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Mechanisms involved in the development of chemotherapy-induced neuropathy

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SUMMARY

Chemotherapy-induced peripheral neuropathy (CIPN) is a debilitating and painful condition seen in patients undergoing treatment with common agents such as vincristine, paclitaxel, oxaliplatin and bortezomib. The mechanisms of this condition are diverse, and include an array of molecular and cellular contributions. Current research implicates genetic predispositions to this condition, which then may influence cellular responses to chemotherapy. Processes found to be influenced during CIPN include increased expression of inflammatory mediators, primarily cytokines, which can create cascading effects in neurons and glia. Changes in ion channels and neurotransmission, as well as changes in intracellular signaling and structures have been implicated in CIPN. This review explores these issues and suggests considerations for future research.

Keywords

chemotherapy; cytokine; glial cells; ion channels; neuropathy; neurotransmission

Chemotherapy-induced peripheral neuropathy (CIPN) is a frequent side effect for many of the most common cancer treatments and is characterized by paresthesia, dysesthesia and often pain, primarily in the hands and feet. Patients most often report sensory symptoms of numbness and tingling, followed by symptoms described as burning, shooting, throbbing and stabbing. All of these symptoms are also associated with diminished ability to detect touch and pinprick sensations as well as sensorimotor impairment [1]. These sensory changes can be debilitating to the extent that a reduction in the dose of therapy given to a patient is required. For example, a recent report found that 17% of patients receiving the

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chemotherapeutic agent paclitaxel required a dose reduction because of CIPN, and such dose reductions have been linked to poorer survival rates [2].

The occurrence of CIPN has been studied for decades and is commonly associated with well-known anticancer drugs. Those therapies most likely to produce CIPN include cisplatin [3] oxaliplatin [4,5], vincristine [6,7], paclitaxel [8] and bortezomib [1]. Each of these agents works to kill cancerous cells in differing ways and produces various rates of CIPN. To illustrate, approximately 40% of patients receiving cisplatin or paclitaxel will experience CIPN, whereas an estimated 80% of patients undergoing treatment with oxaliplatin will report extreme sensitivity to cold [9]. The occurrence of CIPN is generally related to dosing, both in the amount of drug administered and in the number of administrations, and to various risk factors such as diabetes or a history of smoking.

Unfortunately, these symptoms may persist beyond treatment. One report demonstrated that CIPN following paclitaxel or vincristine administration lasting longer than 3 months became chronic. For this cohort of patients, the average time with neuropathy was 5 years, and their pain was poorly managed by current treatments, including opiates [10]. As would be expected, these symptoms significantly reduce quality of life [11]. These factors bolster the need to better understand the mechanisms driving the development of CIPN.

Chemotherapy treatments result in numerous changes to cellular structure and function, including loss of sensory terminals in the skin, and alterations of membrane receptors, intracellular signaling, neurotransmission, excitability and metabolism all of which can negatively influence neuronal and glial cell phenotypes, thereby contributing to CIPN (Figure 1). This complexity has hindered a unified understanding of the specific mechanisms underlying this condition. As a step toward formulating a unifying hypothesis, the scope of this review is to inform the reader of the major biological factors involved in effects of chemotherapy on the nervous system that contribute to CIPN.

Genetic influences

With the growing trend of personalized medicine, recent studies have turned toward understanding CIPN from a pharmacogenomic perspective. This approach would potentially allow practitioners to identify patients who carry genetic variations that would increase their risk of chemotherapy-related side effects such as CIPN and modify treatment as necessary. Multiple studies, with each generally focusing on one type of cancer and treatment, have investigated the relationship between single nucleotide polymorphisms (SNPs) and CIPN risk. A concise review of the genes and SNPs that have been implicated as potentially predictive for CIPN was recently published [12]. Unfortunately, the results from these studies have not always been reproducible. For example, many studies have investigated the *GSTP1* gene. Earlier reports found that polymorphisms in this gene were related to survival outcomes in cancer [13] making it a viable candidate for pharmacogenomics research. While some have indeed found an association between *GSTP1* polymorphisms and CIPN [14], just as many have failed to find a relationship (c.f. [15]), even when controlling for ethnicity, type of cancer and primary treatment. That being said, this line of investigation warrants more research because most studies have focused on genes involved in cancer rather than on

genes likely to contribute more specifically to neuropathy. Some recent studies have shown predictive validity when studying the contribution of SNPs to CIPN. For example, patients undergoing treatment with oxaliplatin had five SNPs identified that predicted CIPN development with 72% accuracy [16]. Others extended these predictive findings to additional polymorphisms found in Charcot-Marie-Tooth disease genes [17]. The genes that were found to be significantly associated with CIPN were related to myelinating Schwann cells (periaxin), nerve conduction velocity (Rho guanine nucleotide exchange factor 10) and tachykinin peptide production (tachykinin precursor 1). This line of research is promising, but future studies will need to elucidate how these mutations influence CIPN development. This is especially important in light of research demonstrating that survival rates are reduced by treatment modifications.

Neuronal alterations associated with CIPN

Much of the research on the mechanisms of CIPN has focused on alterations produced by chemotherapy drugs on neuronal properties, including altered ion channel responses and activation or modification of intracellular signaling pathways.

• Altered activity & expression of voltage-gated ion channels in CIPN

As Na^+ entry into a neuron is usually the primary cause of excitation and depolarization, it is not surprising that changes in the behavior of voltage-gated sodium channels have been found in CIPN. For example, a major metabolite of oxaliplatin, oxalate, can produce prolonged opening of voltage-gated Na^+ channels, leading to altered thresholds and ectopic firing in diverse neurons [18,19]. Consistent with the possibility of enhanced activity in sodium channels (or depressed activity in potassium channels) increased peripheral axonal excitability precedes symptom expression in patients [20,21]. Interestingly, voltage-gated sodium channel blockers, such as the anticonvulsant carbamazepine, have shown some success in treating neuropathy in people [22], although not all clinical studies have supported the effectiveness of this approach [23].

Potassium channel changes in CIPN have been proposed at various levels of the nervous system. Cortical level K^+ channels were down-regulated in rats treated with oxaliplatin, an effect the authors proposed contributes to the ongoing nature of CIPN [24]. Primary afferent fibers also exhibit decreased expression of various potassium channels in both oxaliplatin [25] and paclitaxel models of CIPN [26]. These changes result in a more depolarized resting membrane potential, leading to hyperexcitability in nociceptors and could be related to the development of spontaneous activity in DRG neurons in CIPN rats [26]. Interestingly, both of these studies also found increased expression of hyperpolarization-activated channels (HCNs) permeable to both K^+ and Na^+ , which are known to increase nociceptor excitability and spontaneous firing in other pain conditions [27]. A simulation study has shown that oxaliplatin-induced decreases in potassium channel function and increases in sodium channel function can account for the observed nociceptor hyperexcitability [28]. In support of these findings, use of a voltage-gated K^+ channel opener, retigabine, to encourage neuronal hyperpolarization has been found to be effective in a mouse model of cisplatin neuropathy [29].

Calcium is an important contributor to CIPN in numerous ways. Voltage-gated calcium channels are essential for nociceptive signal transmission, and appear to contribute to CIPN as well. Increased levels of voltage-gated calcium channel mRNA have been reported in DRG following paclitaxel treatment in mice [30], and administration of drugs that interfere with the function of voltage-gated calcium channels, such as gabapentin and ethosuximide, reduced paclitaxel- and vincristine-induced reflex hypersensitivity in rodents [31,32].

• Alterations of neurotransmission in CIPN

Numerous studies have documented alterations in processes involved primarily in neurotransmitter signaling following chemotherapy treatment. 5HT_{2A} knockout mice failed to develop vincristine-induced mechanical hyperalgesia, and rats exposed to vincristine had increased expression of this receptor in the spinal cord [33]. Similar results have been obtained for vincristine-induced neuropathy in mice lacking serotonin transporters [34].

Glutamate signaling is also altered in CIPN. Pharmacological inhibition of glutamate production by blocking the enzyme glutamate decarboxypeptidase (which hydrolyzes the peptide N-acetyl-aspartyl-glutamate to release glutamate) improved nerve conduction deficits and reversed morphological alterations in DRGs associated with CIPN following cisplatin, paclitaxel and bortezomib [35]. Administration of an mGluR5 antagonist reversed bortezomib-induced reflex hypersensitivity and nerve conduction deficits [36]. Furthermore, as glutamate is an excitatory neurotransmitter, its clearance from the synapse prevents excitotoxicity, and reduced clearance by astrocytes can lead to increased responses of spinal neurons to nociceptive input [37]. Bortezomib-, paclitaxel- and vincristine-induced hyperalgesia in the rat have all been associated with decreased expression of the glutamate transporter GLAST in spinal astrocytes [38,39]. Given that spinal neurons show pronounced after discharges that appear to be related to the downregulation of glutamate transporters and that similar changes in spinal neuron physiology are observed in vincristine – and cisplatin-induced neuropathies [40,41], downregulation of glutamate transporters may be a common mechanism across CIPN subtypes.

Changes to other neurotransmitter systems have been also observed in animal models of CIPN, including decreased spinal mu-opioid receptor activation by the endogenous ligand, endomorphin-1 [42]. It was proposed that the resulting effect is due to an indirect loss of inhibitory GABA signaling that could be differentially reversed by oxycodone, but not morphine [35]. Unfortunately, clinical use of an array of opiate analgesics does not adequately treat CIPN [10]. Altering levels of endocannabinoids may prove useful in CIPN treatment. Endocannabinoids are broken down by fatty acid amide hydrolase (FAAH), and blocking this enzyme to increase endocannabinoid levels can reverse cold and mechanical sensitivity [43] and decrease C-fiber sensitization in a cisplatin model of CIPN [44]. Recently, translational research aimed at augmentation of signaling by A₃ adenosine receptors has been suggested as an effective treatment for paclitaxel-related CIPN [45].

• Alterations of transient receptor potential channels in CIPN

The transient receptor potential (TRP) channels are a large family of nonselective cation channels. The TRP vanilloid (TRPV) family has been the most widely studied with regard to

pain. TRPV1, the capsaicin receptor, is located on a large subset of nociceptors and plays important roles in sensory transduction and primary afferent sensitization. This channel can be activated in numerous ways, including by various exogenous vanilloid chemicals (e.g., capsaicin, resiniferatoxin) as well as by protons, heat greater than 42°C, and diverse endogenous lipid signals associated with inflammation [46]. Predictably, the sensation evoked by these stimuli when applied to skin is perceived by humans as a burning sensation [47]; but surprisingly is perceived as deep aching pain following intramuscular administration [48,49]. Notably, CIPN patients complain of both these symptoms [1,10]. Indeed, recent evidence indicates that activation of TRPV1 during chemotherapy sensitizes pain pathways. The expression of TRPV1 is increased in rat DRG following paclitaxel administration at a time point corresponding to the onset of thermal hyperalgesia; and use of TRPV1 antagonists in a rodent model reduced heat hypersensitivity [50]. Increases in TRPV1 expression in murine DRG and spinal cord have also been observed following bortezomib [51] and cisplatin treatments [52].

TRPA1 is often colocalized with TRPV1 and can be activated by diverse noxious chemicals including formalin, allyl isothiocyanate and acrolein; and by cold temperatures ($< 17^{\circ}\text{C}$) under some conditions [53]. Oxaliplatin produces a robust sensitivity to cold in most patients, and based on animal studies indicating that TRPA1 channels respond to noxious cold [54], it was assumed that this channel was responsible for this effect. Indeed, studies reported that oxaliplatin-induced sensitivity to cold in animal models was TRPA1 dependent [55,56]. This conclusion was also drawn for paclitaxel-induced cold allodynia [57]. However, recent research has proposed a species-dependent activation of this channel, wherein noxious cold activates TRPA1 in rodents but not humans [58], thereby limiting the potential translational impact of TRPA1 channels as cold sensors. Yet, the possibility remains that TRPA1 may be involved in the induction of long-lasting sensitization of nociceptors during chemotherapy. Ongoing CIPN may be supported by sensitization of TRPV1, TRPV4 and TRPA1 channels by enzymes (protein kinase A, protein kinase C epsilon, phospholipase C) activated by proteinase-activated receptors (PARs) after chemotherapy [59].

Finally, less studied, but also a potentially important modulator of CIPN is the TRPM8 channel. The TRPM8 channel is activated by mild cool stimuli between 25 and 28°C and chemically by menthol [60] and has been implicated as analgesic when activated in some nerve injury models [61]. An analgesic effect of topical menthol has also been reported in paclitaxel-related CIPN patients [62].

• Intracellular signaling pathways associated with CIPN

Activation of protein kinases and caspases occurs during various forms of cellular stress and in response to growth factors and cytokines. Activation of these enzymes can result in mitochondrial damage and apoptosis in neurons and glial cells.

Caspase signaling is thought to contribute to CIPN via its relation to mitochondrial damage and observed DRG cell loss. Animal models indicate that paclitaxel activates the caspase 10 pathway, leading to mitochondrial damage and subsequently to the generation of reactive oxygen species (ROS), as well as potential apoptosis of the neuron [63]. Caspase signaling

was also found to contribute to cisplatin and oxaliplatin neuropathy in rats, with activation of these pathways caused by mitochondrial ROS production [64]. Caspase inhibitors reduce vincristine-induced reflex hypersensitivity in the rat [65] and prevent oxaliplatin-induced DRG cell loss [66].

Activation of protein kinase pathways, especially kinases in the MAPK family, can further contribute to cellular damage. Cisplatin and oxaliplatin activate p38 MAPK and Erk1/2 to promote apoptosis in DRG neurons [67]. A follow up study by this group replicated kinase activation changes and further reported a protection against this apoptosis by NGF [68]. Activation of these pathways influence a number of downstream events that could further promote CIPN, including cytokine release and damage to cellular structures.

Changes to intracellular structures associated with CIPN

Damage to glial and neuronal mitochondria as a result of chemotherapy has been the focus of much of the recent research on CIPN. Some rodent studies have reported swollen and vacuolated mitochondria and or impaired mitochondrial function following treatment with paclitaxel [69–71], oxaliplatin [71,72] and bortezomib [73]. Acetyl L-carnitine (ALCAR) has been reported to improve mitochondrial function following chemotherapy and became a promising avenue of CIPN therapy, with several studies in animal models reporting resolution of chemotherapy-induced mechanical and thermal hyperalgesia [74–77]. Initial clinical trials showed promise with ALCAR [78,79] but, unfortunately, subsequent trials found that ALCAR not only fails to have a significant ameliorating effect [80], but can actually worsen CIPN [81]. Thus, it remains unclear whether the clinical trial results negate the hypothesis of a central role of mitotoxicity in the pathophysiology of CIPN.

Oxidative stress is both a catalyst for and a product of mitochondrial distress. Bortezomib can induce reactive oxygen species (ROS) to produce mitochondrial dysfunction [82]. Paclitaxel can also increase mitochondrial production of ROS, which can sensitize TRPA1 channels to enhance thermal sensitivity in rodents [83]. As mentioned previously, mitochondrial-released ROS can then activate apoptotic and proinflammatory pathways, contributing to chronic CIPN. Further evidence for a role of ROS in CIPN was the finding that administration of ROS scavengers alleviates paclitaxel-induced mechanical hyperalgesia [84,85]. Peroxynitrite, a powerful oxidant and nitrating agent produced by ROS, has been proposed as a potential therapeutic target for ameliorating CIPN based on translational work in rodents [86].

Damage to DNA, due to direct effects of chemotherapeutics on neurons as well as ROS production during mitochondrial distress, has been strongly implicated in CIPN [87]. Cisplatin and oxaliplatin produce DNA adducts, leading to neuron death [62]. Apurinic/aprimidinic endonuclease/redox effector factor (APE1), an enzyme which contributes to DNA repair, has been implicated as a potential therapeutic target for CIPN. Decreased expression of APE1 is associated with increased nociceptive responding following cisplatin and oxaliplatin, and enhancing the activity of this enzyme protected against cisplatin-induced neurotoxicity of cultured neurons [88].

Other cellular components can be damaged in CIPN. Bortezomib and cisplatin can damage organelles, such as lysosomes and endoplasmic reticulum in neurons [89,90] and Schwann cells [91]. Many of the common chemotherapeutics target microtubules in cancer cells to prevent cellular division, and binding of these drugs to neuronal microtubules has been suggested as contributing to CIPN [92–94]. Axonal transport in peripheral nerves is in fact impaired following treatment with vincristine and paclitaxel [94,95]. However, neither oxaliplatin nor bortezomib bind to microtubules when used to produce cancer cell death, yet both still produce a robust neuropathy in a clinical population [1,92]. Interestingly, both bortezomib and oxaliplatin inhibit axonal transport like the antimicrotubule agents [96,97]. Suppression of axonal transport may therefore be induced by a mechanism other than interaction with microtubules for the latter two agents; and potentially this alternate mechanism also contributes to suppression of axonal transport with other chemotherapeutics.

Loss of intraepidermal nerve fibers & Meissner's corpuscle during CIPN

The cumulative effect of the above mechanisms appears to result in a loss of intraepidermal nerve fibers (IENFs) and Meissner's corpuscles (MC) that appear in areas of skin where patients experience their most severe symptoms of CIPN. The observed loss of MCs explains the decreased touch perception of CIPN patients [1]. Paclitaxel [98], oxaliplatin [99] and bortezomib [1] produce IENF loss at a time that corresponds to the peak of CIPN symptoms in humans and in animal models. Although the specific mechanisms driving this loss of IENF are unclear, similar findings are also seen in other diseases that result in painful neuropathy, such as HIV and diabetes [100,101]. Interestingly, prevention of IENF loss by the tetracycline derivative, minocycline, which reduces neuroinflammation, also protects against neuropathy produced by oxaliplatin [99] and paclitaxel [98] in animal models of CIPN. Similarly, interventions directed at the suppressing CCL2, a chemokine prominently involved in proinflammatory responses in dorsal root ganglia that are evoked by chemotherapy treatments, blocked both the behavioral signs of CIPN as well as reduced distal IENF density in rats [102].

Glial cell function

Much of the research on CIPN has focused on neuronal changes; however, the contributions of glial cells should not be overlooked. Changes to Schwann cells in the periphery, satellite cells in the DRG and astrocytes in the spinal cord seem to be an important component of CIPN. As noted above, inhibition of astrocyte glutamate transporters may be a common mechanism among chemotherapeutics in producing CIPN. But there are several other possible mechanisms where glial cells may play roles in the pathophysiology of CIPN. For example, following cisplatin or paclitaxel exposure, Schwann cells activate and begin to release inflammatory cytokines, such as TNF- α [103–105] (see more below). Following activation of apoptotic pathways, peripheral nerves experience a loss of Schwann cells [106], leading to a loss of protection and nourishment to nerve fibers and impairment of action potential propagation.

Likewise, satellite cells, when activated by chemotherapeutics, begin to secrete cytokines [107], which can contribute to apoptosis of DRG neurons. Satellite cells also experience an increase in gap junction coupling, and blocking this effect produced an analgesic response following chemotherapy-induced sensitization in mice [108].

Within the spinal cord, activation of astrocytes, but not microglia contributes to CIPN symptoms [109,110]. Astrocyte activation leads to increased cytokine release, which contributes to behaviors indicative of neuropathic pain in mice [111]. Decreasing astrocyte activation by treatment with minocycline or reducing gap junction coupling with carbenoxolone can decrease chemotherapy-induced mechanical hyperalgesia in rodents [38,112].

Cytokine & chemokine binding

Cytokines historically were viewed as small proteins released by cells of the immune system to promote immune responses such as fever and inflammation. It is now known that cytokines, including chemotactic cytokines (chemokines), are also released by glia and neurons, and these versatile signals have well-established roles in many forms of pain. Injection of proinflammatory cytokines produces a robust hypersensitivity to thermal and mechanical stimulation [113,114], and administration of cytokine receptor antagonists can mitigate hyperalgesia in the mouse [115]. Cytokines can enhance pain responding in a number ways in the peripheral nervous system. Direct sensitization of primary afferent fibers occurs following proinflammatory cytokine exposure, leading to spontaneous discharge [116]. This effect is also seen within the DRG [117] and in dorsal horn neurons [118] following cytokine exposure. TNF- α can decrease GABAergic inhibitory signaling in the spinal cord via a MAPK (p38)-mediated pathway to enhance pain signaling [119]. Cytokines can also indirectly lead to a host of inflammation-related responses, such as the release of bradykinin, serotonin and histamine [120]; and can activate apoptotic pathways within cells to contribute to pain [121].

Chemotherapeutic exposure consistently enhances cytokine release. Administration of paclitaxel [122], cisplatin [123] and vincristine [124] leads to the increased production and release of proinflammatory cytokines such as TNF- α and IL-1 β and chemokines such as MCP-1. These cytokines can bind to receptors located on neurons and glial cells to enhance activity in pain pathways, and in turn, increase expression of cytokines in these same cells, thus leading to a potentially self-sustaining cycle [125].

One receptor important for regulating the release of cytokines shown to be involved in CIPN is the Toll-like receptor (TLR). Toll-like receptors are a family of pathogen-detecting transmembrane proteins that can be activated by chemotherapeutics [126]. While traditionally viewed as being primarily involved in innate immunity, the TLRs have also more recently been implicated in pain. Increased levels of TLR4 are expressed in the DRG of rats displaying paclitaxel-induced hyperalgesia, and that hyperalgesia is significantly ameliorated using an antagonist to TLR4 receptors (a lipopolysaccharide isolated from *Rhodobacter sphaeroides*) [127]. Complementary evidence for an important role of TLR

signaling in CIPN came from observations of attenuated responses after cisplatin treatment in mice in which TLR4 or TLR3 were knocked out [128].

MCP1 (also called CCL2), a chemokine, and its receptor CCR2 have also been shown to be altered in CIPN. MCP1 is increased in spinal astrocytes and nociceptive DRG neurons in rats with paclitaxel-induced CIPN, and CCR2 numbers increased in large- and medium-sized DRG cells during paclitaxel-induced hyperalgesia [102]. Antagonism of CCR2 [129] mitigated neuropathic pain in mice, a finding similar to the effect of CCR2 gene knockout [130].

Conclusion

Chemotherapy remains a frontline treatment for many forms of cancer, but unfortunately is associated with the painful and debilitating condition of neuropathy. While research has provided insight into the mechanisms underlying this condition, treatment for CIPN is still limited. This is perhaps due in part to the complexity of these mechanisms. As outlined above, CIPN affects many aspects of neuronal and glial cell function, creating cascading effects and potentially engaging feedback loops that may sustain the neuropathy and pain.

Future perspective

Currently, clinical trials have not revealed effective treatments to prevent the development of CIPN, although many interventions have been tested, including ALCAR, vitamin E, infusions of calcium or magnesium ions, and amitriptyline [131]. Opiates, a mainstay for many forms of chronic pain, provides only limited relief for chemotherapy-induced pain, and does so at the risk of addiction. It is, therefore, important to find alternative treatments. Many of the mechanisms discussed here have been studied as potential avenues of CIPN treatment, but the clinical trials have produced mixed results. For example, inhibition of p38 MAPK was found to decrease pain associated with peripheral injury in one clinical trial [132] but not another [133]. When studying CIPN mechanisms and developing treatments on the basis of preclinical studies, it is important to keep in mind issues of validity and reliability, as was highlighted by the recent finding of species differences in the function of TRPA1 channels [58]. Future research should benefit from further consideration of the role of glial cells in CIPN. Finally, as a newer generation of chemotherapeutics becomes available, such as ixabepilone, researchers can compare and contrast prevalence of CIPN and associated mechanisms to help identify cellular and molecular contributions to CIPN.

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Practice points

- Pharmacogenomics provides insights into potential genetic predictors for chemotherapy-induced peripheral neuropathy (CIPN).
- Changes in cellular activation and signaling, including enhanced cytokine release, changes in voltage-gated ion channels, altered neurotransmission and activation of apoptotic pathways have been observed.
- Structural changes to the cell, especially mitochondrial and microtubule damage, play a role in the chronicity of CIPN.
- Loss of intraepidermal nerve fibers and Meissner's corpuscles further contributes to the ongoing nature of this condition.
- Glial cells are important contributors to CIPN. The most relevant of these cells are the astrocytes, satellite cells and Schwann cells.

Figure 1. Schematic overview of mechanisms of chemotherapy-induced peripheral neuropathy (A) Illustrates neuronal and glial targets for chemotherapeutics, including paclitaxel, bortezomib and oxaliplatin. (B) Indicates the multiple ways these drugs alter neuron and glial cell function, resulting in activation of astrocytes, enhanced cytokine release, mitotoxicity and eventual apoptosis, spontaneous discharge and altered signaling in primary afferent fibers, and loss of cutaneous fibers, ultimately enhancing nociceptive input. CIPN: Chemotherapy-induced peripheral neuropathy; DRG: Dorsal root ganglion; ROS: Reactive oxygen species; TLR: Toll-like receptor; TRP: Transient receptor potential.