Enhancing fractalkine signaling attenuates neuropathic pain through dual pathways

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Backgrounds

1. Neuropathic pain (NP) is one of the most prevalent and incapacitating forms of chronic pain.
2. A better understanding of its pathogenesis at cellular and molecular levels is crucial to developing new therapeutics.
3. Neuroimmune interactions are critical to the mechanism and therapeutics of pain. A major focus has been on the roles of Fractalkine (CX3CL1) signaling between neurons and immune cells in the pathogenesis of NP.
4. In this study, we over-expressed CX3CL1 in mice and investigated the impact of over-expressing CX3CL1 on neuropathic pain and nerve injury-induced differentially expressed genes (DEGs).

Hypothesis: Enhancing CX3CL1 signaling promotes the resolution of neuroinflammation and mitigates neuropathic pain.

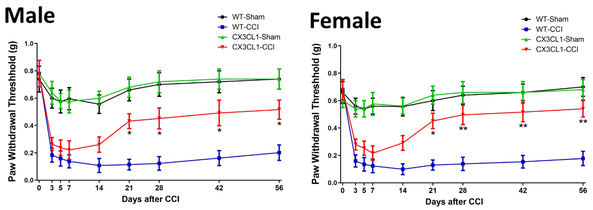
Methods

1. Tg-CX3CL1 was generated by the insertion of HA-tagged CX3CL1 human cDNA between exon 2 and exon 3 of mouse prion protein gene DNA at two unique XhoI sites in the Mo-Prp plasmid vector, and the prion promoter predominantly drives the expression of transgene in neurons (Borchelt et al., 1997).
2. Chronic constriction injury (CCI) was performed on wild-type (WT) and CX3CL1 overexpressing (CX3CL1-Tg/CX3CR1GFP/+) mice.
3. Mechanical hyperalgesia was evaluated using the von Frey Filament test.
4. CCI-induced DEGs were analyzed in the injured sciatic nerve in WT and CX3CL1-Tg mice by RNA sequencing at post-CCI day 28.

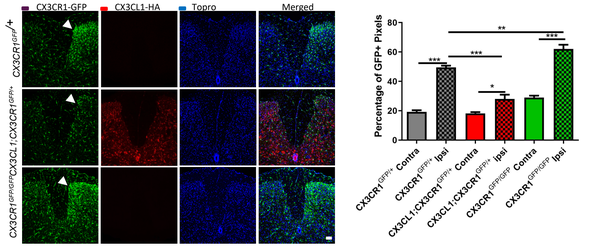
NIH National Institutes of Health
Turning Discovery Into Health
W81XWH-11-1-0672
Grant ID# 10669042)
NINDS/1UG3NS127258-01A1 (UG3/UH3)
NIAMS 3R01AR077452-04S1
NINDS R01 NS052372
NINDS 1 P20 RR15576 01
NCRR 5M01RR007122-18
Lisa Dean Moseley Foundation
Anesthesiology Institute Research Fund
Pain Management Innovation Fund #T56629
Cleveland Clinic

Results

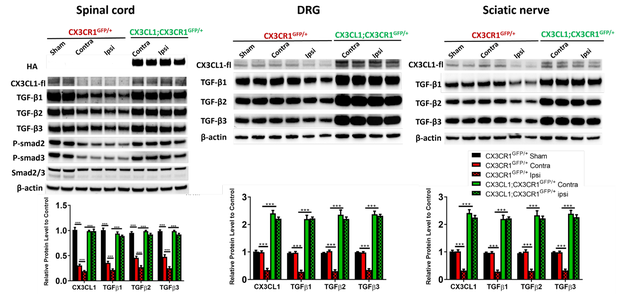
1. CX3LC1 over-expression alleviated CCI-induced hyperalgesia



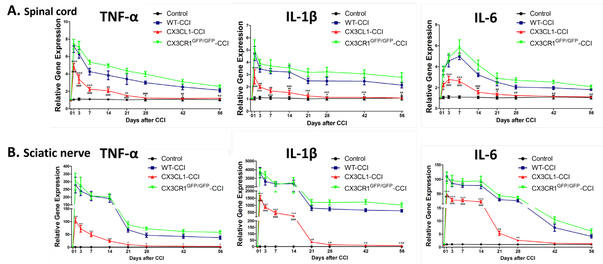
2. CX3CL1-overexpression inhibited microglial activation and CX3CR1 KO exacerbated neuroinflammation



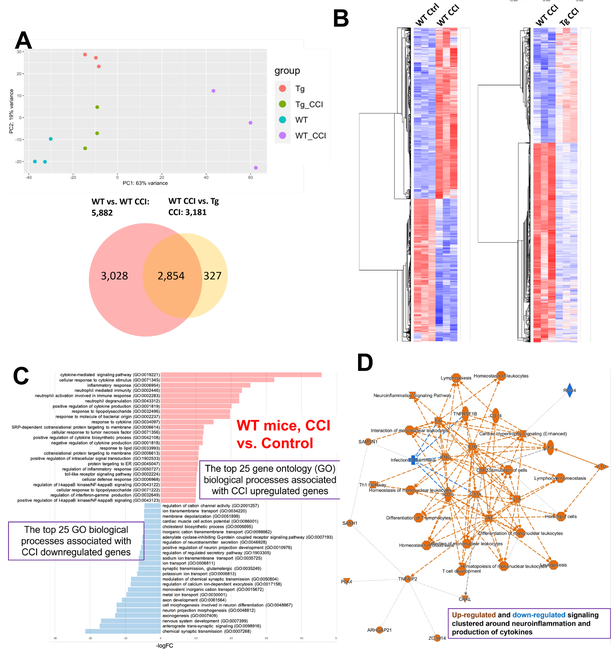
3. CX3CL1-tg mice over-expressed CX3CL1, TGFβ, and Smads (CCI day 7)

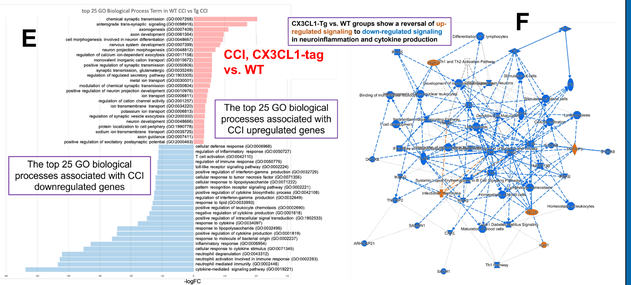


4. CX3CL1 over-expression reduced production of proinflammatory cytokines

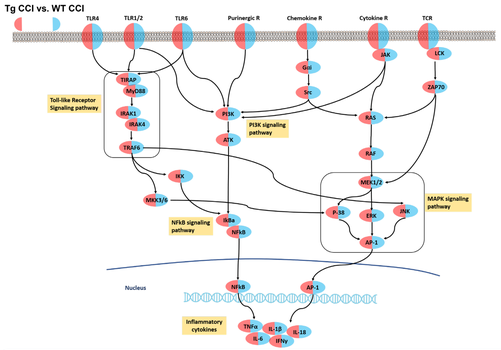


5. CX3CL1 over-expression normalized CCI-induced DEGs that regulate immune and neural functions

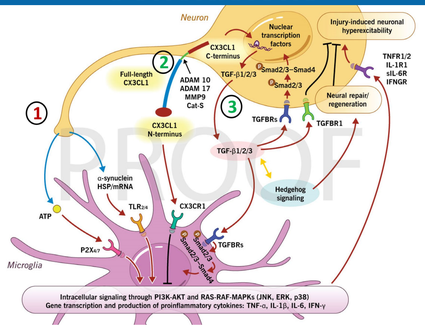




6. CX3CL1 over-expression decreased proinflammatory cytokine synthesis by inhibiting membrane receptors, intracellular signaling pathways, and transcription factors



Conclusions



Enhancing CX3CL1 signaling effectively mitigated neuroinflammation and alleviated NP, likely through CX3CL1 signaling between neuronal and immune cells via two distinct pathways: the CX3CL1 N-terminus mediated, CX3CR1-dependent pathway, and the CX3CL1 C-terminus mediated, TGF-β-dependent pathway.