Exosome-Mediated Crosstalk Between Synovium and Cartilage via the IRF7/Ptma Pathway in Steroid-Induced Osteonecrosis of the Femoral Head

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INTRODUCTION: Osteonecrosis of the femoral head (ONFH) is a devastating condition that often progresses to femoral head collapse and ultimately leads to hip joint dysfunction. Previous studies have predominantly focused on intra-femoral head lesions as the major pathological driver of disease progression. However, clinical observations have revealed that even in cases where necrotic femoral heads no longer undergo further collapse, progressive cartilage degeneration still occurs, inevitably resulting in secondary osteoarthritis of the hip. These findings suggest that the pathogenesis of ONFH extends beyond intraosseous changes and involves pathological alterations of periarticular tissues, including the synovium and joint capsule. Nevertheless, the molecular mechanisms underlying these extra-femoral head lesions, and their regulatory interactions with articular cartilage, remain poorly understood. We therefore hypothesized that synovial fibroblasts contribute to cartilage degeneration in steroid-induced ONFH by exosome-mediated regulation of chondrocyte apoptosis, thereby linking periarticular synovial pathology to progressive joint deterioration.

METHODS: Key genes implicated in synovial lesions associated with steroid-induced osteonecrosis of the femoral head (SIONFH) were identified through RNA sequencing (RNA-seq), and these results were subsequently validated using clinical specimens and cellular experiments. A synovial fibroblast model was employed to confirm the expression of key genes at the cellular level, and we investigated the downstream mechanisms of these genes through lentivirus-mediated gene knockout technology. Fibroblast proliferation and migratory capacity were assessed utilizing CCK-8 assays and migration assays, respectively. Additionally, Transwell co-culture experiments were conducted to elucidate the interactions between fibroblasts and chondrocytes. Subsequently, proteomics analysis of exosomes was performed to explore the downstream targets mediated by the identified key genes.

RESULTS: RNA sequencing (RNA-seq) results indicated that synovial lesions associated with steroid-induced osteonecrosis of the femoral head (SIONFH) are closely linked to immune and inflammatory responses. Validation through clinical specimens and cellular experiments confirmed that interleukin regulatory factor 7 (IRF7) expression was significantly elevated in the synovium of SIONFH patients, and that the proliferation and migratory capacities of SIONFH synovial fibroblasts were markedly increased. Subsequent experimental findings elucidated that the Irf7/Ptma signaling pathway is activated in the synovial fibroblasts of SIONFH, resulting in a significant reduction of Ptma protein levels in the exosomes they secrete, which in turn accelerates chondrocyte apoptosis. These findings suggest that the Irf7/Ptma axis may play a pivotal role in the interactions between synovial fibroblasts and chondrocytes.

DISCUSSION: The findings of this study comprehensively elucidate the potential mechanisms underlying the interactions between the synovium and cartilage in the progression of steroid-induced osteonecrosis of the femoral head (SIONFH), thereby providing novel molecular targets for the treatment of this condition.

SIGNIFICANCE/CLINICAL RELEVANCE: (1-2 sentences): This study highlights that cartilage degeneration in steroid-induced osteonecrosis of the femoral head arises not only from intraosseous lesions but also from synovial pathology, underscoring the importance of whole-joint mechanisms in disease progression. Targeting the synovial exosome–mediated crosstalk with cartilage may offer novel therapeutic strategies to delay or prevent secondary osteoarthritis in affected patients.

IMAGES AND TABLES:

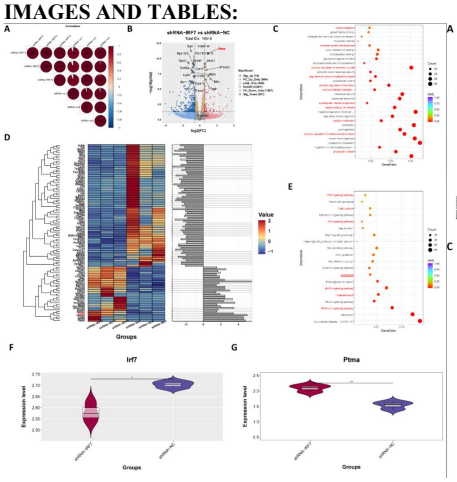

Figure 1

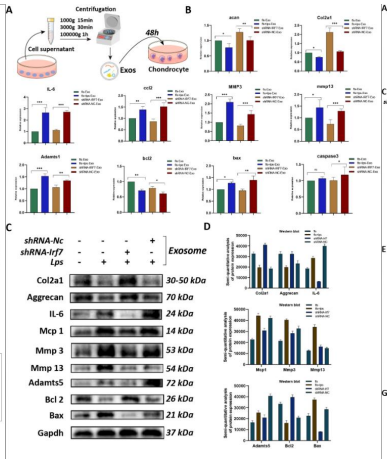

Figure 2

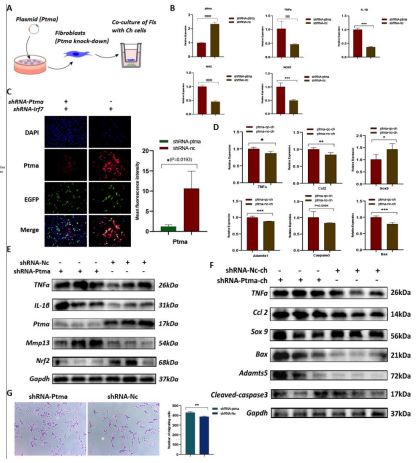

Figure 3

Notes:
Figure 1 Synovial fibroblasts knocked out Irf7 and underwent transcriptomic sequencing.
Figure 2 Isolate fibroblast exosomes, treat chondrocytes with equal amounts, and detect gene expression levels related to chondrocyte proliferation, inflammation, apoptosis, etc.
Figure 3 Further knockout of Ptma on the basis of Irf7 knockout, co-culture with chondrocytes, and detection of proliferation, inflammation, and apoptosis gene expression and protein translation levels.