Pathogenesis of paclitaxel-induced peripheral neuropathy: A current review of *in vitro* and *in vivo* findings using rodent and human model systems

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Abstract

Paclitaxel (Brand name Taxol) is widely used in the treatment of common cancers like breast, ovarian and lung cancer. Although highly effective in blocking tumor progression, paclitaxel also causes peripheral neuropathy as a side effect in 60-70% of chemotherapy patients. Recent efforts by numerous labs have aimed at defining the underlying mechanisms of paclitaxel-induced peripheral neuropathy (PIPN). In *vitro* models using rodent dorsal root ganglion neurons, human induced pluripotent stem cells, and rodent *in vivo* models have revealed a number of molecular pathways affected by paclitaxel within axons of sensory neurons and within other cell types, such as the immune system and peripheral glia, as well skin. These studies revealed that paclitaxel induces altered calcium signaling, neuropeptide and growth factor release, mitochondrial damage and reactive oxygen species formation, and can activate ion channels that mediate responses to extracellular cues. Recent studies also suggest a role for the matrix-metalloproteinase 13 (MMP-13) in mediating neuropathy. These diverse changes may be secondary to paclitaxel-induced microtubule transport impairment. Human genetic studies, although still limited, also highlight the involvement of cytoskeletal changes in PIPN. Newly identified molecular targets resulting from these studies could provide the basis for the development of therapies with which to either prevent or reverse paclitaxel-induced peripheral neuropathy in chemotherapy patients.

1. Introduction

The taxanes are microtubule stabilizing agents that provide great benefits in treating a large number of cancers, including breast, ovarian and lung cancers. Therefore, a large cohort of cancer patients is treated with paclitaxel or other taxanes each year. Unfortunately, neuropathy is a major and dose-limiting side effect of treatment with taxanes. It has been estimated that over half the patients treated with the most commonly used taxane, paclitaxel, experience symptoms; and a subset develop long-lasting, irreversible peripheral neuropathy due to the treatment (Nyrop et al., 2019). The symptoms of neuropathy include pain, tingling, cold-sensitivity and numbness that typically presents in a stocking glove distribution. Many patients experience allodynia, so that normal stimuli such as light touch are experienced as severe pain. As these

symptoms dramatically interfere with quality of life (Miaskowski et al., 2018), multiple recent studies have focused on understanding the mechanisms for paclitaxel-induced peripheral neuropathy and how this condition can be prevented or treated (Flatters et al., 2017; Fukuda et al., 2017).

Diverse approaches have been taken to investigate paclitaxel-induced peripheral neuropathy, including *in vitro* studies investigating the direct effects of paclitaxel on rodent peripheral sensory neurons of the dorsal root ganglia (DRG) and DRGs derived from human induced pluripotent stem cells, *in vivo* studies using rodent models, and genetic approaches in humans (Fukuda et al., 2017; Gornstein and Schwarz, 2014; Smith et al., 2016). These have highlighted several features of the disorder. The initial effects of paclitaxel appear to reflect on-target changes in the axonal microtubules of sensory neurons. Subsequent changes have been found in intracellular Ca^{++} regulation, axonal transport, mitochondrial function, and neuropeptide secretion (Bobylev et al., 2015; Chiba et al., 2016) (Li et al., 2019; Li et al., 2018; Pease-Raissi et al., 2017). Interactions within the peripheral nervous system among these neurons and surrounding Schwann cells, satellite glial cells, immune cells and specialized intradermal mechanoreceptor cells, such as Merkel cells, epidermal keratinocytes, as well as the interactions of the central axon of DRG sensory neurons with astrocytes and microglia may all contribute to the progression of the disease (Sekiguchi et al., 2018; Zhang et al., 2008). The complex interplay of all of these processes is also affected by genetic predisposition of the individual patients.

Here we review recent studies using diverse approaches to understand the pathogenesis of paclitaxel-induced peripheral neuropathy (PIPN) (**Figure 1**). To date, none of these approaches have yielded new clinical methods for preventing or treating this debilitating consequence of chemotherapy. However, integration of these multiple approaches will ultimately yield insights regarding the mechanisms that contribute to this neuropathy, and so will provide new techniques for preventing or treating this devastating, iatrogenic condition.

2. *In vitro* methods to model neuron-autonomous mechanisms for PIPN

Several *in vitro* models, using cultures of primary sensory neurons or neuron-like cell lines have been utilized to identify the mechanisms by which paclitaxel alters neuronal function and structure. While these *in vitro* systems are limited in recapitulating the interactions of neurons within their *in vivo* microenvironment, they do allow for direct manipulation of protein expression and function via pharmacological and genetic tools to interrogate intracellular signaling pathways altered by paclitaxel within the neurons.

Paclitaxel-induced changes in neuronal sensitivity and excitability have been assessed using assays for neurotransmitter release, changes in intracellular calcium levels, and electrophysiological techniques. In primary cultures derived from rodent dorsal root ganglion neurons, exposure of the cultures to paclitaxel causes time- and concentration-dependent alterations in the basal and stimulated release of two neuropeptides, calcitonin-gene related peptide (CGRP) and substance P (SP). Acute exposure of

neuronal cultures to paclitaxel (10nM - 10µM for 10-30 minutes) directly stimulates the release of CGRP and SP in a manner dependent on the activation of protein kinase C (PKC) (He and Wang, 2015; Miyano et al., 2009). A possible mechanism underlying the activation of PKC and neuropeptide release is a transient increase in intracellular calcium, an effect observed after acute treatment of both cultured sensory neurons and neuroblastoma cells with paclitaxel (Boehmerle et al., 2006; Miyano et al., 2009). Putative mechanisms for paclitaxel to acutely enhance intracellular calcium dynamics and neuropeptide release include direct activation of the TLR4 by paclitaxel (Li et al., 2015) and an indirect activation of intracellular calcium release by paclitaxel binding to the neuronal calcium sensor-1 (Boehmerle et al., 2006). In contrast to the acute effects of paclitaxel, chronic exposure of cultures to paclitaxel (300nM - 1µM, for ≥ 3 days) diminishes the release of CGRP stimulated by TRPV1 or TRPA1 agonists (Pittman et al., 2014), which occurs concurrent with a diminution in stimulated calcium release from intracellular stores (Boehmerle et al., 2007). Proposed mechanisms by which extended exposure of neuronal cultures to paclitaxel leads to desensitization of peptide release include disruption of axonal transport and subsequent impairment of the movement of organelles and/or calcium dysregulation (Boehmerle et al., 2007; Shemesh and Spira, 2010; Theiss and Meller, 2000), and the loss of PKC activation (Darby et al., 2017).

Because mechanisms for paclitaxel-induced changes in neuronal sensitivity may differ between rodents and humans, research on human primary neurons and neuron-like cells induced from human pluripotent stem cells has surged in recent years. Some mechanisms for paclitaxel-induced changes identified in rodents have been validated in

human neurons, such as a role for paclitaxel to enhance sensitivity of the TRPV1 through activation of TLR4 (Li et al., 2015); however, fundamental differences between human and rodent DRGs also have been identified. Ru Rong Ji's laboratory has found differential sodium channel expression in human and mouse DRG: human DRG predominantly express Nav1.7, whereas mouse DRG predominantly express Nav1.8. Furthermore, exposure of paclitaxel to cultures derived from human DRG neurons elicits an increase in the expression of Nav1.7, but not that of Nav1.8 (Chang et al., 2018). Another approach to studying the mechanisms of paclitaxel-induced neurotoxicity in cells derived from humans has been to reprogram fibroblasts or embryonic stem cells into sensory neuron-like cells, called induced pluripotent stem cells (IPSCs) (Chambers et al., 2012; Wainger et al., 2015). If these IPSC neurons closely recapitulate the gene expression and cellular functions of sensory neurons, they may provide human-derived cells suitable for *in vitro* mechanistic studies. A distinct advantage of using patient-derived precursor cells is to recapitulate genotype differences between patient populations *in vitro*, potentially allowing for a correlation between patient-specific genotypes with peripheral neuron sensitivity and/or response to injury. To date, the studies using IPSC neurons are mostly limited to using cellular morphology as an endpoint of neurotoxicity. However, one study examined the effects of paclitaxel on the mean firing rate of the IPSC neurons and observed a slight decrease in the firing rate of cells following a 48-hour exposure in the absence of any paclitaxel-induced cell death (Wing et al., 2017).

Patients treated with paclitaxel have a decrease in the density of nerve fibers that innervate the epidermis of the hands and feet (Boyette-Davis et al., 2013), and it is likely that this "dying back" or retraction of nerve endings underlies some of the symptoms of PIPN. A similar length-dependent decrease in intraepidermal innervation is apparent in rodents treated with paclitaxel (Boyette-Davis et al., 2011; Jin et al., 2008; Ko et al., 2014; Siau et al., 2006). The effects of paclitaxel on sensory neuron morphology have been examined in DRG explants and dissociated neuronal cultures derived from both embryonic and adult rodents and, dependent upon the timing of drug administration to the cultures, paclitaxel can either inhibit outgrowth or promote degeneration of existing neurites (Gracias et al., 2011; Malgrange et al., 1994; Melli et al., 2006; Pittman et al., 2016; Yang et al., 2009b). Studies from Ahmet Hoke's laboratory used a compartmentalized microfluidic culture platform to determine whether paclitaxel acts on discrete regions of embryonic neurons to elicit changes in the cellular morphology. Paclitaxel exposure to the axonal compartment caused a reduction in neurite length; however, no changes in neurite length were observed when paclitaxel was applied to the soma (Yang et al., 2009a). These studies suggest that the primary site of paclitaxel uptake or site of action is along the axons and at the peripheral terminals of sensory neurons. Not surprisingly, some of the identified mechanisms by which paclitaxel alters cell morphology are similar to those which underlie functional changes *in vitro* and *in vivo*, including activation of the TLR4 (Ustinova et al., 2013), modulation of calcium dynamics (Pease-Raissi et al., 2017), and the production of ROS/RNS (Duggett et al., 2016; Janes et al., 2013; Melli et al., 2008).

In an elegant series of experiments, investigators demonstrated that paclitaxel's effects on microtubule axonal transport decrease the local translation of a Bcl2 family member, *bclw,* in cultures of embryonic sensory neurons. Loss of axonal *bclw* expression dysregulates calcium flux at the endoplasmic reticulum and can lead to activation of calcium-dependent calpains that subsequently induce axonal degeneration (Pease-Raissi et al., 2017). Based upon some early *in vivo* work, whereby NGF administration alleviated the neurotoxic effects of paclitaxel administration to rodents (Apfel et al., 1991), investigators endeavored to overcome the degenerative effects of chemotherapeutics by increasing growth factors in the *in vitro* culture media (Chen et al., 2017; Konings et al., 1994; Malgrange et al., 1994; Pittman et al., 2016). Although a protective effect of NGF was observed in embryonic neuronal explants treated with paclitaxel (Konings et al., 1994), these findings were not replicated in dissociated neurons derived from adult rats (Pittman et al., 2016), thus there might be a contribution of development in the protective effects of NGF on neuronal morphology. Other neuroprotective agents that have been found to inhibit or counteract the morphological changes of neurons induced by paclitaxel or docetaxel include insulin-like growth factor-1 (Chen et al., 2017), minoxidil (Chen et al., 2017), erythropoietin (Maggioni et al., 2010; Melli et al., 2006), and pirenzepine (Calcutt et al., 2017). Interestingly, one study combined a functional output to the morphological effects of paclitaxel *in vitro*. In this work, paclitaxel-induced changes in the release of CGRP from adult sensory neurons was inhibited by the addition of nerve growth factor to the culture media; however, this growth factor addition did not protect against the neurodegenerative effects of paclitaxel in decreasing neurite length in the same cultures (Pittman et al., 2016), suggesting that

the mechanisms for neuronal sensitivity and neurite growth could be independent. Further studies are warranted to determine whether these growth factors abrogate the effects of paclitaxel or whether they mask the symptoms because of their growth-promoting effects. To assess the effects of paclitaxel on human cells, IPSC neurons have been exposed to paclitaxel and total neurite outgrowth has been shown to decrease with increasing concentrations of paclitaxel. As in rodent models, studies are ongoing to test the ability of putative neuroprotective drugs to reverse the degenerative effects of paclitaxel on neurite outgrowth (Wing et al., 2017). In summary, neuronal cultures provide a reduced system to study the effects of paclitaxel on neuronal signaling and provide clear endpoints to assess neuroprotection by putative therapies. Using these systems, several neuron-autonomous mechanisms by which paclitaxel alters neuronal function and morphology have been identified, providing novel targets for pharmacological intervention.

3. *In vivo* pathophysiology of taxanes

Several animal studies explored the mechanisms involved in paclitaxel-induced peripheral neuropathy (PIPN) *in vivo*. Some non-mammalian models have also been used to understand the mechanisms behind CIPN, such as Zebrafish or Drosophila models, and these are described in detail in another review within this Special Issue. We will therefore focus our review on rodent studies. Paclitaxel is typically administered to mice and rats through intravenous or intraperitoneal injection. The pathophysiological processes induced by paclitaxel include inflammation, oxidative stress, loss of primarily

epidermal nerve fibers, and alterations of mitochondrial function and excitability of peripheral neurons. Various cell types in the peripheral and central nervous system have been shown to be affected by paclitaxel treatment in these models, including dorsal root ganglion neurons, Schwann cells, satellite glial cells, microglia, epidermis and spinal astrocytes. Different mechanisms leading to paclitaxel neurotoxicity in rodent models are summarized below:

3.1 *Peripheral neurons*

It is well established that neuropathic pain induced by paclitaxel treatment is accompanied by damage of small fiber sensory axons. Many publications report the degeneration of fine intra-epidermal nociceptive fibers, as well as axonal demyelination due to the loss of contact between axolemma and Schwann cells, and also a loss of Meissner's corpuscles, the sensory end-organ for one mechanosensitive neuron subtypes (Beh et al., 2019; Bennett et al., 2011; Boehmerle et al., 2014; Li et al., 2014; Pevida et al., 2013; Wozniak et al., 2018). Nociceptive symptoms observed in animals reflect alterations of electrophysiological parameters as well as the degeneration of nerve endings (Boehmerle et al., 2014; Boyette-Davis et al., 2011). Recently, factors, such as Notch1, phosphorylated Janus kinase 2 (p-JAK2), phosphorylated signal transducer and activator of transcription 3 (p-STAT3) have been implicated in neuropathic pain induced by paclitaxel treatment (Al-Massri et al., 2018, 2019). Paclitaxel alters the electrophysiological properties of peripheral neurons *in vivo*, and the effect is dependent upon the modified expression of diverse receptors and voltage-gated ion channels within dorsal root ganglion neurons, including increased expression

of the calcium channels, Cav3.2, Cav2.3, Cav2.2, a decreased expression of the potassium channels, K2P and Kv7, and the upregulation of sodium channel Nav1.7, all of which results in a gain-of-function (Li et al., 2019; Li et al., 2018; Li et al., 2017; Okubo et al., 2011; Shan et al., 2019; Zhang and Dougherty, 2014). Other receptors involved in paclitaxel-induced neuropathic pain in rats include glutamatergic receptors. Paclitaxel induces a tonic activation of presynaptic NMDA receptors, and increases the expression of the voltage-gated calcium channel subunit, $\alpha2\delta$-1, and the NMDA receptor subunits, GluN1, GluN2A, and GluN2B (Chen et al., 2019).

As paclitaxel directly targets microtubules and prevents depolymerization, it is not surprising that microtubule dysfunction is prevalent in axons following treatment with paclitaxel (Flatters and Bennett, 2006; Xiao et al., 2011; Zheng et al., 2011). It is generally accepted from various *in vitro* and *in vivo* studies that paclitaxel impedes fast axonal transport along microtubule tracks (Bobylev et al., 2015; Malacrida et al., 2019; Shemesh and Spira, 2010). While paclitaxel treatment does not directly lead to damage of mitochondrial DNA in neurons (Boyette-Davis et al., 2018), swollen and vacuolated mitochondria in myelinated and unmyelinated sensory nerve fibers have been observed (Flatters and Bennett, 2006), as well as changes in mitochondrial membrane potential and subsequent calcium release (Mironov et al., 2005; Yilmaz and Gold, 2016; Yilmaz et al., 2017). Mitochondrial damage induced by paclitaxel further leads to the formation of reactive oxygen species, resulting in intra-axonal oxidative stress, as indicated by numerous studies (Miao et al., 2018; Singh et al., 2019; Sun et al., 2019; Zhao et al., 2019). For instance, it was found that lipid peroxidation was augmented and glutathione

levels increased, whereas expression of the antioxidant enzyme, superoxide dismutase, was decreased in the sciatic nerve and DRG neurons following paclitaxel treatment (Miao et al., 2018; Sun et al., 2019). Treatment of mice with paclitaxel resulted in impaired Nrf2-antioxidant response element (Nrf2-ARE) function and decreased Nrf2-responsive gene (HO-1, γ-GCLC, and NQO1) expression, associated with neuropathic pain (Zhao et al., 2019). Whether the increase in oxidative stress contributes to degeneration of nerve endings has, however, not been directly tested in rodents. However, a recent study demonstrated in zebrafish that axons do not show increased oxidative stress upon paclitaxel treatment despite that axonal mitochondria are vacuolated (Cirrincione et al., 2019). Intriguingly, rather than a role for intrinsic effects of paclitaxel in axon degeneration, epidermally expressed MMP-13 appears to play a role in neuropathy of rats and mice injected with paclitaxel. MMP-13 was previously shown to mediate axon degeneration in the zebrafish model since it is upregulated upon paclitaxel treatment and its pharmacological inhibition prevented axon degeneration (Lisse et al., 2016); yet vacuolation of axonal mitochondria still occurs in inhibitor treated zebrafish. Pharmacological inhibition of MMP-13 either by intraperitoneal injection or upon topical administration to the paw pad of rats also prevented paclitaxel-induced neuropathy (mechanical and cold hypersensitivity), suggesting that MMP-13 dependent mechanisms are conserved. Taken together, evidence points to a multitude of mechanisms leading to paclitaxel-induced axon damage, including inflammation, microtubule aggregation and transport defects, and mitochondrial changes. Whether these phenotypes are underlying axon degeneration remains to be tested *in vivo.* New molecular players originally identified in zebrafish and validated in mammals, such as

MMP-13, could serve as new targets in the treatment of paclitaxel-induced peripheral neuropathy.

3.2 *Immune cells and glia*

Paclitaxel treatment induces inflammation, with numerous pro-inflammatory chemokines released from either dorsal root ganglion neurons or associated cells. Receptor-mediated signaling by these chemokines can cause neuropathic pain. For example, the chemokine CXCL8 (otherwise known as IL-8) and its receptors CXCR1/2 are upregulated in rat dorsal root ganglion neurons. Importantly inhibition of CXCL8/CXCR1/2 signaling reduced paclitaxel-induced nociception and alleviated mechanical and cold hypersensitivity in a rat model (Brandolini et al., 2017). More recently, it was shown that upregulation of another chemokine, CXCL1, and its receptor CXCR2 and subsequent activation of PI3Kγ contributes to the development and maintenance of paclitaxel-induced mechanical hypersensitivity in mice (Manjavachi et al., 2019). Paclitaxel treatment of mice can cause accumulation of macrophages in the sciatic nerve, and upregulation of the chemokine receptor, CXCR4, and RAGE (Receptor for Advanced Glycation Endproducts) in dorsal root ganglia. Intriguingly, antagonists for CXCR4 and RAGE can prevent paclitaxel-induced allodynia (Sekiguchi et al., 2018). Another chemokine, MCP-1/CCL-2 (Monocyte Chemoattractant Protein 1) and its cognate receptor CCR2 may also play a role in paclitaxel-induced inflammation and macrophage migration, as increased MCP-1 expression was observed in small nociceptive dorsal root ganglion neurons and in spinal astrocytes in rats treated with paclitaxel (Zhang et al., 2013). This chemokine may stimulate CCR2 which is expressed

in large and medium-sized myelinated neurons. Direct addition of MCP-1 to dorsal root ganglion neurons led to calcium spikes selectively in CCR2-positive medium-sized neurons, and injection of anti-MCP-1 antibodies and CCR2 antisense oligonucleotides reduced intra-epidermal nerve fiber loss and mechanical hypersensitivity (Zhang et al., 2016). Similarly, previous studies showed that paclitaxel induces an inflammatory response in dorsal root ganglion neurons by activating the Toll-like receptor 4 (TLR4) pathway and increasing MCP-1 expression (Byrd-Leifer et al., 2001) (Li et al., 2014). Taken together, chemokine signaling plays a critical part in the crosstalk among different dorsal root ganglion neuron subpopulations and so contributes to neuropathic pain and allodynia. Cytokine-dependent nuclear translocation of nuclear factor-κB (NFκB), which regulates nerve growth factor, promotes paclitaxel-induced mechanical, thermal and cold hypersensitivity in outbred ICR mice (Meng et al., 2019). In this study, nuclear NF-κB translocation and peripheral nerve injury could be blocked by inhibiting the activation of p38 phosphorylation via duloxetine.

Recently a mechanistic link between complement, a key component of the innate immune system, and paclitaxel-induced peripheral neuropathy has been found (Xu et al., 2018). Using CRISPR/Cas9 in rats, a major component of this system, C3, was knocked out to study its involvement in paclitaxel-induced neuropathy. Rats lacking C3 showed improved sensitivity to touch and reduced loss of intradermal nerve fibers. Furthermore *in vitro* studies using the neuronal cell line PC12 revealed that paclitaxel treatment enhances C3 activation and this contributes to cytotoxicity.

Increasing evidence indicates that non-neuronal cells, including microglia and astrocytes of the CNS, are also involved in the initiation and resolution of pain. The role of microglia in paclitaxel-induced peripheral neuropathy has therefore been the subject to a few recent studies. It was shown that paclitaxel treatment induces microglia dysregulation in the dorsal horn of the spinal cord and increases the expression of cannabinoid type 2 receptor (CB2), and of the chemokines, CCL2 and interleukin (IL-6, IL-4 and IL-10) (Ha et al., 2019; Pevida et al., 2013; Wu et al., 2019). More recently, there has been a growing interest in cannabinoid receptors in the treatment of neuropathic pain. For example, by modulating microglia these receptors can have analgesic properties and reduce pain associated with paclitaxel-induced neuropathy (Burgos et al., 2012; Wu et al., 2019). Paclitaxel has further been shown to induce neuropathic pain by activation of spinal astrocytes, which causes the secretion of pro-inflammatory cytokines, i.e. tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β) and IL-6 (Ba et al., 2018; Burgos et al., 2012).

Other glia cells, such as satellite glial cells that support and surround DRG neuronal cell bodies, have been shown to play an additional role in paclitaxel-induced peripheral neuropathy. For example, paclitaxel treatment leads to increased gap junction coupling among satellite glial cells, which may contribute to pain sensation (Warwick and Hanani, 2013). It has been suggested that activation of TLR4 in satellite glial cells stimulates the release of TNF-α and subsequent inflammation, TRP channel activation, and pain sensation (Boehmerle et al., 2018; Duggett et al., 2016; Materazzi et al., 2012; Wu et al., 2015). Interestingly, TRPA1 and TRPV4 have also been implicated in paclitaxel-

induced cold hypersensitivity (Alessandri-Haber et al., 2004) Satellite glial cells were further shown to upregulate angiotensin II type 1 receptor (AT1R) following paclitaxel treatment, which increases the expression of inflammatory cytokines, such as IL-1β and TNF-α in the nearby dorsal root ganglion neurons (Kim et al., 2019).

3.3 *Pathogenesis of other taxanes leading to peripheral neuropathy*

Along with paclitaxel, also docetaxel and cabazitaxel belong to the family of taxanes that are used in oncology and which can cause peripheral neuropathy, although not as severe as the effects induced by paclitaxel treatment. However, few studies explored their mechanisms in this condition. Docetaxel binds to tubulin with greater affinity than paclitaxel and causes cell cycle arrest in the S rather than G2-M phase junction as is the case for paclitaxel (Dorr, 1997). Nonetheless, paclitaxel is more commonly associated with the development of CIPN in cancer patients (Chon et al., 2009; Hilkens and ven den Bent, 1997). In animal studies, docetaxel is typically administered to mice and rats through intravenous or intraperitoneal injection. However, few studies have described docetaxel-induced peripheral neuropathies. A decrease in nerve conduction velocity was observed for intravenous injection of docetaxel at doses between 5 and 12.5 mg/kg in rats (Persohn et al., 2005). Nevertheless, no significant changes in sciatic nerve morphology (number of fibers and demyelinization) have been reported (Persohn et al., 2005). Another study showed a decrease in nerve conduction velocity, intraepidermal fiber numbers and myelin protein expression in a docetaxel rat model (10mg/kg, i.v., 4 weeks) (Roglio et al., 2009). More recently, there have been reports of the involvement of TRPA1 receptors (through upward regulation) in the development of

mechanical allodynia induced by docetaxel (Huang et al., 2017). Cabazitaxel is a dimethyl derivative of docetaxel with equivalent efficacy to docetaxel for stabilizing microtubules *in vitro*. Clinical studies suggest that the incidence and severity of peripheral neuropathy may be lower with cabazitaxel compared with other taxanes (de Bono et al., 2010). However, to our knowledge, no animal studies explored the mechanisms involved in peripheral neuropathies and neuropathic pain induced by cabazitaxel.

4. Human genetic studies provide insight into clinical paclitaxel neurotoxicity

Human genetic studies have provided pathomechanistic insight into taxane-induced peripheral neuropathy. The genetic study design takes advantage of an important clinical fact: for a given taxane exposure, neuropathy can have dramatically variable severity or may not occur at all. By comparing genotypes in patients with varying CIPN phenotypes, these studies have uncovered specific genes and pathways that may underlie CIPN susceptibility. There are two broad approaches that are employed in these genetic studies: targeted or unbiased. In the targeted approach, specific genes that are hypothesized to contribute to CIPN susceptibility are investigated (i.e. neuropathy or metabolism genes), whereas in the unbiased studies, genome wide associations are investigated that may uncover unexpected pathways.

A review of available human genetic studies of taxane-induced neuropathy susceptibility on PubMed revealed 30 studies dating back to 2006, which includes both targeted (Abraham et al., 2014; Apellaniz-Ruiz et al., 2015; Apellaniz-Ruiz et al., 2017; Beutler et

al., 2014; Boora et al., 2016; Boora et al., 2015; de Graan et al., 2013; Dou et al., 2017; Eckhoff et al., 2015; Hertz et al., 2014; Hertz et al., 2013; Kulkarni et al., 2015; Leandro-Garcia et al., 2012; Lee et al., 2015a; Leskela et al., 2011; McWhinney-Glass et al., 2013; Mir et al., 2009; Park et al., 2017; Park et al., 2014; Sissung et al., 2006; Sucheston et al., 2011; Tanabe et al., 2017) and unbiased (Baldwin et al., 2012; Bergmann et al., 2013; Hertz et al., 2016; Leandro-Garcia et al., 2013; Schneider et al., 2016; Schneider et al., 2015; Sucheston-Campbell et al., 2018; Wheeler et al., 2013) approaches. Polymorphisms and mutations in genes that have been associated with altered risk of taxane neuropathy include genes in structural and cytoskeletal pathways, such as LIMK2 (Dou et al., 2017; Leandro-Garcia et al., 2013), MAPT (Park et al., 2017), SBF2 (Schneider et al., 2016), PRX (Beutler et al., 2014), TUBB2A (Abraham et al., 2014; Leandro-Garcia et al., 2012), TECTA (Bergmann et al., 2013), FGD4 (Baldwin et al., 2012), in neural developmental pathways, including GSK3B (Park et al., 2017; Park et al., 2014), EPHA4-6 (Apellaniz-Ruiz et al., 2017; Boora et al., 2016; Leandro-Garcia et al., 2013), BDNF (Azoulay et al., 2015), ARGHEF10 (Beutler et al., 2014; Boora et al., 2015), GPR177 (Schneider et al., 2015), SOX10 (McWhinney-Glass et al., 2013), in cell damage and apoptosis, including BCL2 (McWhinney-Glass et al., 2013), RWDD3 (Bergmann et al., 2013), FANCD2 (Sucheston et al., 2011), and in drug metabolism, including ABCB1 (Abraham et al., 2014; Boora et al., 2016; Sissung et al., 2006; Tanabe et al., 2017), CYP genes (Apellaniz-Ruiz et al., 2015; de Graan et al., 2013; Hertz et al., 2014; Hertz et al., 2013; Lee et al., 2015b; Leskela et al., 2011), GSTP1 (Eckhoff et al., 2015; Mir et al., 2009), in addition to several genes that when mutated can cause Charcot-Marie Tooth Disease and other neurodegenerative

diseases (Baldwin et al., 2012; Beutler et al., 2014; Boora et al., 2015; Hertz et al., 2016; Schneider et al., 2016). While these studies have provided mechanistic insights to genes and pathways that might influence taxane-induced peripheral neuropathy, many of these genetic association studies have been fraught with methodological problems and challenges with reproducibility. Varied methods of genetic analysis, underpowered studies, lack of validated cohorts, neuropathy phenotyping, and concomitant neurotoxic chemotherapies (often platinum-based compounds) have unfortunately prevented wide applicability of these studies (Argyriou et al., 2017; Cavaletti et al., 2011). A recent review suggested that ABCB1, TUBB2A, GPR177, and EPHA4-6 were the genes that had the strongest data supporting their role in taxane-induced neuropathy susceptibility and should be validated further (Argyriou et al., 2017).

Attempts at prevention of taxane-induced neuropathy or its treatment have been disappointing in human clinical trials. The only clear success in a large randomized clinical trial was the demonstration that duloxetine provides a modest improvement of pain in patients with established CIPN (Smith et al., 2013). All other studies were either negative or showed benefits in small cohorts that have not been reproduced (Majithia et al., 2016). Failed prevention trials have focused on diffuse neuroprotection and have employed agents that are cytoprotective, antioxidants and improve mitochondria function (Amifostine, glutathione, vitamin E, acetyl-L-carnitine). It is hoped that more targeted prevention strategies that focus on unique aspects of CIPN (drug transporters, axonal degeneration, neuroinflammation) will be able to prevent CIPN while still maintaining taxanes' tumor-killing properties.

In all the human CIPN studies described above, it is critical that researchers are able to accurately determine the presence of a given patient's CIPN and its severity. In the complicated clinical setting of a patient with cancer, this is less straightforward than it may initially seem. There has been intensive research into the methodology of quantitating CIPN in patients, which broadly can be divided into clinician-reported outcomes (ClinROs) and patient reported outcomes (PROs). ClinROs may include very blunt instruments such as the Common Terminology Criteria for Adverse Events (CTCAE) or more sensitive assessments such as, quantitative neurological examinations, neurophysiology, or nerve pathology (Argyriou et al., 2019). PROs in CIPN have become more widely used and are typically questionnaires related to symptoms (sensory, motor and autonomic) (Griffith et al., 2010) or functionality (e.g. activity of daily living) (Binda et al., 2015). Many of the above cited studies used poorly sensitive or specific CIPN tools such as the CTCAE, which raises concerns about the reliability of their findings. Fortunately, the more sensitive CIPN measurements, often a combination of ClinROs and PROs, are now routinely being incorporated into human studies of CIPN (Gewandter et al., 2018).

5. Conclusions

Of the patients given paclitaxel for cancer treatment, about 60-70% suffer from paclitaxel-induced peripheral neuropathy (Seretny et al., 2014). Paclitaxel-induced peripheral neuropathy, among other chemotherapy-induced peripheral neuropathies, is a major reason for early termination of chemotherapy. Although many groups have

begun to uncover mechanisms by which paclitaxel causes neuropathy, there are currently no effective clinical treatments available for this condition. Several questions are being addressed, including (i) What are the direct effects of paclitaxel on sensory axons? (ii) What type of damage causes specific symptoms? and (iii) Are the neurons or other cell types connect to neurons the primary targets of paclitaxel leading to neuropathy? In addition, it will be important to address whether alternative mechanisms, besides microtubule damage, which is the primary effect in cancer treatment, could cause axon degeneration. Addressing these questions is likely to enable the development of new treatments.

Microtubule stabilization has been analyzed as a potential cause of axonal degeneration, but most of the knowledge in this respect has been derived from *in vitro* analyses. An important observation *in vitro* and *in vivo* is that mitochondrial damage associated with oxidative stress also contributes to nerve damage, and given findings in the cancer field, which show that mitochondria can be directly targeted by paclitaxel and damaged (André et al., 2002; Kidd et al., 2002; Varbiro et al., 2001), it is possible that mitochondrial damage is a primary cause of axon degeneration through the formation of reactive oxygen species. Intriguing and consistent with this idea are findings that in some human trials, antioxidants such as Amifostine, acetyl-L-carnitine, β-carotene and α-tocopherol are beneficial to patients. Nevertheless, clinical trials with these agents have also revealed a great variability among between individual patients, which has prevented their widespread clinical use despite FDA approval (Block and Gyllenhaal, 2005; Maestri et al., 2005). The difficulty in using antioxidant therapies in addition to

cancer treatment is that interference with reactive oxygen species may exert widespread toxicities. For instance, cells depend on low-level reactive oxygen species whereas their overproduction in diseases like cancer, or due to chemotherapy treatment, causes cellular damage. Thus, finding the proper balance of antioxidants during treatment will be important but is inherently difficult. Intravenous injections of the antioxidant and anti-inflammatory agent, Amifostine, for instance, led to a wide variety of systemic toxicities like hypotension, nausea, vomiting, and hypocalcemia (Block and Gyllenhaal, 2005). On the other hand, many, but not all, of these toxicities were eliminated upon subcutaneous administration. This further highlights the complexity of oxidation and proper delivery of these agents into inherently different tissues and/ or cell types. Targeted approaches, such as those that manipulate the function of downstream or upstream factors of reactive oxygen species will likely be much more controllable since these approaches target one or few specific pathways. Efforts in the private sector have been under way to target, for instance, mitochondria damage induced by paclitaxel treatment to reduce the formation of reactive oxygen species.

Given a relatively broad understanding of potential mechanisms implicated in paclitaxel-induced peripheral neuropathy, the mechanisms identified thus far need to be carefully dissected in pre-clinical models in order to determine whether any of those might be useful for the development of treatments. Future efforts need to be directed at validating this mechanistic data in humans. One approach could be, for example, to compare data across species and with data in humans, such as patient databases. Conservation of mechanisms across multiple species including non-mammalian and mammalian

vertebrates or invertebrates has a higher chance to also be conserved in humans. Prior to clinical trials, some of the findings could be further validated using patient-derived induced pluripotent stem cells, for example. Generating new data sets from patient samples derived either from tissue storage resources or clinical trials could also be useful. Various efforts are currently under way, such as within the Toxic Neuropathy Consortium, to collect patient data across the globe for comparative purposes, which will be available to clinicians and scientists.

Additional efforts should be made to develop two classes of treatments, one class comprising preventative therapies, and those that can reverse the symptoms in those patients already suffering from the condition. Ideally one therapy shows efficacy toward both. These therapies could either target pathways inducing axon de- and regeneration or mitigate or prevent pain symptoms without opioid-based drugs. To date, most efforts concentrate on preventing painful neuropathies, which could be related to the increased efforts related to pain research. Some studies using non-mammalian *in vivo* models have in contrast been quite successful in their identification of new candidate targeting axon de- and regeneration pathways, which are also discussed in this Special issue.

Conflict of interest

The authors declare no conflicts of interest.

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Fig. 1. Mechanisms of paclitaxel pathogenesis leading to axon degeneration and painful neuropathy based on mammalian studies. Isolated rodent DRG neurons and patient-derived induced pluripotent stem cells have revealed acute and chronic changes in calcium signaling *in vitro*. *In vivo* studies using rodent models have shown various effects directly in sensory neurons and indirectly in skin cells, immune cells and glia. Genetic studies using patient data identified polymorphisms and mutations in various pathways associated with increased risk for paclitaxel-induced peripheral neuropathy (PIPN). Clinical trials for antioxidants have so far failed to prevent or reverse paclitaxel-neurotoxicity.

Highlights

- Inflammation, ion channel function and perturbed calcium homeostasis contribute to paclitaxel-induced neuropathic pain
- Reactive oxygen species formation and altered microtubule function are common in animal models of paclitaxel-induced peripheral neuropathy

- Genetic studies in patients with paclitaxel-induced peripheral neuropathy have revealed genes that are also altered in animal models and could represent new targets in the treatment of this condition