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REVIEW

Biological Mediators and Partial Regulatory Mechanisms on Neuropathic Pain Associated With Chemotherapeutic Agents

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Summary

One of the most common issues caused by antineoplastic agents is chemotherapy-induced peripheral neuropathy (CIPN). In patients, CIPN is a sensory neuropathy accompanied by various motor and autonomic changes. With a high prevalence of cancer patients, CIPN is becoming a major problem for both cancer patients and for their health care providers. Nonetheless, there are lacking effective interventions preventing CIPN and treating the CIPN symptoms. A number of studies have demonstrated the cellular and molecular signaling pathways leading to CIPN using experimental models and the beneficial effects of some interventions on the CIPN symptoms related to those potential mechanisms. This review will summarize results obtained from recent human and animal studies, which include the abnormalities in mechanical and temperature sensory responses following chemotherapy such as representative bortezomib, oxaliplatin and paclitaxel. The underlying mechanisms of CIPN at cellular and molecular levels will be also discussed for additional in-depth studies needed to be better explored. Overall, this paper reviews the basic picture of CIPN and the signaling mechanisms of the most common antineoplastic agents in the peripheral and central nerve systems. A better understanding of the risk factors and fundamental mechanisms of CIPN is needed to develop effective preventive and therapeutic strategies.

Key words

Neuropathy • Bortezomib • Oxaliplatin • Paclitaxel • Inflammation • Proinflammation • Oxidative stress • Mechanical pain • Cold sensitivity

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Introduction

Cancer is a leading cause of mortality worldwide [1]. One of the most common and distressing symptoms suffered by patients with progression of cancer is pain [2]. Cancer pain mainly arises from a tumor compressing or infiltrating tissue; from nerve and other changes caused by a hormone imbalance or immune response; and/or from treatments and diagnostic procedures [2,3]. It is promising that effective treatments including chemotherapeutic agents can increase the number of cancer survivors [1] whereas the side effects are present. Among them, one of the most common problems caused by antineoplastic agents is chemotherapy-induced peripheral neuropathy. It should be noted that chemotherapy produces painful conditions persisting long after treatment has ended [2,4,5]. This side effect caused by chemotherapeutic agents is still a serious clinical issue for cancer patients during treatment. As a result, how to effectively manage neuropathic pain related to these therapies becomes important for treatment and management of cancer patients in clinics. Nonetheless, treatment options for these abnormal sensations have been restricted, partly due to a poor understanding of the underlying mechanisms responsible for neuropathic pain induced by chemotherapy. Also, there are lacking of effective drugs applied to patients; and costs and side effects of drugs affect a treatment strategy of neuropathic pain in patients with chemotherapy. Thus, alternative

treatment strategy of neuropathic pain is noteworthy during chemotherapy on the basis of study findings of basic signaling pathways.

Chemotherapy-induced peripheral neuropathy (CIPN)

CIPN is a nerve-damaging side effect of antineoplastic agents in the common cancer chemotherapy, which involves various symptoms such as tingling, pain, and numbness in the hands and feet in addition to motor, and/or autonomic functions [6]. Patients may experience numbness, tingling, altered touch sensation, gait and balance disturbances, burning pain, thermal allodynia or hyperalgesia, impaired vibration sense, extreme temperature sensitivity, paresthesia, and/or dysesthesia as part of sensory damage [7]. These symptoms can impair activities of daily living, such as typing or dressing, reduce balance, and increase risk of falls and hospitalizations, which can cause to decrease and/or discontinue chemotherapy in cancer patients.

Nonetheless, there are lacking effective interventions preventing CIPN and treating the CIPN symptoms. Therefore, it is important to explore the underlying mechanisms leading to CIPN and develop effective preventive and therapeutic strategies. As following, we will discuss results obtained from recent human and animal studies, including the abnormalities in mechanical pain and cold sensitivity response following chemotherapy. This provides the basic picture of CIPN and the signaling mechanisms of the most common antineoplastic agents such as representative bortezomib (BTZ), oxaliplatin (OXL) and paclitaxel (PLT). The underlying mechanisms of CIPN at cellular and molecular levels are also reviewed for additional in-depth studies needed to be better explored. A better understanding of the risk factors and underlying mechanisms of CIPN is needed to develop effective preventive and therapeutic strategies.

Chemotherapeutic agents causing neuropathy

There are six main agent groups found in chemotherapy treatment that damage the sensory, motor, and autonomic neurons and therefore cause CIPN [1,6,7]. They include proteasome inhibitors, platinum-based compounds, taxanes, vinca alkaloids, epothilones, and immunomodulatory drugs (Table 1). In this review, we focus on the agents which have been recently studied with respect to the signaling pathways responsible for neuropathic pain.

Cellular and molecular mechanisms leading to neuropathy in the peripheral nerve system

There are many signaling pathways in the peripheral nerve system responsible for CIPN. The presented Figure 1 partly summarizes signaling pathways associated with neuropathic pain after antineoplastic treatment. Specifically, inflammation and oxidative stress are generally involved in the process of CIPN. The detailed discussion is followed as below. It is also interesting to pay attentions to a number of interventions to improve neuropathic pain in experimental models discussed in each section.

Pro-inflammatory cytokines (PICs)

PICs are produced predominantly by activated macrophages and are involved in the up-regulation of inflammatory reactions. There is abundant evidence that certain pro-inflammatory cytokines such as IL-1β, IL-6, and TNF-α are involved in the process of pathological pain. Furthermore, BTZ, OXL and PLT were reported to increase the level of IL-1β, IL-6 and TNF-α in the sensory nerve-dorsal root ganglion (DRG) of rats thereby inducing pain behaviors [8,9]. Consistent with these findings, blocking PIC signaling pathways inhibits mechanical and thermal hypersensitivity [10,11].

In particular, *via* PIC signaling proteinase-activated receptor 2 (PAR2) and transient receptor potential ankyrin 1 (TRPA1) are engaged in neuropathic pain induced by BTZ in rats [11]. Results of this prior study demonstrated that systemic injection of BTZ increased mechanical pain and cold sensitivity as compared with control animals. Data of this report further showed that blocking respective PAR2 and TRPA1 attenuated mechanical pain and cold sensitivity observed in control rats and BTZ rats. Notably, the attenuating effect of blocking PAR2 and TRPA1 on mechanical pain and cold sensitivity was significantly smaller in BTZ rats than that in control rats. In addition, protein expression of PAR2 and TRPA1 was upregulated in the lumbar DRG of BTZ rats, and inhibition of PAR2 decreased the levels of TRPA1 and attenuated its downstream pathways (namely, PKCε and PKA). This suggests that there is a specific regulatory pathway PAR2-TRPA1 in involvement of BTZ-induced neuropathic pain and that

Table 1. Chemotherapeutic agents causing neuropathy.

Category	**Examples**	**Treatment**
Proteasome inhibitors	Bortezomib	Multiple myeloma certain types of lymphoma [47,48]
Platinum-based compounds	Oxaliplatin, cisplatin carboplatin	Solid tumors, i.e., stomach, liver, lung, ovarian, brain, uterine cancers [49]
Taxanes	Paclitaxel, docetaxel cabazitaxel	Ovarian, breast, on-small cell lung, and prostate cancers [48,50]
Vinca alkaloids	Vincristine, vindesine, vinblastine, vinorelbine	Hodgkin lymphoma, testicular cancer, and non-small cell lung cancer [51]
Epothilones	Ixabepilone	Non-small lung, ovarian, and prostate cancers [52]
Immunomodulatory drugs	Thalidomide	multiple myeloma [53]

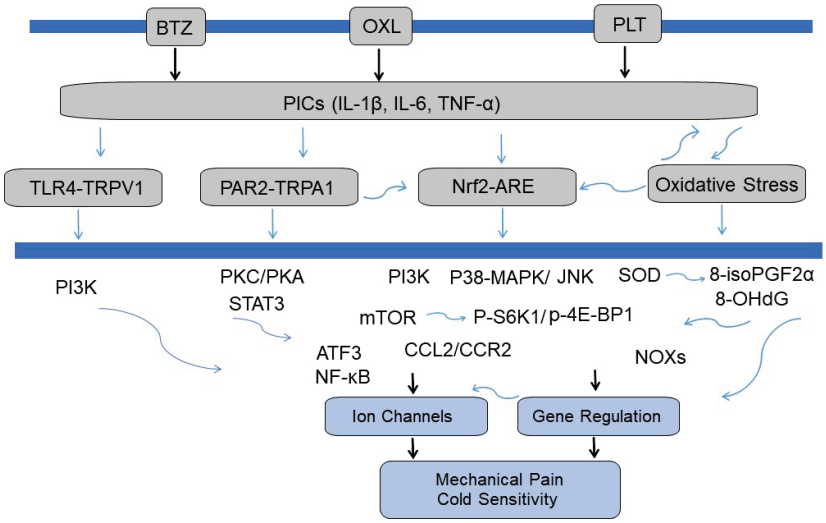

Fig. 1. The diagram describes signaling pathways in the peripheral nerve system for the neuropathic pain following administration of representative agents of chemotherapy. In chemotherapy-induced peripheral neuropathy, the responses of pro-inflammation cytokines and oxidative stress are mainly involved in neuropathic pain. Using experimental models of neuropathy, a number of studies have demonstrated that the protein expression of several receptors in dorsal root ganglion are upregulated and thus alter functions of ion channels in sensory neurons with stimulation of these receptors are increased, thereby leading to the exaggerated mechanical pain and cold sensitivity. Those signaling pathways also alter factors involved by gene regulation and thereby neuropathy. Note that there are many molecular mediators engaged in regulation of neuropathic pain following chemotherapeutic agents. The efforts are made to focus on some commonly shared signaling pathways by those agents.

intracellular PKCε and PKA play a role [11]. In the similar way, blocking PAR2 also significantly decreased TRPA1 expression in the DRG tissue and attenuated mechanical pain and cold sensitivity observed in control rats and OXL rats [10]. Also, the attenuating effect of PAR2 on mechanical pain and cold sensitivity was significantly smaller in OXL-rats than that in control rats.

On top of TRPA1, OXL induced up-regulation of the mRNA of the TRPV1 and TRPM8 in cultured DRG neurons [12] whereas OXL causes cold allodynia and enhance the sensitivity and expression of TRPM8 and TRPA1. Increased levels of CCL2 and CCR2 accompanied by mechanical hypersensitivity [13,14] were found in experimental model after application of OXL. IL-8 signaling pathway is also involved in neuroinflammation [15] and microbiota -TLR4 activation on macrophages.

In addition, several studies have implicated dysregulation of transcription factors in the DRG in the development of BTZ-induced CIPN. Following BTZ administration, nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) is increased in intranuclear fractions, indicating activation of the NF-κB signaling pathway [16,17]. Consistent with this finding, transgenic mice expressing a dominant negative form of IκBα (an endogenous inhibitor of NF-κB), which inhibited NF-κB translocation to the nucleus by preventing endogenous IκBα degradation, did not

develop CIPN [17]. Moreover, BTZ-induced axonal degeneration of the sciatic nerve was less severe in these transgenic mice, while decreased density of intraepidermal nerve fibers occurred at the same level observed in wild type mice [17]. Upregulation of activating transcription factor 3 (ATF3) is also reportedly involved in BTZ-induced CIPN. In DRG neurons of CIPN rodents, ATF3-immunoreactivity was increased in the nucleus, whereas vehicle-treated animals rarely exhibited immunoreactivity [18,19]. The increase of ATF3 elicited by BTZ enhanced the recruitment of c-Jun, a transcription factor known to form a heterodimer with ATF3 that binds the promoter region of CCL2, ultimately resulting in upregulation of CCL2 and the development of neuropathic pain [19]. Signal transducer and activator of transcription-3 (STAT3) is also highly phosphorylated in DRG neurons following BTZ injection [20]. Indeed, both pharmacological and genetic inhibition of STAT3 and treatment prevent the development of BTZ-induced mechanical allodynia in rats and mice [20].

Likewise, PLT was observed to amplify IL-1β, IL-6 and TNF-α in the DRG whereas it increased mechanical and thermal hypersensitivity [21]. Interestingly, EA attenuated increases in IL-1β, IL-6 and TNF-α after PLT and attenuated mechanical and thermal hypersensitivity. Results of this previous report suggest that downregulation of IL-1β, IL-6 and TNF-α in the DRG is involved in the inhibitory effects of EA on mechanical pain and thermal hypersensitivity in PLT-induced neuropathy [21]. It should be noted that other general signaling pathways involved in BTZ and OXL are also found in experimental models of PLT including NF-κB, CCL2/CCR2, TLR4 etc. [1,7,22]. This suggests that BTZ, OXL and PLT have a common regulatory mechanism in engagement of neuropathic pain and it is significant to target those signaling pathways for improve symptoms of neuropathy during chemotherapy in patients.

Oxidative stress and Nrf2-antioxidant response element (Nrf2-ARE)

The role of oxidative stress in CIPN has been studied. A number of studies have demonstrated that BTZ, OXL and PLT increase products of oxidative stress and thus stimulate signaling pathways of oxidative stress in CINP [1,6,7,22]. The side effects due to antineoplastic agents occurs due to activation of nuclear factor NF-κB and free radical injury is also involved in the antineoplastic agent-mediated neurotoxicity as dysregulation of nuclear factor (erythroid-derived 2)-like 2 (Nrf2) is seen. Note that Nrf2 is a transcription factor and as a basic leucine zipper protein it regulates the expression of antioxidant proteins protecting against oxidative damage triggered by injury and inflammation [23]. Numerous drugs that stimulate the Nrf2 pathway were used for treatment of diseases caused by oxidative stress [24]. This protects against the free radical injury by regulating glutathione S-transferases and hemeoxygenase-1 (HO-1). Thus, correcting the imbalance between NF-κB and Nrf pathways is suggested to affect CINP following chemotherapy [25]. *Via* those pathways, BTZ and OXL have been reported to increase activities of oxidative stress and alter Nrf2-ARE mechanisms thereby leading to neuropathic pain [26-29].

In particular, as a non-specific reactive oxygen species (ROS) scavenger, N-tert-butyl-α-phenylnitrone (PBN) was reported to inhibit the development of PLT-induced mechanical hypersensitivity [30]. Also, tempol used for supplement of ROS scavenger inhibited the development and maintenance of PLT-induced mechanical hypersensitivity, but was ineffective on cold allodynia [8,30]. In addition, the activity of different antioxidant enzymes in the DRG and peripheral sensory nerves were examined during the time course of PLT-induced painful neuropathy. Enhanced activity of mitochondrial and cellular endogenous antioxidant enzymes in the DRG and peripheral nerves was observed, however this was inadequate and delayed in its onset leading to excessive ROS in peripheral sensory axons [31]. Others have demonstrated an impaired mitochondrial antioxidant response after PLT [32].

In addition to antioxidants and/or free radical scavengers, it is also interesting to determine the effects of decreasing ROS generation on PLT-induced mechanical and thermal hypersensitivity. One source of ROS production is the enzyme family of NOX. The rodent genome encodes four genes that contain the catalytic NOX subunit, namely NOX1, NOX2, NOX3, and NOX4 [33]. This electron-transferring subunit is constitutively inactive in resting cells and generates ROS only upon activation, e.g. after noxious stimuli [34]. While NOX2 activation is predominantly associated with innate immunity mediated host defense and NOX1 with blood pressure control and related vascular mechanisms [35,36], NOX4 was shown highly expressed under ischemic conditions in the central nervous system, e.g. ischemic stroke [37]. Evidence has also identified

activation of NOX4 as a causative factor that contributes to inflammatory or neuropathic pain role in the peripheral nervous system [38]. A recent study further determined the effects of EA intervention on expression levels of NOX4 in the DRG of PLT rats [39]. It was observed that NOX4 was upregulated after administration of PLT and EA attenuated upregulation of NOX4 as well as increases of oxidative 8-iso PGF2α/8-OHdG [39].

Moreover, results of a recent study demonstrated that the expression of Nrf2-ARE signal and SOD expression were downregulated in the DRG of PLT rats as compared with control rats [21,39]. The expression of NOX4, the levels of oxidative products 8-iso PGF2α/8-OHdG and PICs such as IL-1β, IL-6 and TNF-α were amplified in the DRG of PLT rats. In those prior studies, results further demonstrated that PICs were decreased and mechanical and thermal hypersensitivity were attenuated in PLT rats after inhibition of NOX4 and systemic supplying of SOD and antioxidant vitamin C as well as EA [21,39]. Notably, results of those studies suggest that EA intervention 1) restored impairment of Nrf2-ARE and SOD in the DRG of PLT rats; 2) inhibited amplification of NOX4 and 8-iso PGF2α/8-OHdG and PICs, thereby alleviating neuropathic pain induced by PLT. This provides an alternate potential approach to alleviate neuropathic pain for cancer patients during chemotherapy, which should be considered for application in clinical practice before any better drugs are developed.

TLR4-PI3K-TRPV1 signaling pathways

In addition, TLR4-PI3K-TRPV1 signaling pathways are also involved in the neuropathic pain induced by chemotherapy and EA has improving effects on pain responses *via* this mechanism. i.e., a study reported that PLT-induced pain hypersensitivities *via* TLR4 and EA can significantly alleviate neuropathic pain induced by PLT [40]. As a downstream signaling TRPV1 was observed to be upregulated in DRGs of PLT-treated rats, whereas EA reduced overexpression of TRPV1. Experiments of Ca^{2+} imaging further indicated that TRPV1 channel activity was enhanced in DRG neurons of paclitaxel-treated rats whereas EA suppressed the enhanced TRPV1 channel activity which increases intracellular Ca^{2+}. In this study, pharmacological blocking of TRPV1 mimics the analgesic effects of EA on the pain hypersensitivities, whereas capsaicin opposites EA's effect. EA can also inhibit the activation of spinal astrocytes and microglia activated in PLT-treated rats [40]. Overall, these results suggest that EA alleviates PLT-induced peripheral neuropathic pain *via* the mechanisms by suppressing TLR4-TRPV1 upregulation in DRG neurons and spinal neuronal pathways. An attention is also needed to pay on the central nerve system regarding the mechanisms leading to CIPN.

Cellular and molecular mechanisms leading to neuropathy in the central nerve system (CNS)

It should be mentioned that several signaling pathways in the CNS also play an important role in regulating the neuropathic pain induced by chemotherapy. Some of the cellular and molecular mechanisms are similar to these observed in the PNS, whereas features of signaling pathways responsible for CIPN are seen in the CNS. For example, a prior study reported that administration of BTZ increased hyperalgesia in rats, accompanied by a significant reduction in sensory nerve conduction velocity [41]. Spinal extracellular glutamate levels were also increased in rats treated with BTZ. Interestingly, investigators of this study further observed that the use of antagonists to mGluR5 receptor to inhibit the glutamatergic system decreased development of painful peripheral chemo-neuropathy induced by BTZ [41].

On top of the spinal cord level, a number of brain regions are also involved in CIPN of experimental animal models. In particular, OXL has been found to induce neuropathic pain at the different levels of brain regions *via* multiple signaling pathways. A study has observed that expression levels of the α7 nicotinic acetylcholine receptor (nAChR) subunit were dramatically decreased in the peripheral and central nervous system [42]. The active enantiomer of a novel α7 nAChR agonist, PNU-282987 prevented the α7 nAChR receptor down-regulation and significantly reduced OXL-evoked alterations of the pain threshold after noxious or non-noxious stimuli [42]. Furthermore, it has been reported that intracellular OXL rapidly increased the levels of ROS and endoplasmic reticulum stress [43]. These changes were accompanied by activation of caspase-3 causing extracellular ATP release. The investigators of this study suggested that OXL enters the endothelial cells of the blood brain barrier vessels and triggers a signaling pathway and thus induces the disassembly of the tight junctions [43]. This is likely to cause OXL toxicity and the chemotherapy-induced

neuropathic pain *via* the effects of the CNS. The role of OXL in a higher levels of brain regions has also been reported [44]. i.e., the concentration of choline was increased in the posterior insular cortex of neuropathic animal with administration OXL and this change was closely related to pain response seen in animals. Additionally, in this previous study that several interventions were applied to attenuate OXL-induced neuropathic pain [44]. It was reported that pharmacological activation of cholinergic M2 receptors in the insular cortex using oxotremorine completely reversed OXL-induced mechanical allodynia. A systemic treatment with donepezil, a centrally active acetylcholinesterase inhibitor, prevented and reversed OXL-induced cold and mechanical allodynia [44]. It is important that these findings shed light on the crucial role of cortical cholinergic neurotransmission as a central mechanism of neuropathic pain, and suggest that targeting insular M2 receptors using central cholinomimetics could be used for a potential neuropathic pain treatment.

Regarding PLT-induced peripheral neuropathy numerous studies have been reported. The protective role of the angiotensin II type 2 receptor (AT2) in the central and peripheral nervous systems is well-established. A widely used drug, ramipril, can improve neuroprotection in some rodent models of peripheral neuropathy [45]. PLT was administered in wild type or AT2-deficient mice. It was observed that allodynia was completely absent in AT2-deficient mice and in wild type mice ramipril and PD123319, an AT2 antagonist can inhibit PLT-induced neuropathic pain *via* the involvement of AT2 [45].

An interesting finding from both human and animal studies was to explore traumatic nerve injury and toxic challenge with chemotherapeutic agents involved in the reorganization of neural circuits in the brain [46]. Magnetic resonance imaging was used to identify changes in brain neural circuitry that accompany the development of chemotherapy-induced neuropathic pain. Rats exposed to PLT induced allodynia and it was found that affected brain regions included the prefrontal cortex, amygdala, hippocampus, hypothalamus and the striatum/nucleus accumbens [46]. The investigators of this study further suggested that a reorganization of gray matter microarchitecture formed a continuum of brain areas stretching from the basal medial/lateral forebrain to the midbrain. Resting state functional connectivity showed reorganization between the periaqueductal gray, a key node in nociceptive neural circuitry, and connections to the brainstem. Nonetheless, overall, various regions of the CNS are involved in CIPN.

Future perspective

CIPN is a main side effect of cancer in patients and this common symptom can alter treatment strategy on patients. Neuropathic pain associated with chemotherapy has been studied providing basic mechanisms responsible for CIPN. It is noted that a suitable alternate intervention has benefits for patients with CIPN. Therefore, experimental strategies need to be addressed in the future by 1) performing the similar studies using different experimental models of CIPN and/or a combination of multiple models to address effectiveness of studied interventions, 2) applying the similar experiments corresponding to humans to validate the effectiveness as well as consideration of designing clinical experiments, and 3) utilizing interventions with a less cost to examine their alleviating effect on CIPN in cancer patients with chemotherapy. Nevertheless, in the future experimental models determining CIPN pathophysiology are still desired to be developed.

Conflict of Interest

There is no conflict of interest.

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Abbreviations

4E-BP-1, eukaryotic translation initiation factor 4E-binding protein 1; 8-iso PGF2α, 8-iso-prostaglandin F2α; 8-OHdG, 8-Hydroxy-2'-deoxyguanosine; ARE, antioxidant response element; ATF3, activating transcripttion factor 3; BTZ, bortezomib; CCL2, C-C Motif Chemokine Ligand 2; CCR2, CC chemokine receptor 2; CIPN, chemotherapy-induced peripheral neuropathy; DRG, dorsal root ganglion; EA, electroacupuncture; HO-1, hemeoxygenase-1; IκBα, endogenous inhibitor of NF-κB alpha; IL-1β, interleukin-1β; IL-6, interleukin-6; JNK, c-Jun N-terminal kinase; MAPK, mitogen-activated protein kinase; mTOR, mammalian target of rapamycin; NF-κB, nuclear factor kappa-light-chain-enhancer of

activated B cells; NOX, NADPH oxidase, Nrf2, nuclear factor (erythroid-derived 2)-like 2; OXL, oxaliplatin; PAR2, proteinase-activated receptor 2; PBN, N-tert-butyl-α-phenylnitrone; PI3K, phosphoinositide 3-kinase PIC-proinflammatory cytokine; PKA, protein kinase A; PKC, protein kinase C; PLT, paclitaxel; ROS, reactive oxygen species; S6K1, ribosomal protein S6 kinase beta-1; SOD, superoxide dismutase; STAT3, signal transducer and activator of transcription-3, TLR4, toll like receptor 4; TNF-α, tumor necrosis factor-α; TRPA1, transient receptor potential ankyrin 1; TRPM8, transient receptor potential channel subfamily M8; TRPV1, transient receptor potential vanilloid 1.

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