Ctbp2 and P300-Mediated Epigenetic Regulation of μ-Opioid Receptor in Paclitaxel-Induced Neuropathic Pain

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Abstract:

Paclitaxel (PTX), a chemotherapy agent widely used for cancer treatment, often induces dose-limiting peripheral neuropathy, significantly impairing patients' quality of life. This study uncovers a pivotal role for C-terminal binding protein 2 (CtBP2) in the epigenetic regulation of μ-opioid receptor expression, contributing to PTX-induced neuropathic pain in dorsal root ganglion (DRG) neurons. We found that PTX treatment significantly increased CtBP2 expression in NeuN-positive DRG neurons, correlating with the development of mechanical allodynia in rat models. CtBP2 was shown to interact with p300 by binding to the PXDLS motif. CtBP2 blocks the accessibility of p300 to histones and thus represses p300-mediated histone acetylation and transcriptional activation. This epigenetic remodeling led to μ-opioid receptor gene silencing, a key driver of neuropathic signaling pathways. Notably, knockdown of CtBP2 or p300 in DRG neurons effectively reversed μ-opioid receptor expression and alleviated PTX-induced pain hypersensitivity. Our findings reveal a novel CtBP2-p300 axis that epigenetically decreases μ-opioid receptor expression, driving neuropathic pain development following PTX treatment. Targeting this regulatory mechanism offers promising therapeutic potential for managing chemotherapy-induced neuropathic pain and improving patients' quality of life.

Keywords:

Paclitaxel, CtBP2, p300, μ-opioid receptor, dorsal root ganglion, chemotherapy-induced neuropathy.