CHAPTER

38

Peripheral Neuropathy: Neurochemical and Molecular Mechanisms

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OUTLINE

INTRODUCTION

Peripheral nerve consists of fascicles of nerve fibers with their associated vascular supply and supporting tissues. Sensory and motor deficits arising from pathological processes affecting the microvessels, neuronal soma, axons, and myelin of peripheral nerves can result in severe disability. Diseases that affect the vasa nervorum or microvasculature often present as multifocal neuropathy (also called mononeuritis multiplex). Some disorders are characterized by axonopathy, while others are predominantly demyelinating polyneuropathies. The distinction between the various forms is based on nerve conduction studies and electromyography, as well as nerve biopsy. The latter is useful in establishing the diagnosis of certain inflammatory neuropathies (e.g., vasculitis) and other conditions (e.g., amyloidosis), though used less frequently for the diagnosis of hereditary neuropathies. The recent identification of mutant genes associated with neuropathy has provided important insight into the molecular interaction between Schwann cells and axons and the role of mitochondria, protein trafficking and axonal transport in maintaining peripheral nerve function.

PERIPHERAL NERVE ORGANIZATION

The peripheral nervous system (PNS) includes the cranial nerves, the spinal nerves and nerve roots, the peripheral nerves, and the peripheral component of the autonomic nervous system

The cell bodies of sensory neurons are located in the dorsal root ganglia (DRG), and motor neuron cell bodies are found within the anterior horn of the spinal cord. The autonomic outflow consists of a sequential two-neuron efferent pathway: a preganglionic neuron in the brainstem or intermediolateral columns of the spinal cord, and a postganglionic neuron in the autonomic ganglia.

The axons of the PNS are all intimately associated with Schwann cells, the neural crest–derived glial cells of the PNS (Chapters 1 and 28). Small-caliber axons of less than 1μm are ensheathed in small groups (Remak bundles). The axonal membranes in these bundles are normally completely enveloped by Schwann cell membranes, such that the axonal membranes are not in direct contact. Larger-caliber axons are surrounded by the Schwann cell–produced multilayered myelin membrane sheath. Axon caliber therefore determines whether associated Schwann cells are myelinating or ensheathing (nonmyelinating). The myelin sheath is produced as a specialized extension of the Schwann cell plasma membrane, which wraps around the axon multiple times. As such, myelin is a lipid-rich structure, largely devoid of cytoplasm. One Schwann cell produces an individual segment of myelin, in contrast to oligodendrocytes, each of which has the potential to simultaneously myelinate as many as 50 axonal segments. The highly ordered multilayered structure of the myelin sheath is thought to be the result of interactions within the unique set of proteins and lipids that are produced by the myelinating cell (Chapter 10).

Myelination subdivides the axon into distinct domains. The node of Ranvier is the unmyelinated region of the axon that lies between adjacent segments of myelin; the paranodal domain is the region, surrounded by uncompacted myelin, which flanks the nodal region; and the internodal region, ensheathed by compact myelin, represents by far the largest area of myelinated axons. Distinct sets of proteins are found in each axonal subdomain. The voltage-gated sodium channels are concentrated in the nodal domain, which allows for rapid saltatory conduction. Demyelination results in a loss of these focal sodium-channel domains (Chapter 10).

While the caliber of the axon initially determines if associated Schwann cells will become myelinating, the myelin sheath influences the caliber of the axon. Myelination results in the phosphorylation of neurofilaments, which are the major axonal cytoskeletal proteins. When phosphorylated, neurofilament subunits are spaced farther apart and form more cross-bridges, an effect which is likely responsible for the increased caliber of myelinated axons. This process is reversed in demyelinated axons (Chapter 6).

The synaptic terminals of peripheral neurons are often located at a considerable distance from their cell bodies. This cytoarchitecture requires proteins synthesized in the cell body to be actively transported down the axon. Moreover, trophic factors acquired at nerve terminals need to be transported to the cell body, where they influence the phenotype and viability of the cell. Therefore, neurons possess a sophisticated axonal transport system that is essential for nerve function. Although the underlying molecular mechanism is unclear, myelination influences axonal transport. Disruptions to axonal transport are associated with disorders of both the peripheral nerves and myelin (Chapter 8).

GENETICALLY DETERMINED NEUROPATHIES

The inherited neuropathies are commonly referred to as Charcot-Marie-Tooth disorders (CMT) or hereditary motor and sensory neuropathies (HMSN)

Historically, heritable neuropathies have been classified according to their mode of transmission and whether the primary defect is demyelinating or axonal (Table 38-1). CMT1 and CMT4 are disorders of myelin and are inherited dominantly and recessively, respectively. CMT2 disorders are primarily axonal and can be inherited either dominantly or recessively (Suter & Scherer, 2003).

These classifications, while important for determining the diagnosis and prognosis of these disorders, have not always provided insight into the underlying molecular pathology. For example, depending on the nature of the lesion, individual genes associated with neuropathy can display dominant or recessive inheritance. Furthermore, it has become increasingly clear that the intimate interactions between Schwann cells and axons make determining the cellular origin of neuropathic disorders difficult. Demyelinating disorders are disorders of myelinating Schwann cells that result in a slowing of nerve conduction velocities. Neuropathies with normal or near-normal nerve conduction velocities are classified as axonal and are believed to be due to neuronal abnormalities. Nevertheless, mutations in myelin protein genes (e.g., myelin associated glycoprotein, connexin 32) have been shown to cause axonal defects despite normal-appearing myelin, and recently it was shown in mice that mutations in the prion protein gene result in peripheral nerve demyelination that has been unexpectedly ascribed to a neuronal defect (Bremer et al., 2010).

Transcription factors are likely suspects for tissue-specific diseases; however, few have been associated with genetic neuropathy (Chapter 27). Mutations in the gene encoding EGR2 (formerly known as Krox20), a Schwann cell–specific transcription factor, cause a wide range of demyelinating neuropathies, including CMT1D, which varies in severity, and CMT4, which onsets in infancy, as well as more severe forms of neuropathy: Dejerine-Sottas syndrome (DSS) and congenital hypomyelinating neuropathy (CHN). EGR2 is involved in the upregulation of several myelin genes, such as those encoding PMP22, MPZ, GJB1, and PRX, which are also associated with genetic neuropathy and which will be discussed below. SOX10 is also known to induce the expression of many of the same myelin genes as EGR2, but patients with mutations in *SOX10* demonstrate multiple symptoms, including CNS demyelination, pigmentation abnormalities, and deafness, in addition to peripheral

TABLE 38-1 Genes Associated with Inherited Neuropathies

Gene	Function	Genetic neuropathy	Inheritance	Pathology
ARHGEF10	guanine exchange factor for a small rhoGTPase, cellular morphogenesis	slowed NCV	autosomal dominant	demyelinating
DNM2	large GTPase, endocytosis, actin dynamics	CMTDIB	autosomal dominant	axonal and demyelinating
		CMT2M	autosomal dominant	axonal
EGR2 (Krox20)	Schwann cell transcription factor, upregulates myelin genes	CMT1D	autosomal dominant	demyelinating
		CMT4E (CH)	autosomal recessive	demyelinating
		CH	autosomal dominant	demyelinating
		DSS	autosomal dominant	demyelinating
FGD4	guanine exchange factor for a small rhoGTPase, involved in myelin morphogenesis	CMT4H	autosomal recessive	demyelinating
FIG4	regulates PI(3,5)P2 level by dephosphorylation	CMT4J	autosomal recessive	demyelinating
GAN	stabilizes microtubules, may interact with intermediate filaments	GAN	autosomal recessive	axonal
GARS	glycyl-tRNA synthetase	CMT2D	autosomal dominant	axonal
GDAP1	mitochondrial fission	CMT4A	autosomal recessive	demyelinating
		CMT2K	autosomal dominant or recessive	axonal
		CMTRIA	autosomal recessive	axonal and demyelinating
GJB1 (Cx32)	gap junction protein found in myelin at the paranodal loops and Schmidt-Lanterman incisures	CMTX1	X-linked dominant/intermediate	axonal and demyelinating
HSPB1 (HSP27)	heat shock protein, may be required for NEFL folding	CMT2F	autosomal dominant	axonal
HSPB8 (HSP22)	heat shock protein, may be required for NEFL folding	CMT2L	autosomal dominant	axonal
KIF1B	motor protein, vesicle transport along microtubules	CMT2A1	autosomal dominant	axonal
LITAF (SIMPLE)	function not known, possible transcription factor	CMT1C	autosomal dominant	demyelinating
LMNA	encodes two components of nuclear envelope intermediate filaments	CMT2B1	autosomal recessive	axonal
MFN2	large GTPase, mitochondrial fusion	CMT2A2	autosomal dominant	axonal
MPZ (P0)	predominant protein component of peripheral myelin	CMT1B	autosomal dominant	demyelinating
		CMTDID	autosomal dominant	axonal and demyelinating
		CMT2J	autosomal dominant	axonal
		CMT2I	autosomal dominant	axonal
		CH	autosomal dominant	demyelinating
		DSS	autosomal dominant	demyelinating
MTMR2	PI3P and PI(3,5)P2 dephosphorylation	CMT4B1	autosomal recessive	demyelinating
NDRG1	may be involved in lipid distribution or signaling	CMT4D (HMSN-L)	autosomal recessive	demyelinating

(Continued)

TABLE 38-1 (Continued)

Gene	Function	Genetic neuropathy	Inheritance	Pathology
NEFL	neuronal intermediate filament light subunit	CMT1F	autosomal dominant	demyelinating
		CMT2E	autosomal dominant	axonal
PMP22	integral myelin protein	CMT1A	autosomal dominant (frequently duplication)	demyelinating
		HNPP	autosomal dominant (frequently deletion)	demyelinating
		DSS	autosomal dominant or recessive	demyelinating
PRPS1	purine and pyrimidine biosynthesis	CMTX5	X-linked dominant/intermediate	axonal and demyelinating
PRX	interacts with dystroglycan, connects basal lamina to Schwann cell cytoskeleton	CMT4F (DSS)	autosomal recessive	demyelinating
RAB7	Ras-related GTPase, vesicle transport	CMT2B	autosomal dominant	axonal
SBF2 (MTMR13)	interacts with MTMR2, may regulate phosphatase function	CMT4B2	autosomal recessive	demyelinating
SH3TC2 (KIAA1985)	effector for small GTPase, vesicle transport	CMT4C	autosomal recessive	demyelinating
SOX10	transcription factor, upregulates myelin genes	Waardenburg-Hirschsprung	autosomal dominant	demyelinating
SPTLC1	biosynthesis of sphingolipids	HSN1	autosomal dominant	axonal
YARS	tyrosyl-tRNA synthetase	CMTDIC	autosomal dominant	axonal and demyelinating

demyelination (Niemann et al., 2006). Recently, it has been suggested that lipopolysaccharide-induced tumor necrosis factor α (SIMPLE/LITAF), which has long been associated with CMT1C, may also act as a transcription factor (Gerding et al., 2009).

Most commonly, it is alterations to genes encoding structural components of the myelin sheath that are responsible for genetic neuropathies (Niemann et al., 2006). The gene most frequently associated with genetic neuropathy encodes peripheral myelin protein 22 (PMP22), a tetraspan integral membrane protein of compact myelin. The normal function of PMP22 is not fully understood. In the majority of cases, the region of chromosome 17 that contains this gene is duplicated, resulting in CMT1A (Lupski et al., 1991). Alternatively, most patients with missense mutations in *PMP22* suffer from the more severe DSS, while those carrying a deletion of the gene demonstrate a milder disorder referred to as hereditary neuropathy with liability to pressure palsies (HNPP). While the molecular mechanisms behind the different forms of PMP22-associated neuropathy are not fully understood, both gene dosage and protein regulation appear to play a role. When PMP22 is overexpressed, as occurs in patients with a duplication, the protein, much of which is normally degraded before transport to the cell surface, forms aggregates within the cell, suggesting the cell is unable to cope with the excess amount of protein. Nevertheless, the requirement that overexpressed PMP22 be present on the cell surface for symptoms to manifest is among data that suggest that the ratio of PMP22 molecules to other myelin components may also be important. Altered protein ratios could also be a factor in HNPP patients, who are haploinsufficent for PMP22. In patients with missense mutations, misfolding appears to result in retention of the protein in the endoplasmic reticulum (ER), which may initiate the unfolded protein response (UPR) and apoptosis. Alternatively, the mutant proteins may interact with wild-type PMP22 and other binding partners, disrupting normal function.

Myelin protein zero (MPZ or P0), the predominant protein of peripheral myelin, is another structural protein whose disruption causes neuropathy (CMT1B). MPZ is a single-pass membrane protein that participates in the association of the extracellular membrane faces of the myelinating cell, as well as the compaction of the myelin sheath. Mutations that result in an apparent loss of function indicate that MPZ haploinsufficiency is causative. In other cases, the unfolded protein response may play a role. Mutations that disrupt the folding potential of the MPZ protein are common, and evidence has been presented that indicates that at least a subset of the MPZ point mutations result in the activation of the unfolded protein response in Schwann cells, presumably because of the accumulation of misfolded MPZ in the endoplasmic reticulum.

The X-linked gene *GJB1* encodes the gap junction protein connexin 32 (Cx32). Cx32 forms gap junctions in the noncompact regions of the myelin sheath: the paranodal loops and Schmidt-Lanterman incisures. Although the function of Cx32 in the myelin sheath is unclear, a variety of distinct mutations have been identified in patients that display a demyelinating

neuropathy (CMTX1), which, though less severe in females, is dominantly inherited. Many of these mutations disrupt the intracellular trafficking of the mutant protein. Interestingly, it has recently been shown that axonal abnormalities, axonal transport deficiencies, and cytoskeletal defects appear in *Cx32*-null mutant mice before myelin abnormalities are detected.

Unlike the myelin structural components discussed above, mutations in the gene encoding periaxin (PRX) result in a recessively transmitted demyelinating neuropathy (CMT4F, which is similar to DSS). Like PMP22, PRX mediates a Schwann cell–extracellular matrix interaction. A membrane-bound protein with a protein–protein–associating PDZ domain, PRX interacts with the dystroglycan complex that connects the basal lamina to the Schwann cell cytoskeleton. Inexplicably, considering their presence throughout the PNS, periaxin mutations are specifically associated with sensory neuropathies.

As suggested by PRX's association with neuropathy, disruption of proteins involved with the cytoskeleton can lead to neuropathy (see Chapter 10 for more about cytoskeletal proteins). Alterations to neurofilaments can result in diminished axonal caliber and reduced rates of axonal transport. Dominant mutations in the gene encoding NEFL, the light subunit of neuronal intermediate filaments, cause CMT2E, which varies in severity and age of onset depending on the genetic lesion. Experiments with cultured neurons have shown that some mutant forms of NEFL interfere with neurofilament assembly and transport. Additionally, axonal neuropathies associated with the two small heat-shock proteins HSPB1/HSP27 and HSPB8/HSP22 (CMT2F and CMT2L, respectively) may also result from neurofilament defects. It has been suggested that HSPB1 and HSPB8, which are known to interact, are required for the proper folding of NEFL.

A point mutation in another intermediate filament gene, *LMNA*, is responsible for a recessive axonal form of neuropathy (CMT2B1, formerly AR-CMT2A), one of many tissue-specific diseases arising from distinct mutations of this ubiquitously expressed gene. Both lamin A and lamin C are encoded, via alternate splicing, by *LMNA* and are components of the intermediate filaments of the nuclear envelope. The nuclear lamina play a role in many functions including gene expression, intracellular signaling, and organization of nuclear pore complexes. The specific disease mechanism of CMT2B1 remains unknown. Further demonstrating the importance of intermediate filaments to peripheral nerve function, mutations in gigaxonin result in the early-onset giant axonal neuropathy (GAN), in which intermediate filaments are disorganized. Because gigaxonin is known to stabilize microtubules, it is hypothesized that it plays a communicative role between microtubules and intermediate filaments.

Another cellular function that is commonly affected in neuropathies, and is closely tied to neuronal morphology, is intracellular transport (See Box). Axons are particularly sensitive to transport defects because their extreme lengths demand efficient transport. One clear example of a transport defect is seen in mutations of the gene encoding kinesin family member 1b (KIF1B). The kinesins are motor proteins involved in the transport of mitochondria and synaptic vesicle precursors along microtubules. The reduced motility of the mutant KIF1B results in CMT2A1.

Disruption of organelle transport is also believed to play a role in the disease mechanism of patients with mutations in *RAB7*, *DNM2*, and *SCH3TC2*. RAB7 is a member of the Ras-related GTPases and is important for the transport of vesicles from late endosomes to lysosomes, and from the plasma membrane to the Golgi. Dominant mutations result in axonal CMT2B. DNM2 belongs to the large GTPase family and appears to be involved in endocytosis and the regulation of actin dynamics (Chapter 7). Patients with *DNM2* mutations demonstrate a dominant-intermediate form of CMT, in which both the Schwann cells and neurons may be primarily affected. Meanwhile, specifically in Schwann cells, SCH3TC2 (formerly KIAA1985) acts as an effector for RAB11, a small GTPase involved in returning components to the plasma membrane. Mutations in *SCH3TC2* affect the interaction between SCH3TC2 and RAB11, impairing this process and causing the recessive demyelinating CMT4C (Stendel et al., 2010).

Vesicle transport may also be impaired when phosphotidylinositol phosphate (PIP) metabolism is altered, as it is by mutations in the genes encoding myotubularin-related protein-2 (MTMR2), SBF2 (formerly MTMR13), and FIG4. PIPs are important components of vesicle membranes that tether proteins, including those important for trafficking and membrane dynamics (Chapter 23). Both the MTMR2/MTMR13 complex and FIG4 dephosphorylate PI(3,5)P2, but they have opposing effects on the level of this substrate (Chapter 26). *MTMR2* and *MTMR13* mutations result in CMT4B1 and CMT4B2, respectively, while *FIG4* mutations cause CMT4J, all of which are severe recessive demyelinating neuropathies. Additionally, membrane dynamics are likely affected by mutations in *FGD4*, which encodes a guanine nucleotide exchange factor (GEF) for a small rhoGTPase, and CDC42, that controls cellular morphogenesis in processes including myelination. Patients with mutant *FGD4* develop CMT4H, which may onset in childhood or in adulthood. A link has been suggested between FGD4 and the MTMR2/MTMR13 disease mechanism as well, because FGD4 has PIP-binding domains. Another GEF, ARHGEF10, has also been associated with a mild form of autosomal dominant neuropathy; the mechanism, though not yet understood, is also predicted to be related to morphogenesis during myelination (Verhoeven et al., 2003).

The proper functionality of membranes is dependent on their lipid composition as well as their protein components. SPTLC1, a subunit of serine palmitoyltransferase, is required for the biosynthesis of sphingolipids, a class of lipids particularly important to neuronal function. Mutations in *SPTLC1* are associated with hereditary sensory neuropathy 1 (HSN1). Recent work has shown that HSN1 pathology may arise from an accumulation of toxic species produced by the mutant protein rather than a lack of the wild-type products. Meanwhile, mutations in *NDRG1* may play a role in the lipid composition of Schwann cell membranes, although this role has not been confirmed. NDRG1, when altered, is associated with CMT4D. Observed interactions with apolipoproteins APOA1 and APOA2 suggest that NDRG1 may be important to lipid distribution (Melotte et al., 2010).

Defects specifically affecting the trafficking and dynamics of mitochondria are also associated with neuropathy. Ganglioside-induced differentiation-associated protein-1 (GDAP1) is a protein found in the outer membrane of mitochondria and appears to participate in mitochondrial fission. Recessive mutations can result in severe demyelination (CMT4A) and severe

axonal neuropathy (CMT2K), as well as intermediate forms. Alternatively, mitofusin 2 (MFN2), a large GTPase, acts to bring mitochondria together during fusion and its dysfunction results in a dominant axonal form of CMT (CMT2A) in which both mitochondrial fusion and transport are impaired.

Finally, genes that carry out basic housekeeping functions have been found to cause neuropathy when altered. The X-linked CMTX5 results from certain mutations in the *PRPS1* gene, which encodes phosphoribosylpyrophosphate synthetase I, an enzyme required for purine and pyrimidine biosynthesis (Kim et al., 2007). Additionally, neuronal-specific defects are caused by mutations in *GARS*, which encodes the sole human glycyl-tRNA synthetase. Though GARS is required in every cell type to charge $tRNA^{Gly}$ with glycine, mutations in *GARS* result specifically in dominant axonal CMT2D, as well as a form of distal muscular atrophy (HMN5) (Chapter 45). Although the disease mechanism is not known, it has been suggested that the metabolic requirements of neurons may make them particularly susceptible (Niemann et al., 2006). More recently, a second tRNA synthetase, YARS, was found to be associated with dominant intermediate CMT type C (CMTDIC), in which both axonal and demyelinating features are present (Jordanova et al., 2006). As with GARS, the mechanism of this disorder is not yet understood.

DIABETIC NEUROPATHY

Metabolic/Endocrine diseases such as diabetes mellitus (DM), thyroid diseases, and uremia are frequent causes of peripheral nerve damage

Here, we focus on diabetic neuropathy, which can manifest as diffuse polyneuropathy, focal neuropathy, or multifocal neuropathy. Cell types affected in diabetic neuropathy include endothelial cells, Schwann cells, and dorsal root ganglion neurons and their axons. In sural nerves, axon loss can be diffuse or patchy; the latter would be suggestive of ischemia arising from microvascular mechanisms (Zochodne, 2007).

The debate regarding the role of microangiopathy, polyol flux, oxidative stress, impaired neurotrophic support, and inflammatory mechanisms in diabetic neuropathy continues to this date (Russell et al., 2008; Tomlinson & Gardiner, 2008; Zochodne, 2007). Hyperglycemia leads to sorbitol and fructose accumulation in the peripheral nerves. Aldose reductase (AKR), though it has a lower affinity for glucose than hexokinase, is able to convert glucose to sorbitol during hyperglycemia. Negative consequences of sorbitol accumulation include osmotic stress, the depletion of myoinositol and taurine, and the generation of fructose, which is a more potent glycation agent than glucose. Furthermore, there is depletion of NADPH and redox imbalance, as well as altered protein kinase C (PKC) and Na/K ATPase activity (Fig. 38-1). The role of AKR in the pathogenesis of diabetic neuropathy is further supported by findings of improved nerve function in AKR-deficient mice (Ho et al., 2006).

Other consequences of hyperglycemia include protein glycation and oxidative stress. Glycation is a nonenzymatic reaction of reducing sugars or oxaldehydes with proteins, DNA, or lipids, resulting in the formation of glycation adducts (fructosamines) and advanced glycation end-products (AGE), which bind to their receptor, RAGE. While increased RAGE expression is observed in axons, Schwann cells, and DRG neurons in experimental diabetic neuropathy, RAGE is found to localize primarily to the microvasculature and Schwann cells in sural nerve biopsies from patients with diabetic neuropathy. In addition, mice lacking RAGE ($Ager^{-/-}$) are partially protected from diabetic neuropathy and demonstrate blunted expression of NF-κB and PKCβII, both of which are implicated in the pathogenesis of diabetic neuropathy (Bierhaus et al., 2004; Toth et al., 2008).

Both the polyol and AGE pathways play a major role in creating redox imbalance through the depletion of antioxidants and the activation of inducible nitric oxide synthase and cycloxygenase, respectively (Figueroa-Romero et al., 2008; Obrosova, 2009). Activation of poly (ADP-ribose) polymerase (PARP) as a consequence of oxidative stress-induced DNA strand breakage depletes NAD, causes energy failure, and alters gene expression, although PARP activation may also occur via phosphorylation by pERKs (Kauppinen et al., 2006).

Hyperglycemia and ROS activate other signaling pathways, particularly the mitogen-activated protein kinases (MAPKs). Increases in total levels of p38 and JNK were observed in the sural nerves of patients with type I and type II diabetes (Purves et al., 2001). Aside from regulating transcription factors, MAPKs may influence the development of neuropathy in other ways. The α isoform of p38 phosphorylates serine 553 of Nav1.6, resulting in decreased current density and a conduction defect, while JNK activation is linked to aberrant neurofilament phosphorylation (Fernyhough et al., 1999; Wittmack et al., 2005). JNK and p38 also phosphorylate kinesin, negatively regulating fast axonal transport, which has been shown to be impaired in diabetic nerves (Calcutt et al., 1988; Morfini et al., 2006). Another molecule that is implicated in fast axonal transport is GSK3 beta, which is elevated in diabetes due to impaired insulin signaling (Jolivalt et al., 2008) (Chapter 8).

Diabetes not only causes neuropathy, but also impairs peripheral nerve regeneration following injury. Optimal control of glucose levels remains the best approach to minimize neuropathic complications. Clinical trials of AKR inhibitors have been disappointing. There is some evidence that the antioxidant α-lipoic acid may be of benefit in diabetic neuropathy (Ziegler et al., 2006). It is possible that maximal benefit requires simultaneous targeting of multiple pathways implicated in diabetic neuropathy.

AUTOIMMUNE NEUROPATHIES

An autoimmune attack on the PNS can manifest in various disease forms that include but are not limited to Guillain-Barré syndrome, chronic inflammatory demyelinating polyradiculopathy (CIDP), antibody-mediated neuropathies, and vasculitic neuropathies

Guillain-Barré syndrome (GBS) is a common cause of reversible paralysis and is further classified into acute inflammatory demyelinating polyradiculopathy (AIDP), acute

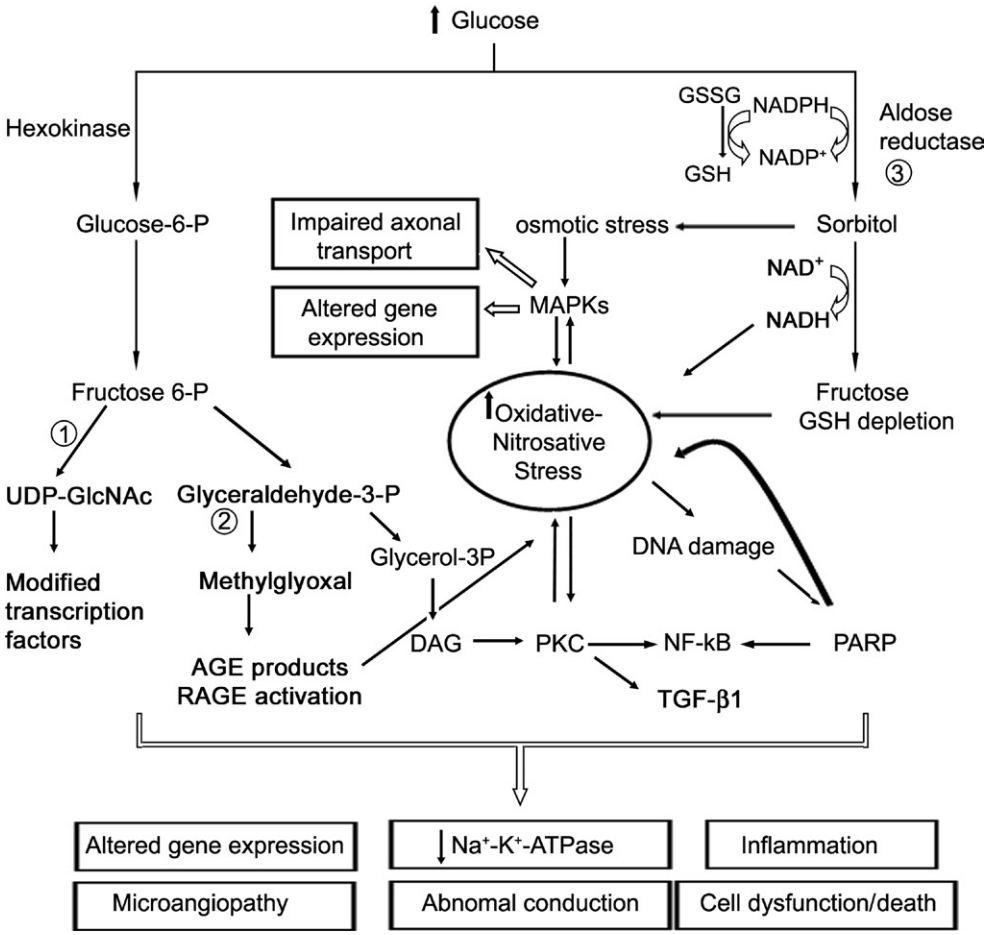

FIGURE 38-1 **Schematic diagram of biochemical pathways and their interactions in diabetic neuropathy.** 1. hexosamine pathway; 2. advanced glycation end-product (AGE) pathway; 3. polyol pathway.

motor axonal neuropathy (AMAN), acute motor and sensory axonal neuropathy (AMSAN), and Miller-Fisher syndrome (MFS). The latter manifests as ophthalmoparesis and sensory ataxia rather than limb paralysis.

Both cell-mediated and humoral immunity are involved in the pathogenesis of autoimmune neuropathies. T-cells and macrophages are found in nerve biopsies from patients with GBS and CIDP and from animal models such as experimental autoimmune neuritis (EAN) and spontaneous autoimmune polyneuropathy (Ho et al., 1998; Kim et al., 2008; Maurer & Gold, 2002). Peripheral nerve injury and demyelination can occur by multiple mechanisms, including T-cell–mediated cytotoxicity, damage from cytokines and oxygen free radicals, complement-dependent attack, and antibody-mediated functional impairment. The triggering mechanisms are not completely understood, but there is evidence for molecular mimicry in GBS, which is often preceded by an infection. The case is strongest for AMAN and Miller Fisher syndrome. It has been noted that certain antigens, surface lipo-oligosaccharide (LOS) structures, found on *Campylobacter* species are able to mimic PNS gangliosides. The sialyltransferase enzyme cstII found in *C. jejuni* has α2,3 activity and is sufficient to produce GM1 and GD1a-like LOS mimics, which induce AMAN. On the other hand, bifunctional α2,3-cstII and α2,8-cstII produce disialosyl mimics, which induce MFS (Fig. 38-2) (Yuki, 2007). The clinical manifestations of antibodies against gangliosides correlate with ganglioside localization in the PNS (Table 38-2). For example, GQ1b is localized to cranial nerves III, IV, and VI and to the DRGs, while GM1 is predominantly found in ventral roots and some DRGs. Modes of injury by anti-ganglioside antibodies vary from reversible functional impairment, to complement-dependent damage to perisynaptic Schwann cells, to α-latrodotoxin-like effects at the neuromuscular junction (Buchwald et al., 2007; Halstead et al., 2004; Plomp et al., 1999).

Other antigenic targets in the PNS include myelin-associated glycoprotein (MAG), sulfated glucuronyl paragloboside (SGPG), neuron-specific Hu proteins (HuB, HuC, HuD), the ganglionic acetylcholine receptor, voltage-gated potassium K^+ channels, and voltage-gated Ca^{2+} channels. MAG, an intrinsic membrane glycoprotein and a member of the immunoglobulin family, is localized to periaxonal membranes, paranodal loops, and Schmidt-Lanterman incisures. Anti-MAG neuropathy is characterized clinically by large fiber sensory dysfunction

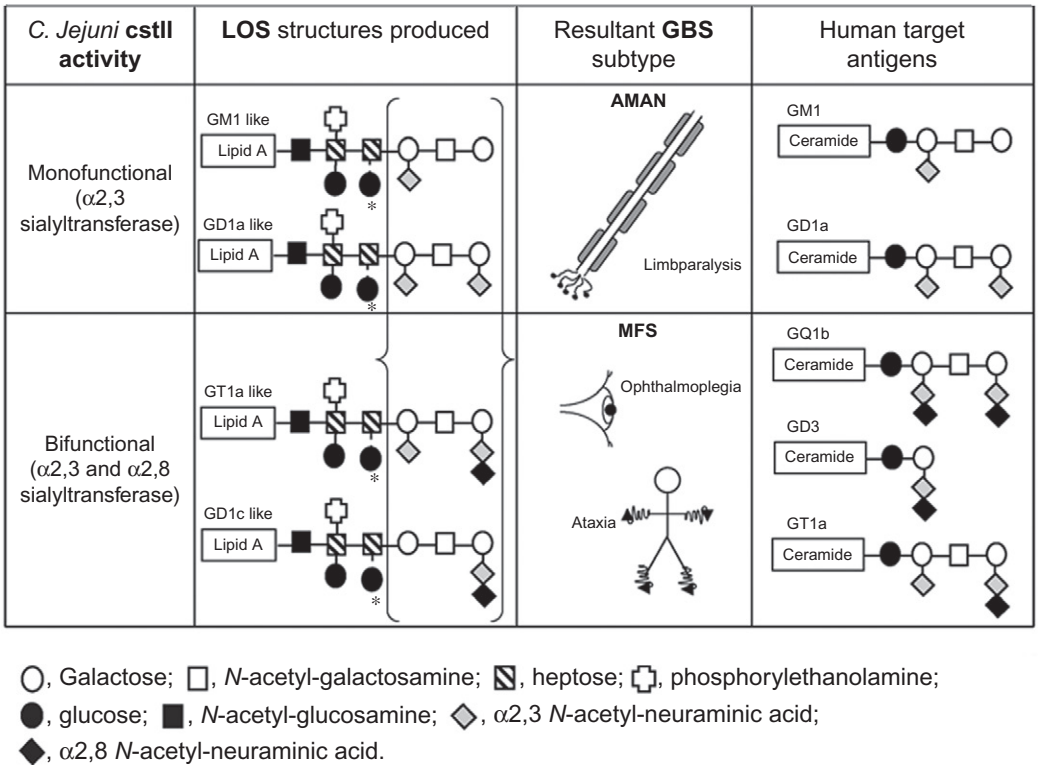

FIGURE 38-2 **Molecular mimicry in GBS.** *Campylobacter* sialyltransferase activity determines the neuropathy subtype. *Campylobacter jejuni* with the cstII allele Thr51 have α2,3-activity and produce GM1 and GD1a-like LOS structures, which induce the production of anti-GM1 and anti-GD1a antibodies, resulting in AMAN. *C. jejuni* strains possessing the Asn51 allele have bifunctional enzyme activity and produce GT1a and GD1c-like LOS structures with terminal disialosyl groups, which induce the production of anti-GQ1b, GD3, and GT1a antibodies, resulting in MFS. AMAN, acute motor axonal neuropathy; *C. jejuni, Campylobacter jejuni*; GBS, Guillain–Barré syndrome; LOS, lipo-oligosaccharide; MFS, Miller Fisher syndrome. {} = ganglioside mimicking structure of LOS. [Modified from the review by Rinaldi et al., 2008, with permission from Lippincott Williams & Wilkins].

TABLE 38-2 **Peripheral Nerve Disorders Associated with Specific Antibodies**

Clinical syndrome	Antibody
A. Acute: GBS variants	
Acute motor axonal neuropathy	IgG α GM1, GM1b, GD1a, GalNAc-GD1a
Miller Fisher syndrome	IgG α GQ1b, GT1a
B. Chronic dysimmune neuropathies	
Distal acquired demyelinating neuropathy	IgM α MAG, SGPG
Multifocal motor neuropathy	IgM α GM1, asialo-GM1, GD1b
Chronic ataxic neuropathy	IgM α GD1b, GD2, GD3
C. Idiopathic autonomic neuropathy	Abs α ganglionic acetylcholine receptor
D. Paraneoplastic sensory neuronopathy	Abs α HuB, HuC, HuD
E. Neuromyotonia (Isaac's syndrome)	Abs α Kv1.1
F. Presynaptic (Lambert Eaton syndrome)	Abs α calcium channels (P/Q, N)
G. Vasculitic neuropathy	Abs to myeloperoxidase, proteinase3
H. Paraproteinemic neuropathy	IgG or IgM monoclonal (unknown target)

with or without distal weakness, and pathologically by demyelination, remyelination, and a wide spacing of myelin lamella (Latov et al., 1980). These histopathologic findings were reproduced in passive transfer experiments in chicks (Tatum, 1993). Antibodies against Hu antigens, which are RNA binding proteins expressed by DRGs and small cell lung cancer, are associated with paraneoplastic sensory neuronopathy, which is sometimes accompanied by limbic encephalitis or cerebellar ataxia. The intracellular location of the antigen, in addition to failed attempts to develop an animal model via passive transfer or immunization, suggests that anti-Hu antibodies are not pathogenic. The presence of oligoclonal cytotoxic $CD8^+$ T-cells in nervous tissues of patients with anti-Hu syndrome supports the role of cellular immunity in this disorder (Plonquet et al., 2002). Other neurologic syndromes associated with antibodies are listed in Table 38-2. In contrast, the antigenic targets of aberrant T-cell or B-cell responses remain elusive in CIDP, as immune responses to myelin proteins, β-tubulin, and glycolipids have been observed with variable frequency and not consistently, perhaps reflecting the heterogeneity of this disease (Connolly et al., 1993; Csurhes et al., 2005; Sanvito et al., 2009).

OTHER CAUSES OF PERIPHERAL NERVE DISORDERS

Infections can damage nerves directly, via exotoxins, or by immune mechanisms

Mycobacterium leprae infects Schwann cells by binding to α-dystroglycan, causing sensory mononeuritis multiplex, a major complication of leprosy. *Clostridium botulinum* secretes a toxin that consists of a heavy chain and a light chain. The heavy chain binds to either polysialogangliosides and synaptotagmin or SV2 in presynaptic terminals, allowing internalization and translocation of the light chain into the cytosol. The light chain cleaves the three SNARE proteins in the cytosol, thereby blocking neurotransmitter exocytosis (Montecucco et al., 2009). Alternatively, an exotoxin that causes myelin injury is secreted by *Corynebacterium diphtheriae*. Immune reaction contributes to the peripheral neuropathy following HIV, Hepatitis C virus, and *Borrelia burgdoferi* infection.

Peripheral nerve damage is a recognized complication of toxins (e.g., alchohol, heavy metals, hexacarbons, organophosphates) and medications

Medications can affect different components of the PNS. Cisplatin causes Bax-dependent apoptosis of DRG neurons and vasa nevorum endothelial cells, and reduce fast axonal transport in vitro. Vinca alkaloids (e.g., vincristine) and taxols (e.g., paclitaxel) block the polymerization of tubulin into microtubules, thereby causing axonal neuropathy. Antiretroviral medications (e.g., zalcitabine, didanosine) induce mitochondrial toxicity, resulting in painful axonal neuropathy. Examples of drugs that may trigger a demyelinating neuropathy include perhexilene, amiodarone, suramin, and FK506 (Peltier & Russell, 2002).

Nutritional and vitamin deficiencies that occur during famine, after gastric surgery for tumors, or, more recently, following bariatric surgery for obesity cause a variety of neurologic syndromes that include neuropathy

Alcohol neuropathy results from a combination of thiamine deficiency, which impairs carbohydrate metabolism, and a direct toxic effect of ethanol on the PNS. Cyanocobalamin (Cbl) deficiency is most commonly seen as a result of B12 malabsorption due to pernicious anemia, and causes myelin damage and spongy vacuolation in the PNS and CNS. Cbl acts as a coenzyme (i.e., methyl-Cbl and adenosyl-Cbl) in the conversion of homocysteine to methionine catalyzed by methionine synthase, and in the conversion of methylmalonic-CoA to succinyl-CoA. It has been postulated that accumulation of methylmalonic acid and homocysteine leads to impaired methylation reactions essential for myelin synthesis and maintenance, though other findings would argue against this hypothesis. Patients with hyperhomocysteinemia due to other causes and methionine synthase knockout mice do not develop the neuropathological features of Cbl deficiency. Studies in experimental Cbl deficiency have revealed that there is a dysregulation of cytokine and growth factor synthesis, accompanied by increased levels of myelinotoxic factors such as tumor necrosis factor-α (Scalabrino, 2009).

AXON DEGENERATION AND PROTECTION

Injuries to axons by traumatic, ischemic, and toxic processes ultimately lead to axonal degeneration. Wallerian degeneration refers to an active process of axonal self-destruction that occurs distal to the transection/injury and takes 7–14 days in mammals (Griffin et al., 1992). Increased intra-axonal calcium, mitochondrial failure, and impaired axonal transport lead to the activation of calpains, which are major Ca^{2+}-dependent proteases involved in microtubule and neurofilament degradation (Coleman & Freeman, 2010). Wallerian degeneration is delayed in Wld^S mutants, whose axons survive for over two weeks, while those of wild-type mice survive for approximately 1.5 days (Glass et al., 1993; Lunn et al., 1989). WLD^S is a fusion protein composed of N-terminal 70 amino acids of UBE4B (or UFD2A) and full-length nicotinamide mononucleotide adenylyltransferase 1 (NMNAT1). UBE4B is an E4-type ubiquitin ligase, while NMNAT1 is a key protein of the NAD^+ salvage pathway in mammals. There is evidence that the N-terminal 16 amino acids (N16) of WLD^S, which are derived from UBE4B, and an enzymatically active NMNAT1 are critical for axon protection, although there is no increase in NAD^+ in Wld^S mice (Coleman & Freeman, 2010).

During Wallerian degeneration, both Schwann cells and macrophages participate in the clearance of myelin debris, which is required for subsequent axonal regeneration. A recent study in B-cell knockout JHD mice showed that endogenous antibodies also promote myelin clearance by macrophages following traumatic injury to axons (Vargas et al., 2010). Axonal regeneration also involves the production of growth factors by denervated Schwann cells, upregulation of growth factor receptors, and interaction of the growth

MOLECULAR MOTORS AND PERIPHERAL NEUROPATHIES

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Several inherited peripheral neuropathies have been associated with mutations in molecular motor proteins, such as members of the kinesin family or cytoplasmic dyneins. Curiously, specific neuronal populations appear to be primarily affected in these diseases, despite the fact that the motor proteins are more widely expressed. The first description of a mutation in kinesin associated with a peripheral neuropathy was the report of a loss of function mutation in the *KIF5B* gene in a Japanese family diagnosed with a dominant form of Charcot-Marie-Tooth 2A or CMT2A (Zhao et al., 2001). KIF1B was expressed in motor neurons, consistent with an axonal defect, and the *KIF1B* gene was mapped near the known locus for CMT2A. A similar phenotype was seen with haploinsufficiency of KIF1B in a mouse model, suggesting that partial loss of function for KIF5B is sufficient to produce a neuropathy. However, subsequent studies in other CMT2A lineages failed to find a mutation in *KIF1B*, so there may be more than one gene near this locus associated with CMT2A.

In 2003, a study of patients with congenital fibrosis of extraocular muscles type 1 (CFEOM1) demonstrated that mutations in the gene encoding another kinesin family member, KIF21A, were the most common cause (Traboulsi & Engle, 2004), showing autosomal dominant inheritance and primarily affecting the occulomotor cranial nerve affecting eye movements. At least seven mutations in *KIF21A* have been reported in CFEOM1 and one additional mutation is associated with a different variant, CFEOM3 (Andrews et al., 2006). The seven mutations associated with CFEOM1 affect a set of amino acids implicated in KIF21A stalk formation and may destabilize the motor or affect interaction with specific cargos. KIF21A is widely distributed in the brain and some non-neuronal tissues, but preferentially affects the occulomotor nerve. This again appears to be a case of haploinsufficiency, but the reason for selective vulnerability in occulomotor neurons remains to be determined.

Mutations in the dynein motor can also produce a selective peripheral neuropathy (Braunstein et al., 2010; Chen et al., 2007; Dupuis et al., 2009; Ilieva et al., 2008; Weedon et al., 2011). A nine-pair deletion in the cytoplasmic dynein heavy chain gene produces a preferential loss of proprioceptive sensory neurons (Chen et al., 2007). In mice with this mutation, motor neurons are spared even at advanced age. Two other mutations in dynein heavy chain similarly preferentially affect proprioceptive sensory neurons (Dupuis et al., 2009; Ilieva et al., 2008) while sparing motor neurons. Curiously, at least one mutation in dynein heavy chain also affects striatal neurons (Braunstein et al., 2010). This variation in phenotype with different mutations in the same gene may allow us to relate the molecular architecture of a protein to specific functional roles of a gene product. In turn, the genetics of disease provide insights into the selective vulnerabilities of different neuronal populations.

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cones of regenerating axons with components of the extracellular matrix (Hoke et al., 2006). A better understanding of the molecular mechanisms underlying the response to axonal injury is required for the development of novel strategies aimed at the protection of axons and the augmentation of regeneration in peripheral neuropathies.

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