Neurotherapeutics (2021) 18:2153–2155
https://doi.org/10.1007/s13311-021-01177-5

EDITORIAL

Peripheral Neuropathy: No Longer the Land of Therapeutic Nihilism

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Accepted: 22 December 2021 / Published online: 6 January 2022

The peripheral neuropathy field has been historically dominated by investigations of clinical manifestations and etiology. While natural history studies have advanced care of patients with diabetic and toxic neuropathies, and careful clinical trials have defined optimal immune modulating treatment regimens for acquired inflammatory neuropathies, progress toward disease-modifying therapeutics for most forms of peripheral neuropathy has been incremental. This is due to the challenges imposed by the rare nature of many forms of peripheral neuropathy, an incomplete mechanistic understanding of disease, and imprecise outcome measurements. These barriers are gradually melting away as a consequence of increasingly thorough understanding of genetic and cellular pathophysiological mechanisms as well as a growing toolbox of therapeutic techniques to target DNA, RNA, and/or enzymes. This dynamic therapeutic environment is paving the road to a new and exciting phase in the field of peripheral neuropathy. In this issue of Neurotherapeutics, we highlight some of the many advances in understanding of disease mechanisms, as well as novel tools and therapies that are making treatment possible.

Basic Biology/Disease Mechanisms

It is increasingly appreciated that impaired axon and myelin development may underlie several forms of genetic neuropathy. Previtali [1] details recent advances in our understanding of radial sorting of axons — the process whereby developing axons and Schwann cells (SCs) interact to form functional peripheral nerves. SCs, axons, and components of the extracellular matrix all play roles in this complex process. Mutations of specific proteins critical for this process, including LAMA2, can cause Charcot-Marie-Tooth (CMT) disease. Bolino [2] next reviews our fundamental understanding of the myelin sheath and Schwann cell biology. Abnormalities in these processes underlie many of the most common forms of inherited peripheral neuropathy. Duplication (CMT1A) or point mutations (CMTIE) in the PMP22 gene produce demyelinating neuropathies of variable severity. Conversely, abnormalities in genes encoding proteins regulating endosomal trafficking such as myotubularin-related phosphatases (MMTR) result in aberrant myelination seen in forms of CMT4B. While most studies have focused on alterations of peripheral nerve structure during disease, Rawat and Morrison [3] detail our increasing understanding of the metabolic demands of peripheral nerves and the vulnerability imposed by very long axons, more permissible blood-nerve barriers, and hydrophobic myelin sheaths. They review how the second most common form of inherited peripheral neuropathy, CMT-X, may be linked to disruption of energy support through mutations in Cx32/GJB1 and might be treatable through gene therapy that restores Cx32 function or inhibition of axonal degeneration through SARM1 inhibition. Augustus Waller first described the morphological process of axonal degeneration after nerve transection 150 years ago. Here, Arthur-Farraj and Coleman [4] describe recent steps characterizing molecular mechanisms of this process. Depletion of NMNAT2 either by axon transection or disease initiates a cascade of NAD depletion and activation of the prodegenerative enzyme SARM, while Schwann cell transformation to a repair state is mediated through the transcription factor c-JUN. These pathways may be relevant to many forms of peripheral neuropathy, and the specific molecular mediators offer novel therapeutic strategies including antagonism of the SARM1 enzyme.

Outcome Measures and Novel Assessments

Several emerging techniques have the potential to simplify patient assessment and timing of therapy. Kollmer and Bendszus [5] describe the growing role that peripheral

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nerve imaging has in different forms of peripheral neuropathy. Improved MRI sequences detect structural changes in peripheral nerves that often occur at proximal sites despite the clinical length-dependent appearance. Changes can also be detected at early stages of disease and offer the potential to identify patients at pre-symptomatic stages in order to optimally time initiation of therapy. Similarly, Wieske et al. [6] review promising data on several peripheral neuropathy liquid biomarkers. The most studied and promising to date is neurofilament light (NfL), a neuronal cytoplasmic protein that is highly expressed in large caliber myelinated axons. While it may miss small fiber involvement, NfL has demonstrated potential in detecting active disease, disease progression, and a treatment effect in several forms of peripheral neuropathy. Such measurements will likely serve as useful adjunct measurements in future clinical trials.

Specific Diseases

Among toxic/metabolic peripheral neuropathies, Cavaletti et al. [7] review the potential of targeting the endocannabinoid system for symptomatic treatment for chemotherapy induced peripheral neuropathy (CIPN). While CIPN results from many different agents that likely involve different pathways, this promising treatment approach offers hope for a dire unmet need. In contrast, Poitras et al. [8] review mechanisms that have been implicated in diabetic polyneuropathy (DPN), a condition that remains refractory to disease-modifying therapeutic advances. It is possible that different mechanisms are at play among different patients, and this has contributed to the refractory nature of the condition in large clinical trials. Among peripheral neuropathies with well-defined disease mechanisms, therapeutic advances have been more dramatic. Obici and Mussinelli [9] elegantly describe treatments for hATTR — an ultra-rare inherited neuropathy tied to dissociation, misfolding, aggregation, and deposition of a single protein, transthyretin, as amyloid. Therapies designed at stabilizing TTR's native 3D-structure (stabilizers), knockdown of TTR synthesis (silencers), and gene editing through CRISPR-cas9 have transformed what was a progressive and ultimately fatal disease into a condition with many treatment options. Similar therapeutic success may await other forms of inherited neuropathy that have been linked to single proteins. Over-expression of PMP-22 due to gene duplication in CMT-1A is one such example discussed in the review by Fridman and Saporta [10]. McCray and Scherer [11] highlight themes underlying genetic neuropathies including defects in axonal transport, mitochondrial dynamics, organelle-organelle contacts, and local axonal protein translation. Many of the protein abnormalities attributed to CMT2 are expressed beyond the peripheral nervous system, yet disproportionately or exclusively manifest as peripheral neuropathy and highlight the vulnerability of peripheral nerves. Restoring axon expression of these proteins or their functional homologues in animal models as has been shown with MFN2 in CMT2A is paving the way for future gene therapy human trials. Querol and Lleixà [12] review how breakdown of the blood-nerve barrier is a seminal event in allowing access of autoantibodies, macrophages, and other immune mediators to the endoneurial space where they initiate nerve damage. Identification of specific autoantibodies such as against SC/axon junction proteins: contactin 1 (CNTN1) and contactin-associated protein 1 (Caspr1) on the axonal side and neurofascin 155 (NF155) increasingly allow neurologists to tailor treatments such as avoiding IVIg in patients with anti-CNTN1 antibodies or following antibody titers as a measure of treatment effect in patients with disyalosil antibodies. Finally, Ebenezer and Scollard [13] review the pathophysiological understanding of the most common infectious neuropathy, leprosy neuropathy, and different antibiotic and anti-inflammatory treatment options.

Together, peripheral neuropathies comprise one of the most common forms of neurological disease affecting more people than multiple sclerosis, ALS, or Parkinson's disease, all of which garner more public attention. This relative obscurity is changing. The next decade promises to bring unprecedented therapeutic options to peripheral nerve diseases as a growing mechanistic understanding reveals druggable targets.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s13311-021-01177-5.

Required Author Forms Disclosure forms provided by the authors are available with the online version of this article.

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