Targeting RIP3 inhibits osteoarthritis development by restoring anabolic-catabolic balance in the bone-cartilage unit

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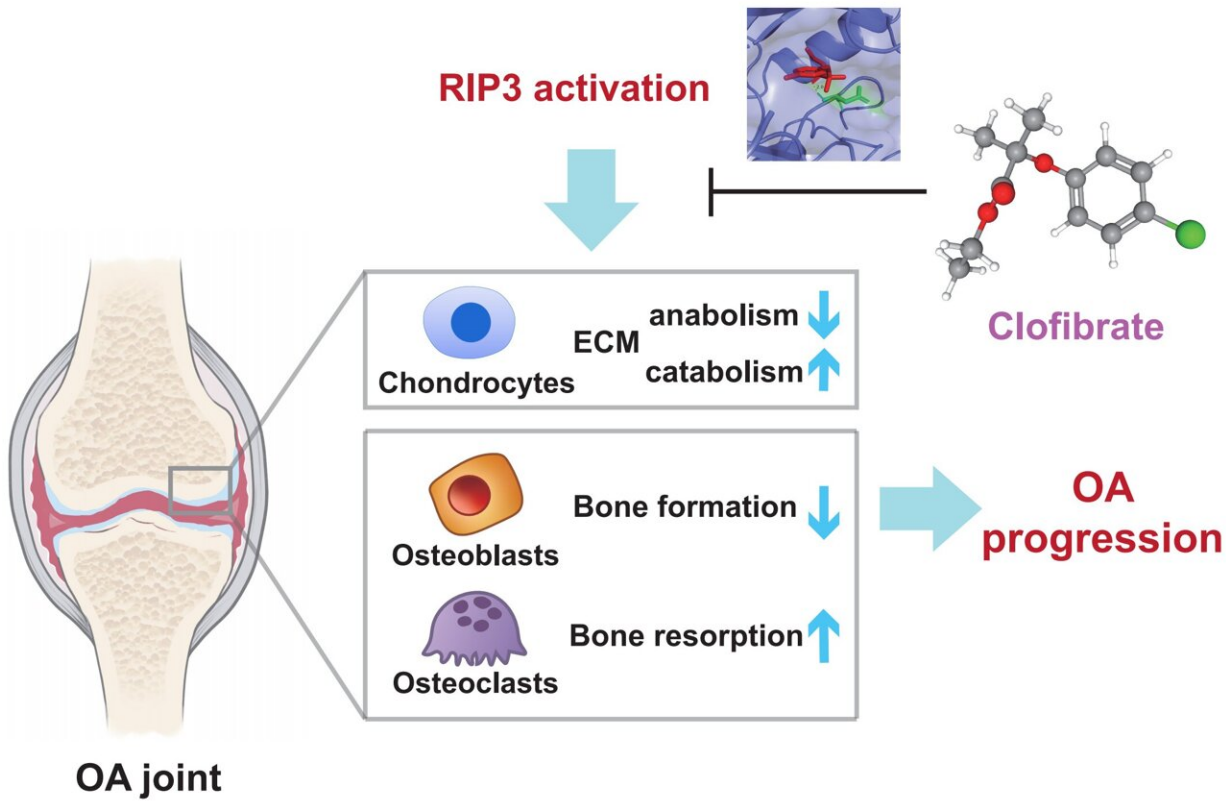

RIP3 plays a pivotal role in the pathogenesis of OA by disrupting cartilage extracellular matrix (ECM) metabolism homeostasis, inhibiting bone formation, and enhancing bone resorption, while clofibrate appears to be a promising drug against OA by targeting RIP3. Credit: Science China Press

Osteoarthritis (OA) represents the most prevalent form of chronic degenerative joint disease worldwide. The dynamic interplay between cartilage and subchondral bone is essential for preserving joint structural and functional integrity. In addition to cartilage degeneration, pathological alterations within the subchondral bone significantly contribute to OA progression. Therefore, there is an urgent need to develop new strategies that target not only cartilage but also subchondral bone for the efficient treatment of OA.

Recently, teams led by Prof. Xiaoqing Hu, Prof. Yingfang Ao, Prof. Jin Cheng from the Department of Sports Medicine, Peking University Third Hospital, Prof. Fengbiao Mao from the Institute of Medical Innovation and Research, Peking University Third Hospital, have systematically investigated the specific role of the key molecule of necroptosis—receptor-interacting protein kinase 3 (RIP3) in OA joints.

It was found that RIP3 expression was upregulated in both OA cartilage and subchondral bone. RIP3 not only induces chondrocyte necrosis and anabolic-catabolic disorders, but also mediates osteoblast necrosis and inhibits the expression of key osteogenic factors. On the other hand, the absence of RIP3 markedly attenuates osteoclastogenic process induced by RANKL in bone marrow macrophages.

Cheng further confirmed that overexpression of RIP3 within the articular cavity is sufficient to elicit typical OA-associated osteochondral pathologies. The absence of RIP3 effectively mitigates pain symptoms, cartilage degeneration, and synovial inflammation induced by trauma and natural aging in the progression of OA.

Additionally, it significantly impedes structural deterioration of the subchondral bone and restores the balance between osteoblasts and osteoclasts. This underscores the pivotal role of RIP3 in the pathophysiology of both OA cartilage and subchondral bone, thereby

presenting a novel two-birds-one-stone target for the development of early-stage OA therapeutics.

Furthermore, based on the transcriptional alterations induced by RIP3 in chondrocytes, a comprehensive screen within the Connectivity Map database was performed to identify small molecule drugs capable of reversing the downstream effects of RIP3, and the lipid-lowering agent clofibrate was identified as an effective modulator to block chondrocyte necroptosis induced by RIP3 and attenuate IL-1β-mediated enhancement of chondrocyte catabolism. Thus, clofibrate has the potential to be repurposed as a novel therapeutic agent for OA treatment.

This study corroborates the significance of RIP3 as a key modulator of joint metabolic homeostasis. The development of novel therapeutic interventions that target RIP3 in both OA cartilage and subchondral bone may effectively achieve the objectives of inhibiting osteochondral degeneration and alleviating pain symptoms in the early stages of the disease.

Subsequent validation of the therapeutic efficacy of RIP3-targeted interventions in the bone-cartilage unit across large animal models and human subjects will enhance our comprehension of RIP3's mechanistic role in OA and offer renewed hope to the patient population.

More information: Jin Cheng et al, Targeting RIP3 inhibits osteoarthritis development by restoring anabolic-catabolic balance in the bone-cartilage unit, *Medicine Plus* (2024). DOI: 10.1016/j.medp.2024.100032

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