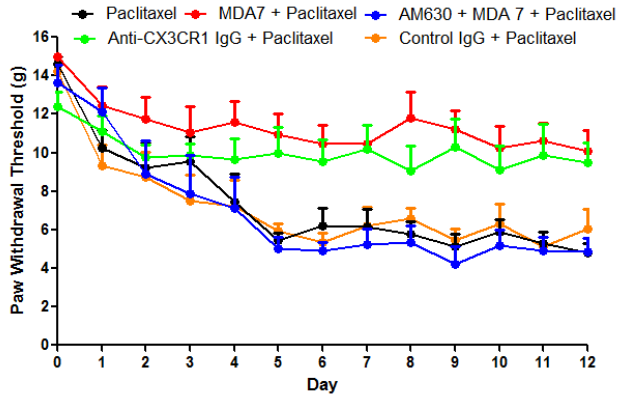
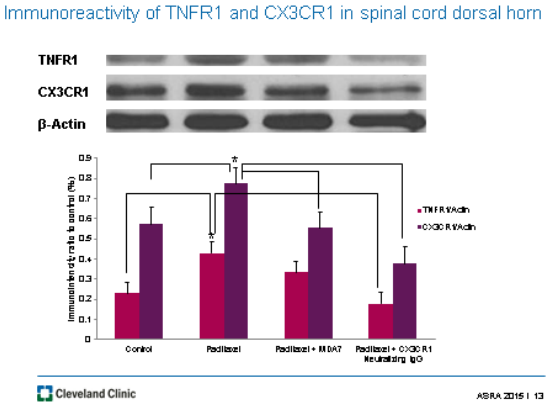
Regulation of Spinal Fractalkine/CX3CR1 and TNF-alpha Signaling in Paclitaxel Induced Peripheral Neuropathy in Rats

Chemotherapy-induced peripheral neuropathy (CIPN) is a common, potentially severe and dose-limiting adverse effect of cancer treatment. Most clinically available drugs have failed to provide adequate pain relief for this neuropathic pain syndrome. Searching for the underlying pathophysiological mechanism to help identify novel therapies for CIPN is of critical importance.

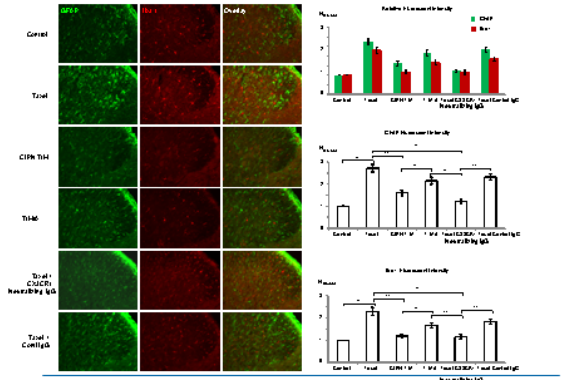
Activation of microglial cells in the spinal cord plays a significant role in different pain syndromes. The chemokine Fractalkine/CX3CR1 and tumor necrosis factor (TNF)-alpha signaling have been recently recognized as crucial players in mediating neuropathic pain conditions. Cannabinoid receptors (CB2) have emerged as a promising therapeutic target for neuropathic pain management. In this study, we hypothesized that administration of the selective CB2 agonist MDA7 (intraperitoneally, i.p.) or CX3CR1 neutralizing antibody (intrathecally, i.t.) may alleviate CIPN neuropathic behaviors induced by paclitaxel in rats by regulating spinal microglial activation and CX3CR1 and/or TNF-alpha signals.

We found that the selective CB2 agonist MDA7 or CX3CR1 neutralizing antibody could inhibit paclitaxel-induced peripheral mechanical allodynia in rats. The upregulation of TNFR1, CX3CR1 and Iba (for microglial activation) immunoactivity induced by paclitaxel was blocked by i.p. MDA7 or i.t. CX3CR1 neutralizing antibody. Targeting fractalkine/CX3CR1 and TNF-alpha signaling may be a novel therapeutic approach to prevent or reverse chemotherapy-induced peripheral neuropathy.





Immunofluorescence staining of Iba1 and GFAP in spinal cord dorsal horn



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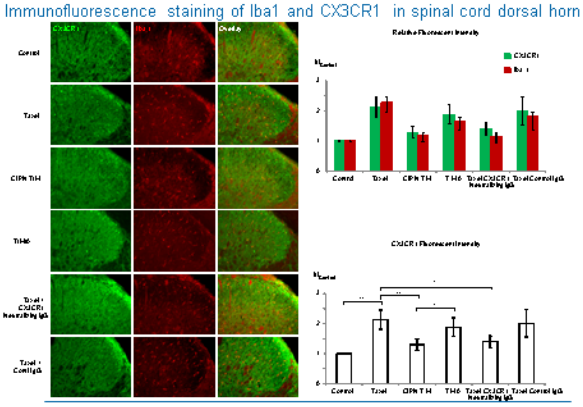
Immunofluorescence staining of Iba1 and CX3CR1 in spinal cord dorsal horn



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