Chemotherapy-Induced Neuropathic Pain

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Chemotherapy-induced peripheral neuropathy (CIPN) is a side effect of chemotherapics such as taxanes, vinca alkaloids, and platinum compounds. The pathways described so far are diverse and target various components of the peripheral Nervous System (PNS). Among the contributors to neuropathic pain, inflammation has been indicated as a powerful driver of CIPN.

chemotherapy peripheral nervous system chemokines\ inflammation

1. Introduction

Chemotherapy-induced peripheral neuropathy (CIPN) is a side effect of chemotherapics, such as taxanes, vinca alkaloids, and platinum compounds. Sensory neuropathy causes symptoms such as pain, allodynia, loss of sensation, paresthesia, numbness, tingling, and gait disturbance [1]. CIPN can result in significant loss of functional abilities and negatively impact quality of life, leading to lowering of the dose and discontinuation of assumption, and ultimately affecting overall survival rates [2]. Some chemotherapeutic drugs have been associated with a higher prevalence and duration of CIPN, such as taxanes and oxaliplatin treatment, which can last up to six months or two years after chemotherapy [1].

The mechanisms described so far are diverse and target various components of the PNS. The Dorsal Root ganglion (DRG), which lacks an efficient blood–brain barrier (BBB) [3], is prone to neurotoxic damage and can account for the sensory symptoms seen in CIPN. Pt compounds trigger DNA damage through Pt adducts and cause changes in the nucleoli of DRG sensory neurons, affecting the transcription machinery [4]. The accumulation of taxanes and vinca alkaloids in the DRG seems to produce nucleolar abnormalities [5] and modifications in the neurofilaments [6]. They also affect microtubule conformation through tubulin acetylation (**Figure 1**) [7]. Bortezomib (BTZ) [8] and vinca alkaloids [9] modify axonal transport by decreasing the supply of trophic factors and energy production, or by increasing Wallerian-degeneration and causing neurological damage, which is often permanent. Energy depletion in axons due to mitochondrial damage may contribute to the neurotoxicity exerted by different chemotherapics [10][11][12]. BTZ affects the integrity of the endoplasmic reticulum, mainly in Schwann cells [8], thus causing degeneration of the myelin sheath. The modulation of axonal ion channels may also be involved in CIPN. Dysfunction in Na^+ channels, mediated mainly by oxaliplatin, but also by paclitaxel and vincristine, can lead to an increase in Na^+ currents in the DRG, predisposing it to paresthesia [13][14][15]. Moreover, Ca^{2+} and K^+ channels are related to paclitaxel [16] and oxaliplatin toxicity [17], respectively. In addition, alterations in proteins involved in Ca^{2+} signaling (such as calpains and caspases) lead to apoptotic phenomena in the DRG [18]. Changes in the expression levels of transient receptor potential channels (TRPV, TRPA, and TRPM), as well as in molecules

related to glutamate signaling induced by Pt compounds, resulting from treatment with paclitaxel and BTZ [19][20][21][22][23], lead to hyper-responsiveness of nociceptors, rendering patients prone to neuropathic pain and peripheral neuropathy development. Chemotherapics also induce increased expression of mitogen-activated protein kinases (MAPKs), leading to neurotoxicity [24]. Vincristine, paclitaxel, and BTZ cause inflammation due to an increase in pro-inflammatory cytokines in the peripheral nerves and the number of antigen presenting cells in the skin [16][25]. Furthermore, the production of reactive oxygen species (ROS), combined with an increase in Ca^{2+} in the DRG, is a common following chemotherapy and leads to neuronal cytotoxicity [26][27][28].

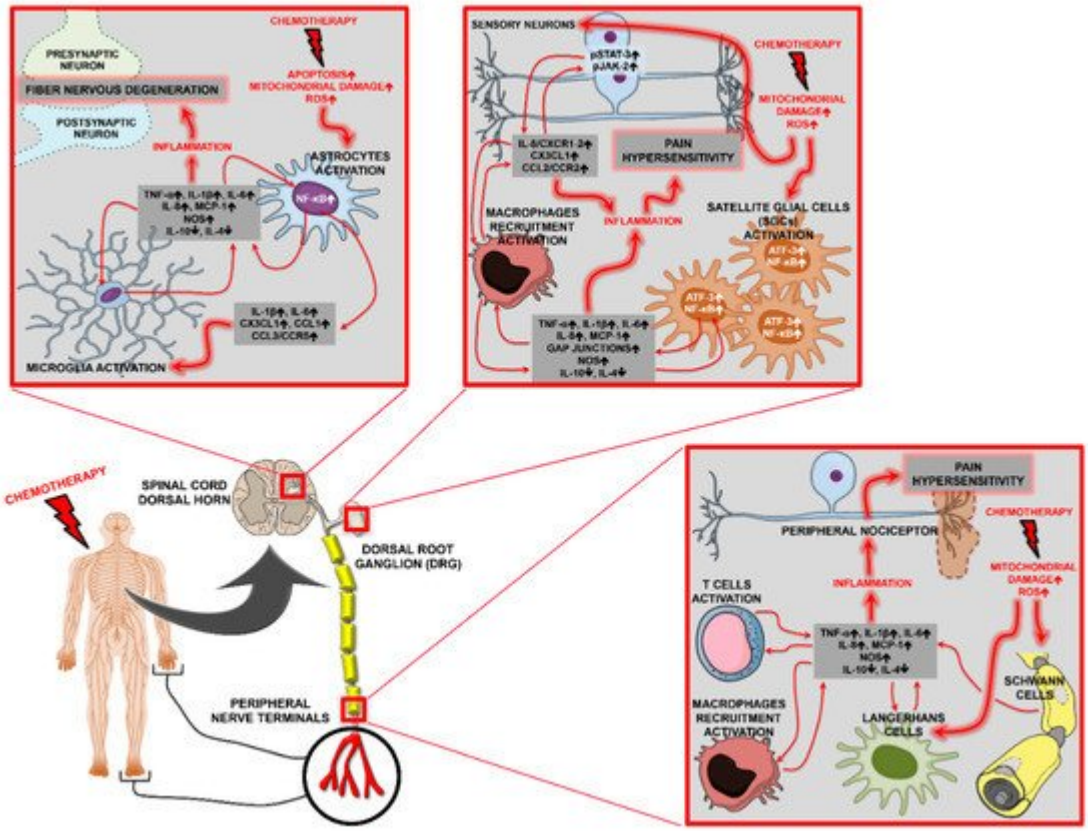

Figure 1. Summary scheme indicating the different players driving chemotherapy-induced peripheral neuropathy (CIPN).

Among the players in neuropathic pain, inflammation has been indicated as a potential common driver of CIPN. Several pieces of evidence have demonstrated a chemotherapy-induced increase in peripheral pro-inflammatory cytokines and a strong correlation with peripheral neuropathy [29][30]. At present, there is no adequate strategy to prevent CIPN, although there are active drugs for treating CIPN, such as duloxetine, that have displayed a moderate effect on CIPN.

2. Chemotherapy-Induced Peripheral Neuropathy

CIPN is a dose-limiting side effect of chemotherapy that affects 30–40% of patients undergoing treatment [31]. It has been described as a functional impairment of neurons characterized by oxidative stress, inflammation,

apoptosis, and electrophysiological failure.

It is generally accepted that, at the neuronal level, chemotherapeutic drugs damage microtubules and affect microtubule-based axonal transport, damage mitochondrial function, alter ionic homeostasis, or directly target DNA [32], leading to peripheral nerve degeneration or small fiber neuropathy. Taxanes and vinca alkaloids exhibit an antiproliferative effect by disrupting mitotic spindles and causing cell cycle arrest [32]. Platinum agents are known to cause CIPN by damaging the DRG through mitochondrial dysfunction and apoptosis, while also causing DNA damage or oxidative stress [33]. New drugs, such as bortezomib, eribulin, and ixabepilone, are also correlated with significant incidences of CIPN by affecting tubulin polymerization [33][34]. Glial cells seem to play a crucial role in CIPN. Alterations of Schwann cells, satellite cells in the DRG, and astrocytes in the spinal cord after chemotherapy lead to the activation of apoptosis [35]. Loss of glial cells results in a decrease in the protection and sustainment of nerve fibers and consequent defects in the propagation of the action potential [36]. Numerous findings indicate that CIPN, in addition to causing morphological changes, triggers the involvement of the inflammation and immune responses. Chemotherapy can cause mitochondrial DNA adducts and defects in electron transport chain proteins, leading to mitochondrial dysfunction [37][38]. This event is accompanied by disequilibrium in the redox potential and an increase in ROS within cells [37]. These reactive species can trigger perturbations in peripheral neurons, such as mitochondrial apoptosis, inflammation, and subsequent nerve degeneration [37][38]. ROS can also damage biomolecules such as phospholipids, resulting in demyelination, oxidized proteins, and an increase in carbonyl by-products, which can activate transient receptor potential vanilloid (TRPV) channels, impair antioxidant enzymes, and destroy microtubules [37]. Adducts to nuclear DNA and peroxynitrite create strand breaks, promoting neuronal apoptosis [39][40]. Intracellular ROS can also cause peripheral nociceptor over-excitation by increasing pro-inflammatory mediators (interleukin (IL)-1β, tumor necrosis factor-α (TNF-α), bradykinin, and nerve growth factors) [37][41]. All these metabolic, bioenergetic, and functional impairments lead to the development and maintenance of peripheral neuropathic injuries in neurons [37]. On the basis of these observations, it appears that preventative therapies for CIPN are urgently required for patients receiving chemotherapy.

Although many strategies have been developed, no specific intervention is presently recommended for the prevention or management of CIPN. In many patients, chemotherapy is discontinued due to CIPN, which increases the risk for patients. No efficient treatment options are presently available for CIPN because its exact pathophysiological mechanisms are not yet fully elucidated. Most of the pharmacologic treatments available for neuropathic pain include tricyclic antidepressants and anticonvulsants, which are minimally effective for CIPN and/or have substantial side effects [42][43][44]. At present, only duloxetine is recommended by the American Society of Clinical Oncology (ASCO) for CIPN treatment, based on a modest positive result obtained in one randomized controlled trial (RCT) [45].

3. Cytokine Signaling in CIPN

The inflammatory response triggered by chemotherapeutics has been indicated as a possible driver of the nociceptive process in CIPN [46][47]. The release of pro-inflammatory and chemotactic cytokines (chemokines) upon treatment has been suggested to be one of the primary mechanisms regulating neuro–immune interactions.

Downstream cytokine effects are pivotal triggers of neuroinflammation in the sensory nervous system [48][49]. Chemotherapeutic administration significantly increases the production and release of cytokines, such as TNF-α, IL-1β, and IL-6, and chemokines, such as IL-8 and MCP-1 [25][50][51]. Pro-inflammatory cytokines may be responsible for neural cytotoxicity, not only through inflammation but also through direct activity, mediated by specific receptors, on neurons and glial cells [52][53][54][55]. Several preclinical observations have indicated the involvement of cytokine signaling in the pathogenesis of CIPN. Several studies have indicated an increase in pro-inflammatory cytokines (TNF-α, IL-1β, and IL-6), combined with a decrease in anti-inflammatory cytokines in the DRG and spinal cord [25][40][56]. The role of inflammation in vincristine-induced PN is still debated. An increase in Langerhans cells (LCs) in the skin, which leads to intraepidermal nerve fiber loss, has been reported as a consequence of inflammatory mechanisms [16]. The onset of pain triggered by an increase in LCs has been attributed to two main events: an increase in nitric oxide release [57] and the release of pro-inflammatory cytokines and neurotrophic factors [58][59], both of which result in the sensitization of nociceptors and mechanical hypersensitivity. In support of these findings, it has been shown that spironolactone, an aldosterone receptor antagonist with anti-inflammatory properties, has a beneficial effect in improving vincristine-related pain [47].

Several inflammation processes (the increase of LCs, the regulation of pro-inflammatory cytokines, macrophage accumulation, and microglia activation) are involved in the onset of neuropathic pain following chronic treatment with paclitaxel. Upregulation of pro-inflammatory cytokine gene expression in lumbar DRG following paclitaxel treatment has been reported [25]. Furthermore, an initial upregulation of ATF-3 in the DRG and Schwann cells, followed by macrophage activation in the DRG and sciatic nerve and microglial and astrocyte activation in the spinal cord, has been described [60]. Paclitaxel increased TNF-α and IL-1β and decreased IL-10 and IL-4 in the spinal cord, in association with peroxynitrite elevation due to the increased activity of nitric oxide synthase and nicotinamide adenine dinucleotide phosphate oxidase. Inhibition of peroxynitrite formation sharply decreased TNF-α and IL-1β and augmented IL-10 and IL-4 expression [40][61]. Genetic and pharmacological inhibition of S1PR1 by selective antagonists in distinct chemical classes decreased and counteracted neuropathic pain in mice models of traumatic nerve injury. The antagonists maintained the capability to inhibit neuropathic pain during sustained drug treatment, and these effects were independent of opioid circuits. Moreover, knockouts of S1PR1 in mice astrocytes led to the absence of neuropathic pain following nerve injury, indicating astrocytes as the primary inducer of S1PR1 activity. At the molecular level, it has been demonstrated that the decrease in neuropathic pain caused by S1PR1 inhibition was due to IL-10, an anti-inflammatory cytokine [62].

Additionally, elevated levels of IL-1β in paclitaxel-treated rats have been associated with glycogen synthase kinase 3β (GSK3β) activation. Inhibition of GSK3β activity counteracted pain hypersensitivity and IL-1β release in the dorsal spinal cord [63]. It has been reported that augmented expression of TNF-α, IL-1β, and IL-6 in the spinal cord following paclitaxel treatment lasted for eight days and was no longer present at day 29, indicating a transient increase in cytokine production in the Central Nervous System (CNS) [64].

In the PNS, elevated expression of IL-1β and TNF-α was reported in the DRG of animals after 36 days of paclitaxel treatment and was decreased by IL-10 gene therapy [25][61]. Moreover, it has been established, in vitro and in vivo, that sensitive neurons are able to modulate cytokine production, thus contributing to the onset of CIPN [65].

Oxaliplatin treatment in rats caused an increase in IL-1β and TNF-α and a decrease in IL-10 and IL-4 in the spinal cord after 25 days of treatment [56].

Pro-inflammatory cytokine expression is generally upregulated in both the CNS and PNS following chemotherapy treatment in animal models.

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