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Cellular Senescence in Metabolic Syndrome–Associated Osteoarthritis

Metabolic syndrome–associated osteoarthritis (MetS-OA) is a distinct osteoarthritis phenotype defined by the coexistence of MetS or its individual components. Despite the high prevalence of MetS-OA, its pathogenic mechanisms are unclear. In the present study, we report that humans and mice with MetS are more likely to develop osteoarthritis-related subchondral bone alterations than those without MetS. MetS-OA mice exhibited a rapid increase in joint subchondral bone plate and trabecular thickness before articular cartilage degeneration. Subchondral preosteoclasts undergo senescence at the pre- or early-osteoarthritis stage and acquire a unique secretome to stimulate osteoblast differentiation and inhibit osteoclast differentiation. Antagonizing preosteoclast senescence markedly mitigates pathological subchondral alterations and osteoarthritis progression in MetS-OA mice. At the molecular level, preosteoclast secretome activates COX2-PGE2, resulting in stimulated differentiation of osteoblast progenitors for subchondral bone formation. Administration of a selective COX2 inhibitor attenuated subchondral bone alteration and osteoarthritis progression in MetS-OA mice. Longitudinal analyses of the human Osteoarthritis Initiative (OAI) cohort dataset also revealed that COX2 inhibitor use, relative to non-selective nonsteroidal anti-inflammatory drug use, is associated with less progression of osteoarthritis and subchondral bone marrow lesion worsening in participants with MetS-OA. Our findings suggest a central role of a senescent preosteoclast secretome-COX2/PGE2 axis in the pathogenesis of MetS-OA.

Biography

Mei Wan, Ph.D. is Frank J. Frassica Professor at the Department of Orthopaedic Surgery in Johns Hopkins University School of Medicine. Dr. Wan's research focuses on the contribution of fundamental aging processes, particularly cellular senescence, to bone health and disease. Another line of Dr. Wan's research is to understand the mechanisms by which the bone-derived cues regulate the aging process of other organs such as vascular system and brain. The impact of Dr. Wan's research extends across different disciplines as testified by her publication record, which includes papers in Cell Metabolism, Nature Communications, Journal Clinical Investigation, Gene & Development, PNAS, Bone Research, etc. Her research program has been continuously funded by NIH. Dr. Wan served on the editorial boards of two leading skeletal-related journals, JBMR and Bone Research. Since 2021, she serves on the Reviewing Editor Board of eLife.

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