Published in final edited form as:
Expert Rev Neurother. 2012 September ; 12(9): 1041–1043. doi:10.1586/ern.12.79.

Therapeutic implications of protein homeostasis in demyelinating peripheral neuropathies

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Keywords

Charcot–Marie–Tooth disease; demyelinating neuropathies; endocytic trafficking; protein quality control; receptor signaling

"A better understanding of the pathogenesis of demyelinating neuropathies may overcome the current limitations in designing therapies for these patients."

Demyelinating peripheral neuropathies describe a group of human disorders where the primary defect is the peripheral demyelination of nerve fibers. Patients suffering from these neuropathies exhibit a combination of motor weakness and sensory loss that can drastically affect quality of life [1]. Demyelinating neuropathies can be caused by a variety of conditions, including abnormal inflammatory responses, environmental exposure to pathogens and toxins and genetic disorders such as Charcot–Marie–Tooth disease (CMT) [2]. In addition, a significant number of cases are found to be idiopathic [2]. Although some of the neuropathic symptoms could be abated by treating the underlying cause [2], no effective therapy currently exists for the majority of demyelinating neuropathies. A better understanding of the pathogenesis of demyelinating neuropathies may overcome the current limitations in designing therapies for these patients. Recent advances in the genetics field have identified specific mutations in more than a dozen genes known to cause demyelinating CMT [3]. Characterization of these CMT-linked mutations has provided novel insights into the pathogenic mechanisms of demyelinating neuro pathies, and recent studies have begun to suggest new therapeutic strategies for treating these diseases.

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Financial & competing interests disclosure
The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.
No writing assistance was utilized in the production of this manuscript.

Protein quality control pathways as potential therapeutic targets for demyelinating neuropathies

Accumulating evidence suggests that protein misfolding is a major etiology of demyelinating CMT [4]. More than 80% of demyelinating CMT cases are caused by mutations that induce the overexpression or single amino acid substitutions of membrane proteins such as PMP22, myelin protein zero and SIMPLE, which result in the increased production of misfolded forms of these proteins in Schwann cells [4]. Misfolded proteins are normally refolded by molecular chaperones at the endoplasmic reticulum (ER) or are retrotranslocated from the ER to the cytosol for proteolysis by the ubiquitin–proteasome system in a process known as ER-associated degradation [4,5]. In addition, these misfolded proteins and their aggregates can be sequestered and degraded by the aggresome–autophagy pathway [4,5]. When the protein quality control systems are overwhelmed or impaired, misfolded proteins start to accumulate and aggregate into toxic oligomers, which can inhibit cellular functions [5]. Recent reports implicate that medications that inhibit proteasome function, such as the chemotherapeutic agent bortezomib, or drugs that block the formation of aggresomes, such as vincristine, docetaxel and cisplatin, cause or exacerbate the demyelinating neuropathic phenotype [4,6]. Therefore, these drugs are contraindicated in patients diagnosed with neuropathic disorders such as CMT.

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A therapeutic strategy currently under investigation involves the reduction of PMP22 synthesis by drugs such as ascorbic acid to prevent the accumulation of misfolded proteins in human patients [3,7]. Studies described earlier support a possible alternative strategy by augmenting the protein quality control systems to protect Schwann cells against misfolded protein-mediated cytotoxicity. Some drugs that have shown promise in cellular and animal studies include curcumin, a sarcoplasmic/ER calcium ATPase inhibitor, which decreases the amount of misfolded myelin proteins accumulated at the ER to reduce the cytotoxicity of these misfolded proteins [3,7]. Recent drug screens have identified chemical agents that facilitate the proteasomal degradation, such as oleuroperin and a USP14 inhibitor, and novel chemical compounds that promote aggresome formation, all of which have demonstrated cytoprotective effects against misfolded proteins [4]. In addition, autophagy activation by rapamycin, which facilitates the degradation of misfolded proteins, has been shown to improve myelination in explant models of demyelinating CMT [8], suggesting that augmentation of autophagy may also be included as a strategy in combating against demyelinating neuropathies. While the pharmacological activation of the protein quality control pathways seems promising, one major challenge is the potential side effects caused by using drugs targeting these pathways that are ubiquitously present in multiple tissues and cell types. For example, rapamycin that activates autophagy by inhibiting mTOR, a signaling molecule upstream of many important cellular pathways, can cause severe side effects such as immunosuppression and metabolic diseases [5]. Therefore, a more in-depth understanding of the molecular pathways that degrade misfolded proteins in Schwann cells, including the identification of E3 ligases and adaptor proteins specifically targeting the

proteolysis of misfolded PMP22, myelin protein zero and SIMPLE, could provide novel agents for targeting demyelinating neuropathies with minimal side effects.

Targeting signaling cascades & endocytic trafficking as potential therapeutic intervention in demyelinating neuropathies

Recent genetic studies have identified loss-of-function mutations in FIG4, MTMR2 and MTMR13, all of which are lipid phosphatases, to cause demyelinating CMT [3,7]. Depletion of the lipid phosphatase PTEN also causes a similar demyelinating phenotype in mice [9]. These enzymes are responsible for downregulating phosphatidylinositol phosphates, such as PIP3, which are normally elevated transiently in response to receptor activation [10]. An increase in PIP3 level reduces the inhibition of the downstream Akt/mTOR signaling pathway that stimulates myelin synthesis by Schwann cells [10]. When lipid phosphatases such as MTMR2 and PTEN are impaired, the toxic build-up of PIP3 in cells drives the overactivation of the protein kinase Akt, which induces uncontrolled myelin synthesis as characterized by infolded and/or outfolded myelin loops at the early stages of a subgroup of demyelinating neuropathies [10,11]. Recurrent myelin loop formation becomes more complex as the disease progresses, and it is possible that the hypermyelination eventually becomes unsustainable, which leads to the demyelination and axonal degeneration seen at late stages of the disease [12]. This hyper-myelination phenotype is also seen in several subtypes of demyelinating CMT, chronic inflammatory demyelinating neuropathy and animal models of peripheral neuropathies [10,11], suggesting that the pathological increase in promyelination signaling could be a common feature in these types of peripheral neuropathies.

> "...modulation of receptor trafficking and signaling could be beneficial in treating demyelinating neuropathies."

Disruption of phosphatidylinositol-regulating enzymes can also affect the endosome-to-lysosome trafficking pathway and inhibit the degradation of cell surface proteins [3,13]. Activated ErbB receptors are normally downregulated by endocytic trafficking to lyso-some for degradation, and the blockage of this degradative pathway by MTMR2 depletion causes sustained ErbB receptor activation of the Akt signaling [13]. In addition to MTMR2, mutations in endocytic proteins, such as SIMPLE and SH3TC2, are also linked to subtypes of demyelinating CMT. SIMPLE is an endosomal protein implicated in the regulation of endosome-to-lysosome traffick ing based on its interaction with TSG101, a component of the endosomal sorting complexes required for transport machinery [14]. We have found that CMT1C-linked mutations in SIMPLE cause its mislocalization from the early endosome to the cytosol [14], suggesting an involvement of impaired endosome-to-lysosome traffick ing in demyelinating CMT. SH3TC2 is an endosomal protein that regulates endosomal recycling, and loss-of-function mutations in SH3TC2 cause CMT4C, which is associated with decreased receptor recycling to the cell surface and decreased myelin protein synthesis in the peripheral nerves [15,16]. As a result, loss-of-function in SH3TC2 causes hypomyelination at the early stages [15], rather than hypermyelination and irregular myelin folding associated with MTMR2 mutations [10,11]. Together, these reports indicate that

imbalance in receptor trafficking and downstream signaling could be a major cause of demyelinating neuropathies.

The studies described earlier suggest an intriguing possibility that modulation of receptor trafficking and signaling could be beneficial in treating demyelinating neuropathies. For selected types of neuropathies with an initial hyperactivation of promyelination signaling, pharmacological agents that decrease receptor activation of the Akt/mTOR pathway might be a promising therapeutic approach. Some examples of this approach include the finding that PKI 166, a drug that inhibits ErbB receptor signaling, is efficacious in preventing *Mycobacterium leprae*-induced ErbB receptor activation and demyelination in mice [17]. In addition, rapamycin, a drug that has been investigated for its ability to promote proper myelination [8,9], inhibits mTOR, which may have a therapeutic effect not only from its ability to activate autophagy [8] but also from its action in blocking signaling downstream of ErbB receptor activation to prevent the dysregulation of promyeli-nation signaling [9]. Although PKI 166 and rapamycin are probably not the drugs of choice in treating peripheral neuropathy due to their side effects, the development of pharmacological agents targeting receptors and downstream effectors of the Akt/mTOR pathway should help provide novel treatments for these types of demyelinating neuropathies.

For demyelinating neuropathies where promyelination signaling pathways are impaired, drugs that stimulate promyelination signals may prove beneficial to these patients. Recently, the trkB receptor agonist 7,8-dihydroxyflavone has been examined as a treatment for several neurodegenerative diseases [18]. A small-molecule screen for agonists of promyelination receptors, such as ErbB receptors, may help identify drugs that could promote myelination to treat certain types of demyelinating neuropathies. Moreover, lithium, a drug that has been used as a long-term mood stabilizer in treating bipolar and depressive disorders, was recently found to stimulate peripheral myelin gene expression and myeli-nation of peripheral nerves *in vivo* by inducing the nuclear trans-location of β-catenin without stimulating Akt [19]. Compounds such as lithium could be tested for their ability to reverse subtypes of demyelinating neuropathies where hypomyelination occurs at the early stages. Finally, modulation of phosphatidylinositol metabolic enzymes and/or endocytic sorting protein machineries to restore receptor trafficking and signaling back to homeostatic levels could be explored as therapeutic options in the future. A better understanding of the molecular pathways regulating receptor trafficking and signaling will facilitate the development of novel therapies for treating these debilitating neuropathic disorders.

Acknowledgments

This work was supported by NIH grants NS050650 (L-S Chin), AG034126 (L-S Chin), ES015813 (L Li), GM082828 (L Li) and NS063501 (SM Lee).

Biography

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