Multi-omics integration in osteoarthritis: Unraveling cell-type-specific gene-metabolite networks for precision medicine (Review)

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Abstract. Osteoarthritis (OA) is a heterogeneous joint disorder lacking disease-modifying therapies. Recent advances in single-cell transcriptomics, metabolomics, lipidomics, and spatial omics have enabled the reconstruction of cell-type-specific gene-metabolite networks and revealed that metabolic reprogramming differs markedly across chondrocyte subsets, synovial fibroblasts and immune cells. Lipid metabolism disturbances, particularly those involving glycerophospholipids, sphingolipids and cholesterol, are consistently linked to OA severity and pain generation. Integrative multi-omics approaches further facilitate molecular endotyping, informing patient stratification and endotype-driven clinical trial design. However, a systematic synthesis of these emerging findings is still lacking. This review critically synthesizes current multi-omics integration strategies, delineates cell-type-specific metabolic networks derived from transcriptomic and metabolomic data and discusses their implications for precision medicine in OA, while also considering the emerging contributions of spatial omics technologies.

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Abbreviations: OA, osteoarthritis; scRNA-seq, single-cell RNA sequencing; MSI, mass spectrometry imaging; CH25H, cholesterol 25-hydroxylase; CYP7B1, cytochrome P450 family 7 subfamily B member 1; RORα, retinoic acid-related orphan receptor α; LPC, lysophosphatidylcholine; ASIC3, acid-sensing ion channel 3; PPAR, peroxisome proliferator-activated receptor; LXR, liver X receptor; SREBP1, sterol regulatory element-binding protein 1; SESN2, Sestrin 2; ABCD2, ATP-binding cassette subfamily D member 2; ACSL4, acyl-CoA synthetase long-chain family member 4; LPCAT3, LPC acyltransferase 3; ABCA1, ATP-binding cassette subfamily A member 1; IPFP, infrapatellar fat pad; EV, extracellular vesicle; DMOAD, disease-modifying osteoarthritis drug; OARSI, Osteoarthritis Research Society International; AI, artificial intelligence

Key words: osteoarthritis, multi-omics integration, single-cell transcriptomics, metabolomics, gene-metabolite networks, lipid metabolism, molecular endotypes, precision medicine

Contents

1. Introduction

Osteoarthritis (OA) is a leading cause of chronic disability worldwide, yet no disease-modifying therapy has been approved to date. The increasing prevalence of OA, driven by population aging and increasing obesity rates, imposes a substantial socioeconomic burden on health care systems globally. Vicenti *et al* (1) performed an early multi-omics analysis of synovial fluid and reported that conventional approaches based on radiographic grading and symptomatic management fail to capture the molecular heterogeneity of OA, which largely explains the recurrent failures of clinical trials for structure-modifying drugs. Despite decades of research, current pharmacological interventions remain limited to

pain relief without altering long-term disease progression, underscoring the urgent need for a deeper mechanistic understanding that can guide precision therapeutic strategies.

The traditional view of OA as a simple 'wear and tear' disease resulting from mechanical overloading has been progressively supplanted by a more nuanced understanding of OA as a multifactorial disorder involving metabolic, inflammatory and genetic components. Iijima *et al* (2) integrated meta-analysis with multi-omics data from murine models of age-related knee OA and demonstrated that pathways associated with oxidative stress, mitochondrial dysfunction and inflammation converge to drive cartilage degeneration, thereby challenging the exclusive biomechanical paradigm. In parallel, Bensa *et al* (3) systematically reviewed preclinical evidence on corticosteroid injections and revealed a wide spectrum of effects ranging from detrimental to disease-modifying, highlighting that therapeutic responses are highly context-dependent and likely influenced by underlying molecular endotypes. Bajpai and Chandra (4) recently reviewed the emerging anti-inflammatory attributes of curcumin and proposed that targeting inflammatory cascades represents a promising avenue, yet they critically noted that the heterogeneous nature of OA pathogenesis complicates the identification of universally effective interventions. Collectively, these observations have shifted the conceptual framework toward recognizing OA as a systemic metabolic and immune disorder with localized joint manifestations, thereby necessitating molecular-level stratification.

The inherent complexity and heterogeneity of OA demand analytical approaches capable of capturing molecular events across multiple biological layers. Liu *et al* (5) recently synthesized advances in omics technologies and emphasized that while bulk transcriptomics, proteomics and metabolomics have individually identified OA-associated pathways, their integration is essential to disentangle causal relationships from correlative noise. Similarly, Wei *et al* (6) comprehensively reviewed progress in multi-omics studies of OA and concluded that single-platform approaches are insufficient to capture the intricate interplay between genes, proteins and metabolites that drives disease heterogeneity. The advent of single-cell RNA sequencing (scRNA-seq) has further revolutionized the field by resolving cell-type-specific transcriptional programs that bulk analyses average across millions of cells. Gu *et al* (7) provided a systematic overview of scRNA-seq applications in OA and highlighted that this technology has unveiled previously unrecognized chondrocyte and synovial cell subsets with distinct metabolic and inflammatory signatures. Danzeng *et al* (8) extended this paradigm by demonstrating that single-cell sequencing can dissect the immune microenvironment in OA, revealing macrophage and T-cell heterogeneity that correlates with disease severity. However, a critical appraisal of these studies reveals that while descriptive catalogs of cell types have multiplied, functional validation and integration with metabolite data remain limited, representing a major knowledge gap.

The present review synthesizes current advances in multi-omics integration applied to OA, with a specific focus on reconstructing cell-type-specific gene-metabolite networks and their implications for precision medicine. This review synthesizes advances in single-cell transcriptomics, metabolomics, lipidomics and spatial omics, presenting their collective contributions to a coherent understanding of OA. While spatial omics technologies have provided valuable insights into the spatial organization of joint tissues, their systematic integration with cell-type-specific gene-metabolite networks remains an ongoing challenge that is critically discussed in this review. While previous comprehensive reviews have summarized omics advances in OA and highlighted the importance of multi-omics integration, they have not systematically bridged transcriptional and metabolic alterations at cellular resolution nor comprehensively synthesized the mechanistic links between lipid metabolic reprogramming and pain generation, which are gaps that the present review specifically addresses. Recent systematic reviews by Boffa *et al* (9) and Sourugeon *et al* (10) have comprehensively evaluated cell-based therapies in animal models, demonstrating disease-modifying effects across multiple cell sources, yet these studies also highlighted that the mechanisms of action remain poorly understood due to insufficient molecular characterization. D'Arrigo *et al* (11) further called for standardization in secretome and extracellular vesicle (EV) research, noting that heterogeneous protocols have precluded definitive conclusions about therapeutic mechanisms. Tan *et al* (12) integrated single-cell sequencing with genetics and epigenetics to reveal mesenchymal stem cell (MSC) senescence in OA, providing a molecular basis for age-related susceptibility. Wang *et al* (13) recently performed multi-omics analysis of small EVs and proposed that integrating vesicle cargo with tissue-level omics can bridge molecular insights and clinical applications. By critically evaluating these emerging findings, the present review aims to delineate cell-type-specific gene-metabolite networks across chondrocytes, synovial fibroblasts and immune cells; synthesize evidence linking lipid metabolic reprogramming to OA severity; and discuss how multi-omics-derived molecular endotypes can inform patient stratification and endotype-driven clinical trial design.

2. Omics technologies in OA research: From bulk to single-cell and spatial resolution

The evolution from conventional bulk omics to high-resolution single-cell and spatial technologies has fundamentally reshaped the landscape of OA research. Traditional platforms provided the first molecular maps of diseased joints but averaged signals across millions of cells, masking critical heterogeneity. The subsequent advent of scRNA-seq enabled unbiased dissection of cell-type-specific transcriptomes, while emerging spatial omics technologies now add back the lost tissue context. A comparative overview of these technological platforms, their principal contributions to the understanding of OA and their current methodological limitations is summarized below (Fig. 1).

Traditional bulk omics platforms. Bulk transcriptomics, proteomics and metabolomics laid the groundwork for understanding OA pathogenesis by profiling average molecular alterations from whole tissues. In a comprehensive review, Rai *et al* (14) examined three decades of OA omics studies and concluded that while bulk approaches have consistently identified pathways such as extracellular matrix dysregulation and

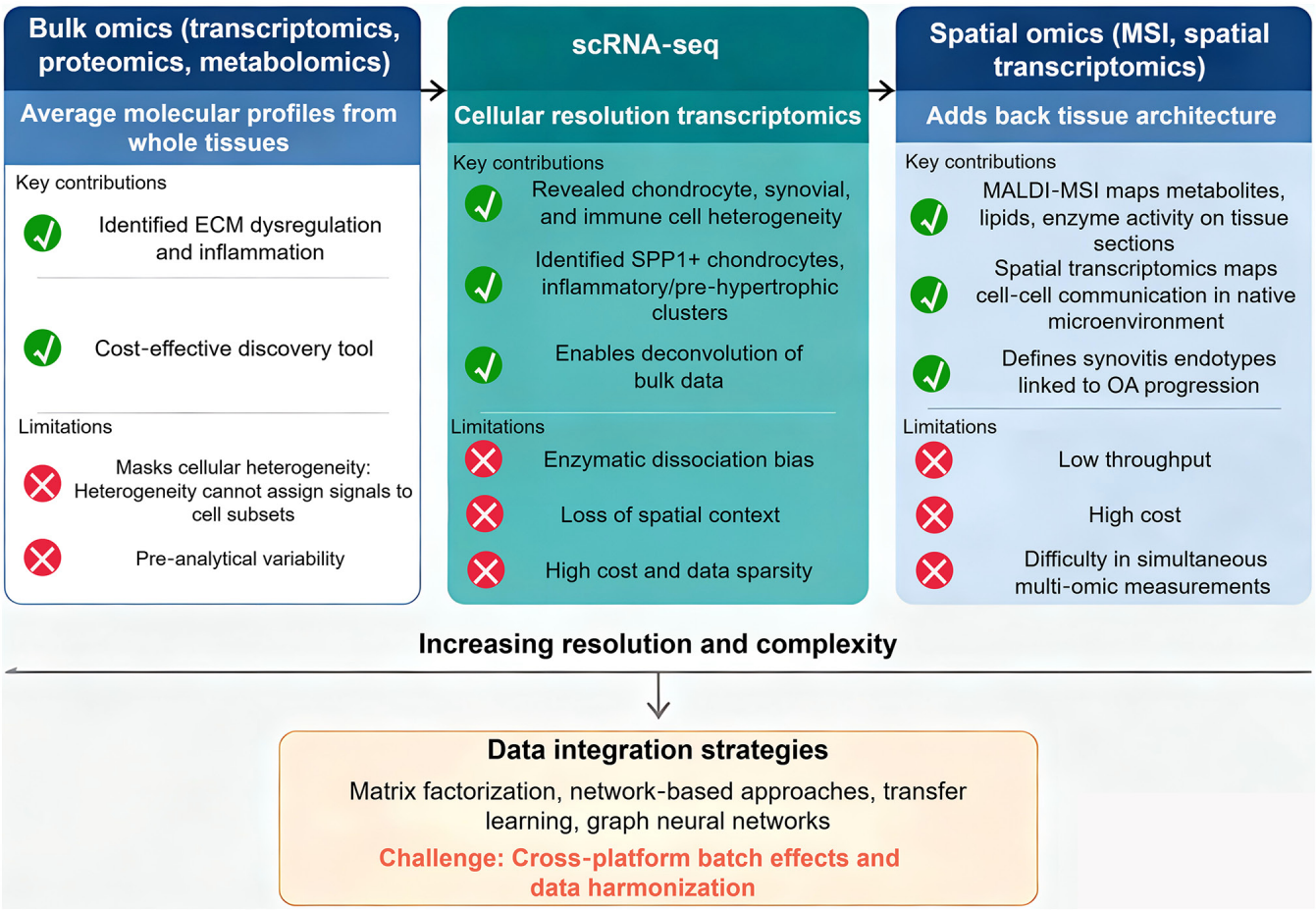

Figure 1. Evolution of omics technologies in OA research: From bulk to single-cell and spatial resolution. Overview of key technological platforms, their main contributions to the understanding of OA and current methodological limitations. Limitations for bulk omics include 'Masks cellular heterogeneity: Heterogeneity cannot be resolved; molecular signals cannot be assigned to distinct cell subsets' and 'pre-analytical variability'. The figure was generated with Figdraw (www.figdraw.com; copyright code: AOAIIbbbda). OA, osteoarthritis; ECM, extracellular matrix; scRNA-seq, single-cell RNA sequencing; MALDI, matrix-assisted laser desorption ionization; MSI, mass spectrometry imaging; SPP1, secreted phosphoprotein 1.

inflammation, they cannot resolve whether these signals originate from distinct cell subsets. Similarly, Van Pevenage *et al* (15) performed a systematic review of metabolomics studies and found that disturbed amino acid and lipid metabolism are reproducible findings in OA biofluids, but pre-analytical variability and cohort heterogeneity remain major barriers to clinical translation. More recently, Liu *et al* (5) emphasized that bulk transcriptomics, when combined with deconvolution algorithms, can still yield valuable insights, yet the accuracy of such inferences depends heavily on the quality of single-cell reference data. Despite their inherent limitations, bulk platforms continue to serve as cost-effective discovery tools and provide essential datasets for integrative analyses.

scRNA-seq. The introduction of scRNA-seq has revolutionized OA research by mapping transcriptional landscapes at cellular resolution, revealing previously unrecognized heterogeneity within cartilage, synovium and infrapatellar fat pad. Using scRNA-seq on human OA cartilage, Ji *et al* (16) first identified multiple chondrocyte clusters with distinct metabolic and inflammatory signatures, setting the stage for cell-level investigations. More recent work by Fan *et al* (17) integrated single-cell and bulk transcriptomics to uncover inflammatory and pre-hypertrophic chondrocyte subpopulations as key drivers of cartilage degeneration, and they validated these findings using spatial transcriptomics. In the synovial compartment, Liao *et al* (18) performed comprehensive scRNA-seq profiling of synovial macrophages and identified a subset of secreted phosphoprotein 1 (SPP1)+ macrophages that correlates with OA severity, suggesting that macrophage heterogeneity is directly linked to disease progression. Using a murine model, Sebastian *et al* (19) demonstrated that post-traumatic OA induces early transcriptomic changes in immune cells within the synovium, including the emergence of a novel neutrophil population, highlighting the dynamic nature of the synovial immune landscape. A major methodological advance came from Huang *et al* (20), who developed a computational strategy to deconvolute bulk synovial transcriptomes using scRNA-seq references, enabling retrospective analysis of existing datasets without new experiments. Furthermore, Wang *et al* (21) provided a forward-looking review on how scRNA-seq is shaping orthopedics, emphasizing that the generation of comprehensive joint cell atlases will be essential for identifying cell-specific therapeutic targets. Nevertheless, challenges persist, including enzymatic dissociation biases and the inevitable loss of spatial context.

Spatial omics: Mass spectrometry imaging and spatial transcriptomics. While scRNA-seq provides cellular resolution, it disrupts native tissue architecture, which is particularly problematic for OA given the zonal organization of cartilage and synovium. Spatial omics technologies, including mass spectrometry imaging (MSI) and spatial transcriptomics, have emerged to fill this gap. A comprehensive review by Fan *et al* (22) synthesized the current state of spatial analysis in the OA microenvironment, noting that matrix-assisted laser desorption ionization-MSI can map metabolites, lipids and even enzyme activities directly on tissue sections. In a functional study, Fan *et al* (23) used MSI to visualize phospholipase A2 activity across OA joints, demonstrating that active enzyme localization is spatially restricted to cartilage fissure edges and adjacent synovium, thereby linking local lipid metabolism to tissue damage. Lee *et al* (24) applied high-resolution N-glycan MSI to subchondral bone and revealed that complex-type N-glycans accumulate at high mechanical loading sites, providing a direct molecular bridge between biomechanical stress and post-translational modifications.

In the synovial membrane, Rocha *et al* (25) identified a distinct lipidomic signature in OA compared to rheumatoid arthritis, with specific phosphatidylcholines enriched in hyperplastic synovial areas, suggesting that local lipid alterations drive synovitis independent of systemic inflammation. More recently, Zhu *et al* (26) integrated spatially resolved proteomic and metabolomic imaging to define synovitis endotypes associated with OA progression, demonstrating that spatial multi-omics can stratify patients beyond conventional histology. For spatial transcriptomics, a review by Xie *et al* (27) emphasized that this technology holds great promise for mapping cell-cell communication networks within their native microenvironment, such as ligand-receptor interactions between superficial chondrocytes and synovial lining cells. Despite these advances, current limitations include low throughput, high cost and the difficulty of performing simultaneous multi-omic measurements on the same tissue section. Critically, while spatial omics technologies have provided valuable descriptive maps of metabolite and protein distributions across joint tissues, their integration with cell-type-specific gene-metabolite networks, including the assignment of spatially resolved metabolic signals to defined cell populations, remains a significant technical and analytical challenge that has yet to be fully resolved (26,27). This limitation is acknowledged throughout the present review, and the spatial findings discussed here are presented as complementary evidence rather than as fully integrated network components.

Data integration strategies and remaining challenges. Integrating data from bulk, single-cell and spatial platforms represents a major computational frontier. Kreitmaier *et al* (28) discussed state-of-the-art integration strategies for complex diseases, including matrix factorization and network-based approaches, and stressed the importance of tissue-specific context when combining datasets. A systematic evaluation by Rai *et al* (14) noted that while integrative analyses have successfully identified novel OA pathways such as glycerophospholipid metabolism, cross-platform batch effects and data sparsity frequently compromise reproducibility. As an example, Huang *et al* (29) combined metabolomics with transcriptomics from the same cartilage samples and identified glycerophospholipid metabolism as a central hub, but they acknowledged that the cellular origin of these signals could not be definitively assigned without single-cell resolution. More recently, Wei *et al* (6) provided a comprehensive summary of multi-omics OA studies and concluded that harmonizing data from different omics layers requires standardized computational pipelines and prospective validation in well-phenotyped cohorts.

An emerging trend is the use of single-cell data as a reference to deconvolute bulk and spatial data, a strategy that has yielded insights into synovial macrophage heterogeneity. Liu *et al* (5) further emphasized that recent advances in multi-omics integration, including the use of transfer learning and graph neural networks, are beginning to address cross-platform batch effects, but these methods remain inaccessible to many clinical researchers. Therefore, while individual omics technologies have matured considerably, their effective integration into a cohesive and clinically translatable understanding of OA continues to be an active area of method development.

3. Cell-type-specific gene-metabolite networks in OA

Single-cell transcriptomics integrated with metabolomics has enabled the reconstruction of cell-type-specific gene-metabolite networks in OA. These approaches have revealed that metabolic reprogramming is highly heterogeneous across chondrocyte subsets, synovial fibroblasts and immune cells, with distinct pathway alterations driving disease progression in a cell-type-dependent manner (Fig. 2).

Methodological framework for network reconstruction. Reconstructing cell-type-specific gene-metabolite networks requires computational strategies that integrate single-cell transcriptomic data with metabolomic or lipidomic profiles. Ojha *et al* (30) developed a multi-omics integration framework at cellular resolution to uncover gene-metabolite mechanisms underlying OA heterogeneity, demonstrating that coupling scRNA-seq with metabolomics enables the assignment of metabolic signatures to specific cell populations. This approach addresses a fundamental limitation of bulk analyses, where tissue-level averaging obscures cell-type-specific contributions. A critical methodological advance came from Fan *et al* (17), who integrated single-cell and bulk transcriptomics with spatial transcriptomics to identify inflammatory and prehypertrophic chondrocyte subpopulations as key drivers of cartilage degeneration, and importantly, validated these findings across multiple omics layers. However, several challenges persist. Katsoula *et al* (31) emphasized that while multi-omics integration has matured considerably, cross-platform batch effects and the difficulty of obtaining matched multi-omic data from the same single cells remain substantial hurdles. Furthermore, the computational complexity of integrating heterogeneous data types often requires specialized expertise, limiting accessibility for many clinical research groups. Taken together, these methodological advances have established a foundation for dissecting cell-type-specific metabolic networks, but standardized pipelines and prospective validation cohorts are urgently needed.

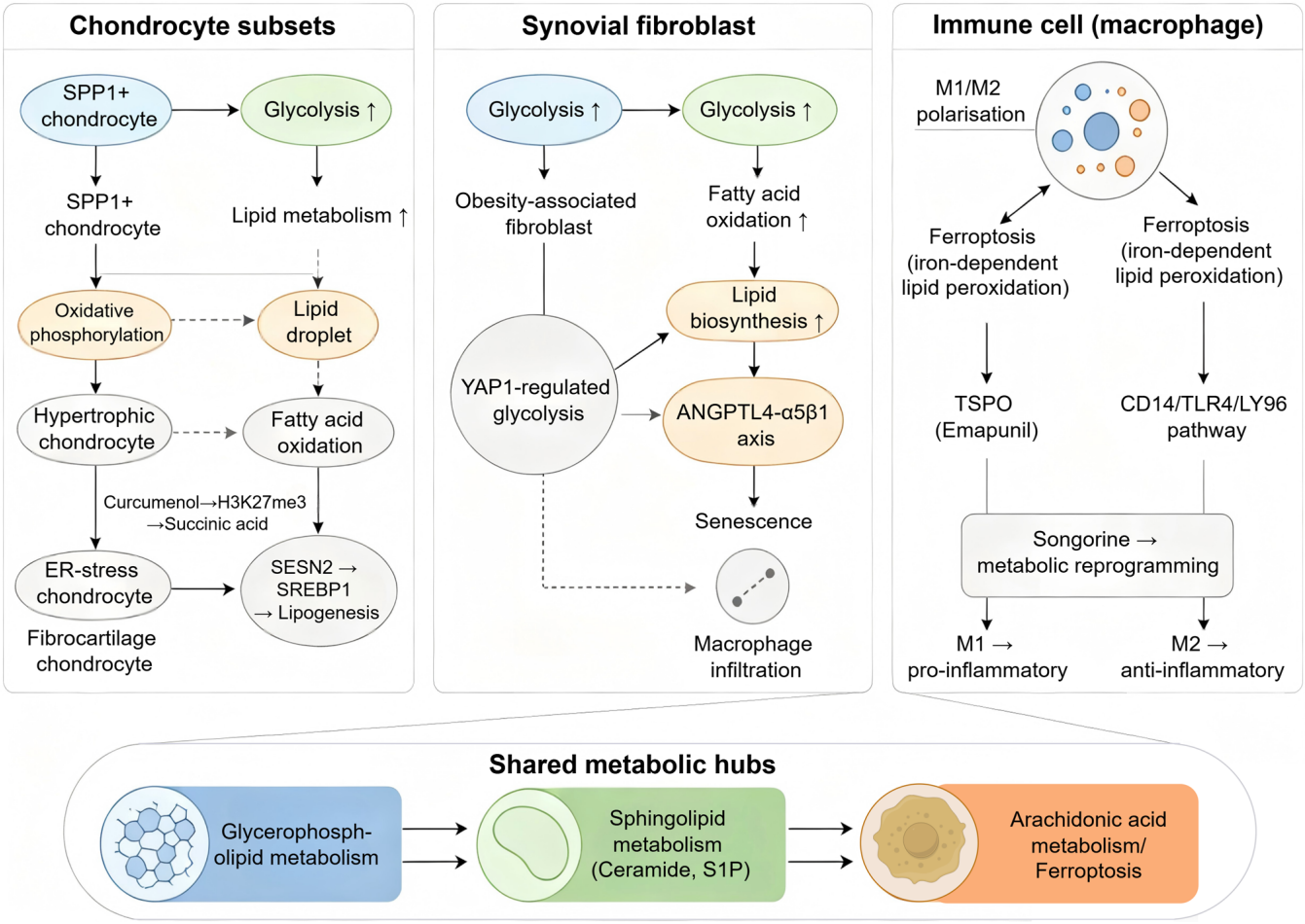

Figure 2. Cell-type-specific gene-metabolite networks in OA. Chondrocyte subsets (left), synovial fibroblasts (middle) and immune cells (right) exhibit distinct metabolic signatures. Shared hubs (bottom) include glycerophospholipid, sphingolipid and arachidonic acid metabolism. Arrows indicate pathway activation or crosstalk. The figure was generated with Figdraw (www.figdraw.com; copyright code: ORRUT47e0e). ANGPTL4, angiopoietin-like 4; ER, endoplasmic reticulum; LY96, lymphocyte antigen 96; SPP1, secreted phosphoprotein 1; S1P, sphingosine-1-phosphate; SESN2, sestrin 2; SREBP1, sterol regulatory element binding transcription factor 1; TLR, Toll-like receptor; TSPO, translocator protein 18 kDa; YAP1, Yes1 associated transcriptional regulator.

Shared metabolic hubs across cell types. Despite cell-type-specific metabolic features, integrative analyses have identified several metabolic hubs that are consistently altered across multiple joint cell populations in OA. Wang *et al* (32) performed integrated multi-omics analyses and revealed a lipid metabolic signature characterized by dysregulated glycerophospholipid and sphingolipid metabolism that spans chondrocytes, synovial fibroblasts and infiltrating immune cells. Similarly, He *et al* (33) employed integrated machine learning and multi-omics approaches to demonstrate that immune-metabolic signatures, particularly those involving arachidonic acid metabolism and ferroptosis-related pathways, are shared across different cell types in the OA joint. Notably, Wu *et al* (34) integrated bulk and scRNA-seq data and discovered that arachidonic acid metabolism is consistently upregulated in OA chondrocytes, suggesting that this pathway represents a convergent metabolic alteration across cellular compartments. By contrast, Wijesinghe *et al* (35) identified obesity-defined molecular endotypes in the synovium, revealing that metabolic pathway alterations can vary substantially depending on systemic metabolic status, with certain gene-metabolite associations being present only in obese patients with OA. This finding underscores that shared metabolic hubs may be context-dependent and modulated by host factors. Collectively, these observations indicate that while certain lipid metabolic pathways are broadly dysregulated in OA, their manifestation and functional consequences are modulated by both cell type and systemic metabolic context.

Chondrocyte-specific gene-metabolite associations. A critical synthesis of single-cell transcriptomic studies reveals both convergent and divergent findings regarding chondrocyte metabolic heterogeneity (16,36-41) (Table I). Southan *et al* (36) performed an integrated transcriptomics and metabolomics analysis of articular cartilage following mechanical injury and identified that chondrocyte metabolic responses are characterized by altered amino acid and lipid metabolism, with specific gene-metabolite pairs distinguishing injured from healthy cartilage. This study provided early evidence that chondrocyte metabolic reprogramming is directly linked to mechanical insult. Using scRNA-seq, Qu *et al* (37) identified a unique SPP1^{+} chondrocyte subpopulation in human OA cartilage that exhibits distinct metabolic gene expression signatures, including enrichment of glycolysis and lipid metabolism pathways, suggesting that these cells may represent a metabolically active pathogenic subset. Importantly, the definition of SPP1^{+}

Table I. Comparative synthesis of chondrocyte subpopulations and their gene-metabolite signatures in OA.

Authors, year	Cell population	Definition/marker genes	Key metabolic signature	Validation approach	Consistency with other studies	(Refs.)
Ji *et al*, 2019	Seven chondrocyte subtypes (ProC, preHTC, HTC, FC, EC, RegC, HomC)	Transcriptional clustering of human OA cartilage	SPP1 high-expressing cells associated with energy metabolism and anabolic-catabolic balance (KEGG pathway analysis)	scRNA-seq on human OA cartilage	First comprehensive scRNA-seq atlas; SPP1+ metabolic associations differ from Qu *et al* (37)	(16)
Southan *et al*, 2020	Injured vs. healthy chondrocytes	Mechanical injury model in articular cartilage	Altered amino acid and lipid metabolism; specific gene-metabolite pairs distinguish injured from healthy cartilage	Integrated transcriptomics + metabolomics	Early evidence linking mechanical insult to chondrocyte metabolic reprogramming	(36)
Qu *et al*, 2023	SPP1+ chondrocytes	High SPP1 expression	Glycolysis and lipid metabolism enrichment; angiogenic and senescence-associated gene signatures	Animal model; spatial heterogeneity of SPP1 confirmed	SPP1 pathway enrichment also reported by Kang *et al* (42); metabolic details differ from Ji *et al* (16)	(37)
Kang *et al*, 2023	Multiple chondrocyte subtypes (not discrete SPP1+ cluster)	SPP1 as signaling pathway (not cluster marker)	SPP1 pathway enrichment scores increased in OA; pleiotrophin, visfatin, TGF-β pathways also altered	Bulk RNA-seq validation	SPP1 involvement confirmed; differs from Qu *et al* (37) in not defining SPP1+ as discrete metabolic cluster	(42)
Chen *et al*, 2024	Chondrocytes (epigenetic regulation)	Curcumenol regulation of H3K27me3 demethylases KDM6B	Succinic acid metabolism altered; alleviates cartilage degeneration	*In vitro* + *in vivo* pharmacological intervention	Links epigenetic regulation to chondrocyte-specific metabolic alterations	(39)
Zhang *et al*, 2025	ER stress-responsive chondrocytes	Endoplasmic reticulum stress gene signatures	Lipid droplet formation; ceramide accumulation	Single-cell + transcriptomic profiling	Novel pathway; not directly comparable to SPP1+ studies; links ER stress to lipid metabolic reprogramming	(40)
Pan *et al*, 2024	FCs	Fibrocartilage markers from scRNA-seq	Fundamentally different metabolic gene expression vs. resident chondrocytes; six FC-related biomarkers identified (BCL6, ABCA5, ABCA6, CITED2, NR1D1, SLC7A8)	Bulk + single-cell transcriptomics; exploratory risk model	Highlights heterogeneity across repair vs. resident cells	(41)

EC, effector chondrocyte; ER, endoplasmic reticulum; FC, fibrocartilage chondrocyte; HomC, homeostatic chondrocyte; HTC, hypertrophic chondrocyte; KEGG, Kyoto Encyclopedia of Genes and Genomes; OA, osteoarthritis; preHTC, pre-hypertrophic chondrocyte; ProC, proliferative chondrocyte; RegC, regulatory chondrocyte; scRNA-seq, single-cell RNA sequencing; SPP1, secreted phosphoprotein 1 (osteopontin).

chondrocytes varies across studies: While Qu *et al* (37) defined this population primarily by high SPP1 expression coupled with angiogenic and senescence-associated gene signatures, Kang *et al* (42) identified SPP1 as one of several signaling pathways (alongside pleiotrophin, visfatin and TGF-β) that mediate altered cell-cell communication among chondrocyte subtypes in OA, without characterizing $SPP1^+$ cells as a discrete metabolic cluster. Extending these findings, Matta *et al* (38) provided a comprehensive review of chondrocyte populations at single-cell resolution and highlighted that hypertrophic chondrocytes display a distinct metabolic profile characterized by altered oxidative phosphorylation and fatty acid metabolism compared with healthy articular chondrocytes. Notably, the metabolic signatures attributed to $SPP1^+$ cells are not entirely consistent: Qu *et al* (37) reported enrichment of glycolysis and lipid metabolism pathways, whereas a subsequent study associated SPP1 high-expressing cells with energy metabolism and anabolic-catabolic balance through a Kyoto Encyclopedia of Genes and Genomes pathway analysis (16). This discrepancy may reflect differences in dataset composition, analytical pipelines or the stage of OA progression sampled. Mechanistically, Chen *et al* (39) demonstrated that Curcumenol regulates histone H3K27me3 demethylases to affect succinic acid metabolism, thereby alleviating cartilage degeneration in knee OA, revealing a direct link between epigenetic regulation and chondrocyte-specific metabolic alterations. More recently, Zhang *et al* (40) employed single-cell and transcriptomic profiling to decode endoplasmic reticulum (ER) stress on chondrocytes driving OA development, showing that ER stress-responsive chondrocytes exhibit a unique gene-metabolite network involving lipid droplet formation and ceramide accumulation. A critical insight from Pan *et al* (41) was the identification of key biomarkers related to fibrocartilage chondrocytes, demonstrating that these cells, which populate repair tissue, show fundamentally different metabolic gene expression profiles compared with resident articular chondrocytes. Across these studies, the lack of standardized cell-type annotation and metabolic pathway scoring represents a major barrier to direct cross-study comparison. In aggregate, these findings establish that chondrocyte metabolic heterogeneity is substantial, with specific subpopulations exhibiting distinct gene-metabolite networks that may represent therapeutic opportunities, though harmonized analytical frameworks are urgently needed to reconcile apparent discrepancies across datasets.

Synovial fibroblast and immune cell metabolic signatures. The synovial compartment harbors diverse fibroblast and immune cell populations, each displaying characteristic gene-metabolite networks. Wijesinghe *et al* (35) performed multi-omic analysis of synovium from patients with OA and identified that fibroblast subsets defined by obesity status exhibit distinct metabolic signatures, with certain fibroblast clusters showing enrichment of glycolysis and lipid biosynthesis pathways specifically in obese individuals. This observation suggests that systemic metabolic factors directly shape synovial cell metabolism. In a related study, Acharjee *et al* (43) conducted cross-species transcriptomics to identify obesity-associated genes between human and mouse studies, revealing that synovial fibroblasts from obese patients with OA upregulate genes involved in fatty acid oxidation and oxidative stress responses compared with non-obese patients. Yang *et al* (44) demonstrated that targeting Yes1-associated transcriptional regulator-regulated glycolysis in fibroblast-like synoviocytes impairs macrophage infiltration and ameliorates diabetic OA progression, providing functional evidence that fibroblast metabolic reprogramming directly influences immune cell recruitment. Regarding immune cells, Wu *et al* (45) integrated single-cell transcriptome and multi-omics data to reveal ferroptosis-driven immune microenvironment remodeling in knee OA, showing that synovial macrophages undergo iron-dependent lipid peroxidation that alters their inflammatory phenotype. Furthermore, Wei *et al* (46) identified shared M0 macrophage infiltration-related gene signatures in OA and osteomyelitis, suggesting that metabolic reprogramming of infiltrating macrophages may represent a common pathogenic mechanism across inflammatory joint diseases. A recent study by Deng *et al* (47) revealed that senescent synovial intimal fibroblasts aggravate OA by regulating macrophage polarization and chondrocyte phenotype through the angiopoietin-like 4-α5β1 axis, demonstrating a direct metabolic-immune crosstalk mechanism. Collectively, these studies indicate that synovial fibroblasts and immune cells possess distinct metabolic signatures that are modulated by systemic metabolic status and directly contribute to OA pathogenesis through paracrine and cell-cell interaction mechanisms.

Integration with disease severity and progression. Linking cell-type-specific gene-metabolite networks to clinical disease severity and progression represents a critical translational goal. Komaravolu *et al* (48) investigated sex-specific effects of injury and beta-adrenergic activation on metabolic and inflammatory mediators in a murine model of post-traumatic OA, revealing that male and female mice exhibit different metabolite profiles in response to joint injury, suggesting that sex-specific metabolic networks may influence disease trajectories. This finding has important implications for precision medicine, as it suggests that therapeutic targeting of metabolic pathways may need to be sex-stratified. Huang *et al* (49) performed multi-omics integrative analyses and identified two distinct endotypes of hip OA based on metabolic profiles, with one endotype characterized by altered amino acid metabolism and the other by lipid metabolism dysregulation, and importantly, these endotypes correlated with different rates of radiographic progression. Using spatially resolved proteomic and metabolomic imaging, Zhu *et al* (26) defined synovitis endotypes associated with OA progression, demonstrating that patients with specific metabolic signatures in the synovium show accelerated cartilage loss over 24 months. Tang *et al* (50) constructed a single-cell atlas of human infrapatellar fat pad and synovium and implicated apolipoprotein E (APOE) signaling in OA pathology, showing that APOE-expressing cells exhibit metabolic gene signatures that correlate with pain severity and joint function decline. More recently, Lu *et al* (51) performed an integrated multi-omics analysis to identify a glutamine metabolism-related gene signature as a diagnostic and therapeutic target, demonstrating that glutamine metabolism scores derived from single-cell data correlate with OA severity grades. A critical contribution reviewed omics-driven insights into OA pathogenesis and emphasized that while

cross-sectional associations between cell-type-specific networks and disease severity are increasingly robust, prospective studies linking baseline metabolic signatures to long-term clinical outcomes remain sparse (52). In summary, existing evidence supports the notion that cell-type-specific gene-metabolite networks are associated with OA severity, but prospective validation and standardization of network reconstruction methods are required before clinical application.

4. Lipid metabolism and metabolic reprogramming in OA pathogenesis

Emerging evidence positions lipid metabolism dysregulation as a central driver of OA pathogenesis, extending beyond the traditional view of OA as a purely mechanical disease. Lipidomic profiling has consistently revealed profound alterations in glycerophospholipids, sphingolipids and cholesterol metabolism across joint tissues (Table II). These metabolic perturbations not only correlate with disease severity but also actively contribute to chondrocyte dysfunction, synovial inflammation and pain generation.

Overview of OA-associated lipid pathways. Integrative lipidomic and transcriptomic analyses have identified several interconnected lipid metabolic pathways that are consistently perturbed in OA joints. Cholesterol metabolism represents a major hub, with the cholesterol 25-hydroxylase (CH25H)-cytochrome P450 family 7 subfamily B member 1 (CYP7B1)-retinoic acid-related orphan receptor alpha (RORα) axis identified as a critical regulator of OA pathogenesis. Choi *et al* (53) demonstrated that cholesterol metabolite 25-hydroxycholesterol, produced by CH25H, is converted to 7α,25-dihydroxycholesterol by CYP7B1, which then acts as a natural ligand for RORα, and genetic ablation of Ch25h or Cyp7b1 in mice protected against experimental OA. Conversely, enhancing cholesterol efflux from chondrocytes has emerged as a protective strategy. Lee *et al* (54) recently showed that pharmacological promotion of intracellular cholesterol efflux alleviated OA progression, suggesting that cholesterol accumulation within chondrocytes is directly pathogenic. Glycerophospholipid metabolism is another prominently altered pathway, with multiple studies reporting dysregulated phosphatidylcholines and lysophosphatidylcholines (LPCs) in OA synovial fluid and cartilage (55,56). Sphingolipid metabolism, particularly involving ceramide and sphingosine-1-phosphate (S1P), has also been consistently implicated across human and animal studies (56). A systematic review by Steinmeyer (56) consolidated these findings, concluding that phospholipids and sphingolipids are not merely passive markers but active participants in OA pathophysiology. Importantly, these pathways are interconnected: Cholesterol metabolism influences membrane lipid raft composition, which in turn modulates sphingolipid signaling, creating a complex metabolic network that requires integrated investigation.

Key lipid species and their pathogenic mechanisms. Specific lipid species have been mechanistically linked to distinct pathogenic processes in OA, including cartilage degradation, synovial inflammation and pain generation. Among sphingolipids, ceramide accumulation directly induces chondrocyte apoptosis and matrix degradation. Ma *et al* (57) demonstrated that myriocin, an inhibitor of ceramide synthesis, alleviated oleate/palmitate-induced chondrocyte degeneration, confirming that ceramide mediates lipotoxic chondrocyte injury. Conversely, Cherifi *et al* (58) showed that inhibition of S1P protected mice against chondrocyte catabolism and OA development, indicating that different sphingolipid species exert distinct biological effects. LPC species have emerged as key mediators of OA pain. Jacquot *et al* (59) identified LPC as a chronic joint pain mediator acting through acid-sensing ion channel 3, providing a direct molecular link between lipid metabolism and nociception. This finding was corroborated by Pousinis *et al* (60), who demonstrated that specific plasma lipids, including LPC, were associated with pain behavior in a mouse OA model. For cholesterol metabolism, Cao *et al* (61) revealed that cholesterol-induced low-density lipoprotein receptor-related protein 3 downregulation promotes cartilage degeneration by targeting Syndecan-4, establishing a mechanistic axis linking hypercholesterolemia to OA pathogenesis. The pathogenic effects of lipids are cell-type specific: While cholesterol accumulation drives chondrocyte catabolism, specific phospholipid species activate fibroblast-like synoviocytes through the autotaxin-lysophosphatidic acid receptor axis, as shown by Zhao *et al* (62). Taken together, these findings indicate that rather than viewing lipids as a homogeneous group, individual lipid species must be considered as discrete signaling molecules with specific receptor-mediated actions.

Cross-species lipidomics and translational models. Comparative lipidomic studies across species have proven invaluable for identifying conserved metabolic perturbations and evaluating potential therapeutic interventions. Kosinska *et al* (55) performed a comparative lipidomic analysis of synovial fluid from human and canine OA, revealing remarkably similar alterations in phospholipid profiles, including decreased phosphatidylcholine and increased sphingomyelin compounds in both species. This cross-species conservation supports the translational relevance of animal models for studying OA lipid metabolism. In rodent models, Pousinis *et al* (60) established associations between plasma lipid profiles and pain behavior, demonstrating that lipidomic readouts can serve as surrogate markers of OA pathology. More recently, Zhou *et al* (63) conducted temporal profiling of lipid mediators in synovium and tibial plateau during joint inflammation in a collagenase-induced mouse model, revealing dynamic changes in eicosanoids and specialized pro-resolving mediators that correlate with disease progression. Importantly, pharmacological interventions targeting lipid pathways have shown efficacy across multiple species. Lee (64) demonstrated that MSC injection in monosodium iodoacetate-induced OA rats altered lipid metabolism gene expression, suggesting that cell-based therapies may exert part of their effects through metabolic modulation. However, species-specific differences exist: While human OA shows pronounced alterations in sphingolipid metabolism, certain mouse models exhibit more subtle changes, necessitating careful interpretation of preclinical data (56). These cross-species comparisons highlight both conserved pathogenic mechanisms and species-specific metabolic adaptations that must be considered when translating findings to human OA.

Table II. Key studies on lipid metabolism and metabolic reprogramming in OA pathogenesis.

Author/s, year	Study design/sample source	Key findings	Lipid pathway/metabolite(s)	Species/model	Technology platform	(Refs.)
Choi *et al*, 2019	Experimental animal study	Identified CH25H CYP7B1 RORα axis as a critical catabolic regulator of OA pathogenesis; genetic ablation of Ch25h or Cyp7b1 in mice protected against experimental OA	Cholesterol metabolism	Mouse	Knockout mouse model	(53)
Lee *et al*, 2025	Experimental animal study	Pharmacological promotion of intracellular cholesterol efflux from chondrocytes alleviated OA progression, establishing that cholesterol accumulation within chondrocytes is directly pathogenic	Cholesterol metabolism	Mouse	Pharmacological intervention	(54)
Kosinska *et al*, 2016	Comparative lipidomic analysis	Synovial fluid phospholipid profiles showed remarkably similar alterations between human and canine OA, including decreased phosphatidylcholine and increased sphingomyelin	Glycerophospholipids, sphingolipids	Human, canine	Mass spectrometry-based lipidomics	(55)
Steinmeyer, 2025	Systematic narrative review	Concluded that phospholipids and sphingolipids are not merely passive markers but active participants in OA pathophysiology, involved in joint lubrication, inflammation and cartilage degradation	Phospholipids, sphingolipids	Human, animal models	Literature review	(56)
Ma *et al*, 2020	*In vitro* cell study	Myriocin, an inhibitor of ceramide synthesis, alleviated oleate/palmitate induced chondrocyte degeneration, confirming that ceramide mediates lipotoxic chondrocyte injury	Ceramide (sphingolipid)	Rat chondrocytes	Pharmacological inhibition	(57)
Cherifi *et al*, 2021	Experimental animal study	Inhibition of S1P protected mice against chondrocyte catabolism and OA development, indicating that different sphingolipid species exert distinct biological effects	S1P	Mouse	Pharmacological inhibition	(58)
Jacquot *et al*, 2022	Human cohort + mouse model	Identified lysophosphatidylcholine (LPC) 16:0 as a chronic joint pain mediator acting through acid sensing ion channel 3 (ASIC3); LPC16:0 levels correlated with pain outcomes in OA patients	Lysophosphatidylcholine (LPC 16:0)	Human, mouse	Lipidomics, electrophysiology, behavioral assays	(59)
Pousinis *et al*, 2020	Mouse model study	Demonstrated that specific plasma lipids, including LPCs, were associated with pain behavior in a mouse OA model, suggesting lipidomic readouts as surrogate markers of OA pathology	LPC	Mouse	Lipidomics	(60)

Table II. Continued.

Author/s, year	Study design/sample source	Key findings	Lipid pathway/metabolite(s)	Species/model	Technology platform	(Refs.)
Cao *et al*, 2022	Experimental animal + *in vitro* study	Revealed that cholesterol induced LRP3 downregulation promotes cartilage degeneration by targeting Syndecan 4, establishing a mechanistic axis linking hypercholesterolemia to OA pathogenesis	Cholesterol metabolism	Mouse, human chondrocytes	Molecular biology, knockout models	(61)
Zhao *et al*, 2021	*In vitro* cell study	Showed that specific phospholipid species activate fibroblast like synoviocytes through the autotaxin LPA receptor axis, demonstrating cell type specific lipid actions	Phospholipids, LPA	Human fibroblast like synoviocytes	Proteomics, lipidomics, cell signaling	(62)
Zhou *et al*, 2025	Mouse model study	Conducted temporal profiling of lipid mediators in synovium and tibial plateau during joint inflammation, revealing dynamic changes in eicosanoids and specialized pro resolving mediators correlating with disease progression	Eicosanoids, oxylipins, PUFAs	Mouse	Lipid mediator profiling (LC MS/MS)	(63)
Lee, 2018	Rat model study	Demonstrated that mesenchymal stem cell injection in monosodium iodoacetate induced OA rats altered lipid metabolism gene expression, suggesting cell based therapies exert part of their effects through metabolic modulation	Lipid metabolism (global)	Rat	Microarray analysis	(64)
Huang *et al*, 2021	Comprehensive review	Reviewed PPAR functions in OA; noted PPARγ activation exerts chondroprotective effects by reducing inflammation and promoting fatty acid oxidation, while PPARα primarily regulates lipid catabolism	PPAR signaling (lipid metabolism)	Human, animal models	Literature review	(65)
Liu *et al*, 2025	Experimental animal + *in vitro* study	Demonstrated that SESN2 maintains cartilage homeostasis by modulating SREBP1 mediated lipid metabolism; SESN2 deficiency exacerbated OA through dysregulated lipogenesis	SREBP1 mediated lipogenesis	Mouse, human chondrocytes	Transcriptomics, lipidomics, molecular biology	(66)
Sun and Beier, 2020	*In vitro* cell study	Showed that LXR activation regulates genes involved in lipid homeostasis in developing chondrocytes, including ABC transporters that mediate cholesterol efflux	Cholesterol efflux (LXR ABCA1 axis)	Rat growth plate chondrocytes	Gene expression analysis	(67)
Park *et al*, 2018	Human tissue + *in vitro* study	Demonstrated that suppression of ABCD2 dysregulates lipid metabolism via dysregulation of the miR 141 ACSL4 axis in human OA, revealing a non coding RNA mediated regulatory mechanism	Very long chain fatty acids, ACSL4	Human chondrocytes	miRNA profiling, lipid analysis	(68)

Table II. Continued.

Author(s), year	Study design/sample source	Key findings	Lipid pathway/metabolite(s)	Species/model	Technology platform	(Refs.)
Wang *et al*, 2025	Human multi omics study	Integrated multi omics analyses identified a lipid metabolic signature encompassing multiple regulators, including ACSL4, that distinguishes patients with OA from healthy controls	Glycerophospholipids, sphingolipids, ACSL4	Human	Transcriptomics, metabolomics integration	(32)
Kondreddy *et al*, 2025	Mouse model + *in vitro* study	Identified the LPCAT3 ABCA1 axis as a critical regulator of steroid drug dose sparing effects in OA mice, suggesting that lipid metabolic regulators can modulate therapeutic responses	LPCAT3 ABCA1 axis (phospholipid remodeling)	Mouse, human chondrocytes	Gene silencing, protein degradation assays	(69)

OA, osteoarthritis; CH25H, cholesterol 25-hydroxylase; CYP7B1, cytochrome P450 family 7 subfamily B member 1; RORα, retinoic acid receptor-related orphan receptor alpha; LPC, lysophosphatidylcholine; ASIC3, acid-sensing ion channel 3; LRP3, low-density lipoprotein receptor-related protein 3; PLA1A, phospholipase A1 member A; LPA, lysophosphatidic acid; PUFA, polyunsaturated fatty acid; PPAR, peroxisome proliferator-activated receptor; SREBP1, sterol regulatory element-binding protein 1; SESN2, sestrin 2; LXR, liver X receptor; ABCA1, ATP-binding cassette subfamily A member 1; ABCD2, ATP-binding cassette subfamily D member 2; ACSL4, acyl-CoA synthetase long-chain family member 4; LPCAT3, lysophosphatidylcholine acyltransferase 3.

Regulators of lipid metabolism in OA. Multiple molecular regulators have been identified that control lipid homeostasis in joint tissues, representing potential therapeutic targets for OA. The peroxisome proliferator-activated receptor (PPAR) family plays a central role in lipid metabolism regulation in OA. Huang *et al* (65) comprehensively reviewed PPAR functions in OA, noting that PPARγ activation exerts chondroprotective effects by reducing inflammation and promoting fatty acid oxidation, whereas PPARα primarily regulates lipid catabolism. The transcription factor sterol regulatory element-binding protein 1 (SREBP1) has emerged as a critical regulator of chondrocyte lipid metabolism. Liu *et al* (66) demonstrated that sestrin 2 (SESN2) maintains cartilage homeostasis by modulating SREBP1-mediated lipid metabolism during OA progression, and SESN2 deficiency exacerbated OA through dysregulated lipogenesis. Liver X receptors (LXRs) are additional key regulators. Sun and Beier (67) showed that LXR activation regulates genes involved in lipid homeostasis in developing chondrocytes, including ATP-binding cassette (ABC) transporters that mediate cholesterol efflux. Epigenetic and post-translational mechanisms also contribute to lipid metabolism dysregulation. Park *et al* (68) demonstrated that suppression of ABC subfamily D member 2 dysregulates lipid metabolism via dysregulation of the microRNA-141-Acyl-CoA synthetase long-chain family member 4 (ACSL4) axis in human OA, revealing a non-coding RNA-mediated regulatory mechanism. Recently, Wang *et al* (32) performed integrated multi-omics analyses and identified a lipid metabolic signature encompassing multiple regulators, including ACSL4, that distinguishes patients with OA from healthy controls. Notably, Kondreddy *et al* (69) identified the LPC acyltransferase 3-ABCA1 axis as a critical regulator of steroid drug dose-sparing effects in OA mice, suggesting that lipid metabolic regulators can modulate therapeutic responses. A critical appraisal of these findings reveals that while numerous regulators have been identified, most studies are descriptive and lack functional validation in human tissues. Furthermore, the tissue-specific and cell-type-specific roles of these regulators remain poorly defined, representing a key knowledge gap for future investigation.

5. Multi-cellular crosstalk and inter-tissue communication in OA

The OA joint operates as an integrated organ system where articular cartilage, subchondral bone, synovium, infrapatellar fat pad (IPFP) and meniscus engage in dynamic bidirectional communication. Disruption of these inter-tissue signalling networks drives disease progression through coordinated metabolic and inflammatory responses. This section synthesizes how intercellular communication propagates and amplifies metabolic reprogramming across tissue compartments, identifying specific ligand-receptor axes that couple cellular crosstalk to metabolic dysfunction (Fig. 3).

The OA joint as an integrated organ system. Mounting evidence has superseded the traditional view of isolated cartilage degeneration, establishing OA as a whole-joint disease where all tissues contribute to and are affected by pathogenic processes. Pandey and Bhutani (70) provided a

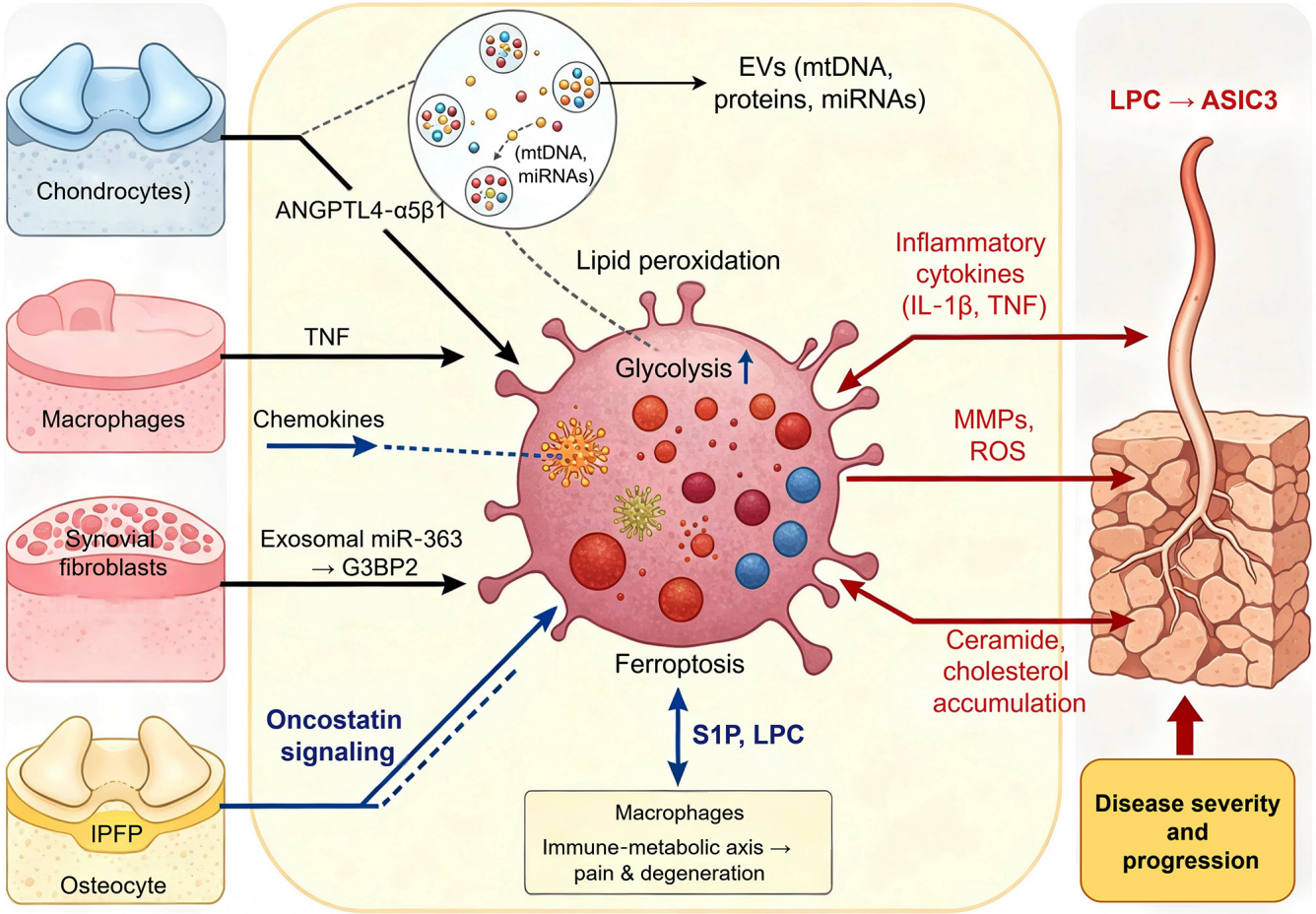

Figure 3. Multi-cellular crosstalk and inter-tissue communication in the OA joint. The figure was generated using Figdraw (www.figdraw.com; copyright code: WYWSUb4bf1). OA, osteoarthritis; FB, fibroblast; Mac, macrophage; Chon, chondrocyte; EV, extracellular vesicle; IPFP, infrapatellar fat pad; S1P, sphingosine-1-phosphate; LPC, lysophosphatidylcholine; ASIC3, acid-sensing ion channel 3; ANGPTL4, angiopoietin-like 4; miR/miRNA, microRNA; G3BP2, G3BP stress granule assembly factor 2; ROS, reactive oxygen species; mtDNA, mitochondrial DNA; TNF, tumor necrosis factor; IL, interleukin.

comprehensive review of single-cell resolution profiling of joint tissues, emphasizing that the molecular connectivity among bone, cartilage and synovium must be understood collectively. Using a multi-tissue human knee single-cell atlas, Raut *et al* (71) identified that OA reduces regenerative tissue stem cells while increasing inflammatory pain-associated macrophages, directly demonstrating that cell populations across different compartments change in a coordinated manner. The structural basis of this integration was further clarified by Hu *et al* (72), who showed that mechanical and structural properties of articular cartilage and subchondral bone are tightly coupled in human OA knees. From a therapeutic perspective, Wang *et al* (73) reviewed that the Notch signalling pathway regulates bone and cartilage homeostasis in a highly integrated fashion, suggesting that pathway modulators could simultaneously affect multiple tissues. A critical appraisal by Semenistaja *et al* (74) noted that while tissue crosstalk is well accepted, most studies remain descriptive and lack functional validation of the causal direction between compartments. Collectively, these findings establish that the OA joint functions as a mechanically and biochemically connected system where disruption in one compartment propagates pathology throughout, but prospective interventional studies are still needed to prove causality.

Chondrocyte-synoviocyte-immune cell interaction networks. Direct communication among chondrocytes, synovial fibroblasts and immune cells creates interaction networks that not only amplify inflammation but also propagate metabolic alterations across cell types (Fig. 3). Using scRNA-seq, Kang *et al* (42) revealed that cell-cell communication alterations mediated by interactive signalling pathways are a hallmark of OA cartilage, with particular enrichment of ligand-receptor pairs involving inflammatory cytokines. In the synovial compartment, Wang *et al* (75) mapped single-cell communication patterns and their intracellular information flow in OA synovial fibroblasts, identifying that fibroblast-macrophage crosstalk is dominated by chemokine and TNF signalling axes. Critically, these ligand-receptor interactions have downstream metabolic consequences: TNF signalling induces glycolytic reprogramming in recipient fibroblasts, while chemokine axes promote lipid biosynthetic pathway activation in macrophages, creating a feed-forward loop where metabolic dysfunction begets further inflammatory signalling (75). A comprehensive review by Chen *et al* (76) synthesised the role of crosstalk between synovial cells and chondrocytes in OA, concluding that targeting this bidirectional communication holds therapeutic promise. Critically, a study by Laouteouet *et al* (77)

using advanced co-culture systems uncovered that monocyte-derived macrophage-synovial fibroblast crosstalk drives an oncostatin signalling network as a key driver of synovitis in OA, representing a novel therapeutic target. Collectively, these observations indicate that the OA joint operates through interconnected ligand-receptor axes that simultaneously drive inflammation and metabolic reprogramming, with therapeutic intervention at any node potentially disrupting this integrated network.

EVs as intercellular messengers. EVs have emerged as critical mediators of intercellular communication in OA, transporting proteins, lipids and nucleic acids between cell types and across tissue compartments. A comprehensive review by Chen *et al* (78) highlighted the communication role of EVs in the OA microenvironment, noting that EV cargo reflects the pathological state of donor cells and can propagate disease signals across joint tissues. Kong *et al* (79) further synthesised evidence on crosstalk among macrophages, chondrocytes and MSCs via EVs, proposing that EV-based therapies could simultaneously target multiple cell types. In a mechanistic study, Liu *et al* (80) demonstrated that osteocyte-derived EVs mediate bone-to-cartilage crosstalk and promote OA progression, providing direct evidence that EVs from subchondral bone can drive cartilage degeneration. From the IPFP perspective, Li *et al* (81) recently reported that EVs from IPFP-MSCs trigger OA by transferring mitochondrial DNA, revealing a previously unrecognised pathogenic mechanism where EVs carry deleterious cargo. On the therapeutic side, Wu *et al* (82) engineered TNF-α preconditioned IPFP-MSC-derived exosomes that enhanced both yield and therapeutic efficacy for OA, suggesting that EV engineering can redirect crosstalk from pathogenic to protective. A critical review by Clarke *et al* (83) noted that while EV research has advanced rapidly, standardisation of isolation, characterisation and quantification methods remains a major barrier to clinical translation, and most studies lack direct comparison of EV efficacy across different cell sources. Therefore, EVs represent both a mechanistic understanding of cell-cell communication and a potential therapeutic modality, but methodological harmonisation and head-to-head comparative studies are urgently needed.

Immune-metabolic axis in OA progression. The convergence of immune cell activation and metabolic reprogramming defines a central feedback loop driving OA progression, where metabolically reprogrammed cells secrete factors that further alter the metabolic state of neighboring cells. Yin *et al* (84) provided a systematic review of macrophage polarisation during OA disease progression, establishing that the M1/M2 balance is dynamically regulated and represents a tractable therapeutic target. A comprehensive review by Zou *et al* (85) further emphasised that macrophage polarisation is central to both OA pathogenesis and treatment, linking immune status directly to disease outcomes. The mechanistic basis for this axis was recently elaborated by He *et al* (86), who demonstrated that Songorine modulates macrophage polarisation and metabolic reprogramming to alleviate inflammation in OA, showing that small molecules can simultaneously target immune phenotype and cellular metabolism.

In the context of synovial macrophages, Yin *et al* (87) reported that Emapunil relieves OA by regulating the CD14/Toll-like receptor 4/lymphocyte antigen 96 pathway through translocator protein 18 kDa, providing a new molecular entry point for immune-metabolic intervention. A multi-omics integration study by Wu *et al* (45) revealed ferroptosis-driven immune microenvironment remodelling in knee OA, demonstrating that iron-dependent lipid peroxidation in synovial macrophages links metabolic stress to inflammatory activation. These findings collectively establish a model wherein metabolic perturbations in one cell type are transmitted to neighboring cells through soluble mediators and EVs, creating self-reinforcing feedback loops that drive disease progression. From a translational perspective, Henry and O'Neill (88) critically appraised that metabolic reprogramming in stromal and immune cells presents therapeutic possibilities, but cautioned that targeting metabolism may have off-tissue effects and that most preclinical studies use young, healthy animals that do not fully recapitulate human OA. Furthermore, a spatial transcriptomic study by Wang *et al* (89) uncovered the spatial and signalling dynamics of immune infiltration in OA synovium, revealing that immune-metabolic interactions are highly localised and vary across synovial subregions. Collectively, these findings establish the immune-metabolic axis as an integrating hub for multi-cellular crosstalk in OA, but prospective validation in well-phenotyped patient cohorts and development of tissue-specific delivery strategies remain critical challenges.

6. Molecular subtyping, endotypes, and precision medicine in OA

The heterogeneity of OA has long hindered the development of disease-modifying therapies. Emerging evidence has shifted the paradigm from a one-size-fits-all approach toward molecularly guided patient stratification. This section synthesizes current advances in clinical phenotyping, multi-omics-driven endotyping and precision medicine strategies that collectively aim to deliver the right treatment to the right patient at the right time (Table III).

Clinical phenotypes vs. molecular endotypes. Traditional OA classification has relied on clinical features such as joint involvement, pain patterns and radiographic severity. However, the heterogeneity of OA has long hindered the development of disease-modifying therapies, prompting a shift toward molecularly guided patient stratification. A hierarchical taxonomy has been proposed to organize this complexity: Clinical phenotypes (observable patient characteristics), molecular endotypes (distinct underlying biological mechanisms) and theratypes (endotypes with validated differential treatment responses) (90,91). This framework provides a structured path from molecular discovery to precision therapeutics. However, it must be acknowledged that while endotype discovery has advanced considerably, the validation of theratypes, demonstrating that a molecularly defined patient subgroup responds differently to a specific therapy, has not yet been achieved in OA. This critical gap is emphasized throughout the present section.

Mobasheri *et al* (90,92) distinguished clinical phenotypes, observable patient characteristics, from molecular endotypes,

Table III. Molecular subtyping, endotypes and precision medicine studies in OA.

Authors, year	Study type	Omics data types	Analytical approach	Key findings	Endotype/subtype characteristics	(Refs.)
Rockel *et al*, 2025	Original research	Multi omics (metabolomics, microRNAs) from three biofluids	Multimodal deep learning (VAE based clustering)	Identified three distinct KOA endotypes that predicted 1-year post TKA pain/function outcomes	Three endotypes with differential post-surgery prognosis	(97)
Huang *et al*, 2024	Original research	Metabolomics, genomics	Integrative multi-omics, pathway enrichment	Discovered two hip OA endotypes with differential amino acid vs. lipid metabolism, correlating with radiographic progression rates	Endotype 1: Amino acid metabolism perturbation; Endotype 2: Lipid metabolism dysregulation	(49)
Fan *et al*, 2024	Original research	scRNA-seq, bulk transcriptomics, spatial transcriptomics	Multi omics integration, cell-type annotation	Uncovered inflammatory and pre hypertrophic chondrocyte subpopulations as key drivers of cartilage degeneration	inflammatory and pre-hypertrophic chondrocyte subpopulations as cellular level endotype associated populations	(17)
Karsdal *et al*, 2025	Perspective/expert opinion	Biochemical markers, clinical data	OARSI symposium synthesis	Proposed the inflammatory endotype as a feasible target for clinical development, with enrichment strategies reducing trial sample sizes	Inflammatory endotype (elevated synovial cytokines, acute phase reactants)	(98)
Thudium *et al*, 2025	Perspective/expert opinion	Biochemical markers	Biomarker panel analysis	Outlined practical tools for single-patient endotyping and considerations for recognizing inflammatory endotype in clinical trials	Inflammatory molecular endotype as clinically actionable	(99)
Hannani *et al*, 2025	Original research	Biochemical markers (biomarker panel)	Longitudinal stability analysis	Demonstrated molecular endotypes of knee OA remain stable over 12-24 months, supporting their utility as clinical trial stratification tools	Structurally stable molecular endotypes	(102)
Mobasheri & Loeser, 2024	Perspective/expert opinion	Clinical phenotypes, molecular markers	Hierarchical taxonomy framework	Articulated clinical phenotypes → molecular endotypes → theratypes as hierarchical taxonomy for OA therapeutic development	Hierarchical endotype theratype framework	(91)
Ghirardi *et al*, 2024	Perspective/expert opinion	Chronic joint diseases	Molecular taxonomy	Argued defining theratypes enables repurposing of existing drugs for molecularly defined patient subsets	Theratype enabled drug repurposing	(104)
Wang *et al*, 2024	Original research	Bulk RNA seq, scRNA seq	Integrative multi omics, machine learning	Characterized Hedgehog pathway features in senescence associated OA, identifying potential theratype specific targets	Hedgehog pathway defined theratype	(105)
Wu *et al*, 2024	Original research	Multi omics	Integrative analysis, 7 ML algorithms	Characterized mitochondrial features in OA; proposed mitochondrial dysfunction defines a distinct theratype amenable to metabolic interventions	Mitochondrial dysfunction theratype	(106)

Table III. Continued.

Authors, year	Study type	Omics data types	Analytical approach	Key findings	Endotype/subtype characteristics	(Refs.)
Ojha *et al*, 2025	Original research	Metabolomics (bone marrow), scRNA-seq	Multi omics integration at cell type resolution	Reconstructed gene metabolite networks assigned to specific cell populations; demonstrated cell-type-specific networks can nominate theratype-specific drug targets	Cell type specific theratype targets	(30)
Lu *et al*, 2026	Original research	Multi-omics (blood based)	Integrated multi omics, gene signature analysis	Identified glutamine metabolism related gene signature as diagnostic marker and therapeutic target; signature correlated with OA severity grades	Glutamine metabolism defined theratype	(51)
Hao *et al*, 2025	Original research	Multi omics	Integrative analysis	Identified OA associated chondrocyte subpopulations and key gene regulating drugs, providing direct bridge from molecular subtyping to drug repurposing	Chondrocyte subpopulation specific theratypes	(107)

InfC, inflammatory chondrocyte; KOA, knee osteoarthritis; OARSI, Osteoarthritis Research Society International; preHTC, pre hypertrophic chondrocyte; scRNA seq, single cell RNA sequencing; TKA, total knee arthroplasty; VAE, variational autoencoder.

which are defined by distinct underlying biological mechanisms. Henrotin (93) emphasized that biochemical markers reflecting cartilage degradation, synovial inflammation and bone turnover can help stratify patients beyond conventional imaging. Hannani *et al* (94) provided a systematic review of validated biomarkers and proposed that combinations of soluble markers define discrete molecular endotypes with prognostic value. By contrast, Pattappa *et al* (95) critically noted that terminological inconsistency between preclinical and clinical studies hampers translation, as basic research often uses 'endotype' differently from clinical investigators. Karalilova *et al* (96) recently demonstrated that ultrasound-detected synovitis phenotypes correlate with distinct biomarker profiles, suggesting that imaging-based phenotyping can approximate underlying endotypes. A critical appraisal of this literature reveals that while numerous candidate biomarkers exist, few have been prospectively validated for endotype assignment and most studies remain cross-sectional rather than longitudinal.

Multi-omics-driven molecular classification. Integrative multi-omics approaches have enabled unbiased discovery of OA molecular subtypes. Rockel *et al* (97) employed deep learning-based clustering of multi-omic data from three biofluids and identified three distinct knee OA endotypes that predicted post-arthroplasty pain outcomes, demonstrating the clinical utility of data-driven classification. Huang *et al* (49) performed multi-omics integrative analyses of hip OA and discovered two endotypes characterized by differential amino acid vs. lipid metabolism perturbations, which correlated with radiographic progression rates. As discussed in Section 2, Fan *et al* (17) integrated single-cell and bulk transcriptomics with spatial data to uncover inflammatory and prehypertrophic chondrocyte subpopulations. Similarly, the lipid metabolic signature identified by Wang *et al* (32) supports the feasibility of metabolic endotyping using peripheral biofluids. Welsing *et al* (52) provided a comprehensive review of omics-driven insights and concluded that while molecular classification has advanced considerably, standardization of computational pipelines and prospective validation remain critical gaps. Collectively, these studies establish that multi-omics integration yields reproducible molecular subtypes, but head-to-head comparisons across cohorts and platforms are lacking.

Endotype-driven trial design and targeted therapies. The identification of molecular endotypes has direct implications for clinical trial design and therapeutic development. Karsdal *et al* (98) synthesized discussions from the Osteoarthritis Research Society International clinical trials symposium and proposed that the inflammatory endotype, which is characterized by elevated synovial cytokines and acute-phase reactants, represents a feasible target for clinical development, with enrichment strategies potentially reducing trial sample sizes. Thudium *et al* (99) further elaborated that diagnosing, treating and monitoring the inflammatory endotype requires a panel of validated biochemical markers, including C-reactive protein and matrix metalloproteinase-derived fragments. Kim *et al* (100) comprehensively reviewed the OA drug development pipeline and emphasized that most failed disease-modifying osteoarthritis drug (DMOAD) trials

did not employ molecular stratification, potentially masking efficacy in responsive subgroups. Jenei-Lanzl *et al* (101) critically appraised emerging concepts in DMOAD development and argued that endotype-driven enrichment should become standard practice, though they cautioned that regulatory frameworks for biomarker-guided trial design are still evolving. Hannani *et al* (102) provided longitudinal evidence that molecular endotypes of patients with knee OA remain stable over 12-24 months, supporting their utility as stratification tools for clinical trials. Oo (103) comprehensively reviewed prospects for DMOADs and concluded that endotype-driven approaches are necessary but not sufficient; concomitant advances in imaging and patient-reported outcomes are equally essential. A critical synthesis of this evidence indicates that while the conceptual framework for endotype-driven trials is well established, prospective implementation in phase 3 studies remains limited.

From endotypes to theratypes and target identification. Translating molecular endotypes into actionable therapeutic strategies requires the concept of 'theratypes', endotypes with validated treatment responses. Mobasheri and Loeser (91) articulated this framework, proposing that clinical phenotypes, molecular endotypes and theratypes form a hierarchical taxonomy for OA therapeutic development. Ghirardi *et al* (104) extended this concept to chronic joint diseases generally, arguing that defining theratypes enables repurposing of existing drugs for molecularly defined patient subsets.

Several studies have identified potential theratype-specific targets through multi-omics integration (30,51,105-107). Wang *et al* (105) employed integrative multi-omics and machine learning to characterize Hedgehog pathway features in senescence-associated OA, identifying potential theratype-specific targets. Wu *et al* (106) similarly characterized mitochondrial features in OA through multi-omics integration, proposing that mitochondrial dysfunction defines a distinct theratype amenable to metabolic interventions. Ojha *et al* (30) developed a multi-omics integration framework at cellular resolution to uncover gene-metabolite mechanisms underlying OA heterogeneity, demonstrating that cell-type-specific networks can nominate theratype-specific drug targets. Lu *et al* (51) identified a glutamine metabolism-related gene signature as both a diagnostic marker and therapeutic target, exemplifying how multi-omics can directly inform target discovery. Hao *et al* (107) identified OA-associated chondrocyte subpopulations and key gene-regulating drugs through multi-omics analysis, providing a direct bridge from molecular subtyping to drug repurposing.

Critically, however, none of these studies have demonstrated differential treatment response in endotype-defined patient subgroups, the defining feature of a true theratype. As noted by Winthrop *et al* (108), the broader rheumatology community still faces substantial unmet needs in translating molecular taxonomy into clinical practice. The path from endotype to theratype requires iterative integration of multi-omics discovery, biomarker development, and crucially, endotype-enriched clinical trials that prospectively validate differential treatment responses. This represents the central translational gap in the field.

7. Integrative bioinformatics, machine learning and clinical translation

Over the past five years, the exponential growth of multi-omics data in OA has driven the development of advanced computational strategies for meaningful integration and interpretation. Machine learning and artificial intelligence (AI) have become indispensable tools for pattern recognition, molecular subtyping and predictive modeling across imaging and omics domains, as summarized in Table IV. These approaches have enabled translational genomic discoveries, including the identification of diagnostic and prognostic biomarkers, yet persistent roadblocks ranging from batch effects and data heterogeneity to poor model generalizability and lack of prospective validation still hinder clinical implementation.

Computational strategies for multi-omics integration. Integrating heterogeneous omics data requires sophisticated bioinformatic pipelines that can handle dimensionality, batch effects and biological complexity. As summarized in Table IV and discussed in Section 6, unsupervised learning approaches such as those employed by Rockel *et al* (97) have demonstrated utility in patient stratification through multi-omic clustering. Similarly, integrative multi-omics analyses have enabled the discovery of molecular endotypes in OA (33,49). At the cellular resolution, Ojha *et al* (30) developed a framework that assigns metabolic signatures to specific cell populations, addressing the limitation of tissue-level averaging. In a critical appraisal, Liu *et al* (5) noted that while transfer learning and graph neural networks are beginning to address cross-platform batch effects, these methods remain inaccessible to many clinical researchers. Taken together, these computational strategies have established proof of concept for multi-omics integration, but standardized pipelines and prospective validation cohorts are urgently needed before clinical deployment.

Machine learning (ML) and AI applications. ML has become an essential tool for integrating and interpreting multi-omics data in OA research, enabling pattern recognition, molecular subtyping and predictive modeling. As detailed in Section 6, Rockel *et al* (97) employed deep learning-based clustering for OA endotyping, while He *et al* (33) applied multiple ML algorithms to identify immune-metabolic signatures. Beyond these, Jamshidi *et al* (109) developed an interpretable metabolomic-driven ML model for early prediction of knee structural OA progression, demonstrating that serum metabolite signatures outperform clinical variables alone, with a six-metabolite panel achieving excellent predictive performance in validation cohorts. Rafiei *et al* (110) developed personalized prediction models for changes in knee pain among patients participating in supervised exercise and education, showing that ML can inform patient-specific treatment responses. These studies collectively illustrate that ML approaches, when applied directly to multi-omics data, can generate clinically relevant insights ranging from molecular endotyping to prognostic prediction.

A critical appraisal reveals that while ML models achieve promising performance in controlled research settings, studies combining ML with multi-omics data in OA remain relatively limited. Most published ML applications in OA focus on

Table IV. Summary of integrative bioinformatics, machine learning and translational genomics studies in OA.

Authors, year	Method/algorithm	Data source/omics layer	Application domain	Main findings/key outcome	Key limitation(s)	(Refs.)
He *et al*, 2025	Seven ML algorithms (LASSO, RF, GBM, XGBoost, decision tree, bagging) + WGCNA	Bulk and single cell RNA seq transcriptomics	Immune metabolic signature discovery	Identified 13 hub immune metabolism genes (including CX3CR1, ADIPOQ, IL17RA, SPP1); stratified patients into two subgroups with distinct immune/drug response profiles	*In vitro* validation only; no prospective clinical validation	(33)
Jamshidi *et al*, 2026	ML/DL prognostic model (LightGBM, XGBoost, neural network)	Serum metabolomics	Early prediction of knee structural OA progression	Metabolomic signatures outperformed clinical variables alone; interpretable model with SHAP analysis; six metabolite panel achieved excellent predictive performance (AUC 0.89 in validation)	Cross cohort heterogeneity; no external validation in diverse populations	(109)
Kang *et al*, 2025	LightGBM + SHAP explainability	Plasma proteomics (1,463 proteins, n=45,307, UK Biobank)	Future OA risk prediction	COL9A1 and CRTAC1 predicted incident OA (HR 1.54 and 1.65); 5-10 year prediction AUC ~0.72-0.82; protein trajectories deviate >10 years pre onset	UK Biobank primarily European ancestry; lacks cross population validation	(114)
Lu *et al*, 2026	WGCNA + LASSO + ML pipeline	Multi tissue transcriptomics (cartilage, synovium, bone, blood) + plasma metabolomics	Diagnostic biomarker and therapeutic target discovery	Identified 3 gene signature (F13A1, IRS2, RELA); AUC up to 0.966; plasma creatine as severity predictor; drug repurposing candidates nominated	Small validation cohort (n=62); cross sectional design	(51)
Yan *et al*, 2025	LASSO, RF + Mendelian randomization + scRNA seq	GWAS, eQTL, transcriptomics, scRNA seq, *in vitro*/*in vivo* experiments	Diagnostic biomarker discovery	FGF1 identified as diagnostic biomarker (AUC 1.000/0.790/0.761); MR supports causal link (OR 1.04, 95% CI 1.002-1.081); validated via RAS MAPK pathway	MR effect size modest; functional validation in animal models only	(113)
Pang *et al* 2024	Multiple ML methods + WGCNA + two sample MR	Transcriptomics (GSE89408, GSE143514) + GWAS (n=24,955 cases, 378,169 controls)	Immune related biomarker discovery	Identified three immune biomarkers (FCER1G, HLA DMB, HLA DPA1); MR supports causal effects (OR 1.118, 1.057 and 1.030)	Expression data from bulk tissues; cell type specificity undetermined	(115)

Table IV. Continued.

Authors, year	Method/algorithm	Data source/omics layer	Application domain	Main findings/key outcome	Key limitation(s)	(Refs.)
Liao *et al*, 2026	Multi omics integration (genetic correlation, transcriptomics, proteomics)	GWAS + eQTL + pQTL	Shared genetic architecture of OA and metabolic traits	Uncovered shared genetic mechanisms between OA and metabolic traits; identified novel OA MT genes, proteins and pathways; lipid metabolism genes represent druggable targets	Functional validation lacking; tissue specificity remains undetermined	(116)
Tu *et al*, 2025	WGCNA + machine learning + scRNA seq + flow cytometry	Multi tissue transcriptomics (4 joint tissues) + scRNA seq (217,983 cells) + peripheral blood	Age specific blood biomarkers	Identified 5 gene blood panel (MAPK1, MAP3K8, ING1, LDLR, NUP153) with AUC 0.966; age specific performance (elderly AUC 0.8 vs. younger 0.7); B-cell remodeling in elderly OA	Cross sectional design; causal direction not established	(117)
Rafiei *et al*, 2025	Random forest regression	Self reported patient information + functional measures (GLA:D registry)	Personalized pain prediction after exercise/education	Concise 6 variable model correctly predicted pain change in 58% of cases (vs. 51% using average values); R^2 0.31-0.32	Modest predictive performance; guidance needed on clinically acceptable accuracy threshold	(110)

AI, artificial intelligence; AUC, area under the receiver operating characteristic curve; CI, confidence interval; COL9A1, collagen type IX alpha 1 chain; CRTAC1, cartilage acidic protein 1; DL, deep learning; eQTL, expression quantitative trait locus; FGF1, fibroblast growth factor 1; GBM, gradient boosting machine; GLA:D, Good Life with osteoArthritis in Denmark; GWAS, genome wide association study; HR, hazard ratio; KL, Kellgren-Lawrence; LASSO, least absolute shrinkage and selection operator; LightGBM, light gradient boosting machine; LLM, large language model; ML, machine learning; MR, Mendelian randomization; MT, metabolic trait; OA, osteoarthritis; OR, odds ratio; pQTL, protein quantitative trait locus; RF, random forest; scRNA seq, single cell RNA sequencing; SHAP, SHapley Additive exPlanations; UK Biobank, United Kingdom Biobank; VAE, variational autoencoder; WGCNA, weighted correlation network analysis; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; XGBoost, extreme gradient boosting.

radiographic image analysis rather than molecular data integration. Furthermore, the translation of ML-driven omics models to diverse clinical settings is hampered by data heterogeneity, lack of interpretability, cross-cohort generalizability and insufficient prospective validation (52,111). As Russell *et al* (112) noted, until ML systems consistently outperform conventional approaches in well-designed prospective trials, they should be viewed as decision support tools rather than replacements for clinical judgment.

Translational genomics and multi-omics biomarker discovery. Multi-omics integration coupled with translational genomics has accelerated the discovery of diagnostic and prognostic biomarkers for OA. Lu *et al* (51) identified a glutamine metabolism-related gene signature as both a diagnostic marker and therapeutic target through integrated multi-omics analysis, with the signature correlating with OA severity grades. Yan *et al* (113) performed multi-omics integration to identify fibroblast growth factor 1 as a diagnostic biomarker for OA, validating their findings using Mendelian randomization, transcriptomics and *in vitro* experiments. Kang *et al* (114) demonstrated that plasma proteomic profiles predict individual future OA risk, with a panel of 12 proteins achieving high predictive accuracy years before radiographic onset. Pang *et al* (115) employed Mendelian randomization and transcriptome analysis to identify immune-related biomarkers for OA, establishing causal relationships between specific cytokines and disease risk. Liao *et al* (116) unraveled the shared genetic architecture of OA and metabolic traits through multi-omics insights, revealing that lipid metabolism genes contribute to both conditions and may represent druggable targets. Tu *et al* (117) performed multi-omics profiling of blood samples and identified age-specific biomarkers, demonstrating that aging drives B-cell remodeling in OA and that biomarker performance varies across age strata. A critical appraisal of these biomarker studies reveals that while discovery phases are increasingly robust, few candidates have been prospectively validated in independent cohorts, and even fewer have been integrated into clinical decision tools. Furthermore, as noted by Welsing *et al* (52), cross-sectional associations between molecular signatures and disease severity are abundant, but longitudinal studies linking baseline biomarkers to long-term clinical outcomes remain sparse.

Bottlenecks and future directions for clinical implementation. Despite substantial progress, multiple roadblocks hinder the clinical translation of integrative bioinformatics and AI tools for OA. Glinkowski *et al* (118) reviewed the clinical performance, limitations and translational readiness of AI in orthopaedics, concluding that most models lack external validation, regulatory clearance, and integration into clinical workflows. Luo *et al* (119) highlighted the translational gap between algorithmic development and real-world implementation, noting that issues of data privacy, model interpretability, and health economics are rarely addressed in published studies. Awasthi *et al* (120) discussed future prospects for AI in OA diagnosis and treatment, emphasizing that prospective randomized trials comparing AI-guided vs. standard care are needed before widespread adoption. Kim *et al* (121) identified key challenges including data standardization, algorithm generalizability and clinician acceptance as critical barriers to AI adoption in orthopaedic practice. Fairley *et al* (122) conducted a systematic scoping review of generative AI in OA and found that while large language models and image generation tools show promise for patient education and synthetic data creation, their current applications remain experimental without proven clinical utility. A critical synthesis indicates that the path forward requires not only technical improvements in model robustness and interpretability but also concerted efforts in prospective validation, regulatory science and health economic assessment. As Russell *et al* (112) forcefully argued, until AI systems consistently outperform expert clinicians in well-designed prospective trials, they should be viewed as decision support tools rather than replacements for clinical judgment. Therefore, the successful translation of integrative bioinformatics and AI into OA precision medicine will depend on interdisciplinary collaboration, rigorous validation frameworks and a clear focus on patient-centered outcomes.

8. Future perspectives

The multi-omics landscape of OA has advanced considerably, yet several frontiers remain underexplored. Emerging technologies and conceptual shifts promise to address current limitations and accelerate clinical translation. However, a critical appraisal of feasibility, cost and scalability is essential to distinguish realistically achievable advances from longer-term aspirations. This section prioritizes opportunities according to their anticipated timeframes for clinical translation.

Realistically achievable in the next 5 years. The application of AI and machine learning represents another transformative direction. Sharma (111) recently synthesized how omics data integration with AI can enhance patient stratification, though prospective validation in independent cohorts remains scarce. Ou *et al* (123) comprehensively reviewed AI applications across OA clinical, imaging and omics domains, concluding that deep learning excels at pattern recognition but generalizability across diverse populations is unproven. Given the rapid pace of computational method development and the increasing availability of public multi-omics datasets, AI-driven endotyping and biomarker discovery are realistically achievable within 5 years, provided that prospective validation cohorts are established.

Drug repurposing based on multi-omics-defined molecular subtypes also represents a near-term opportunity. Kuswanto and Baker (124) systematically evaluated drug repurposing opportunities for OA, arguing that molecularly defined patient subgroups may respond to existing agents targeting metabolic pathways. Maroun *et al* (125) identified senescence-regulatory factors as both circulating biomarkers and therapeutic targets, suggesting that cellular senescence represents a tractable node for intervention. Repurposing of approved drugs for endotype-defined patient subsets is feasible within 5 years, as it bypasses *de novo* drug development timelines and leverages existing safety data, though endotype-enriched trial designs remain to be validated.

Medium-term opportunities with significant barriers. The integration of multi-omics with human-relevant experimental

models holds substantial promise but faces considerable technical and standardization challenges. Osteochondral organoids offer a direct platform for functional validation of the cell type-specific gene-metabolite networks identified from patient multi-omics datasets. This integrated paradigm, which combines multi-omics discovery with organoid-based functional testing, enables researchers to interrogate whether specific gene-metabolite perturbations observed in patient tissues, such as dysregulated glycerophospholipid metabolism in inflammatory chondrocyte subpopulations, are sufficient to drive pathological phenotypes when recapitulated in a controlled 3D microenvironment (17,32). Furthermore, osteochondral organoids allow for systematic manipulation of candidate metabolic regulators, such as ACSL4 or SREBP1, while monitoring downstream metabolomic and phenotypic outcomes (32,66). Synovium-cartilage organoid co-culture systems further enable validation of cell-cell crosstalk mechanisms identified in single-cell transcriptomic studies (3). Such functional validation is essential because multi-omics data, while powerful for hypothesis generation, cannot distinguish causal drivers from passive correlates. Complementing this, microphysiological systems now allow co-culture of multiple joint tissues under controlled mechanical and biochemical conditions, facilitating causal testing of cell-type-specific metabolic hypotheses (126). However, these platforms remain technically challenging to standardize, have limited throughput and lack validation against human disease progression. Widespread adoption within 5 years is unlikely; rather, they will serve as specialized mechanistic tools in research settings.

Long-term challenges. The emerging concept of 'pre-OA' offers opportunities for early intervention. Multi-omics evidence has begun to distinguish pre-OA from mild OA at the molecular level. Del Río (127) proposed a multidimensional definition of pre-OA that incorporates molecular, imaging and clinical parameters, arguing that subclinical detection is essential for disease modification. Lipidomic profiling has provided particularly compelling evidence in this regard. Eichner *et al* (128) systematically quantified 91 lipid species from 6 major classes (phosphatidylcholine, phosphatidylethanolamine, phosphatidylserine, phosphatidylinositol, phosphatidic acid and sphingomyelin) in serum and synovial fluid from 44 joint-healthy donors and 58 early OA or late OA patients, demonstrating that significant lipidomic alterations are already detectable at an average Outerbridge score of <2, before radiologic detection is possible. Notably, nearly 10% of phospholipid species were elevated exclusively in OA serum, indicating a systemic metabolic response that parallels the local lipid metabolic response to OA (128). Single-cell transcriptomics has further enabled the identification of early cell-state transitions, including pre-hypertrophic chondrocyte populations that precede overt cartilage degeneration (17). Spatial multi-omics has revealed distinct synovitis stages, namely quiescent, microvasculopathic, pre-fibrotic and post-fibrotic, providing a molecular trajectory of disease progression from subclinical inflammation to established pathology (26).

Longitudinal cohort studies have substantiated the utility of molecular screening for early OA detection. A nested case-control study within the UK Biobank (n=30,490 incident OA cases) demonstrated that systemic metabolic perturbations, particularly involving energy metabolism (lactate, citrate, amino acids), chronic low-grade inflammation (glycoprotein acetyls) and adverse lipid composition (apolipoprotein B, very low density lipoprotein cholesterol), are detectable a median of 7.3 years before OA diagnosis (129). Large-scale proteomic profiling of 45,307 UK Biobank participants further revealed that plasma protein trajectories, particularly collagen type IX alpha 1 chain and cartilage acidic protein 1, begin to deviate from normal more than a decade before OA onset (114). Similarly, a case-cohort study within the OA Initiative (603 participants, 237 incident knee OA cases, 8-year follow-up) demonstrated that blood-based metabolites reflective of the gut microbiome, including 3-(3-hydroxyphenyl) propanoic acid, N,N-dimethylglycine and butyric acid, are associated with incident knee OA risk (130). The APPROACH cohort further demonstrated that biomarker-based molecular endotypes remain stable over 6-, 12- and 24-month follow-ups, with more than half of knee OA participants exhibiting a longitudinally stable endotype (average overall stability, 55%; Fleiss' Kappa, 0.53; 95% CI 0.46-0.60), supporting the applicability of biomarker-based subtyping in clinical trial settings (102). Despite these promising findings, pre-OA detection requires prospective longitudinal cohorts with deep phenotyping, as exemplified by the OPTIMA-C study protocol (131), and validation of biomarkers across diverse populations. This remains a long-term goal beyond 5-10 years, as it requires large-scale, expensive longitudinal studies with extended follow-up.

The critical barrier of cost and scalability. A fundamental roadblock that underpins many of the challenges discussed above is the prohibitive cost and limited scalability of current multi-omics technologies. Spatial transcriptomics and single-cell metabolomics, while offering unprecedented resolution, remain prohibitively expensive for application to large patient cohorts. The cost of generating spatially resolved omics data from a single tissue section can exceed thousands of dollars, making it infeasible for routine clinical application or large-scale biomarker discovery studies. Similarly, comprehensive multi-omics profiling combining genomics, transcriptomics, proteomics and metabolomics from the same patient sample is currently confined to small, well-funded research cohorts. As noted by several comprehensive reviews, the lack of cost-effective, high-throughput platforms for multi-omics analysis represents a major translational roadblock that limits both discovery-phase sample sizes and clinical validation studies (5,14,52). Furthermore, the computational infrastructure required to store, process and integrate these massive datasets is not readily available in most clinical settings. Acknowledging these cost and scalability barriers is essential for setting realistic expectations for clinical translation.

Off-target risks and delivery limitations of lipid modulators. A critical barrier to translating lipid-targeted strategies into clinical practice is that most currently discussed therapeutic targets remain at preclinical cell or animal model stages, with limited data on off-target effects and tissue-specific delivery in human joints (52). Systemic lipid-modulating

agents repurposed for OA, including statins and PPAR agonists, carry well-documented off-target risks. Statins have been associated with increased OA risk in large-scale observational studies (odds ratio, 1.099; 95% CI 1.002-1.206), with higher doses conferring greater risk, and Mendelian randomization has revealed population-specific effects on skeletal outcomes (2,6). PPAR agonists present cardiovascular safety concerns with limited clinical evidence for OA-specific efficacy (5). For novel multi-omics-identified targets such as SREBP1 and ACSL4 (32,66,68), systemic inhibition could theoretically disrupt hepatic lipid metabolism and essential fatty acid homeostasis in other tissues, yet the off-target landscape remains largely uncharacterized. Beyond molecular risks, the unique anatomical features of the joint, including rapid synovial fluid turnover and dense negatively charged cartilage extracellular matrix, pose formidable barriers to drug delivery, limiting therapeutic accumulation at target cells (14,15). Lipid-based nanocarriers have been developed to address these limitations, but they introduce their own safety challenges, including potential inflammatory responses and unresolved issues of long-term biocompatibility, scalable manufacturing and regulatory classification (14). Emerging strategies such as microenvironment-responsive delivery systems and chondrocyte-biomimetic nanoparticles remain largely at preclinical stages (12,13). In summary, the translation of multi-omics-identified lipid metabolic targets requires systematic evaluation of off-target risks, development of delivery strategies overcoming joint-specific barriers and rigorous safety assessment of nanocarrier systems themselves (14).

In summary, the roadmap to precision medicine in OA requires prioritized, realistic goals: Short-term (5 years): AI-driven endotyping and drug repurposing based on existing omics data, with prospective validation in well-phenotyped cohorts; medium-term (5-10 years): Integration of organoid and microphysiological systems for mechanistic validation of omics-derived hypotheses, alongside development of cost-reduced multi-omics platforms; and long-term (>10 years): Pre-OA detection strategies and endotype-enriched clinical trials of novel therapeutics. Achieving these goals will demand interdisciplinary collaboration among omics scientists, computational biologists, bioengineers and clinician-researchers, as well as sustained investment in scalable technologies and prospective longitudinal cohorts.

9. Conclusions

Integrating single cell transcriptomics, metabolomics and lipidomics has uncovered cell type-specific gene-metabolite networks in OA. Dysregulated glycerophospholipid and sphingolipid metabolism across chondrocytes, synovial fibroblasts and immune cells correlates with disease severity. These insights enable molecular endotyping and support the conceptual framework for precision medicine. However, the validation of theratypes, demonstrating differential treatment responses in endotype-defined patient subgroups, has not yet been achieved in OA. Prospective, endotype-enriched clinical trials represent the critical next step for translating multi-omics discoveries into clinical practice.

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YY and RZ contributed equally to conceptualization, literature review and drafting the original manuscript. YZ and DY performed the literature search and figure preparation. JX and CZ critically revised the manuscript for important intellectual content and gave final approval. All authors agree to be accountable for all aspects of the work and have read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Use of artificial intelligence tools

During the preparation of this work, artificial intelligence tools (DeepSeek-V3.2; https://chat.deepseek.com/) were used to improve the readability and language of the manuscript or to generate images, and subsequently, the authors revised and edited the content produced by the artificial intelligence tools as necessary, taking full responsibility for the ultimate content of the present manuscript.

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