Targeting HDAC6 in the Dorsal Root Ganglia for the Management of Mechanical Allodynia in Models of Peripheral Nerve Injury

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Histone deacetylase 6 (HDAC6) is a Class IIb histone deacetylase, which is primarily located in the cytoplasm and plays an important role in cell cycle progression and transcriptional regulation. Earlier studies from our group and others have shown that HDAC6 inhibitors alleviate sensory signs of chemotherapy-induced and nerve injury-induced peripheral neuropathy. Furthermore, our recent data show that downregulation of HDAC6 in the dorsal root ganglia (DRG), achieved by injection of the sciatic nerve of adult male HDAC6fl/fl mice with AAV8-Cre-EGFP vectors, results in recovery from mechanical allodynia in paclitaxel chemotherapy induced peripheral neuropathy (CIPN) model.

We demonstrate that DRG-knockdown of HDAC6 prevents the development of mechanical allodynia after the paclitaxel CIPN model. We also use the murine spared nerve injury (SNI) model of neuropathic pain to determine the impact of the peripherally acting HDAC6 inhibitor ACY1215 (Regenacy Pharmaceutics) on the alleviation of sensory hypersensitivity behaviors. Using the von Frey assay, we demonstrate that treatment with ACY1215 (30mg/kg) leads to recovery from mechanical allodynia developed after SNI injury in both male and female mice without affecting locomotor activity. We performed bulk tissue RNA Sequencing analysis to understand transcriptomic events and pathways in the DRG associated with the antiallodynic actions of ACY1215. We found over 800 differentially expressed genes (DEG) in the SNI condition between vehicle and ACY1215-treated animals. Most of the pathways affected by these DEGs are associated with inflammatory disorders and B-cell mechanisms, suggesting a potential impairment of circulating immune cell infiltration into the DRG after injury, which has been shown to be necessary for the induction of sensory hypersensitivity. Furthermore, a separate bulk RNA-seq analysis of L3-6 DRGs 7 weeks after SNI highlighted a significant upregulation of several alpha- and beta-tubulin transcripts. Prior work by others suggests that this may be a compensatory response to nerve injury-induced tubulin destabilization. Therefore, we hypothesize that HDAC6 inhibition may address this molecular maladaptation by increasing acetylated tubulin levels and promoting stability and we are using Western Blot analysis to assess alpha- and beta- tubulin acetylation in the DRG following peripheral nerve injury with and without treatment with HDAC6 inhibitors. An alternative hypothesis is that HDAC6 acts as a transcription factor, and it targets several genes that are associated with hereditary neurodegenerative diseases. We hypothesize that several of these genes are regulated under SNI conditions that are rescued under the presence of ACY1215. We are testing this hypothesis by use of qPCR and Western Blot analysis.

Our findings highlight a promising therapeutic role of HDAC6 inhibitors for the alleviation of sensory hypersensitivity behaviors associated with peripheral nerve injury. Future work will define the mechanisms underlying HDAC6 action in the DRG and will test if interventions in HDAC6 activity in subjects suffering from prolonged peripheral nerve injury may reverse sensory and affective manifestations of neuropathic pain.

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