



MINI-REVIEW

Similarities between Inherited Demyelinating Neuropathies and Wallerian Degeneration

An Old Repair Program May Cause Myelin and Axon Perturbation under Nonlesion Conditions

Rudolf Martini, Dennis Klein, and Janos Groh

From the Section of Developmental Neurobiology, Department of Neurology, University of Würzburg, Würzburg, Germany

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Address correspondence to
Rudolf Martini, Ph.D.,
Department of Neurology,
University of Würzburg,
Josef-Schneider Strasse 11,
Würzburg D-97080,
Germany. E-mail: rudolf.martini@mail.uni-wuerzburg.de.

Wallerian degeneration (WD) and inherited demyelinating neuropathies of the Charcot-Marie-Tooth type 1 (CMT1) appear to represent completely distinct events. CMT1-like diseases are chronic disorders of peripheral nerves that are genetically caused and lead to secondary neurodegenerative events, resulting in usually non-treatable disabilities, whereas WD is an acute, usually transient, reaction on injuries, aiming to allow peripheral nerve regeneration. Despite these differences, there are some striking similarities regarding molecular characteristics of neural cells in the affected peripheral nerves. The most conspicuous similarities might comprise the inflammatory component in both situations, as identified in appropriate mouse models. However, although inflammation is a beneficial component in WD, leading to removal of regrowth-repellent myelin debris, inflammation in CMT1 mouse models causes damage of initially intact nerve fibers. We hypothesize that, in CMT1 models, molecular pathways are activated that are shared with an important repair program after peripheral nerve injury, but lead to neural perturbation when activated under nonlesion conditions, as is the case in CMT1. These novel insights into the pathogenesis of CMT1 might be instrumental for the development of new therapeutic options in humans. (*Am J Pathol* 2013, 183: 655–660; <http://dx.doi.org/10.1016/j.ajpath.2013.06.002>)

Inherited demyelinating neuropathies of the Charcot-Marie-Tooth type 1 (CMT1) strongly reduce quality of life because of typical neuropathological features, such as length-dependent axonal degeneration, muscle atrophy, skeletal deformities, and sensory dysfunctions. In the most common forms of the CMT1 diseases, CMT1A, CMT1B, and CMT1X, these uniform features are caused by gene mutations related to distinct peripheral myelin-associated proteins, such as peripheral myelin protein 22 (PMP22), myelin protein zero (P0), or connexin 32 (Cx32),¹ respectively, suggesting some shared disease mechanisms with a similar outcome. Studies in the corresponding mouse models identified components of the immune system as possible common pathomechanistic pathways of the disorders.^{2–5} Based on these studies, the question emerges why, under the genetic disease conditions, a highly coordinated series of cellular and molecular events occur that lead to nerve damage.

The answer may be related to Wallerian degeneration (WD), the reactive degeneration of axons and myelin of nerves that experienced traumatic, adverse metabolic, toxic, or other noxious conditions.^{6,7} In the peripheral nervous system, this process occurs rather rapidly and is an important prerequisite for successful axonal regeneration,⁸ possibly explaining the high evolutionary preservation of this process in different species.⁹ One important feature that enables the rapid speed of Wallerian degeneration is the inclusion of the innate immune system, implicating a sophisticated cross talk between lesioned axons, Schwann cells, and monocytic phagocytes that remove nerve growth–attenuating components of the myelin

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sheaths.^{8,10} Interestingly, there is increasing evidence that, in models for CMT1, inflammation by innate immune cells is mediated by similar mechanisms as found in WD.^{4,10,11} Other common immune-related features implicate intrinsic antibodies that mark myelin for macrophage phagocytosis in WD and potentially also in CMT1 models (R.M. and D.K., unpublished data).¹² Moreover, apart from the immune system, mediators of Schwann cell dedifferentiation, such as c-Jun, appear to be common molecular players of both WD and CMT1.^{13–16} Last, molecular pathways that are involved in WD-related axon degeneration^{7,17,18} have also been identified to participate in axon loss in CMT models.

The present minireview will compare inherited peripheral neuropathies of the CMT1 type with WD, with the aim to analyze cellular and molecular similarities between both processes affecting peripheral nerves as a result of primarily different pathogenic events.

Axon-Related Molecular Changes in Models for Demyelinating Peripheral Neuropathies and WD

Although demyelinating forms of inherited neuropathies are often caused by mutations in Schwann cell genes, a common feature of these disorders is axonal perturbation, particularly at distal aspects of long nerves.^{1,19–21} These axonal changes are most important with regard to the clinical outcome of the diseases. Although a trophic role of Schwann cells is likely,^{21–23} it is not known why axons degenerate when the Schwann cell–related genes are mutated. The minimum knowledge about the degenerative pathways of axons in rodent models of demyelinating inherited neuropathies concerns the partial molecular overlap with mechanisms underlying WD.^{7,17,18} This process usually occurs as a result of nerve injury and is an active process, rather than a passive degenerative event of axons separated from their cell bodies, as revealed by the analysis of the slow Wallerian degeneration (*Wld^S*) mutant mouse.⁷ In this gain-of-function mutant, axon stumps survive 10 times longer than normal after injury because of neuronal overexpression of a chimeric fusion protein.⁹ This fusion protein contains the NAD⁺ biosynthetic enzyme, nicotinamide mononucleotide adenylyltransferase 1 (*Nmnat1*), and 70 amino acids of *Ube4b*, an E4-type ubiquitin ligase. A series of studies indicated that *Wld^S* expression results in increased extranuclear *Nmnat1*, probably substituting for the protective activity of its isoform, *Nmnat2*, which is quickly degraded after axonal injury, or its mitochondrial isoform, *Nmnat3*.²⁴ Recent observations strongly suggest that *Wld^S/Nmnat*-mediated axonal protection results from stabilization of mitochondrial motility and Ca²⁺ buffering capacity, thus preserving the physiological functions of mitochondria, despite axonal injury.²⁵

More important, the protective effect of *Wld^S* is conserved among different species and delays axonal degeneration in noninjury models of distinct neurological disorders, including peripheral neuropathies.⁷ As a first contribution to

this topic, Samsam et al¹⁷ showed that axonal degeneration in mice homozygously lacking P0 and mimicking CMT3 is significantly delayed when the mice are crossbred with *Wld^S* mutants. Corresponding experiments with PMP22 overexpressing rats mimicking CMT1A and transgenic *Wld^S* rats revealed similar results.¹⁸ Another important mechanism during WD is the implication of a recently identified prodegenerative axonal signaling program, comprising dSarm/Sarm1.²⁶ In analogy to studies with *Wld^S* mutants,^{17,18} it remains to be determined if blockade of Sarm1 might attenuate axonal perturbation in peripheral neuropathies and other disorders with axonal loss.

Schwann Cell–Related Molecular Changes in Models for Demyelinating Peripheral Neuropathies and WD

Inherited demyelinating neuropathies and WD have common molecular features regarding axonal degeneration and concerning molecular alterations and dedifferentiating phenotypes of the Schwann cells. For instance, Schwann cells of models for inherited neuropathies express the same cell surface molecules (eg, L1 and neural cell adhesion molecule) as Schwann cells of lesioned nerves.^{27,28} Another important molecule regarding Schwann cell phenotype is the transcription factor component c-Jun.¹³ Parkinson et al¹⁴ identified this molecule as an antagonist of the promyelinating transcription factor Krox-20 and as a dedifferentiation- and demyelination-promoting molecule. In inherited peripheral neuropathies²⁹ and in the respective models,¹⁴ c-Jun is up-regulated, possibly keeping the Schwann cells in a state of demyelination and low differentiation phenotype. Regarding WD, it is most interesting that c-Jun defines the phenotype of the so-called Büngner cells (ie, Schwann cells sharing features of both Schwann cell precursors and immature Schwann cells that enable axonal regrowth).¹⁵

Inflammatory Pathways in Models for Demyelinating Peripheral Neuropathies and WD

MEK/ERK Signaling and Cytokine Induction in Schwann Cells and Fibroblasts

The generation of Büngner cells is dependent on c-Jun activity and on elevated levels of phosphorylated extracellular signal–regulated kinase (ERK), a downstream intracellular signaling component of the Ras/Raf/mitogen-activated protein/ERK kinase (MEK)/ERK pathway.³⁰ To enable stimulation of ERK signaling and investigate the respective consequences related to Schwann cell dedifferentiation/Büngner cell formation, as they may similarly occur under lesion conditions, mice that express the Raf kinase/estrogen receptor fusion protein under the control of the Schwann cell–specific P0 promoter have been generated.¹¹

In this way, activation of the ERK pathway induced a dedifferentiated phenotype of Schwann cells and an elevated expression of the inflammation-related cytokines, monocyte chemoattractant protein (MCP)-1 (chemokine ligand 2), macrophage inhibitory factor-1, IL-11, and CXCL10.¹¹ Moreover, an inflammatory response in the form of an influx of inflammatory cells partially reminiscent of WD occurred, although expression levels of other cytokines relevant in WD, such as IL-6 and tumor necrosis factor- α , were either not elevated or have not been considered in the study, respectively.¹¹

Although this study established that the MEK-ERK signaling pathway is an important player in WD, it is not clear how this pathway is initiated after injury. In a recent study, Schwann cells have been identified to express the neuregulin-1 isoform I (NRG1/I) as an important prerequisite for autocrine-mediated regenerative myelin formation after WD.³¹ Proof of this concept was provided by generating Schwann cell-specific NRG1-null mice, which displayed a strongly reduced regenerative myelin formation. As an interesting observation, the NRG1-deficient Schwann cells fail to show substantial ERK activation after nerve injury,³¹ but the consequences for MCP-1 expression and macrophage influx/inflammation have not been addressed in this study.

MEK-ERK activation has implications for WD, and for CMT1 models, because activation of this pathway has been identified as a typical feature of mutant Schwann cells in three distinct forms of inherited peripheral neuropathies, as exemplified by mice heterozygously deficient for P0 (CMT1B), hemizygotously or homozygotously deficient for Cx32 (CMT1X), or mildly overexpressing PMP22 (line C61; CMT1A).^{3–5} Moreover, there is strong evidence that, in these models, activation of the respective pathway leads to an elevation of MCP-1, which is one of at least two important components for macrophage recruitment and macrophage-related demyelination in these models.¹⁰ The link between MEK-ERK activation and MCP-1 expression has been shown by systemically treating the CMT1 models or isolated Schwannoma cells with the synthetic MEK inhibitor, CI-1040, resulting in the expectedly lowered ERK phosphorylation and in an attenuated expression of MCP-1.^{3–5} In one model, even macrophage influx and some macrophage-related pathological changes could be attenuated by MEK/ERK inhibition, although systemic treatment was limited to only 3 weeks.⁴ Thus, in models of CMT1 (ie, under conditions initially distinct from WD), the molecular axis of MEK/ERK activation—MCP-1 expression—macrophage activation also occurs as in WD and appears to be crucially implicated in the pathogenesis.^{3–5,10,11,32}

By trying to combine the observations by Napoli et al¹¹ and by Stassart et al³¹ and adapt them to potential mechanisms in peripheral neuropathies, the following pathophysiological model could emerge: mutant Schwann cells might lose communication with axons (possibly by hypothetical ErbB2/3 dysregulation), resulting in increased NRG1/I

expression that leads to autocrine MEK-ERK phosphorylation. This will cause elevated downstream expression of MCP-1 and activation of macrophages. Alternatively, it has been speculated that in models for demyelinating inherited neuropathies, MEK-ERK activation might be the result of cellular stress, related to an unfolded protein response.^{10,33}

In addition to MCP-1, colony-stimulating factor (CSF)-1 has been identified as another pathogenic player in distinct models of CMT1.^{34,35} This was clearly demonstrated by the observation that, in the CMT1 models, myelin and axons were substantially and persistently preserved when CSF-1 expression was genetically inactivated, thus identifying macrophages as myelin perturbators and not as innocent scavengers or bystanders. Unexpectedly, this cytokine is not a product of mutant Schwann cells but is expressed by endoneurial fibroblasts.³⁵ It is presently not known which signals let the fibroblasts know about the genetic alteration of the Schwann cells and induce them to secrete CSF-1. According to our present observations, it is conceivable that downstream products of the Schwann cell-related MEK-ERK pathway distinct from MCP-1 could serve as a molecular bridge between Schwann cells and CSF-1-producing fibroblasts.

Possible Roles of Antibodies

Considering the impact of macrophages in myelin phagocytosis in both inherited neuropathies and WD, the question emerges how macrophages may recognize their phagocytotic target. In 2010, Vargas et al¹² showed that endogenous antibodies accumulate rapidly after crush injury at the distal myelin fragments. They also demonstrated that mice lacking B lymphocytes (and, therefore, incapable of producing antibodies) displayed delayed macrophage recruitment and activation after nerve injury. This resulted in reduced myelin clearance and slightly compromised axonal regeneration, suggesting a significant role of endogenous antibodies in the course of macrophage-related myelin removal and subsequent axon regeneration.¹² Interestingly, in models of CMT1, a similar antibody accumulation can be detected, even in the absence of mechanical nerve lesions. Moreover, by investigating myelin-mutant mice lacking endogenous antibodies, one model displayed reduced macrophage activation, with attenuated phagocytic activity and attenuated deterioration of myelin integrity (R.M. and D.K., unpublished data). Our recent unpublished observations are consistent with previous findings in recombination activating gene-1-deficient myelin mutants that displayed an amelioration of myelin degeneration in the absence of mature T and B lymphocytes.^{36,37} It remains to be proven if endogenous antibodies are involved in myelin degeneration in some or most CMT1 models and whether other serum components, such as complement,^{38,39} might also contribute to the primarily genetically caused myelin degeneration.

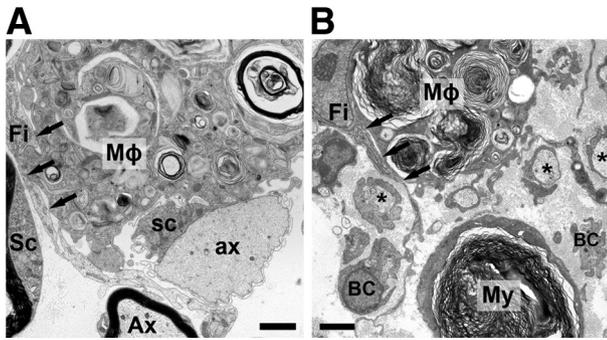


Figure 1 Representative electron micrographs of a ventral root of a CMT1 model (6-month-old Cx32-deficient mouse; **A**) and of an injured plantar mouse nerve (14 days after crush injury; **B**). Both in the CMT1 model and in WD, myelin-laden macrophages (MΦ) are major cellular components at this stage of active demyelination (**A**) and phagocytosis of myelin debris (**B**), respectively. In both situations, macrophages are contacted by endoneurial fibroblasts (Fi; **arrows**). **A**: A demyelinated axon (ax) is associated with a Schwann cell (sc) that likely lost myelin because of the active phagocytosis of the macrophage. Other myelinated axons (Ax) and their myelinating Schwann cells (Sc) appear (still) intact. **B**: Small regenerating axonal sprouts (**asterisks**) are visible. Büngner cells (BCs), still devoid of regrowing axons, are typical cellular components of the injured nerve after axons are degenerated. My, myelin ovoid. Scale bars: 2 μm (**A** and **B**).

Open Questions

It appears that in inherited demyelinating neuropathies, secondary inflammatory mechanisms may occur, which are

normally activated under lesioning conditions. However, it is presently not clear whether there is only partial or extended overlap between the genetic disorders and WD. For instance, it remains to be shown which pathways mediate the expression of the many other cytokines related to WD, such as tumor necrosis factor-α, IL-1α, IL-1β, IL-6, IL-10, and granulocyte-macrophage CSF,^{6,10,40,41} and whether these may also have implications for inherited neuropathies. For inherited neuropathies, it is also not yet known whether M1 or M2 macrophage types are prevalent, as opposed to WD, in which it is known that M2 macrophages appear to be predominant.⁴² On the other hand, the pivotal role of CSF-1 and its cellular source have been only identified in CMT1 models,^{34,35,43} whereas its function in WD is not well investigated.¹⁰ Moreover, neurotrophic factors appear to be important in WD,^{6,40} but there is little knowledge about their implications in inherited peripheral neuropathies.

Conclusions and Future Perspectives

At first glance, WD and CMT1-like disorders appear to represent completely distinct events regarding cause, initiation, progression, duration, and hypothetical therapeutic interventions. While WD is an acute, usually transient, event with inflammatory components, CMT1-like diseases are viewed as chronic disorders that are genetically caused and

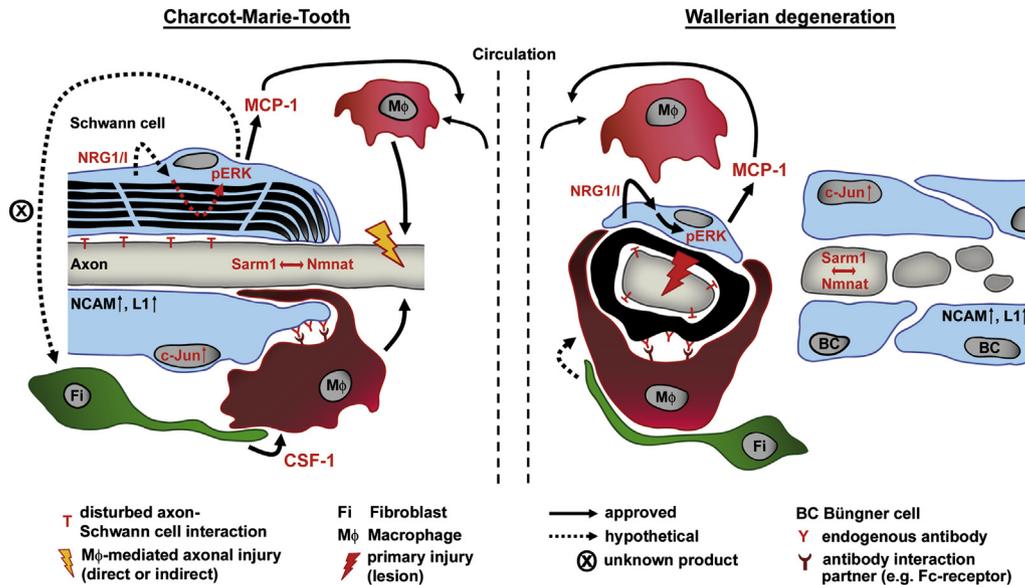


Figure 2 Synoptic view of cellular and molecular interactions in models of demyelinating CMT neuropathy (**left panel**) and in WD (**right panel**). In CMT1 models, mutant Schwann cells show an activated ERK pathway (pERK) that leads to MCP-1 (chemokine ligand 2) expression that fosters macrophage (MΦ) transmigration into the nerve. Hypothetically, ERK activation could be triggered by autocrine NRG1/I secretion, because it occurs in WD, in which it appears to cause ERK activation. In CMT1 models, a postulated (but unknown) secreted molecule downstream of Schwann cell-related ERK activation may activate endoneurial fibroblasts (Fi), which have been shown to deliver CSF-1 to myelin-phagocytosing macrophages that directly or indirectly perturb axons (yellow flash). These macrophages may recognize myelin of the mutant Schwann cells by the presence of decorating endogenous antibodies (possibly recognizing myelin components), as has been proven in WD, in which myelin ovoids are phagocytosed predominantly by immigrating macrophages. Other mechanistic similarities between CMT1 and WD are pathways implicated in axon degeneration (Sarm1; Nmnat) and the up-regulation of glial dedifferentiation markers, L1, neural cell adhesion molecule (NCAM), and c-Jun. The latter is a transcription factor component fostering demyelination and, in the case of WD, is necessary for the generation of axon-regrowth-promoting Büngner cells (BCs). In the WD model, axon damage (red flash) is the primary cause for the molecular alterations and phagocytosis, whereas in the CMT1 model, axon damage (yellow flash) is a downstream result of the molecular alterations triggered by Schwann cell-related mutations and phagocytosis in the initial presence of noninjured axons.

lead to secondary degenerative events, resulting in usually non-treatable disabilities. For the first scenario, the primary research focus is on better/quicker axonal regeneration and target finding^{8,44}; basic interest in the latter is usually on updating our knowledge with novel genetic data on CMT1-like disorders, summarizing and categorizing clinical issues, presenting hypotheses and models for the possible pathogenetic pathways of gene mutations, and eventually discussing possible biomarkers and hypothetical and past therapeutic approaches.^{1,45–53} The present minireview tried to bridge between both pathological conditions, identifying remarkable similarities with possible therapeutic implications, particularly for the inherited disorders.

Regarding CMT1, clear similarities to WD are some neural processes implicating axon-specific degeneration mechanisms, but also glial-related changes, such as steps related to Schwann cell dedifferentiation. According to our present view, the most conspicuous similarity is the inflammatory component in both events (Figure 1). Although inflammation is viewed as a beneficial event in WD, because of removal of inhibitory myelin (thus, enabling axons to regrow substantially),⁸ inflammation appears detrimental to myelin integrity and axonal preservation in models for CMT1. Based on these findings and considering the molecular similarities between WD and CMT1 (Figure 2), it is plausible to assume that, in the genetic disorders, some pathways related to the initially beneficial and, thus, evolutionary preserved mechanisms of WD are ectopically and inappropriately activated. As an adverse effect of this ectopic activation, the inflammatory component appears to be deleterious to the initially non-injured axons. It is conceivable that other forms of CMT show cellular and molecular characteristics common to WD, including inflammation. This is particularly expected for the primarily axonal forms of inherited peripheral neuropathies (CMT2), which, starting with axonal perturbations, might be even closer related to WD than CMT1. However, corresponding studies in animal models disclosing such similarities are rare, so that future studies are necessary for a more complete understanding of the respective disorders and their possible relationship to WD.

Although in the CMT1 models discussed herein, the detailed macrophage-related mechanisms that lead to axon damage have not yet been elucidated, reducing this macrophage-related inflammation might emerge as a therapeutic option for inherited demyelinating diseases.^{10,33,53} There are several hypothetical possibilities regarding how this could be achieved. i) Because ERK activation is upstream of the macrophage-activating chemokine, MCP-1, inhibitors of this pathway (some of which are under clinical consideration for malignancies⁵⁴) might theoretically be an option. However, the pleiotropic implication of the ERK pathway in many cellular processes might be limiting regarding long-term treatment of a chronic disorder. ii) Pharmacological interventions of the CSF-1 pathway could be a promising direction in attenuating macrophage-related myelin attack in CMT1.⁵⁵ iii) Systemic application of mesenchymal stem

cells^{56–59} might be a third option. These cell types can modulate the inflammatory milieu of the organism and might, in this way, attenuate chronic inflammatory conditions that occur in CMT1 neuropathies and other disorders of the nervous system.

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