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PGC1α: an emerging therapeutic target for chemotherapy-induced peripheral neuropathy

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***Abstract*:** Chemotherapy-induced peripheral neuropathy (CIPN)-mediated paresthesias are a common complication in cancer patients undergoing chemotherapy. There are currently no treatments available to prevent or reverse CIPN. Therefore, new therapeutic targets are urgently needed to develop more effective analgesics. However, the pathogenesis of CIPN remains unclear, and the prevention and treatment strategies of CIPN are still unresolved issues in medicine. More and more studies have demonstrated that mitochondrial dysfunction has become a major factor in promoting the development and maintenance of CIPN, and peroxisome proliferator-activated receptor gamma (PPARγ) coactivator 1α (PGC1α) plays a significant role in maintaining the mitochondrial function, protecting peripheral nerves, and alleviating CIPN. In this review, we highlight the core role of PGC1α in regulating oxidative stress and maintaining normal mitochondrial function and summarize recent advances in its therapeutic effects and mechanisms in CIPN and other forms of peripheral neuropathy. Emerging studies suggest that PGC1α activation may positively impact CIPN mitigation by modulating oxidative stress, mitochondrial dysfunction, and inflammation. Therefore, novel therapeutic strategies targeting PGC1α could be a potential therapeutic target in CIPN.

Keywords: chemotherapy-induced peripheral neuropathy, mitochondrial biogenesis, mitochondrial dysfunction, oxaliplatin, oxidative stress, paclitaxel, PGC1α

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Introduction

Cancer is one of the top death causes across the globe, and despite the enormous efforts to implement novel chemotherapy strategies, the disease remains one of the major concerns worldwide. According to the International Agency for Research on Cancer (IARC), it is estimated that over 19.3 million new cancer cases were diagnosed in 2020, followed by 10.0 million deaths.[1,2] With the rapid development of modern cancer diagnosis and treatment technology, cancer patients' survival rate has increased year by year, and the survival period has been prolonged.[3] Statistical analysis shows that the cancer mortality rate in the United States is decreasing at an annual rate of 1.5%, and the overall reduction in 2020 is 29% compared with 1991. Among them, the 5-year survival rate of prostate cancer and female breast cancer is as high as 90%.[4] Consistently, the 5-year survival rate of cancer patients in China also showed a significant upward trend.[5] Cancer is gradually changing from a 'terminal illness' to a chronic disease, and the goal of cancer treatment is changing from 'survival' to 'quality survival'. Chemotherapy is the most extensively used approach for cancer treatment, while chemotherapy-induced peripheral neuropathy (CIPN) is the major side effect that hinders cancer treatment. Up to 80% of chemotherapy patients develop CIPN, and 40–60% of the patients have to terminate or delay the treatment.[6]

Chemotherapy-induced peripheral neuropathy

Many first-line cytotoxic agents inducing peripheral neuropathy have been used in solid tumors

and hematological malignancies, including blockbuster anti-tumor agents, paclitaxel, lenalidomide, and oxaliplatin. CIPN severely limits the use of chemotherapy agents and is a common cause of chemotherapy discontinuation. Besides, immune checkpoint inhibitors such as programmed cell death protein 1 (PD-1) and cytotoxic-T-lymphocyte-antigen-4 (CTLA4) have recently been found to cause similar neurological side effects.[7,8] CIPN symptoms initially manifested as typical 'glove and stocking' neuropathy, symmetrical numbness of the extremities, with pinning and burning paresthesias, and then progressed to sensory and motor disturbances, and eventually to muscle weakness, difficulty moving, burning sensations, and severe pain in the extremities.[6] Some patients suffer CIPN even if their cancer has been cured, such as numbness or burning pain in the hands and feet for years, with major and permanent consequences for life barriers. However, CIPN does not respond well to conventional analgesics and is extremely difficult to treat. There is no specific drug that can prevent and treat CIPN in clinical practice.[9] The American Society of Clinical Oncology (ASCO) acknowledged this dilemma, recommending only duloxetine for the relief of CIPN symptoms in its published clinical practice guidelines on the prevention and management of CIPN. The difficulties faced in the development of CIPN drugs mainly include (1) The pathogenic mechanism of CIPN is still unclear; (2) Disease factors such as cancer increase the complexity of CIPN treatment as cancer and CIPN can synergize on a common signaling pathway; (3) The prevention and treatment of CIPN should not affect the anticancer effect of chemotherapy. Therefore, elucidating the pathogenesis of CIPN and developing specific agents for CIPN prevention and treatment have very important scientific significance and clinical practical value. Prevention and treatment of CIPN represent a critical unmet medical need. This demand has also shifted from academic research to industrial investment. In August 2018, Pfizer, Eli Lilly, and AbbVie have jointly invested US$31 million to launch drug development for the prevention of peripheral neuropathy and cognitive impairment caused by chemotherapy.[10] Therefore, the prevention and treatment of CIPN is a medical need that needs to be urgently met.

Mitochondrial dysfunction in CIPN

The pathogenesis of CIPN induced by chemotherapy mainly includes, (1) abnormal expression and activation of cell membrane receptors and ion channels, (2) changes in intracellular signal transduction, (3) mitochondrial damage and oxidative stress, (4) the activation of glial cells and the generation of neuroinflammation eventually lead to the sensitization of peripheral sensory neurons and the damage of neurons and nerve fibers.[6] Among them, mitochondrial dysfunction is reported to be significant pathogenesis of CIPN, which corresponds to the clinical manifestations.[11–15]

Mitochondria, as highly active organelles, carry out their own 'renewal and regeneration' through biosynthesis, division/fusion, and autophagy to maintain their morphological and functional integrity. Disruption of mitochondrial homeostasis and subsequent mitochondrial dysfunction plays a key role in peripheral neuropathy caused by multiple pathological factors.[16–19] Accumulating evidence indicates that many chemotherapeutic agents cause mitochondrial damage in the peripheral sensory nerves by disrupting mitochondrial structure and bioenergetics, increasing nitro-oxidative stress, and altering mitochondrial transport and fission, fusion, and mitophagy. The mitotoxicity theory of CIPN has proposed that the abnormal and dysfunctional mitochondria in sensory neurons are led to axonal growth defects and the loss of intraepidermal nerve fibers, which in turn increased spontaneous discharge and the sensitization of peripheral sensory neurons and the central nervous system that promote the establishment of chronic pain state.[20] Mitochondrial damage has been reported to be involved in the pathological process of paclitaxel-induced CIPN. Flatters *et al.* found that mitochondrial swelling and vacuolization in both C-fibers and myelinated axons are the main neuropathological features for paclitaxel-induced painful peripheral neuropathy.[21] Besides, a clinical study has demonstrated that mitochondrial swelling and vacuolization were observed in sensory axons by electron microscopy in sural nerve biopsies from CIPN patients induced by paclitaxel[22] and docetaxel.[23] This phenomenon has also been observed in C-fiber and A-fiber of oxaliplatin, and bortezomib-induced CIPN rats.[24,25] In addition, paclitaxel-induced changes in

neuronal mitochondria in C fiber and myelinated axons are correlated to paclitaxel-induced pain syndrome.[21]

Recent research shows that mitochondrial swelling and vacuolization in C-fibers and myelinated axons disrupt the maintenance of the proton gradient, impair mitochondrial ATP production, and result in severe energy insufficiency, and increased reactive oxygen species (ROS) production in neurons.[26,27] Chemotherapy-evoked changes in bioenergetics are also associated with decreased ATP production.[28,29] The maximal respiration and respiratory ability were significantly decreased in dorsal root ganglia (DRG) neurons of paclitaxel-induced CIPN rats. Duggett *et al.* found enhanced basal glycolysis and maximal glycolytic ATP production in peripheral sensory neurons during peak pain in absence of altered respiration or respiratory capacity, suggesting the energy supplement of sensory neurons switched from relying on oxidative phosphorylation through less efficient glycolysis.[29] Moreover, the function of mitochondrial was also decreased in complex I-stimulated and complex II-stimulated respiration in sciatic nerves from paclitaxel-, oxaliplatin-, and bortezomib-induced CIPN rats.[25,28] It has been reported that a complex III inhibitor, antimycin A significantly prevented the development of paclitaxel-induced CIPN, but had no therapeutic effect on CIPN.[30] Mitochondrial DNA damage has been demonstrated to be a novel process for the induction of CIPN induced by chemotherapeutic agents.[31] Mannelli *et al.* reported that the DNA oxidation product 8-Hydroxy-2'-deoxyguanosine (8-OH-dG) has increased in the sciatic nerve and spinal cord with a rat model of oxaliplatin-induced CIPN.[32]

The therapies targeting chemotherapy-induced mitochondrial oxidative stress have the potential to protect mitochondrial function and alleviate neuropathological damage. Antioxidant pharmacological strategies using ROS/RNS scavengers, superoxide dismutase (SOD) mimetics, and peroxynitrite decomposition catalysts have shown success in attenuating chemotherapy-induced neurotoxic effects in cellular and animal models, including n-tert-Butyl-a-phenylnitrone (PBN)-a global free-radical scavenger,[33] 4-hydroxy-2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPOL)-a nonselective nitroxyl antioxidant,[34] the active metabolite of amifostine [N-2-mercaptoethyl]-1-3-diaminopropane (WR-1065), a ROS/RNS scavenger,[35] and the SOD mimetic, polyamine-polycarboxylate-MnII complex 4,10-dimethyl-1,4,7,10 tetraazacyclododecane-1,7-diacetic acid MnII (MnL4).[36] Other strategies attempt to protect against nerve damage by indirectly hindering mitochondrial oxidative stress. Meclizine, a histamine H1 receptor antagonist, has been reported to switch cells to glycolysis and pentose phosphate pathways to improve ATP production and neurite outgrowth in DRG neurons treated with cisplatin.[37] Recent research has shown that oxidative stress can drive matrix metalloproteases 9 (MMP9) mitochondria translocation and induce mitochondria dysfunction,[38] while intrathecal administration of the monoclonal antibody of MMP9 attenuated ROS production in the DRG and resulted in decreased IENF loss and paclitaxel-induced neuropathic pain in mice.[39] Targeting the oxidative stress-sensitive poly (ADP-ribose) polymerase (PARP)/p53 pathway has been reported to prevent mitochondrial dysfunction and neural damage. Pifithrin-μ, a p53 inhibitor, has been reported to prevent mitochondrial damage in the DRG by preventing the accumulation of p53 in the mitochondria and protects against paclitaxel- and cisplatin-induced mechanical allodynia and loss of intraepidermal nerve fiber in mice.[40,41] Therefore, promoting and repairing mitochondrial function may be a new strategy for the treatment of CIPN.

PGC1α, a master coactivator, triggers mitochondrial biogenesis in CIPN

Peroxisome proliferator-activated receptor gamma (PPARγ) coactivator 1α (PGC1α) was first discovered in brown adipose tissue as a PPARγ coactivator in response to cold stimulation.[42] The major function of PGC1α is to regulate mitochondrial biosynthesis to promote aerobic metabolism and resist oxidative stress, and its expression level directly determines mitochondrial function and self-renewal level.[43,44] PGC1α is highly expressed in multiple tissues, including brown adipose tissue, liver, heart, pancreas, skeletal muscle, and kidney,[45,46] as well as in the nervous system, including the cerebral cortex, spinal cord, and DRG neurons, and mediates various neurological diseases.[43,47] It has been reported that PGC1α regulates the expression of

enzymes for ROS detoxifying, such as SOD1 and 2, catalase, and glutathione peroxidase-1.[48] Besides, PGC1α acts as a coactivator with other transcription factors including the nuclear respiratory factor (NRF), transcriptional factor A mitochondrial (TFAM), and myocyte enhancer factor 2.[49] The PGC1α-NRF1/2-TFAM axis plays an important role in the regulation of mitochondrial regeneration. PGC1α promotes the expression of TFAM through NRF1/2. TFAM is a key factor in initiating mitochondrial transcription, promoting mitochondrial DNA (mtDNA) replication, and regulating mitochondrial regeneration.[50] In models of Parkinson's disease, Alzheimer's disease, and aging, the expression levels of TFAM and mtDNA are reduced and mitochondrial function is impaired, while overexpression of TFAM in mitochondria is neuroprotective against these neurodegenerative diseases.[50] A recent study reveals that PGC1α inhibitor SR-18292 reverses the analgesic effect of ZLN005 and abolishes the analgesic effect of formoterol against CIPN.[51]

In sensory neurons, AMP-activated protein kinase (AMPK) mediates muscarinic ACh type 1 receptor (M1R) antagonists induced PGC1α and mitochondrial activity to promote neurite outgrowth from adult sensory neurons and to protect animal models against peripheral neuropathy induced by diabetes, the chemotherapeutic agents such as dichloroacetate and paclitaxel, or human immunodeficiency virus (HIV) envelope protein gp120.[52,53] Furthermore, overexpression of PGC1α can increase the number and quality of mitochondria in DRG neurons of diabetic mice.[54] PGC1α-mediated mitochondrial biogenesis has also been reported to be involved in the attenuation of neuropathic pain at the spinal level in peripheral nerve injury. Activation of PGC1α in the spinal cord attenuates established mechanical allodynia in rats with neuropathic pain.[55] NRF2 attenuates chronic constriction injury-induced neuropathic pain *via* the induction of PGC1α-mediated mitochondrial biogenesis in the spinal cord.[56] In addition, PGC1α also regulates a series of nuclear receptors including the thyroid hormone receptor, and the estrogen receptor.[49]

PGC1α acts as an oxidative stress regulator in CIPN

Intracellular ROS is mainly derived from mitochondrial and excessive production of ROS leads to mitochondrial dysfunction. ROS-induced oxidative stress and the subsequent injury of the myelin sheath, mitochondrial proteins, and antioxidant enzymes in peripheral neurons is a substantial initiator for CIPN.[13] *In vivo* study has demonstrated that scavenge ROS inhibited the development of CIPN induced by paclitaxel and bortezomib.[57,58] Elamipretide (SS-31), a mitochondria-targeted antioxidant, attenuated oxaliplatin-induced CIPN.[59] MitoVitE attenuated the development of paclitaxel-induced mechanical hypersensitivity.[60] Previous *in vivo* study has also demonstrated that ROS production was significantly increased in the spinal cord and lumbar DRG after chemotherapeutic agent treatment.[59,61] Besides, ROS levels were also significantly increased in the superficial spinal and DRG neurons *in vivo* before the onset of paclitaxel-induced mechanical allodynia, suggesting ROS works as an initiating factor.[62] However, antioxidant enzymes were also enhanced in the DRG and peripheral sensory nerves in CIPN animals.[62] These data reveal that mitochondrial ROS increase is an initiating factor for the development and maintenance of CIPN (Figure 1).

Recent research has shown that the administration of Ghrelin, an endogenous ligand for the growth hormone secretagogue receptor, decreases plasma oxidative stress, increases the expression of PGC1α and mitochondrial antioxidant proteins, alleviates mechanical and thermal hypersensitivity, and partially prevents neuronal loss of small unmyelinated intraepidermal nerve fibers. In addition, evodiamine, a plant-derived natural compound, has been reported to prevent paclitaxel-induced loss of mitochondrial membrane potential, increase PGC1α expression in DRG cells, and maintain mitochondrial anti-oxidant functions, and ameliorate paclitaxel-induced neuropathic pain.[63] However, the mechanism of PGC1α in mitochondrial anti-oxidative stress in CIPN is still unclear and needs further exploration.

PGC1α acts as a therapeutic target in peripheral neuropathy

PGC1α is increasingly recognized as an important target in the prevention and regulation of CIPN and other forms of neuropathy. A series of literature have reported the potential of natural compounds or molecules to treat CIPN by modulating PGC1α expression or function. Resveratrol has been reported to reduce apoptosis by SIRT1/PGC1α signal pathway, prevent paclitaxel-induced

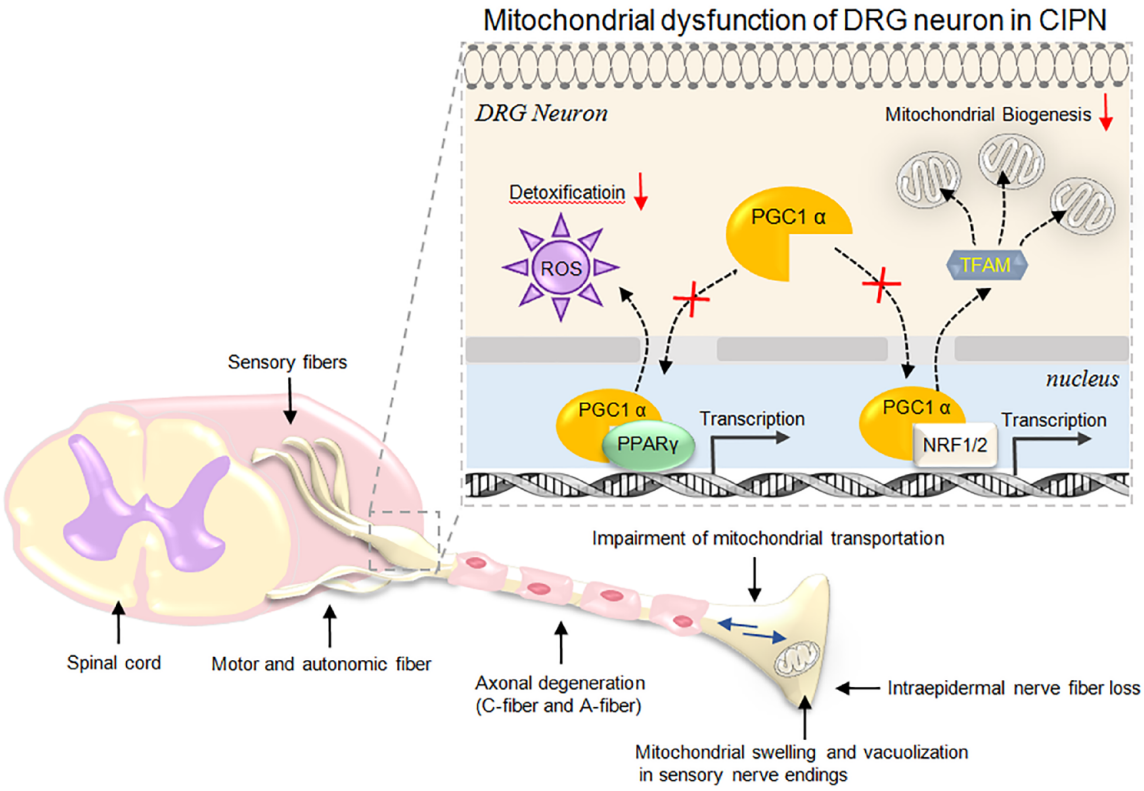

Figure 1. The peripheral neuropathological features and mitochondrial dysfunction of dorsal root ganglia (DRG) neurons in chemotherapy-induced peripheral neuropathy (CIPN).
The pathological characterizations of peripheral nerves in CIPN are indicated by arrows, including axonal degeneration, intraepidermal nerve fiber loss, mitochondrial swelling and vacuolization in sensory nerve endings, and impairment of mitochondrial transportation. The enlarged illustration on the upper right shows the central role of peroxisome proliferator-activated receptor gamma coactivator 1α (PGC1α) in mitochondrial dysfunction of DRG neurons in CIPN.

mitochondrial damage, and improve the relevant pain symptoms.[64] Evodiamine prevented paclitaxel-induced loss of mitochondrial membrane potential and paclitaxel-induced neuropathic pain *via* regulating PGC1α expression in DRG neurons.[63] Ghrelin alleviates paclitaxel-induced CIPN by reducing oxidative stress and enhancing PGC1α expression in mice.[65] Nuclear sirtuin 1 (SIRT1)/PGC1α signaling has been reported to be involved in the analgesic effect of translocator protein in a rat spinal nerve ligation model.[66] SIRT1 activation alleviates oxidative damage and enhances PGC1α-NRF1/2-TFAM axis-mediated mitochondrial biogenesis in diabetic neuropathy rats.[67–69] Furthermore, multiple lines of evidence suggest that PGC1α mediates the mitochondrial function promotion and neuroprotection effect of multiple upstream regulators. Berberine exposure augmented PGC1α-mediated mitochondrial biogenesis in DRG neurons in experimental diabetic neuropathy rats.[70] Impaired AMPK signaling in DRG neurons is associated with PGC1α-mediated mitochondrial dysfunction and peripheral neuropathy in diabetes.[71] Salvianolic acid A application and potassium voltage-gated channel subfamily B member 1 (Kv2.1) inhibition protect the peripheral nerve function in diabetic rats through the regulation of the AMPK/PGC1α pathway.[72,73] Furthermore, overexpression of human TFAM in mice can prevent type 1 diabetes-induced nerve conduction slowdown, improve epidermal fiber loss, and alleviate mechanical hyperalgesia.[74] As an upstream regulator of TFAM, knockout of PGC1α leads to mitochondrial damage, increases oxidative stress, leads to mitochondrial dysfunction, and exacerbates diabetic neuropathy.[75] Therefore, promoting mitochondrial regeneration mediated by the PGC1α-NRF1/2-TFAM axis might be a potential approach for exploring the prevention and treatment of diabetic peripheral neuropathy.

In addition, several natural compounds and molecules targeting PGC1α, including resveratrol, evodiamine, berberine, and ghrelin have shown neuroprotective effects against CIPN and diabetic neuropathy in preclinical studies as discussed above, further clinical trials refer to these molecules are highly recommended. The pan-PPAR agonist bezafibrate, ferulic acid, and co-activation of PPARγ and PGC1α with N-(2-benzoylphenyl)-O-[2-(methyl-2-pyridinylamino) ethyl]-l-tyrosine (GW1929) and alpha-lipoic acid have shown strong therapeutic potential in animal models of degenerative disease like Huntington's and Parkinson's disease in the central nervous system, which can be further investigated in the treatment of peripheral neurodegenerative diseases.[76–78] Several substances that have been proven to promote PGC1α expressions in human skeletal muscle, such as mitoquinone (mitoQ) and pyrroloquinoline quinone, were recommended to test their clinical potential in the treatment of peripheral neuropathy.[79,80] Other substances including hydrogen gas and inorganic nitrate targeting the PGC1α pathway to promote mitochondrial function are also tested in the prevention and treatment of CIPN.[81,82] Thus, modulation of the PGC1α-NRF1/2-TFAM axis in DRG neurons has the potential to promote mitochondrial regeneration or protect peripheral nerve fibers and prevent CIPN (Figure 1).

Other potential mitochondrial markers for CIPN diagnostics

To date, no specific biomarkers of mitochondrial dysfunction have been identified to determine the earliest changes or the severity of CIPN. There are indications that modulators of mitochondrial dysfunction may aid in CIPN diagnosis and predict the outcome of CIPN treatments. These modulators include 8-hydroxy-2'-deoxyguanosine (8-OHdG), mtDNA, and heat shock proteins (HSPs). 8-OHdG, the predominant production of free radical-induced oxidative lesions, has been widely used as a biomarker of oxidative stress and oxidative DNA damage in diseases.[83] Preclinical studies have shown that paclitaxel induces a rise of 8-OHdG in DRG and amplified oxidative stress to lead the neuropathic pain in rats.[84] These results suggested the potential diagnostic value of 8-OHdG as a biomarker in clinical trials.

Moreover, as transcription of mitochondrial genes and level of mitochondrial activity is often proportional to mtDNA copy number, circulating mtDNA has been wildly used as a biomarker for predicting mitochondrial dysfunction and diseases, including cardiovascular disease, metabolic diseases, and cancer.[85,86] Recently preclinical studies assessed the potential of circulating mtDNA as a blood biomarker to predict the progression of CIPN. Paclitaxel and bortezomib-induced increases in mtDNA levels were synchronized with the peak of pain behavioral manifestations. Especially, the mtDNA content (determined by mtDNA/nDNA ratio) in blood was increased in the early phase of oxaliplatin-induced CINP, before the emergence of pain-like behaviors. These results suggested that circulating mtDNA in the blood may use as a potential biomarker to identify early stages of CIPN. Furthermore, mtDNA copy number has often been used to evaluate the treatment of CIPN targeting mitochondrial dysfunction in the peripheral and central nervous system in preclinical research.[37,51] Together, these findings indicate that mtDNA may serve as a potential biomarker to predict and access the development stage of CIPN and its therapeutic effects.

In addition, several studies have also shown that HSP modulation is the underlying mechanism to prevent chemotherapy-induced neurotoxicity.[87–89] Recent findings have reported that human Hsp27 prevents mitochondrial dysfunction, neurotoxicity, and subsequent painful behavior induced by paclitaxel or vincristine.[90,91] These preclinical results suggest the potential of Hsp27 as a biomarker for the conservation of mitochondrial function and efficacy of CIPN treatment. However, studies on the conservation of mitochondrial function that refer to mitochondrial function are limited. Therefore, mechanism-based biomarkers, including PGC1α-modulators may potentially overcome this shortcoming. Taken together, these markers might be potential biomarkers in the clinical diagnosis for the stage and severity or efficacy of treatment in CIPN regarding mitochondrial dysfunction.

Conclusions and future perspective

In this review, we propose a scientific conclusion that PGC1α-mediated recovery of mitochondrial

function might be a novel target for the treatment and prevention of CIPN. The ideas are clear and the theoretical basis is sufficient. As a transcriptional co-activator, PGC1α plays a key role in regulating oxidative stress and mitochondrial biosynthesis. Not limited to the traditional pain pathway, takes PGC1α as the target to study its mechanism of action in CIPN, which has important reference and guiding significance for elucidating the pathogenesis of CIPN, developing innovative drugs and clinical treatment for the prevention and treatment of CIPN. Therefore, targeting PGC1α is expected to be rapidly transformed and applied to fill the gap in the prevention and treatment of CIPN.

Regulation of PPARγ/PGC1α in sensory neurons activates mitochondrial transcription and achieves 'purification and renewal' of mitochondria. However, directly targeting PGC1α might cause severe side effects as PGC1α is majorly involved in non-shivering thermogenesis and temperature homeostasis in humans. Whereas indirectly regulating the expression level of PGC1α is an ideal means to interfere with mitochondrial regeneration. Besides, the upstream regulating and downstream responding signals of PGC1α-mediated mitochondrial regeneration also need to be further explored.

Last but not the least, several natural compounds and molecules targeting PGC1α, including resveratrol, evodiamine, berberine, and ghrelin have shown neuroprotective effects against CIPN and diabetic neuropathy in preclinical studies, further clinical trials refer to these molecules are highly recommended. The pathogenesis of CIPN discussed here is mainly derived from animal models of 'pain induced by chemotherapy agents' from preclinical studies. It does not fully represent the real situation of cancer patients treated with neurotoxic chemotherapy. Therefore, future clinical trials could also pave the way for the clinical translation of CIPN therapy targeting mitochondrial dysfunction.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

The paper has been read and approved by all authors. All authors approved the submission of this paper to '*Therapeutic Advances in Neurological Disorders*' for publication. All authors confirmed that neither the manuscript submitted nor any part of it has been published or is being considered for publication elsewhere.

Author contributions

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Benqing Wu: Conceptualization; Funding acquisition; Supervision; Writing – original draft; Writing – review & editing.

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