An updated understanding of the mechanisms involved in chemotherapy-induced neuropathy

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The burdensome condition of chemotherapy-induced peripheral neuropathy occurs with various chemotherapeutics, including bortezomib, oxaliplatin, paclitaxel and vincristine. The symptoms, which include pain, numbness, tingling and loss of motor function, can result in therapy titrations that compromise therapy efficacy. Understanding the mechanisms of chemotherapy-induced peripheral neuropathy is therefore essential, yet incompletely understood. The literature presented here will address a multitude of molecular and cellular mechanisms, beginning with the most well-understood cellular and molecular-level changes. These modifications include alterations in voltage-gated ion channels, neurochemical transmission, organelle function and intracellular pathways. System-level alterations, including changes to glial cells and cytokine activation are also explored. Finally, we present research on the current understanding of genetic contributions to this condition. Suggestions for future research are provided.

First draft submitted: 30 April 2018; Accepted for publication: 14 June 2018; Published online: 13 September 2018

Keywords: chemotherapy • cytokine • ion channels • mitochondria • neuropathy • neurotransmission

Anywhere between 50 and 90% of patients receiving chemotherapy will experience a burdensome condition termed chemotherapy-induced peripheral neuropathy (CIPN) [1]. Patients with CIPN report paresthesia and dysesthesia, which generally progresses from sensations of numbness and tingling to sensory and motor impairments, and eventually symptoms include pain that is described as burning, shooting, throbbing and stabbing [1]. Once CIPN develops, there is a high likelihood that it will become a chronic condition. CIPN lasting longer than 3 months is associated with symptoms that continue for years after treatment ends for paclitaxel, vincristine and oxaliplatin [2–4].

These symptoms significantly impair quality of life in a number of ways, ranging from self reports of poorer quality of life related to alterations in lifestyle [3], increased need for assistance from others, and changes in emotional, cognitive and social function [5,6]. Such impairments in function and quality of life cannot be overlooked as they may lead to decreases in the dose of therapy administered, which can potentially have negative treatment outcomes for the patient. To illustrate this idea, Bhatnagar and colleagues [2] found that paclitaxel-induced CIPN was significant enough that a relative dose intensity of 73.4% was required for patients, and unfortunately, relative dose reductions of <85% significantly decrease survival rates.

There are numerous factors that are related to the occurrence of CIPN. For example, pre-existing conditions such as diabetes and obesity [7] are known to increase the risk of developing CIPN during cancer treatment. Lifestyle choices, such as smoking and chronic alcohol use [8], can also increase this risk. The type of chemotherapeutic agent used is widely regarded as one of the most significant predictors of CIPN, with cisplatin [9] oxaliplatin [10,11], vincristine [12,13], paclitaxel [14] and bortezomib [1] being the drugs found to most likely produce symptoms. As implied above, the dose administered also contributes to CIPN incidence and severity. For example, treatment regimens of paclitaxel or bortezomib, which call for doses producing higher peak plasma levels of these compounds, produced more severe CIPN when compared with regimens that included lower doses, even if lower doses are given more frequently [15].

Table 1. Summary of notable cellular and molecular changes observed in chemotherapy-induced peripheral neuropathy.

Ion channels	
Sodium	Upregulation in DRG and spinal dorsal horn; blockade can decrease CIPN
Potassium	Downregulation in cortical neurons and DRG; activation can decrease CIPN
Calcium	Upregulation in DRG; blockade can decrease CIPN
Neurotransmitters	
Glutamate	Levels increase; receptor antagonism can reverse CIPN
Norepinephrine	Receptor agonists can reduce CIPN
Serotonin	5HT2a knockout mice fails to develop CIPN
Cannabinoid	Exogenous administration can decrease CIPN
Opioids	Exogenous administration can lessen CIPN
Orexins	Agonists can alleviate CIPN
Cellular structures	
Mitochondria	Increased mitochondrial ROS observed in CIPN
DNA	Decreased APE1 activity in CIPN
Intracellular signaling pathways	
MAPK	Activation associated with apoptosis in CIPN
Caspases	Induction of negative neuronal and glial outcomes in CIPN
Neuronal and glial	
Innervation	Loss of IENFs, MCs and corneal innervation in CIPN
Astrocytes	Enhanced activation in CIPN; decreased activation can reverse CIPN
Cytokines/chemokines	
TNF- α , IL-1 β	Increased in CIPN
IL-8, MCP-1	Increased in CIPN
CIPN: Chemotherapy-induced neuropathy; DRG: Dorsal root ganglion; IENF: Intra-epidermal nerve fiber; MC: Meissner's corpuscles; ROS: Reactive oxygen species.	

Chemotherapy treatments result in numerous changes to cellular structure and function, including loss of sensory terminals in the skin, and alterations to membrane receptors and ion channels, organelles, intracellular signaling and neurotransmission, all of which can negatively influence neuronal and glial cell phenotypes, thereby contributing to CIPN. This review will provide an updated perspective to our current understanding of the various mechanisms involved in CIPN. Table 1 provides a brief overview of the most notable changes discussed in more detail below.

Cellular & molecular level changes of CIPN

CIPN results in a host of cellular-level alterations, ranging from electrical signaling enhancement through voltage-gated ion channels to increases (or decreases) in neurotransmission and changes in specific receptor subtypes. Further, there are impairments in cellular structures, many of which are related to the activation of various intracellular pathways.

Changes observed in voltage-gated ion channels

Sodium

The Na_v channels, one of the most abundant voltage-gated ion channels, are strongly implicated in CIPN development and maintenance for particular agents. For example, various *in vivo* and *in vitro* studies have revealed that Na_v subunits are associated with CIPN. In human and rat, dorsal root ganglion (DRG) tissue Na_v1.7 channels were found to be upregulated following paclitaxel treatment, resulting in a gain of function in this ion channel [16]. Na_v1.7 is also indicated in oxaliplatin-induced CIPN. Blocking this ion channel reversed hyperalgesia measured in rats following oxaliplatin treatment [17]. The use of murine knockout models to disrupt Na_v1.9 expression results in the prevention of oxaliplatin-induced cold allodynia, which demonstrates the importance of this ion channel in CIPN following oxaliplatin treatment [18]. Interestingly, voltage-gated sodium channel blockers, such as the anticonvulsant carbamazepine, lamotrigine or lidocaine patch/cream have shown some success in treating neuropathy in people [19], although not all clinical studies have supported the effectiveness of this approach [20,21].

Potassium

Potassium channels, specifically Kv7, can contribute to neuropathic pain (for example, the review [22]). Oxaliplatin [23,24] and paclitaxel [25] have been shown to produce downregulation of K⁺ channels in cortical and DRG neurons *in vitro*. The result of such changes in nociceptors is spontaneous activity that corresponds to the development of CIPN in rodent models [25]. In support of these findings, the Kv7 channel activator retigabine has been found to be effective in a mouse model of cisplatin neuropathy [26]. Recently, it was demonstrated that subcutaneous administrations of H₂S can result in pain relief in mice with paclitaxel and oxaliplatin therapy through Kv7 potassium channel activation [27].

Calcium

The voltage-gated calcium channels consist of a diverse family of subtypes, with several indicated as contributing to CIPN. For example, increased expression of Ca_v3.2, a T-type calcium channel, was recently observed in a rodent model of paclitaxel-induced CIPN [28], and chemical inhibition of this subtype reverses hyperalgesia, also in a rodent model [29]. Similar findings are found with vincristine-induced CIPN [30]. Inhibition of N-type [31] and $\alpha_2\delta$ [32] calcium channels likewise minimizes or reverses paclitaxel and oxaliplatin-induced rodent models of CIPN [33]. However, clinical trials, including a Phase III randomized, double-blind, placebo-controlled, crossover trial to assess the efficacy of gabapentin showed unsatisfactory outcome [34,35]. The Na⁺-Ca²⁺ exchanger was thought to contribute to neuropathic pain due to alterations in primary afferent-mediated changes [36], but follow-up studies in rats administered paclitaxel indicate that Na⁺-Ca²⁺ exchanger contributions to neuropathy are mitochondrial driven [37,38].

Neurotransmitter involvement

Numerous studies have documented alterations in processes involved primarily in neurotransmitter signaling following chemotherapy treatment.

Glutamate

The contributions of glutamate to CIPN have generally been investigated by either antagonizing glutamate receptors and/or production or by quantifying expression of glutamate transporters in neurons and glial cells. Use of 2-methyl-6-(phenylethynyl)pyridine, a glutamate receptor antagonist, reversed bortezomib-induced changes in nerve conduction in a rodent model of CIPN [39], and inhibiting glutamate production diminished nerve conduction changes associated with bortezomib, cisplatin and paclitaxel (see the review [40]). Glutamate levels increase following oxaliplatin exposure in rats, and use of a polyamine-deficient diet to modify glutamate levels, and subsequent NR2B activation, prevented oxaliplatin-induced hypersensitivity to cold and mechanical stimulation [41]. Further evidence of the involvement of the NR2B glutamate receptor in oxaliplatin-induced CIPN was found with the administration of an NR2B antagonist, ifenprodil. In this study, ifenprodil administration reversed hypersensitivity in rats treated with oxaliplatin [42]. Glutamate transporters have been shown to be diminished following treatment with bortezomib, paclitaxel and vincristine in spinal astrocytes in *in vitro* studies using rat tissue [43,44].

Norepinephrine

The α -2 adrenoceptor agonist clonidine has been reported to significantly reduce hyperalgesia in animal models by reducing the release of glutamate and substance P and by hyperpolarizing spinal dorsal horn neurons [45–47]. Recently, one rodent study demonstrated that intraperitoneally administered clonidine decreased allodynia induced by oxaliplatin, likely through a spinal p38 MAPK pathway [48].

Serotonin

The functions of serotonin (5HT) are incredibly diverse, and there is evidence that 5HT receptor changes are involved in CIPN. Specifically, mice lacking 5HT receptors (2A) [49] or transporters [50] show protection against the development of vincristine-induced CIPN. Clinically, serotonin and norepinephrine reuptake inhibitors, such as duloxetine, have demonstrated modest efficacy for CIPN treatment [51]. However, venlafaxine, another serotonin and norepinephrine reuptake inhibitor, showed limited efficacy for pain relief [51].

Cannabinoids

Consideration of the contributions of the cannabinoid system is a rather recent inclusion in the CIPN literature, with increasing interest seemingly corresponding to increasing legalization of medicinal and recreational marijuana. Murine models have shown that cisplatin [52,53] and paclitaxel-induced CIPN [54] can be alleviated by increasing cannabinoid activity. An animal study found that the single or combined effects of nonpsychoactive phytocannabinoid cannabidiol and Δ^9 -tetrahydrocannabinol (THC) attenuated mechanical allodynia in mice treated with paclitaxel. Cannabidiol alone and a low-dose combination also decreased oxaliplatin, but not vincristine, induced mechanical sensitivity, while tetrahydrocannabinol significantly reduced vincristine-induced mechanical sensitivity [55]. However, a small sample size double-blind-randomized crossover trial did not show any significant differences in pain scores and quality of life between oral cannabinoid extract and placebo [56].

Opioids

As one especially difficult symptom of CIPN is pain, a logical inclusion in the discussion of CIPN would involve the endogenous opioid system. Indeed, a recent study using rodent spinal cord and DRG tissue *in vitro* found that vincristine-induced allodynia was associated with decreased endogenous activity on mu-opioid receptors [57]. However, it is important to point out that exogenous administration of mu-opioid receptor agonists (i.e., morphine and other opioid-based analgesics) do not address the array of CIPN symptoms or even fully control CIPN-induced pain clinically [2]. This finding reiterates the complexity of understanding the mechanisms of, and identifying treatments for, CIPN.

Orexins

Orexins are neuropeptides mainly localized in neurons in the lateral and dorsal hypothalamus, but receptors are distributed to many different regions of the CNS. Recently, a novel pharmacological therapy, Ox1R agonists showed promise in alleviating oxaliplatin-associated CIPN in a murine model [58]. The author attributed its analgesic effect to its roles in descending pain inhibition due to the finding that orexin-producing neurons send projections to the periaqueductal gray, raphe nucleus and locus coeruleus, and to the spinal dorsal horn. New *in vitro* research further indicates that nonpeptide orexin receptor agonists that are able to cross the blood–brain barrier are promising for pain [59].

Additional receptor changes: the nonselective cation transient receptor potential channels

The transient receptor potential (TRP) channels, and especially the TRP vanilloid (TRPV) family, have been widely studied with regard to CIPN. Evidence collected from *in vitro* and *in vivo* studies in rats and mice supports the idea that TRPV1 is responsible for the heat-sensitive hyperalgesia and mechanical allodynia in sensory neurons induced by cisplatin, oxaliplatin, bortezomib and paclitaxel [60–63]. Conversely, other two channels, TRPA1 and TRPM8 are activated by cold temperature. *In vitro* and *in vivo* studies using rats and mice have additionally found that antagonists of TRPA1 and TRPM8 can relieve mitochondrial oxidative stress, inflammation, cold allodynia and hyperalgesia induced by cisplatin, oxaliplatin, bortezomib and paclitaxel [64–69]. TRPM8, which is activated by cool temperature (<25°C), menthol and icilin, was found to be highly expressed in the DRG of rodents with oxaliplatin-induced cold hyperalgesia [70]. A case report and a small sample size non-randomized clinical trial (RCT) study showed that topic menthol was effective for CIPN [71,72]. More research on the contributions of new members of the TRP superfamily (e.g., TRPM2, TRPM3, TRPM7, TRPV3, TRPC5) to CIPN is warranted (e.g., [73]).

Changes to neuronal & glial structures associated with CIPN

Various intracellular neuronal and glial structures are altered by chemotherapy, ranging from damage to large organelles to alterations in DNA. For example, bortezomib and cisplatin exposure produces damage to lysosomes and endoplasmic reticulum in cultured neurons [74,75]. Paclitaxel and vincristine arrest cellular division, and therefore cancer growth, by targeting microtubules, and this has been reported to contribute to the development of CIPN based on *in vitro* findings [76].

Mitochondria damage has been shown in rodent studies to result from treatment with bortezomib [77], oxaliplatin [78,79] and paclitaxel [79–81], likely as a result of oxidative stress. Both bortezomib and paclitaxel can lead to mitochondrial production of reactive oxygen species (ROS), which can in turn worsen mitochondrial function [82]. ROS production can also damage DNA, and both cisplatin and oxaliplatin produce DNA adducts,

leading to neuron death [72]. Cisplatin can produce damaging p53 accumulation in the mitochondria of DRG, spinal cord neurons and peripheral nerves. Pretreating rats with pifithrin- μ (PTF- μ), an inhibitor of p53, prevented mitochondrial damage and incidence of CIPN [83].

DNA damage in sensory neurons after chemotherapy correlates with symptoms of CIPN. As evidence of this idea, studies have shown that altering expression of enzymes involved in DNA repair, such as apurinic/apyrimidinic (AP) endonuclease/redox factor-1 (APE1), is associated with changes in CIPN. For example, CIPN-related symptoms increase following cisplatin and oxaliplatin in relation to decreasing levels of APE1, and enhancing the activity of this enzyme-protected cisplatin-treated cultured neurons from neurotoxicity [84,85]. A first-generation-targeted APE1 small molecule, E3330, has been approved for Phase I clinical trials, and a second-generation APE1-targeted molecule, APX2009, demonstrated a neuroprotective against cisplatin and oxaliplatin-induced toxicity [86].

Intracellular signaling pathways

Much of the damage to intracellular structures results from direct [87] or indirect (via chemical mediators such as the cytokines discussed below) activation of protein kinases and caspases by chemotherapy. Such activation initiates an array of cellular pathways that can ultimately produce damage or even apoptosis in both glia and neurons.

Of the over 500 known protein kinases, MAPK has been the most consistently studied in terms of CIPN [88]. MAPK has been found to contribute to paclitaxel-induced hyperalgesia in a rodent model through activation of TLR4 receptors located on DRG [89]. Cisplatin and oxaliplatin can also produce MAPK-related apoptosis in DRG neurons [90] that can be prevented by treatment with NGF [74]. Administration of MAPK inhibitors partially prevented paclitaxel-induced hyperalgesia [89] and prevented DRG damage induced by cisplatin and oxaliplatin in cultured cells [90].

The caspases are a family of cysteine proteases that signal apoptosis. In regard to CIPN, activation of caspases contributes further to neuron damage. For example, paclitaxel [75], cisplatin and oxaliplatin [91] produce a range of damaging effects via caspase signaling, including mitochondrial damage, ROS production and neuron-level apoptosis. Inhibition of caspases was found to prevent oxaliplatin-induced DRG apoptosis [92] and decrease vincristine-induced hypersensitivity in the rat [93].

A newly explored kinase, adenosine kinase, has very recently provided insight into oxaliplatin-induced pain. Wahlman *et al.* [94] reported that astrocytes displayed decreased signaling on the A3 adenosine receptor following oxaliplatin exposure in rodents. Administration of an A3 adenosine receptor agonist decreased proinflammatory cytokine production in this study, but it should be pointed out that clinical trials targeting adenosine receptors have either been terminated due to adverse events or failed to find positive outcomes [95].

System-level changes of CIPN

Beyond the intracellular events outlined about, there are various other chemotherapy-related modifications that occur that may impact sensation at the level of sensory transduction. Additionally, by impacting the function of glial cells, CIPN may be maintained or worsened.

Changes in sensation related to damaged nerve endings

In considering the symptoms of motor and sensory loss and eventual pain, changes in sensory transduction should be expected, and indeed, there are findings of damage in conjunction with chemotherapy exposure. Corneal innervation has also been found to be altered in rats treated with paclitaxel [96]. Most notably, intraepidermal nerve fibers (IENFs) and Meissner's corpuscles (MC) are lost or damaged, and such changes correspond to the bodily areas where symptoms are worst (i.e., hands and feet). Significant loss of IENFs has been found clinically following bortezomib [1] and in rodent models of paclitaxel [97] and oxaliplatin [98] CIPN. It has been hypothesized that IENF loss is related to cytokine or chemokine signaling, an idea that was supported by the finding that decreasing levels of the chemokine MCP-1/CCL-2 could not only minimize IENF loss but also prohibit CIPN-indicative behaviors in a paclitaxel-based rodent model [99]. Other methods of minimizing neuroinflammation, such as the use minocycline, protect against oxaliplatin and paclitaxel induced CIPN in animal models [100]. While a recent clinical trial using minocycline did not effectively prevent CIPN, this commonly used and relatively safe antibiotic did alleviate paclitaxel-induced pain [101]. Another line of work indicates that mitochondrial damage may play a role in IENF loss. A recent study found that cisplatin leads to p53 accumulation in the mitochondria of nerve fibers, producing damage and eventual loss of IENFs. Blocking p53 with pifithrin- μ protected against IENF loss and allodynia in this murine study [83]. Nicotinic acetylcholine receptor-mediated pathways may also contribute

to CIPN-related IENF loss [102,103]. An animal study demonstrated that inhibiting these receptors can prevent paclitaxel-induced IENF loss [104]. Human biopsies reveal that MCs are lost following bortezomib treatment [1] and in areas of the body where touch perception is most significantly impaired [105]. Unlike the reversal of CIPN that has been found following IENF protection, research has not yet shown how salvaging MCs may impact CIPN.

Glial cell function

While neuronal mechanisms were historically viewed as the primary mechanism of CIPN, more recent research has discovered important contributions from glial cells. Bortezomib [44], paclitaxel [106] and oxaliplatin [94,107] all activate astrocytes, and decreasing this activation with minocycline or carbenoxolone was found to decrease bortezomib [44] and oxaliplatin-induced hyperalgesia [108]. Mice lacking expression of the cAMP receptor, Epac, showed decreased astrocyte activation, IENF loss and paclitaxel-induced hyperalgesia compared with wild-type mice, further implicating the intracellular pathways discussed above in CIPN development [100]. A possible intermediary factor for Epac activation of these pathways is the release of cytokines from activated glial cells and damaged neurons, but further research is needed to more clearly elucidate this relationship. Interestingly, *in vitro* studies find that microglia do not show heightened activation following chemotherapy [107], and instead appear in reduced number following both paclitaxel and oxaliplatin [109]. It is unclear at this point how this decrease may contribute to CIPN. Rodent studies provide evidence that satellite cells may undergo apoptosis and thereby contribute to CIPN, either by secretion of apoptotic cytokine signaling [110] or gap junction coupling [111]. Schwann cells may likewise release cytokines that produce their own apoptosis [112]. Oxaliplatin, but not paclitaxel, produces mitochondrial dysfunction in Schwann cells [113].

Neuronal & glial cell mediators: cytokines, chemokines & their receptors

CIPN is a complex condition that is best understood when incorporating mechanisms that extend beyond traditional neuron and neuron/glial function. Not only are traditional neurotransmitters and ion channels important, recognition of additional chemical mediators of neuron and glial behavior have provided a more complete understanding of CIPN. Specifically, cytokines and chemokines can have a profound impact on cells.

Cytokines are small molecules released by various cells, including traditional immune cells, glial cells and neurons. Their role in inflammation and pain is well established and includes the ability to directly activate primary afferent fibers [114], DRG neurons [115] and spinal dorsal horn neurons [116]. *In vitro* studies show enhanced release of 'proinflammatory' cytokines such as TNF- α and IL-1 β occur following exposure to cisplatin [117], paclitaxel [118] and vincristine [119]. These cytokines can then encourage CIPN in a host of manners, including GABA-mediated disinhibition of neuronal firing via an MAPK pathway [120], apoptosis signaling [121] and neuronal sensitization. The release of cytokines from cells following chemotherapy may be related to the ability of these agents to activate the Toll-like receptor (TLR) family [122], especially TLR4. In rodent models of paclitaxel-induced hyperalgesia, DRG cells show increased expression of TLR4 [123]. Antagonizing [123] or knocking out [124] that receptor in mice decreased pain behaviors following paclitaxel and cisplatin. In addition to the contributions of proinflammatory signaling, it was recently found that IL-10, an 'anti-inflammatory' cytokine, can assist in resolving paclitaxel-induced CIPN [125] and oxaliplatin-induced CIPN via adenosine signaling [94] in murine models.

Like cytokines, chemokines are also implicated in CIPN. For example, IL-8, and its receptor CXCR1/2, contribute to CIPN, as it was recently found that inhibiting CXCR1/2 reduced paclitaxel-induced hyperalgesia in rats [126]. Another chemokine, MCP-1/CCL-2, is released from neurons and activated astrocytes and is a major contributor to neuropathic pain [127]. Paclitaxel leads to increased expression of this chemokine and its receptor, CCR2, in DRG in a paclitaxel model of CIPN [99], and neutralizing MCP-1/CCL-2 in DRG blocked macrophage infiltration and subsequent hyperalgesia in a paclitaxel rodent model of CIPN [128]. Oxaliplatin is also capable of increasing MCP-1/CCL-2, primarily released from astrocytes, at the time that hyperalgesia is occurring in rats; a finding that was decreased by treatment with melatonin [129]. Melatonin may further protect against oxaliplatin-induced CIPN by preventing mitochondrial dysfunction and eventual neuronal apoptosis, as was evidenced in a recent extensive study using a combination of *in vitro* and *in vivo* methods in human tissue and behavioral assessments in rats exposed to paclitaxel [130]. Rats with bortezomib-induced pain behaviors were found to have enhanced release of MCP-1/CCL-2 in DRG, and as with paclitaxel, neutralizing the chemokine-produced decreased pain responding [131].

Genetic influences

As mentioned elsewhere in this review, there are various risk factors associated with the occurrence of CIPN; one possible risk factor that may prove to be especially important is genetic predisposition. The field of pharmacogenomics has grown in the last decade and much work has been dedicated to understanding the influence of genetics on the response to chemotherapy. Beginning in the early 2000s, there were reports that particular single nucleotide polymorphisms (SNPs) could increase the risk of CIPN, but unfortunately, replication of these findings has been inconsistent. A recent meta-analysis investigating 93 studies was, however, able to identify consistent SNP changes for some chemotherapeutic agents. For example, CIPN resulting from paclitaxel treatment was associated with *CYP2C8*3*, and vincristine-related CIPN risk was increased with *CYP3A5*3* [132]. Both of these genes belong to the CYP450 family, which have known effects on drug metabolism, but it is currently unclear what the pathway for producing neuropathy might be. Although targeting these SNPs may one day allow for prevention of CIPN, researchers are currently far from determining how doing so may interfere with chemotherapy effectiveness.

Conclusion

In conclusion, there are a host of molecular and cellular changes that contribute to CIPN. Symptoms can negatively impact patient quality of life to such an extent that chemotherapy doses are lowered, potentially harming treatment outcomes. It is therefore essential to better understand the factors that produce this condition. Currently, significant alterations have been found in ion channels and neurotransmitters, especially those involved in neuronal excitability, mitochondrial function, and intracellular pathways. Cytokine activity can worsen symptoms. Associated damage to IENFs and glial cells further complicate CIPN outcomes.

Future perspective

Clearly, CIPN negatively impacts the life of a patient who is already experiencing significant stress related to a diagnosis of cancer. The side effects of cancer treatment, of which CIPN is only one of many, are incredibly burdensome and can even harm survival rates when dose modifications are needed to control these side effects. While many side effects, such as vomiting or hair loss, resolve following treatment cessation, CIPN is especially impactful because it frequently becomes a chronic condition that continues long after treatment ends. Yet, for various reasons, there are currently no consistent treatment options for CIPN. Some of these reasons include the complexity of the mechanisms of CIPN. Targeting ion channels, for example, may or may not alter neurotransmission; altering cytokine levels may provide benefits against the activation of certain cellular pathways but not others. Other barriers to identifying treatments are related to both diagnosis of CIPN and the way that new treatments are investigated. Literature reporting on CIPN uses inconsistent diagnostic tools for instance [133]. Additionally, cancer itself can produce neuropathy that may be present prior to chemotherapy. For example, patients with subclinical neuropathy showed increased loss of nerve fibers following bortezomib treatment for multiple myeloma [105]. Interestingly, corneal innervation was found to be lower in patients with upper gastrointestinal cancer compared with healthy control, and increased following treatment with cisplatin or oxaliplatin. The implications of this finding warrant further research. The primary means of controlling pain clinically are by the use of opiates, but opiates are not only highly addictive, they are also ineffective against CIPN. Although much more work is needed, it is clear from the abundance of literature cited in this review, there are promising treatments currently being investigated that will hopefully yield more effective interventions in the future.

Executive summary

- Chemotherapy-induced peripheral neuropathy (CIPN) results in changes to ion channels, and mitigating these changes can lessen CIPN symptoms.
- Various neurotransmitters, including glutamate, norepinephrine and serotonin, are altered in CIPN, and may provide a viable target for treatment.
- Mitochondrial damage, which is associated with multiple chemotherapeutic agents, is heavily implicated in CIPN symptoms.
- Activation of various caspase and kinase intracellular pathways following chemotherapy exposure can trigger neuronal and glial apoptosis.
- Inflammatory mediators such as TNF- α and MCP-1 are activated in CIPN.
- Human and animal studies illustrate a loss of innervation in CIPN.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

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