[BIOINFO 2025]

Molecular Convergence and Divergence in Osteoarthritis: A Cross-Cohort 12-Gene OA Common Signature and Contrasting Molecular Programs

Hojun Kim[1], Ju-Ryoung Kim[2], Man Soo Kim[2,*], and Ji-Hwan Park[1,*]

[1]Department of Biological Science, Ajou University
[2]Department of Orthopedic Surgery, Seoul St. Mary's Hospital,
College of Medicine, The Catholic University of Korea
**Corresponding authors: Ji-Hwan Park(parkjihwan@ajou.ac.kr), Man Soo Kim(kms3779@naver.com)*

Osteoarthritis (OA) is a heterogeneous disease in which multiple factors act across cartilage, synovium, and subchondral bone. Consequently, therapeutic responses vary among patients, underscoring the need for molecular stratification to enable precision medicine. We investigated OA's molecular features through a dual approach: discovery of an OA common signature and patient subtyping. We integrated a clinical cohort from Seoul St. Mary's Hospital (Seoul, Korea) with multiple public RNA-seq datasets to compute cohort-wise differentially expressed genes (DEGs) between OA and controls and to derive a cross-cohort, reproducible transcriptomic signature. Through this analysis, we identified a 12-gene OA common signature, addressing the reproducibility limitations inherent in single-cohort analyses. Using an independent patient cohort, we applied missing-value-aware principal component analysis (PCA) followed by k-means clustering (k=5) to partition OA into five molecular clusters. These clusters aligned along a spectrum from an inflammation–destruction program at one extreme to a tissue–reconstruction program at the other. DEG- and pathway-level contrasts across clusters indicated that variation in the relative activities of these two programs underlies OA heterogeneity. We propose a conceptual model of OA as a molecular spectrum governed by the balance between two antagonistic programs. The OA common signature provides a foundation for diagnostic biomarker development, whereas subtype-specific gene sets offer potential leads for targeted therapeutics and patient stratification in clinical trials.