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Mechanisms of Paclitaxel-Induced Peripheral Neuropathy

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Abstract

Peripheral neuropathy is a common adverse effect associated with the use of a group of chemotherapeutic agents including paclitaxel (PTX) which negatively affect the quality of life of cancer survivors. In addition, it is considered as a dose-limiting side effect that hinder completion of appropriate chemotherapy regimen. In spite of 27 years of research in mechanisms of PTX neuropathy, there is no approved therapy for prevention of PTX-induced peripheral neuropathy (PIPN). Thus, there is a continuous need to characterize the possible mechanisms associates with PIPN in order to find appropriate targeted therapy for this clinical problem. In this review, most of the recent findings of the cellular targets implicated in PIPN are summarized.

Keywords
Paclitaxel, neuropathy, mitochondrial dysfunction, immune response, axon transport, lipid mediators

Introduction

Cancer is a leading cause of morbidity and mortality globally. In 2020, about 19 million new cancer cases were diagnosed and almost 10 million cancer deaths were recorded [1]. Thus, the overall demand of chemotherapeutics is rising with an estimated increase of 53 % in number of patients who need chemotherapy by 2040 compared to 2018 [2]. Many of those chemotherapeutics cause debilitating adverse effects that further increases the overall burden of therapy and increase the mortality rate of cancer. Some of these adverse effects include hepatotoxicity [3], renal [4] and pulmonary toxicities [5] as well as neurotoxicity [6]. Thus, there is a compulsive need to find drugs that reduce the adverse effects associated with chemotherapies. Peripheral neuropathy is a common adverse effect of many chemotherapeutic agents, such as platinum derivatives [7], taxanes [8], vinca alkaloids [9], epothilones [10] and bortezomib [11]. Chemotherapy induced peripheral neuropathy affects from 19 % to more than 85% of patients receiving anticancer therapy [12].

Between 1960 and 1981, the National Cancer Institute (NCI) and the United States department of agriculture (USDA) worked in partnership of a plant screening program to find out naturally occurring compounds with anticancer activity. Samples from Pacific yew tree, *Taxus brevifolia*, were acquired by Arthur Barclay in 1962. Crude extracts of different parts of the tree were tested, the bark extract was found cytotoxic [13]. By 1967, Mansukh Wani and Monroe Wall had isolated and identified the active ingredient from the bark of *Taxus brevifolia* and called it taxol, to refer to the species of the plant and the presence of hydroxyl groups in its chemical structure [14]. Taxol was not considered the most promising plant product due to the scarcity of the compound, since taxol is found in minute concentrations of 0.01%–0.05% in the bark [15].

However, the interest in taxol was invigorated in 1979 when the unique mechanism of its antitumor effect was identified [16]. Then, clinical trials showed that 30% of patients with advanced ovarian cancer responded to taxol therapy [17]. However, its further use in clinical trials resulted in severe depletion of T. brevifolia, since removing the bark killed the trees. In 1990, T. brevifolia appeared on the list of endangered species, and the Pacific Yew Act was passed in 1992 to safeguard the tree [18]. Thus, the NCI made the decision to transfer taxol to a pharmaceutical company for commercialization. The request for applications received four responses, and Bristol-Myers Squibb (BMS) was selected who trademarked the name “Taxol” and created the new generic name paclitaxel [19], despite the fact that the term taxol had been used in hundreds of manuscripts published over the course of 30 years.

The unique antitumor mechanism of PTX depends on interfering with mitosis [20]. During the metaphase of mitosis, chromatids attach to spindle microtubules via their kinetochores. In order to guarantee that each daughter cell will receive one copy of every chromatid, all kinetochores should make stable connections to their microtubules. Mitotic checkpoint is a signal transduction cascade that is activated when any of the kinetochores is not attached to its microtubule or the tension on microtubule resulting from microtubule depolarization, is insufficient to separate daughter chromatids [21-23]. In this way, mitotic checkpoint prevents premature chromosomal segregation and arrest cell in mitosis. [24].

Paclitaxel binds to the N-terminal 31 amino acids of the beta-tubulin subunit in the microtubule. Thus, PTX inhibits depolymerization of microtubules with the resultant decrease in tension on kinetochores during metaphase [25] resulting in activation of the mitotic checkpoint and mitotic arrest [22]. However, questions were raised regarding the fate of mitotically arrested cells. Mitotic arrest results in either death during mitosis

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or mitotic slippage in which cells exit from mitosis, without chromosome segregation. After slippage, cells may die, arrest, or continue cycling. What defines the fate of cells after mitotic arrest is still mysterious [26, 27]. In contrast, in cultured human cells, treated with the clinically relevant PTX concentrations (5–10 nM), mitosis is not arrested. After a few hours the cells satisfy the checkpoint and complete division to produce 2–3 daughters. The study by Zasadil, Andersen [28] showed that PTX permits the cells to pass through mitosis via formation of multipolar spindle. However, a portion of the cytokinetic tracks usually fail, and most divisions in paclitaxel produce two or three daughter cells. Moreover, a recent study showed that PTX promotes nuclear multiple micronucleation by nuclear budding in cells during interphase. The multi-nucleated cells die, through ill-defined mechanisms. Therefore, the non-mitotic mechanisms of PTX can explain the activity of PTX in tumors with low proliferative index [29].To our knowledge, the exact mechanism and consequences of mitotic catastrophe induced by PTX remains elusive.

Beside mitotic arrest, PTX has immunomodulatory effect. Tumor cells produce local mediators that stimulate tumor-associated macrophages to adopt a M2-like phenotype which assists tumor immune escape and angiogenesis. A current study demonstrated that PTX reset tumor-associated macrophages back into a pro-inflammatory M1 profile via TLR4 signaling [30]. PTX also boosts maturation and phagocytic activity of antigen-presenting cells [31] and inhibits the function of T-regulatory cells [32] in a TLR4-independent mechanism. Thus, PTX supports the immune system to arrest tumor cells.

In addition, PTX triggers intrinsic apoptosis through activation of caspase-3, caspase-9 and poly (ADP-ribose) polymerase as a result of release of mitochondrial cytochrome c (Cyt-c) due to PTX-induced opening of mitochondrial transition pore [33, 34]. However, [35] showed that PTX induced the intrinsic apoptosis was independent on release of Cyt-c. Moreover, the release of reactive oxygen species (ROS) induced by PTX induces cell death via DNA damage and inhibition of EGFR/PI3K/AKT/mTOR Signaling [36, 37]. However, the role of autophagy in cytotoxicity of PTX is controversial. Khing, Choi [35] showed that PTX increases the expression of Beclin-1 and light chain 3B (LC3-II) and concluded that autophagy is responsible for PTX-induced cell death specially after prolonged mitotic arrest. However, others showed that inhibition of autophagy enhance cell sensitivity to PTX [38].

Paclitaxel-induced peripheral neuropathy (PIPN) is a dose-limiting toxicity at doses of 200 mg/m^2 or higher, per cycle [39]. However, it remains mild or subclinical up to a cumulative dose of 1400 mg/m^2 [40, 41]. In a study on breast cancer patients using paclitaxel (PTX), PIPN persisted for 1 year in 64 % of patients while, 41% of patients suffered for 3 years after initiating PTX [42]. However, the incidence rate of PIPN shows a great variability among studies due to difference in the delivered dose-density, duration of therapy and applied screening systems of neuropathy.

Chronic neuropathy induced by PTX is mainly sensory while, motor and autonomic neuropathies are quite rare. Neuropathic pain is manifested as positive and negative symptoms. Positive symptoms include various painful symptoms e.g spontaneous pain episodes such as tingling and prickling sensations as well as tactile and thermal allodynia or hyperalgesia. Negative symptoms usually include neurological sensory deficits such as numbness and continuous feeling of wearing socks that diminishes the ability to feel ground properly that contributes to loss of balance and falls [43]. Symptoms are generally symmetrical, but may start in an asymmetrical manner [44].

Factors which increase the risk of PIPN includes the dose per cycle (more than 250 mg/m^2) [41] and the total cumulative dose of PTX (more than 1,400 mg/m^2) [40]. However, the infusion rate is not implicated in neurotoxicity at a dose of 135 mg/m^2. However, at a dose of 175 mg/m2, the 24 hours-infusion was found less neurotoxic compared to 3 hours infusion [45, 46]. Genetic variations in CYP2C8 are associated with more susceptibility to PIPN [47]. Furthermore, old [48] and obese patients as well as those with progesterone positive tumors show greater incidence and severity of PIPN [49]. Additional risk factors include diabetes mellitus and low level of physical activity.

To date, there is no approved drug for the prevention of peripheral neuropathy associated with cancer therapy. In order to find candidate agents for this purpose, it is important to understand the cellular and molecular pathways involved in PIPN. In this review, we will summarize the most recent studies exploring the pathogenesis of PIPN.

Mechanisms of paclitaxel induced peripheral neuropathy

Paclitaxel predominately causes sensory rather than motor neuropathy. This selectivity can be attributed to the inability of PTX to cross the intact blood brain barrier [50] and the anatomical differences between sensory and motor nerves which permits the access of PTX to sensory rather than motor fibers. Cell bodies of motor neurons are in the ventral horn of the spinal cord and thus protected by the blood-spinal cord barrier, whereas sensory neuron cell bodies reside in the dorsal root ganglia found outside the spinal cord. In addition, cell bodies of sensory neurons, but not motor neurons, are vascularized by fenestrated capillaries permeable to small molecules. Therefore, it is reported that PTX accumulation was much higher in the cell bodies of sensory neurons than motor neurons which persisted for at least 7 days after the last injection [51]. Moreover, the sustained retention of PTX has been attributed to a failure of efflux and chemical degradation to overcome intracellular target binding [52, 53].

1. Axonal transport

The main mechanism of antitumor activity of PTX relies on its ability to stabilize the bundles of microtubules, which disrupts cell proliferation. Interference with the dynamic nature of microtubules impair cell division but unfortunately, may disrupt the axonal transport system [54]

Microtubules (MTs) are one of the principal cytoskeleton components present in all eukaryotic cell types. Both α- and β-tubulin subunits binds to form a polarized linear protofilaments. Therefore, one end of a protofilament will have the α-subunits exposed which represent (-) end while the other end will have the β-subunits, (+) end. A cluster of 13 protofilament associated laterally together creates the MT with a negative and a positive ending [55]. MTs are extremely dynamic structures, existing in either a growing state (polymerization) or catastrophic state (depolymerization). Polymerization proceeds via addition of a GTP-bound heterodimer at the MT plus end, at the exchangeable (E-site) of β-tubulin. However, it is rapidly hydrolyzed to GDP. When most of tubulin in the MT is linked to GDP, the protofilaments splay apart and the MT depolymerizes [56, 57].

Microtubules play a major role during neuronal development [58]. MTS creates small bundle that invade lamellipodia in multiple points to help in formation of neurites and specify the

neuronal axon [59]. Moreover, MTs are also implicated in axonal elongation through cross talks with the growth cone, a dynamic structure at the tip of a growing axon [60]. MTs are also involved in synapse formation as well as transport of organnells, signaling proteins along the axis [61-64]. PTX stabilize the bundles of microtubules, via binding to the luminal side of GDP-tubulin β subunit resulting in inhibition of microtubule catastrophic phase. On one hand, there is evidence that paclitaxel diminishes the transport of proteins and organelles [65] which includes the mitochondrial. Thus, the delayed delivery of mitochondria due to transport deficits could impair functionality and even viability of long peripheral neurons Gornstein and Schwarz [66] due to the energy consuming nature of the neuronal tissues.

One example of the deteriorative effect of impaired axonal transport is the reduced transport of B-cell lymphoma-w (BCLw) to the axon ending of long nerves. B-cell lymphoma-w is able to bind and prevent activation of inositol 1,4,5-trisphosphate receptor (IP3R). The activated IP3R increases calcium flux into mitochondria and leads to activation of calcium-dependent calpains that subsequently induce axonal degeneration. Therefore, due to the impairment of axonal trafficking during paclitaxel treatment, Bclw is not transported to the axons. Thus, the brakes over IP3R are removed and the calpain-mediated axonal degenerative cascade is initiated [67].

On the other hand, stabilization of microtubules permits some forms of post transitional modification of microtubules such as acetylation, polyglutamylation and detyrosination. Those modifications can disrupt the axonal transport system [54, 68, 69]. However, the changes associated with PTX treatment do not consistently inhibit axonal transport. At high doses, PTX results in accumulation of bundles of MTs in axons which could impair the transport along the axon. However, aggregation of microtubules was not observed in sural nerve biopsies of patients with PIPN [70]. In addition, it has been proposed that binding of PTX to MTS might affect velocity of motor proteins e.g. kinesin 1. However, in vitro study by showed that PTX has no effect on velocity of kinesin 1 [71].

Moreover, studies by Gornstein and Schwarz [72], [73] showed that the impaired axonal transport is not implicated as an early mechanism of paclitaxel neurotoxicity. The study used microfluidic chambers to investigate the specific effect of PTX on soma and different parts of the axon. The distal axons were primarily vulnerable to neurotoxic effect of PTX, indicating that neurotoxicity is a direct effect of PTX on the distal part of the axon. The study showed that PTX neurotoxicity was evident after only 2.5 h of exposure of the entire axon. Meanwhile, the neurotoxic effect was lost when PTX was applied for two days but prevented from contacting the distal portion of the axon. Thus, interference with axonal transport might not be an initial mechanism of PIPN.

2. Mitochondrial dysfunction

Mitochondria are considered the metabolic hub of the cell, responsible for cellular energy production, control of the level of ROS and initiation of apoptosis. Thus, maintaining high-quality mitochondria is essential to maintain cellular function and viability. The mitotoxic effect of PTX was showed by earlier studies, since many articles reported the presence of numerous atypical mitochondria in sciatic and saphenous nerve of PTX-treated animals. In addition, PTX induces mitochondrial derived apoptosis through enhancement of the expression of apoptotic proteins such as caspase 3 which are involved in precipitation of PIPN [74, 75]. However, Figueroa-Masot, Hetman [76] showed that other bcl2-independent mechanism mediates the neurotoxic effect of PTX on cortical neurons.

Besides association with apoptosis, the neurotoxic effects of mitochondrial dysfunction can be attributed to the energy demanding nature of neurons. A huge amount of ATP is consumed by neurons for maintenance of resting membrane potential after each membrane depolarization. According to the type of neuron, a single action potential consumes 10^7 to 10^9 of ATP molecules [77, 78]. Thus, mitochondrial dysfunction and subsequent energy deficits very likely reduce the capacity of Na^+ /K^+ ATPase exchanger which consumes up to 50 % of neuronal energy [78, 79]. Thus, the electrochemical gradient across the cellular membrane is disrupted. The upset of resting membrane potential would facilitate spontaneous firing in sensory neurons, which is responsible for the burning pain that many patients of neuropathy report [54, 80]. Furthermore, the absence of an adequate energy supply has been linked to the inability of intraepidermal nerve fibers (IENFs) to sprout within the epidermis which subsequently leads to reduced number of IENFs, the clinical diagnostic marker of CIPN [81].

The mechanisms of PTX-induced mitochondrial damage have been intensively studied and revealed the involvement of the ability of PTX to alter the permeability of the mitochondrial membrane resulting in release of mitochondrial Ca^{2+} and cytochrome C [33, 82]. In addition, PTX induces deficits of oxygen consumption mediated via inhibition of complex I- and II-mediated respiration [83].

Furthermore, Wu and Chen [84] found that PTX reduces the expression of mitochondrial peroxisome proliferator-activated receptor γ co-activator 1α (PGC-1α) in rat dorsal root ganglia (DRG). PGC-1α is a crucial regulator of mitochondrial biogenesis. Activation of PGC-1α is required to promote the expression of most nuclear-encoding mitochondrial proteins, and triggers mitochondrial DNA replication and transcription. In addition, PGC-1α reduces phosphorylation of NFκB subunit p65 and diminishes the production of inflammatory cytokines which are considered one central regulator of PIPN. Moreover, PTX leads to impaired manipulation of reactive species (ROS and RNS) which further foster the mitochondrial dysfunction and energy deficit. It was observed that N-tert-Butyl-α-phenylnitrone (PBN), a non-specific ROS scavenger, prevented the development of paclitaxel-induced peripheral neuropathy [85].

To study the role of mitochondrial dysfunction as an initial cause of PIPN, Duggett, Griffiths [86] studied mitochondrial bioenergetics at 3 key behavioral timepoints; before, during and after resolution of pain in the cell bodies of sensory neurons of PTX-treated rats. They show that before onset of pain, PTX acutely provokes deficits in mitochondrial bioenergetics in DRG neurons, which is convoyed by decreased ATP levels. In presence of PTX-induced pain, DRG neurons were still deficient in ATP and favorably shifted to aerobic glycolysis. Glycolysis is the part of glucose metabolism that occurs in the cytosol and results in conversion of glucose to pyruvate with resultant 2 ATP/ glucose. This is associated with reduction of 2 molecules of NAD into NADH. Normally the step is followed by translocation of pyruvate to the mitochondria for further oxidation. However, under hypoxic conditions, pyruvate is converted into lactate via lactate dehydrogenase in the process called anerobic glycolysis. Some cells, shift to glycolysis even under normoxic conditions such as active immune cells as well as cancer cells. Epstein, Xu [87] showed that cells shift to aerobic glycolysis to meet the abrupt change in energy needs specially if related to the membrane pumps.

The shift to aerobic glycolysis is also suggested to be an adaptive mechanism to lower the production of ROS, the obligate byproduct of oxidative phosphorylation. The increase in oxidative stress would otherwise induces apoptosis. Therefore, switch to aerobic glycolysis prevents ROS-induced damage on account of less ATP. Although ATP deficiency has been considered a crucial contributor to both initiation and maintenance of PIPN, Ludman and Melemedjian [88] suggest that products of glycolysis, lactate and protons, are implicated in the neuropathic changes.

On one hand, lactate activates TLR4 resulting in recruitment of immune cells to DRG [89]. The active immune cells would produce inflammatory mediators that further sensitize DRG [90, 91]. On the other hand, the acidified extracellular space stimulates a variety of channels that enhance the excitability of the axons e.g transient receptor potential cation channel subfamily V member 1 (TRPV1) and ATP-gated P2X receptor cation channels, activation of those channels is involved in PIPN [92, 93].

A large body of evidence supports the pathological role of aerobic glycolysis. First, pharmacological inhibition of pyruvate dehydrogenase kinase- 1 (PDHK1) and lactate dehydrogenase (LDH), key enzymes of aerobic glycolysis, attenuated spontaneous pain behaviors in mice. Although it was demonstrated in a model of bortezomib-induced neuropathy [88], Duggett, Griffiths [94]showed that both enzymes PDHK1 and LDH are overexpressed in PIPN. Second, replenishing of cytosolic pool of NAD^+, known inhibitor of LDH, which also serves the ultimate goal of aerobic glycolysis to suppress oxidative stress was able to reverse PIPN. Third, The inhibition of the transcription factor HIF-1α, which increases the abundance of lactate dehydrogenase (LDH), and pyruvate dehydrogenase kinase was able to manage PIPN [95-97].

3. Immune response

A mounting body of evidence indicates that the neuropathic pain is not limited to changes in neuronal cells but may include a mutual interaction among neurons and immune cells. When nerve integrity is affected, activation of immune cells, which may be resident or recruited to the injured tissue, peripheral axons or the dorsal root ganglia and spinal cord, takes place. The activated immune cells lead to the release of several mediators from the damaged peripheral sensory neurons such as high mobility group box-1 (HMBG1), fibronectin, and heat shock proteins which triggers neuronal inflammation, hyperexcitability and potentiation of pain. Similarly, PTX-induced changes in microbiota and gut barrier dysfunction results in elevated systemic exposure to bacterial metabolites, which drives pain sensitivity [98, 99].

Paclitaxel has been associated with enhanced activation of neuronal toll-like receptors, TLR2, TLR4 and TLR9. PTX is considered a direct agonist of TLR4 which leads to increased expression of monocyte chemoattractant protein-1 (MCP-1) by DRG neurons resulting in macrophage infiltration to the DRG with subsequent increase in inflammatory cytokines. These events were accompanied with IENF loss and the development of behavioral signs of PIPN [100]. In a model of nerve injury, sialyltransferase *St3gal2* was upregulated in sensory neurons and associated with neuropathic changes. *St3gal2* led to an increase in the expression of the sialylated glycosphingolipid, GT1b which is a TLR2 agonist which induces proinflammatory microglia activation and central sensitization [101]. Although inhibition of TLR2 attenuates PIPN [102], the *St3gal2*-GT1b-TLR2 axis has not been studied in a model of PIPN.

The high mobility group box 1 (HMGB1), a non-histone nuclear protein, is mainly secreted by macrophages to act as a damage-associated molecular pattern (DAMP). PTX causes cytoplasmic translocation and extracellular secretion of HMGB1. A recent study by Domoto, Sekiguchi [103] showed that PIPN can be attenuated via HMGB1 neutralization or macrophage depletion. They demonstrated that PTX induces the release of HMBG1 from macrophages via activation of $P2X_7$ and $P2X_4$ mediated by neuron-derived ATP in a co-culture of macrophage-like RAW264.7 cells and neuron-like NG108-15 cells. Furthermore, HMBG1 activates TLR4 by binding to MD-2 [12,43] and binds to receptors of advanced glycation end products (RAGE) to enhance translocation of TLR4 to the cell membrane. Thus, HMBG1 promotes both surface expression and activation of TLR4 [104, 105].

Moreover, PTX activates different types of immune cells. Macrophages are predominantly skewed to the pro-inflammatory M1 type, which release pro-inflammatory cytokines that activate and sensitize the sensory neurons [91] while the number of M2 macrophages (anti-inflammatory phenotype) is reduced. In addition, PTX fosters a rise in the number of antigen-presenting cells, $CD3^+$ lymphocytes, and activated microglia [106-108]. Furthermore, the number of regulatory T lymphocytes (Treg) decreases [109, 110]. Recently, Brandolini, d'Angelo [111]demonstrated that PTX binds and activates complement component 5a receptor 1 (C5aR1) which is involved in PIPN as well as PTX-induced anaphylaxis.

PTX-activated immune cells secrete a plethora of inflammatory mediators, such as interleukins (IL): IL-1β [112], IL-6 [113], IL-8 [114], tumor necrosis factor α (TNFα), and interferon γ (IFN-γ)] and chemokines (e.g., CCL2, and CXCL12, CCL11, CCL3, and CCL4) [115], all are implicated in precipitation of neuropathy. Moreover, a lower expression of anti-inflammatory cytokines e.g. IL-10 [116] and IL-4 [117] is observed after the administration of several chemotherapeutics including paclitaxel.

4. Neuronal excitability

Paclitaxel alters the electrophysiology of peripheral neurons towards increased neuronal excitability via modulation of the expression of diverse receptors and voltage-gated ion channels. PTX enhances the expression of calcium channels Cav2.3, Cav2.2, Cav3.2 [118, 119] and sodium channel Nav1.7 [120]. Moreover, the potassium channel Kv7 responsible for maintaining resting membrane potential and controlling neuronal excitability, has been down-regulated by PTX in mouse DRG neurons [121].

Cation-chloride cotransporters, such as Na^+-K^+-$2Cl^-$ cotransporter-1 (NKCC1) critically regulate the intracellular chloride concentrations. PTX has been associated with enhanced expression of NKCC1 with subsequent decline in GABA-induced membrane hyperpolarization of dorsal horn neurons [122].

Transient receptor potential channels family. TRPV4, TRPA1 are mainly implicated in thermal sensitivity. TRPM8 is associated with sensation of cold. TRPV1, and TRPV4 are directly stimulated under oxidative stress conditions through modification of specific cysteine residues present in the pore-forming or cytoplasmic N and C terminal region of the channels [123, 124]. Meanwhile, activation of TRPM8 is directly linked to H_2O_2 and ROS production under oxidative stress and indirectly by ADP-Ribose (ADPR), a molecule generated by oxidative

stress-induced DNA damage, translocated from the nucleus to the cytoplasm and binds to the NUDT9-H domain present in the C terminal of the channel resulting in conformational changes that opens the pore [125]. PTX increases both expression and sensitivity of TRPV4 and TRPA1 in the rat DRG neurons resulting in boosting DRG neurons excitability [126].

5. Lipid mediators

Lipids, such as sphingolipids, sterols, glycerophospholipids (GPLs), and fatty acids (FAs) are essential structural components of the cell membrane. Lipids are the major component of myelin sheath; the structure which is mostly not intact in various types of neuropathies. Furthermore, the lipid rafts are involved in neuronal communication with the extracellular microenvironment. Thus, lipids serve as crucial signaling molecules.

Recent studies showed that linoleic acid metabolites, such as hydroxyoctadecadienoic acids (HODEs), 9,10-epoxyoctadecenoic acids (9,10-EpOME), are increased in the DRG after PTX treatment. These HODEs and 9,10-EpOME have been demonstrated to sensitize TRV1 channels [127]. Furthermore, lysophosphatidic acid (LPA) species (16:0- LPA, 18:0-LPA, and 18:1-LPA) transiently increase in the spinal dorsal horn within 1–3 days after the first PTX dose. Uchida, Nagai [128] demonstrated that LPA_1 and LPA_3 receptors mediates additional production of spinal LPA which is vital for the development of PTX-induced neuropathic pain. Importantly, the amount of certain LPA species in the cerebral spinal fluid of patients was correlated with pain intensity and symptoms, especially 18:1-LPA and 20:4-LPA [129].

Moreover, blockade of sphingosine- 1- phosphate (S1P) receptor 1 prevents and reverses paclitaxel-induced mechanical allodynia. S1P is synthesized primarily from hydrolysis of ceramide under the effect of both serine palmitoyl transferase activity and sphingomyelinase resulting in release of sphingosine which is then phosphorylated via sphingosine kinase. PTX increases the levels of ceramide and sphingosine as well as the activity of serine palmitoyl transferase activity and sphingomyelinase. Moreover, enzymatic activity of sphingosine kinase and the level of S1P in the spinal cord are markedly increased after PTX [130]. More importantly, clinical trials are ongoing to examine the efficacy of blocking S1P1 signaling by treatment with fingolimod [131].

6. Targets not related to the peripheral neurons

6.1. Brain effects

Omran, Belcher [132] decided to tweet out of the tune and proposed that the brain should be accused for CIPN. They suggested that the theoretical paradigm of PIPN should be shifted to include the effects of PTX on the brain. Although PTX per se is almost undetectable in the brain, Omran *et al* suggested that the brain is affected indirectly via altered afferent input including bizarrely excessive input from some sensory nerves and loss of input from others, similar to what happens with phantom limb pain [133]. They based their assumption on the predictive coding theory, which suggests that perceptual experience is determined principally by the brain's predictions at a given moment [134]. Therefore, neurotoxic chemotherapy might alter the brain's circuitry responsible for creating predictions (and thus perceptions), which explains the chronicity of PIPN.

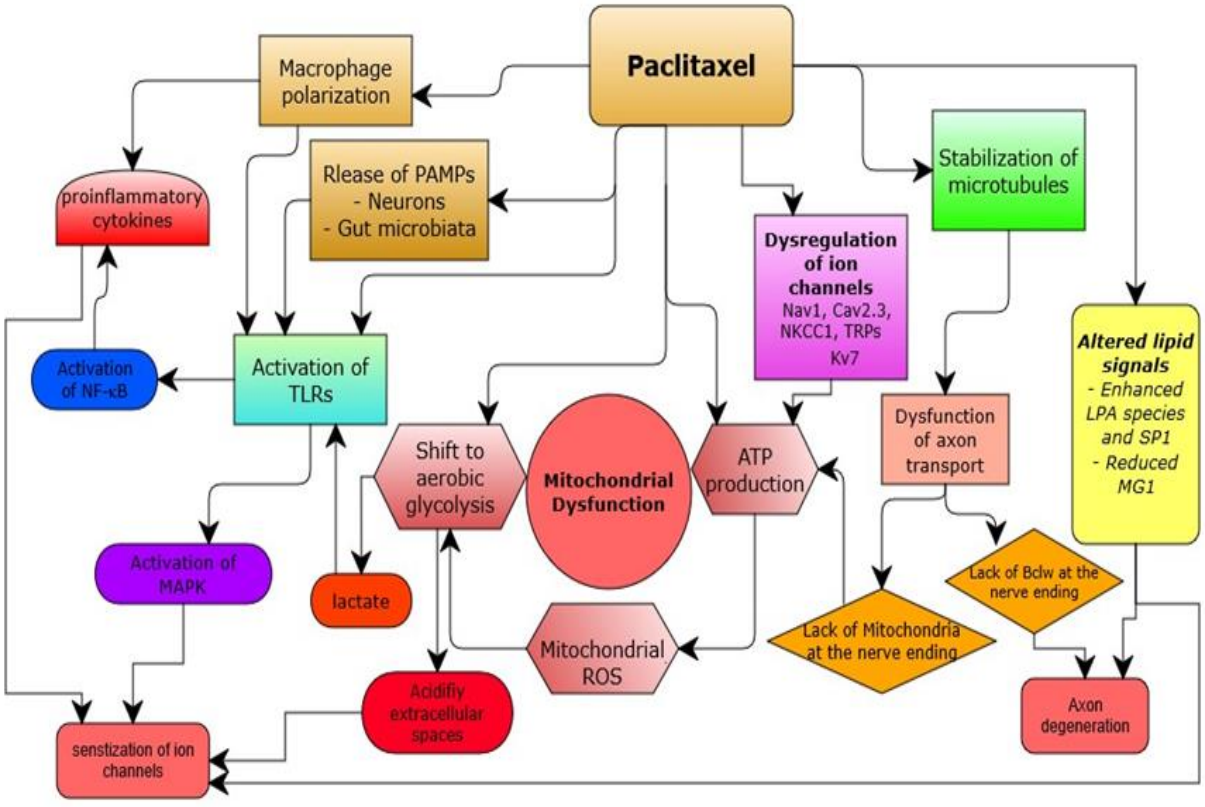

Figure 1. Summary of possible mechanisms implicated in paclitaxel neuropathy

This suggetion is supported by two main concepts. First, PTX triggers a state of hyperexcitability in several brain regions including the periaqueductal gray, thalamus, secondary somatosensory cortex, and insula, all of which are part of a well-known circuitry related to sensation and perception including pain [135-137]. Thus, they suggest that the state of pain is derived from impaired central modulation of pain rather than peripheral hyperexcitability. Second, PTX reduces GABAergic inhibition in the brain, thereby generates a molecular environment fostering neuronal hyperactivity [138].

6.2. Skin effects

Cirrincione, Pellegrini [139] demonstrated that PTX results in upregulation of matrix metalloproteinase- 13 (MMP-13) in keratinocytes via a ROS mediated mechanism. The study shows that PTX results in vacuolated mitochondria in both keratinocytes and epidermal neurons. Inhibition of MMP-13 results in resolution of PIPN without affecting the vacuolated mitochondria in the neuronal ending. Interestingly, MMP13 is not expressed in neurons, it is only expressed in keratinocytes and the protective effect of MMP-13 inhibition was demonstrated when DB004760 or CL-82198; MMP-13 inhibitors, were applied topically and the effect was lost when added to DRG. The study was initially done in zebra fish and then similar results were obtained in mice.

Conclusion

Herein, we provided an overview of the recent findings of the possible targets implicated in PIPN which include; dysfunction of axonal transport, mitochondrial dysfunction, activation of immune system, hyperexcitability of the axons as well as the role of lipid metabolites as shown in Figure 1. Although, medications based on these mechanisms and a variety of techniques has shown some neuroprotective effect against PIPN in experimental setting and clinical settings such as acupuncture [140], cryotherapy [141], compression therapy [142], exercise therapy [143], scrambler therapy [144]. In addition to a plethora of natural products and clinically used drugs including all-trans retinoic acid [145], amifostine [146], cannabinoids [147], goshajinkigan [148], metformin [149], minocycline [150], pregabalin [151], and venlafaxine [152]. However, none of these agents have been listed in ASCO guidelines for prevention of PIPN [153]. Thus, further studies are encouraged to uncover mechanisms needed to create a unifying hypothesis of PIPN and possibly produce a clinically-effective preventative strategy against PIPN.

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