PERIPHERAL NEUROPATHY – OVERVIEW OF ANATOMY AND PATHOLOGY

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The cell types of the PNS

The PNS is usually considered to be comprised of cell bodies and axons of motor, sensory, and autonomic neurons, and their associated glial cells (the Schwann cells and satellite cells that ensheathe axons and cell bodies, respectively), and skeletal muscle. In addition, the neurons and glia of the enteric nervous system and all but one of the cranial nerves (the optic) are part of the PNS.

Motor neurons (motoneurons) innervate skeletal muscle fibers, and autonomic (sympathetic and parasympathetic) neurons innervate and regulate the function of secretory cells and smooth muscle cells.

Because skin and sensory nerves are typically biopsied, it is important to understand the diversity of sensory neurons, which can be distinguished by their function (Zimmermann et al., 2009), trophic dependence (Luo et al., 2009), and synaptic connections (Marmigere and Ernfors, 2007; Zampieri et al., 2014). For example, proprioceptors (IA afferents) innervate muscle spindles, have large myelinated axons, synapse on motoneurons, and depend on neurotrophin-3 signaling via their TrkC receptors for their normal development. Unmyelinated axons (C fibers) and thinly myelinated axons (Aδ) subserving nociception terminate in the superficial laminae of the spinal cord, and depend on NGF and/or neurturin signaling via their respective receptors (TrkA and c-ret) for their normal development. Mechanoreceptor sensory fibers (Aα/β) innervating specialized sensory appendages (Merkel cells, Pacinian corpuscles, hair follicles, Meissner corpuscles) have precise connections in the dorsal horn of the spinal cord, and depend on a variety of trophic factors for their normal development (Table 1).

The myelin sheath

In the mature peripheral nervous system, Schwann cells form myelin sheaths around most axons that are 1 micron in diameter or larger. All axons that innervate skeletal muscle (both intrafusal and extrafusal muscle cells) as well as a subset of sensory axons are myelinated. The bulk of the myelin sheath is formed by layer upon layer of closely apposed cell membranes, called compact myelin. The cell membrane itself is highly specialized, containing a higher proportion of lipids than typical cell membranes, as well as specialized lipids (galactocerebroside and sulfatide) and proteins (myelin protein zero; P0, peripheral myelin protein 22 kDa; PMP22) that are not found in most cell membranes. P0 is the "molecular glue" that holds together the apposed cell membranes. The function of PMP22 is unknown, but genetic evidence strongly suggests that precisely the right amount is required for the stability of the myelin sheath: halving the amount of PMP22 causes hereditary neuropathy with liability to pressures palsies (HNPP) and increasing the amount of PMP22 by one-half causes Charcot-Marie-Tooth disease type 1A (CMT1A).

A different set of molecular specializations characterize regions other parts of the myelin sheath – so-called "non-compact myelin". Non-compact myelin is found in the paranodes (at the lateral edges of the myelin sheath) and incisures (funnel shaped disruptions of compact myelin). Non-compact myelin contains the molecules that form specialized junctions, including gap junctions that form a pathway for the diffusion of small molecules and ions directly across the myelin sheath. Mutations of the *GJB1*, the gene that encodes the gap junction protein connexin32, cause CMT1X, presumably because the mutant proteins do not form functional gap junctions in the myelin sheath.

Kinds of injury in the PNS

The cells of the PNS can be injured:

Neurons. Neurons can be "injured" in a number of ways – toxins (e.g., too much B6), metabolic disorders (e.g., genetic causes of ALS), autoimmune disorders (sensory neuronopathy associated with small cell cancer), and physical injury (e.g., axonal injury near the cell body). For some causes, there appears to be a continuum between neuronopathy and neuropathy. In vitamin B6 intoxication, a large acute dose causes a sensory neuronopathy (Albin et al., 1987), whereas smaller, chronic doses produces an axonal sensory neuropathy (Xu et al., 1989). Selective cell death is typical. Motor neurons selectively die in spinal muscular atrophy and amyotrophic lateral sclerosis. Similarly, preganglionic autonomic neurons, post-ganglionic autonomic neurons, and sensory neurons are selectively affected in other diseases. Dead neurons are not replaced, but surviving neurons may be able to compensate if their terminals can sprout and effectively replace the terminals of the dead neurons.

Axons. A variety of genetic diseases, toxins, and acquired metabolic disorders (e.g., diabetes mellitus) damage axons, typically affecting the longest ones first, producing the clinical picture of length-dependent sensory and motor deficits. Trauma to peripheral nerves is less common kind of lesion, but has been best characterized injury owing to its reproducible nature in the laboratory animals. Axonal regeneration is possible in the PNS, but its success depends on the nature of the lesion (the continuity of the Schwann tubes is key) and the distance that axons must regenerate.

Myelinating Schwann cells. Injury to these cells usually results in demyelination (loss of myelin sheaths with preservation of axons), but does not typically cause cell death. Autoantibodies to one or more components of myelinating Schwann cells cause acquired demyelinating neuropathies (Guillain-Barre syndrome and chronic inflammatory demyelinating neuropathy), and mutations in the genes that encode various components of the myelin sheaths cause inherited demyelinating neuropathies (Charcot-Marie-Tooth disease). Remyelination is typically robust unless a genetic lesion compromises the Schwann cells themselves.

Axonal Neuropathies

The physical length of axons may be the reason for their selective vulnerability – they are the longest cells in the body. Axons have a prominent cytoskeleton composed of intermediate filaments and microtubules. Because axonal protein synthesis is scant, proteins must be transported down the axon after they are synthesized in the cell body. Orthograde (from the cell body) axonal transport is mediated by microtubule-activated ATPases, known as kinesins, molecular motors that use microtubules as tracks; different kinesin transport different organelles.

A complex of dynein and p150 mediate retrograde axonal transport. Axons have plentiful mitochondria, which are presumably the main source of axonal ATP.

In most neuropathies, a progressive, "dying back" of the longest axons produces the clinical picture of a length-dependent neuropathy. The axonal loss is usually indolent and progressive, so that actively degenerating axons are rarely detected in nerve biopsies. Distal to the site of the "lesion", myelinated axons are transformed into cords of Schwann cells that are not associated with any axons (bands of Büngner), and even these disappear with time, such that severe chronic neuropathies leave the nerves atrophied, with few Schwann cells and abundant collagen. Marked axonal with conspicuous myelin debris indicates that the neuropathy is acute – such as vasculitis and GBS.

Wallerian degeneration is the term that is used to describe the changes that occur in nerves distal to the site of a lesion (Scherer and Salzer, 2001). Although originally described for mechanically injured nerves, the same events appear to happen after toxic, metabolic, and genetic injuries to axons, and even after neuronal cell death. During Wallerian degeneration, the axon degenerates, which in turn, initiates the degeneration of myelin sheaths. The myelin sheaths break down and are phagocytosed, in part by Schwann cells, but also by the macrophages that invade the nerve. The basal lamina of the Schwann cell, however, remains intact and the Schwann cells remain within these basal lamina tubes. Previously myelinating, but now "denervated", Schwann cells cease expressing the genes encoding components of myelin sheaths (proteins and glycolipids), and express genes that likely support regenerating axons.

Clusters of regenerated axons are found in some chronic neuropathies (CMT2, CMTX, and chronic vasculitis), but it is unlikely that these regenerating axons succeed in reaching their former targets.

Many sensory neurons (including those that convey pain information) and autonomic neurons (which innervate glands and smooth muscle) have unmyelinated axons. The term "small fiber neuropathy" denotes a neuropathy in which unmyelinated axons are selectively involved. With a few exceptions (e.g., Fabry disease), these are mostly acquired neuropathies, and chronic diabetes is the most common cause. In some kinds of Hereditary Sensory (and Autonomic) Neuropathies, unmyelinated axons are missing owing to the congenital loss of their associated cell bodies. In most small fiber neuropathies, the longest axons are affected first - the skin of the foot is denervated before the skin of the thigh.

Demyelinating Neuropathies

Individual axons are myelinated nearly synchronously along their length, and the subsequent growth in that region of the body results in the elongation of myelin sheath. The axons destined to become the largest are the first to be myelinated; the smallest myelinated axons are the last to be myelinated. The result of these developmental processes is that the myelin sheaths (called internodes) of individual myelinated axons have remarkably similar lengths, and that the internodal lengths are linearly related to their axonal diameter. In addition, the myelin sheath and axon itself constitute about 40% and 60%, respectively, of the total diameter of the myelinated axon, regardless of the axonal diameter (this the basis of the "g-ratio" = diameter of axon/diameter of the myelinated fiber). If a myelin sheath breaks down, for whatever reason, the

demyelinated region is typically remyelinated. Because there is little turnover of myelin sheaths in normal nerves, abnormally thin myelin sheaths and abnormally short internodes are important pathological findings that are used to diagnose demyelinating neuropathies.

Most of the dominantly and recessively inherited demyelinating neuropathies also show evidence of repeated demyelination and remyelination, particularly the more severe forms, which are known as Dejerine-Sottas Neuropathy and Congenital Hypomyelinating Neuropathy. In these neuropathies, the "left over" Schwann cells (generated by proliferation during demyelination) that surround the remyelinated internode form "onion bulbs". In addition to the demyelinating forms of CMT, de/remyelination is a feature of some dominant and recessive syndromes. Some inherited demyelinating neuropathies have particular pathological findings (Tables 2 and 3) – "tomaculi" in HNPP, uncompacted myelin in some cases of CMT1B, "focally folded" myelin sheaths in CMT4B1 and CMT4B2, focal accumulations of glycolipids in lysosomes in the Schwann cells in metachromatic and globoid cell leukodystrophies.

Demyelination is also a feature of the demyelinating forms of GBS and of CIDP. In acute inflammatory demyelinating polyneuropathy (AIDP), complement is deposited on the outer surface of myelinating Schwann cells, followed by the vesicular degeneration of the outmost myelin lamellae (Hafer-Macko et al., 1996). In animal models, antibodies against the gangliosides GM1 (Susuki et al., 2007) and GD1a (McGonigal et al., 2010; Susuki et al., 2012) can disrupt the molecular architecture of the node in a complement-dependent manner. More recent work has shown that, in addition to gangliosides, antibodies against proteins that are localized in the nodal region may be the key for pathogenesis of GBS, CIDP, and acquired neuromyotonia (Table 4). Some of these antibodies are IgG4, which do not fix complement and likely cause demyelination in a complement-independent manner (Querol et al., 2014).

IgM kappa and IgG or IgA lamba paraproteins are associated with acquired demyelinating neuropathies. This paraproteins cause widening of compact myelin, presumably because they paraproteins infiltrate it.

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Table 1. Trophic factors for PNS neurons (with the help of Dr. Wenqin Luo).

Neuronal type	Trophic factor	Receptor
α-motoneurons	BNDF, NT-4 NT-3 LIF CNTF CT-1 CRLF1+CLCF1	TrkB TrkC LIFβR+gp130 CNTFRα+gp130 CNTFRα+gp130 CNTFRα+gp130
γ-motoneurons	GDNF	GFRα1+ret
pre-ganglionic autonomic	NT-4 GDNF TGF-betas	TrkB GFRα1+ret type I & II receptors
sympathetic	NGF artemin	TrkA GFRα3+ret
parasympathetic	GDNF neurturin CRLF1+CLCF1	GFRα1+ret GFRα2+ret CNTFRα+gp130
trkA nociceptive	NGF	TrkA
IB4 nociceptive	NGF neurturin	TrkA (prenatal) GFRα2+ ret (postnatal)
Merkel cells	NT3	TrkC
Pacinian corpuscles	neurturin	GFRα2+ret
Meissner corpuscles	BDNF neuturin	TrkB GFRα2+ret
Aβ lanceolate endings	neuturin	GFRα2+ret
Aδ lanceolate endings	NT-4	TrkB
C lanceolate endings	NGF neurturin	TrkA (prenatal) GFRα2+ ret (postnatal)
muscle spindle afferents	NT-3	TrkC

Table 2: Non-syndromic inherited neuropathies that have unique pathological findings.
The table groups non-syndromic inherited neuropathies by their patterns of inheritance and phenotypes. Some diseases are thus listed more than once. The genes are named by the HUGO gene nomenclature (http://www.genenames.org/), and hyperlinked to this database. Dominant diseases are **bolded**. The diseases, their chromosomal locus, and genes are hyperlinked to OMIM (http://www.ncbi.nlm.nih.gov/Omim/).

Disease (OMIM)	Gene (OMIM)	Comments
CMT1 (autosomal or X-linked dominant demyelinating)		
HNPP (162500)	*PMP22* (601097)	Tomaculi superimposed on an underlying chronic, mild demyelinating neuropathy
CMT1A (118220)	*PMP22* (601097)	Demyelinated axons are more prevalent in children; "hypomyelinated" axons are more numerous with age
CMT1B (118200)	*MPZ* (159440)	Some mutations are associated with non-compact myelin; other have abnormally folded myelin sheaths
CMT1X (302800)	*GJB1* (304040)	Chronic axonal neuropathy, with rudimentary onion bulbs and clusters of regenerated axons; unique pathology in the adaxonal Schwann cell cytoplasm
Autosomal recessive demyelinating neuropathy ("CMT4")		
CMT4B1 (601382)	*MTMR2* (603557)	Severe, demyelinating neuropathy, with irregular folding and redundant loops of myelin
CMT4B2 (604563)	*SBF2* (607697)	
CMT4B3 (615284)	*SBF1* (603560)	
CMT4C (601596)	*SH3TC2* (608206)	Severe, demyelinating neuropathies
CMT4D (601455)1	*NDRG1* (605262)	
CMT4E (605253)	*EGR2* (129010)	
CMT4F (614895)	*PRX* (605725)	
CMT4H (609311)	*FGD4* (11104)	Severe, demyelinating neuropathy with outfolded myelin sheaths in the paranodal region
CMT4J (611228)	*FIG4* (609390)	Severe, demyelinating neuropathies
CMT4 (no OMIM)	*PMP22* (601097)	
CMT4 (no OMIM)	*MPZ* (159440)	
Severe, demyelinating neuropathies; dominant or recessive		
Déjérine-Sottas neuropathy (145900)	Diverse genetic causes	Most biopsies show severe, demyelinating neuropathy. Some show endoneurial edema.
congenital hypomyelinating neuropathy (605253)	Diverse genetic causes	Some biopsies show an even greater paucity of myelin than DSN, and a failure of myelinating Schwann cells to progress beyond the promyelinating stage; some have "basal lamina onion bulbs".
CMT2 (autosomal dominant axonal) and dominant CMTX		
CMT2E (607684)	*NEFL* (162280)	Masses of neurofilaments within axons
giant axonal neuropathy 2 (610100)	*DCAF8* (615820)	Masses of neurofilaments within axons
Autosomal recessive axonal neuropathy (ARCMT2)		
ARCMT2	*NEFL* (162280)	Axons are small, and lack neurofilaments
Hereditary Sensory (and Autonomic) Neuropathy (HSN or HSAN)		
HSAN3 (223900)	*IKBKAP* (603722)	Progressive loss of C-fibers and some myelinated fibers
HSAN4 (256800)	*NTRK1* (191315)	C-fibers and small myelinated axons are congenitally absent
HSAN5 (608654)	*NGF* (162030)	

Table 3: Syndromic inherited neuropathies that have unique pathological findings..
Dominant diseases are **bolded**. The genes are named according to the HUGO gene nomenclature (http://www.genenames.org/), and hyperlinked to this database. The diseases, their chromosomal locus, and genes are hyperlinked to OMIM (http://www.ncbi.nlm.nih.gov/Omim/).

Disease (OMIM)	Gene (OMIM)	Comments
Syndromic demyelinating neuropathies		
metachromatic leukodystrophy (250100)	*ARSA* (607574)	lysosomal material in Schwann cells
globoid cell leukodystrophy (245200)	*GALC* (606890)	lysosomal material in Schwann cells
gonadal dysgenesis with minifascicular neuropathy (607080)	*DHH* (605423)	minifascicular neuropathy
Syndromic axonal neuropathies		
FAP-1 (105210) **FAP-2** (115430)	*TTR* (176300)	amyloid
FAP-3 (105200)	*APOA1* (107680)	
FAP-4 (105120)	*GSN* (137350)	
familial visceral amyloidosis (105200)	*B2M* (109700)	
Somatic and autonomic neuropathy	*PRNP* (176640)	
giant axonal neuropathy-1 (256850)	*GAN* (605379)	Masses of neurofilaments within axons
HP1 (259900)	*AGXT* (604285)	intraneural oxalate deposition
Fabry disease (301500)	*GLA* (300644)	dark osmiophilic deposits in the perineurium and blood vessels
adrenoleukodys-trophy (300100)	*ABCD1* (300371)	inclusions in Schwann cells
APBD (263570)	*GBE1* (607839)	polyglucosan bodies in axons
galactosialidosis (256540)	*CTSA* (613111)	vacuoles in Schwann cells

APBD: polyglucosan body neuropathy, adult form;
FAP: familial amyloidotic polyneuropathy;
HP1: Hyperoxaluria, primary type 1

Table 4. Autoantibody against nodal proteins and associations with demyelinating diseases.

nodes		
gliomedin	GBS	(Devaux et al., 2012)
	CIPD	(Devaux et al., 2012)
Nr-CAM	GBS	(Devaux et al., 2012)
	CIPD	(Devaux et al., 2012)
moesin	GBS	(Sawai et al., 2014)
paranodes		
NF155	GBS	(Devaux et al., 2012; Kawamura and al., 2013; Ng et al., 2012; Pruss et al., 2011)
	CIDP	(Devaux et al., 2012; Kawamura and al., 2013; Ng et al., 2012; Querol et al., 2014)
	DADS	(Kawamura and al., 2013; Mathey et al., 2007)
	MMN	(Kawamura and al., 2013)
	CCPD	(Kawamura and al., 2013)
contactin	GBS	(Devaux et al., 2012; Doppler et al., 2015)
	CIDP	(Devaux et al., 2012; Doppler et al., 2015; Querol et al., 2014)
juxtaparanodes		
TAG-1	GBS	(Devaux et al., 2012)
	CIDP	(Devaux et al., 2012)
Caspr2	GBS	(Rosch et al., 2014; Tuzun et al., 2013)
	NMT	(Irani et al., 2010; Irani et al., 2012; Klein et al., 2012; Lancaster et al., 2011)

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