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Review

Targeting dorsal root ganglia for chemotherapy-induced peripheral neuropathy: from bench to bedside

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Eliana Ege, Daniel Briggi, Peter Vu, Jianguo Cheng, Feng Lin and Jijun Xu

Abstract: Chemotherapy-induced peripheral neuropathy (CIPN) is a debilitating condition affecting an increasing number of cancer survivors worldwide. However, insights into its pathophysiology and availability of effective therapies remain lacking. Dorsal root ganglia (DRG) have been studied as a key component of chemotherapeutic drug toxicity and a potential therapeutic target for CIPN treatment. This comprehensive review aims to synthesize, summarize, and correlate the results of both preclinical and clinical studies relevant to the pathophysiology and management of CIPN in relation to the DRG. Design: Review. A thorough literature search was conducted using the terms 'dorsal root ganglion' and 'chemotherapy-induced peripheral neuropathy', along with appropriate variations. Searched databases included PubMed, EMBASE, Medline, Cochrane Library, Wiley Library, and Web of Science. Inclusion criteria targeted all English language, peer-reviewed original research from the inception of these databases to the present year. Review articles, book chapters, and other nonoriginal publications were excluded. Of 134 relevant studies identified, the majority were preclinical studies elucidating how various chemotherapeutic agents, especially taxanes, disrupt neurotransmission, inflammatory processes, and apoptotic pathways within sensory neurons of DRG. Not only do these effects correlate with the presentation of CIPN, but their disruption has also been shown to reduce CIPN symptoms in preclinical models. However, clinical studies addressing DRG interventions are very limited in number and scope at this time. These results reveal various pathways within DRG that may be effective targets for CIPN treatment. While limited, clinical studies do offer promise in the utility of DRG neuromodulation in managing painful CIPN. In the future, clinical trials are needed to assess interventions aimed at these neuronal and nonneuronal pathological targets to better treat this complex condition.

Keywords: chemotherapy, dorsal root ganglia, management, neuromodulation, neuropathy, pathophysiology, stimulation

Correspondence to:
Jijun Xu
Department of Pain Management and Inflammation and Immunity, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195, USA
Xuj3@ccf.org

Eliana Ege
Daniel Briggi
Department of Physical Medicine and Rehabilitation, Baylor College of Medicine, Houston, TX, USA

Peter Vu
Department of Physical Medicine and Rehabilitation, University of Texas Health Science Center at Houston, Houston, TX, USA

Jianguo Cheng
Department of Pain Management, Cleveland Clinic, Cleveland, OH, USA

Department of Neuroscience, Cleveland Clinic, Cleveland, OH, USA

Feng Lin
Department of Inflammation and Immunity, Cleveland Clinic, Cleveland, OH, USA

Introduction

Chemotherapy-induced peripheral neuropathy (CIPN) is a common complication of antineoplastic treatment affecting more than half of the 28 million cancer survivors in the United States.[1–3] Symptoms typically include sensory changes, impaired motor function, and neuropathic pain in the distal parts of the limbs. CIPN can occur in up to 80% of patients receiving chemotherapy.[4] Symptoms may persist in 60% of patients at 3 months after treatment and in 30% at 6 months and beyond.[5] These symptoms often limit the dose or even lead to discontinuation of chemotherapy, resulting in suboptimal cancer treatment. Long-term functional impairment from chemotherapy can also significantly reduce

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quality of life.[6] As the number of cancer survivors increases worldwide, understanding and mitigating these effects become increasingly critical.

Current therapeutic alternatives for the management of CIPN are far from satisfactory. There is a lack of evidence-based treatment and no Food and Drug Administration (FDA)-approved therapy for CIPN, in part due to the limited understanding of its pathophysiology. Numerous pathophysiological mechanisms have been proposed for commonly implicated chemotherapeutic agents, which include taxanes, platinum-based agents, alkylating agents, vinca alkaloids, proteasome inhibitors, and immunomodulators.[7] These agents interact with deoxyribonucleic acid (DNA), mitochondria, ion channels, and inflammatory pathways that induce axonal degeneration and peripheral neuropathy.[8] A common target of toxicity among these agents are the dorsal root ganglia (DRG), which are responsible for the transmission of sensory input and pain signals from the peripheral to the central nervous system (Figure 1).[9] Due to a lack of protection by the blood–brain barrier and the high permeability of surrounding capillaries,[10] DRG are particularly vulnerable to chemotherapy drug penetration and toxicity. Given that drug–ganglia interactions are central to CIPN, understanding them is essential in developing effective treatment options.

Neuromodulation through electrical stimulation and targeted drug delivery has proven effective in a variety of neuropathic pain conditions.[11–15] It has also been proposed as a treatment modality for CIPN.[16,17] We have recently reported that

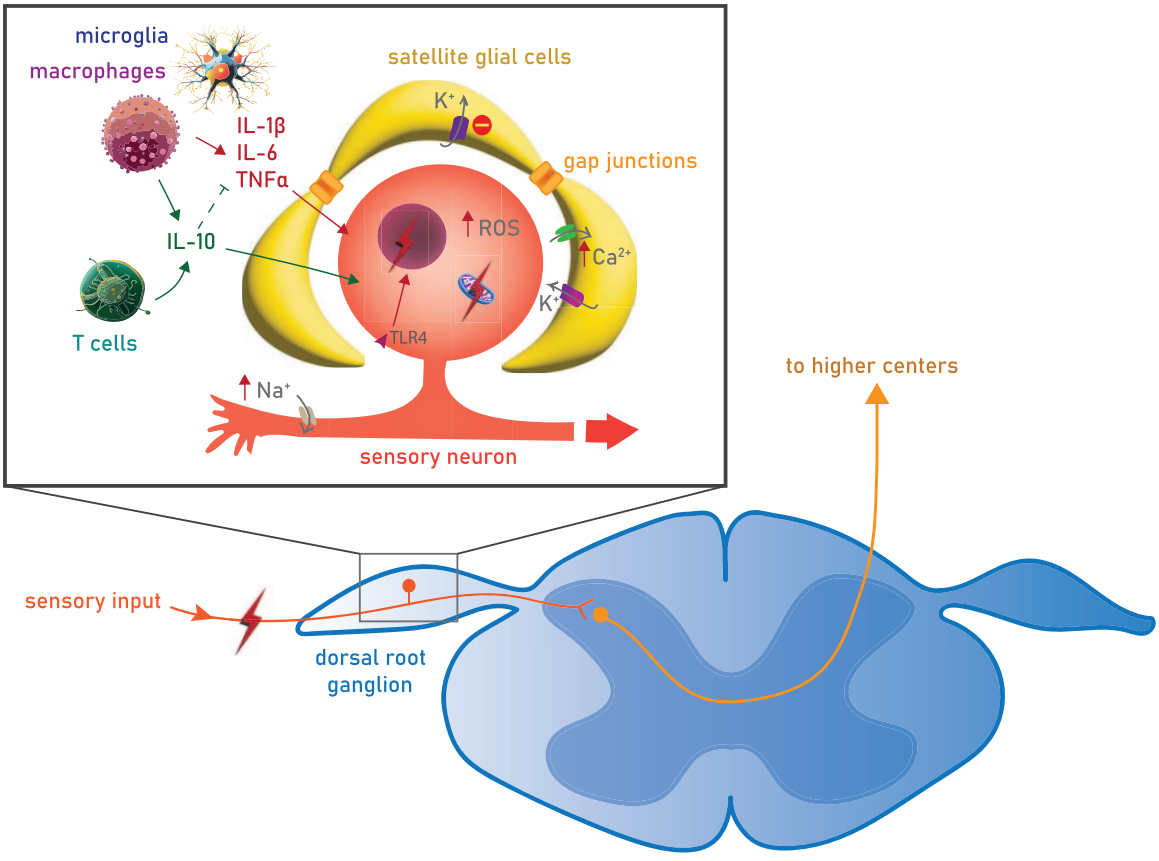

Figure 1. Chemotherapeutic insults affect sensory transmission through the dorsal root ganglia of the spinal cord through the involvement of microglia and immune cells, as well as the modification of various ion channels and inflammatory pathways. Neuronal damage is indicated by the red lightning strike. Proinflammatory processes are shown in red and anti-inflammatory processes are in green.
ROS, reactive oxygen species; TLR4, Toll-like receptor 4; TNF-α, tumor necrosis factor alpha.

dorsal root ganglion stimulation (DRG-S) could have potential for meaningful symptom relief in patients suffering from CIPN,[18] indicating that DRG could be a therapeutic target for CIPN. This review aims to synthesize, summarize, and interpret the results of preclinical and clinical research related to the role of DRG in CIPN as an effort to guide future research and management strategies for this debilitating pain syndrome.

Methods

A thorough literature search was conducted using the terms 'dorsal root ganglion' and 'CIPN', along with appropriate variations and corresponding Boolean operators. Searched databases included PubMed, EMBASE, Medline, Cochrane Library, Wiley Library, and Web of Science. Inclusion criteria targeted all English language, peer-reviewed abstracts, and original research from the inception of these databases to the present year (September 2023). Review articles, book chapters, and other nonoriginal publications were excluded. Multiple database queries and article back searches were conducted to identify relevant literature and experimental findings. All results and relevant references were reviewed by the authors and included as appropriate.

Results

Our literature search yielded 1159 articles, from which 134 relevant studies were identified (Figure 2). The majority (111) were preclinical studies related to the mechanisms and management of CIPN, while the rest consisted of clinical reports.

Pathophysiology of CIPN

There is an increasing body of evidence supporting DRG as a critical pathophysiology hub and therapeutic target in animal models of CIPN. This evidence emerges from studies focusing on a variety of chemotherapeutic agent classes, particularly taxanes.

Taxane-induced CIPN. Taxanes are common first-line solid-tumor chemotherapies that inhibit microtubule–tubulin disassembly.[19] The two most widely used, and implicated in CIPN, are paclitaxel and docetaxel.[20] The prevalence of taxane-induced CIPN is as high as 90% in taxane-treated patients on standard chemotherapy doses (300 mg/m^2 for paclitaxel and 100 mg/m^2 for docetaxel) or accumulated doses (exceeding 1400 mg/m^2).[6,19] Taxane-induced neuropathy, particularly with paclitaxel, has been linked to pathological changes in ion channels, inflammatory responses, intracellular signaling, transcription factors, and mitochondrial oxidative stress within the DRG.[21]

Neuronal damage and hypersensitivity. Treatment with taxanes can lead to direct damage to the primary sensory neurons in the DRG. DRG neurons show early signs of injury after paclitaxel treatment in rats.[22] The pathophysiological changes in the DRG include the upregulation of activating transcription factor 3 (ATF3, a marker of cell injury/regeneration), macrophage hyperplasia/hypertrophy, and satellite cell hypertrophy.[22] Paclitaxel's toxic effects on DRG neurons result in the enlargement of neuronal cell bodies and a reduction in the neurite length,[23,24] upregulation of pronociceptive ion channels, mitochondrial damage, and reactive oxygen species (ROS) formation.[4,25]

Paclitaxel treatment has been shown to upregulate transient receptor potential channels [TRPV1,[26,27] TRPA1 (transient receptor potential ankyrin-1), and TRPV4[28]] in DRG neurons, promoting the release of tumor necrosis factor-α (TNF-α) from immune cells and glial cells to mediate mechanical and cold allodynia in rats. Biochemical analyses of DRG showed that epigenetic modulation is involved in the paclitaxel-induced *TRPV1* gene expression and neuropathic pain in rats.[29] Blocking TRPV1, TRPV4, or TNF-α signaling, in turn, reduces paclitaxel-induced pain.[30] Paclitaxel also increases the expression of voltage-gated sodium channels (Nav1.7) in rats and human DRG neurons.[31] Recent live imaging studies demonstrated that paclitaxel enhances vesicular trafficking and surface expression of Nav1.7 in the cell bodies of DRG neurons.[32] The upregulation of Nav1.7 in DRG neurons and its expression in the cell bodies contribute to ectopic spontaneous activity, which can be blocked by Pro-TX II, a selective Nav1.7 inhibitor.[31] *In vitro* treatment of paclitaxel on human DRG primary culture increased Nav1.7 expression, transient sodium currents, and action potential frequency in small DRG neurons.[33] Epigenetically, the repression of DRG Nav1.7 using the adeno-associated virus intrathecal

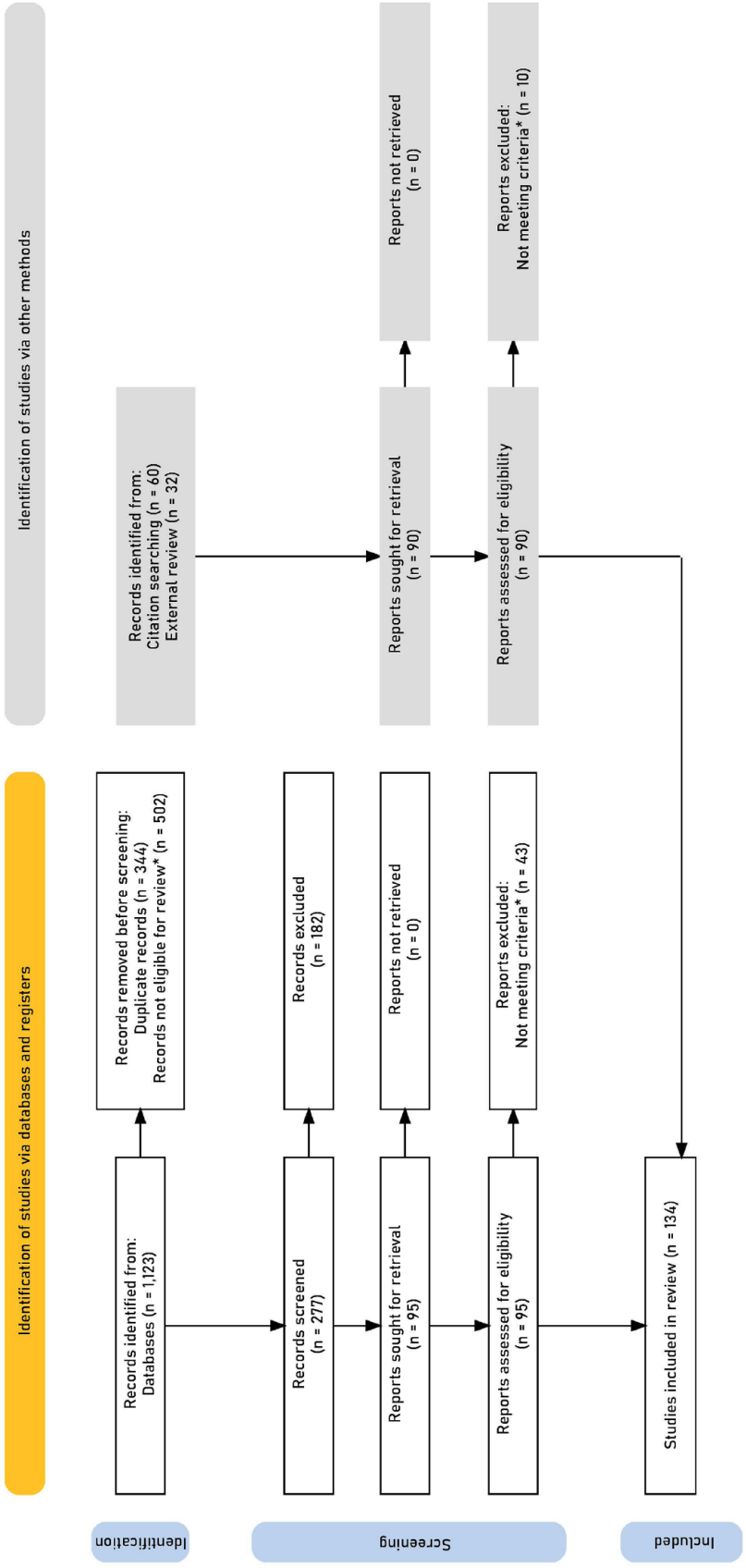

Figure 2. This flow diagram details our search strategy.
*Records were excluded if they were not in English, not peer-reviewed, not original research (e.g. reviews), or not focusing on DRG as a primary target of toxicity or treatment in the context of CIPN.
CIPN, chemotherapy-induced peripheral neuropathy; DRG, dorsal root ganglia.

delivery approach demonstrated effective and long-lasting reduction of tactile allodynia mediated by paclitaxel without changes in normal motor function in mice.[34] Paclitaxel-induced transcriptional downregulation of potassium channels in mouse DRG neurons also contribute to membrane depolarization and increased excitability of nociceptors, and consequently the development of pain.[35] Furthermore, the paclitaxel-induced increase in current in the calcium channels of DRG neurons may lead to increased pain in rat models of CIPN.[36,37]

In addition to these changes in ion channels, paclitaxel also induces swelling and vacuolation of sensory axonal mitochondria that are thought to contribute to CIPN. In a long-term longitudinal study in a rat model of paclitaxel CIPN, axonal degeneration or dysfunction of axonal microtubules was not observed.[38] Instead, the mitochondrial abnormality resulted in a chronic axonal energy deficiency that likely caused the CIPN symptoms.[38,39] Oxidative stress from chemotherapy is known to induce mitochondrial damage, which in turn amplifies oxidative stress.[40] These damages may lead to neuronal apoptosis, neuroinflammation, and finally neurodegeneration.[40] Studies using DRG neuronal cell lines and a phenotypic drug screening approach have identified ethoxyquin and its novel derivatives as a potential neuroprotective therapy for CIPN in rodents without affecting paclitaxel's antitumor effect.[41]

Neuroimmune interactions. Neuroimmune interactions have also been identified as critical mechanisms for CIPN.[42] Paclitaxel binds to Toll-like receptor 4 (TLR4),[27] activating a proinflammatory intracellular signaling pathway *via* nuclear factor kappa B (NF-κB) and increasing inflammatory cytokine production. Blocking TLR4 signaling can reduce paclitaxel-induced CIPN.[43] We found that complement C3, a key component in innate immune response, is essential in paclitaxel-induced neuropathic pain.[44] We further demonstrated that blocking the anaphylatoxin C3a receptor (C3aR1) proinflammatory signaling could reduce CIPN by suppressing DRG neuronal hypersensitivity.[28] Paclitaxel-induced changes in inflammatory markers and mediators have also demonstrated influences on DRG-mediated mechanisms of CIPN. In mouse models, paclitaxel has been shown to promote CIPN *via* proinflammatory markers such as interleukin-1 beta (IL-1β), IL-6, and TNF-α, while suppressing anti-inflammatory factor IL-4 in DRG.[45,46] Resveratrol improved the paclitaxel-induced pain symptoms in rats by increasing IL-10 and decreasing IL-1b.[47]

Nonneuronal cells in the DRG also play an important role in CIPN. Satellite glial cells (SGCs) are glial cells that closely envelop sensory neurons, and represent the largest glial population in the DRG.[48] DRG SGCs play an important role in neuropathic pain by increasing gap junction coupling[49] between SGCs and by augmenting neuronal activity.[50,51] Activation and gliosis of SGCs were reported in multiple studies of paclitaxel CIPN.[22,49,52,53] A recent single-cell RNA sequencing study identified enriched expression of the tissue inhibitor metalloproteinase 3 (TIMP3) in SGCs, which was decreased after paclitaxel treatment. Intrathecal treatment with recombinant TIMP3 reversed mechanical allodynia in both *Timp3* knockdown mice and in wild-type mice treated with paclitaxel.[54]

Macrophage infiltration in the DRG is another key process in the development of CIPN.[55,56] Upregulation of markers such as matrix metalloproteinase-3, which recruits and activates macrophages and ROS in DRG neurons, was noted in rat models with paclitaxel-induced neuropathy.[57] One particular role attributed to macrophages is the release of proinflammatory markers, sensitizing the DRG and invoking neuropathic pain.[58] In addition, macrophage infiltration has been implicated as an upstream mechanism in the necroptosis of DRG neurons, which has been linked with the development of paclitaxel-induced peripheral neuropathy.[59] Paclitaxel induced the release of high-mobility group box 1 (HMGB1) from macrophages to mediate CIPN through the ROS/p38 mitogen-activated protein kinases (MAPK)/NF-κB/histone acetyltransferases (HAT) pathway.[60] We found that blocking complement C3aR1 signaling could suppress the expansion of both CCR2+ and CX3CR1+ macrophages in DRG after paclitaxel treatment.[28]

Besides macrophages, T lymphocytes also contribute to CIPN.[61] Paclitaxel induces a significant increase in the percentage of CD3+ T cells in mouse DRG.[62,63] Flow cytometric analysis revealed that the majority of T cells in the DRG were CD8+ T cells.[63] CD8+ T cells may play

different roles in the development and resolution of CIPN. An early study reported that adoptive transfer of proinflammatory CD8+ T cells exacerbated neuropathic pain, whereas adoptive transfer of anti-inflammatory Treg cells or intrathecal injection of CD8-neutralizing antibody reduced pain hypersensitivity.[64] A more recent study reported that paclitaxel-induced mechanical allodynia was prolonged in T cell-deficient (Rag1(−/−)) mice.[63] Adoptive transfer of either CD3+ or CD8+ T cells to Rag1(−/−) mice normalized resolution of CIPN. Paclitaxel also increased DRG IL-10 receptor expression, an effect which required CD8+ T cells.[63] Both T cell receptor and co-stimulator signals are required for T cell activation. Intrathecal injection of the inducible co-stimulatory molecule agonist antibody to activate DRG T cells has been shown to facilitate the resolution of paclitaxel-induced mechanical hypersensitivity by increasing IL-10 expression in the DRG of female mice.[62]

Signal transduction in the DRG. Intracellular pathways, transcription factors, and mitochondrial damage in cells of the DRG appear to play significant roles in the pathophysiology of CIPN.[65] Activated intracellular pathways, such as protein kinase A, protein kinase B, protein kinase C, protein phospholipase C, phosphoinositide 3-kinase (PI3K), and proteinase-activated receptor 2, could induce hyperalgesia in paclitaxel-treated mice.[66,67] The calcium ion is the main secondary messenger that mediates depolarization and synaptic activity of a neuron. An increase in cytosolic calcium can lead to membrane excitability, release of neurotransmitter, and excitotoxicity.[68,69] Intrathecal administration of drugs that decrease the extracellular and intracellular availability of calcium could ameliorate taxane-induced mechano-allodynia and mechano-hyperalgesia in rodents.[70] However, Boehmerle *et al.*[71] found that paclitaxel-induced calcium oscillations were independent of extracellular and mitochondrial calcium but dependent on the interaction of a paclitaxel binding protein, neuronal calcium sensor 1 (NCS-1), with inositol 1,4,5-trisphosphate receptors (IP_3R). The interaction of NCS-1 with IP_3R and aberrant calcium signaling can be inhibited by lithium, a mood stabilizer that could prevent paclitaxel-induced peripheral neuropathy in rodents.[72,73] Role of IP_3R has also been indicated in paclitaxel-induced axonal degeneration. Paclitaxel treatment significantly reduced ATP-evoked IP_3R-mediated calcium release in DRG neurons. Paclitaxel causes degeneration by reducing the synthesis of Bclw, a Bcl2 family member that binds to axonal IP_3R and prevents axon degeneration.[74]

Transcriptome analysis has demonstrated that crosstalk between neuroactive ligand-receptor and cytokine–cytokine receptor plays a critical role in the dysregulation of neuronal function in the DRG.[65] Paclitaxel increases the expression of pERK, pp38, C–C chemokine ligand 2, TLR4, MyD88, and IL-6 in primary rat DRG cultures.[75] Other pathways involving Wnt/β-catenin signaling, TLR4, and receptor-interacting protein kinase 3/mixed-lineage kinase domain-like protein have been found to influence the mediation of neuropathic pain in paclitaxel-treated rats.[43,59,76–78] Transcription factors such as nuclear factor erythroid 2-related factor 2 have shown a significant antioxidant role in the DRG, but are actively suppressed by paclitaxel.[79] Transcriptome profiling has revealed long noncoding RNAs and mRNAs that impact immune and inflammatory responses to induce neuronal apoptosis, contributing to CIPN.[80] A similar pathway linked to a mitochondrial etiology of CIPN is the sirtuin 1/peroxisome proliferator-activated receptor gamma coactivator 1-α (PGC-1α) pathway. The use of resveratrol has been demonstrated to prevent paclitaxel-induced mitochondrial damage and apoptosis by the PI3K and PGC-1α signaling pathways.[47]

CIPN induced by other agents. Animal models of CIPN induced by several other chemotherapy agents have been used to study the mechanisms and potential therapeutic strategies. In this section, we review evidence from studies focusing on platinum-based agents, vinca alkaloids, proteasome inhibitors, immunomodulators, and alkylating agents.

Platinum -based agents. Platinum-based chemotherapeutic agents, such as oxaliplatin and cisplatin, have generally been used to treat solid-based tumors, including lung, breast, ovarian, colorectal, and testicular cancer.[81] The anticancer activity of platinum-based agents is believed due to their interaction with DNA.[82] Platinum agents form DNA–platinum interstrand crosslink compounds that interfere with tumor cell proliferation *via* DNA inhibition.[19] These chemotherapeutic agents have been associated with high rates of

CIPN, affecting 70–92% of patients treated with these medications.[83] Cumulative doses of cisplatin as low as 350–600 mg/m^2 could produce CIPN, with higher doses resulting in worse symptoms.[84] For oxaliplatin, CIPN has been found with doses starting at 540 mg/m^2.[85]

Platinum-based agents have been associated with CIPN mechanisms similar to those of taxanes.[86] Sensory neuronal cells and mitochondria in the DRG are the main target for neurotoxicity induced by these agents.[87,88] Novel *in vitro* assays have been developed to mirror *in vivo* pathways in DRG explants to better elucidate toxic processes.[89] Postulated mechanisms of injury involve channel-based, proinflammatory, and apoptotic pathways.

Oxaliplatin has been reported to induce CIPN by downregulating Kv4.3 potassium channels and A-type potassium currents, disrupting nerve depolarization, and elevating nerve excitability.[90] Similarly, it was found to increase sodium current and compound action potentials through voltage-gated sodium channels within DRG.[91] Oxaliplatin-induced cold hyperalgesia has been identified as a downstream effect of calcium influx *via* L-type calcium channels through the transient receptor potential melastatin 8 pathway.[92] Cisplatin was also shown to upregulate N-type voltage-gated calcium channels in rat DRG, leading to thermal and mechanical hyperalgesia even in the absence of structural cell damage.[93–95]

The effects of ion channel disruption parallel the influence of inflammatory mediators and biochemical pathways in the presentation of CIPN. Activation of proinflammatory markers and macrophages by TLR4 cascade signaling creates a positive feedback loop, further increasing inflammatory mediators and ROS in the DRG.[96,97] Similar to taxanes, oxaliplatin activates SGCs and increases gap-junction-mediated coupling of SGCs in the DRG.[49] Platinum-induced proinflammatory molecules, such as IL-1β, IL-6, and TNF-α, accelerate inflammatory DRG neuron destruction, thereby promoting CIPN.[98] Recent studies have shown that CD8+ T cells alleviate CIPN induced by cisplatin *via* an increase in the expression of IL-10 receptors in the DRG.[99] Adoptive transfer of CD8+ T cells facilitates resolution of cisplatin-induced mechanical allodynia and spontaneous pain. Interestingly, the effect of CD8+ T cells requires *in vivo* exposure ('education') of these cells to cisplatin.[99]

Cellular uptake of platinum derivatives in the DRG has been considered vital in understanding CIPN development.[86] Accumulation of these platinum DNA adducts inhibits DNA repair pathways, inducing apoptosis and damaging DRG to induce CIPN.[100,101] Apoptosis of neuronal and glial cells in the DRG *via* oxidative stress-activated caspases and mitogen-activated kinases have also contributed to platinum-induced CIPN.[102] These apoptotic pathways are postulated to be induced by MAPKs, which activate p38 and ERK1/2 pathways to further promote neuronal DRG death and resultant neuropathy.[103] *In vitro* studies have also suggested that oxaliplatin-induced oxidative stress can destroy neuronal DRG bodies.[104] Organic cation transporter 2 (OCT2), which facilitates oxaliplatin accumulation in these neurons, has been implicated in increasing oxidative stress and inhibiting neurite regrowth.[89,105] Inhibiting this mechanism through agents such as l-tetrahydropalmatine and duloxetine has been demonstrated to reduce oxaliplatin uptake in DRG and attenuate peripheral neurotoxic effects.[106,107]

Vinca alkaloids. Among vinca alkaloids, vincristine is the most likely to induce dose-dependent CIPN compared to its counterparts: vinblastine, vinflunine, and vinorelbine.[108,109] The incidence and prevalence of CIPN after treatment with vinca alkaloids have been reported at 17.5% and 91%, respectively, with symptoms often continuing beyond 12 months post-cessation.[110] This group works by manipulating microtubule assembly and mitotic spindle formation, disrupting and inhibiting cell structure and cytoskeleton axonal transport.[111] This mechanism of action has a direct influence on CIPN, with obstructed neural axoplasmic transport inducing nerve failure and fiber apoptosis *via* organelle axonal accumulation, length-dependent nerve conduction inhibition, and disrupted neuronal growth and swelling.[112,113] The tubular mechanism also disrupts mitochondrial membrane structure and excitability, vacuolating channels and pores to disrupt mitochondrial concentration gradients and electron transport chains, especially with calcium ion gradients.[70,114] Studies have shown that the acute exposure of isolated sensory neurons to vinca alkaloids results in CIPN by generating a TrpA1-dependent depolarizing sodium current to increase the excitability of the sensory neurons. The hypersensitization to painful stimuli in response to the acute exposure to vinca alkaloids

is reduced in TrpA1-mutant flies and mice.[115] Other biochemical enzymatic pathways, such as SARM1, have mediated vinca-induced axonal destruction.[116] Mice deficient in SARM1 are protected from vincristine-induced neuropathy (VIN).[116] In addition, similarly to other chemotherapeutic agents, vinca alkaloids can increase inflammatory markers (TNF-α, IL-1β) and cells (macrophages) that promote CIPN symptoms.[117]

Proteasome inhibitors. Proteasome inhibitors are commonly used for the treatment of multiple myeloma and certain types of lymphoma. Common proteasome inhibitors include bortezomib, ixazomib, and carfilzomib.[118] With bortezomib, 31–37% of patients in phase II trials have been diagnosed with CIPN[119]; the incidences of CIPN in ixazomib and carfilzomib are significantly less.[120,121] As with other chemotherapies, dosage and duration greatly affect CIPN symptoms.[122] This group of agents induces the accumulation of abnormally folded proteins by inhibiting the β proteolytic tubulin subunits of proteasome, resulting in cellular apoptosis.[123] Similar to taxanes and vinca alkaloids, bortezomib has been shown to influence tubulin function, microtubule stability, and structural dynamics of neurons, resulting in axonopathy and axonal degeneration in the DRG.[124,125] Chronic treatment with bortezomib induced a marked upregulation of ATF3 in most DRG neuron nuclei as well as damage of sensory neurons and satellite cells.[126] This is further explained by long neuritic processes susceptible to insults and axonal transport disruption in the DRG of rat models of bortezomib-induced neuropathy.[127] Additionally, ion channels, especially calcium, are deranged by bortezomib, leading to caspase activation, membrane potential disruption, and eventual neuronal apoptosis.[128] Further studies have also shown direct peripheral nerve fiber insults and swelling *via* mitochondrial damage and energy disruption induced by bortezomib treatments.[129] Inflammatory activation of cell signaling cascades *via* NF-κB, TNF-α, sphingosine-1 phosphate, and dihydrosphingosine-1-phosphate in dorsal horn neurons have demonstrated similar CIPN mechanisms and presentations as other chemotherapeutic agents.[130–132]

Immunomodulators. The immunomodulatory agent most commonly associated with CIPN is thalidomide, with 25–75% of patients diagnosed in relation to dose and severity.[133] In many cases, a minimal 200 mg/m^2 daily dose with a cumulative dose of 20 g can result in CIPN symptoms.[134] Its mechanism of action is poorly expounded, however, with few studies elucidating its pathophysiology.[135] Current hypotheses have centered on the inhibition of TNF-α and NF-κB to accelerate DRG hypoxia *via* neurotrophin blockade.[136] Its antiangiogenic effect *via* fibroblast growth factor and vascular endothelial growth factor blockade also influence tumor and CIPN presentations *via* further neuronal cell death.[136]

Alkylating agents. Alkylating agents, such as cyclophosphamide, nitrosoureas, procarbazine, and thiotepa, rarely cause CIPN.[8] The alkylating agent most likely to produce CIPN is ifosfamide, at about 8% of cases; however, its mechanism and effect on the DRG are poorly studied to date.[7,137,138]

Management of CIPN

At present, there are no medications recommended by the American Society of Clinical Oncology for the prevention of CIPN. Out of numerous alternatives purported both for preventative and therapeutic use, duloxetine is the only agent that has established efficacy for the treatment of painful CIPN, and even then with limited benefit.[139] While many preclinical studies have proposed pharmacological approaches targeting the various affected pathways within the DRG, clinical evidence remains lacking. An alternative treatment strategy that may simultaneously target more mechanisms, DRG neuromodulation, has also been explored in both preclinical and clinical settings.

Pharmacological therapies

Preclinical studies. The majority of preclinical research on DRG-focused management of CIPN involves pharmacologic interventions. Many cellular mechanisms have been targeted in preclinical models, including drug transport, neuronal degeneration and apoptosis, oxidative stress, and channel dysfunction.

One preventative strategy has been to limit the accumulation and direct neurotoxicity of chemotherapeutic drugs within DRG neurons. For instance, tyrosine kinase inhibitors such as nilotinib and dasatinib may be able to block anion and cation transporters, such as OCTs, to inhibit drug accumulation without affecting antitumor efficacy.[4] Ethoxyquin may prevent paclitaxel- and

cisplatin-induced axonal degeneration *via* heat shock protein 90 (HSP 90) modulation without compromising antitumor effects.[140] In addition, agents such as fingolimod and nicotine that have downstream inhibition of NF-κB may be able to prevent and treat CIPN associated with different chemotherapeutic classes by preventing neuronal apoptosis.[4] However, these effects remain to be demonstrated clinically.

Other agents have been proposed to target oxidative stress. Carvedilol, which has been studied a cardio-protective drug in cancer patients, has also been shown to reduce mitochondrial superoxide dismutase expression in rat DRG, consequently attenuating oxaliplatin-induced sensorimotor deficits.[141] The neurohormone melatonin prevented the loss of antioxidant enzymes and expression of proinflammatory cytokines in human colon cancer cell lines treated with oxaliplatin and prevented neuronal apoptosis through the LC3A/3B pathway in rat DRG, preventing cold and mechanical allodynia and hyperalgesia.[142,143] The reversal of these symptoms with melatonin was also demonstrated in paclitaxel-treated rats.[144]

Finally, given their ubiquitous role in chemotherapeutic toxicity, several drugs have targeted ion channels. Carbamazepine and arylsulfonamides, which are sodium channel antagonists, have been demonstrated to reverse hyperalgesia in preclinical models.[91,145] Multiple calcium channel blockers, such as verapamil, nifedipine, diltiazem, and mexiletine, have also been reported to inhibit L-type calcium channels and nuclear factor of activated T-cell translocation in DRG and oxaliplatin-induced cold hyperalgesia in animal models.[89,92] Unfortunately, none of these drugs are supported by clinical evidence at this time.

Clinical studies. A small number of DRG-targeting pharmacological agents have been tested in the clinical setting with variable results on CIPN. For instance, calmangafodipir, which mimics manganese superoxide dismutase, is known to reduce ROS and hyperalgesia in rat models.[146] One double-blinded randomized controlled phase II trial showed that calmangafodipir significantly reduced sensory disturbances in patients with colon cancer treated with oxaliplatin.[147] However, in two subsequent international trials studying this population (POLAR A and M), calmangafodipir actually exacerbated CIPN incidence, likely due to redox interactions between the metal cations.[148,149]

More promising evidence has emerged with glutathione and its precursor *N*-acetylcysteine, which can increase antioxidant activity and downregulate proinflammatory (e.g. IL-1b and TNF-α) and apoptotic (e.g. p53) pathways in animal models of platinum-induced CIPN.[150,151] Some randomized controlled trials have reported subjective neuroprotective effects of these agents when administered along with platinum drugs.[152–154] However, no objective benefits were shown in nerve studies, and some trials reported conflicting results.[155]

Lithium, which is known to interfere with IP3R and aberrant calcium signaling in rat DRG, was associated with a decreased incidence of CIPN in cancer patients in a retrospective study.[156] However, a double-blinded randomized clinical trial showed that, compared to placebo, 300-mg lithium once daily for 5 days was not effective in preventing CIPN in breast cancer patients.[157] A larger phase II trial using lithium to prevent paclitaxel-related neurological side effects is underway.[158]

Interventional therapies

Preclinical studies. DRG interventions targeting CIPN include DRG stimulation (DRG-S) and ablation, which may be able to modulate multiple neurotoxic mechanisms co-occurring within DRG. In contrast to pharmacological evidence, our literature search yielded no preclinical studies evaluating the use of DRG-S or radiofrequency ablation for CIPN. Two related publications evaluated the effectiveness of focused ultrasound ablation for VIN in rodent models.

In their 2018 publication, Youn *et al.*[159] applied internal high-intensity focused ultrasound (HIFU) therapy to exposed DRG of VIN rats. Rodents in the treatment group received ultrasound therapy to the left L5 DRG at 3 W for 3 min at 11 MHz, pulsed at 38 Hz with a period 90 ns and a width of 13 ms. Utilizing von Frey Fibers (VFF) to evaluate innocuous mechanical thresholds, Randall–Selitto testing for noxious mechanical thresholds, and hot plate testing (HPT) for thermal mechanical thresholds, the authors noted significant reductions in mechanical allodynia as well as mechanical and thermal hyperalgesia with HIFU therapy. Histological

evidence of transient cellular edema was found within the HIFU-treated group, though this was diminished 48 h after treatment. The first of its kind, this study revealed the potential for neuromodulation targeting the DRG in chemotherapy-induced neuropathy.

In a similar 2020 publication from the same group of authors, internal or external low-intensity focused ultrasound (LIFU) (2.5 or 8 W, respectively) was evaluated as a treatment for VIN in rats.[160] VFF were again used to evaluate mechanical nociceptive thresholds, and HPT to evaluate thermal nociceptive thresholds. Mechanical and thermal thresholds were significantly improved in both internal and external treatment groups. Internal LIFU did not result in histological evidence of edema but did result in significant increases in mechanical and thermal nociceptive thresholds. Interestingly, VFF nociceptive thresholds also increased in the untreated right hind paw following internal LIFU, and though the significant ipsilateral threshold changes had been observed to be similar between internal and external LIFU treatment groups, only the internal LIFU treatment group was found to have significant contralateral sensory threshold improvement. External LIFU resulted in a less rise in mean temperature. This study, in redemonstrating the potential for DRG-targeted neuromodulation in VIN, also suggests that benefit may be realized with contralateral improvement and without the histological changes accompanying HIFU.

Clinical studies. Clinical evidence on the efficacy of neuromodulation in treating CIPN also remains lacking.[16] At present, published research on the use of DRG-S and ablation for CIPN consists mostly of case reports. Our literature search yielded a total of 10 reports representing eight unique cases (Table 1)[161–170] and one retrospective study describing 9 additional cases.[18]

The isolated cases included patients of both genders, with ages ranging from 23 to 63 years old. Where specified, DRG-S leads were placed anywhere from L3 to S3, with half of the cases reporting multiple levels. Pain reduction with DRG-S ranged from 50% to 100%, with a maximum follow-up of 36 months. Pain reduction with the single case of DRG radiofrequency ablation was described as good but transient, worsening after 8 months. Additional outcomes with DRG-S included improvements in standing tolerance, pain-free-walking distance, mood, sleep, and phantom limb pain. Complications included dorsal lead migration and S1 nerve root compression in separate cases, both of which required subsequent revision.

More recently, we published the only retrospective review available on this topic describing nine patients who underwent DRG-S for CIPN.[18] This study demonstrated significant reductions in pain scores after DRG-S trial and implantation for up to a year of follow-up. Reported improvements also included reduced sensory symptoms, improved mobility, and decreased pain medication burden within the first year. No complications were reported.

Discussion

The results of this literature review highlight several important themes among existing studies on the role of the DRG in the development and management of CIPN. Nearly all agents known to cause CIPN have been shown to induce neuronal damage and cell death within the DRG, resulting in sensory disturbances and neuropathic pain in various *in vivo* models. Some classes of chemotherapeutics, such as platinum agents, have been reported to increase apoptosis of neuronal and glial cells within the DRG directly through DNA damage, axonal destruction, and oxidative stress. Others, such as taxanes and immunomodulators, appear to induce neuronal hypoxia and necroptosis *via* downstream effects of macrophage infiltration and inflammatory pathways. Moreover, similar to other peripheral neuropathies, the increases in inflammatory mediators and decreases in anti-inflammatory mediators and antioxidants in the DRG appear to contribute to the pathophysiology of CIPN. Importantly, the disruption and reversal of many of these processes has shown the potential to reduce CIPN symptoms and increase analgesia in animal models.

Taxanes, platinum-based agents, vinca alkaloids, and proteasome inhibitors have also been implicated in dysregulation of sodium, potassium, and calcium channels within the DRG, resulting in hyperexcitability in pain signaling in both rats and humans. Through complementary effects on ion channels, receptors, and neurotransmission, the increased depolarization and spontaneous activity in injured DRG neurons are imperative

Table 1. Summary of case reports on the use of DRG interventions for CIPN.

Author	Patient age (years)	Patient gender	Chemotherapy	Modality	Pain reduction	Follow-up (months)	Other outcomes
Chapman[161]	52	Female	Cyclophosphamide, thalidomide	DRG-S	VAS 8/10 to 1/10	5	Improvements in standing tolerance, EQ-5D, SF-36
Finney[163]	47	Male	Oxaliplatin	DRG-S	50%	1	NR
Grabnar[164]	50	Female	NR	DRG-S	100%	36	NR
Rao[165]	53	Male	NR	DRG-S	75% with trial	NR	S1 nerve root compression requiring device replacement
Sindhi[166]	23	Male	Rituximab	DRG-S	60%	5	Dorsal migration of leads requiring revision
Yelle[167]	49	Female	Rituximab	DRG-S	>60%	NR	Increased pain-free walking distance, improved mood, improved sleep
Ahmadi[168]	61	Female	NR	DRG-S	75% with trial	NR	Improved phantom limb pain
Yadav[169]	63	Male	Docetaxel	DRG RFA	'Good'	8	Pain worsened after 8 months

CIPN, chemotherapy-induced peripheral neuropathy; DRG-S, dorsal root ganglion stimulation; EQ-5D, EuroQol-5D; NR, not reported; RFA, radiofrequency ablation; SF-36, Short Form 36; VAS, Visual Analog Scale.

to the progression and persistence of CIPN. Again, the disruption of these toxic effects has been reported to reduce neuropathic symptoms *in vivo*. This suggests that targeting these pathways may be key to developing effective therapies for CIPN.

While neuroprotective agents have been trialed in preclinical studies, the multimodality of chemotherapeutic toxicity and the sheer amount of involved pathways make it difficult to treat CIPN with targeted drug therapy. Pharmacological interventions that block specific processes only have partial protective effects and have demonstrated conflicting results in clinical trials.[4] Though such agents may eventually play a role in the prevention and even management of subclasses of CIPN, there currently remain no FDA-approved therapies and only one general anti-neuropathic drug recommended for this condition. Given the availability of minimally invasive interventions such as neurostimulation and neuroablation, this offers promise in the possibility of managing CIPN symptoms through the modulation of multiple pathways at the level of the DRG.

When exploring the management of CIPN through neuromodulation of DRG, existing studies have addressed three potential modalities: ultrasound therapy, DRG-S, and radiofrequency ablation. The two animal experiments studying the use of HIFU and LIFU on the DRG of vincristine-induced rodents found significant increases in mechanical and thermal nociceptive thresholds, one even noting sensory improvement on the nontreated side. In humans, case reports and the single retrospective study on DRG-S demonstrated improvements in pain scores as well as other functional measures related to CIPN. Overall, though limited in scope, these results suggest that interventional treatments targeting the DRG carry promise in the management of CIPN.

While these findings are promising, the true therapeutic potential of DRG modulation in the management of CIPN remains underexplored. A notable limitation to this literature review is the relatively small number of studies published on this topic, especially in the clinical space. The low level of evidence on therapeutic modalities, such as DRG-S, ablation, and ultrasound therapy, makes it difficult to draw conclusions on their efficacy at this time. Furthermore, the majority of the reviewed publications are animal studies that may have limited applicability to human subjects. While human DRG show overall similar immunoreactivities for pain-related molecules to those of laboratory animals, they do differ in aspects such as neuronal size, electrophysiology, and expression of channel proteins and receptors.[9] These differences and the lack of subjective feedback (e.g. pain scoring) further amplify the need for better clinical research studying human responses.

In the future, investigators should explore potential therapies through larger studies designed specifically to evaluate their effects on the physiologic mechanisms and symptoms associated with CIPN. When applicable, randomized, controlled, prospective study designs should be utilized. Clinically under-explored modalities such as ultrasound stimulation deserve further consideration in human populations, and more widely used treatments such as DRG-S deserve more rigorous evaluation in patients with CIPN. Alternative modalities, such as rhizotomy and radiofrequency ablation of the DRG, are also being trialed in similar populations, including patients with cancer pain.[170] Given the mechanistic evidence supporting DRG-targeted therapies in the treatment of peripheral neuropathy, such interventions should be further considered in cancer survivors suffering from refractory CIPN symptoms.

Conclusion and perspectives

CIPN remains a pressing challenge in cancer chemotherapy. The National Cancer Institute's Symptom Management and Health-Related Quality of Life Steering Committee has prioritized CIPN for translational research.[171] Numerous animal studies have targeted neuronal and nonneuronal (SGCs, macrophages, and T cells) pathological mechanisms in DRG to reverse or prevent CIPN. However, there is a paucity of clinical trials studying therapies that pursue these mechanisms. Because the DRG are a major target of neurotoxicity caused by multiple chemotherapy agents, DRG neuromodulation warrants further exploration for the management of persistent CIPN that has not responded to conventional therapies.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Author contributions

Eliana Ege: Conceptualization; Data curation; Investigation; Methodology; Project administration; Supervision; Visualization; Writing – original draft; Writing – review & editing.

Daniel Briggi: Data curation; Investigation; Methodology; Writing – original draft.

Peter Vu: Data curation; Investigation; Writing – original draft.

Jianguo Cheng: Conceptualization; Funding acquisition; Investigation; Resources; Writing – review & editing.

Feng Lin: Conceptualization; Funding acquisition; Investigation; Resources; Writing – review & editing.

Jijun Xu: Conceptualization; Data curation; Funding acquisition; Methodology; Project administration; Resources; Supervision; Writing – original draft; Writing – review & editing.

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Competing interests

The authors declare that there are no competing interests.

Availability of data and materials

Figures and tables are available for use with written permission from the corresponding author by reasonable request.

ORCID iD

Eliana Ege https://orcid.org/0000-0003-4928-4051

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