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Traumatic Osteoarthritis Induces Mechanical Hyperalgesia through IL-1β/TNF-α-Mediated Upregulation of the Sema4D Gene Expression

Authors : Hsiao-Chien Tsai, Yu-Pin Chen, Ruei-Ming Chen

Abstract : Introduction: Osteoarthritis (OA) is characterized by joint destruction and causes chronic disability. One of the prominent symptoms is pain. Alleviating the pain is necessary and urgent for the therapy of OA patients. However, currently, understanding the mechanisms that drive OA-induced pain remains challenging, which hampers the optimistic management of pain in OA patients. Semaphorin 4D (Sema4D) participates in axon guidance pathway and bone remodeling, thus, may play a role in the regulation of pain in OA. In this study, we have established a rat model of OA to find out the mechanisms of OA-induced pain and to deliberate the roles of Sema4D. Methods: Behavioral changes and the pro-inflammatory cytokines (IL-1β, TNF-α, and IL-17) associated with pain were measured during the development of OA. Sema4D expression in cartilage and synovial membrane at 1, 4, and 12 weeks after inducing OA was analyzed. To assess if Sema4D is related to the neurogenesis in OA as an axon repellant, we analyzed the expression of PGP9.5 as well. Results: Synovitis and cartilage degradation were evident histologically during the development of OA. Mechanical hyperalgesia was most severe at week 1, then persisted thereafter. It was associated with stress coping strategies. Similar to the pain behavioral results, levels of IL-1β and TNF-α in synovial lavage fluid were significantly elevated in the OA group at weeks 1 and 4, respectively. Sema4D expression in cartilage and the synovial membrane was also enhanced in the OA group and was correlated with pain and pro-inflammatory cytokines. The marker of neurogenesis, PGP9.5, was also enhanced during the development of OA. Discussion: OA induced mechanical hyperalgesia, which might be through upregulating IL-1β/TNF-α-mediated Sema4D expressions. If anti-Sema4D treatment could reduce OA-induced mechanical hyperalgesia and prevent the subsequent progression of OA needs to be further investigated. Significance: OA can induce mechanical hyperalgesia through upregulation of IL-1β/TNF-α-mediated Sema4D and PGP9.5 expressions. And the upregulation of Sema4D may indicate the severity or active status of OA and OA-induced pain.

Keywords : traumatic osteoarthritis, mechanical hyperalgesia, Sema4D, inflammatory cytokines
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