

BONE MORPHOGENETIC PROTEIN TYPE IA RECEPTOR MIMETIC PEPTIDE CK2.1 ACTIVATES CHONDROGENESIS IN CHONDROCYTES FROM OSTEOARTHRITIS PATIENTS

K. DEGEORGE ¹, V. PANDIT ²,
D. HALLORAN ³, A. NOHE ^{2, *}

¹ Department of Biology, Northeastern University

² Department of Biological Sciences, University of Delaware

³ Childrens Hospital of Philadelphia

* Corresponding author: Nohe A., e-mail: anohe@udel.edu

Osteoarthritis (OA) represents the most prevalent form of joint disease, leading to considerable pain and functional disability. While surgical interventions and pain relief modalities are available, there is an urgent necessity for effective therapeutic strategies to restore the damage. Our research investigates CK2.1, an innovative peptide that has exhibited significant promise in stimulating chondrogenesis, specifically within articular chondrocytes, for the treatment of OA. In our study, we employed micromass cultures derived from chondrocytes of human OA patients to evaluate the effectiveness of CK2.1. We demonstrated that CK2.1 significantly enhanced proteoglycan synthesis in chondrocytes isolated from OA patients. This observation highlights CK2.1's targeted action and potential as a novel therapeutic strategy for treating osteoarthritis.

Key words: Osteoarthritis, BMP pathway, peptide drug, chondrogenesis, hypertrophy, musculoskeletal diseases.

ПЕПТИД СК2.1, МІМЕТИК РЕЦЕПТОРА
КІСТКОВОГО МОРФОГЕНЕТИЧНОГО БІЛКА
ТИПУ ІА, АКТИВУЄ ХОНДРОГЕНЕЗ У
ХОНДРОЦИТАХ ПАЦІЄНТІВ
З ОСТЕОАРТРИТОМ

Остеоартрит (ОА) є найпоширенішою формою захворювання суглобів, що призводить до значного болю та функційної недієздатності. Хоча наразі доступні хірургічні втручання та методи знеболювання, є нагальна потреба в ефективних терапевтичних стратегіях для відновлення після пошкод-

жень. Наше дослідження присвячене СК2.1 інноваційному пептиду, який виявив значний потенціал у стимулюванні хондрогенезу, зокрема в суглобових хондроцитах, для лікування ОА. У нашому дослідженні ми використовували культури мікромаси, отримані з хондроцитів пацієнтів з ОА, щоб оцінити ефективність СК2.1. Ми продемонстрували, що СК2.1 значно посилює синтез протеогліканів у хондроцитах, отриманих від пацієнтів з ОА. Це спостереження підкреслює цільову дію СК2.1 та його потенціал як нової терапевтичної стратегії для лікування остеоартриту.

Ключові слова: остеоартрит, шлях ВМР, пептидний препарат, хондрогенез, гіпертрофія, захворювання опорно-рухового апарату.

REFERENCES

- Abramoff, B., and Caldera, F.E., Osteoarthritis: Pathology, Diagnosis, and Treatment Options, *Med. Clin. North. Am.*, 2020, vol. 104, no. 2, pp. 293–311. <https://doi.org/10.1016/j.mcna.2019.10.00>
- Akkiraju, H., Bonor, J., and Nohe, A., CK2.1, a novel peptide, induces articular cartilage formation *in vivo*, *J. Orthop. Res.*, 2017, vol. 35, no. 4, pp. 876–885. <https://doi.org/10.1002/jor.2334>
- Akkiraju, H.; and Nohe, A., Role of Chondrocytes in Cartilage Formation, Progression of Osteoarthritis and Cartilage Regeneration. *J. Dev. Biol.*, 2015, vol. 3, no. 4, pp. 177–192, <https://doi.org/10.3390/jdb3040177>
- Akkiraju, H., et al., CK2.1, a bone morphogenetic protein receptor type Ia mimetic peptide, repairs cartilage in mice with destabilized medial meniscus. *Stem. Cell Res. Ther.*, 2017, vol. 8, no. 1, pp. 82–88. <https://doi.org/10.1186/s13287-017-0534-1>
- Allen, K.D.; Thoma, L.M.; and Golightly, Y.M., Epidemiology of osteoarthritis, *Osteoarthritis Cartilage*, 2022, vol. 30, no. 2, pp. 184–195. <https://doi.org/10.1016/j.joca.2021.04.020>
- Baker, N.A., et al., Associations Between Arthritis and Change in Physical Function in U.S. Retirees, *J. Gerontol. A Biol. Sci. Med. Sci.*, 2017, vol. 72, no. 1, pp. 127–133. <https://doi.org/10.1093/gerona/glw145>
- Bharadwaj, U., et al., Targeting Janus Kinases and Signal Transducer and Activator of Transcription 3 to Treat Inflammation, Fibrosis, and Cancer: Rationale, Progress, and Caution, *Pharmacol. Rev.*, 2020,

- vol. 72, no. 2, pp. 486–526. <https://doi.org/10.1124/pr.119.018440>
- Bonor, J., et al., Initiation of BMP2 signaling in domains on the plasma membrane, *J. Cell Physiol.*, 2012, vol. 227, no. 7, pp. 2880–2888. <https://doi.org/10.1002/jcp.23031>
- Bouhaddou, M., et al., The Global Phosphorylation Landscape of SARS-CoV-2 Infection, *Cell*, 2020, vol. 182, no. 3, pp. 685–712.e19. <https://doi.org/10.1016/j.cell.2020.06.034>
- Bragdon, B., et al., Casein kinase 2 regulates *in vivo* bone formation through its interaction with bone morphogenetic protein receptor type Ia, *Bone*, 2011, vol. 49, no. 5, pp. 944–954. <https://doi.org/10.1016/j.bone.2011.07.009>
- Bragdon, B., et al., Casein kinase 2 beta-subunit is a regulator of bone morphogenetic protein 2 signaling. *Biophys. J.*, 2010, vol. 99, no. 3, pp. 897–904. <https://doi.org/10.1016/j.bpj.2010.04.070>
- Carballo, C.B., et al., Basic Science of Articular Cartilage, *Clin. Sports Med.*, 2017, vol. 36, no. 3, pp. 413–425. <https://doi.org/10.1016/j.csm.2017.02.001>
- Carragee, E.J., Hurwitz, E.L., and Weiner, B.K., A critical review of recombinant human bone morphogenetic protein-2 trials in spinal surgery: emerging safety concerns and lessons learned, *Spine J.*, 2011, vol. 11, no. 6, pp. 471–491. <https://doi.org/10.1016/j.spinee.2011.04.023>
- Charlier, E., et al., Chondrocyte dedifferentiation and osteoarthritis (OA), *Biochem. Pharmacol.*, 2019, vol. 165, pp. 49–65. <https://doi.org/10.1016/j.bcp.2019.02.036>
- Chen, A.L., et al., Expression of bone morphogenetic proteins, receptors, and tissue inhibitors in human fetal, adult, and osteoarthritic articular cartilage, *J. Orthop. Res.*, 2004, vol. 22, no. 6, pp. 1188–1192. <https://doi.org/10.1016/j.orthres.2004.04.001>
- Chen, G., Deng, C., and Li, Y.P., TGF- β and BMP signaling in osteoblast differentiation and bone formation, *Int. J. Biol. Sci.*, 2012, vol. 8, no. 2, pp. 272–288. <https://doi.org/10.7150/ijbs.2929>
- Chen, H., et al., Molecular Mechanisms of Chondrocyte Proliferation and Differentiation, *Front. Cell Dev. Biol.*, 2021, vol. 9, pp. 664168. <https://doi.org/10.3389/fcell.2021.664168>
- Chen, M., et al., Advancements in tissue engineering for articular cartilage regeneration, *Heliyon*, 2024, vol. 10, no. 3, pp. e25400. <https://doi.org/10.1016/j.heliyon.2024.e25400>
- Concoff, A., et al., The efficacy of multiple versus single hyaluronic acid injections: a systematic review and meta-analysis, *BMC Musculoskelet Disord*, 2017, vol. 18, no. 1, pp. 542. <https://doi.org/10.1186/s12891-017-1895-2>
- Ding, L., et al., IL-37 is associated with osteoarthritis disease activity and suppresses proinflammatory cytokines production in synovial cells, *Sci. Rep.*, vol. 7, no. 1, pp. 11601. <https://doi.org/10.1038/s41598-017-11397-5>
- Dreier, R., Hypertrophic differentiation of chondrocytes in osteoarthritis: the developmental aspect of degenerative joint disorders, *Arthritis Res. Ther.*, 2010, vol. 12, no. 5, pp. 216. <https://doi.org/10.1186/ar3117>
- Elahi, S.A., et al., Contribution of collagen degradation and proteoglycan depletion to cartilage degeneration in primary and secondary osteoarthritis: an *in silico* study, *Osteoarthritis Cartilage*, 2023a, vol. 31, no. 6, pp. 741–752. <https://doi.org/10.1016/j.joca.2023.01.004>
- Fortier, L.A., et al., The role of growth factors in cartilage repair, *Clin. Orthop. Relat. Res.*, 2011, vol. 469, no. 10, pp. 2706–2715. <https://doi.org/10.1007/s11999-011-1857-4>
- Gamer, L.W., et al., The Role of Bmp2 in the Maturation and Maintenance of the Murine Knee Joint, 2018, *J. Bone Miner. Res.*, vol. 33, no. 9, pp. 1708–1717. <https://doi.org/10.1002/jbmr.3465>
- Hame, S.L., and Alexander, R.A., Knee osteoarthritis in women, *Cur. Rev. Musculoskelet Med.*, 2013, vol. 6, no. 2, pp. 182–187. <https://doi.org/10.1007/s12178-013-9164-0>
- Hawker, G.A., Osteoarthritis is a serious disease, *Clin. Exp. Rheumatol.*, 2019, vol. 37, Suppl 120, no. 5, pp. 3–6.
- Hogan, B.L., Bone morphogenetic proteins in development. *Curr. Opin. Genet. Dev.*, 1996, vol. 6, no. 4, pp. 432–438. [https://doi.org/10.1016/S0959-437X\(96\)80064-5](https://doi.org/10.1016/S0959-437X(96)80064-5)
- Horváth, E., et al., Inflammatory and Metabolic Signaling Interfaces of the Hypertrophic and Senescent Chondrocyte Phenotypes Associated with Osteoarthritis, *Int. J. Mol. Sci.*, 2023, vol. 24, no. 22. <https://doi.org/10.3390/ijms242216447>
- Hussain, S.M., et al., Knee osteoarthritis: a review of management options, *Scott. Med. J.*, 2016, vol. 61, no. 1, pp. 7–16. <https://doi.org/10.1177/0036933015619588>
- Jay, G.D., and Waller, K.A., The biology of lubricin: near frictionless joint motion, *Matrix Biol.*, 2014, vol. 39, pp. 17–24. <https://doi.org/10.1016/j.matbio.2014.08.008>
- Ji, B., et al., Activation of the P38/CREB/MMP13 axis is associated with osteoarthritis, *Drug. Des. Devel. Ther.*, 2019, vol. 13, pp. 2195–2204. <https://doi.org/10.2147/DDDT.S201831>
- Jing, J., et al., BMP receptor 1A determines the cell fate of the postnatal growth plate, *Int. J. Biol. Sci.*, 2013, vol. 9, no. 9, pp. 895–906. <https://doi.org/10.7150/ijbs.7291>

- Komori, T., Molecular Processes in Chondrocyte Biology, *Int. J. Mol. Sci.*, 2020, vol. 21, no. 11, pp. 3968. <https://doi.org/10.3390/ijms21113968>
- Kotlarz, H., et al., Insurer and out-of-pocket costs of osteoarthritis in the US: evidence from national survey data, *Arthritis Rheum.*, 2009, vol. 60, no. 12, pp. 3546–3553. <https://doi.org/10.1002/art.24984>
- Kovermann, N.J., et al., BMP2 and TGF- β Cooperate Differently during Synovial-Derived Stem-Cell Chondrogenesis in a Dexamethasone-Dependent Manner, *Cells*, 2019, vol. 8, no. 6, pp. 636. <https://doi.org/10.3390/cells8060636>
- Kugimiya, F., et al., Involvement of endogenous bone morphogenetic protein (BMP) 2 and BMP6 in bone formation, *J. Biol. Chem.*, 2005, vol. 280, no. 42, pp. 35704–35712. <https://doi.org/10.1074/jbc.M505166200>
- Kumar, P., et al., Common hip conditions requiring primary total hip arthroplasty and comparison of their post-operative functional outcomes, *J. Clin. Orthop. Trauma*, 2020, vol. 11, no. Suppl 2, pp. S192–S195. <https://doi.org/10.1016/j.jcot.2019.05.003>
- Mang, T., et al., BMPRI A is necessary for chondrogenesis and osteogenesis, whereas BMPRI B prevents hypertrophic differentiation, *J. Cell Sci.*, 2020, vol. 133, no. 16, pp. jcs246934. <https://doi.org/10.1242/jcs.246934>
- Moseychuk, O., et al., Inhibition of CK2 binding to BMPRIa induces C2C12 differentiation into osteoblasts and adipocytes, *J. Cell Commun. Signal*, 2013, vol. 7, pp. 265–278. <https://doi.org/10.1007/s12079-013-0201-1>
- Nazempour, A., and Van Wie, B.J., Chondrocytes, Mesenchymal Stem Cells, and Their Combination in Articular Cartilage Regenerative Medicine, *Ann. Biomed. Eng.*, 2016, vol. 44, no. 5, pp. 1325–1354. <https://doi.org/10.1007/s10439-016-1575-9>
- Nohe, A., et al., The mode of bone morphogenetic protein (BMP) receptor oligomerization determines different BMP-2 signaling pathways, *J. Biol. Chem.*, 2002, vol. 277, no. 7, pp. 5330–5338. <https://doi.org/10.1074/jbc.M102744200>
- Nohe, A., et al., Effect of the distribution and clustering of the type I A BMP receptor (ALK3) with the type II BMP receptor on the activation of signalling pathways, *J. Cell Sci.*, 2003, vol. 116, no. Pt 16, pp. 3277–3284. <https://doi.org/10.1242/jcs.00639>
- Occhetta, P., et al., Developmentally inspired programming of adult human mesenchymal stromal cells toward stable chondrogenesis, *Proc. Natl. Acad. Sci. USA*, 2018, vol. 115, no. 18, pp. 4625–4630. <https://doi.org/10.1073/pnas.1720658115>
- Palazzo, C., et al., Risk factors and burden of osteoarthritis, *Ann. Phys. Rehabil. Med.*, 2016, vol. 59, no. 3, pp. 134–138. <https://doi.org/10.1016/j.rehab.2016.01.006>
- Redman, S.N., et al., The cellular responses of articular cartilage to sharp and blunt trauma, *Osteoarthritis Cartilage*, 2004, vol. 12, no. 2, pp. 106–116. <https://doi.org/10.1016/j.joca.2003.09.004>
- Rodriguez-Merchan, E.C., The Current Role of Disease-modifying Osteoarthritis Drugs, *Arch. Bone Jt. Surg.*, 2023, vol. 11, no. 1, pp. 11–22. <https://doi.org/10.22038/ABJS.2022.65650.3146>
- Rosen, V., BMP2 signaling in bone development and repair, *Cytokine Growth Factor Rev.*, 2009, vol. 20, no. 5–6, pp. 475–480. <https://doi.org/10.1016/j.cytogfr.2009.10.018>
- Rountree, R.B., et al., BMP receptor signaling is required for postnatal maintenance of articular cartilage, *PLoS Biol.*, 2004, vol. 2, no. 11, pp. e355. <https://doi.org/10.1371/journal.pbio.0020355>
- Singh, P., et al., Phenotypic instability of chondrocytes in osteoarthritis: on a path to hypertrophy, *Ann. N Y Acad. Sci.*, 2019, vol. 1442, no. 1, pp. 17–34. <https://doi.org/10.1111/nyas.13931>
- Taköcs, R., et al., Isolation and Micromass Culturing of Primary Chicken Chondroprogenitor Cells for Cartilage Regeneration, *Curr. Protoc.*, 2023, vol. 3, no. 7, pp. e835. <https://doi.org/10.1002/cpz1.835>
- Tschon, M., et al., Gender and Sex Are Key Determinants in Osteoarthritis Not Only Confounding Variables. A Systematic Review of Clinical Data, *J. Clin. Med.*, 2021, vol. 10, no. 14, pp. 3174. <https://doi.org/10.3390/jcm10143178>
- Veronese, N., et al., Type 2 diabetes mellitus and osteoarthritis, *Semin. Arthritis Rheum.*, 2019, vol. 49, no. 1, pp. 9–19. <https://doi.org/10.1016/j.semarthrit.2019.01.005>
- Weaver, C.M., et al., The National Osteoporosis Foundation's position statement on peak bone mass development and lifestyle factors: a systematic review and implementation recommendations, *Osteoporos Int.*, 2016, vol. 27, no. 4, pp. 1281–1386. <https://doi.org/10.1007/s00198-015-3440-3>
- Wojdasiewicz, P., Poniatowski Ł, A., and Szukiewicz, D., The role of inflammatory and anti-inflammatory cytokines in the pathogenesis of osteoarthritis, *Mediators Inflamm.*, 2014, vol. 2014, pp. 561459. <https://doi.org/10.1155/2014/561459>
- Yang, Y., Skeletal morphogenesis during embryonic development, *Crit. Rev. Eukaryot. Gene Expr.*, 2009, vol. 19, no. 3, pp. 197–218. <https://doi.org/10.1615/CritRevEukaryotGeneExpr.v19.i3.30>
- Yao, Q., et al., Osteoarthritis: pathogenic signaling pathways and therapeutic targets, *Signal Transduct Target Ther.*, 2023, vol. 8, no. 1, pp. 56. <https://doi.org/10.1038/s41392-023-01330-w>

- Yoshioka, N.K., et al., Structural changes in the collagen network of joint tissues in late stages of murine OA, *Sci Rep*, 2022, vol. 12, no. 1, pp. 9159. <https://doi.org/10.1038/s41598-022-13220-3>
- Youn, I., et al., Zonal variations in the three-dimensional morphology of the chondron measured *in situ* using confocal microscopy, *Osteoarthritis Cartilage*, 2006, vol. 14, no. 9, pp. 889–897. <https://doi.org/10.1016/j.joca.2006.02.016>
- Zhai, G., Clinical relevance of biochemical and metabolic changes in osteoarthritis, *Adv. Clin. Chem.*, 2021, vol. 101, pp. 95–120. <https://doi.org/10.1016/bs.acc.2020.06.002>
- Zhang, W., et al., OARSI recommendations for the management of hip and knee osteoarthritis, Part II: OARSI evidence-based, expert consensus guidelines, *Osteoarthritis Cartilage*, 2008, vol. 16, no. 2, pp. 137–162. <https://doi.org/10.1016/j.joca.2007.12.013>
- Zhou, N., et al., BMP2 induces chondrogenic differentiation, osteogenic differentiation and endochondral ossification in stem cells, *Cell Tissue Res.*, 2016, vol. 366, no. 1, pp. 101–111. <https://doi.org/10.1007/s00441-016-2403-0>
- Zhu, M., et al., Chondroinductive/chondroconductive peptides and their-functionalized biomaterials for cartilage tissue engineering, *Bioact. Mater.*, vol. 9, pp. 221–238. <https://doi.org/10.1016/j.bioactmat.2021.07.012>

Received October 08, 2025

Received January 21, 2026

Accepted May 18, 2026