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Minireviews

Mini-Review: Mitochondrial dysfunction and chemotherapy-induced neuropathic pain

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ABSTRACT

Chemotherapy-induced peripheral neuropathy (CIPN) is a somatosensory axonopathy in cancer patients receiving any of a variety of widely-use antitumor agents. CIPN can lead to long-lasting neuropathic pain that limits the dose or length of otherwise life-saving cancer therapy. Accumulating evidence over the last two decades indicates that many chemotherapeutic agents cause mitochondrial injury in the peripheral sensory nerves by disrupting mitochondrial structure and bioenergetics, increasing nitro-oxidative stress and altering mitochondrial transport, fission, fusion and mitophagy. The accumulation of abnormal and dysfunctional mitochondria in sensory neurons are linked to axonal growth defects resulting in the loss of intraepidermal nerve fibers in the hands and feet, increased spontaneous discharge and the sensitization of peripheral sensory neurons that provoke and promote changes in the central nervous system that establish a chronic neuropathic pain state. This has led to the propose mitotoxicity theory of CIPN. Strategies that improve mitochondrial function have shown success in preventing and reversing CIPN in pre-clinical animal models and have begun to show some progress toward translation to the clinic. In this review, we will review the evidence for, the causes and effects of and current strategies to target mitochondrial dysfunction in CIPN.

1. Introduction

Chemotherapy-induced peripheral neuropathy that leads to a long-lasting bilateral neuropathic pain state (CIPN) is a common adverse side effect that develops in patients receiving treatment with first-line anticancer drugs for breast, gastrointestinal, lung, ovarian and testicular cancers and multiple myeloma [30,93]. These agents include taxanes (e.g., paclitaxel and docetaxel) [30,93] that disrupt microtubule depolymerization [38,75], vinca alkaloids (e.g., vincristine) [30,93] that disrupt microtubule polymerization [6], platinum-based antineoplastic agents (e.g., cisplatin and oxaliplatin) [30,93] that disrupt DNA replication [43], proteasome inhibitors (e.g., bortezomib) [30,65,93] and targeted monoclonal antibody therapies (e.g., brentuximab and trastuzumab) [93]. However, despite their diverse mechanisms of action in cancer, these agents induce a somatosensory axonopathy hallmarked by reductions in the density of intraepidermal nerve fibers (IENF) of axon terminals that innervate the cutaneous layer of glabrous skin [88,102,108], which may or may not be accompanied by axonal atrophy, axonal demyelination and/or neuronal degeneration of sensory neurons in the dorsal root ganglia [7,36]. An increase in the incidence of low frequency, irregularly-patterned spontaneous discharges in the sensory neurons [100,103] also develops with this axonopathy and is thought to initiate and contribute to changes in the processing and amplification of pain sensations that lead to the transition to a chronic pain state [7,50].

Evidence over the last two decades has shown that these features are associated with abnormal and dysfunctional mitochondria in peripheral sensory neurons (Fig. 1). Mitochondria play an essential role in neuronal bioenergetics, calcium buffering, lipid and protein biosynthesis and antioxidant status that drive the health, growth and synaptic function of neurons [16,20,45]. Strategies discussed in this review that improve or prevent mitochondrial abnormalities in peripheral sensory neurons have shown effectiveness in preclinical studies in reducing pain symptoms during CIPN or preventing the development of CIPN altogether. This has led to a propose hypothesis that chemotherapeutic agents are mitotoxic in the peripheral sensory neurons and the ensuing mitochondrial dysfunction drives the development and maintenance of CIPN [7].

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2. Evidence for mitochondrial dysfunction in CIPN

2.1. Abnormal mitochondrial morphology.

A greater incidence of abnormal swollen and vacuolated mitochondria in peripheral nerve sensory axons was first noted in myelinated A-fibers and unmyelinated C-fibers in the saphenous nerves of rats treated with paclitaxel treatment prior to the development of CIPN and at peak hypersensitivity, but not during the resolution of CIPN [29]. Abnormal mitochondria have been observed in the saphenous nerves [39,41,71], sciatic nerves [99] and the sensory axons of the dorsal root [103] in rodents treated with paclitaxel. Moreover, direct paclitaxel treatment of mouse sciatic nerve explants increased axonal mitochondrial swelling as early as one day after treatment [74]. Similar increases in abnormal mitochondria have been reported peripheral sensory axons in animal models of vincristine- [15,17,104], oxaliplatin- [102], cisplatin- [61] and bortezomib- [108] induced painful peripheral neuropathy. Increased abnormal mitochondria in small distal cutaneous nerves have also been reported in skin biopsies of female non-diabetic patients receiving treatment with the microtubule-stabilizing epothilone chemotherapy, ixabepilone [25].

The occurrence of abnormal mitochondria morphologies following chemotherapeutics is largely restricted to the sensory axons [99,103] with little evidence of abnormal mitochondria associated with paclitaxel in motor axons [103], Schwann cells [99,103] or in the spinal cord [99]. This has led to the suggestion that abnormal mitochondrial morphologies are largely a sensory axon phenomenon during the development of CIPN [7]. However, increased numbers of swollen and vacuolated mitochondria have been reported in the dorsal root ganglia (DRG) cell bodies following paclitaxel [5] or cisplatin treatments [61,77] and in Remak Schwann cells during ixabepilone treatment [25].

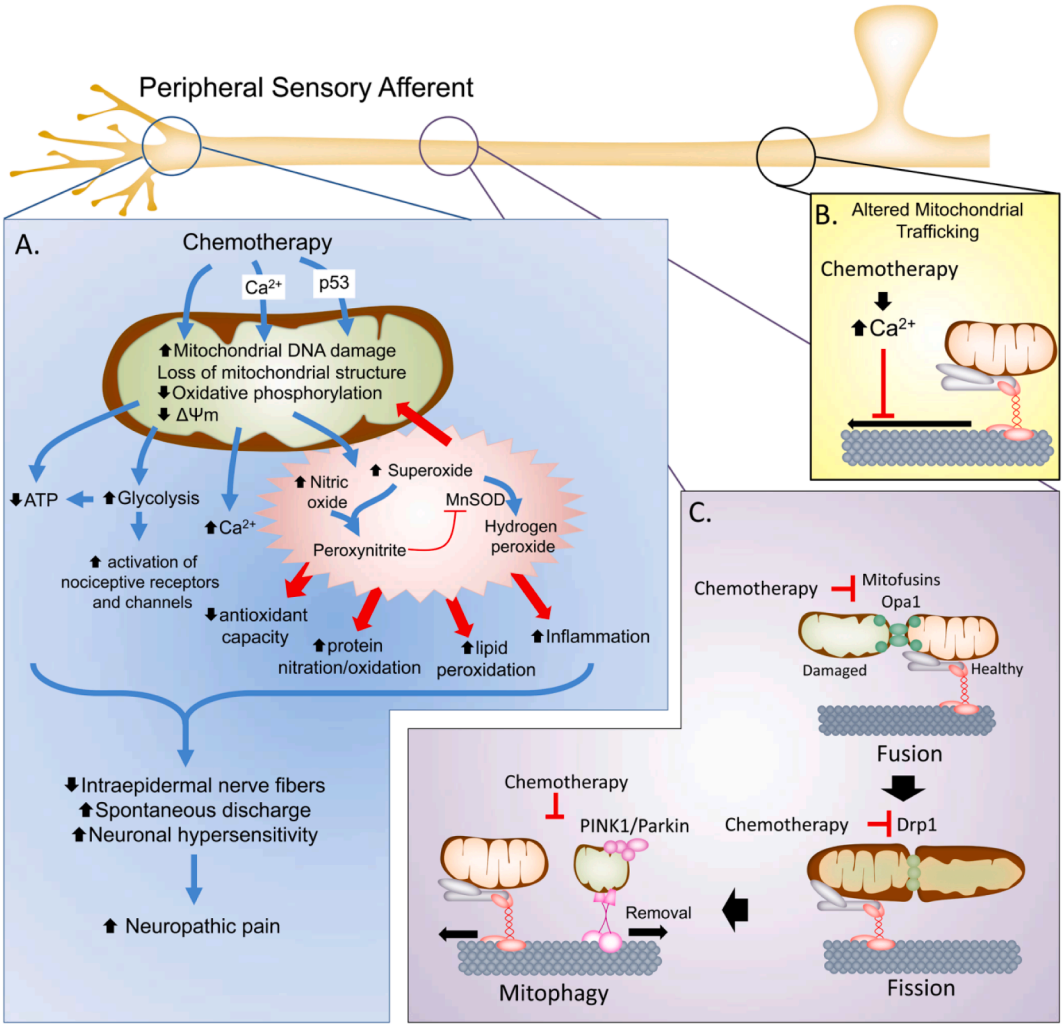

Fig. 1. Mitochondrial dysfunction in chemotherapy-induced neuropathy. A. In the peripheral sensory neurons, chemotherapeutic agents can cause direct or indirect (e.g., through Ca^{2+} influx or p53 accumulation) injury to mitochondria that include damage to mitochondrial DNA, loss of mitochondrial morphology and disruption of oxidative phosphorylation and mitochondrial membrane potential. This leads to reduced ATP production and increased reliance on glycolysis that result the net reduction of cellular bioenergetic capacity to respond to increase cellular activity and potential activation of nociceptive receptors and channels. Moreover, mitochondrial dysfunction also leads to increased production of SO and PN to drive nitroxidative stress that initiate protein, lipid and nucleic acid modifications. This reinforces nitro-oxidative stress and mitochondrial dysfunction as well as contribute to neuronal signaling pathways and inflammation. Collectively this leads to reduced axonal growth, loss of IENFs, increased spontaneous discharge and neuronal hypersensitivity that contribute to establishment of the chronic neuropathic pain state. B. Chemotherapeutics also contribute to mitochondrial dysfunction by altering the axonal transport of mitochondria to the axon terminals, depriving the axonal terminals of bioenergetics support. C. The health of mitochondria is maintained in part by mitochondrial fission and fusion processes that allow healthy mitochondria to fuse and mix with damage mitochondria, then sort the damaged areas for removal (mitophagy). In addition to altering transport, chemotherapeutics may down-regulate the expression of mitochondrial fusion (mitofusins and Opa1) and fission (Drp1) proteins to disrupt the renewal of mitochondria in the axonal terminals and prevent mitophagy resulting in the accumulation of abnormal, dysfunctional mitochondria.

2.2. Dysfunctional mitochondrial bioenergetics.

Mitochondrial swelling and vacuolization disrupts the maintenance of the proton gradient and impairs mitochondrial ATP production [31]. *Ex vivo* preparations of sciatic nerve axons from rats with CIPN following paclitaxel, oxaliplatin, or bortezomib treatment exhibited significant reductions in the oxygen consumption rates (OCR) and ATP production after maximal stimulation of Complex I-mediated and Complex II-mediated respiration prior to the development of CIPN (day 7) and lasting at least three weeks after the last dose of chemotherapy [39,103,108]. This suggested functional impairment of mitochondria during CIPN. Recent studies by Maj et al. in mice with cisplatin-induced neuropathy confirmed compromised OCR, indicating compromised respiration, in isolated DRG cells and tibia nerves at baseline, during the production of ATP and at maximal respiratory capacity [61]. The spare respiratory capacity, which indicates the ability of mitochondria to respond to energy demands, was reduced in DRG cells, but not tibial nerves [61]. That same year, Duggett et al., demonstrated DRG cells isolated from rats treated with paclitaxel had significant reductions in maximal respiratory capacity and spare respiratory capacity after paclitaxel, but only prior to the pain manifestation [23]. ATP formation and ion exchange in the mitochondria is determined by the transmembrane potential energy established by the chemical hydrogen ion gradient (ΔpH) and charge gradient (mitochondrial membrane potential; ΔΨm) resulting from the proton pumping activity of Complex I, II and IV proteins within the mitochondrial oxidative phosphorylation chain (OXPHOS) on the inner mitochondrial membrane [109]. In sciatic nerve mitochondria from rats with CIPN following oxaliplatin, protein levels and activities of the OXPHOS Complex I, II and IV were reduced and the ΔΨm and ATP production was compromised [1,3]. Similar reductions of ΔΨm have recently been reported in DRG neurons isolated from mice treated with one dose of cisplatin [61] and in segmental motor neurons of Drosophila larvae treated with cisplatin [78].

Much of a neuron's bioenergetics expenditure is in maintaining membrane potential, neurite growth and the formation and stability of synapses [84]. Impairment of mitochondrial ATP production in the peripheral sensory neurons has been posited as one mechanism by which mitochondrial dysfunction contributes to CIPN [7] (Fig. 1A). This has been supported by findings that treatments supporting mitochondrial function attenuate CIPN, whereas, mitochondrial toxins exacerbate CIPN. For example, acetyl-L-carnitine (ALCAR) administration in paclitaxel-treated rats prevents and reverses mechano-hypersensitivities [29,41]. ALCAR is metabolized in the mitochondria to yield carnitine for fatty acid transport and acetyl-CoA production to generate nicotinamide adenosine dinucleotide (NADH) for ATP production via the oxidative phosphorylation [82]. ALCAR prevented swelling and vacuolation of mitochondria in primary afferent C-fibers, but not A-fibers, in paclitaxel-treated rats [41]. ALCAR also attenuated spontaneous discharge in rats treated with vincristine- [100], paclitaxel- [100] and oxaliplatin- [102] induced peripheral neuropathy. This was accompanied by reductions of sensory axonal Complex I & II respiration and ATP production and attenuated the development of mechano-hypersensitivity in rats treated with paclitaxel, oxaliplatin, or bortezomib [107,108]. In contrast, inhibition of the ATPase with oligomycin increased spontaneous discharge in animals with CIPN following paclitaxel [101]. Moreover, nicotinamide adenine nucleotide (NAD^+) levels in the hind paw and sciatic nerves, but not the DRG, have been shown to be significantly reduced in animals treated with paclitaxel [53]. The depletion of NAD^+ corresponded with mitochondrial dysfunction, reduced IENF and neuropathic pain, which was prevented by the stimulation of the NAD^+ salvage pathway using a pharmacological activator of nicotinamide phosphoribosyl transferase (NAMPT) [53].

Other strategies that are thought to improve mitochondrial OXPHOS also show that ability to attenuate chemotherapy-induced neuropathic pain, IENF loss and spontaneous discharge. For example, deletion of the exchange factor directly activated by cyclic AMP 1 (EPAC1) prevented paclitaxel-induced reductions in mitochondrial OCR [89]. Its inhibition prevented the loss of IENF and the development of pain. The proposed mechanism of action is through EPAC1 translocation to the plasma membrane in response to increased cyclic AMP [89]. This is then thought to activate PKCε and cause its accumulation in mitochondria where it can inhibit OXPHOS [89].

The loss of mitochondrial ATP has been suggested to reduce the capacity of neurons to maintain the Na^+/K^+ ATPase to maintain membrane potential allowing a slow leak of Na^+ to trigger spontaneous discharge [7,69,102]. However, quantitative measurements of ATP in brain neurons suggests that maintaining resting membrane potential for a neuron through the Na^+/K^+ ATPase is easily maintained by ATP produced through glycolysis [81]. Oxidative phosphorylation is then stimulated by neuronal activity to meet the additional bioenergetic burden associated with maintaining synaptic integrity, organelle transport and protein synthesis [81,84]. In animals treated with repeated paclitaxel, Duggett et al., found evidence of enhanced basal glycolysis and maximal glycolytic ATP production in peripheral sensory neurons during peak pain in absence of altered respiration or respiratory capacity [23]. This suggests that sensory neurons switch from a reliance on oxidative phosphorylation to less efficient ATP production through glycolysis for their bioenergetics needs [23] (Fig. 1A). The implications of such a switch would be that glycolysis would no longer be sufficient to maintain basal Na^+/K^+ ATPase activity and facilitating spontaneous discharge as its ATP production would be directed to areas normally supplied by oxidative phosphorylation. Ludman and Melemedjian found a similar switch towards glycolysis in the DRG cells from animals with bortezomib-induced neuropathic pain [57]. However, in their model, they found that pyruvate dehydrogenase kinase 1 (PDHK1) and lactate dehydrogenase expression increased, which led to reduced pyruvate dehydrogenase-mediated conversion of pyruvate to acetyl-CoA and increased pyruvate conversion to its downstream metabolite lactate by lactate dehydrogenase [57]. Instead of CIPN being driven by a lack of ATP production due to glycolysis, they proposed that CIPN pain stemmed from the release of lactate and protons extracellular space that allowed lactate to potentiate voltage-gated sodium channels and immune signaling while the acidification of the extracellular space triggered proton-sensitive ion channels, such as acid-sensing ion channels, transient receptor potential cation channel subfamily V member 1 (TrpV1) and ATP-gated P2X receptor cation channels that have been associated with nociception [57] (Fig. 1A). To support their model, pharmacological inhibition of PDHK1 and lactate dehydrogenase attenuated spontaneous bortezomib-induced pain behaviors in mice [57].

3. Mitochondrial dysfunction and nitro-oxidative stress.

3.1. Evidence of mitochondrial nitro-oxidative stress in CIPN.

Nitro-oxidative stress is the imbalance between the production of reactive oxygen species (ROS; e.g. superoxide and hydrogen peroxide) and reactive nitrogen species (RNS; e.g., peroxynitrite) and the cellular antioxidant capacity bolstered by a number of antioxidant enzymes that include glutathione peroxidases (Gpx), catalase, cytosolic copper/zinc superoxide dismutase (Cu/Zn-SOD) and the mitochondrial manganese superoxide dismutase (MnSOD) [9,40,70,80]. This imbalance leads to uncontrolled release of ROS/RNS that can undergo oxidative, nitrosylative and nitrative reactions with proteins, lipids and nucleic acids [9,40,70,80]. Nitro-oxidative stress has been implicated in the development of CIPN (Fig. 1A). For example, increased levels of lipid peroxidation and protein oxidation products have been found in plasma, sciatic nerves and spinal cord in animals with oxaliplatin-induced neuropathic pain [21]. Increased lipid peroxidation products have also been reported in the sciatic nerve of animals with vincristine- [68], cisplatin- [85] and oxaliplatin- [2] induced neuropathic pain. The DNA oxidation product 8-OH-dG increased in animal sciatic nerve and spinal

cord with oxaliplatin treatment [21]. In neuronal cell cultures, oxaliplatin increased cellular ROS and mitochondrial superoxide production [1,3], lipid peroxidation [2] and nitrite [2] formation. Cisplatin also induced cellular and mitochondrial production of ROS/RNS in SH-5Y5Y neuroblastoma [18] and N2a cells [79]. Direct measurements of ROS/RNS are difficult to do in vivo; however, studies using indicator dyes have reported increased ROS/RNS in the DRG of animals with paclitaxel-induced neuropathic pain [24,94]. Moreover, when nitro-oxidative stress was augmented in rats using auranofin, an inhibitor of the mitochondrial antioxidant thioredoxin (Trx)-thioredoxin reductase (TrxR) system, paclitaxel- and oxaliplatin-induced neuropathic pain in rats was exacerbated [101].

Mitochondria are a major source of superoxide production, which is primarily generated by electron leak at complex I and complex III of oxidative phosphorylation chain [92]. Platinum-based chemotherapeutics form DNA adducts in nuclear and mitochondrial DNA causing intrastrand nucleotide adducts that impact protein production [49,51]. In the nucleus, these adducts can be efficiently repaired by the nuclear excision repair mechanisms [49]; whereas, little or no repair of these adducts occurs in mitochondria [49,51]. This may lead to inadequate levels of oxidative phosphorylation proteins that exacerbates superoxide production [70]. Paclitaxel also causes disruptions in the mitochondrial $\Delta\Psi m$ through changes in mitochondrial structure, mitochondrial calcium flux and/or mitochondrial permeability transition pore [13]. However, once superoxide is formed in the mitochondria, it will undergo a dismutation reaction by MnSOD to hydrogen peroxide that then oxidizes reduced glutathione via glutathione peroxidases or degraded by catalase to generate water and oxygen [37,40,59]. Reductions in the levels of glutathione have been reported in the sciatic nerve of rats with vincristine-induced neuropathic pain [68]. Once superoxide exceeds these antioxidant mechanisms, it can cause lipid peroxidation, protein and DNA oxidation or undergo diffusion-limited reaction with nitric oxide to form peroxynitrite [9,40,70,80]. Peroxynitrite will nitrate tyrosine-34 on MnSOD via a Mn-catalyzed process that reduces its activity by 80% and impairing antioxidant capacity [59,60]. In CIPN models, we have found significant increases in tyrosine nitrated MnSOD in saphenous nerves of rats treated with paclitaxel, oxaliplatin or bortezomib [39]. Reductions in MnSOD have been reported by others in the sciatic nerve of paclitaxel-treated rats and N2a cells [2]. Such reductions in MnSOD activity and other mitochondrial antioxidant systems can lead to reinforcement of superoxide and peroxynitrite formation by further impairing ATP synthesis [80] or indirectly via protein kinase C activation and subsequent triggering of the cellular nicotinamide adenine dinucleotide phosphate (NADPH) oxidase complex, which will produce a burst of cellular superoxide [4,14].

3.2. *Targeting chemotherapy-induced mitochondrial nitro-oxidative stress.*

Strategies that target nitro-oxidative stress have been successful in animal and cellular models in combating chemotherapy-induced neurotoxicity. In addition to their metabolic functions, ALCAR [97], α-lipoic acid [73], ascorbic acid [54] and α-tocopherol [54] can also act as antioxidants. Intravenous and intradermal injections of ALCAR, α-lipoic acid, or ascorbic acid dose-dependently reversed oxaliplatin-induced hyperalgesia [44]. Alpha-tocopherol and the plant-based polyphenolic flavonoid, silibinin, reduced oxaliplatin-induced lipid peroxidation and protein oxidation products in the plasma and sciatic nerves of rats and attenuated the formation of 8-OH-dG in the sciatic nerve [21]. Other studies used the mitochondrial-targeted alpha-tocopherol, MitoVitE, to attenuate paclitaxel-induced neuropathic pain [64]. Rosmarinic acid is a plant polyphenol that has can act as an antioxidant or stimulate PPARγ signaling [35]. PPARγ activation increases mitochondrial function, mitochondrial biogenesis and the transcription of a number of antioxidant enzymes through action with retinoid X receptor or by stimulating the antioxidant response transcription factor nuclear factor E2-related factor 2 (Nrf2) [48]. In N2a cells, oxaliplatin-induced lipid peroxidation and nitrite formation were reduced and antioxidant Nrf2 and MnSOD levels increased with rosmarinic acid [2]. Rosmirinic acid also improved mitochondrial function, reduced inflammation in the sciatic nerves and blocked the development of oxaliplatin-induced pain in animals [2]. However, there has been limited success thus far in human CIPN clinical trials using these approaches [83,105].

More directed antioxidant pharmacological strategies using ROS/RNS scavengers, SOD mimetics and peroxynitrite decomposition catalysts have shown success attenuating chemotherapy-induced neurotoxic effects in cellular and animal models. For example, n-*tert*-Butyl-a-phenylnitrone (PBN), a global free-radical scavenger, and TEMPOL, a non-selective nitroxyl antioxidant [67], attenuated the development of and reverse established paclitaxel-induced neuropathic pain in rats [28]. In cisplatin-treated mice, PBN attenuated reductions in conductance velocity and increases in electro-stimulated action potential in the tibial nerve [87]. The active metabolite of amifostine, WR-1065, is a ROS/RNS scavenger [32] and activates MnSOD [66]. In neurons, WR-1065 attenuated cisplatin-induced ROS, reduced neurite outgrowth and apoptosis. [79]. The SOD mimetic, MnL4, reduced superoxide production and lipid peroxidation in SH-SY5Y neuronal cells and attenuated decreased oxaliplatin-induced mechano-hyperalgesia and allodynia and cold allodynia in rats [22]. Mangafodipir, a manganese-based contrast dye, and its calcium-substituted derivative, calmangafodipir (PLEDOx), have SOD mimetic properties [12,19]. In animal models of oxaliplatin-induced neuropathic pain, mangafodipir reduced the level of oxidized proteins in the serum in mice. Both compounds prevented peripheral nerve damage and attenuated the development of mechanical and cold hypersensitivity in mice [12,19]. In Phase II trials with 22 cancer patients whose oxaliplatin-treatment was ceased due to the development of grade 2 or greater CIPN, 77% patients that resumed at least 4 cycles of oxaliplatin therapy with a cotreatment of mangafodipir showed improved pain outcomes [19]. When compared to non-responding patients, those with improved pain had reduced oxidized proteins products and increased SOD activity in their serum [19]. In Phase II clinical trials, calmangafodipir also appeared to provide favorable pain outcomes in patients with grade 2 or higher oxaliplatin-induced neuropathy [33] and is now currently in Phase III trials for CIPN (NCT03654729) [76]. In our own studies, we have found that using a compound with both SOD mimetic and peroxynitrite-decomposition catalytic activities prevented increased abnormal mitochondria in the saphenous nerves of paclitaxel-treated rats [39]. This compound also prevented MnSOD nitration and inactivation and protected ATP production in the saphenous nerves of rats treated with paclitaxel, oxaliplatin or bortezomib [39].

Other strategies attempt to address nitro-oxidative stress in CIPN by indirectly blocking the production of ROS/RNS. In DRG neurons treated with cisplatin, meclizine improved ATP production and neurite outgrowth by shifting the cells towards glycolysis and the pentose phosphate pathway to replenish depleted NADPH and antioxidant glutathione [34]. In mouse models of paclitaxel-induced neuropathic pain, matrix metalloproteases 9 (MMP9) levels increased in the DRG and intrathecal administration of a monoclonal antibody, MMP9 mAb, attenuated ROS/RNS production and stimulated Cu/Zn SOD in the DRG that resulted in reduced IENF loss and neuropathic pain [94]. The authors suggested that blocking MMP9 attenuated inflammation that then led to reduced oxidative stress [94]. However, expression of matrix metalloprotease 9 is stimulated by oxidative stress and recent work shows that oxidative stress can drive MMP9 to translocate to mitochondria and act on substrates such as connexin-43, hsp 60 and 70 and drive mitochondrial dysfunction [42]. In other studies, the Szeto–Schiller (SS) peptides, SS-31 (Elamipretide) [95] and SS-20 [96] have been shown to attenuate pain and IENF loss in mice treated with oxaliplatin. SS peptides interact with cardiolipin [10,98], which is a phospholipid of the inner mitochondrial membrane that maintains cristae structure and stabilizes cytochrome *c* for the OXPHOS [56]. Cardiolipin

peroxidation disrupts the OXPHOS, increases ROS/RNS generation, mitochondrial swelling and the release of cytochrome *c* [10,72,98]. SS-31 is in early and late phase clinical trials for cardiological, opthalmological and neurological mitochondrial diseases (NCT02805790, NCT02976038, NCT02693119 and NCT03323749).

Other studies targeting the oxidative stress-sensitive PARP/p53 pathway have also reduced mitochondrial dysfunction and nerve injury. The selective serotonin and norepinephrine reuptake inhibitor, duloxetine, attenuated peroxidation and PARP/p53-dependent apoptosis in primary DRG rat neurons after paclitaxel [55]. The p53 inhibitor, pifithrin α, in cisplatin-treated animals prevented the accumulation of p53 in the mitochondria and preserved mitochondrial membrane potential, ATP production and normal morphology in the DRG [61]. This was associated with reductions in pain and loss of IENF [61].

4. Axonal mitochondrial transport and mitochondrial dysfunction.

Axonal transport of protein, messenger RNA and mitochondria from the cell soma to the axonal end terminal and nodes of Ranvier are critical to maintaining healthy mitochondrial pools and energy supply necessary for proper neurotransmission, axonal growth and synaptic function [62,86]. Mitochondria will travel anterograde along axonal microtubules via kinesin motor complexes and anchor at a regions with high intracellular calcium concentrations detected by the Miro1 protein in the motor complex [62,86]. To maintain anchored mitochondria function in the presence of increasing protein turnover, oxidative stress and accumulation of mitochondrial DNA errors, younger mitochondria traveling along the axon will fuse their outer and inner membranes via mitofusins and Opa1 proteins with older mitochondria, mix contents and sort regions of mitochondrial damage that then are removed by mitochondrial fission processes directed by Drp1 [62]. In damaged mitochondria fractions, the PTEN-induced kinase 1 (PINK1), which is usually translocated to and sequestered within the inner mitochondrial membrane, accumulates on the outer membrane to recruit the Parkin complex and ubiquitinate the damaged mitochondrial fraction for mitophagy [62,86]. Disruption along any of these pathways leads to mitochondrial dysfunction and nitro-oxidative stress [62,86].

There is growing evidence that dysregulated mitochondrial trafficking and fission/fusion may contribute to mitochondrial dysfunction and neuropathic pain during CIPN (Fig. 1B,C). Smith et al., demonstrated that microtubule-stabilizing chemotherapeutics (paclitaxel and ixabepilone) reduced anterograde mitochondrial movement in human neuroblastoma cells and mouse sciatic nerves [91]. In mice with cisplatin-induced neuropathic pain, the levels of mitofusin-2 have been found to be reduced in both the DRG and tibial nerves; implicating reduced anterograde trafficking. Moreover, the levels of fission/fusion mRNA, *Opa1* and *Drp1*, were reduced in the tibial nerve [11]. Inhibiting mitochondrial fission with a Drp1 inhibitor was found to attenuate oxaliplatin-induced neuropathic pain [27].

In addition to abnormal trafficking and fission/fusion, mitophagy is also altered by chemotherapeutics. For example, cisplatin activated PINK1/parkin mitophagy, but blocked its late stages in PC12 cells. Reducing parkin in these cells increased cisplatin toxicity in mitochondria and drove further depletion of ATP levels; whereas increasing parkin expression increased neurite outgrowth [106]. Similar beneficial effects were observed in the *Drosophila* CIPN model when PINK1 was overexpressed [46]. Restoration of NAD^+ production by overexpressing nicotinamide nucleotide adenylyltransferase 1 (Nmnat1) restored the fission/fusion rates in DRG neurons treated with vincristine [8]. This prevented the slowing of mitochondrial velocity down the axon, mitochondrial fragmentation and neurodegeneration induced by vincristine [8].

Histone deacetylase 6 (HDAC6) deacetylates α-tubulin to destabilize microtubules necessary for mitochondrial trafficking [63,90]. The HDAC6 inhibitors, ACY-1083 [47] and ACY-1215 [58] have shown beneficial effects on mitochondrial function and CIPN in cisplatin-treated mice. ACY-1083 prevented and reversed the development of cisplatin-induced mechano-allodynia and IENF loss, while increasing mitochondrial mass and restoring mitochondrial bioenergetics in the tibial nerves [47]. Similar effects were observed with ACY-1215 [58]. This suggested that HDAC6 inhibition may have improved mitochondrial trafficking [47,58]. However, HDAC6 has a number of mechanisms that could alter the development of CIPN [52]. When HDAC6 was specifically knocked out in the DRG, it had little or no effect on CIPN [58]. When ACY-1215 was tested in Rag2 knockout mice that are T cell depleted, ACY-1215 lost its effects, suggesting that the beneficial effects of these compounds may be on inflammatory processes.

5. Conclusions and future directions.

A substantial body of evidence has accumulated over the last 30 years to suggest a vital role of mitochondria in the development of CIPN. Mitochondrial dysfunction does occur in the sensory afferents and rectifying their function improves the health, axonal growth and regulation of neurotransmission of sensory afferents to prevent and reduce peripheral and central sensitization that leads to chronic neuropathic pain. This has opened new research for novel therapeutic pharmacological approaches to treat CIPN for which there are currently limited options for clinicians and patients [26]. Moreover, several peripheral neuropathies of various etiologies (e.g., diabetes, human immunodeficiency virus and nucleoside reverse transcriptase inhibitors) share similar mitochondria defects with in the peripheral afferents [7]. Despite the rapid expansion in our knowledge of mitochondrial dysfunction and CIPN over the last decade, the limited success in clinical trials thus far for strategies that target mitochondrial dysfunction suggests that substantial gaps remain in our understanding of how chemotherapy triggers mitochondrial dysfunction and how that mitochondrial dysfunction drives CIPN. Questions as to what triggers mitochondrial dysfunction and whether these effects are due to chemotherapeutic agent on the mitochondria or due to pathological changes in the cell soma in the DRG are among the questions that still remain. Further understanding of how chemotherapeutics cause mitochondrial dysfunction and the role of mitochondrial dysfunction has on CIPN is necessary for the development of strategies to combat this devastating adverse side-effect of otherwise life-saving therapies.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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