LSU Health NEW ORLEANS School of Medicine

Department of Orthopaedics

Targeting arthralgia in knee osteoarthritis via non-psychoactive cannabinoid mechanisms

Collin Toups[1], Grace Guillot[1], Sydney Jensen[2], Kaitlyn Redondo[2], Vinod Dasa[2], Luis Marrero[2,3]
Louisiana State University Health Sciences Center School of Medicine[1], Department of Orthopaedics[2], and Morphology and Imaging[3]

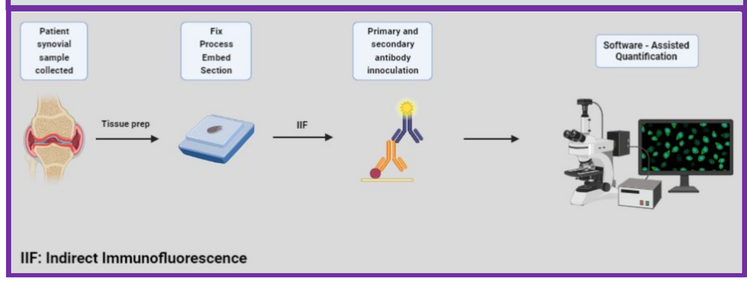
Introduction

- Before total knee arthroplasty (TKA) is imminent, the current non-surgical standard of care for knee osteoarthritis (KOA) involves administration of non-steroidal anti-inflammatory drugs, corticosteroids, and opioids; however, these treatments provide short-term pain relief and may even worsen KOA in the long term.
- As TKA procedures are projected to exceed 3.4 million annually by 2040, it is crucial to develop non-addictive, long-lasting, and cost-effective methods to manage KOA arthralgia, reducing the burden on individuals, and minimizing disparities in surgical outcomes.
- Further research on nociceptive receptors in the synovium, objective pain measures, and targeted pharmacotherapies would refine pain management, identify novel analgesic alternatives, and improve on non-surgical strategies for arthropathy.
- The activation of the transient receptor potential vanilloid 1 (TRPV1) cation channel plays a role in KOA-related pain and inflammation when bound by high-affinity, endogenous ligands such as 12-HETE, which results in measurable CGRP production.
- In neurodegenerative diseases and arthropathy, TRPV1 co-activates with cannabinoid 2 receptor (CB2R) to modulate pain and inflammation.
- For example, cannabidiol (CBD) can co-activate CB2R and TRPV1 but with low affinity and the potential to bind psychoactive CB1R.
- By exploring the anti-inflammatory properties of CB2R and TRPV1 desensitization in the joint, we aim to test the effectiveness of CBD analogs engineered with highly selective affinity for CB2R and TRPV1 co-activation without binding to CB1R.
- Assessing TRPV1 and CB2R levels in synovial material, alongside knee injury and osteoarthritis outcome scores (KOOS), can help identify individuals with severe arthralgia who may benefit from cannabinoid-related supplementation.
- Testing the anti-inflammatory and analgesic effect of CB2R-specific agonist such as JWH133 on diseased synoviocytes *in vitro* and intra-articular delivery in a mouse model of KOA, respectively, will shed light on novel CBD-based pharmacotherapies for painful arthropathy.

Objectives

1. ***Test the prediction that self-reported pain will correlate to TRPV1 activation in the KOA synovium***
   - ✓ Relate severity of KOA-attributable synoviopathy to TRPV1 density metrics in sensory nerves and synoviocytes of banked synovium relative to KOOS pain scores.
   - ✓ Measure TRPV1 activation status and validate histological synovitis and fibrosis by synovial fluid analytics.
2. ***Test that responsiveness of KOA patient-derived synoviocytes to CB2R agonists in vitro will vary in relation to measures of CB2R modulation and TRPV1 activation in vivo.***
   - ✓ Measure histological CB2R density in synovium and endocannabinoids in SF relative to KOOS.
   - ✓ Test responses of synoviocytes derived from KOA patients in high and low KOOS pain groups to CB2R-specific analogs.

Methods



IIF: Indirect Immunofluorescence

Results

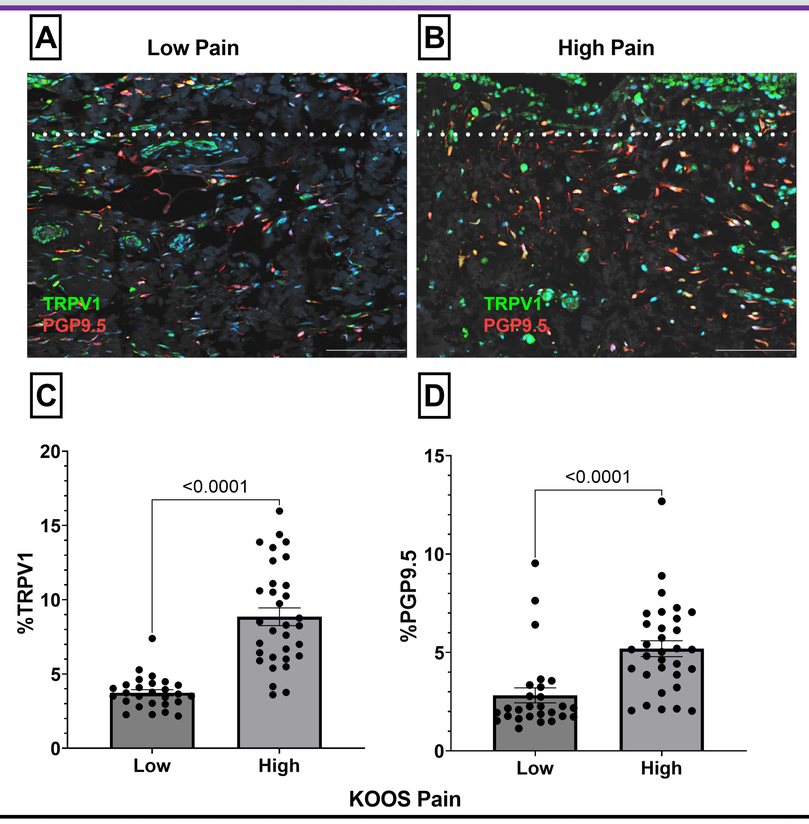


Figure 1: Representative 200x confocal photomicrographs of TRPV1 (green) and PGP9.5 (red) in the synovium of KOA patients grouped by (A) low and (B) high self-reported pain. Bar = 100µm. The mean expression percentage of (C) TRPV1 and (D) PGP9.5 was compared between groups. Student's t-test with α=0.05

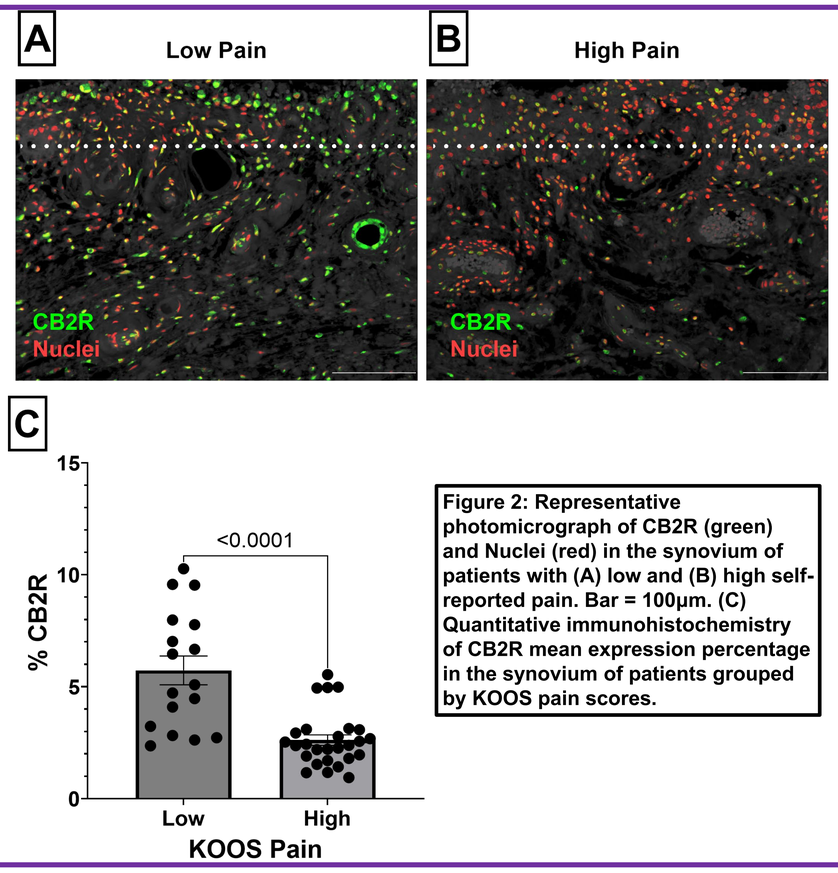


Figure 2: Representative photomicrograph of CB2R (green) and Nuclei (red) in the synovium of patients with (A) low and (B) high self-reported pain. Bar = 100µm. (C) Quantitative immunohistochemistry of CB2R mean expression percentage in the synovium of patients grouped by KOOS pain scores.

Discussion

- TRPV1 and PGP9.5 expression is significantly increased in the synovium of patients reporting high pain and could be used as one predictor of patient responsiveness to intra-articular supplementation with CB2R-specific analogs to co-modulate arthralgia and inflammation.
- Examining levels of 12-HETE and CGRP in the synovial fluid of these patients will expand on these findings and help determine the activation status of TRPV1, which will be used to measure a correlation with KOOS pain scores.
- CB2R is distributed in synoviocytes of the synovial intima and scattered synoviocytes and immune cells in the intima, with significantly higher expression in the low pain (high KOOS) group.
- Based on these preliminary results, we would predict that elevated expression of CB2R in patients reporting low pain would indicate higher endocannabinoid production, which would allow for increased TRPV1 cross-talk and thus greater desensitization.
- The variability in CB2R expression between patients grouped by self-reported pain emphasizes the role of the KOA synovium as a target for endocannabinoid modulation that is highly accessible to local, intra-articular administration of novel CB2R-specific analogs.

Conclusions

- Measures of CB2R and TRPV1 density, along with endocannabinoid-based activation levels could help objectively identify patient responders to novel cannabinoid-based pharmacotherapy.
- Intra-articular injections targeting CB2R and its interaction with TRPV1 could provide a safer and more effective therapeutic approach for managing arthropathy-related pain and inflammation.

Limitations

- High variability in the inflammatory and fibrogenic secretome between patients inconsistent with histological inflammation is possible, which could be predicted as the result of chronic cytokine build-up or that the histology is not representative.
- Intraoperative collection of adequate SF volumes can be challenging, since some patients present with "dry knees," but we expect to retain enough power to complete the experiments.
- Patient failure to self-report perioperative cannabis usage may result in misleading KOOS pain scores or skewed responses to CB2R analogs.

References

1. Singh JA, Yu S, Chen L, Cleveland JD. Rates of Total Joint Replacement in the United States: Future Projections to 2020-2040 Using the National Inpatient Sample. *J Rheumatol.* 2019;46(9):1134-1140. doi:10.3899/jrheum.170990

2. von Banchet GS, Richter J, Hückel M, Rose C, Bräuer R, Schaible HG. Fibroblast-like synovial cells from normal and inflamed knee joints differently affect the expression of pain-related receptors in sensory neurones: a co-culture study. *Arthritis Res Ther.* 2007;9(1):R6. doi:10.1186/ar2112

3. Fernihough J, Gentry C, Bevan S, Winter J. Regulation of calcitonin gene-related peptide and TRPV1 in a rat model of osteoarthritis. *Neurosci Lett.* 2005;388(2):75-80. doi:10.1016/j.neulet.2005.06.044

4. Wernecke C, Braun HJ, Dragoo JL. The Effect of Intra-articular Corticosteroids on Articular Cartilage: A Systematic Review. *Orthop J Sports Med.* 2015;3(5):2325967115581163. doi:10.1177/2325967115581163

5. Bianchi BR, Lee CH, Jarvis MF, et al. Modulation of human TRPV1 receptor activity by extracellular protons and host cell expression system. *Eur J Pharmacol.* 2006;537(1-3):20-30. doi:10.1016/j.ejphar.2006.03.00

6. Muller C, Morales P, Reggio PH. Cannabinoid Ligands Targeting TRP Channels. *Front Mol Neurosci.* 2018;11:487. doi:10.3389/fnmol.2018.00487

7. Kelly S, Chapman RJ, Woodhams S, et al. Increased function of pronociceptive TRPV1 at the level of the joint in a rat model of osteoarthritis pain. *Ann Rheum Dis.* 2015;74(1):252-259. doi:10.1136/annrheumdis-2013-203413

Acknowledgements

We would like to thank all study participants and members of the Marrero Laboratory and the Morphology and Imaging Core for technical assistance and thoughtful discussions. Collection, preservation, and storage of samples in the LSU Integrated Musculoskeletal Biobank (LIMB) and used in study was supported by an award from the LSU Health Research Enhancement Program.