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Full-length Article

# Triggering receptor expressed on myeloid cells 2 (TREM2) dependent microglial activation promotes cisplatin-induced peripheral neuropathy in mice

Lang-Yue Hu [1], Yang Zhou [1], Wen-Qiang Cui, Xue-Ming Hu, Li-Xia Du, Wen-Li Mi, Yu-Xia Chu, Gen-Cheng Wu, Yan-Qing Wang, Qi-Liang Mao-Ying *

*Department of Integrative Medicine and Neurobiology, State Key Laboratory of Medical Neurobiology, School of Basic Medical Science, Institutes of Brain Science, Collaborative Innovation Center for Brain Science, Institute of Acupuncture and Moxibustion, Fudan Institutes of Integrative Medicine, Fudan University, Shanghai 200032, People's Republic of China*

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ABSTRACT

Chemotherapy-induced peripheral neuropathy (CIPN) is a common adverse side effect of many antineoplastic agents. Patients treated with chemotherapy often report pain and paresthesias in a "glove-and-stocking" distribution. Diverse mechanisms contribute to the development and maintenance of CIPN. However, the role of spinal microglia in CIPN is not completely understood. In this study, cisplatin-treated mice displayed persistent mechanical allodynia, sensory deficits and decreased density of intraepidermal nerve fibers (IENFs). In the spinal cord, activation of microglia, but not astrocyte, was persistently observed until week five after the first cisplatin injection. Additionally, mRNA levels of inflammation related molecules including IL-1β, IL-6, tumor necrosis factor (TNF)-α, inducible nitric oxide synthase (iNOS) and CD16, were increased after cisplatin treatment. Intraperitoneal (i.p.) or intrathecal (i.t.) injection with minocycline both alleviated cisplatin-induced mechanical allodynia and sensory deficits, and prevented IENFs loss. Furthermore, cisplatin enhanced triggering receptor expressed on myeloid cells 2 (TREM2) /DNAX-activating protein of 12 kDa (DAP12) signaling in the spinal cord microglia. The blockage of TREM2 by i.t. injecting anti-TREM2 neutralizing antibody significantly attenuated cisplatin-induced mechanical allodynia, sensory deficits and IENFs loss. Meanwhile, anti-TREM2 neutralizing antibody prominently suppressed the spinal IL-6, TNF-α, iNOS and CD16 mRNA level, but it dramatically up-regulated the anti-inflammatory cytokines IL-4 and IL-10. The data demonstrated that cisplatin triggered persistent activation of spinal cord microglia through strengthening TREM2/DAP12 signaling, which further resulted in CIPN. Functional blockage of TREM2 or inhibition of microglia both benefited for cisplatin-induced peripheral neuropathy. Microglial TREM2/DAP12 may serve as a potential target for CIPN intervention.



## 1. Introduction

Patients treated with antineoplastic agents frequently suffer progressive, enduring, often irreversible and dose-limiting nerve damage, termed as chemotherapy-induced peripheral neuropathy (CIPN). The symptoms are characterized as a glove-and-stocking distribution of sensory changes: dysesthesia, paraesthesia and persistent pain (Miltenburg and Boogerd, 2014). CIPN severely limits the application of antineoplastic agents and affects the quality of life of cancer patients. However, there is no effective strategy available for CIPN prevention and treatment, because of its complexity of mechanism.

Accumulating evidence indicates that the initiation and progression of CIPN are tightly related with the loss of intraepidermal nerve fibers (IENFs), oxidative stress, abnormal spontaneous discharges, ion channel activation, leukocyte infiltration into dorsal root ganglion (DRG), and the activation of the neuro-immune system (Sisignano et al., 2014; Zhang et al., 2016). Quite a few studies have focused on the role of central glia in CIPN in recent years (Di Cesare Mannelli et al., 2014; Pevida et al., 2013; Robinson et al., 2014; Zheng et al., 2011). Vincristine induced astrocyte activation in the spinal cord, together with up-regulated production of interleukin-1β (IL-1β). IL-1β further induced the phosphorylation

* Corresponding author at: P.O.Box 291, 138 Yi Xue Yuan Road, Department of Integrative Medicine and Neurobiology, School of Basic Medical Science, Fudan University, Shanghai 200032, China.
*E-mail address:* maoyql@fudan.edu.cn (Q.-L. Mao-Ying).
[1] Lang-Yue Hu and Yang Zhou are equally contributed to this work.

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