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Mechanisms of Distal Axonal Degeneration in Peripheral Neuropathies

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Abstract

Peripheral neuropathy is a common complication of a variety of diseases and treatments, including diabetes, cancer chemotherapy, and infectious causes (HIV, hepatitis C, and *Campylobacter jejuni*). Despite the fundamental difference between these insults, peripheral neuropathy develops as a combination of just six primary mechanisms: altered metabolism, covalent modification, altered organelle function and reactive oxygen species formation, altered intracellular and inflammatory signaling, slowed axonal transport, and altered ion channel dynamics and expression. All of these pathways converge to lead to axon dysfunction and symptoms of neuropathy. The detailed mechanisms of axon degeneration itself have begun to be elucidated with studies of animal models with altered degeneration kinetics, including the slowed Wallerian degeneration (Wld^S) and Sarmknockout animal models. These studies have shown axonal degeneration to occur througha programmed pathway of injury signaling and cytoskeletal degradation. Insights into the common disease insults that converge on the axonal degeneration pathway promise to facilitate the development of therapeutics that may be effective against other mechanisms of neurodegeneration.

Keywords

Peripheral neuropathy; Guillain-Barré syndrome; Diabetes; HIV; HIV neuropathy; Mitochondrial aging; Hepatitis C; *Campylobacter jejuni*; Chemotherapy induced peripheral; neuropathy; Wld^S; Mechanisms of neuropathy; Nodo-paranodopathy; Post-infectious neuropathy

I. INTRODUCTION

Peripheral nerve degeneration is a common disorder of the nervous system whereby sensory and/or motor axons no longer effectively communicate between the periphery and central

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nervous system. The prevalence of peripheral neuropathy in the United Stateshas been reported to be nearly 15% in adults over the ageforty[108].

Peripheral neuropathy is not a single, homogenous disease, but is instead a mix of different clinical presentations, natural histories, and pathologies. Patients may present with motor insufficiency (weakness), sensory abnormalities (numbness, parethesias, hyperalgesia/allodynia, pain), autonomic symptoms, or a combination of all, often depending on the particular disease. Thesevariousconstellations of neurological symptoms suggest motor, sensory, and autonomic axons have differingsusceptibilities to various disease processes. Additionally, while most neuropathies are chronic, slowly progressive conditions, some neuropathies have a more acute onset and gradual recovery[111] (reviewed in[140, 275, 293]). The heterogeneity of peripheral neuropathies is likely secondary to the initiating event. Few neuropathies are present in isolation, but, rather, are often secondary to other systemic illnesses, including diabetes and infectious causes such as human immunodeficiency virus and hepatitis C virus. Additionally, peripheral neuropathies may be iatrogenic, arising from the toxicity of drugs given as part of antiretroviral or chemotherapy regiments.

Despite the great variety of cause and symptoms, the pathophysiology of peripheral neuropathies is limited to only a handful of mechanisms. In this article, the pathophysiological mechanisms of various types of peripheral neuropathy – diabetic neuropathy, chemotherapy induced peripheral neurotoxicity (CIPN), HIV and non-HIV infectious neuropathies – will briefly be reviewed in an effort to examine how many different disease process converge onto a handful of cellular targets involved in the axonal degradation pathway to produce peripheral nerve dysfunction. As it is among the most heavily studied, diabetic neuropathy will serve as the prototypical example for many of the mechanisms, then additional detail added for particular diseases.

1.1 Clinical Overview of Selected Diseases

1.1.1 Diabetic neuropathy—Diabetes mellitus is a very common chronic disease. In 2014, over 9% of the United States population (21 million people) has been diagnosed with diabetes [47], and the prevalence is expected to increase[220]. Diabetes is the most common cause of peripheral neuropathy, accounting for over half of the cases in a recent Dutch study[207].

Diabetic peripheral neuropathy is classically a sensory neuropathy presenting as numbness and parethesias in a length dependent “stocking glove” distribution, whereby the feet are affected earlier and more severely than the hands (as reviewed in [51]), but painful, autonomic, or motor neuropathies may also occur (reviewed in [249]). In two studies of patients with type-I diabetes, intense glucose control reduced the risk of peripheral neuropathy by 60%[102, 110]. This finding suggests that the elevated glucose levels in the body may be pathogenic. While hyperglycemia may be a large component of the pathogenesis of diabetic neuropathy, non-hyperglycemic effects of diabetes, including reduced trophic support (hypoinsulinemia in type I and advanced type II diabetes) and mitochondrial health and function, may also be important.

1.1.2. Chemotherapy induced peripheral neurotoxicity—While improved cancer treatment regimes and higher rates of remission are a boon to modern medicine and cancer biologists, many of the commonly used anti-neoplastics have long term toxic effects that currently are not well mitigated during treatment [45]. Indeed, chemotherapy induced peripheral neurotoxicity (CIPN)has increased in incidence as cancer remission rates continue to climb due to improved cancer therapies (as reviewed in [12, 45]). While the incidence and prevalence of CIPN varies by agent, in general, 30-80% of treated patients develop a peripheral neuropathy (as reviewed in [96]). Patients experience motor and sensory symptoms, including numbness, pain, and weakness[248], so severely that they may be dose-limiting. The wide variety of symptoms suggests chemotherapeutic agents may harm multiple types of neurons, as well as different parts of neurons, including the axon (axonopathy) or the soma/ganglion (ganglionopathy) (as reviewed in [118]). The most common causes of CIPN include taxanes, such as paclitaxel, platinum agents including cisplatin and oxaloplatin, and proteasome inhibitors such as bortezomib and will, thus, be the focus of discussion. For other compounds, readers are referred to Argyriou et al's excellent, recent review [12]. Within a pharmacological class, there is also heterogeneity. For example, cisplatin has chiefly chronic affects, but oxaliplatin has toxic neurological effects in both the acute and chronic setting, suggesting different processes may underlie early and late pathology. Thus, the particular pathophysiology of CIPN depends not only on the family of chemotherapeutic but also on the specific member of the family.

1.1.3. Human immunodeficiency virus neuropathy—The global prevalence of the human immunodeficiency virus (HIV) in 2009 was found to be 33.3 million [1], and nervous system defects, including a peripheral neuropathy, is common in the disease [159, 229]. Interestingly, while control of the virus has improved over the past few decades, the incidence of neuropathy has increased from 13% in 1993 to 42% in 2006[229]. This increase in prevalence during the eraof effective treatments suggests that the neuropathy is not caused by the virusalone, but also by the drugs used to treat it [87]. HIV neuropathy is chiefly a sensory neuropathy of pain, paresthesias, and absent ankle reflexes[67]. Direct viral infection of neurons or Schwann cells has not been well demonstrated, but the virus has been recovered from some nerve samples [52, 74]. Viral concentration in these samples is remarkably low, suggesting viral particles and proteins must enter the nerve through other cells, such as macrophages or T-cells. Indeed, careful studies of viral tropism have shown that particles recovered from nerve are consistent with macrophage and T-cell infectious particles [127] and that viral proteins colocalize with macrophages in vivo [115]. These findings suggest the virus is brought to the nerve by immune cells, but does not directly infect neuronal cells [66, 115]. The viral proteins gp120 and protein R (VPR) are especially important toward the observed neurotoxicity. The primary mechanisms of the neuropathy appear to be immune damage from viral proteins and mitochondrial toxicity from the antiretrovirals (as reviewed in [131, 133]).

1.1.4 Non-HIV infectious causes: Hepatitis C and Campylobacter jejuni—In addition to HIV, hepatitis C virus (HCV) and *Campylobacter jejuni* infection are also associated with peripheral neuropathy. Hepatitis C is a viral infection that may become an intractable, chronic infection,best known for causing liver cirrhosis and hepatocellular

carcinoma. In 2011, the best estimate of prevalence was 2.35% of the world population(160 million people), making it five times more common than HIV [143]. HCV has long been known to be associated with neurological complications including peripheral neuropathy and encephalopathy [241]. A study in France of 321 patients with hepatitis C infection found 9% and 10% develop a sensory or motor neuropathy, respectively [40]. HCV-associated peripheral neuropathy has been further divided into four subtypes based on distribution: polyneuropathy, mononeuritis multiplex, cranial neuropathy, and a combination of polyneuropathy/cranial neuropathy, with axonal degeneration and demyelination on biopsy [180]. Importantly, the hepatitis C virus has not been shown to replicate or infect muscle or nerves directly [14], so, as was the case with HIV, neuropathy must develop through indirect, inflammatory mechanisms instead of direct viral infection.

In these studies of HCV and peripheral neuropathy, cryoglobulinaemia was found to alter the complication profile associated with HCV infection [40] and be associated with more widespread neuropathy [180]. Cryoglobulins are immunoglobulins that reversibly aggregate at cooler (less than 37°C) temperatures and are associated with a variety of chronic and autoimmune diseases, with HCV infection being one of the best characterized (as reviewed in [95]). Between 30[213] and 78% [180] of patients with HCV have been reported to have cryoglobulinaemia. Although the presence of cryoglobulinemia as a risk factor for neuropathy has been debated, it is interesting to consider Nemni, et al's findings that, while cryoglobulinaemia may not increase the severity of neuropathy, it changes the profile to one of a more generalized syndrome [180]. This observation is pertinent since cryoglobulinaemia is known to lead to systemic vasculitis, suggesting ischemic injury and inflammation may be important for the development and/or advancement of HCV induced peripheral neuropathy[14].

The bacteria *Campylobacter jejuni* is a common causeof gastroenteritisandis associated [100]with a post-infectious neuropathy in 1 of 1000 infections [5]. First described by Guillian, Barré and Strohl [111], the neuropathy often occurs a week after infection and is classically an acute, ascending, motor neuropathy (as reviewed in[275]). With an estimated incidence of 1/100,000[5], Guillian-Barrésyndrome (GBS) is somewhat rare but may cause permanent disability or be fatal secondary to diaphragmatic paralysis and respiratory failure [275]. While some viruses may also cause GBS, *C. jejuni* is believed to cause 30% of all cases[5]. GB has recently been appreciated to have multiple subtypes[275], including acute inflammatory demyelinating polyradiculoneuropathy (AIDP) and acute motor axonal neuropathy (AMAN)[109, 119, 162]. The pathophysiology of AMAN is more thoroughly understood than AIDP, and, thus will be used to discuss principles that may be generalized to other subtypes.

II. MECHANISMS OF PERIPHERAL NEUROPATHY

2.1 Metabolic Dysr egulation

In diabetes, hyperglycemia leads to dysregulation of the polyol, hexosamine, and pentose phosphate pathways that ultimately leads to reactive intermediates that damage the axon and Schwann cells. Glucose-6-phosphate (G6P) can be diverted by the enzyme glucose-6-phosphate dehydrogenase (G6PD) from glycolysis into the anaerobic pentose phosphate

pathway to produce more NADPH. When intracellular glucose (and, thus, glucose-6-phosphate) levels are very high, G6PD is inhibited [300]and glucose is instead diverted into the polyol pathway by the enzyme aldose reductase to produce the alcohol sorbitol (see figure 1). Sorbitol and other polyols accumulate in various tissues throughout the body, including the sciatic nerve of experimental rat models [101]. Sorbitol reduces the level of membrane component myo-inositol in cultured neuroblastoma cells exposed to high levels of glucose by inhibiting its cellular import [290]. This disruption of the axonal membrane could reduce the ability of the axon to propagate an action potential [290] or impair the ability to regenerate following injury since a “wave” of lipogenesis is necessary for regeneration [156], and nerves from patients with diabetes demonstrate areas of focal demyelination and remyelination, a lipid intensive process [245]. Additionally, myo-inositol depletion in a rat model of type II diabetes is associated with reduced Na^+-K^+-ATPase activity, leading to a nerve conduction deficits[107].

NADPH is one of the primary intracellular antioxidants, so its depletion reduces the ability of a cell to protect against oxidant damage, ultimately leading to apoptosis. The polyol pathway also depletes NADPH, since it is used in the conversion of glucose into sorbitol (see figure 1). The pentose phosphate pathway is an anaerobic metabolic pathway used to create NADPH reducing equivalents and other biomolecules. G6PD is the gateway to this pathway, so its inhibition by high glucose levels is a second hit against the production of antioxidants, ultimately leading to increased rates of apoptosis [247, 300]. Thus, dysregulation of the polyol pathway by hyperglycemia may cause nerve damage through multiple mechanisms:membrane damage by reduced levels of myoinositol, and increased radical damage from a reduced antioxidant capacity.

2.2 Covalent Modification

In addition to the potential toxicityfrom alternative metabolic pathways in diabetes, glucose itself can be toxic as a result of non-enzymatic addition of glucose to proteins via the Amadori product[6] of the Maillard reaction [155]whereby glucose condenses with the amine group of amino acidsto form modified proteins, “advanced glycation end products” (AGEs),as reviewed in[35]. AGEs have been observed in both the axons and Schwann cells of peripheral nerves, with enrichment of AGEs in samples from patients and animal models of diabetes [261],[234],[84]. These molecules work through direct modification of biomolecules.

Among the modified proteins is collagen, which leads to increased thickness [240], immune complex deposition[36], and LDL trapping *in vitro* [37]in comparison to non-modified collagen. All of these are characteristics of an atherosclerotic plaque, which can lead to luminal narrowing of a vessel and greater risk of occlusion, thereby reducing blood flow and exposingthe nerve to hypoxic conditions. This hypoxic risk is increased byAGEsthat quenchthe vasodilator nitric oxide released from endothelial cells[38], demonstrating how multiple aspects of the response to hyperglycemic synergize to damage tissue.

One of the principal components of the basement membrane, laminin is critical for the health and development of neurons and Schwann cells(as reviewed in [62]) and is directly modified by AGEs. Modified laminin inhibits neurite outgrowth in vitro when compared to

nonmodified laminin [90], and this reduction in outgrowth persists despite neurotrophin stimulation or preconditioning [84]. One can imagine the AGE modifications of collagen and laminin combining to produce recurrent injury to axons: the modified collagen facilitates hypoxic conditions which damages the axon, but the modified laminin is not permissive to axon regrowth, thereby limiting peripheral nerve recovery and producing an axonopathy.

Glyceraldehyde-3-phosphate, a metabolic intermediate of the polyol and glycolytic pathway, can nonenzymatically bindto, and, thus interfere with, other proteins[42] (as reviewed in [246]). Glyceraldehyde-3-phosphate may also activate the protein kinase C (PKC) pathway, since it can be degraded into diacylglycerol, one of the secondary messenger of the canonical PKC signaling cascade [203]. This pathway has been shown to be particularly relevant for vascular complications associated with diabetes (as reviewed in [73]).

The hexosamine pathway produces glucosamine-6-phosphate and glutamate from fructose-6-phosphate and glutamine (see figure 1). Glucosamine-6-phosphate is ultimately converted into UDP-*N*-acetylglucosamine (UDP-GlcNAc) and other hexosamines to serve as substrates for glycoprotein sugar moieties (reviewed in [39]). UDP-GlcNAc can be covalently bound to proteins by O-GlcNAc transferase. These modifications are believed to regulate protein function by competing with kinase phosphorylation [63]. Indeed, O-GlcNAcylation has been observed on numerous proteins regulating transcription, including RNA polymerase II [63], Sp-1 [287], and insulin receptor substrates 1 and 2 (IRS1/2) [89]. In the case of Sp-1, O-GlcNAcylation leads to increased expression of more pathogenic proteins such as TGFß [81]. Thus, over activity of the hexosamine biosynthetic pathway modifies the activity of numerous transcription factors, ultimately leading to gross changes in cell state and signaling.

In addition to proteins, other biomolecules,such as DNA, can also be modifiedby AGE products. Plasmid DNA incubated with reactive AGE products produced double strand DNA breaks and base modifications [174]. A small study of 31 type II diabetic patients in Turkey found higher AGE DNA adduct concentration in patients with diabetes compared to controls, despite the use of oral hypoglycemic drugs [198]. This study confirms the ability of AGE compounds to react with other biomolecules *in vivo* as well as illustrates how modified molecules remain in the tissue despite initiation of hypoglycemic therapy, although it remains unclear what effect the modified DNA has in these tissues.

DNA modification is also believed to be one of the mechanisms responsible for the chronic symptoms of CIPN, particularly following treatment with platinum containing compounds like cisplatin and oxaliplatin. Incubation of DRG neurons in vitro with oxaliplatin and cisplatindecreases neurite outgrowth, increases platinum/DNA adducts[160, 238], and apoptosis-mediated cell death [238]. The exact mechanisms of toxicityis platinum adduct formation with nuclear and mitochondrial DNA [160, 197]which initiatesapoptosis [161]. Interestingly, the increased accumulation of platinum/DNA adducts is selective for DRG neurons, over cancer cells, in vitro [160], likely due to expression of aselective organic cation transporter[231]. This pattern may explain the particular vulnerability of sensory neurons to platinum compounds like cisplatin and oxaliplatin.

2.3 Organelle Damage and Reactive Oxygen Species

Mitochondria, the site of oxidative phosphorylation, are intrinsically linked to the development of reactive oxygen species(as reviewed in [175]). Damage or pathology associated with these organelles may lead to cell death through apoptosis or energetic failure, thereby increasing sensitivity to ischemia. Given the constant flux of electrons and oxygen in mitochondria, it is not surprising that they are likely the primary site(more than 90%) of reactive oxygen species production (as reviewed in [19]). Mitochondrial dysfunction, both in its normal function and increased ROS production, has been implicated in the pathogenesis of many different neuropathies.

In addition to mitochondria, (dys)function of the endoplasmic reticulum also facilitates development of neuropathy. As a fundamental component of the protein synthesis and modification pathway, insults that may inhibit the proteasome or increase the concentration of unfolded proteins may trigger stress, thereby releasing calcium and initiating the unfolded protein response, leading to cell deaththrough multiple pathways (as reviewed in[282]). Impairment in both the endoplasmic reticulum and mitochondria are acommon mechanism to all of the pathologies discussed.

2.3.1 Impaired mitochondria function—While it is perhaps expected that mitochondria, as the primary energy production site for the mammalian cell, would display certain pathology in the setting of a hyperglycemia and aberrant metabolism, recent work has suggested that the mitochondria play a much more active role in the development of neuropathy through cell death and injury.

In a murine model of type II diabetes,Vincent and colleagues found abnormal mitochondrial morphology insensory neuronsdespite an increased mitochondrial density in their axons, neurites, and cell bodies compared to healthy control mice[86, 255]. Vincent, et al, suggest increased mitochondrial fission is necessary to meet the greater energetic requirements of a hyperglycemic state, but too rapid mitogenesis leads to unhealthy mitochondria[255]. Alternatively, mitochondria fission may represent a response to toxicity. In a 2005 review, Youle and Karbowski proposed a model of the induction of apoptosis whereby the machinery necessary for fission also mediates apoptosis[145, 291].

Mitochondrial dysfunction is also evident with an impaired respiratory capacity. Indeed, in an animal model of type I diabetes, mitochondria in sensory neurons displayed depressed respiratory function compared to control animals due to lower activity of complex I and IV secondary to reduced protein expression of certain complex components [56]. The reduced protein levels, in turn, are likely due to reduced PGC-1α/AMPK axis signaling that occurs in the setting of hyperglycemia and metabolic derangement [55]. Impaired electron transport chain function also causes an increase in ROS generation (as reviewed in [177]), which will be discussed in more detail later.

Mitochondrial dysfunction is a major mechanism of CIPN across all of the various chemotherapeutic agents. The taxane family of chemotherapeutics, including paclitaxel, exercises its antineoplastic effects through inhibition of tubulin depolymerization (as reviewed in [128]), thereby interfering with the stabile/labile balance of microtubules [128],

including the axons of neurons [17]. Swollen and vacuolated mitochondria are commonly observed in the axons of sensory nerves of animal models CIPN caused by paclitaxel [98, 279, 280]. By interfering with microtubule dynamics, paclitaxel has been shown to interfere with calcium signaling in mitochondria and the endoplasmic reticulum by the opening of the mitochondrial membrane permeability pore, leading to calcium triggered calcium release from the ER [135, 171]. The opening of the mitochondrial permeability transition pore (MPTP) also leads to release of ROS and cytochrome C [252]. For these reasons, the MPTP has been hypothesized to be a major, convergent effector of axonal degeneration [21] via induction of apoptosis[205] and downstream calcium activated effectors. The increase in calcium may also facilitate cellular injury by activating the calcium dependent protease calpain. Indeed, paclitaxel treated animals that were also administered a calpain inhibitor displayed improved neurological scores and fewer signs of sensory axon degeneration, even though apoptotic rates were unaffected [270]. Furthermore, calpain also degrades the neuronal calcium sensor-1 protein, leading to reduced IP_3 signaling [27, 28]. In addition to direct toxic and apoptotic effects, the abnormal mitochondria may also be pathogenic because of reduced respiratory ability, thereby contributing to energetic failure [280, 301].

Mitochondrial dysfunction has also been observed in axons following CIPN caused by oxaliplatin and bortezomib [279, 301]. Commonly used for multiple myeloma, bortezomib is a chemotherapeutic that inhibits the proteasome. Like platinum agents and taxanes, it is well known to cause painful sensory neuropathy in humans and animals [166]. Bortezomib, like paclitaxel, has been shown to lead to mitochondrial calcium release leading to activation of the apoptotic cascade [142] and energetic collapse [302].

In HIV neuropathy, both the virus and the drugs used to treat the infection lead to mitochondrial dysfunction. When cultured DRG neurons were exposed to HIV infected macrophages, mitochondrial membrane potential in the soma decreased as reactive oxygen species formation increased, but there was no effect on neurite mitochondria,suggesting there are distinct mechanisms of injury between the soma and axon [115]. This separation has been well characterized in studies on inflammatory and apoptotic signaling (discussed below).

In addition to induction of apoptosis and increased calcium from the MPTP (as reviewed in [206]), mitochondria are functionally impaired because of damaged DNA. In a recent study of sural nerve mitochondria in HIV patients with and without sensory neuropathy, mitochondrial deletions were more common in those with neuropathy[144], with more mutations observed in distal mitochondria versus those in more proximal aspects [144]. These mutations were correlated with reduced mitochondrial respiratory function [144]. Interestingly, mitochondrial defects were not observed in the proximal sciatic nerve, only the sural nerve, which suggests the distal aspect of axons are more sensitive to toxicity [144]. Lehman, et al's study of mitochondrial mutations and dysfunction lead to the development of a novel, unifying theory of neuropathy based on mitochondrial aging and, thus, distal axon susceptibility. Mitochondria must travel from the soma to the periphery, which may take months to years. During this process, mitogenesis takes place, but in an imperfect manner, leading to an accumulation of mitochondrial DNA (mtDNA) mutations, and, thus deficits. This process would make the distal most aspect of an axon more

susceptibly to further injury than the proximal aspect, mirroring the length dependency of many neuropathies. Additionally, Lehman, et al also suggested that the higher density of mitochondria in small, lightly or non-myelinated fibers [144] will make these fibers especially sensitive to mitochondrial dysfunction, as is observed with the primarily sensory component of many neuropathies. Lastly, one can imagine that processes that affect axonal transport will only exacerbate mitochondrial dysfunction distally since it takes longer to reach distal points. This hypothesis of mitochondrial aging is an exciting development toward a unifying explanation of many different peripheral neuropathies, but more testing is needed, especially toward the development of therapeutics that protect mitochondria from chronic damage and aging. This hypothesis suggests that agents that directly damage mitochondrial DNA may exacerbate neuropathic symptoms, and this is indeed what is observed in the treatment of HIV infection.

Mitochondrial dysfunction in HIV neuropathy occurs througha variety of antiretroviral treatments (as reviewed in [71]). Treatment of rabbits with a nucleoside analog (2',3'-dideoxycytidine; ddC) show robust dysmyelination, abnormal Schwann cell morphology, and slowing of nerve conduction velocity [9, 91]. Treated patients display an increased density of swollen, vacuolated mitochondria with inclusions in the axons and Schwann cells of the sural nerves in those treated with ddC [72]. These abnormal mitochondria correlate with a reduced level of mtDNA[72], likely as a result of inhibition of mtDNA polymerase[158] (as reviewed in [130, 131]) and subsequently reduced protein levels [144]. This reduced amount of mtDNA may exacerbate the mtDNA damage from aging as described in the hypothesis above. Indeed, the ratio of mtDNA to nuclear DNA in nerve samples is reduced with infection and drug over infection only, and marginally recovers upon drug cessation [68]. Like HIV itself, the antiretroviral-induced damage to mtDNA also leads to impaired mitochondria function.

Antiretrovirals are sufficient to interfere with mitochondrial function. By inhibiting replication of the mitochondrial genome, a number of the necessary components of the electron transport chain may not be produced, thereby leading to uncoupled transport and decreased oxidative phosphorylation, as is observed in neuronal mitochondria treated with ddC in vitro [132]. Interestingly, patients on nucleoside analogues often display hyperlactemia, which resolves upon drug cessation. One could imagine systemic mitochondrial inhibition would lead to decreased oxidative phosphorylation, and, thus a concomitant increase in glycolysis and lactic acid fermentation. Thus, antiretroviral drugs and HIV infection synergize to cause greater injury[305]. As with other neuropathies, mitochondrial dysfunction may cause additional cellular injury through the production of reactive radical species, as outlined below

2.3.2 Endoplasmic reticulum dysfunction—The endoplasmic reticulum (ER) is also vulnerable to various toxicities, as evidenced by the induction of the unfolded protein response. While ER inhibition in diabetes is not well characterized, bortezomib has been shown to induce a transient stress response in the Schwann cell ER, leading to myelination deficiency and an increased cytokine expression [224]. This off target effect is perhaps unsurprising, given bortezomib's mechanism of action as a proteasome inhibitor one would expect the unfolded protein response to increase, as well.

While most of the work has examined mitochondrial dysfunction in the setting of HIV neuropathy and anti-retroviral therapy, the ER may also be adversely affected by viral proteins. Indeed, in a study by Höke, et al, the HIV envelope protein gp120 induced ER calcium release by binding to the chemokine receptor to activate the canonical IP_3 signaling cascade leading to rapid increase of intracellular calcium [123]. When calcium storage in the ER was experimentally reduced, the neurons were more resistant to gp120 triggered cell death, reinforcing the important role of the ER in mediating degeneration [123]. A similar calcium response has been described upon DRG neuron exposure in vitro to Vpr [2]. While the downstream effect of the increased calcium has not been well studied, one could imagine a similar mechanism to what is observed in CIPN with calpain protease activation and the induction of apoptosis (as reviewed in [116]).

2.3.3 Reactive oxygen and nitrogen species—The electron transport chain (ETC) produces superoxide as a byproduct of electron uncoupling followed by reduction of oxygen to form the free radical[20], but mitochondria also produce hydrogen peroxide, hydroxide radicals, and nitric oxide, all of which are reactive species that can directly damage other proteins or DNAthrough covalent modification (as reviewed in[177, 227]). While superoxide production is a common feature of all eukaryotic cells, the nervous system may be particularly vulnerable to free radical damage because of large energetic demands and high lipid content (as reviewed in [168]).

Natural antioxidants help mitigate this damage, such that the depletion of these molecules increases the susceptibility of the cell the oxidative damage. Uncoupling proteins serve to reduce the electrochemical potential across the mitochondrial inner membrane by bypassing ATPsynthase, thereby uncoupling the hydrogen ion gradient from the generation of ATP (as reviewed in [208, 228]). ROS generation may be reduced by uncoupling since the electron transport chain (ETC) complexes that may generate superoxide radical are bypassed (as reviewed in [173, 228]). The uncoupling protein (UCP) family includes three proteins, UCP-1, UCP-2, and UCP-3, which are all hydrogen ion channels or transporters. UCP-1 was identified to be involved in thermogenesis from brown fat [181], while UCP-2 and UCP-3 were found [85]to be important for homeostasis [99] and thermogenesis [31] in a variety of tissues including white adipose tissue and brain for UCP-2[99] and DRG, brown adipose tissue, and skeletal muscle for UCP-3[257, 284]. UCP-2 and UCP-3were also quickly identified as inhibitors of ROS generation in the mitochondria [179, 253] since null mice displayed evidence of increased ROS production and damage (as reviewed in [30]). UCPs are also critical for the attenuation of damage from ROS secondary to hyperglycemia. A variety of studies have shown all three UCP family members to protect cells from hyperglycemia induced ROS generation when the proteins are overexpressed [209, 257]. Interestingly, in the setting of hyperglycemia, UCP-3 expression is actually reduced [257]. These data suggest development of damage secondary to hyperglycemia may be facilitated by a reduction of UCPs in vivo, or, alternatively, loss of UCPs in vivo may facilitate the development of diabetic complications. This relationship makes UCP expression an enticing therapeutic target, but the development of drugs to alter expression must move forward with great caution since overexpression of UCP-2, for example, reduces insulin secretion, thereby potentially worsening the hyperglycemia characteristic of diabetes[49, 50]. Thus, while there

is some conflicting evidence on the utility of increased UCP expression toward the protection from, or development of, the complications of diabetes, there is clear evidence that the coupling of the ETC to ATP production becomes dysregulated in diabetes which may lead to increased ROS and altered energetics (as reviewed in [173]).

Superoxide production may be a unifying mechanism that initiates, or least propagates, many of the mechanisms of neuropathy in diabetes.The aforementioned pathogenic elements from metabolic derangements (sorbitol, AGEs, PKC signaling) decreased upon inhibition of superoxide [183]. Mitochondrial function and DNA health was also improved upon inhibition of superoxide production in the retina in a model of diabetes [242]. The ROS control of these mechanisms is effected by DNA damage activated poly(ADP-ribose) polymerase (PARP). PARP catalyzes the inhibitory ADP-ribosylation of proteins, including GAPDH [80](as reviewed in [177]), inhibition of which increases activity of the hexosamine pathway, PKC signaling activation, and AGE concentration[80]. Additionally, recent evidence has implicated PARP as not just a downstream signal of oxidative damage, but, instead, as a promulgator of ROS damage in a variety of tissues, including Schwann cells and the peripheral nerve[185]. PARP is directly neurotoxic due to the depletion of its cofactor, NAD^+, when it is catalytically active [113]. Severe reduction of NAD^+ results in energetic collapse of the cell and necrotic death [113].

In addition to ADP-ribosylation, superoxide may directly oxidize proteins to form carbonyl adducts that may modify protein function (as reviewed in [177]). Indeed, these modified proteins have been identified in the brain [70, 202], although their function is not well studied. In addition to oxygen modification, ROS may leadto PARP mediated up regulation of iNOS followed by reaction of nitric oxide with superoxide to produce the reactive nitrogen radical[185]. Regardless of its source, nitric oxidemay also modify proteins [185] to act in both damaging and protective capacities [168]. Nitric oxide and its radical may be a particularly importantpathogenic mechanisms in the nervous system due to its use as both a neurotransmitter by neurons and regulator of blood flow secondary to nitric oxide mediated vasodilation [168]. The balance between nitric oxide and its radical likely explains the observed protective and damaging effects of nitric oxide, since nitric oxide with its vasodilatory activity is likely protective, but its radical, that accumulates with increased ROS, likely mediates protein, and, thus, cellular, injury (as reviewed in [258]).Thus, the development of ROS and reactive nitrogen species (RNS) are a critical component of diabetes-induced damage that extends beyond simple radical chemistry to prolonged alterations of cellular signaling pathways.

CIPN, like diabetes, is also mediated by ROS (as reviewed in [65]). Both oxaliplatin and cisplatin have been shown to generate ROS [126], and mitochondria are damaged by ROS/RNS secondary to drug treatment[125].Regardless of the source, these ROS damage additional cellular components such as proteins and lipids [65, 77], ultimately leading to energetic failure [125]and apoptosis [126, 218]. The result of these derangements include increased nociception as well as distal degeneration of intraepidermal nerve fibers, as is seen in animal models of CIPN caused by paclitaxel [23]. These data suggest that studies of CIPN must consider the distal most aspect of axons, and not just proximal segments seen in the sciatic nerve or dorsal roots since damage is not uniform.

ROS and RNS are alsoa prominent component of HIV,and its treatment, induced injury. The generation of these species appears to be most harmful to the neuronal cell body[115]. Antioxidant treatment improves cell survival but not neurite outgrowth [115], emphasizing the importance of ROS to somal, but not axonal, injury. Lehman and colleagues confirmed these observations in animal models of HIV infection, whereby the virusincreased hydrogen peroxide production as well as oxidative and nitrosative protein modification in the sural, but not the sciatic, nerve [144]. The selectivity of sural nerve versus sciatic nerve may be due to the increased sensitivity of distal sensory fibers to mitochondrial dysfunction, as discussed previously [144].

2.4 Intracellular and Inflammatory Signaling

In diabetes, in addition to non-enzymatic modification of biomolecules, AGEs are also bioactive as ligands for two major types of cell surface receptors. The first discovered receptor, receptor for AGE (RAGE), was identified through the selective binding of glycosylated albumin to the surface of mouse macrophages with subsequently AGE/RAGEinternalization[260, 262], leading to macrophage proliferation in a granulocyte/macrophage colony stimulating factor (GM-CSF) dependent manner [292]. Since its identification, RAGE has been found to be expressed by a variety of cell types, including neurons (as reviewed in [230]). Vlassara and colleagues hypothesized that RAGE acts to clear harmful AGE modified proteins from the body [260]. Interestingly, the RAGE receptor also has a soluble isoform that is believed to be a scavenger receptor for AGEs and found in many tissues, including the adult nervous system [53]. A reduced level of this scavenger isoform is correlated with increased risk of peripheral neuropathy in patients with type II diabetes [13]. RAGE, however, is not simply a net to clear AGEs, but also can initiate an inflammatory response through cytokine release [289], including NF-κB mediated transcriptional activation of pro-inflammatory cytokines TNF-α, IL-1ß, and MCP-1 [289], a pattern of cytokine expression that may facilitate tissue remodeling, as occurs in atherosclerosis [263]. RAGE has been identified on endothelial cells [178],[217] and neurons [32], in vivo, which suggests an immune response with the concomitant increase in ROS could be initiated by AGEs in these tissues, thereby effecting additional vascular or neuronal injury [273]. In addition to tissue remodeling, the downstream effect of the induction of these cytokines may be the production of ROS, as monocytes from patients with diabetes have greater ROS production than control cells [79]. Cultured endothelial cells and AGE infused mice also demonstrate a RAGE dependent increase in oxidative stress and NF-κB induction upon exposure to AGEs [285]. Indeed, the antioxidantα-lipoic acid protects Schwann cells from AGE induced apoptosis in vitro [219]. Thus, RAGE converts the transient inflammatory signal of the AGE into a sustained inflammatory response that may lead to a long term inflammatory state, thereby hindering treatment [25, 79].

After the identification of RAGE, three other receptors were identified (AGE-R1, AGE-R2, and AGE-R3) as part of a large AGE-receptor complex [288], [264] (as reviewed in [259]). As a complex, AGE-R1/R2/R3 has been shown to be up regulated in the presence of AGEs with AGE-R3 demonstrating the greatest induction after exposure, and AGE-R2 phosphorylation increased in vitro upon exposure of human umbilical vein endothelial cells to AGE-BSA [232]. Together, these data suggest that AGE-R1 may serve as a stable

receptor, while AGE-R2 effects the intracellular response through AGE-R3 following AGE-R2 tyrosine phosphorylation. The role of intracellular signaling by the AGE-R complex and the relevance of the previously identified activities of each component in the larger complex remain to be elucidated. Interestingly, early data on the AGE-R complex suggested AGE binding leads to a IL-1 dependent late induction of progrowth cytokine insulin-like growth factor (IGF-1) in monocytes in vitro [137], linking RAGE cytokine release to AGE-R response.

It should be noted that much of the work on the AGE-Rs has been performed in endothelial cells, reinforcing the importance of vascular injury, with concomitant ischemia, in the development of neuropathy, as is seen with RAGE. Current models suggest a delicate balance between the pro-inflammatory and tissue remodeling effects of RAGE and AGE clearance by the AGE-R complex [150], whereby AGE binding facilitates tissue remodeling and inflammatory cell recruitment, leading to vascular occlusion and neuronal/axonal injury. While this model remains to be tested in vivo, other work has elucidated the importance of mitochondrial (dys)function toward the development of diabetic peripheral neuropathy.

While the function of PARP in the regulation of metabolism through GAPDH modification and as an effector of ROS injury was previously discussed, it is also responsible for the regulation of inflammatory signaling.PARP was elegantly demonstrated to, upon exposure to inflammatory particles like LPS and TNF-α, increase transcription factors that lead to an increased expression of inflammatory cytokinesand iNOS [112]. The expression of iNOS is particularly interesting, as its up regulation varied by cell type and stimulus [112]. Nitric oxide can also initiate damage through its radical as well as signal through in an independent cascade.

Nitric oxide serves as both a vasodilator and neurotransmitter that has a complex activity in neuronal signaling, damage, and repair with mixed data describing its protection from or contribution toward cellular damage and neuropathy (as reviewed in [306]). As described above, iNOS is induced in glia by PARP [113] where it serves an inflammatory function. However, in cultured endothelial cells, endothelial nitric oxide synthase (eNOS) has been shown to be downregulated in the setting of hyperglycemia, as a result of O-linked N-acetylglucosamine modifications secondary to activation of the hexosamine pathway, thereby increasing the risk of atherosclerosis and/or microvascular ischemia[82].Interestingly, an early study conflicted with the previous data and found NOS and TNF-α to be induced in endothelial cells upon exposure to glycated albumin [7]. The authors of this study postulated that the NOS and AGE balance is critical for early and late development of diabetic complications, where nitric oxide is increased early in the disease through theactivity of NOS, thereby damaging glomeruli through hyperfiltration, whereas AGE products serve to quench NO in the vasculature later in disease, thereby reducing vasodilatory capacity [7]. Thus, in the setting of hyperglycemia, reactive nitrogen intermediates may be produced within the nervous system as a result of PARP activation secondary to ROS damage while, concurrently, oxygen flow may be reduced through impaired mechanisms of vasodilation. Together, the increase in iNOS and decrease in eNOS are two hits toward a toxic knockout of neurons and glia.

In addition to PARP and NOS signaling, neurotrophic factor signaling is also altered in diabetes. While all of the research discussed thus far has focused on the effect of hyperglycemia on nerve pathology, recent work has suggested that insulin, or the lack thereof, may also facilitate the development of the complications associated with type I diabetes. Indeed, Sima and colleagues suggest different nerve conduction properties between typeI and type II diabetes may be a result of the loss of insulin and C peptide that classically occurs in type I diabetes [227].C-peptide is derived from the same prohormone as insulin and is increasingly recognized as having distinct, albeit complementary, effects to the action of insulin (as reviewed in [265]). C-peptide will be lost at the same time as insulin, since they are both part of the same precursor peptide. Theimportance of the loss of C-peptide and insulin toward the development of the complications of diabetes was supported by more recent experiments showing diabetic animals had a reduced ability to up regulate neurotrophic factors (IGF-1, IGF-1 receptor, p75, and TrkA) in response to nerve crush injury, ultimately leading to reduced regenerative ability and decreased nerve fiber density[190, 196]. This deficiency was largely selective for type I, not type II, diabetic models, suggesting that the deficiency of insulin and C-peptide, not hyperglycemia, leads to axonopathy and decreased nerve fiber density [196]. Evidence for the importance of insulin and C-peptide to the development of axonal defects in type I diabetes comes from rescue experiments where exogenous C-peptide improved conduction deficits, myelination defects, regenerative capacity, and nerve fiber number [226].

Additional work has clarified the protective role of the insulin induced neurotrophic factor insulin-like growth factor 1 (IGF-1).Given a decrease an insulin, as is seen in type I diabetes, it is perhapsunsurprising that IGF expression is decreased in patients with type I diabetes versus normoglycemic controls [190], Long appreciated for its anti-apoptotic activity in cancer and injury (as reviewed in [256]), IGF-1 was recently found to protect DRG neurons from hyperglycemia induced apoptotic signaling [145].

Other signaling axes have been identified to be dysregulated in diabetes. Nerve growth factor (NGF) is well known to support sensory fiber survival in vitro and in vivo[58-60, 146, 147] and was recently demonstarted to be transiently upregulated in the DRGs of an animal model of type II diabetes during the onset of mechanical allodynia, suggesting dysregulated NGF signaling may facilitate the development of one of the hallmarks of diabetic neuropathy - pain [54]. NGF levels may be elevated at the onset of injury [54], facilitating the development of neuropathic pain, but then fall later in the course of the disease[93], thereby reducing regenerative capacity, although this pattern of expression may be dependent on the type of diabetes.

Altered signaling to increase inflammation is a prominent component of CIPN. In animals models of paclitaxel toxicity, ATF3, a general, transientmarker of neuronal injury[250], is up regulated in DRG neurons within a day of drug administration, while glia increase expression of injury markers nearly a week after the first dose of the drug[195]. Additionally, markers of macrophage (CD68) and microglia (CD11b) activation increase one week following treatment[195]. These data show an evolving pathology whereby the DRG neurons are first harmed, then supporting glia in the DRG and nerve, which ultimately leads to recruitment or activation of inflammatory cells (macrophages, microglia)

concomitant with symptom onset[194, 195, 272] and increased expression of many pro-inflammatory cytokines (as reviewed in [271]). Macrophage activation leads to matrix metalloproteinases-3 and -9 and, as a result, increased tissue degradation[182, 225]. Thus, the chemotherapeutic agents increase inflammation in the nerve and ganglia, which may then lead to tissue damage andmore severe deficits.

Inflammatory signaling is a critical mechanism of HIV neuropathy. Indeed, both HIV proteins and systemic inflammation secondary to the viral infection may damage neurons and axons (as reviewed in [133, 251]). Recent work has shown gp120 induces separate processes of injury in the neuronal soma versus the axon. In a compartmentalized culture of DRG neurons, gp120 reduces axonal length in an axon/Schwann cell only compartment and triggers apoptotic cell death when applied to the soma [165]. Interestingly, in the absence of Schwann cells, DRG soma were protected from apoptosis, but axons were still sensitive to the application of gp120 [165], suggesting different injury pathways were active in the two areas.Ultimately, Melli et al found that this response is due to selective binding of gp120 to chemokine receptors on axons which leads to caspase activation, and, thus, injury and degeneration [165]. The engagement of apoptotic machinery in the soma, however, was distinct from the mechanisms in the axons as suggested by the Schwann cell dependence of soma apoptosis in response to gp120 [165]. Additional work found gp120 binding to chemokine receptor CXCR4 on Schwann cells in the DRG to result in the release of the ligand RANTES (regulated upon activation, normal T-cell expressed and secreted). RANTES then binds to a different chemokine receptor (CCR5) on the neuron, leading to release of TNF-α by neurons and autocrine apoptotic signaling through its receptor and the c-Jun cascade[26, 134]. The importance of CXCR4 and CCR5 to the development of HIV neuropathy also extends to the initiation of inflammation[127]. VPR has been shown to evoke very similar, pro-inflammatoryresponses in DRG neurons [2]. In addition to the activation of cell mediated inflammation, Apostolski, et al showed gp120 may mediate DRG neuron cell death by activation of the complement cascade [11]. Thus, HIV may enter the peripheral nervous system through other cells, but its proteins and the immune response may indirectly damage neuron cell bodies and axons, albeit through slightly different mechanisms.

In addition to the inflammation from the virus, recent work hasidentifiedantiretrovirals to also increase inflammatory signaling[303] and activation of apoptotic machinery [26]. To this end, ddC increases expression of TNF-α in GFAP^{+}cells in the dorsal horn and neurons in the DRG[303]. In addition to TNF-α, BDNF has also been shown to facilitate the development of mechanical and thermal hyperalgesia following treatment by a nucleoside analogue by increasing firing rates of dorsal horn neurons to stimuli [204]. This finding suggests ddCincreases BDNF release which ultimately leads to enhanced synaptic connectivity between primary nociceptors and dorsal horn neurons. Thus, in addition to the inflammatory signaling from the virus itself, the antiretrovirals may also initiate damage through modulation of the inflammatory response via TNF-α and synaptic connectivity via BDNF.

Aberrant inflammatory signaling is the primary pathogenic mechanism of HCV neuropathy. As discussed previously, while cryoglobulinaemia is not necessary for the development of

peripheral neuropathy, it changes the symptom constellation from a localized neuropathy to a more generalized disorder affecting multiple nerves. Cryoglobulinemia has long been appreciated to precipitate peripheral neuropathy [48]. Sural nerve histology of a patient with cryoglobulinemia showed small and medium vessel perivascular inflammation with some vessels completely occluded and myelin degeneration[48]. IgM and IgG were found deposited on smaller vessels, while fibrinogen was readily stained on the larger vessels [48]. The authors of this report suggest the patient's neuropathy was precipitated by the cryoglobulinemia, whereby IgGs bound to myelin, leading to direct immune attack, as well as to the small and medium vessels, leading to vascular occlusion and ischemia. A different study found that the antibodies binding to myelin were largely against myelin associated glycoprotein (MAG)[244]. Thus, the IgG and IgM antibodies may cause damage through two mechanisms: activation of complement on myelin and ischemia by precipitation of immune complexes and lymphocytic inflammation within the vasa nervorum, causing luminal narrowing or occlusion[29, 244]. While these mechanisms may explain the neuropathy in patients with HCV and cryoglobunemia, recall that 30-70% of patients with HCV neuropathy may not have cryoglobulins. In these patients a different mechanism must be responsible for their symptoms.

Interferon-α (IFN-α)modulates the development of peripheral neuropathy in patients infected with HCV. Both IFN-γ and IFN-α are cytokines that are released during viral infection to induce an "antiviral," intracellular state.IFN-α can be induced by most cells, while IFN-γ is specifically released by lymphocytes as part of the cell mediated immune response (as reviewed in [92]). In addition to endogenous induction of IFN-$\alpha$by HCV, given its general antiviral activity, exogenous IFN-α has become a critical component of combination therapy for certain HCV infections (as extensively reviewed in [222]).Interestingly, autoimmunity increases following IFN-αmonotreatment in HCV infection[88], despite a decrease in cryoglobulins and viral titer. This suggests that IFN-α produces a pro-inflammatory state that may facilitate damage to the vasa nevorum and myelin. Thus, it is a fine balance between inflammation to clear the virus and autoimmunity. This autoimmunity likely initiates the development of neuropathy in HCV;there is a combination of ischemia due to occluded small vessels and direct attack against the myelin. This model is consistent with the non-dependence of neuropathy on the presence of cryglobulins. While the cryoglobulins may increase vascular inflammation, leading to ischemia and more widespread neuropathy, anti-myelin proteins may still be present in the absence of cryoglobulins, so neuropathy may still develop. It is still unclear how ribavirin may reduce the incidence of neuropathy, but one possibility is by leading to more complete viral clearance, ribavirin reduces systemic inflammation, including cryglobulins and anti-MAG antibodies. By reducing these compounds, IFN-α autoimmunity, and, thus, neuropathy, is less likely to develop. This hypothesis remains to be tested.

2.5 Axonal Transport Defects

Diabetes also affects axonal health by modulation of axonal transport. Nearly 30 years ago, Medori, et al. identified impaired slow axonal transport of cytoskeletal proteins neurofilament (light and medium subunits), tubulin, and actin in an animal model of type I diabetes versus healthy controls [164]. The authors also observed increased axonal cross

sectional area in the proximal aspect of the axon, but a reduced area in the distal aspect. They hypothesized that this pattern may be a result of reduced accumulation of cytoskeletal elements distally because of impaired transport [164]. Additional cytoskeletal protein defectsinclude direct actin and neurofilament glycation in the setting of hyperglycemia in vitro [34], andin vivo [69, 191](as reviewed in [163]), as well as reduced expression of heavy and light neurofilament, and α-tubulin in the DRGs of type I diabetic animals [172]. It should be noted, however, that while actin glycationdoes not interfere with its ability to polymerize [191], glycosylated tubulin has a reduced polymerization ability [274]. The expression and modification of these cytoskeletal proteins (actin, neurofilament, tubulin) is believed to interfere with cytoskeletal assembly, and, thus, axonal transport [163].RAGE is predicted to interactwith actin through its effector mDia1[124, 129, 157], but recent work has elegantly shown that slowed axonal transport in diabetic animals is independent of RAGE expression [129]. Despite the slowed transport of the RAGE/actin effector protein mDia1 in diabetic animals (wild type and RAGE knockout), RAGE itself was not differentially present between diabetic and control animals. While the exact mechanisms of slowed axonal transport in diabetes, and how it may effect other cellular processes, remains to be elucidated, one can imagine that such large scale changes in the cell may alter its ability to respond to its environment, perhaps making it more susceptible to damage through other mechanisms or less efficient with cellular repair and regeneration.

Microtubule defects with the concomitant transport difficulties is a critical component of paclitaxel-induced CIPN with much work focusing on how microtubule stabilization by taxanes, in particular, may interfere with axonal transport (as reviewed in [106]). Incubation of DRG neurons with high levels of paclitaxel has been shown to interfere with anterograde transport of HRP [243]. Interestingly, while paclitaxel binds to the lumen of microtubules and, thus, cannot directly hinder motor movement [106], electron microscopy shows decreased rates of microtubule crosslinks and reduced density of the cross-linking microtubule associated proteins upon DRG neuron exposure to paclitaxel in vitro [243]. Thedearth of these crosslinks could alter transport dynamics. Alternatively, increased microtubule density and aggregation [46, 106, 243]may hinder motor movement. However, these microtubule abnormalities havenot been observed in patient sural nerve biopsies [211], perhaps due to lower drug concentrations.

An alternative hypothesis of transport interference in paclitaxel mediated CIPN is covalent modification of tubulin interfering with molecular motor function. As a microtubule polymerizes, the tubulin components that are not on the elongating end can be acetylated, glutamated, and detyrosinated to increase stability (as reviewed in [106]). Investigations of dendrite/axon identity have found tubulin detyrosination to organize distribution and movement of kinesin along the axon[83, 139]. Paclitaxel enhances all three posttranslational modifications, thereby disrupting axon/soma/dendrite polarity [117, 276]. The role of posttranslational modification is complex, however, as each modification can alter motor binding and motility[106], and different motor subtypes may bind to different modified tubulins preferentially [41]. Nonetheless, interruption of transport may lead to poor anterograde transport of vesicles and organelles, as well as retrograde transport of trophic factors [106]. Transport dynamics may also be affected at the end of the axon, where motors

must release from and reattach to different microtubules. Indeed, a recent paper has shown that in a drosophila model of a degenerative motor neuron diseasewith a tubulin binding domain mutation in a subunit of dynein, dynein accumulates in the terminal bouton because of a failure to bind to the end of the microtubule [149]. The microtubule end and motor dynamics are critical for maintaining proper and equitable delivery of vesicles to terminal boutons [277]. This model suggests dysfunction of transport could lead to derangements at the axon terminal and, thus, interfere with communication or organelle delivery and lead to terminal degeneration, although this hypothesis has not been tested.

Surprisingly, low dose paclitaxel has been shown to facilitate regeneration, rather than degeneration, in the central nervous system [120]. The authors of this initial study suggested paclitaxel may facilitate regeneration by reducing scarring [120]. An additional hypothesis was proposed three years prior to the discovery of the regenerative benefit of low dose paclitaxel. Witte, et al suggested that since paclitaxel modifies neuron polarity to create multiple axons from one cell, perhaps low dose paclitaxel may be helpful to “convert a nongrowing minor neurite into a growing axon” to facilitate central nervous system regeneration[276]. Thus, the microtubule stabilizing dynamics must be delicately balanced between stable and unstable, polymer and monomer, such that paclitaxel may either cause axonal degeneration through interruption of axonal transport or regeneration by stabilization of growing neurites.

Axonal transport defects are also observed in CIPN caused by cisplatin and bortezomib. As with paclitaxel, in a model of bortezomib CIPN, tubulin polymerization is increased in vivo and in vitro upon clinically appropriate drug concentration[167]. The exact mechanism of bortezomib tubulin stabilization remains to be elucidated. In addition to bortezomib and paclitaxel, early studies on cisplatin neurotoxicity showed impaired anterograde and retrograde fast transport in vitro with no gross morphologic abnormalities [210]. The authors of this study suggested cisplatin may be directly toxic to kinesin and dynein through crosslinking or motor ATPase inhibition[210], although little work has been pursued in this line of research.

2.6 Channelopathy

While diabetes does have some sodium/potassium channel dysfunction[107], as discussed with respect to metabolic deregulation and conduction velocity, the details of direct channel modulation in diabetes is still unclear[254]. However, channel defectsaresome of the fundamental dysfunctions in CIPN and GBS.

In CIPN, channel toxicity is especially relevant for platinum compounds and proteasome inhibitors.Of the platinum chemotherapeutics, oxaliplatin has the largest effect on channels. Indeed, recall that oxaliplatin has two types of neuropathy: an acute as well as a more chronic form[22]. Thus far, the chronic neuropathy with numbness and functional impairmenthas been discussed. However, the acute neuropathy is characterized by transient cold hypersensitivity and parasthesias, which generally resolve on their own and do not require dose changes [22]. Acute abnormalities of nerve, hippocampal neurons, and DRG neurons are observed in vitro after just 45 minutes of oxaliplatin exposure, where sodium current is drastically increased to produce larger compound action potentials in response to

depolarization [4]. These abnormalities were abrogated with a sodium channel blocker, suggesting modification of these channels likely contribute to the abnormality [4], and the increased refractory period of the neuron suggested that it was the modification of the voltage gated ion channel inactivation, in particular, that was altered by exposure to oxaliplatin [4], with no effect on potassium channels [33]. The mechanisms of specific sodium channel sensitization remain to be elucidated, however, and a general increase in sodium current does not explain the specific cold hypersensitivity observed in oxaliplatin CIPN.

Cold hypersensitivity is instead most likely due to oxaliplatin triggered sensitivity in TRP channels, including the capsaicin receptor (TRPV1) and “cold” receptors (TRPA1 or TRPM8) [8]. While oxaliplatin fails to directly modulate these receptors, cAMP rapidly increases in concentration upon drug exposure, suggesting cAMP is a second messenger to a signaling cascade initiated by oxaliplatin that leads to TRP channel modification [8]. Additionally, Descoeur and colleagues identified two potassium channels, TREK1 and TRAAK, to be drastically reduced in expression, while the expression of two depolarizing channels, the sodium channel and hyperpolarization activated channel (HCN), were slightly elevated[75]. These changes appeared to specific for cold sensing neurons[75]. Thus, oxaliplatin treatment causes a global change in ion channel expression that leads to a higher membrane potential and, thus, more robust firing of TRP channels. Additionally, modeling experiments have suggested that the reduction in potassium current in internodal regions of myelinated axons could lead to the nerve fiber defects first observed by Adelsberger, et al with action potential trains, and thus a stronger central response following a small peripheral stimulus[78]. The acute and chronic ion changes, however, were not considered.

In addition to cisplatin, bortezomib has also been shown to interfere with ion channels. In a recent animal study with both acute (single dose) and chronic (multiple dose) administration of bortezomib, the authors found mechanical hyperalgesia and an increase in protein levels of TRPV1 in DRGs and spinal cord [201]. Interestingly, the transcript levels of TRPV1 and CGRP were reduced in these tissues, suggesting the protein levels likely increase because of bortezomib’s inhibition of the proteasome [201], thereby potentially increasing neuronal response to nociceptive stimuli.Additionally,patients treated with bortezomib had increased resting membrane potential, which would lead to increased neuronal response for a given input. This change in potential preceded axonal degeneration[176]. Degeneration was suggested by the authors to be due to energetic collapse in the axon, from mitochondrial dysfunction leading to impaired Na^+/K^+ ATPaseactivity and, thus, intraaxonal accumulation of sodium ions [176]and increased calcium influx by reversal of the sodium/calcium exchanger [233]. This influx of calcium may begin the path to apoptosis. This hypothesis remains to be tested, however.Nonetheless, channel dysfunction and changes in membrane polarization appear to be a critical mechanism for the development of hyperexcitability and acute symptoms of CIPN, especially from platinum chemotherapeutics and proteasome inhibitors.

While little work has examined the electrophysiological effect of HIV or its proteins on DRGs, there do appear to be some subtle changes. Chiefly, bothgp120 [188] and Vpr [2]have been shown to increased DRG neuron excitability, perhaps through the influx of

calcium following activation of the chemokine receptors. In macrophages, gp120 binding to chemokine receptors has been shown to directly regulate calcium, potassium, and chloride transport [148].

While channel dysfunction has not been identified as a pathogenic mechanism in HCV neuropathy, the node of Ranvieris the primary insult in GBS. Much work by Yuki and others have shown molecular mimicry between *C. jejuni* antigens and gangliosides results in immune attack of the node of Ranvier. The first clues to the pathophysiology were the association of anti-GM1 ganglioside antibodies with the AMAN form of GBS following *C. jejuni* infection[121, 296]. The presence of these antibodies predicted a reversible conduction block, believed to be due to disruption of the node of Ranvier[138, 141].The deposition of these antibodies leads to complement deposition on the axolemma [114]and, thus, disruption of axons/Schwann cell architecture at the node and paranodal regions[43], ultimately leading to disruption of ion channel organization at the node of Ranvier[235]. More specifically, antibody deposition and complement activation increases potassium current in the paranodal region and decreases sodium current in the node, thereby leading to conduction failure [239]. While this may be the mechanism of block, it does not link *C. jejuni* to the development of autoantibodies.

A key breakthrough in the understanding of the pathophysiological link between *C. jejuni* and GBS came from Yuki and colleagues when they found rabbits that were inoculated with GM1 ganglioside developed the axonal phenotype of GBS[295]. In a follow up study using this in vivo model, Yuki, et al. found the lipooligosaccharide of *C. jejuni* to be sufficient to induce anti-GM1 antibodies and paralysis consistent with GBS, and that the anti-GM1 antibodies were sufficient to induce the symptoms [294]. The findings suggest GBSis the result of molecularmimicry between *C. jejuni* antigens and host gangliosides [294]. Much like Koch’s postulatesfor infectious organisms, Ang, Jacobs, and Laman proposed a number of criteria to define molecular mimicry between pathogen antigens and host tissue as a cause of autoimmune disease [10]. These include 1. Epidemiological association between pathogen and disease, 2. Identification of antibodies against self antigens, 3. Identification of the pathogen’s antigen that elicits the self antibodies, and 4. Recapitulation of the disease in an animal model [10]. *C. jejuni* and GBS successfully filled all criteria and is thus considered to be a genuine example of molecular mimicry between a pathogen and host molecular that leads to an autoimmune disease [10]. After the identification of the *C. jejuni*/GM1 relationship, other pathogen/antigen links were identified for GBS, including anti-GD1a ganglioside [122], anti-neurofascin [76, 200] as well as antibodies against other nodal/paranodal proteins including gliomedin and contactin [76]. The motor selectivity of the AMAN subtype of GBS may be due to differential ganglioside expression between motor and sensory axons and myelin [186], with GM1 found mainly in motor myelin [187]. However, these results were challenged in a later, larger study [237], suggesting more work is needed to separate the ganglioside composition of both motor and sensory axons and myelin in both healthy controls and patients who develop GBS. Nonetheless, anti-ganglioside antibodies that interfere with the node of Ranvier appear to be common in many of the sensory and motor subtypes of GBS, with specific ganglioside targets being more prevalent in certain subtypes [236].

Thus, a variety of diseases and neuropathies are caused by only a few mechanisms: mitochondrial dysfunction and ROS, altered signaling and inflammation, and finally reduced axonal transport and channel dysfunction. While these pathophysiological mechanisms inevitably will be valuable for therapeutic design, recent advances into the downstream effectors of degeneration reveal fundamental mechanisms of axonal degeneration and promise to be essential for the development of treatments that may be applied universally to degeneration caused by disease as well as trauma.

III. NEW INSIGHTS INTO MECHANISMS OF DEGENERATION

Wallerian degeneration is the process whereby an injured axon degrades and debris is cleared to facilitate axonal regeneration and recovery. Axonal degeneration is not a passive process like a wire being broken, however. Rather, it is an active process that requires axon to soma signaling. This type of self destructive pathway is reminiscent of apoptosis, but the pathways of axonal degeneration have been shown to be independent of caspases and apoptotic signaling [97]. One can imagine this signaling may be through an active “injury” signal or the loss of a “survival” signal. Early studies suggested axonal degeneration is a result of the former case. After axotomy, there is a delayed influx of calcium with subsequent activation of the calcium activated protease calpain and other proteases that is necessary and sufficient for axon degenerationand digestion of the cytoskeleton [103, 153, 286].Interestingly, inhibition of calpain does delay Wallerian degeneration, but chelation has a much more robust effect, suggesting the influx of calcium likely has multiple roles, in addition to the activation of calpain [297]. This calcium influx marks a late step toward axonal degeneration (once proteins begin to be degraded, the process cannot be reversed), suggesting it is the result of up stream signaling, but what is this signal, and what are the components of this pathway?

A curious inbred mouse strain was reported to have delayed Wallerian degeneration where the axons in a transected nerve remained largely intact three days after injury, a time point where robust degeneration normally has begun [151].Later studies identified the mutant gene responsible for this slowed Wallerian degeneration, Wld^S,[152, 193] as a fusion ofubiquitination factor E4B (Ube4b) and Nicotinamide mononucleotide adenylyltransferase (Nmnat). The fusion protein is chiefly found in the nucleus of these animals[154], although its protective activity depends on its activity in the axon[57, 214]. The Ube4b:Nmnat fusion results in increased stability of Nmnat versus wild type Nmnat [105]. Studies in mice and drosophila have shown that the axon protective effects of the Wld^S gene product requires the activity of Nmnat[16, 215], while the Ube4b fusion allows the Wld^S gene product to bind to another protein, which may localize the protein fusion to the axon or mitochondria and/or allow it to interact with additional, unknown proteins [16]. WhileNmnat appears to be critical for axonal protection [16, 216, 298], the classic product of Nmnat reactions, NAD, is not required intracellularly for resistance to degeneration[216], despite protection from degeneration with exogenous, extracellular NAD application in vitro [267]. These data suggest that both extracellular NAD and preserved Nmnat function protect axons from degeneration but through two distinct mechanisms[216, 298]. The secondary activity of Nmnat may be chaperone activity[299]or regulation of mitochondrial metabolism[283]. Nmnat has been shown to be active within the mitochondria. Several studies have shown

Nmnat to reduce calcium spikes after axotomy[3, 15], which ties the early stages of axonal degradation signaling to the later calcium dependent phase discussed above. Additionally, the Wld^S gene product has been shown to modulate energy metabolism within the axon to maintain ATP levels following injury[221] as well as to reduce ROS production[184, 199].

This arrangement of the pathway suggests that, in contrast to the late injury signal of calcium, Nmnat may produce a survival signal that is lost during axonal injury.Indeed, when the MPTP is activated in Wld^S mice, axons degenerate, which confirms the upstream position of Nmnat to calcium signaling [21]. If Nmnat is transported throughout the axon [105], reduced transport may increase distal axon sensitivity to degeneration due to reduced Nmnat levels, tying this mechanism to the axonal transport defect pathways. Additionally, E3 ligases have been shown to balance degeneration and regeneration, where increased activity of an E3 ligase reduces Nmnatexpression, thereby initiating degeneration[18, 281], while inhibition of the proteasome system resists Wallerian degeneration [297]. Thus, Nmnat likely acts as a survival signal that is actively distributed throughout the axon. Once an axon is injured, Nmnat levels decrease, ultimately leading to calcium influx and activation of calcium dependent proteases and degradation of the axon (as reviewed in [61]). Wld^S interferes with this process by resisting decreases in NMNAT concentration.

A loss of function mutation of a component of Toll-like receptor signaling has been found to phenocopy the gain of function of the Wld^S gene product, presenting an additional therapeutic target for protection from axon degeneration. A member of the Toll-like receptor (TLR) adaptor family, SARM/MyD88-5, was first identified to negatively regulate TLR signaling [44] and to be expressed in vivo in neuronal mitochondria and microtubuleswhere it associates with JNK3 in vitro [136], a pathway known to be critical for axon degeneration[223]. SARM null mice are resistant to cell death following oxygen and glucosedeprivation, suggesting SARM, like Nmnat, may be critical for neuron degeneration and death signaling [136]. These findings were extended to axon degeneration more specifically, where SARM loss of function resulted in resistance to axon degeneration following axon transection [189] and withdrawal of trophic support in vitro [104]. SARM may also be activated by CaM kinase, linking this pathway to the calcium influx characteristic of axonal degeneration [189]. It is likely that SARM is a common pathway toward axon degeneration from various insults, as is the case with the downstream JNK signaling, which may be activated by SARM or by an additional emerging pathway involving dual leucine kinase (DLK) [170]. Thus, the axon degeneration pathway appears to contain many points of convergence such that many different types of insults may result in initiation of a common degradation pathway.

These data suggest a model of the active process of axon degradation. The balance of proteasomal degradation and active transport maintain Nmnat expression at a constant, steady state level. In the setting of an injury, either one of these processes may be affected such that Nmnat levels fall below a threshold. The decrease in Nmnat then triggers calcium influx and release from mitochondria,which activates calpain. Alternatively, calpain may be activated by SARM (which is itself stimulated by injury) with JNK signaling. Calpain then leads to protein degradation. Additionally, DLK may activate JNK in parallel to Nmnat loss or act to signal a different type of insult. Clearly, the details of the axonal degeneration

process continue to be elucidated and much work must be done to clarify how Wld^S (Nmnat), SARM, and DLK converge or diverge. Any insult that activates this pathway or modulates any of the components, as in mitochondrial dysfunction or slowed axonal transport, will lead to axonal degeneration, as is seen in diabetes, CIPN, HIV neuropathy, HCV neuropathy, and GBS (figure 2). Interestingly, Nmnat has been shown to be regulated by PKC and to modulate PARP, which links Nmnat activity to two additional points of injury in neuropathy, as discussed above [24].

IV. CONCLUSION

While a variety of insults, including diabetes, chemotherapy, HIV, HCV, and *C. jejuni* may lead to peripheral neuropathy, there are only a handful of mechanisms that cause it. These include altered metabolism, covalent modification of proteins, reduced organelle efficiency with concomitant increases inROS and RNS production, altered intracellular signaling (e.g. PKC, RAGE) and increased inflammation, reduced axonal transport, and modulation of ion channel expression and/or dynamics (figure 2). Alterations in metabolism, as seen in diabetes, may modulate the flux through different metabolic pathways with concomitant changes in reactive metabolite. Many of these mechanisms are intrinsically linked, such as slowed mitochondrial transport exacerbating the accumulation of mitochondrial mutations during the normal aging process, or the increase in ROS associated with mitochondrial dysfunction.

Downstream of the damage from the pathophysiological processes, in a paradigm reminiscent of apoptosis, degeneration occurs in an early, non-committed (“survival”) and late (“death”) stage of degeneration marked by the increasein calcium and protease activation. While the details of this processes is still being elucidated, current data suggest that withinthe axon, Nmnatacts as a survival signal that decreases during axonal injury. This fall leads to the initiation of the degeneration pathway. While the mechanism whereby Nmnat modulates downstream effectors such as calcium, its potential role in mitochondrial metabolism is particularly interesting, given the importance of this organelle to the generation of neuropathy through many diseases. The multipurpose role of Nmnat in NAD metabolism, chaperone activity, and mitochondrial function regulation suggests that it may protect different pathologies in a variety of ways, with one modality not being protective for all diseases (as proposed in [64] and observed in transection versus Charcot-Marie-Tooth disease [169]). Clearly, the protective effect of the Wld^S transgene is multifaceted and only now starting to be understood.

The promise of the$Wld^S$and SARM models of resistance of axonal degeneration in the generation of pan-disease neuroprotectants is reflected in the many experiments showing the Wld^Sgene to protect against neuropathy in a variety of diseases, including models of spinocerebellar ataxia[299], CIPN[268, 269], diabetes [278, 304], myelinopathy[212], progressive motor neuronopathy [94], Charcot-Marie-Tooth disease [169], traumatic axon injury[169, 266], and spinal muscular atrophy [169]. However, the Wld^S gene does not cure all deficits of these diseases. Indeed, Wld^S does not protect against disease onset or synapse abnormalities inthe model of spinal muscular atrophy[169], and it loses its effectiveness in protection from degeneration with advanced age [192]. While research continues to uncover

the axonal degeneration pathway, the initiating components of this pathway and how it interacts with other pathways (i.e. DLK) or components (SARM, e.g.) have still not been uncovered.

Clearly, while there are many new exciting avenues of research into the unifying mechanisms of neuropathy, and how modulation of these mechanisms may help treat or prevent neuropathy, there is still much work that needs to be done in understanding how axons become more susceptible to injury and degeneration with age, as well as what, if any, commonality there is between the pathways of development, degeneration, and regeneration (figure 2).

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ABBREVIATIONS

AGE	Advanced glycation end products
AIDP	Acute inflammatory demyelinating polyradiculoneuropathy
AMAN	Acute motor axonal neuropathy
CIDP	Chemotherapy induced peripheral neurotoxicity
ddC	2’,3’-dideoxycytidine
ETC	Electron transport chain
G6P	Glucose-6-phosphate
G6PD	Glucose-6-phosphate dehydrogenase
GBS	Guillain-Barré syndrome
HCV	Hepatitis C virus
IGF-1	Insulin-like growth factor-1
IFN-α/γ	Interferon α or γ
MPTP	mitochondrial permeability transition pore
Nmnat	Nicotinamide mononucleotide adenylyltransferase
PARP	Poly(ADP-ribose) polymerase
RAGE	Receptor of advanced glycation end products
RNS	Reactive nitrogen species
ROS	Reactive oxygen species
TLR	Toll-like receptor
Ube4b	Ubiquitination factor E4B

Wld^S Slowed Wallerian degeneration gene

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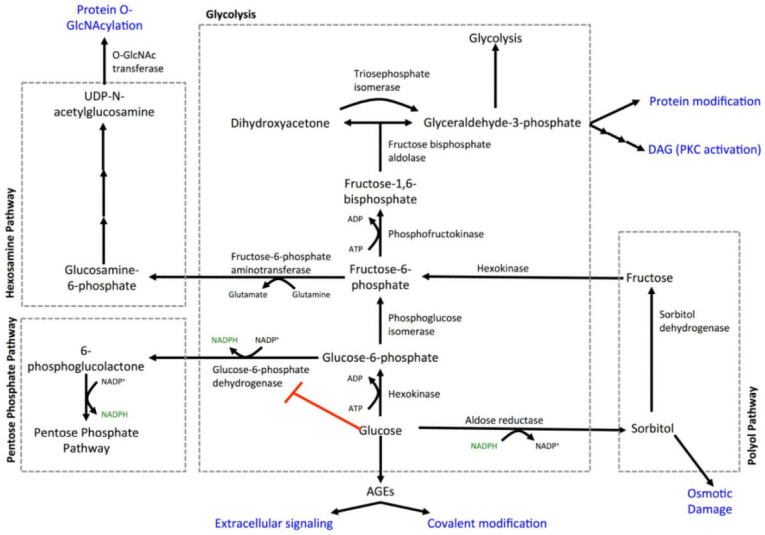

Figure 1. Summary of metabolic pathways

A variety of metabolic processes that branch off of glycolysis are dysregulated in diabetes, including the polyol, pentose phosphate, and hexosamine pathways. This dysregulation leads to protein modification, changes in extra- and intracellular signaling (effectors in blue text), and decreased antioxidant capacity secondary to reduced NADPH levels (shown in green). Red arrow indicates inhibition of the pentose phosphate pathway by elevated glucose levels.

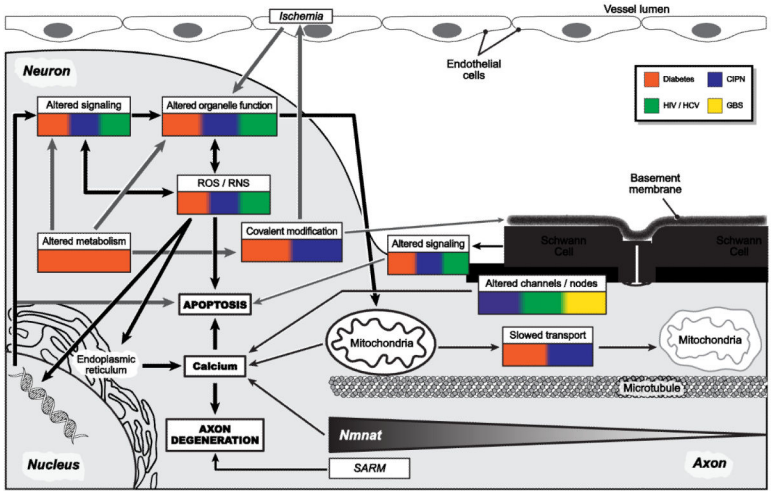

Figure 2. Summary of the mechanisms of peripheral nerve degeneration

Peripheral neuropathy in a wide range of disease, including diabetes, CIPN, viral infections, and GBS, develops as a result of the interaction of various combinations of just six processes: altered metabolism, covalent modification, impaired organelle function with ROS/RNS, altered signaling, slowed axonal transport, and altered ion channel dynamics. The figure delineates which process is active in which disease by color, as shown in the key. All of these processes interact to ultimately converge on the neuronal death and/or axonal degeneration pathways, with the major interactions outlined in the above figure. The different black, dark gray, and light gray coloring of the arrows is for clarity only.