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Molecular Mechanisms of Inherited Demyelinating Neuropathies

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ABSTRACT
The past 15 years have witnessed the identification of more than 25 genes responsible for inherited neuropathies in humans, many associated with primary alterations of the myelin sheath. A remarkable body of work in patients, as well as animal and cellular models, has defined the clinical and molecular genetics of these illnesses and shed light on how mutations in associated genes produce the heterogeneity of dysmyelinating and demyelinating phenotypes. Here, we review selected recent developments from work on the molecular mechanisms of these disorders and their implications for treatment strategies.

NOSOLOGY

Dominantly Inherited Demyelinating Neuropathies

More than a century ago, Charcot, Marie, and Tooth described patients who we now understand to have a dominantly inherited, progressive neuropathy that affects myelinated motor and sensory axons in a length-dependent manner (Lupski and Garcia, 2001; Shy et al., 2005b; Wrabetz et al., 2004a). This disorder is usually called Charcot-Marie-Tooth disease, or simply CMT. Soon thereafter, presumed recessive cases of more severely affected individuals (Déjérine–Sottas neuropathy; DSN) as well as X-linked kindreds (CMT1X) were described. Dyck et al. introduced the currently used classification scheme, although they used the term "hereditary motor and sensory neuropathy" (HMSN) rather than CMT. They demonstrated that most kindreds had CMT1/HMSN I, characterized by slowed motor conduction velocities in the arms (10–40 m/s) and histological evidence of segmental demyelination and remyelination, in addition to axonal loss. CMT2/HMSN II kindreds tended to have a later age of onset, little if any nerve conduction slowing, and loss of myelinated axons but little segmental demyelination/remyelination. Several groups extended these findings, and forearm motor conduction velocities of less than 38 m/s were proposed to separate CMT1 from CMT2 (Harding and Thomas, 1980). This criteria was a heuristic aid, but can be misleading if applied too rigidly, particularly for several forms of CMT that have been termed "dominant intermediate" (Nicholson and Myers, 2006).

Mapping the genetic loci led to the identification of the causative genetic defects, and to the realization that multiple genes cause CMT1 (http://www.molgen.ua.ac.be/CMTMutations/ and Table 1). This began with the discovery that a partial intrachromosomal duplication of chromosome 17 leads to a duplication of the *PMP22* gene (which encodes an intrinsic membrane protein of compact myelin, peripheral myelin protein 22 kDa; PMP22) that causes CMT1A (Patel et al., 1992), and the corresponding deletion causes hereditary neuropathy with liability to pressure palsies (HNPP; Chance et al., 1993). Mutations in genes already known to be expressed by myelinating Schwann cells were found to cause other kinds of dominantly inherited demyelinating neuropathies—myelin protein zero (*MPZ*; Hayasaka et al., 1993), which encodes the major adhesive protein of compact myelin, and (*EGR2*; Warner et al., 1998), which encodes a transcription factor, Krox20. In addition, mutations in genes not previously known to be expressed by myelinating Schwann cells were found to cause CMT1—*GJB1*, which encodes the gap junction protein connnexin32 (Cx32; Bergoffen et al., 1993), and *LITAF/SIMPLE*, which encodes a protein that may be involved in the degradation of intracellular proteins (Street et al., 2003), or regulate gene expression (Tang et al., 2006).

Recessively Inherited Demyelinating Neuropathies

These are much less common than dominantly inherited neuropathies (Dubourg et al., 2006; Ouvrier et al., 2007; Vallat et al., 2005), and these are mainly caused by mutations in a different group of genes (Table 1). The demyelinating forms (sometimes referred to as "CMT4") are caused by mutations in *GDAP1*, *MTMR2*, *MTMR13*, *EGR2*, *PRX*, *NDRG1*, *KIAA1985*, *FGD4*, or *FIG4*.

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TABLE 1. Nonsyndromic Inherited Demyelinating Neuropathies

Disease (OMIM)	Linkage or gene
CMT1 (autosomal or X-linked dominant)	
HNPP (162500)	*PMP22* (601097)
CMT1A (118220)	*PMP22* (601097)
CMT1B (118200)	*MPZ* (159440)
CMT1C (601098)	*SIMPLE* (603795)
CMT1D (607678)	*EGR2* (129010)
CMT1X (302800)	*GJB1* (304040)
CMT4 (autosomal recessive)	
CMT4A (214400)	*GDAP1* (606598)
CMT4B-1 (601382)	*MTMR2* (603557)
CMT4B-2 (604563)	*MTMR13* (607697)
CMT4C (601596)	*KIAA1985* (608260)
CMT4D (601455)	*NDRG1* (605262)
CMT4F (145900)	*PRX* (605725)
HMSN-R (605285)	10q23.2
CMT4H (609311)	*FGD4* (611104)
CMT4 (605253)	*EGR2* (129010)
CMT4J (611228)	*FIG4* (609390)

TABLE 2. Syndromic Inherited Demyelinating Neuropathies

Disease (OMIM)	Linkage or gene
Dominant	
Waardenburg-Shah syndrome (277580)	*SOX10* (602229)
PCWH (609136)	*SOX10* (602229)
Recessive or X-linked	
Metachromatic leukodystrophy (250100)	*ARSA* (607574)
Krabbe disease (245200)	*GALC* (606890)
Refsum disease (266500)	*PHYH* (602026)
Cockayne syndrome type A (216400)	*ERCC8* (609412)
	ERCC6 (609413)
CDG1A (212065)	*PMM2* (601785)
Gonadal dysgenesis with minifascicular neuropathy (607080)	*DHH* (605423)
MDC1A (607855)	*LAMA2* (156625)
MNGIE (603041)	*ECGF1* (131222)
PMD (312080)	*PLP1* (300401)
Hypomyelination and congenital cataract (610532)	*DRCTNNB1A* (610531)
CCFDN (604168)	*CTDP1* (604927)

Myelinating Schwann cells express all of these genes, and each of the corresponding proteins probably plays an essential role in Schwann cells so that recessive mutations result in demyelination. *GDAP1* may be an exception, as some patients have a neuropathy with demyelinating features, whereas in other kindreds, the neuropathy appears to be axonal.

Congenital Hypomyelinating Neuropathy and Déjérine-Sottas Neuropathy

These terms are used to describe individuals with severe neuropathy and a clinically recognized onset in infancy (congenital hypomyelinating neuropathy, CHN; 605253) or before two years of age (DSN, also known as CMT3/HMSN III; 145900). In both, nerve conduction velocities (typically less than 10 m/s) and even amplitudes are reduced, and nerve biopsies show more profound loss of normally myelinated axons than biopsies from most CMT1 patients, indicating that the axons were never properly myelinated (hence the term dysmyelinated). Surprisingly, the long-term prognosis for some DSN patients is similar to that in patients with "severe CMT" (Ouvrier et al., 1999). Dominant mutations in *MPZ* or *PMP22* can be found in the majority of patients, but dominant and recessive mutations in *EGR2*, as well as recessive mutations in *MPZ*, *PMP22*, *PRX*, and *FIG4* have been described. Recessive mutations in *GDAP1*, *MTMR2*, or *KIAA1985* can also cause a DSN-like phenotype, and many cases of CMT, sometimes referred to as "severe CMT", could have just as well have been labeled DSN. Whereas experienced clinicians likely can meaningfully separate CHN, DSN, and severe CMT, the literature describing the mutations is replete with incompletely documented cases and even frank errors.

MECHANISMS

Demyelination is Cell Autonomous

The earlier classification underscores the idea that CMT1 is caused by mutations in genes that are expressed by myelinating Schwann cells, whereas CMT2 is caused by mutations in genes expressed by neurons. The former possibility was first formally demonstrated by grafting nerve segments from *Trembler* mice (which have a dominantly inherited demyelinating neuropathy caused by a missense mutation in *Pmp22*) into the sciatic nerves of normal mice (Aguayo et al., 1977). The host axons that regenerated into the donor nerve grafts were abnormally myelinated by the donor Schwann cells, thereby demonstrating that the demyelination defect was intrinsic to the Schwann cells. In keeping with the idea that inherited demyelinating neuropathies are Schwann cell autonomous, Schwann cells express each of the genes that cause demyelinating neuropathies (Table 1). Why myelinating Schwann cells are selectively affected when other cell types also express the same genes (including *SIMPLE*, *GJB1*, *MTMR2*, *KIAA1985*, *FGD4*, and *FIG4*) remains to be explained.

Myelinating Schwann cells also express genes that cause demyelination as part of a syndrome (Table 2). Refsum disease may be an exception, as phytanic acid cannot be metabolized, so that the systemic accumulation of phytanic acid may lead to demyelination. There may be other exceptions to the idea that demyelinating neuropathies are Schwann cell autonomous, such as the dominant mutations of *NEFL* (the gene that encodes the light subunit of neurofilaments) that appear to cause a demyelinating neuropathy. In these cases, demyelination may be a secondary consequence of a primary axonopathy (Fabrizi et al., 2004, 2007). Finally, the very term "dominant intermediate" CMT emphasizes the uncertainty as to whether these are primary demyelinating or primary axonal disorders; as mentioned earlier, this uncertainty extends to *GDAP1* mutations.

Structural Components of the Myelin Sheath—*LAMA2, PRX, PMP22, MPZ, GJB1*

A myelin sheath is a multilamellar spiral of specialized cell membrane that surrounds a segment of an

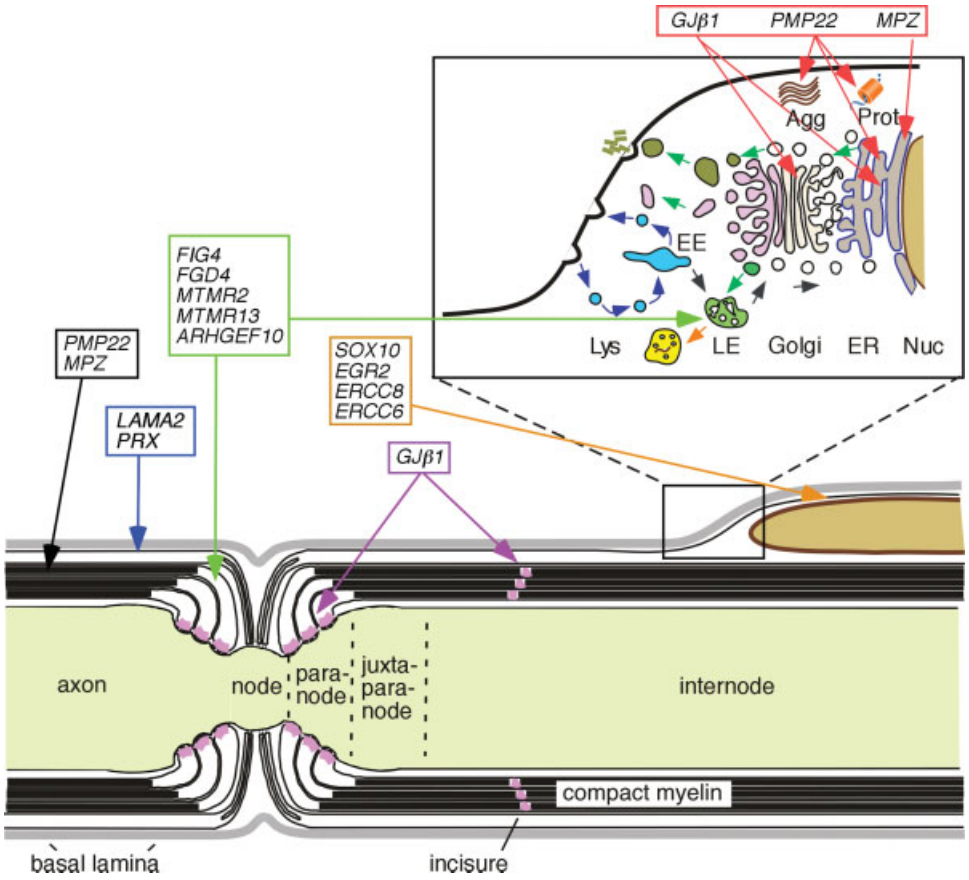

Fig. 1. Heterogeneous pathogenesis represents a challenge for developing unifying treatment strategies. This is a schematic representation of a myelinated axon, and the variety of subcellular locations that have been implicated as sites where mutant proteins disrupt myelination. The color code represents hypothetical grouping of genes by pathogenetic alteration. Red, protein quality control; brown, transcription; violet, gap junctions; green, membrane homeostasis; blue, extracellular matrix interactions; black, stability of compact myelin. The inset depicts the major pathways for the synthesis and degradation of intrinsic membrane proteins. Agg, aggresome; EE, early endosome, ER, endoplasmic reticulum; LE, late endosome; Lys, lysosome; Nuc, nucleus; Prot, proteasome.

axon that is typically larger than 1 μm in diameter (Trapp and Kidd, 2004). By reducing the capacitance of the internodal axonal membrane and clustering ion channels at nodes, myelin sheaths facilitate saltatory conduction. Demyelination increases internodal capacitance and disrupts the organization of ion channels in the nodal region, resulting in conduction slowing and even conduction block (Smith et al., 2005; Waxman et al., 1995).

By analogy to epithelial cells, the basal/abaxonal cell membrane apposes the basal lamina (see Fig. 1). Laminin-2 (formerly known as merosin), comprised of α2, β1, and γ1 subunits, is the principle laminin. In humans, recessive mutations in *LAMA2*, which encodes α2, cause a congenital muscular dystrophy (MDC1A in Table 2) and a mild demyelinating neuropathy (Di Muzio et al., 2003), whereas in mice, recessive mutations of *Lama2* cause a more profound phenotype, with large bundles of unsorted axons (Feltri and Wrabetz, 2005); these have not been described in humans.

The abaxonal membrane contains several receptors for laminins—the integrins α6β1, α6β4, α7β1, and dystroglycan (Feltri and Wrabetz, 2005). The intracellular domain of dystroglycan β forms a complex with periaxin and dystroglycan-related protein 2 (DRP2), both of which are specifically localized to the regions of the abaxonal membrane that lack cytoplasm (Sherman and Brophy, 2004). The importance of the dystroglycan complex in myelinating Schwann cells remains to be fully elucidated, but conditional deletion of dystroglycan in myelinating Schwann cells causes mild changes in myelination but slowed nerve conduction likely owing to a decreased density of nodal voltage-gated Na^+ channels (Occhi et al., 2005; Saito et al., 2003).

Recessive *Periaxin* mutations in humans cause CMT4F (Sherman and Brophy, 2004). *Prx*-null mice have disrupted cytoplasmic channels on the outside of the myelin sheath (called Cajal bands); this may decrease intracellular transport and result in abnormally short myelin internodes (and consequently, slowed conduction; Court et al., 2004), but how this leads to demyelination remains to be shown.

The myelin sheath is chiefly comprised of two domains—compact and noncompact myelin—each of which contains a nonoverlapping set of proteins (see Fig. 1). Compact myelin forms the bulk of the myelin

sheath, and it is composed of closely packed membranes. Lipids are the main constituents, mainly cholesterol and sphingolipids, including galactocerebroside and sulfatide. The targeted disruption of the genes required for the synthesis of sulfatide or galactocerebroside and sulfatide (*cst*-null and *cgt*-null mice, respectively) provided an unprecedented opportunity to perturb the lipid components of myelin. Surprisingly, except for the splitting of some CNS myelin sheaths, compact myelin has a normal ultrastructure (Dupree et al., 1998). In spite of this normal appearance, axonal conduction velocity is dramatically slowed, which is related to the lack of paranodal septate-like junctions (for details, see Salzer et al., 2008, in this issue). Conversely, the inability to degrade galactocerebroside and/or sulfatide results in their massive accumulation in myelinating glial cells and demyelination in metachromatic and globoid cell leukodystrophies. Finally, studies in mice demonstrate that the lack of cholesterol results in a severe reduction of myelination (Saher et al., 2005). Cholesterol, galactocerebroside, and sulfatide, as well as PMP22 and P_0, are all components of compact myelin, which is similar to a liquid crystal (Lecar et al., 1971; Schmitt et al., 1935), so that perturbations in the stoichiometry of any one component could conceivably alter the integrity of entire structure.

PMP22 is a hydrophobic, intrinsic membrane protein of unknown function (Suter, 2004). As shown in Fig. 1, PMP22 is synthesized in the endoplasmic reticulum (ER), where it is glycosylated, transported to the Golgi (where further glycosylation occurs), and then to the cell membrane (Pareek et al., 1993). Although it is a relatively minor constituent, the amount of PMP22 in compact myelin may be critical. Three (instead of two) copies of the *PMP22* gene cause CMT1A, the commonest form of CMT, leading to modestly more PMP22 in compact myelin (Vallat et al., 1996). An increased amount of PMP22 in compact myelin could lead to demyelination, an early pathological finding (Gabreëls-Festen et al., 1992), but this remains to be demonstrated directly. The effects of PMP22 overexpression can be detected clinically by the age of five; pathological findings and slow nerve conduction velocities are evident even earlier (Berciano et al., 2003; Fabrizi et al., 1998; Gabreëls-Festen et al., 1992; Thomas et al., 1997). There is considerable variability in the degree of neurological deficits within families, and even between identical twins, indicating that epigenetic, environmental, and/or stochastic factors modulate disease severity (Garcia et al., 1995).

Having only one copy of the *PMP22* gene causes HNPP, perhaps owing to a modest decrease of PMP22 in compact myelin (Vallat et al., 1996). Episodic mononeuropathies at typical sites of nerve compression are the hallmark, leading to the suggestion that myelin sheaths with too little PMP22 are more easily damaged by compression. Although it is plausible that severe focal demyelination (causing conduction block) followed by remyelination (restoring conduction) underlie the transient focal neuropathies, this remains to be directly demonstrated. Because patients are asymptomatic or do not seek medical attention, HNPP may actually be more common than CMT1A. Biopsies of unpalsied nerves show focal thickenings (tomacula) caused by folding of the myelin sheath, as well as segmental demyelination and remyelination.

In addition to the deletion and duplication of the *PMP22* gene, a variety of missense (amino acid substitutions), nonsense (premature stop), and frameshift mutations have been discovered. The mutations associated with HNPP presumably cause loss-of-function. Most mutations, however, cause a much more severe phenotype—usually reported as "severe CMT" or even DSN, as described earlier. These mutations, therefore, must have a toxic gain-of-function that has yet to be fully elucidated (Suter, 2004). For most of these mutations, the clinical phenotype can be related to the degree of demyelination as judged by conduction slowing and dys/demyelination (and possibly axonal loss) seen in nerve biopsies.

In transfected cells, several human PMP22 mutants are retained in the endoplasmic reticulum and/or intermediate compartment, indicating that they fold improperly (Suter, 2004). Similar results were found in myelinating Schwann cells that express epitope-tagged versions of the *Pmp22* mutations found in *Trembler* (G150D) and *TremblerJ* (L16P) mice by viral infection (Colby et al., 2000). Immunostaining a nerve biopsy from a "severe CMT1" patient with the L16P (*TremblerJ*) mutation showed PMP22 (wild-type and mutant protein cannot be distinguished in patients) colocalized with an ER marker, BiP (Hanemann et al., 2000). Three additional, abnormal characteristics of the G150D and/or L16P mutants that may relate to their ability to cause dys/demyelination have been described: (1) They form abnormally stable aggregates with themselves and even with wild-type PMP22 (Tobler et al., 2002); (2) they have abnormally prolonged association with the ER chaparone calnexin, so that sequestered calnexin may contribute to the pathogenesis of demyelination (Dickson et al., 2002; Shames et al., 2003); (3) they reduce the proteasomal activity, which in turn increases the levels of polyubiquitinated proteins (including PMP22), and cause proteins (including PMP22) to accumulate in special intracellular structures known as aggresomes (Fortun et al., 2005).

There are animal models of various human *PMP22* mutations (Wrabetz et al., 2004b). In addition to *Trembler* (G150D) and *TremblerJ* (L16P) mice, mice with other point mutations have been discovered (delExonIV, H12R, Y153X); all have a demyelinating neuropathy. Several models of PMP22 overexpression, including a model of tetracycline-regulated PMP22 expression (Huxley et al., 1996, 1998; Magyar et al., 1996; Robaglia-Schlupp et al., 2002; Robertson et al., 2002; Sereda et al., 1996), have been generated as models of CMT1A. A loss-of-function allele has also been generated in mice. Mice that are heterozygous for this allele ($Pmp22^{+/-}$) have a demyelinating neuropathy with focal myelin thickenings (tomacula); this is a model of HNPP (Adlkofer et al., 1997a). Furthermore, $Pmp22^{Tr/-}$ mice have a worse phenotype than do $Pmp22^{-/-}$ mice, con-

firming that *Pmp22*^{Tr} is more deleterious than the null *Pmp22* allele, and that *Pmp22*^{Tr} can have a dominant effect in the absence of wild-type PMP22 (Adlkofer et al., 1997b).

Myelin protein zero (P_0) is the main protein of compact myelin (Kirschner et al., 2004). It is an immunoglobulin (Ig)-like cell adhesion molecule with a single intramolecular disulfide bond. P_0 is glycosylated and thus traffics through the Golgi (see Fig. 1). Its extracellular domain probably forms tetramers that interact with each other both in *cis* (in the plane of the membrane) and in *trans* (from apposed membranes); they are the molecular glue of PNS myelin (Shapiro et al., 1996). Whereas Schwann cells can form a multilamellar spiral of membrane in *Mpz*-null mice, the myelin is not compact (Giese et al., 1992). Mice that are heterozygous for a null *Mpz* allele (*Mpz*$^{+/-}$) also develop a late-onset demyelinating neuropathy (Shy et al., 1997; Zielasek et al., 1996). This finding raises the possibility that a reduction in P_0 causes instability of compact myelin (Martini, 1997), albeit with a different morphological phenotype than in *Pmp*22$^{+/-}$ mice.

Some human *MPZ* mutations likely cause demyelination owing to haplotype insufficiency. A few mutations (such as E71X, D75frameshift, and V102frameshift) are obvious candidates, as the mutant proteins would be unlikely to function as cell adhesion molecules because they lack a transmembrane domain. The V102frameshift was discovered in two siblings with DSN (who were both homozygous for this mutation), but their heterozygous parents and grandparents were mildly affected, including their electrophysiological studies (Sghirlanzoni et al., 1992). Thus, if the mild phenotypes caused by the V102 frameshift mutation result from a simple loss-of-function, then *MPZ* mutations that cause more severe phenotypes must have a toxic gain-of-function (see below).

More than 100 different *MPZ* mutations have been identified (Shy et al., 2004). For many mutations, the clinical phenotype can be related to the degree of dys/demyelination as judged by conduction slowing and nerve biopsies - ranging from CHN to typical CMT1, and even to exceptionally mild phenotypes noted above. About 25 mutations, however, have a peculiar clinical presentation: individuals are clinically normal until at least young adulthood, then develop what has been often termed an "axonal neuropathy" between 30–50 years old. In these patients, nerve conductions are variably slowed as the neuropathy develops, but axonal loss (and not de/remyelination) is the chief finding in nerve biopsies. An apparently axonal neuropathy is particularly provocative because P_0 is expressed by Schwann cells and not by neurons.

The mutations themselves provide a few clues about the possible molecular pathogenesis. A few result in an extra cysteine in the extracellular domain; these may result in intermolecular disulfide bonds, and all are associated with a severe demyelinating neuropathy. In transfected cells, mutations that cause neuropathy (including the "axonal" mutations) are associated with decreased adhesion (Grandis et al., 2008; Matsuyama et al., 2002; Shames et al., 2003; Zhang and Filbin, 1998), but the genotype-phenotype correlation needs to be investigated further. In a mouse model of the S63C mutation, the mutant protein traffics to the myelin sheath, but causes a packing defect of compact myelin (Wrabetz et al., 2006). Mutations that result in a premature stop codon or frameshift that affect the intracellular C-terminus also cause severe phenotypes. For these mutations, the absence of nonsense-mediated decay (NMD), the degradation of mRNA activated by premature stop codons (Shyu et al., 2008), may contribute to the more severe phenotype (Inoue et al., 2004). Finally, at least one mutation, S63deleted, is associated with a maladaptive unfolded protein response (UPR). The severity of demyelination in mice expressing this mutation is ameliorated if one of the effectors of the UPR, CHOP, is deleted (Pennuto et al., 2008).

Non-compact myelin is found in the paranodes, the lateral borders of the myelin sheath that flank nodes of Ranvier, and in Schmidt-Lanterman incisures (the funnel-shaped cytoplasmic interruptions in the compact myelin). Non-compact myelin contains adherens junctions, tight junctions, and gap junctions; these join adjacent layers of the myelin sheath. Of these junctional specializations, gap junctions have been clearly implicated in demyelinating neuropathies. Small gap junction plaques had been noted between the rows of tight junctions in the PNS myelin sheath by freeze-fracture EM for decades. Their obscurity ended when mutations in *GJB1* were discovered to cause CMT1X, an inherited demyelinating neuropathy (Bergoffen et al., 1993). *GJB1* encodes Cx32, which belongs to a family of about 20 connexin genes that encode gap junction proteins. Gap junctions appear to provide a direct pathway for the diffusion of ions and small molecules across the layers of the myelin sheath (Balice-Gordon et al., 1998). Mutations in *GJB1* may disrupt the function of these gap junctions, but this was not demonstrated in *GJB1*-null mice. Cx29 (the human ortholog is Cx31.3) is also localized to paranodes and incisures, but its functional role is unclear, as Cx31.3/Cx29 do not appear to form functional gap junctions on their own and do not appear to interact with Cx32 (Ahn et al., 2008; Altevogt et al., 2002; Sargiannidou et al., 2008).

More than 300 different mutations in *GJB1* have been described, including missense, nonsense, and frameshift mutations, as well as mutations in the promoter and 5′UTR; all are associated with neuropathy. Further, the clinical severity caused by these *GJB1* mutations appears to be relatively uniform in affected men, including those with a deleted gene, indicating that all mutants cause loss-of-function (Shy et al., 2007). Cx32 is synthesized in the ER, where it is prenylated (Huang et al., 2005) and likely assembles into hexamers/hemichannels (Koval, 2006). When expressed in heterologous cells, most Cx32 mutants are mislocalized to the ER or Golgi, and hence could not form functional channels; these mutants are degraded in proteosomes and lysosomes (VanSlyke et al., 2000; Yum et al., 2002). Some

mutants, however, form functional gap junctions, a subset even have normal electrophysiological characteristics (Abrams et al., 2000); how these cause disease is an enigma. Expressing two such mutants (C280G or S281X) in myelinating Schwann cells did not clarify this issue, as both properly localized to incisures and paranodes, and appeared to ameliorate demyelination in *GJB1*/*cx32*-null mice (Huang et al., 2005).

Transcription—*SOX10, EGR2, ERCC8, ERCC6*

Given that altered dosage of myelin-related genes produces hereditary demyelinating neuropathies, it follows that mutations of transcription factors that regulate myelin gene expression might do the same. *EGR2* (encoding Krox20) and *SOX10* are key regulators of Schwann cell differentiation and of myelin-related gene expression (Schreiner et al., 2007; Topilko et al., 1994), and mutations in both cause demyelinating neuropathies (for details, see Svaren and Meijer, 2008, in this issue).

Dominant *SOX10* mutations are associated with complex "neurocristopathies" - PCWH (peripheral demyelinating neuropathy, central demyelinating leukodystrophy, Waardenburg-Shah syndrome, and Hirschsprung disease), or partial variants (Inoue et al., 2004). PCWH phenotypes include moderate (CMT1-like) or severe (CHN-like) demyelinating neuropathies (Inoue et al., 2004, 2002, 1999; Pingault et al., 2000; Verheij et al., 2006), but *SOX10* mutations have not been identified in non-syndromic CMT (Pingault et al., 2001). *SOX10* alterations are typically nonsense mutations that produce premature termination and dose-dependent effects suggesting toxic gain-of-function. Most mutants have reduced transcriptional activity and dominant-negative effects on wild-type SOX10 *in vitro*. Inoue et al. (2004) have proposed that SOX10 mutants that showed NMD *in vitro* were associated with milder phenotypes, whereas those resistant to NMD were associated with more severe phenotypes (including neuropathy). This hypothesis should be explored further in animal models expressing mutant *SOX10* alleles.

In mice, Krox20 is necessary for the differentiation of myelinating Schwann cells (Topilko et al., 1994), and even the maintenance of a myelinating phenotype (Decker et al., 2006). Because of these findings, *EGR2* (the human homologue) was considered to be a candidate gene for CMT (Warner et al., 1998). One recessive and many dominant mutations of *EGR2* are associated with severe (DSN) or moderate (CMT1) dys/demyelinating neuropathy have been described. Krox20 increases the expression of many myelin-related genes, including those encoding P_0, PMP22, MBP, Cx32, periaxin, and HMG CoA reductase (Le et al., 2005a; LeBlanc et al., 2005; Nagarajan et al., 2001). Most dominant mutations are located in zinc finger domains of Krox20 and alter DNA binding *in vitro* (Warner et al., 1999). Coexpressing one such mutant with wild-type Krox20 in Schwann cells interfered with activation of these target genes, not by a dominant negative effect on wild-type Krox20, but instead on another protein (Nagarajan et al., 2001).

The analysis of Sox10 and Krox20 on the promoters of myelin-related genes fit with the above observations. Putative Sox10 and Krox20 binding sites have been found in the *GJB1* promoter, and three different mutations in the Sox10 binding site are associated with CMT1X (Beauvais et al., 2006; Bondurand et al., 2001; Houlden et al., 2004). The *Mpz* gene provides a more complicated, but illuminating example. Here, both Krox20 and Sox10 bind to an important transcriptional enhancer within intron 1 (LeBlanc et al., 2006). Expressing mutant Krox20 reduces the activation of wild-type Krox20 at this site, but not at the other sites where Krox20 binds alone. Sox10 binding is required for the dominant negative effect of mutant Krox20, and is reduced by mutant Krox20 expression, so that Krox20 mutants appear to interfere with Sox10 binding at sites of combinatorial Sox10/Krox20 activation (LeBlanc et al., 2007). Because similar composite Sox10/Krox20 binding sites have been detected in the *Mbp*, *Mag, GJB*1, and *Prx* genes (Bondurand et al., 2001; Denarier et al., 2005; Jang et al., 2006; Jones et al., in press; LeBlanc et al., 2005), dominant *EGR*2 mutations may cause partial loss of function of multiple myelin-related genes (Nagarajan et al., 2001), thereby producing severe dysmyelinating phenotypes.

In addition to acting as a transcriptional activator, Krox20 may also directly repress other genes (Mager et al., in press). The recessive I268N mutation in *EGR*2 was predicted to interfere with the binding of NAB1 (NGFI-A/Egr-binding 1) and/or NAB2, transcriptional corepressors that were thought to be negative modulators of Krox20 activation (Svaren et al., 1996; Warner et al., 1998). Hence, I268N might have been predicted to cause overexpression of myelin genes, but the peripheral nerves of NAB1/NAB2-double null mice, or mice homozygous for the targeted *Egr*2-I268F mutation (which blocks interactions with NABs *in vitro*) had diminished myelination but with reduced, not increased, expression of myelin-related genes (Desmazieres et al., 2008; Le et al., 2005b). These findings lead to the proposal that Krox20 and NABs cooperatively repress transcription factors (like Sox2 and c-Jun) that can block differentiation of Schwann cells when inappropriately expressed (Le et al., 2005a).

The idea that Krox20 represses genes that actively promote dedifferentiation of Schwann cells fits with their response to nerve injury. It is well known that myelinating Schwann cells dedifferentiate if they lose contact with axons; this includes the down-regulation of many genes that encode the components of the myelin sheath but also Krox20 (Murphy et al., 1996; Zorick et al., 1996), and the reactivation of genes (including *cJun*) that are associated with a dedifferentiated phenotype (Scherer and Salzer, 2001). Parkinson and colleagues (Parkinson et al., 2008) have delineated reciprocally antagonistic roles of Krox20 and c-Jun in Schwann cells. Forced expression of c-Jun blocks myelination and the activation of myelin-related genes by Krox20,

whereas ablation of c-Jun expression magnifies the activation of myelin-related genes by Krox20 and even (albeit temporarily) maintains a myelinating phenotype after the loss of axonal contact. Thus, *EGR*2 mutations could interfere with Krox20 repression and activate a program of genes that favor dedifferentiation of Schwann cells in neuropathy. Conditional ablation of "dedifferentiation" genes in neuropathic Schwann cells will provide further evidence for this idea.

Cockayne syndrome is characterized by UV sensitivity, growth retardation, premature aging, and neurological abnormalities including dys- or demyelinating neuropathy (Ohnishi et al., 1987; Smits et al., 1982). It is an autosomal recessive disorder caused by mutations in either *ERCC8* (excision-repair cross-complementing group 8) or *ERCC6*, thereby producing defective transcription-coupled nucleotide excision repair, which removes DNA damage that obstructs transcription. In the absence of repair, specific gene expression is reduced. Work in animal models of Cockayne syndrome suggests that reduced transcription of growth hormone/insulin-like growth factor 1 may explain growth retardation (van der Pluijm et al., 2007). Genes targeted by loss of DNA repair and relevant to demyelinating neuropathy have yet to be identified.

Signals and Membranes—*MTMR2, MTMR13, FIG4, FGD4, ARHGEF10*

A series of recent reports emphasize the importance of phosphotidylinositol phosphate (PIP) and small rhoGTPase signaling in myelination. PIPs tag vesicles and organelles to coordinate membrane traffic and homeostasis (Di Paolo and De Camilli, 2006). Myotubularin-related phosphatases (MTMRs) were the first of these signaling molecules found to be mutated in neuropathy (Azzedine et al., 2003; Bolino et al., 2000; Senderek et al., 2003b). Recessive *MTMR2* and *MTMR13* mutations are associated with CMT4B1 and CMT4B2, respectively, both of which are severe demyelinating neuropathies, with characteristic focal myelin outfoldings (Previtali et al., 2007). MTMR2 and MTMR13 form a tetramer in which MTMR2 requires the "dead" phosphatase MTMR13 to produce appropriate activity—to dephosphorylate the 3′ phosphate of PI(3)P or PI(3,5)P2 (Berger et al., 2006, 2002; Robinson and Dixon, 2005).

The analysis of mice with homozygous targeted genetic alterations of *Mtmr2* or *Mtmr13* confirm that loss of function causes demyelination (Bolino et al., 2004; Bonneick et al., 2005; Robinson et al., 2008; Tersar et al., 2007). Ablation of *Mtmr2* in Schwann cells reproduced myelin outfolding, whereas ablation of *Mtmr2* in neurons produced no detectable phenotype (Bolis et al., 2005). However, since the complete loss of *Mtmr2* function in mice does not reproduce the severe axonal changes seen in CMT4B1 patients (Houlden et al., 2001), an additional cell autonomous role in neurons is possible. MTMR2 interacts with DLG1, a scaffolding protein enriched in paranodal loops in the myelin sheath, the origin of most outfoldings (Bolino et al., 2004). These findings, together with the role for PI(3,5)P2 in late endosome/lysosome activity in other cells, suggest that MTMR2 regulates membrane homeostasis at the lateral edge of the myelin sheath. In neurons, MTMR2 may interact with neurofilament-light (Previtali et al., 2003), with as yet unknown consequences.

The discovery that mutations in *FIG4*, a PI(3,5)P2 5′ phosphatase, cause CMT4J (or DSN), provides further evidence for a role of PI(3,5)P2 in myelinating Schwann cells (Chow et al., 2007). Like MTMR2/13, FIG4 is a phosphatase, but it forms a complex with Vac14 and Fab1 kinase that ultimately activates PI(3,5)P2 production. Thus, loss of FIG4 or Vac14 function produces less, not more, PIP2 in yeast and vertebrate cells—the opposite of what is expected in CMT4B1 and B2. CMT4J also differs from CMT4B1 and B2 in that part of the neuropathy probably owes more to cell autonomous effects of lost *FIG4* function in neurons. At least some cases of CMT4J are clinically distinctive from CMT, with abrupt declines of strength, and an electrophysiological appearance of a motor neuronopathy (Zhang et al., in press). In accord, both *FIG4*-deficient (*pale tremor* mice; (Chow et al., 2007) and *Vac14*-null mice (Zhang et al., 2007) have a widespread neuronopathy (including sensory and motor neurons) with characteristic intracellular vacuoles. Nevertheless, some patients with compound heterozygous *FIG4* mutations (producing partial loss of function in yeast) have compelling evidence of demyelination, but the contribution of the demyelination to the clinical picture is unclear (Chow et al., 2007; Zhang et al., 2008).

CMT4H is an autosomal recessive hypomyelinating neuropathy caused by homozygous, putative loss-of-function mutations in *FGD4* (Delague et al., 2007; Stendel et al., 2007). *FGD4* encodes Frabin, a guanine nucleotide exchange factor (GEF) for Cdc42, one of the small rhoGTPases (including Rac1 and RhoA) that regulate cellular morphogenesis, including myelination (for details, see Feltri et al., 2008, in this issue). Because the GTP-bound form of Cdc42 is active, loss of Frabin function is predicted to decrease Cdc42 activity. The milder demyelination seen in CMT4H than in Cdc42-null nerves (Benninger et al., 2007) may owe to the other GEFs for Cdc42. Further support for the role of RhoGTPases in myelination is the identification of a mutation in another GEF, *ARHGEF10*, in an autosomal dominant, asymptomatic syndrome of slowed NCVs and thin myelin sheaths (Verhoeven et al., 2003).

Mutants of both Frabin and MTMRs are associated with myelin outfolding and Frabin may interact with phophoinositides, as do MTMRs. Could the pathogenesis of CMT4H and CMT4B be related (Suter, 2007)? Signaling paths with mediators in common (e.g. phosphoinositides) are able to function distinctly by segregation in the cytoplasm. Certainly, the complex organization of membranes and cytoplasm in myelinating Schwann cells provides myriad opportunities for segregation. A central objective for MTMRs, Frabin and other signaling mole-

cules is to specify where they function in myelin Schwann cells.

Mutations with Unknown Consequences—*SIMPLE, KIAA1985/SH3TC2, NDRG1*

Apart from the identification of mutations in *SIMPLE*, *KIAA1985/SH3TC2*, and *NDRG1* in CMT1C (Street et al., 2003), CMT4C (Senderek et al., 2003a), and CMT4D (Kalaydjieva et al., 2000), respectively, little is known about the pathogenesis of the neuropathy (Niemann et al., 2006). Myelinating Schwann cells, but not neurons or axons, express NDRG1 (Berger et al., 2004), whereas the expression of SIMPLE/LITAF (Bennett et al., 2004) and *KIAA1985/SH3TC2* appears more widespread. Both *Ndrg*-null (Okuda et al., 2004) and *Sh3tc2*-null (R. Chrast, personal communication) mice develop a demyelinating neuropathy, supporting that *NDRG1* and *KIAA1985/SH3TC2* mutations result in demyelination because mutant proteins fail to function (probably in myelinating Schwann cells). SIMPLE/LITAF has been suggested to be involved with ubiquitination, and modify gene expression in macrophages (Saifi et al., 2005). A conditional allele of *Litaf* has been introduced into mice (Tang et al., 2006); whether a loss of function model will illuminate the mechanism of demyelination seen in CMT1C has not yet been explored.

TREATMENT STRATEGIES

Haplotype insufficiency has been well established for *PMP22* (causing HNPP), and appears likely for some *MPZ* mutations (causing adult onset CMT1B). The duplication and consequent overexpression of *PMP22* is likely the cause of CMT1A. Because CMT1A is the most common inherited neuropathy seen clinically, finding ways to reduce PMP22 expression is a high priority. Two strategies have been found to date—anti-progestins and ascorbic acid. An anti-progestin, onapristone, can reduce PMP22 mRNA levels in nerves and improve motor function in a rat model of CMT1A (Meyer zu Horste et al., 2007; Sereda et al., 2003). The side effects of onapristone, however, have motivated a search for other anti-progestins as candidates for chronic therapy in CMT (Nave et al., 2007). In a mouse model of *Pmp22* overexpression with hypomyelination, ascorbic acid improved myelination and prolonged lifespan (Passage et al., 2004), inspiring clinical trials (Pareyson et al., 2006; Shy 2006). Both anti-progestins and ascorbic acid were selected owing to prior evidence of their effects on myelination, but high thoughput screening in cell-based assays offers a powerful, unbiased way to identify compounds that decrease PMP22 expression.

Other mutations of PMP22 or P_0 cause a toxic gain-of-function. Altered trafficking of mutant proteins has led to the idea that mutant proteins can induce an UPR, form abnormal aggregates, including aggresomes, or overwhelm the cell's ability to degrade them. These pathways are already being considered to be therapeutic targets—stimulating chaperone activity to help fold misfolded proteins (Khajavi et al., 2005, 2007), stimulating autophagy (Fortun et al., 2007), or eliminating maladaptive mediators of the UPR (Pennuto et al., 2008).

For recessive mutations and *GJB1* mutations, demyelination appears to stem from loss-of-function. At this time, however, there are no known methods for replacing the function of missing genes in myelinating Schwann cells. Delivering genes to all the Schwann cells, which are distributed widely throughout the body, seems implausible. Restoring the function of the missing gene, however, may be possible in a few instances. For example, if drugs can effectively allow read through of stop codons (Welch et al., 2007), then this would be an appropriate potential therapy for patients who have recessive nonsense mutations.

Given the genetic heterogeneity of hereditary neuropathies, finding common pathogenetic mechanisms as targets for treatment strategies would be a major advance. Reversing conduction block with K^+ channel blockers has long been considered to be an attractive target (Bostock et al., 1981). This approach has not caught on, perhaps because the currently available medications have important side effects (Solari et al., 2003).

Preventing axonal degeneration has also been considered to be an attractive target (Suter and Scherer, 2003), as all demyelinating neuropathies produce axonal degeneration, and disability correlates best with axonal damage (Berciano et al., 2003; Dyck et al., 1974, 1989; Krajewski et al., 2000). Axonal loss has been documented for $Pmp22^{-/-}$ (Sancho et al., 1999), $Mpz^{-/-}$ (Frei et al., 1999), $Gjb1^{-/-}$ (Scherer et al., 1998), and *Mpz*S63del (Wrabetz et al., 2006) mice, but likely occurs in other mutants, too. The degree of axonal loss these animal models is much less than what has been described in humans, presumably because human nerves are much longer and most biopsies come from older individuals. The cause of axonal loss in demyelinating diseases has remained elusive; energetically inefficient conduction, loss of trophic support, disturbed axonal transport, and even superimposed inflammatory changes could be involved (Martini, 2001). Nevertheless, the finding that the *Wlds* mutation partially prevents axonal loss in *Mpz*-null mice provides a proof-of-concept that axonal loss is a therapeutic target (Samsam et al., 2003). The means for intervening in patients is limited. Exogenous trophic factors prevent axonal loss in a number of animal models. One trophic factor has been safely given to patients with CMT1A (Sahenk et al., 2005), but in a large clinical trial, nerve growth factor was not effective in treating diabetic neuropathy (Apfel, 2002).

The availability of rodent models for many inherited demyelinating neuropathies should facilitate these efforts. In addition to clarifying the pathogenesis of various neuropathies, these animals should enable preclinical trials. Performing clinical trials with patients will be facilitated by well-validated rating scales of disease progression (Shy et al., 2005a), these may be further refined

in the first large clinical trials that are currently underway.

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