication	Direct Indirect	- Viral proteins highjack axonal transport machinery - Macrophage activation causes mitochondrial dysfunction - Altered signaling pathways involved in axonal transport - Anti-viral drugs cause mitochondrial damage	(Berth et al., 2015, 2009) (Bachis et al., 2006; Berth et al., 2015; Cashman and Höke, 2015; Laast et al., 2011; Pardo et al., 2001; Ristoiu, 2013; Woolf, 2004) (Avdoshina et al., 2016; Kaul et al., 2005; Takeuchi et al., 2005) (Avdoshina et al., 2016; Huang et al., 2013; Niescier et al., 2013; Wallace et al., 2007)

CIPN	- Vascular changes - Neuroinflammation - Oxidative stress and ROS production - DNA and protein damage - Nerve compression - Neurotoxicity of anti-cancer medication	Direct Indirect	- Structural damage to cytoskeletal proteins - Disturbance of microtubule dynamics by binding tubulin - Oxidative stress and ROS production - Nutrient insufficiency - Ischemia - Proteasome dysfunction and protein aggregation - Mitochondrial dysfunction (complex I and II) - Ion channel dysfunction	(Grisold et al., 2012) (LaPointe et al., 2013; Meregalli et al., 2010; Nicolini et al., 2015; Poruchynsky et al., 2008; Shemesh and Spira, 2010; Silva et al., 2006; Staff et al., 2013; Xiao et al., 2006) (Meregalli, 2015; Richardson et al., 2002) (Kathirvel et al., 2013; Zheng et al., 2012) (Nicolini et al., 2015)
Disease	**Contributing Mechanism(s)**	**Links to Axonal Transport**		**References**
Alcohol induced peripheral neuropathies	- Stimulation of mGluR5 and HPA - Neuroinflammation - Oxidative stress and ROS production - Neurotoxicity of ethanol (metabolites)	Direct Indirect	- Structural damage to cytoskeletal proteins by metabolites - Post-translational modification of microtubules - Activation MAPK pathway and phosphorylation of motor proteins - Oxidative stress and ROS production - Nutrient stress	(Chopra and Tiwari, 2012) (Kannarkat et al., 2006; Malatová and Cízková, 2002) (Dina et al., 2000; Tong et al., 2011) (Albano, 2006; Alfonso-Loeches et al., 2013; Canton Santos et al., 2013; Hama, 2003)

Abbreviations: APNs (acquired peripheral neuropathies), CIPN (chemotherapy induced peripheral neuropathies), DIPN (diabetes induced peripheral neuropathies), mGluR5 (glutamate subtype-5 receptor), HPA (hypothalamic-pituitary-adrenal), MAPK (mitogen-activated protein kinases), and ROS (reactive oxygen species).