

FOXO TRANSCRIPTION FACTORS IN JOINT AGING AND OSTEOARTHRITIS PATHOGENESIS

This study examines the role of FoxO transcription factors in regulating mechanisms of joint homeostasis and consequences of reduced FoxO expression in cartilage for joint aging and osteoarthritis pathogenesis. Experimental approaches to increase FoxO will be tested for therapeutic potential in experimental osteoarthritis.

Funding

NIH/NIA R37 AG059418 04/01/18-03/31/28

ROLE: Lotz (PI)

Publications

[Targeting FoxO transcription factors with HDAC inhibitors for the treatment of osteoarthritis.](#)

Ohzono H, Hu Y, Nagira K, Kanaya H, Okubo N, Olmer M, Gotoh M, Kurakazu I, Akasaki Y, Kawata M, Chen E, Chu AC, Johnson KA, Lotz MK.

Ann Rheum Dis. 2022 Sep 15;annrheumdis-2021-221269. doi: 10.1136/ard-2021-221269. Online ahead of print.

PMID: 36109140

[Genome-Wide Occupancy Profiling Reveals Critical Roles of FoxO1 in Regulating Extracellular Matrix and Circadian Rhythm Genes in Human Chondrocytes.](#)

Duffy T, Bekki H, Lotz MK.

Arthritis Rheumatol. 2020 Sep;72(9):1514-1523. doi: 10.1002/art.41284. Epub 2020 Aug 9. PMID: 32281255

[FOXO1 and FOXO3 transcription factors have unique functions in meniscus development and homeostasis during aging and osteoarthritis.](#)

Lee KI, Choi S, Matsuzaki T, Alvarez-Garcia O, Olmer M, Grogan SP, D'Lima DD, Lotz MK.

Proc Natl Acad Sci U S A. 2020 Feb 11;117(6):3135-3143. doi: 10.1073/pnas.1918673117. Epub 2020 Jan 24.

PMID: 31980519

[FOXO1 transcription factor regulates chondrogenic differentiation through transforming growth factor \$\beta\$ 1 signaling.](#)

Kurakazu I, Akasaki Y, Hayashida M, Tsushima H, Goto N, Sueishi T, Toya M, Kuwahara M, Okazaki K, Duffy T, Lotz MK, Nakashima Y.

J Biol Chem. 2019 Nov 15;294(46):17555-17569. doi: 10.1074/jbc.RA119.009409. Epub 2019 Oct 10. PMID: 31601652

[Identification of transcription factors responsible for dysregulated networks in human osteoarthritis cartilage by global gene expression analysis.](#)

Fisch KM, Gamini R, Alvarez-Garcia O, Akagi R, Saito M, Muramatsu Y, Sasho T, Koziol JA, Su AI, Lotz MK.

Osteoarthritis Cartilage. 2018 Nov;26(11):1531-1538. doi: 10.1016/j.joca.2018.07.012. Epub 2018 Aug 3.

PMID: 30081074

[FoxO transcription factors modulate autophagy and proteoglycan 4 in cartilage homeostasis and osteoarthritis.](#)

Matsuzaki T, Alvarez-Garcia O, Mokuda S, Nagira K, Olmer M, Gamini R, Miyata K, Akasaki Y, Su AI, Asahara H, Lotz MK.

Sci Transl Med. 2018 Feb 14;10(428):eaan0746. doi: 10.1126/scitranslmed.aan0746. PMID: 29444976

[FoxO transcription factors support oxidative stress resistance in human chondrocytes.](#)

Akasaki Y, Alvarez-Garcia O, Saito M, Caramés B, Iwamoto Y, Lotz MK.

Arthritis Rheumatol. 2014 Dec;66(12):3349-58. doi: 10.1002/art.38868. PMID: 25186470

[Dysregulated FOXO transcription factors in articular cartilage in aging and osteoarthritis.](#)

Akasaki Y, Hasegawa A, Saito M, Asahara H, Iwamoto Y, Lotz MK.

Osteoarthritis Cartilage. 2014 Jan;22(1):162-70. doi: 10.1016/j.joca.2013.11.004. Epub 2013 Nov 21. PMID: 24269635

KLF4 TRANSCRIPTION FACTORS IN JOINT DEGRADATION AND REGENERATION

The goal of this project is to determine the role of KLF4 in cartilage homeostasis and the consequences of KLF4 suppression for joint aging and OA pathogenesis. We will also establish proof of concept for KLF4 as a therapeutic target in OA.

Funding

NIH/NIA R01 AG056144 09/01/18-05/31/23

ROLE: Lotz PI

Publications

[Krüppel-like factor-4 and Krüppel-like factor-2 are important regulators of joint tissue cells and protect against tissue destruction and inflammation in osteoarthritis.](#)

Kawata M, Teramura T, Ordoukhanian P, Head SR, Natarajan P, Sundaresan A, Olmer M, Asahara H, Lotz MK.

Ann Rheum Dis. 2022 May 9;annrheumdis-2021-221867. doi: 10.1136/annrheumdis-2021-221867. Online ahead of print. PMID: 35534137

[Mocetinostat activates Krüppel-like factor 4 and protects against tissue destruction and inflammation in osteoarthritis.](#)

Kawata M, McClatchy DB, Diedrich JK, Olmer M, Johnson KA, Yates JR, Lotz MK. JCI Insight. 2023 Sep 8;8(17):e170513.doi: 10.1172/jci.insight.170513.

INTEGRATIVE OMICS ANALYSIS OF HUMAN CARTILAGE IN AGING AND OSTEOARTHRITIS

This project examines gene expression patterns and epigenetic mechanisms that characterize cartilage homeostasis, healthy aging and osteoarthritis using human knees.

Funding

NIH/NIA R01 AG049617 01/15/16-11/30/25

ROLE: Lotz (PI)

Publications

[Identification of transcription factors responsible for dysregulated networks in human osteoarthritis cartilage by global gene expression analysis.](#)

Fisch KM, Gamini R, Alvarez-Garcia O, Akagi R, Saito M, Muramatsu Y, Sasho T, Koziol JA, Su AI, Lotz MK.

Osteoarthritis Cartilage. 2018 Nov;26(11):1531-1538. doi: 10.1016/j.joca.2018.07.012. Epub 2018 Aug 3.

PMID: 30081074

[Impaired Proteasomal Function in Human Osteoarthritic Chondrocytes Can Contribute to Decreased Levels of SOX9 and Aggrecan.](#)

Serrano RL, Chen LY, Lotz MK, Liu-Bryan R, Terkeltaub R.

Arthritis Rheumatol. 2018 Jul;70(7):1030-1041. doi: 10.1002/art.40456. Epub 2018 May 27. PMID: 29457374

[Platelet-derived growth factor-coated decellularized meniscus scaffold for integrative healing of meniscus tears.](#)

Lee KI, Olmer M, Baek J, D'Lima DD, Lotz MK.

Acta Biomater. 2018 Aug;76:126-134. doi: 10.1016/j.actbio.2018.06.021. Epub 2018 Jun 14. PMID: 29908335

[Genome-Wide Occupancy Profiling Reveals Critical Roles of FoxO1 in Regulating Extracellular Matrix and Circadian Rhythm Genes in Human Chondrocytes.](#)

Duffy T, Bekki H, Lotz MK.

Arthritis Rheumatol. 2020 Sep;72(9):1514-1523. doi: 10.1002/art.41284. Epub 2020 Aug 9. PMID: 32281255

[Suppression of circadian clock protein cryptochrome 2 promotes osteoarthritis.](#)

Bekki H, Duffy T, Okubo N, Olmer M, Alvarez-Garcia O, Lamia K, Kay S, Lotz M. Osteoarthritis Cartilage. 2020

Jul;28(7):966-976. doi: 10.1016/j.joca.2020.04.004. Epub 2020 Apr 24. PMID: 32339698

[Mohawk is a transcription factor that promotes meniscus cell phenotype and tissue repair and reduces osteoarthritis severity.](#)

Lee KI, Gamini R, Olmer M, Ikuta Y, Hasei J, Baek J, Alvarez-Garcia O, Grogan SP, D'Lima DD, Asahara H, Su AI, Lotz MK.

Sci Transl Med. 2020 Oct 28;12(567):eaan7967. doi: 10.1126/scitranslmed.aan7967. PMID: 33115953

[Both microRNA-455-5p and -3p repress hypoxia-inducible factor-2 \$\alpha\$ expression and coordinately regulate cartilage homeostasis.](#)

Ito Y, Matsuzaki T, Ayabe F, Mokuda S, Kurimoto R, Matsushima T, Tabata Y, Inotsume M, Tsutsumi H, Liu L, Shinohara M, Tanaka Y, Nakamichi R, Nishida K, Lotz MK, Asahara H.

Nat Commun. 2021 Jul 6;12(1):4148. doi: 10.1038/s41467-021-24460-7. PMID: 34230481

[Transcriptomic analyses of joint tissues during osteoarthritis development in a rat model reveal dysregulated mechanotransduction and extracellular matrix pathways.](#)

Hu Y, Li K, Swahn H, Ordoukhanian P, Head SR, Natarajan P, Woods AK, Joseph SB, Johnson KA, Lotz MK.

Osteoarthritis Cartilage. 2022 Oct 28:S1063-4584(22)00880-9. doi: 10.1016/j.joca.2022.10.003. Online ahead of print. PMID: 36354073

[Senescent cell population with ZEB1 transcription factor as its main regulator promotes osteoarthritis in cartilage and meniscus.](#)

Swahn H, Li K, Duffy T, Olmer M, D'Lima DD, Mondala TS, Natarajan P, Head SR, Lotz MK.

Ann Rheum Dis. 2022 Dec 23;ard-2022-223227. doi: 10.1136/ard-2022-223227. Online ahead of print. PMID: 36564153

MAPPING THE JOINT-NERVE INTERACTOME OF THE KNEE

The goal is to use transcriptomic analyses at single cell and tissue levels to determine interactions between joint tissues and the peripheral nervous system that are involved in joint pain.

The project is part of the Restoring Joint Health and Function to Reduce Pain (**RE-JOIN**) Consortium is a new program within the NIH Helping to End Addiction Long-term (**HEAL**) program. The overall goals of HEAL are 'Understanding, managing, and treating pain and consequently 'Improving prevention and treatment for opioid misuse and addiction'. Joint and back pain are the major indications for the prescription of pain medications, including opioids. The **RE-JOIN** Consortium aims to understand how patterns of sensory neuron networks in joints change with disease and aging. Our goal is to use transcriptomic analyses at single cell and tissue spatial levels of the knee joint tissues and dorsal root ganglia to determine interactions between joint tissues and the peripheral nervous system that are involved in joint pain. Mechanisms and mediators of these interactions would be potential new targets for tissue destruction and joint pain.

Funding

NIH UC2 AR0821860 9/23/22-08/31/27
ROLE: Lotz (Co-PI) with Anne-Marie Malfait and Richard Miller

FOXO TRANSCRIPTION FACTORS AS CRITICAL REGULATORS OF INTERVERTEBRAL DISC AGING

The objective of this project is to determine the role of FoxO in intervertebral disc homeostasis, how FoxO deficient promotes intervertebral disc degeneration and whether enhancing FoxO activation has therapeutic potential.

Funding

NIH/NIA R01 AG062533 08/01/19-04/30/24
ROLE: Lotz (PI)

Publications

[Age-related reduction in the expression of FOXO transcription factors and correlations with intervertebral disc degeneration.](#)

Alvarez-Garcia O, Matsuzaki T, Olmer M, Masuda K, Lotz MK.

J Orthop Res. 2017 Dec;35(12):2682-2691. doi: 10.1002/jor.23583. Epub 2017 May 4. PMID: 28430387

[FOXO are required for intervertebral disk homeostasis during aging and their deficiency promotes disk degeneration.](#)

Alvarez-Garcia O, Matsuzaki T, Olmer M, Miyata K, Mokuda S, Sakai D, Masuda K, Asahara H, Lotz MK.

Aging Cell. 2018 Oct;17(5):e12800. doi: 10.1111/accel.12800. Epub 2018 Jul 2. PMID: 29963746

[The cellular landscape of the healthy human intervertebral disc: identification of new immature cell populations and their relationship with mature populations at single cell resolution.](#)

Mertens J, Swahn H, Olmer M, Myers K, Mondala TS, Natarajan P, Head SR, Alvarez-Garcia O, Lotz MK.

Submitted

[Shared and compartment-specific processes in nucleus pulposus and annulus fibrosus during intervertebral disc degeneration.](#)

Swahn H, Mertens J, Olmer M, Myers K, Mondala TS, Natarajan P, Head SR, Alvarez-Garcia O, Lotz MK.

Submitted

HIGH RESOLUTION 3D MAPPING OF CELLULAR HETEROGENEITY WITHIN MULTIPLE TYPES OF MINERALIZED TISSUES

The Human BioMolecular Atlas Program (**HuBMAP**) is working to create a Human Reference Atlas at the cellular level. We will map the cellular composition of the human knee joint at single cell resolution.

This project is part of the HuBMAP consortium and applies single cell and spatial transcriptomics to build three-dimensional maps of normal human articular cartilage.

Funding

NIH/NIAMS 5 U54 AR078664 09/01/22-08/31/23
ROLE: Lotz Co-PI with David Rowe

Publications

[Senescent cell population with ZEB1 transcription factor as its main regulator promotes osteoarthritis in cartilage and meniscus.](#)

Swahn H, Li K, Duffy T, Olmer M, D'Lima DD, Mondala TS, Natarajan P, Head SR, Lotz MK.

Ann Rheum Dis. 2022 Dec 23;ard-2022-223227. doi: 10.1136/ard-2022-223227. Online ahead of print. PMID: 36564153

MECHANO SIGNALS REGULATING TENDON AND LIGAMENT HOMEOSTASIS

The goal is to determine the function of mechanoreceptors in tendon development, homeostasis, and regeneration.

Funding

NIH/NIAMS R01 AR080127

09/20/22-08/31/27

ROLE: Lotz Co-I; Asahara PI

Publications

[The mechanosensitive ion channel PIEZO1 is expressed in tendons and regulates physical performance.](#)

Nakamichi R, Ma S, Nonoyama T, Chiba T, Kurimoto R, Ohzono H, Olmer M, Shukunami C, Fuku N, Wang G, Morrison E, Pitsiladis YP, Ozaki T, D'Lima D, Lotz M, Patapoutian A, Asahara H.

Sci Transl Med. 2022 Jun;14(647):eabj5557. doi: 10.1126/scitranslmed.abj5557. Epub 2022 Jun 1. PMID: 35648809