Review

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Lipid metabolic networks in osteoarthritis pathogenesis: from systemic regulation to intrinsic control in chondrocytes

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Abstract: Osteoarthritis (OA) is a leading cause of chronic joint degeneration, and recent research increasingly highlights the pivotal role of lipid metabolism in its development. This review offers a comprehensive analysis of how systemic lipid metabolic dysfunction, local joint tissue remodeling, and intracellular lipid regulation in chondrocytes contribute to OA progression. We examine how obesity, dietary patterns, and gut microbiota imbalances promote systemic lipid disturbances, which, in turn, drive chronic inflammation and cartilage degradation. At the joint level, disrupted lipid metabolism in the infrapatellar fat pad (IPFP), synovial tissue, and macrophages creates a pro-inflammatory environment that accelerates cartilage damage. Additionally, alterations in intracellular lipid homeostasis in chondrocytes are linked to oxidative stress, mitochondrial dysfunction, and ferroptosis, which further contribute to cell death and joint destruction. This review presents an integrated framework that connects these multi-level lipid metabolic disturbances, emphasizing their combined effects on OA progression. It also explores emerging therapeutic strategies targeting lipid metabolic pathways at the systemic, local, and cellular levels. The findings provide a solid theoretical foundation for the development of precision therapies focused on lipid metabolism modulation, offering new possibilities for OA management and potential intervention.

Key words: Osteoarthritis; Lipid metabolism; Obesity; Gut microbiota; Synovial inflammation; Cartilage degeneration; Metabolic dysfunction.

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1 Introduction

OA is the most common chronic degenerative joint disease worldwide and places a substantial economic burden on public health systems because of population aging and rising obesity rates (Hunter and Bierma-Zeinstra, 2019). Current treatment options focus mainly on symptom relief or joint replacement, but both approaches have important limitations because the pathogenesis of OA remains incompletely understood (Hunter and Bierma-Zeinstra, 2019; Cao H et al., 2024). Although OA was once regarded as a mechanical "wear-and-tear" disease, advances in medical research have identified metabolic dysregulation as a central mechanism in disease progression (Wei G et al., 2023). Within this metabolic framework, abnormal lipid me-

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tabolism is increasingly recognized not as a secondary event, but as an important driver of OA (Chen X et al., 2024).

Abnormal lipid metabolism contributes to cartilage degeneration throughout the progress of the disease through systemic endocrine effects and changes in the local cellular environment. At the systemic level, obesity, unhealthy diets, and gut dysbiosis alter circulating lipid profiles and promote a persistent pro-inflammatory state (Friedland et al., 2002; Suren Garg et al., 2023; Meng et al., 2024). For example, excess adipose tissue functions as an active endocrine organ that releases adipokines and free fatty acids (FFAs), which can enter the synovial fluid (Wang T and He, 2018). In addition, diets with an imbalanced ratio of n-6 to n-3 polyunsaturated fatty acids (PUFAs) (Dai et al., 2021), together with changes in the gut microbiota that impair protective short-chain fatty acid metabolism (Dabke et al., 2019; Karim et al., 2025), further increase oxidative stress and inflammation.

At the local level, abnormal lipid metabolism markedly alters the intra-articular environment. Major joint tissues show distinct metabolic changes: the infrapatellar fat pad (IPFP) adopts a pro-inflammatory phenotype with altered lipolysis (Tang et al., 2024), fibroblast-like synoviocytes (FLSs) undergo changes that increase their proliferation and invasiveness (Cao X et al., 2022b), and resident joint macrophages shift toward pro-inflammatory M1 polarization (Ma S et al., 2021). Notably, local lipid metabolic dysfunction may represent an independent response, distinct from systemic lipid metabolism. Conversely, systemic lipid metabolic disorders can directly affect cartilage or indirectly alter the periarticular microenvironment. Collectively, these local disturbances trigger the release of inflammatory cytokines and lipotoxic molecules, which disrupt chondrocyte homeostasis and directly accelerate cartilage matrix degradation.

At the cellular level, lipid metabolic reprogramming in chondrocytes influences cell fate and disrupts cartilage matrix homeostasis. OA chondrocytes exhibit significant metabolic changes, such as lipid droplet accumulation due to increased fatty acid uptake and de novo synthesis (Liu Z et al., 2025; Mei et al., 2025), abnormal intracellular accumulation of cholesterol and activation of related metabolic pathways (e.g., the CH25H-CYP7B1-RORα axis), which upregulates catabolic enzymes like MMP13 (Choi et al., 2019). Furthermore, altered phospholipid metabolism, along with phospholipase overactivation (Huang G et al., 2025), leads to mitochondrial dysfunction and inflammation (Steinmeyer, 2025). Besides, lipid peroxidation-induced ferroptosis, mediated by enzymes like acyl-CoA synthetase long-chain family member 4 (ACSL4), acts as a critical link between lipid dysmetabolism and chondrocyte death (He et al., 2023).

In light of this evolving understanding, OA treatment strategies are shifting from traditional symptom management toward comprehensive and personalized approaches that target lipid metabolism (Liao T et al., 2023; Shawl et al., 2024; Fu et al., 2025; Su J et al., 2025). Although several reviews on lipid metabolism and OA have been published, most have focused on a single perspective, such as obesity-related systemic effects or metabolic changes in specific cell types. Multilevel analyses that integrate systemic factors, the local joint environment, and cell-intrinsic mechanisms remain limited. Accordingly, this review examines the role of lipid metabolic networks in OA pathogenesis across three dimensions: systemic, local, and cellular. It specifically addresses how systemic metabolic dysregulation affects the joint environment, how local cells in joints influence intercellular communication through metabolic reprogramming, and how intracellular lipid regulatory networks in chondrocytes shape cell fate. Our aim is to provide a theoretical basis for precision therapies targeting lipid metabolic pathways in OA.

2 Systemic lipid dysregulation as an upstream driver of OA

Recent research suggests that OA is a complex inflammatory joint disorder associated with systemic metabolic dysregulation. Among the factors influencing OA, systemic lipid metabolism disturbance plays a central role in the onset and progression of the disease (Zhao Y and Gan, 2023). Obesity, dietary patterns, and the gut microbiota affect this process and collectively link systemic lipid metabolism to joint health by altering

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immune responses, oxidative stress, and the intra-articular environment (Table S1).

2.1 Obesity-driven dyslipidemia and adipose–joint crosstalk

Obesity is a major risk factor for OA and promotes its onset and progression through both mechanical and metabolic mechanisms. Beyond increased joint loading, accumulating evidence, including Mendelian randomization studies, supports a causal role of obesity in OA via chronic inflammation and metabolic dysregulation (Nedunchezhiyan et al., 2022; Sun H et al., 2025). In obesity, adipose tissue functions as an active endocrine organ, releasing adipokines, FFAs, and other pro-inflammatory mediators that disturb systemic lipid homeostasis and contribute to low-grade inflammation and insulin resistance (Yu C et al., 2024; Kim et al., 2025).

These metabolic abnormalities are closely linked to dyslipidemia. A sustained positive energy balance drives white adipose tissue (WAT) expansion and dysfunction (Reyes-Farias et al., 2021), leading to lipotoxicity, altered adipokine secretion, and impaired insulin signaling (Yazıcı et al., 2024). As a result, hepatic synthesis and secretion of very low-density lipoprotein (VLDL) increase (Sparks et al., 2012), followed by elevated circulating low-density lipoprotein (LDL). In addition, visceral adipose tissue in obesity releases large amounts of free fatty acids, which further promote hepatic cholesterol and VLDL production (Ebbert and Jensen, 2013). At the same time, reduced hepatic LDL receptor expression impairs LDL clearance (Klop et al., 2013), while oxidative stress promotes the formation of oxidized LDL (ox-LDL), a highly bioactive lipid mediator (Koite et al., 2022).

Together, these systemic changes contribute to joint degeneration at both systemic and local levels. Circulating FFAs, cholesterol, and ox-LDL can enter the synovial fluid and promote synovial inflammation (Mustonen and Nieminen, 2021). Locally, obesity also alters cartilage lipid metabolism and fatty acid composition. For example, aetyl-CoA carboxylase 1 (ACC1) activation in chondrocytes from obese mice has been shown to increase de novo lipid synthesis, resulting in abnormal accumulation of palmitic, oleic, and linoleic acids in cartilage (Liu H et al., 2022). Collectively, systemic lipid infiltration and local metabolic disturbance may accelerate OA progression by amplifying oxidative stress, synovial inflammation, and chondrocyte dysfunction (Fig. 1).

2.1.1 Adipokine signaling as a link between obesity and cartilage catabolism

2.1.1.1 Leptin

Leptin levels are elevated in obesity-associated OA and aggravate joint degeneration through multiple pathways (Collins et al., 2025). After binding to the leptin receptor long isoform (Ob-Rb) receptor on chondrocytes, leptin activates the Janus kinase 2 (JAK2)-signal transducer and activator of transcription 3 (STAT3) signaling pathway and modulates the cluster of the differentiation 14 (CD14)/Toll-like receptor 4 (TLR4) axis, thereby promoting synovial inflammation and cartilage damage (Jiang M et al., 2021a). It also increases the secretion of catabolic factors, including interleukin-1 beta (IL-1β), IL-18, and matrix metalloproteinases (MMPs), by activating the NOD-like receptor family pyrin domain-containing 3 (NLRP3) inflammasome through NADPH oxidase 4 (NOX4)-dependent reactive oxygen species (ROS) production (Mourmoura et al., 2022). In addition, leptin inhibits chondrocyte autophagy by upregulating lysyl oxidase-like 3 (LOXL3) through the mechanistic target of the rapamycin (mTOR) pathway (Wei Q and Bhagyaveni, 2022). Recent studies further suggest that leptin contributes to chondrocyte senescence. It induces senescence and growth arrest through mechanisms such as activation of the p53/p21 pathway and increases the senescence-associated secretory phenotype (SASP). This leads to increased release of catabolic and inflammatory factors, including MMPs and nitric oxide, thereby accelerating joint tissue degeneration (Liu Z et al., 2024).

2.1.1.2 Visfatin

Visfatin, an adipokine produced by visceral adipose tissue and several joint tissues, contributes to cartilage degradation and synovial inflammation. Although circulating visfatin levels have been reported to be elevated

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in patients with OA (Chen WP et al., 2010), it remains unclear whether obesity independently leads to a further increase in visfatin. In patients with hip OA, serum visfatin concentrations were not significantly correlated with body mass index (BMI), despite increased visfatin expression in the synovial tissue of obese patients (Philp et al., 2021). Similarly, in another clinical cohort only a non-significant increase in serum visfatin levels was found in patients with knee OA, compared with obese controls without OA (Lambova et al., 2023). Therefore, circulating visfatin concentrations may not accurately reflect its abundance or biological activity within the joint. Visfatin can be produced locally by the synovium, cartilage, IPFP, and subchondral bone (Laiguillon et al., 2014). Its expression is increased in synovial tissue from obese patients with OA and is enriched in regions of cartilage damage (Philp et al., 2021). These findings suggest that visfatin may contribute to OA mainly through local production and cell-to-cell signaling within the joint, rather than through changes in circulating levels.

At the cellular level, locally derived visfatin directly disrupts chondrocyte homeostasis through several catabolic and pro-inflammatory pathways. In chondrocytes, visfatin promotes apoptosis by activating the nuclear factor kappa B (NF-κB) pathway, upregulating microRNA-34a (miR-34a) and miR-181a and thereby suppressing B-cell lymphoma 2 (BCL2) (Cheleschi et al., 2019). It also reduces mechanical stability by inactivating glycogen synthase kinase 3 beta (GSK3β) through p38 signaling (Chang et al., 2021). In synovial fibroblasts, visfatin worsens joint pathology through three miRNA-mediated pathways. Specifically, it activates extracellular signal-regulated kinase (ERK)/p38/ c-Jun N-terminal kinase (JNK) signaling to inhibit miR-199a-5p, thereby increasing IL-6 and tumor necrosis factor-alpha (TNF-α) production (Wu MH et al., 2018). It also activates the AMP-activated protein kinase (AMPK)/p38 pathway to downregulate miR-320a, which upregulates intercellular adhesion molecule 1 (ICAM-1) and promotes monocyte adhesion (Law et al., 2020). Furthermore, it uses the phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt) pathways to suppress miR-485-5p, leading to vascular endothelial growth factor (VEGF)-driven synovial angiogenesis and pathological remodeling (Tsai CH et al., 2020).

2.1.1.3 Resistin

Serum resistin levels are significantly elevated in patients with knee OA, particularly in those with obesity (BMI $\geqslant$ 30) (Lambova et al., 2021). It promotes joint degeneration by targeting both chondrocytes and synovial fibroblasts. In chondrocytes, resistin binds to the adenylyl cyclase-associated protein 1 (CAP1) receptor and activates the p38-MAPK and NF-κB pathways, inducing the release of pro-inflammatory chemokines, such as C-C motif chemokine ligand 3 (CCL3) and CCL4, and matrix-degrading enzymes, including MMP13 and a disintegrin and metalloproteinase with thrombospondin motifs 4 (ADAMTS-4) (Zhao CW et al., 2022). It also upregulates autophagy-related genes, including autophagy-related 5 (ATG5), Beclin-1, and microtubule-associated protein 1 light chain 3 (LC3) (Aboudeya et al., 2022). In synovial fibroblasts, resistin suppresses miR-381 through the protein kinase C (PKC), p38, and JNK signaling pathways, upregulates vascular cell adhesion molecule 1 (VCAM-1) expression, and promotes monocyte adhesion, thereby contributing to OA pathogenesis (Chen WC et al., 2020a). Concurrently, it triggers the mitogen-activated protein kinase kinase (MEK)/ERK pathway to suppress miR-149, unleashing the production of IL-1β and TNF-α and exacerbating synovial inflammation at the joint site (Chen WC et al., 2020b).

2.1.1.4 Other Adipokines

Adiponectin exerts context-dependent effects on OA progression. At high intra-articular concentrations, adiponectin binds to the adiponectin receptor 1 (AdipoR1) receptor on chondrocytes and synovial fibroblasts. This activates several kinase pathways, including AMPK/NF-κB, p38 MAPK, liver kinase B1 (LKB1)/ calmodulin-dependent protein kinase II (CaMKII), and JAK2/PI3K, which increase the production of pro-inflammatory cytokines (IL-6), matrix-degrading enzymes (MMP-1/3/13), and adhesion molecules (ICAM-1/VCAM-1), thereby promoting inflammation and cartilage destruction. Under some conditions, however, adiponectin may also have protective effects by promoting chondrocyte autophagy through the AMPK/mTOR pathway and stimulating osteogenic repair through Wnt/β-catenin signaling and phosphatase and tensin homolog (PTEN) inhibition. This dual behavior may help explain why, in obesity-associated OA, elevated local adiponectin levels in the joint may be linked to disease progression even when systemic adi-

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ponectin levels are low (Ilia et al., 2022; Kim et al., 2025). Additionally, newly identified adipokines such as apelin (Wang YH et al., 2020b) and omentin-1 (Ko et al., 2023) have been found to exhibit abnormal expression in obese OA patients and contribute to OA progression.

2.1.2 Fatty acid lipotoxicity in obesity-associated OA

2.1.2.1 *Palmitic acid and stearic acid*

Palmitic acid, a long-chain saturated fatty acid, is significantly elevated in the serum of obese patients (Hierons et al., 2022). In chondrocytes, it induces endoplasmic reticulum (ER) stress by activating the inositol-requiring enzyme 1 alpha (IRE1α)/ protein kinase RNA-like endoplasmic reticulum kinase (PERK) pathway, upregulating X-box binding protein 1 (XBP1) and activating transcription factor 4 (ATF4), and subsequently increasing C/EBP homologous protein (CHOP) expression (Tan et al., 2021). Elevated CHOP further upregulates nuclear protein 1 (Nupr1), which directly promotes cytochrome c release and cleaved caspase-3 (CC3) activation while also inducing tribbles pseudokinase 3 (TRB3) expression and inhibiting Akt activity, thereby intensifying chondrocyte apoptosis through two pathways (Tan and Yammani, 2019). Zhao et al. (2025a) showed that palmitic acid also induces DNA damage in chondrocytes, activates the p53-Akt- forkhead box O3 (FOXO3) pathway, and leads to chondrocyte apoptosis. Furthermore, palmitic acid activates the TLR2/4 pathway, inducing M1 polarization of macrophages and exacerbating systemic and joint inflammation (Tsai YW et al., 2021).

In addition to palmitic acid, stearic acid, another saturated fatty acid, promotes chondrocyte inflammation through a distinct metabolic pathway. It enhances lactate dehydrogenase A-dependent lactate production, thereby stabilizing hypoxia-inducible factor 1α (HIF-1α) and increasing the expression of VEGF and pro-inflammatory cytokines (Miao et al., 2015).

2.1.2.2 *Oleic Acid/Linoleic Acid*

Linoleic acid, an n-6 polyunsaturated fatty acid, and oleic acid, an n-9 monounsaturated fatty acid, are elevated in patients with obesity-associated OA. These elevated levels suppress chondrocyte autophagy by downregulating the sirtuin 1 (SIRT1)/FOXO1 signaling pathway (Li X et al., 2024c). In OA chondrocytes, impaired autophagy reduces degradation of the STING1 protein, leading to its accumulation. This activates the stimulator of interferon genes 1 (STING1)- TANK-binding kinase 1 (TBK1)-interferon regulatory factor 3 (IRF3) and STING1-MAP2K3-p38 signaling pathways, induces the expression of inflammatory mediators such as IFN-β, and upregulates matrix-degrading enzymes, including MMP3, MMP13, and ADAMTS4/5 (Kang X et al., 2025). Lee et al. (2018) found that chondrocytes resist lipotoxicity by sequestering FFAs through PKCK2/ six-transmembrane epithelial antigen of prostate 2 (STAMP2)/ fat-specific protein 27 (FSP27)-mediated lipid droplet accumulation, which reduces cytoplasmic FFA concentrations. However, high concentrations of oleic and palmitic acids reduce lipid droplet volume in chondrocytes by downregulating STAMP2, thereby weakening cellular resistance to lipotoxicity and promoting chondrocyte death.

2.1.3 Lipoprotein and cholesterol stress in Joint Degeneration

Low levels of high-density lipoprotein (HDL), elevated ox-LDL, and increased circulating cholesterol levels are key features of obesity-related dyslipidemia (Sampath et al., 2023). Among these factors, ox-LDL exerts particularly deleterious effects on joint tissues. By binding to lectin-like oxidized- LDL receptor LOX1 on chondrocytes, ox-LDL increases intracellular ROS production, activates NF-κB signaling, and promotes local inflammatory responses (Nishimura et al., 2004). It also stimulates peroxisome proliferator-activated receptor gamma (PPAR-γ) signaling and upregulates VEGF expression, thereby facilitating vascular invasion, chondrogenic calcification, and extracellular matrix degradation (Kanata et al., 2006). Ox-LDL has been shown to inhibit autophagic flux through the ERK1/2–mTOR–transcription factor EB (TFEB) axis, leading to chondrocyte necroptotic death and accelerated OA progression (Lee JS et al., 2024).

Elevated cholesterol further aggravates joint degeneration through direct effects on chondrocytes and pathological intercellular crosstalk. In chondrocytes, excessive cholesterol downregulates LDL receptor-related

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protein 3 (LRP3), activates Ras/ERK signaling, and increases syndecan-4 (SDC4) expression, thereby promoting ADAMTS-5-mediated matrix degradation (Cao C et al., 2022a). High-cholesterol conditions also reduce circular RNA actin-related protein 2/3 complex subunit 1B (circARPC1B) expression, weakening its protective effect on vimentin and enhancing synoviolin 1 (SYVN1)-mediated ubiquitination and degradation of this structural protein, which further compromises cartilage homeostasis (Li J et al., 2023). Ma et al. (2025) showed that elevated intra-articular cholesterol disrupts nudix hydrolase 8 (Nudt8)-rich mitochondria in subchondral osteoblasts in mouse OA models by promoting coenzyme A degradation and increasing mitochondrial membrane permeability. These dysfunctional mitochondria release mitochondrial DNA and migrate to chondrocytes through intercellular nanotubes, where they directly activate the cyclic GMP-AMP synthase (cGAS-STING) pathway and markedly increase synovitis and cartilage matrix degradation.

2.1.4 Adipose-derived exosomal miRNAs in obesity-promoted OA

A recent study revealed that adipose tissue-derived exosomes (Ad-EVs) also contribute to obesity-promoted OA progression. Geranylgeranyl diphosphate synthase (Ggpps), a key protein-modifying enzyme, regulates the fusion of intracellular vesicles with the plasma membrane through its downstream protein Ras-related protein Rab-27A (Rab27A). Prospective research by Li et al. (2024a) found that Ggpps expression increases in adipose tissue under obesity conditions, promoting the secretion of adipose tissue-derived exosomes. Ad-EVs carry high concentrations of miR-3074-5p, which circulate to temporomandibular joint chondrocytes, where they target and suppress SMAD family member 4 (SMAD4) expression. This leads to increased chondrocyte apoptosis and reduced matrix synthesis, ultimately exacerbating OA (Li B et al., 2024a).

2.2 Dietary lipid inputs and pro-inflammatory nutritional patterns in OA

Dietary patterns play a central role in shaping circulating lipid profiles and thereby influence OA progression. Unhealthy dietary habits, particularly high-fat diets, increase systemic levels of FFAs and triglycerides. After absorption, these lipids can accumulate in joint tissues and contribute to cartilage damage, synovial inflammation, and subchondral bone remodeling. Importantly, the pathological effects of dietary FFAs depend strongly on their carbon chain length and degree of saturation (Fig. 2).

2.2.1 Saturated fatty acids (SFAs) and chain-length-related lipotoxicity

Numerous studies have shown that dietary SFAs are generally associated with a pro-inflammatory metabolic profile and may contribute to OA progression by increasing the systemic lipid burden (Goldring and Otero, 2011). The harmful effects of SFAs on chondrocytes are closely associated with carbon chain length. Long-chain SFAs, such as palmitic acid and stearic acid, have strong pro-inflammatory effects. In contrast, medium- and short-chain SFAs, such as lauric acid and myristic acid, show limited chondrotoxicity. Lauric acid may even have protective effects by counteracting IL-1β-induced autophagy (Sekar et al., 2018). Therefore, the dietary relevance of SFAs may lie not only in their total intake, but also in the composition of fatty acid species that enter the circulation and subsequently influence the joint microenvironment.

2.2.2 PUFA imbalance and inflammatory lipid mediators

The effects of PUFAs on OA depend largely on the dietary ratio of n-6 to n-3 fatty acids. Excessive n-6 PUFAs, such as linoleic acid and arachidonic acid, may favor pro-inflammatory lipid mediator production and cartilage catabolism (Chen GY et al., 2023; Li X et al., 2024c). In contrast, n-3 PUFAs, such as docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), exert protective effects on cartilage by activating SIRT1, inhibiting the high mobility group box 1 (HMGB1)-receptor for the advanced glycation end products (RAGE)/TLR4 signaling axis, and activating G protein-coupled receptor 120 (GPR120) to suppress NF-κB signaling (Xiong et al., 2024). A systematic review by Deng et al. (2023) found that supplementation with n-3 PUFAs effectively reduces pain and improves joint function in patients with OA, supporting their protective role in joint health.

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Maintaining a balanced dietary n-6/n-3 PUFA ratio, ideally between 1:1 and 4:1, is important for preserving joint homeostasis and normal systemic inflammatory status (Simopoulos, 2011; Dai et al., 2021;). Experimental studies in rat models of OA showed that high dietary n-6/n-3 ratios increased n-6 concentrations in trabecular bone and markedly worsened paw swelling, particularly at a ratio of 365:1. In contrast, lower ratios ranging from 1:1 to 6:1 reduced joint inflammation, protected cartilage, and lowered MMP-13 expression to levels comparable to those in healthy controls (Yu H et al., 2015). Similarly, in ovariectomized mice with OA, a low n-6/n-3 diet combined with DHA-rich Antarctic krill oil reduced intra-cartilage n-6/n-3 ratios and improved cartilage matrix structure. Mechanistically, this intervention reduced systemic low-grade inflammation by activating GPR120 and inhibiting NF-κB signaling (Dai et al., 2021). Clinical evidence is consistent with these findings. A cross-sectional study of patients with knee OA aged 45 to 85 years found that serum n-6/n-3 ratios above 5 were associated with more severe pain and poorer lower-limb physical function (Sibille et al., 2018). Thus, the balance between n-6 and n-3 PUFAs appears to critically shape the inflammatory and metabolic microenvironment of the joint, thereby influencing both the severity and progression of OA.

2.2.3 High-sugar diets and hepatic lipid dysregulation

Excessive sugar intake may accelerate OA progression mainly by promoting hepatic lipid dysregulation rather than simply worsening obesity. For example, combining a high-fat diet with excess sucrose markedly aggravates knee cartilage destruction, osteophyte formation, and synovitis in surgically induced mouse models of OA. Mechanistically, this dietary pattern causes abnormal accumulation of free cholesterol in the liver. This hepatic lipotoxicity then upregulates inflammatory pathways, including TLR4, TNF-α, IL-6, and monocyte chemoattractant protein 1 (MCP1), as well as fibrotic markers such as transforming growth factor beta (TGF-β) and collagen type I alpha 1 chain (COL1A1). As a result, excess sucrose may indirectly promote joint degeneration through a systemic pathological axis linking hepatic free cholesterol accumulation, inflammation, and fibrosis (Min et al., 2023).

2.2.4 Mediterranean and western diets in OA progression

Overall dietary patterns strongly influence OA progression by modulating systemic inflammation and plasma fatty acid profiles. The Mediterranean diet is a plant-based dietary pattern in which olive oil is the main source of fat, with moderate intake of fish, poultry, and dairy products. It is considered beneficial in OA because it is rich in antioxidants, anti-inflammatory compounds, and n-3 PUFAs (Veronese N et al., 2024). Substantial clinical evidence indicates that close adherence to the Mediterranean diet, or similar prudent dietary patterns, is associated with a lower prevalence of OA and with slower symptomatic and radiographic progression (Veronese N et al., 2017; Veronese N et al., 2018; Veronese et al., 2019; Zeng et al., 2023). In contrast, the Western diet, which is rich in red and processed meats, refined grains, sweets, and fast food, appears to worsen OA pathology (Quan et al., 2021). Adherence to this pro-inflammatory dietary pattern consistently accelerates both structural and symptomatic progression in knee OA (Xu C et al., 2020). These findings underscore the therapeutic potential of dietary interventions.

2.3 Gut microbiota–lipid crosstalk in OA

Recent research indicates that the composition and functional state of the gut microbiota strongly influence systemic metabolism, especially lipid metabolism. Gut dysbiosis is closely associated with metabolic disorders such as obesity and hyperlipidemia, supporting the concept of a “gut-joint axis” that contributes to OA progression through systemic inflammation and disordered lipid metabolism (Fig. 3).

2.3.1 Short chain fatty acids (SCFAs) and butyrate: barrier protection and chondroprotective signaling

Under normal conditions, SCFAs, mainly acetate, propionate, and butyrate, are produced by microbial fermentation of dietary fiber and enter the circulation, where they exert protective effects on joints. Among

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them, butyrate appears to be a key metabolite linking gut homeostasis to cartilage health through several interconnected mechanisms (Koh et al., 2016).

Butyrate, as a core metabolite of the gut microbiota, has anti-inflammatory and chondroprotective effects (Cho et al., 2022). A prospective study of patients with knee OA reported that daily butyrate supplementation improved intestinal barrier function, reduced the translocation of bacterial toxins into the bloodstream, lowered systemic inflammation, and significantly ameliorated pain and joint function (Karim et al., 2025). Mechanistic studies showed that butyrate acts through GPR43 to reduce the expression of pro-inflammatory mediators such as nitric oxide (NO) and IL-6, adipokines such as lipocalin 2 (LCN2), and adhesion molecules such as VCAM1. It also suppresses inflammatory pathways, including NF-κB, mitogen-activated protein kinase (MAPK), and AMPKα/Akt, while increasing the expression of C-X3-C motif chemokine ligand 1 (Cx3cl1) and the anti-inflammatory protein annexin A1 (AnxA1), thereby promoting the resolution of inflammation (Pirozzi et al., 2018). Furthermore, butyrate helps maintain extracellular matrix balance by inhibiting MMP13 expression, promoting type II collagen synthesis, and restoring autophagy in inflamed chondrocytes, which may help prevent necrotic cell death mediated by receptor-interacting serine (RIPK3)/ mixed lineage kinase domain-like protein (MLKL) (Cho et al., 2022). These findings suggest that SCFAs, especially butyrate, may function as more than simple microbial metabolites in OA. By simultaneously regulating intestinal barrier integrity, systemic inflammation, chondrocyte autophagy, and extracellular matrix balance, butyrate provides a mechanistic link between gut microbial activity and joint tissue homeostasis.

The therapeutic relevance of this axis is further supported by exogenous interventions such as gold nanoparticles (GNPs), which can modify host immune responses (Metch et al., 2018). GNP treatment has been reported to enrich beneficial bacteria, including Akkermansia and Lactobacillus, thereby increasing endogenous SCFA and butyrate production. This increase strengthens the gut barrier by upregulating tight junction proteins such as zonula occludens-1 (ZO-1) and occludin and promotes anti-inflammatory M2 macrophage polarization, which may reduce inflammation and protect articular cartilage (Deng Z et al., 2024). This observation also indicates that the protective effect of beneficial genera may not depend solely on their abundance, but on their capacity to reshape microbial metabolic outputs.

2.3.2 Microbial lipid signatures linking dysbiosis to joint damage

Dysregulation of lipid metabolism alters the intestinal environment, which may lead to gut microbiota imbalance. Conversely, studies indicate that the gut microbiota also plays a critical role in influencing lipid metabolism (Dabke et al., 2019; Chen H et al., 2026;). For example, the abundance of *Blautia* is negatively correlated with visceral fat content (Ozato et al., 2019); *Bacillus subtilis B10* promotes lipid breakdown by upregulating hepatic PPARα and 3-hydroxy-3-methylglutaryl-CoA synthase 2 (HMGCS2) expression (Lei et al., 2015); *Pediococcus pentosaceus PP04* and *Lactobacillus plantarum LP104* inhibit lipid synthesis by activating the AMPK pathway, suppressing ACC activity, and downregulating sterol regulatory element-binding protein 1 (SREBP-1), fatty acid synthase (FAS), and stearoyl-CoA desaturase (SCD) expression (Rahman et al., 2021). Additionally, *Lactobacillus sakei* reduces serum total cholesterol and triglyceride levels (Kang Y et al., 2022), while *Lactobacillus acidophilus* upregulates key transcription factors, including PPARα, PPARγ, and CCAAT/enhancer-binding protein alpha (C/EBP-α) (Kang Y *et al.*, 2022). *Bifidobacterium* regulates hepatic FAS and PPARγ protein expression through its metabolites, reducing triglycerides and LDL cholesterol, thereby ameliorating lipid metabolism abnormalities in obese mice (Chen M et al., 2021).

In recent years, increasing evidence has highlighted a role for gut microbiota in OA progression through its regulation of systemic lipid metabolism. Gut dysbiosis may contribute to joint disease by reshaping circulating lipid profiles and promoting pro-inflammatory metabolic states. In temporomandibular joint disorder, for example, lipid metabolism appears to be a key mediator of microbiota-related effects: pro-inflammatory genera such as *RUG147* are associated with increased free cholesterol in small VLDL particles, whereas protective taxa such as *Bifidobacterium* may help preserve HDL3 levels and limit joint damage (Jiang Y et al., 2025). Consistently, dysbiosis involving species such as *Bacteroides uniformis*, *Klebsiella pneumoniae*, *Intestinibacter*

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bartlettii, and *Streptococcus anginosus* has been linked to increased linoleic acid and glycerophospholipid metabolism, elevated choline-related metabolites, and increased cartilage degradation (Wang Y et al., 2025c).

Microbiota-driven lipid dysregulation also appears to vary across OA phenotypes, suggesting that the gut–lipid–joint axis is unlikely to be a uniform pathway in all forms of OA. Symptomatic hand OA has been associated with increased *Bilophila* and *Desulfovibrio* abundance and reduced *Roseburia*, together with impaired sphingolipid metabolism (Wei J et al., 2021a). In knee OA, enrichment of pro-inflammatory taxa such as *Paraprevotella*, *Barnesiella*, *Coprobacter*, and *Christensenellaceae*, along with depletion of anti-inflammatory genera including *Bacteroides*, *Anaerostipes*, *Ruminococcus*, and *Blautia*, may promote persistent pain and synovial inflammation. Mechanistically, *Paraprevotella* may increase the conversion of phosphatidylcholine to lysophosphatidylcholine, thereby releasing arachidonic acid and increasing pro-inflammatory eicosanoid production (Huang J et al., 2024). More broadly, an increased *Firmicutes*/*Bacteroidetes* ratio disrupts leucine and geraniol metabolism, increases serum 3-hydroxyisovaleric acid, and decreases ferulic acid levels. This metabolic profile may suppress the circulating anti-inflammatory protein tumor necrosis factor-like weak inducer of apoptosis (TWEAK), induce compensatory upregulation of its receptor in the synovium, and worsen synovial inflammation (Wang X et al., 2026).

Taken together, these findings support the concept that gut microbiota may regulate OA progression through lipid-related metabolic outputs, rather than through bacterial composition alone. The gut–lipid–joint axis appears to be shaped by a dynamic balance between lipid-protective and lipid-disruptive microbial functions. On the protective side, taxa such as *Akkermansia*, *Lactobacillus*, *Blautia*, and *Bifidobacterium* are associated with SCFA production, improved lipid breakdown, reduced lipid synthesis, or lower cholesterol and triglyceride levels. In contrast, dysbiosis-associated taxa, including *RUG147*, *Bilophila*, *Desulfovibrio*, *Paraprevotella*, *Klebsiella pneumoniae*, *Intestinibacter bartlettii*, and *Streptococcus anginosus* are linked to disturbed cholesterol, sphingolipid, linoleic acid, glycerophospholipid, and eicosanoid-related metabolism (Table S2). Importantly, these observations suggest that gut microbiota should not be viewed simply as an upstream inflammatory trigger, but as a metabolic regulator that may determine how systemic lipid signals are translated into synovial inflammation, pain, and cartilage degeneration.

3 Local lipid reprogramming in the OA joint microenvironment

The joint is a complex microenvironment in which several local tissues—notably the IPFP, synovium, and resident macrophages—undergo substantial metabolic remodeling during OA. These tissues are not passive bystanders; rather, disturbed lipid metabolism within these compartments contributes directly to disease progression. Local lipid dysregulation promotes inflammatory changes in the IPFP and enhances the pathological activation of FLSs and intra-articular macrophages. Through the paracrine release of inflammatory cytokines, lipotoxic mediators, and altered metabolic signals, these tissues disrupt the anabolic-catabolic balance of neighboring chondrocytes and accelerate cartilage degeneration (Table S3).

3.1 IPFP metabolic remodeling and adipokine amplification

The IPFP is an active intra-articular endocrine and metabolic tissue rather than merely a mechanical cushion. In OA, it undergoes marked metabolic reprogramming characterized by disrupted lipid homeostasis, fibrosis, and inflammatory cell infiltration. These changes transform the IPFP from a supportive energy store into a local contributor to joint degeneration through three main mechanisms (Fig. 4a).

3.1.1 OA-IPFP lipidome remodeling revealed by multi-omics

Multi-omics analyses have revealed profound lipid metabolic dysregulation in the IPFP during OA. Lipidomic profiling shows that OA markedly reshapes the IPFP lipid landscape and impairs its anabolic capacity. Single-cell analyses further identified a pathological shift in adipocyte subpopulations, characterized by a marked reduction in lipid-synthesizing adipocytes (AD1) and a reciprocal expansion of lipid-catabolizing ad-

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ipocytes (AD3) (Pu et al., 2024). This impaired lipogenesis is driven in part by interstitial inflammatory fibroblasts (iiFBs) through TWEAK, granulin precursor (GRN)/ sortilin 1 (SORT1), and noncanonical wingless-type MMTV integration site family (WNT) signaling (Tiller et al., 2009; Su X et al., 2023; Pu et al., 2024), resulting in depletion of local energy reserves and reduced mechanical buffering. Concurrently, the OA-IPFP accumulates a disease-associated lipidome enriched in pro-inflammatory oxidized lipids, including arachidonic acid and thromboxane B2 (Gierman et al., 2013).

Proteomic alterations further link IPFP lipid dysregulation to disease progression and pathogenic crosstalk with adjacent joint tissues. Upregulation of perilipin 4 (PLIN4) and apolipoprotein B (APOB)-100 suggests abnormal lipid droplet stabilization and triglyceride storage, potentially favoring the release of lipotoxic lipoprotein particles (Smith and Ordovás, 2012; Sztalryd and Brasaemle, 2017; Timur et al., 2021). In addition, intermediate fibroblasts and macrophages within the IPFP overexpress APOE, which acts in a paracrine manner to activate MAPK/ERK and NF-κB signaling in neighboring chondrocytes. This APOE-driven signaling suppresses cartilage anabolism, including COL2A1, aggrecan (ACAN), and SRY-box transcription factor 9 (SOX9), while enhancing catabolic mediators such as MMP3/13 and ADAMTS4/5 (Tang et al., 2024). Moreover, increased microsomal glutathione S-transferase 1 (MGST1) expression in IPFP promotes oxidative stress and prostaglandin E2 (PGE2) production, thereby establishing a vicious cycle of IPFP fibrosis, matrix degradation, and persistent pain (Emanuel et al., 2024).

3.1.2 IPFP-derived adipokines as local amplifiers of synovial inflammation

In OA, the IPFP acts as a local endocrine and paracrine source of adipokines rather than merely reflecting systemic adipose dysfunction. Increased release of leptin, adiponectin (Scotece and Mobasheri, 2015; Yan M et al., 2018; Feng et al., 2022; Wisniewska et al., 2023), and WISP2 from the OA-IPFP (Conde et al., 2015) may amplify inflammatory and catabolic responses in adjacent synovial fibroblasts and chondrocytes. In this way, IPFP-derived adipokines may convert obesity-associated metabolic signals into local intra-articular inflammation and cartilage degradation through tissue crosstalk.

3.2 FLSs lipid metabolic heterogeneity and synovial invasiveness

FLSs are key effector cells in OA synovitis and joint destruction. In the OA microenvironment, FLSs do not show a uniform pattern of lipid metabolic change. Instead, current evidence suggests a context-dependent metabolic plasticity, involving lipid synthesis, lipolysis, fatty acid oxidation (FAO), phospholipid remodeling, and apolipoprotein-mediated crosstalk. These lipid-related changes influence FLS proliferation, invasiveness, inflammatory mediator secretion, and their pathological communication with chondrocytes. Therefore, FLS lipid metabolism should not be interpreted simply as either “activated” or “suppressed”, but as a dynamic process shaped by FLS subset identity, inflammatory stress, disease stage, and systemic metabolic background (Fig. 4c).

3.2.1 Subset-specific lipid programs in OA-FLSs

FLSs are increasingly recognized as a metabolically heterogeneous cell population rather than a uniform stromal compartment. Single-cell and metabolomic studies provide relatively direct evidence that different OA-FLS subsets have distinct lipid metabolic programs. The subserosal Thy-1 cell surface antigen$^+$ (THY1$^+$) FLS subtype shows a highly invasive phenotype and promotes synovitis through marked secretion of pro-inflammatory cytokines, including IL-6, IL-8, and granulocyte-macrophage colony-stimulating factor (GM-CSF). To support these demands,THY1$^+$ FLSs exhibit metabolic reprogramming characterized by enhanced glycolysis. In addition, OA-FLSs show elevated expression of lipid metabolism-related enzymes, including acetyl-CoA acetyltransferase (ACAT), compared with mesenchymal stromal cells. (Damerau et al., 2022).

Adenylate cyclase 7$^+$ (ADCY7$^+$) FLSs represent another OA-associated subset characterized by inflam-

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matory lipolysis. Activation of the PKA-perilipin 1 (PLIN1)/hormone-sensitive lipase (HSL) pathway in these cells increases the release of glycerol and FFAs. These FFAs act as signaling molecules that induce epithelial-mesenchymal transition–like changes and enhance the invasive and catabolic properties of FLSs (Cao X et al., 2022b). These findings support the view that lipid metabolism in OA-FLSs is functionally linked to synovial pathogenicity rather than being a passive consequence of inflammation.

3.2.2 Context-dependent FAO remodeling and conflicting evidence

The pattern of fatty acid metabolism in OA-FLSs remains unclear. Some studies suggest that increased lipid metabolism promotes inflammatory activation. For example, in patients with OA and metabolic syndrome, which is characterized by central obesity, hypertension, hyperglycemia, and hypertriglyceridemia, elevated circulating resistin binds to CAP1 on FLSs and activates the PKA/cAMP response element-binding protein (CREB) pathway. This process increases carnitine palmitoyltransferase 1A (CPT1A) expression and increases FAO. Increased FAO promotes the secretion of inflammatory mediators, including TNF-α and CCL3, and aggravates synovitis (Ding et al., 2025). These findings suggest that FLSs may mediate the local effects of systemic metabolic disorders within the joint.

In contrast, other evidence indicates that mitochondrial fatty acid use may be impaired under severe inflammatory or senescent conditions. Regulator of calcineurin 1^{+} ($RCAN1^{+}$) $IL1\alpha^{+}$ FLSs show increased lipid synthesis and reduced FAO through the RCAN1–ATF4 axis. This change promotes saturated fatty acid secretion, oxidative stress, chondrocyte senescence, and matrix degradation (Hu et al., 2025). Similarly, reduced glutamine amidotransferase-like class 1 domain-containing 3A (GATD3A) expression in OA-FLSs causes mitochondrial dysfunction, disrupts tricarboxylic acid cycle activity, and decreases fatty acid use, thereby promoting a shift toward glycolysis (Shen et al., 2024). Public gene expression analyses and in vitro studies also show that several enzymes involved in long-chain FAO and lipid synthesis, including AMPK, ACC, CPT1A, and fatty acid synthase (FASN), may be reduced in OA-FLSs (de Jong et al., 2023; Liao T et al., 2023; Liao CS et al., 2024).

These findings are not necessarily contradictory. One possible explanation is that FAO activation may promote inflammatory and tissue-destructive behavior in specific FLS subsets or in metabolic syndrome-associated OA, whereas impaired FAO and compensatory glycolysis may predominate in senescent, mitochondrial-dysfunctional, or strongly inflammatory states. Overall, current evidence supports a stage- and subset-dependent model of FLS lipid metabolism rather than a single uniform pathway.

3.2.3 Phospholipid remodeling and synovium–cartilage crosstalk

Compared with fatty acid metabolism, phospholipid remodeling in OA-FLSs is more closely associated with changes in the synovial fluid environment and cartilage surface function. Inflammatory stimulation, particularly by IL-1β, can alter cholesterol-derived oxysterol signaling and promote phospholipid release from FLSs through cholesterol 25-hydroxylase (CH25H)/oxysterol 7α-hydroxylase (CYP7B1)–liver X receptor (LXR)-related pathways (Thottakkattumana Parameswaran *et al.*, 2022). IL-1β also increases phosphatidylethanolamine-related synthesis through NF-κB, p38 MAPK, and JNK signaling (Sluzalska et al., 2017a), whereas growth factors such as TGF-β1 and insulin-like growth factor 1 (IGF-1) mainly promote phosphatidylcholine production (Sluzalska et al., 2017b). These changes may disrupt the balance between phosphatidylcholine and phosphatidylethanolamine, increase the release of pro-inflammatory lipid mediators, and weaken the hydrophobic lubricating layer on cartilage (Kosinska et al., 2013). Therefore, phospholipid remodeling in FLSs may be important because it links synovial inflammation to impaired boundary lubrication and mechanical cartilage damage.

Apolipoprotein-mediated communication may also contribute to synovium–cartilage interactions. APOD appears to have protective effects in both FLSs and chondrocytes by limiting abnormal FLS proliferation, reducing ROS and inflammatory mediator production, supporting chondrocyte survival, and suppressing matrix-degrading enzymes. However, APOD expression is markedly reduced in OA, which may weaken this

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protective mechanism and allow harmful synovium–cartilage interactions to persist (Xu W et al., 2024). Compared with the broader evidence supporting FLS metabolic heterogeneity and inflammation-related lipid remodeling, evidence for APOD-mediated protection remains preliminary and requires further validation in human cohorts and disease-stage-specific models.

Overall, current evidence suggests that FLS lipid metabolism is a dynamic and context-dependent regulator of OA synovitis. The strongest evidence supports an association between FLS metabolic heterogeneity and inflammatory or tissue-destructive phenotypes, particularly in lipid-related FLS subsets. In contrast, the direction of FAO remodeling remains unclear, as both increased and reduced FAO have been reported under different pathological conditions. This discrepancy likely reflects differences in FLS subset identity, inflammatory severity, disease stage, and systemic metabolic background. Future studies should therefore move beyond measuring single lipid metabolic enzymes and instead define stage-specific and subset-specific metabolic states in FLSs. This approach may help clarify which FLS lipid programs directly drive OA progression, and which represent adaptive or secondary responses to the inflammatory joint environment.

3.3 Macrophage lipid reprogramming and M1 persistence

In the chronic low-grade inflammatory environment of OA, tissue-resident macrophages in the synovium and IPFP serve as key immune regulators of joint homeostasis and tissue damage. Their inflammatory phenotype, particularly polarization toward the pro-inflammatory M1 state or the anti-inflammatory M2 state, is closely linked to lipid metabolism. Changes in lipid uptake, synthesis, and oxidation in these cells contribute to persistent synovial inflammation and cartilage degeneration (Fig. 4b).

3.3.1 M1/M2 imbalance and inflammatory joint damage

The OA joint microenvironment contains pathogen-associated molecular patterns (PAMPs), damage-associated molecular patterns (DAMPs; for example, HMGB1 and S100 calcium-binding protein B), and extracellular matrix degradation products (Palumbo et al., 2023; Henry and O'Neill, 2025). These signals continuously activate Toll-like receptors, especially TLR4, on macrophages and promote a shift toward the classically activated M1 phenotype (Hsieh et al., 2020). Clinically, this is reflected by an increased M1/M2 ratio ($CD14^+CD80^+$/$CD14^+CD163^+$) in the OA-IPFP compared with subcutaneous adipose tissue (Ma S et al., 2021). In addition, macrophages in OA joints often show a pathogenic phenotype, such as $CD11c^+CD206^+$, characterized by increased secretion of inflammatory cytokines, including IL-1β, IL-6, and TNF-α, as well as matrix-degrading enzymes such as MMP-9 and MMP-13 (Hengtrakool et al., 2024). These changes directly worsen local tissue damage.

3.3.2 Metabolic support for pro-inflammatory M1 activation

To support pro-inflammatory activation, M1 macrophages undergo a Warburg-like metabolic shift (Batista-Gonzalez et al., 2019). This reprogramming is characterized by increased glycolysis and de novo lipogenesis (DNL), together with reduced FAO and oxidative phosphorylation (OXPHOS) (Yan and Horng, 2020).

3.3.2.1 Enhanced fatty acid synthesis sustains M1 macrophage activation

After TLR4 stimulation by DAMPs, M1 macrophages increase DNL and glycolysis, in part through upregulation of glucose transporter 1 and pyruvate kinase M2 (Henry and O'Neill, 2025). Concurrently, these cells undergo changes in the tricarboxylic acid (TCA) cycle caused by reduced activity of isocitrate dehydrogenase and succinate dehydrogenase, leading to intracellular accumulation of citrate and succinate (Langston et al., 2017). To support DNL, citrate is transported to the cytoplasm and converted into acetyl-CoA by ATP-citrate lyase (ACLY). The LXR-SREBP1 pathway then increases expression of key lipogenic enzymes, particularly ACC, ACLY and FASN (Batista-Gonzalez et al., 2019). Increased fatty acid synthesis helps maintain the M1 phenotype by providing substrates for membrane remodeling and for production of inflammatory mediators such as arachidonic acid (Rodriguez et al., 2025).

3.3.2.2 FAO suppression maintains the glycolytic inflammatory state

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In addition to enhanced fatty acid synthesis, reduced FAO is another mechanism that helps M1 macrophages maintain their phenotype and function. During pro-inflammatory activation, reduced AMPK activity decreases phosphorylation of ACC, thereby increasing its activity and promoting conversion of acetyl-CoA to malonyl-CoA (Batista-Gonzalez et al., 2019). As an inhibitor of CPT-1, malonyl-CoA limits the entry of long-chain fatty acids into mitochondria for β-oxidation (Liang, 2023). Concurrently, hypoxia-inducible factor-1α (HIF-1α) is upregulated in macrophages. In the hypoxic joint environment, reduced expression of prolyl hydroxylase (PHD) inhibits HIF-1α hydroxylation and subsequent ubiquitin-mediated degradation, leading to intracellular accumulation of HIF-1α (Zhang J et al., 2025). In addition, TCA-cycle reprogramming in M1 macrophages redirects citrate through aconitate decarboxylase 1 (ACOD1) to produce itaconate, which inhibits succinate dehydrogenase, promotes succinate accumulation, and further stabilizes HIF-1α (Henry and O'Neill, 2025). HIF-1α has been shown to suppress FAO by inhibiting CPT1A transcription (Du et al., 2017). This reduction in FAO helps preserve reliance on glycolysis and lipid synthesis, thereby sustaining the pro-inflammatory phenotype of M1 macrophages (Rodriguez et al., 2025).

3.3.2.3 Ceramide accumulation links golgi stress to oxidative injury

In addition to these broader metabolic changes, joint-resident macrophages also show organelle-specific lipid abnormalities. In OA, macrophages experience marked Golgi stress, which disrupts ceramide metabolism. The resulting intracellular accumulation of ceramides promotes excessive ROS production and further contributes to local inflammation and cartilage degeneration (Deng C et al., 2025).

3.4 Alterations in the synovial fluid (SF) lipid profile during OA progression

SF is an ultrafiltrate of plasma that helps maintain joint biomechanical homeostasis and regulates cartilage metabolism (Peters et al., 2025). In OA, systemic lipid disturbances together with local metabolic changes lead to the accumulation of pro-inflammatory phospholipids in SF (Steinmeyer, 2025). These lipid abnormalities contribute to OA progression by promoting inflammation, accelerating cartilage damage, and enhancing pain signaling (Su Z et al., 2022).

3.4.1 Stage-dependent phospholipid remodeling in synovial fluid

Phospholipids are the most abundant lipid class in SF and exhibit profound stage-dependent alterations during OA progression. Total phospholipid concentrations surge significantly. For instance, phosphatidylcholine (PC) increases 2.7-fold in early OA and 5.4-fold in late stages (Steinmeyer, 2025). Importantly, phospholipid composition also shifts toward a more pro-inflammatory profile. Levels of lysophosphatidylcholine (LPC), particularly LPC 16:0, and its derivative lysophosphatidic acid (LPA) are significantly increased. These molecules promote synovial inflammation, cartilage injury, and activation of dorsal root ganglia (DRG), thereby contributing to neuropathic joint pain (McDougall and Reid, 2022; Timm et al., 2023; Peters et al., 2025). Metabolomic analyses have also shown increased LPC (16:0) levels in OA SF, together with reduced levels of LPC(18:2) and LPC(18:3). At the same time, increased phosphatidylethanolamine (PE) levels suggest enhanced membrane breakdown associated with oxidative stress (Nieminen et al., 2022).

OA synovial fluid also shows distinct phospholipid patterns at different disease stages. Patients with OA have increased levels of phosphatidylserine (PS) and phosphatidylinositol (PI) in SF, whereas phosphatidic acid (PA) and phosphatidylglycerol (PG) levels are reduced. In early OA, several PUFA-containing PC species, including PC(32:2), PC(34:2), and PC(36:4), are significantly increased. The abundance of these PC species is negatively correlated with the degree of cartilage damage, suggesting a possible compensatory or protective role. In advanced OA, however, these initially elevated PC species decline markedly, approaching or falling below control levels, while other phospholipid classes, such as PS, continue to increase (Rocha et al., 2021). This pattern suggests a transition from an early compensatory state to later metabolic decompensation during OA progression.

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3.4.2 Fatty acid depletion and lipid-based OA phenotyping

In addition to phospholipids, the broader fatty acid composition of OA SF is also altered. One notable change is the depletion of PUFAs, particularly linoleic acid (n-6) and docosahexaenoic acid (n-3). This depletion appears to be joint-specific and is more pronounced in weight-bearing joints such as the knee than in the shoulder, suggesting a local metabolic response to chronic inflammation and mechanical stress (Mustonen et al., 2021). These fatty acids serve not only as energy substrates but also as precursors of signaling molecules involved in inflammation and tissue homeostasis. Their reduction in SF may reflect increased consumption during disease progression and may contribute to synovial inflammation and cartilage degradation (Mustonen and Nieminen, 2021).

High-resolution metabolomic studies further show that lipid dysregulation in SF, including changes in glycerophospholipids, sphingolipids, and fatty acids, is heterogeneous and may define distinct molecular phenotypes of OA. For example, inflammation-dominant OA subtypes show increased activity of pathways that generate pro-inflammatory lipid mediators such as leukotrienes. In contrast, structure-dominant OA subtypes are characterized by marked abnormalities in glycolipid metabolism associated with tissue degeneration (Carlson et al., 2019). These findings suggest that dynamic changes in SF lipid profiles not only reflect OA progression but may also help identify biologically distinct patient subgroups, thereby supporting the development of more precise therapeutic strategies.

4 Chondrocyte-intrinsic lipid dysregulation in cartilage degeneration

Articular cartilage consists of the cartilage matrix and chondrocytes, and its morphology, tissue structure, and physiological functions are maintained mainly by healthy chondrocytes (Zhao Y et al., 2025b). Recent research has shown that lipid homeostasis in chondrocytes is critical for maintaining the overall stability of cartilage (Adam et al., 2024). In OA, chondrocytes experience lipid metabolic imbalances, including abnormal lipid accumulation, excessive FAO, cholesterol metabolism disorders, and lipid peroxidation damage. These changes disrupt the energy and material metabolic homeostasis of chondrocytes, promoting phenotypic alterations, functional impairments, and extracellular matrix degradation, ultimately leading to cartilage degeneration (Table S4).

4.1 Fatty acid reprogramming drives chondrocyte dysfunction

Fatty acid metabolism is essential for cellular energy supply and biosynthesis, encompassing fatty acid uptake, de novo lipogenesis, and β-oxidation. In OA, chondrocytes undergo marked fatty acid metabolic reprogramming characterized by increased lipid synthesis, enhanced fatty acid uptake, and elevated mitochondrial FAO. These alterations promote lipid accumulation and lipotoxic stress, disturb mitochondrial and redox homeostasis, and trigger inflammatory, catabolic, and apoptotic responses, thereby accelerating cartilage degeneration (Fig. 5a).

4.1.1 Lipogenesis-driven lipid accumulation and chondrocyte senescence

A prominent feature of OA chondrocytes is the abnormal activation of de novo lipogenesis, which drives intracellular lipid deposition and contributes directly to cartilage degeneration (Liu Z et al., 2025). Several studies have shown that key lipogenic regulators are dysregulated in OA. Gong et al. (2023) reported that circular RNA Ras-responsive element-binding protein 1 (CircRREB1) is highly expressed in second-passage chondrocytes and inhibits the acetylation-dependent ubiquitination and proteasomal degradation of FASN, leading to FASN accumulation, cellular senescence, and OA progression. In parallel, sestrin 2 (SESN2), a stress-responsive regulator of lipid homeostasis, normally suppresses SREBP1 nuclear translocation by binding SREBP cleavage-activating protein (SCAP) and thereby limits the transcription of lipogenic enzymes such as ACLY and FASN. However, SESN2 is downregulated in OA chondrocytes, resulting in excessive SREBP1-mediated fatty acid synthesis, lipid accumulation, oxidative stress, apoptosis, and senescence (Liu Z et

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al., 2025).

Other signaling pathways reinforce this lipogenic phenotype. Wang et al. (2025a) showed that TGF-β and BMP signaling are both upregulated in human OA chondrocytes, and that this imbalance induces simultaneous enhancement of fatty acid synthesis and oxidation through nuclear factor I A (NFIA) upregulation. In addition, reduced expression of PPARα and its downstream target acyl-CoA thioesterase 12 (ACOT12) in OA cartilage promotes acetyl-CoA accumulation, overactivates lipid synthesis, and leads to abnormal lipid droplet deposition, matrix-degrading enzyme expression, and chondrocyte apoptosis (Park et al., 2022). Organelle dysfunction also contributes to lipid overload (Wu X et al., 2023). For example, downregulation of the peroxisomal enzyme carnitine O-acetyltransferase (CRAT) impairs oxidation of very-long-chain fatty acids, resulting in their accumulation and further promotion of chondrocyte apoptosis (Song et al., 2017).

4.1.2 Joint-specific and stress-dependent control of lipogenic remodeling

Although increased lipogenesis is a general feature of OA chondrocytes, the regulatory mechanisms may vary across joint sites and pathological contexts. In temporomandibular joint (TMJ) OA, abnormal lipogenesis appears to be driven mainly by increased PPARγ activity. Under physiological conditions, growth differentiation factor 11 (GDF11) suppresses lipogenesis by promoting SUMOylation-dependent inhibition of PPARγ transcription. Under abnormal fluid shear stress, however, GDF11 expression is reduced, leading to increased PPARγ activity and enhanced adipogenic remodeling (Wang H et al., 2022). Further work identified the histone deacetylase 3 (HDAC3)–Nrf2–GDF11 axis as a key upstream regulatory pathway in this process: abnormal biomechanical stress increases HDAC3, which inhibits Nrf2 activity, suppresses GDF11 transcription, and ultimately promotes PPARγ-driven adipogenesis (Shi et al., 2025).

Not all fatty acid metabolic alterations in OA are characterized by pathway activation. Some protective lipid metabolic regulators are reduced. For example, SCD1, the rate-limiting enzyme for monounsaturated fatty acid synthesis, is downregulated in OA cartilage (Yu C et al., 2023). Because SCD1 converts saturated fatty acids into monounsaturated fatty acids and helps maintain membrane lipid homeostasis, its loss may disturb the balance between saturated and unsaturated fatty acids, impair membrane integrity, and reduce the ability of chondrocytes to respond appropriately to mechanical and signaling stimuli (Wei G et al., 2023).

4.1.3 Excessive FAO: from metabolic compensation to matrix catabolism

In addition to increased lipogenesis, OA chondrocytes show increased FAO. This increase likely reflects both greater substrate availability due to elevated fatty acid production and upregulation of FAO-related enzymes. Wang et al. (2025a) reported increased expression of key FAO enzymes, including acetyl-CoA carboxylase alpha (ACACA) and CPT2, in human OA cartilage. Acetylomics studies further suggest that increased FAO in OA chondrocytes forms a self-amplifying metabolic loop. Under stimulation with palmitic acid and IL-1β, acetyl-CoA generated by FAO promotes acetylation of hydroxyacyl-CoA dehydrogenase trifunctional multienzyme complex subunit alpha (HADHA), particularly at lysine 728, which increases its catalytic activity and further enhances oxidative flux (Mei et al., 2025).

Although this increase in FAO may initially appear compensatory, excessive FAO is ultimately deleterious to chondrocyte function. Mei et al. (2025) showed that increased FAO inhibits AMPK activity, leading to dephosphorylation, ubiquitination, and degradation of SOX9, thereby weakening chondrogenic capacity. Meanwhile, the large amount of acetyl-CoA produced during FAO promotes catabolic gene expression through epigenetic mechanisms, including increased histone H3 lysine 27 (H3K27) acetylation, upregulation of matrix-degrading enzymes such as MMP13 and ADAMTS7, and repression of cartilage-specific genes including ACAN and COL2A1 (Mei et al., 2025). Furthermore, increased FAO leads to elevated intracellular ROS levels (Morant-Ferrando et al., 2023). Increased intracellular ROS promotes lipid peroxidation, disrupts mitochondrial membrane integrity, induces cytochrome c release, and activates caspase-3-dependent apoptosis. In addition, lipid peroxidation products such as 4-hydroxy-2-nonenal further amplify apoptotic signaling by activating JNK and MAPK pathways and inducing endoplasmic reticulum stress (Chen Z et al., 2019; Wang B et al., 2023).

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Therefore, excessive FAO contributes to OA progression through coordinated metabolic, epigenetic, oxidative, and apoptotic mechanisms.

Taken together, OA chondrocytes exhibit a broad fatty acid metabolic imbalance characterized by increased lipid synthesis and fatty acid uptake, reduced protective lipid remodeling, and excessive FAO. These alterations do not act independently. Rather, they interact to promote lipid accumulation, mitochondrial dysfunction, oxidative stress, inflammatory activation, and extracellular matrix catabolism. Thus, fatty acid metabolic reprogramming should be viewed as a central pathogenic mechanism linking metabolic stress to chondrocyte dysfunction and progressive cartilage degeneration in OA.

4.2 Cholesterol overload and oxysterol signaling in OA chondrocytes

Cholesterol is an essential component of cellular membranes and is required for membrane organization, lipid raft formation, and signal transduction. Although chondrocytes are not traditionally regarded as highly active cholesterol-metabolizing cells, accumulating evidence indicates that cholesterol homeostasis is profoundly disturbed in OA. Under OA conditions, chondrocytes show increased cholesterol uptake, increased cholesterol synthesis, impaired cholesterol efflux, and excessive production of oxysterol metabolites. These alterations promote intracellular cholesterol overload and create a metabolic environment that favors catabolic activation, senescence, and progressive cartilage degeneration (Choi et al., 2019) (Fig. 5c).

4.2.1 Coordinated defects in cholesterol influx, synthesis, efflux, and oxysterol conversion

A defining feature of cholesterol metabolic dysregulation in OA chondrocytes is the abnormal intracellular accumulation of cholesterol and its metabolites. This process reflects not an isolated defect, but a coordinated disturbance involving increased influx, sustained biosynthesis, defective efflux, and increased conversion to bioactive oxysterols.

In the inflammatory OA microenvironment, cholesterol uptake is markedly increased. Choi et al. (2019) showed that stimulation with IL-1β and TNF-α upregulates oxidized LOX1 in chondrocytes, thereby facilitating cholesterol influx. At the same time, CH25H and CYP7B1 are also elevated, promoting the generation of 25-hydroxycholesterol (25-HC) and 7α,25-dihydroxycholesterol (7α,25-HC). These oxysterols activate the nuclear receptor retinoic acid receptor-related orphan receptor alpha (RORα), which increases the transcription of catabolic mediators such as MMP3, MMP13, and ADAMTS5 while suppressing matrix-associated regulators including SOX9. Subsequent studies confirmed that the upregulation of CH25H and CYP7B1 is mediated by the downregulation of microRNA-10a-3p expression in OA chondrocytes (Li X et al., 2021).

Alongside increased uptake and oxysterol generation, cholesterol biosynthesis is also increased in OA chondrocytes. Elevated TGF-β within the OA joint microenvironment activates SREBP-2 through the integrin subunit alpha V (ITGAV)/PI3K/Akt pathway, thereby inducing expression of HMG-CoA reductase (HMGCR), a key enzyme governing cholesterol synthesis. This anabolic shift not only promotes intracellular cholesterol accumulation but is also associated with increased expression of MMP-13, linking sterol biosynthesis more directly to cartilage catabolism (Kostopoulou et al., 2012).

Cholesterol retention is further aggravated by defective efflux. LXR is a major regulator of intracellular lipid homeostasis and normally promotes the expression of efflux transporters such as ATP-binding cassette transporter A1 (ABCA1) and ATP-binding cassette transporter G1 (ABCG1) (Sun MM and Beier, 2020). In human OA chondrocytes, however, LXR expression is reduced, resulting in decreased expression of these transporters and diminished cholesterol export capacity (Collins-Racie et al., 2009). This impaired efflux reinforces cholesterol accumulation and sustains the abnormal lipid state of OA chondrocytes.

Additional regulatory molecules further shape this cholesterol-overloaded phenotype. Superoxide dismutase 3 (SOD3) appears to play a protective role by suppressing C/EBPβ nuclear translocation, thereby limiting APOE transcriptional activity and cholesterol uptake. During OA progression in post-traumatic OA models, SOD3 expression gradually declines, suggesting loss of this protective brake (Wu Y et al., 2025b). Apolipoprotein A-I binding protein (AIBP), another factor involved in cholesterol efflux, is likewise down-

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regulated in OA models, which may further restrict cholesterol clearance (Lee G et al., 2025). Furthermore, Kostopoulou et al. (2015) discovered that miR-33a expression is upregulated in OA chondrocytes compared to normal chondrocytes. In OA chondrocytes, miR-33a regulates cholesterol metabolism by simultaneously increasing cholesterol synthesis through the TGF-β1/Akt/SREBP-2 pathway and suppressing efflux via direct targeting of the ABCA1 3′UTR to suppress its expression, indirectly reducing apolipoprotein A1 (ApoA1) levels and impairing cholesterol efflux. A recent study also identified ABCA6 as a novel pathogenic gene in OA. Its deletion inhibits cholesterol efflux, leading to cellular senescence and cartilage degeneration (Wang Y et al., 2025b). Taken together, these findings indicate that cholesterol accumulation in OA chondrocytes is driven by an integrated regulatory network rather than by a single abnormal pathway.

4.2.2 Cholesterol overload as a driver of catabolism and senescence-associated inflammation

The pathological significance of cholesterol dysregulation in OA extends beyond lipid accumulation. Excess cholesterol and its metabolites actively reshape chondrocyte behavior and accelerate cartilage degeneration through catabolic and senescence-associated mechanisms.

During OA progression, the abnormal accumulation of cholesterol and its metabolites in chondrocytes significantly accelerates cartilage degeneration. As described earlier, intracellular cholesterol in chondrocytes can be metabolized via the CH25H–CYP7B1 axis to produce oxysterols such as 25-HC and 7α,25-HC. These compounds activate the nuclear receptor RORα, upregulating the expression of matrix-degrading enzymes like MMP3 and MMP13, which directly leads to cartilage structural destruction.

Abnormal cholesterol accumulation in OA chondrocytes is also closely linked to cellular senescence and inflammation. Research by Roh et al. (2023) indicates that senescent chondrocytes maintain the SASP by accumulating cholesterol in lysosomes under OA pathological condition. This process is regulated by the GATA binding protein 4 (GATA4)-NF-κB axis, which upregulates ABCA1 expression and directs its localization to the lysosomal membrane. ABCA1, as a cholesterol transporter, facilitates cholesterol aggregation in lysosomes, forming microdomains rich in mTORC1 scaffold complexes. This continuous activation of the mTORC1 signaling pathway sustains the expression of the SASP and drives senescence-associated inflammation, further promoting cartilage degeneration. These findings suggest that cholesterol dysregulation not only initiates catabolic signaling, but also stabilizes a self-perpetuating inflammatory state within OA chondrocytes.

Overall, cholesterol metabolic dysregulation in OA chondrocytes is characterized by a convergence of increased uptake and synthesis, impaired efflux, and excessive oxysterol production. These alterations collectively drive intracellular cholesterol overload and promote a pathogenic switch toward matrix degradation, cellular senescence, and persistent inflammatory activation. Cholesterol metabolism should therefore be viewed not merely as a secondary metabolic disturbance in OA, but as an active contributor to chondrocyte dysfunction and progressive cartilage degeneration.

4.3 Phospholipid remodeling, membrane instability, and ferroptotic injury

Phospholipids are fundamental components of cellular membranes and are essential for maintaining membrane fluidity, structural integrity, intracellular signaling, and lipid mediator generation. In OA, phospholipid homeostasis in chondrocytes is profoundly disturbed. This disturbance is reflected not only in altered phospholipid composition and reduced fatty acid unsaturation, but also in excessive phospholipid degradation mediated by increased phospholipase activity. Together, these changes destabilize membrane structure, disrupt membrane-associated signaling, and promote the release of free fatty acids and inflammatory lipid mediators, thereby contributing to oxidative stress, inflammatory activation, and cartilage matrix degradation (Fig. 5b).

Multi-omics studies have confirmed that chondrocytes from different joint sites exhibit significant alterations in phospholipid metabolic profiles. Lipidomic analysis revealed elevated levels of ceramides and dihydroceramides in hip OA chondrocytes compared to normal chondrocytes, while cholesterol esters, diacylglycerols, triacylglycerols, sphingomyelins, and certain glycolipids were generally reduced (Zhou et al., 2025). Gene-level evidence further supports the existence of this abnormal phospholipid remodeling. In knee OA

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chondrocytes, UDP-glucose ceramide glucosyltransferase (UGCG) and extended synaptotagmin 1 (ESYT1) have been identified as key lipid metabolism-related hub genes (Li H et al., 2024b). UGCG, which encodes UDP-glucose ceramide glucosyltransferase, catalyzes the first committed step in most sphingoglycolipid biosynthetic pathways (Sabatini et al., 2000). Its downregulation is likely to suppress sphingoglycolipid synthesis, promote ceramide accumulation, disrupt lipid raft organization, and thereby increase apoptosis, inflammation, and matrix degradation. In contrast, ESYT1 is upregulated in OA chondrocytes. As a phospholipid transport protein that mediates lipid exchange between the endoplasmic reticulum and mitochondria, ESYT1 is important for membrane lipid homeostasis across organelles. Its overexpression promotes mitochondrial phospholipid accumulation and is associated with mitochondrial dysfunction, indicating that phospholipid imbalance in OA extends beyond the plasma membrane and affects organelle integrity as well (Steinmeyer, 2025).

In parallel with changes in phospholipid composition, OA chondrocytes also show enhanced phospholipid degradation. A consistent observation across studies is the abnormal upregulation of phospholipases, particularly phospholipase A2 (PLA2) family members, which directly couple membrane phospholipid turnover to inflammatory mediator production. Increased expression of secretory phospholipase A2 (sPLA2) has been observed in knee OA cartilage (Wei Y et al., 2021b), and PLA2G5 activity is also significantly elevated in OA chondrocytes, where it catalyzes the conversion of phosphatidylcholine into lysophosphatidylcholine (Zhai et al., 2019). These enzymes hydrolyze the sn-2 ester bond of glycerophospholipids, thereby releasing free fatty acids such as arachidonic acid and generating lysophospholipid species with pro-inflammatory potential (Burke and Dennis, 2009; Zhai et al., 2019).

In addition, phospholipid metabolism also affects the fate of chondrocytes through another type of programmed cell death, namely ferroptosis. Ferroptosis has emerged as an important form of regulated cell death in OA and provides a mechanistic link between lipid metabolic dysregulation and chondrocyte loss (Xia et al., 2025). Unlike apoptosis or necrosis, ferroptosis is characterized by the iron-dependent accumulation of lipid peroxides, particularly in phospholipids enriched with PUFAs. In OA chondrocytes, disturbances in fatty acid metabolism and phospholipid remodeling create a cellular environment that strongly favors lipid peroxidation. When intracellular Fe^{2+} accumulates and promotes ROS generation through the Fenton reaction, PUFA-containing phospholipids become vulnerable to oxidative damage, resulting in membrane injury and ferroptosis (Jiang X et al., 2021b).

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5 Discussion

Lipid metabolic abnormalities contribute to OA through interactions among systemic metabolic disturbance, local joint inflammation, and chondrocyte dysfunction. Obesity, unhealthy dietary patterns, and gut microbiota dysbiosis disrupt systemic lipid homeostasis and increase joint susceptibility to inflammatory injury. Within the joint, the IPFP, synovial macrophages, FLSs, and synovial fluid further amplify lipid-related inflammation, thereby accelerating cartilage degeneration. The chondrocytes in OA may experience lipid metabolic imbalances, including abnormal lipid accumulation, excessive FAO, cholesterol metabolism disorders, and lipid peroxidation damage. Current therapeutic strategies include lifestyle intervention, nutritional regulation, microbiota modulation, and joint-specific metabolic remodeling. However, their clinical translation remains limited by disease heterogeneity and insufficient biomarker validation.

5.1 Systemic-to-local lipid–inflammation cascade in OA

Systemic lipid metabolic disorders provide an important pathological background for OA, but their contribution to joint degeneration should not be viewed as a simple one-way process. Obesity, unhealthy dietary patterns, and gut microbiota dysbiosis may create a systemic metabolic and inflammatory state that increases the vulnerability of joint tissues to lipotoxic injury (Wang T et al., 2013; Dabke et al., 2019; Min et al., 2023; Sampath et al., 2023; Karim et al., 2025; Kim et al., 2025). However, systemic metabolic abnormalities alone are unlikely to fully explain OA progression. The joint is not a passive recipient of circulating lipids; rather, it

functions as a semi-independent local environment in which systemic lipid signals can be selectively amplified, reshaped, or uncoupled from circulating lipid profiles.

Within this framework, local lipid remodeling may serve as a key intermediate step between systemic metabolic stress and cartilage degeneration. The IPFP, synovium, FLSs, macrophages, and synovial fluid do not merely reflect systemic dyslipidemia; they also actively convert metabolic stress into persistent inflammation, impaired lubrication, altered cell-to-cell communication, and cartilage-destructive signaling (Hsieh et al., 2020; Cao X et al., 2022b; Damerau et al., 2022; Palumbo et al., 2023; Tang et al., 2024). This may help explain why systemic lipid abnormalities and local joint pathology are often related but do not always fully correspond. In some patients, systemic dyslipidemia may act as the dominant upstream driver, whereas in others, local metabolic remodeling within the joint may become self-sustaining and continue to promote OA progression even when systemic metabolic changes are less evident.

Chondrocytes represent the final cellular target of this lipid–inflammation cascade, and their damage should be understood as the result of both external stress and intrinsic metabolic vulnerability. Systemic lipid imbalance and local inflammatory lipid remodeling can impose sustained stress on chondrocytes, while intrinsic defects in chondrocyte lipid handling may further reduce their ability to maintain matrix homeostasis (Choi et al., 2019; Liu Z et al., 2025; Mei et al., 2025). Therefore, cartilage degeneration may occur not only because harmful lipid signals reach the joint but also because chondrocytes lose the ability to buffer, adapt to, or resolve lipid metabolic stress.

Systemic lipid metabolic disorders, local lipid remodeling, and chondrocyte metabolic dysfunction do not occur in isolation. Instead, they form a cascade in which systemic lipid imbalance promotes a harmful local joint environment, which then drives chondrocyte degeneration and OA progression. Although this pathway is important in OA development, it is not universally applicable. Some OA cases may originate from intrinsic lipid dysregulation within local joint cells, such as chondrocytes (Wang Y et al., 2025b), whereas others may be triggered by direct stimuli, such as abnormal mechanical loading in temporomandibular joint OA (Wang H et al., 2022), without detectable systemic metabolic abnormalities. These observations highlight the heterogeneity of OA pathogenesis and suggest that lipid metabolism-related OA should be viewed as a disease spectrum shaped by systemic metabolic stress, local joint remodeling, and intrinsic chondrocyte vulnerability.

5.2 Current clinical applications and future treatment strategies

As lipid metabolism has emerged as an important contributor to OA progression, lipid-targeted interventions have received increasing attention. However, current evidence does not support a simple therapeutic model in which systemic lipid lowering directly translates into joint protection. Available strategies can be broadly divided into three categories: lifestyle and nutritional interventions with relatively stronger clinical evidence, microbiota-related interventions with early translational potential, and local or cellular metabolic remodeling strategies that remain largely preclinical.

5.2.1 Lifestyle and nutritional interventions: clinical evidence and uncertainty

At the systemic level, dietary intervention and exercise are the most clinically relevant approaches for reducing lipid-related metabolic risk in OA. Reduced-energy diets and weight management have shown beneficial effects on pain, physical function, and body weight in patients with OA, suggesting that improvement of the systemic metabolic environment may indirectly reduce joint burden and inflammation (Messier et al., 2018). Evidence for specific lipid-oriented dietary patterns is less consistent. The Mediterranean diet is biologically plausible because it is rich in anti-inflammatory nutrients and may improve the balance between n-3 and n-6 fatty acids. However, current evidence remains insufficient to establish the Mediterranean diet as an independent disease-modifying intervention, and further well-designed clinical and mechanistic studies are needed to clarify its effects on OA progression and lipid-mediated joint inflammation (Sadeghi et al., 2022; Veronese N et al., 2024). Similarly, omega-3 fatty acids have been widely studied for their anti-inflammatory and lipid-modulating properties, but clinical findings remain mixed. A randomized clinical trial comparing low- and

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high-dose fish oil in knee OA reported greater improvements in pain and function in the low-dose group than in the high-dose group (Hill et al., 2016). More recently, a randomized clinical trial reported that 2 g/day krill oil did not improve knee pain over 24 weeks compared with placebo in patients with knee OA and effusion-synovitis (Laslett et al., 2024). These findings suggest that the efficacy of lipid-targeted nutritional interventions may depend on dose, formulation, baseline metabolic status, inflammatory phenotype, and patient selection, rather than representing a universal treatment effect.

5.2.2 Exercise as a metabolic and biomechanical therapy

Exercise is another clinically important intervention because it can improve both joint function and systemic metabolism. Animal studies have shown that aerobic exercise reduces serum triglyceride and total cholesterol levels in high-fat and high-sugar diet-induced obese OA models and alleviates cartilage and subchondral bone damage caused by metabolic abnormalities (Abughazaleh et al., 2024). Clinical metabolomic evidence also supports the metabolic effects of lifestyle intervention. In the IDEA trial, 18 months of diet, exercise, or combined diet and exercise intervention altered the serum metabolome of individuals with knee OA, with changes involving lipid, amino acid, carbohydrate, vitamin, and matrix metabolism (Welhaven et al., 2024). These findings indicate that exercise may not only reduce mechanical load but also improve the systemic metabolic environment. Mechanistic studies further suggest that swimming may protect cartilage by increasing superoxide dismutase 3 expression, reducing oxidative stress, and limiting APOE-related lipid accumulation in chondrocytes (Wu Y et al., 2025b). Therefore, exercise should be considered both a metabolic intervention and a biomechanical therapy.

5.2.3 Microbiota modulation along the gut–lipid–joint axis

Microbiota-related interventions may provide another approach to systemic lipid and immune regulation, but their clinical translation in OA remains at an early stage. Probiotics and postbiotics, such as butyrate, may improve intestinal barrier function, regulate serum lipid metabolites, and suppress low-grade inflammation associated with obesity or high-fat diets (Basak et al., 2023). These effects are relevant to the gut–lipid–joint axis. However, most microbiota-based evidence in OA remains mechanistic or exploratory, and large randomized trials are needed to determine which microbial taxa, metabolites, and patient subgroups are most responsive to these interventions.

5.2.4 Joint-specific metabolic reprogramming: preclinical opportunities

At the local cellular level, lipid-targeted therapy is shifting from systemic metabolic correction toward joint-specific metabolic remodeling. In macrophages, Fu et al. (2025) identified salt-inducible kinase 1 (SIK1) as an immune-related gene in OA and developed a 5-aminoimidazole-4-carboxamide ribonucleotide (AICAR)-loaded nanoliposome hydrogel for intra-articular delivery. This approach suppressed macrophage glycolysis, promoted phospholipid synthesis, inhibited M1 polarization, and slowed cartilage degradation. Early correction of mitochondrial dysfunction in synovial macrophages may also promote a shift toward an anti-inflammatory phenotype (Zhang L et al., 2022). In FLSs, L-carnitine activated the AMPK-ACC-CPT1 pathway, promoted fatty acid β-oxidation, reduced lipid accumulation, improved mitochondrial function, and suppressed synovial inflammation (Liao T et al., 2023). Cyasterone similarly restored lipid metabolic balance in synovial cells by activating AMPK signaling, enhancing autophagic flux, and reducing inflammatory FLS activation (Liu D et al., 2026). These studies highlight the therapeutic potential of targeting cell-specific lipid metabolic programs, although most strategies require further validation in clinically relevant models and human trials.

5.2.5 Restoring chondrocyte lipid homeostasis: fatty acid, cholesterol, and ferroptosis targets

Chondrocyte-directed lipid regulation is another promising but largely preclinical therapeutic direction. Strategies targeting FAO, cholesterol metabolism, and lipid peroxidation may help restore chondrocyte home-

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ostasis. Inhibition of CPT1A reduced oxidative stress, improved mitochondrial function, and activated mitophagy, thereby delaying chondrocyte senescence (Jiang N et al., 2022). Natural compounds such as arctiin may regulate cholesterol metabolism through the CH25H-CYP7B1-RORα axis and reduce inflammation-associated matrix degradation (Mai et al., 2025). Local simvastatin release has been reported to delay cartilage degeneration by inhibiting the mevalonate pathway in chondrocytes (Robby et al., 2025), whereas enhanced cholesterol efflux through fenofibrate treatment or AIBP overexpression may mitigate OA progression (Lee G et al., 2025). In addition, inhibition of lipid peroxidation-related ferroptosis through targets such as ACSL4 may provide a potential strategy for preventing chondrocyte death (Zou et al., 2025). Nevertheless, clinical evidence for lipid-targeted drugs remains limited. For example, although statins have theoretical anti-inflammatory and cholesterol-lowering benefits, population-based studies and meta-analyses have produced inconsistent results, and some analyses do not support a clear protective effect against OA progression (Wang J et al., 2020a). This discrepancy may reflect differences between systemic lipid lowering and intra-articular lipid remodeling.

Overall, lipid-targeted OA therapies should be developed according to clear levels of evidence. Lifestyle interventions, especially weight control and exercise, currently have the strongest clinical relevance because they improve both symptoms and systemic metabolic status. Nutritional lipid interventions, including omega-3 supplementation and Mediterranean-style dietary patterns, are biologically plausible but require better patient stratification and more consistent trial evidence. Microbiota modulation and local metabolic reprogramming of macrophages, FLSs, and chondrocytes offer mechanistically attractive strategies, but they remain largely preclinical. Future therapeutic development should therefore combine clinical metabolic phenotyping, lipidomic biomarkers, joint-specific delivery systems, and patient selection based on OA subtype, inflammatory status, and systemic metabolic background. This approach may help transform lipid metabolism regulation from a broad intervention concept into a precision treatment strategy for OA.

5.3 Evidence gaps and translational challenges in lipid-metabolism OA research

Despite growing recognition of the central role of lipid metabolism in OA pathogenesis, current research has several important limitations. Most studies still examine isolated aspects of lipid dysregulation, such as systemic metabolic changes caused by obesity or lipid metabolic remodeling in specific joint cell types. However, OA progression is likely driven by interactions among systemic metabolism, the local joint environment, and intracellular regulatory networks. This issue is further complicated by OA heterogeneity. Metabolic OA, post-traumatic OA, aging-related OA, and mechanically driven OA may not share the same lipid metabolic patterns or pathological drivers. Individual factors, including age, sex, menopausal status, obesity, and metabolic comorbidities, may also influence lipid distribution, adipokine secretion, inflammatory responses, and joint vulnerability. Future studies should therefore combine clinical stratification with metabolic phenotyping to clarify how lipid-related mechanisms differ among OA populations.

Current studies on glucose and lipid metabolism in OA remain largely descriptive. Many omics findings have not been sufficiently linked to specific pathological processes. Alterations in glycerophospholipid, sphingolipid, fatty acid, and energy metabolism may reflect different pathological states of the joint rather than merely serving as molecular signatures. For example, these metabolic changes may be associated with synovial inflammation, impaired lubrication, mitochondrial dysfunction, cartilage matrix degradation, pain sensitization, and chondrocyte death. Synovial fluid metabolomic phenotyping has shown that distinct metabolic profiles are associated with inflammatory, oxidative stress-related, and structural deterioration-related OA states (Carlson et al., 2019). Serum and synovial fluid lipidomic profiles have also been linked to obesity-associated OA severity, synovitis, adipokine changes, and wound repair responses (Wu CL et al., 2017). These findings suggest that lipidomic alterations may serve as indicators of ongoing pathological processes within the joint, rather than merely representing downstream consequences of OA.

Lipid profiles may also have value for OA staging, subtyping, and precision treatment, although this potential remains insufficiently validated. Targeted phospholipidomic analysis of synovial fluid can distinguish

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non-OA controls from early- and late-stage OA and may further identify distinct subtypes within early OA (Rocha et al., 2021). Serum lipidomic evidence also suggests that phospholipids and sphingolipids may change during early-stage OA, supporting their potential value for disease monitoring before obvious radiographic progression (Eichner et al., 2025). This is clinically important because OA diagnosis still relies mainly on symptoms and imaging changes, which often appear only after substantial joint damage has occurred. If validated in large longitudinal cohorts, lipid biomarkers may help identify early metabolic OA, distinguish lipid-dominant from inflammation-dominant phenotypes, monitor disease progression, and select patients who are more likely to benefit from lipid-targeted interventions (Zhai, 2021; Mobasheri et al., 2023).

Important translational barriers also remain. Systemic and local lipid metabolism may be partly uncoupled, as synovial fluid lipid profiles do not always correspond to plasma lipid profiles (de Visser et al., 2018). This suggests that circulating lipids may not fully reflect metabolic abnormalities within the joint. Although basic and clinical studies suggest potential chondroprotective effects of lipid-related interventions, such as omega-3 fatty acids, clinical results remain inconclusive (Hill et al., 2016; Zhang L et al., 2022). Future lipid-targeted therapies should therefore move beyond systemic lipid lowering and place greater emphasis on joint-specific metabolic remodeling, local delivery, and patient stratification. Combination strategies involving dietary intervention, microbiota modulation, exercise, and cellular metabolic remodeling may also be needed. Large-scale longitudinal and multicenter studies that integrate lipidomics with other omics approaches and clinical phenotyping will be essential for translating lipid profiles into practical tools for OA staging, subtyping, prognosis prediction, and individualized treatment.

Summary

Abnormalities in lipid metabolism play a central role in the pathogenesis of OA, involving multiple pathological processes at the systemic, local, and cellular levels. Studies have shown that systemic lipid disorders lead to low-grade inflammation through adipokines and dyslipidemia. In the local joint tissues, such as the IPFP and FLS, metabolic reprogramming occurs, driving the transformation into pro-inflammatory phenotypes that disrupt cartilage homeostasis. Furthermore, within chondrocytes, fatty acid imbalance, cholesterol accumulation, and phospholipid peroxidation directly contribute to mitochondrial dysfunction and ferroptosis, resulting in matrix degradation. Based on these findings, future therapeutic strategies for OA should focus on targeting lipid metabolism at multiple levels throughout the disease progression.

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Author contributions

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Declaration of competing interest

The authors declare that they have no competing financial interests/ personal relationships that may appear to influence the work reported in this paper.

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Declaration on the use of generative AI tool

Generative AI tool (ChatGPT) was used only for linguistic polishing, grammar checking and reference formatting during the revision of this manuscript. The AI tool was not involved in the research design, data collection, data analysis, interpretation of results, or drafting of core arguments and conclusions. The generative AI tool is not designated as an author of this article. All authors have reviewed, revised and approved the entire manuscript, and take full responsibility for all contents of this work.

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Supplementary information

Tables S1-S4

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Figure Legends

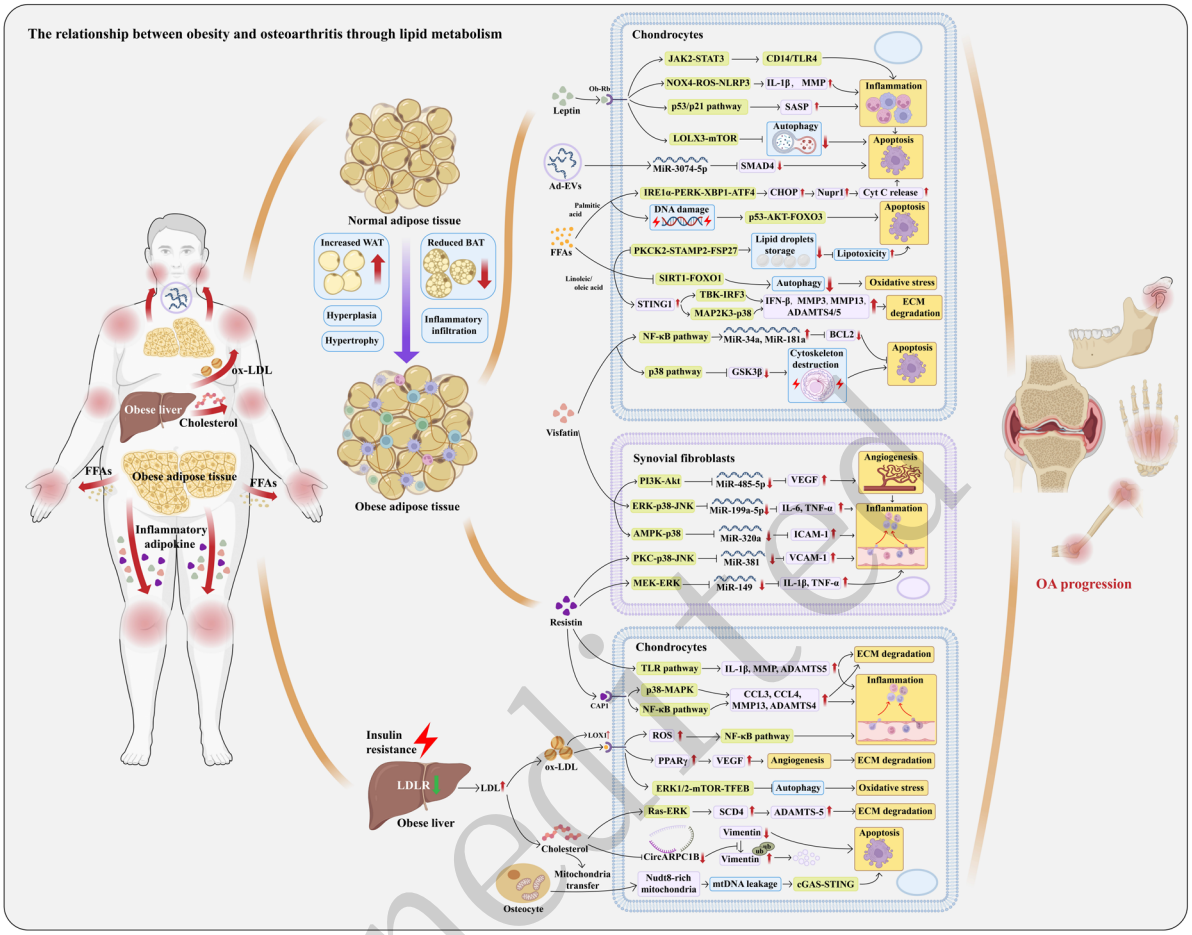


Fig.1 Mechanistic links between obesity and the onset and progression of OA. Obesity promotes OA through systemic lipid metabolic disturbances and chronic low-grade inflammation. In obesity, excessive adipose tissue functions as an active endocrine organ and releases increased levels of adipokines, FFAs, and inflammatory mediators, leading to disrupted lipid homeostasis, insulin resistance, oxidative stress, and persistent inflammation. These alterations are associated with abnormal circulating levels of free cholesterol and LDL, which may enter the joint microenvironment and contribute to synovial inflammation, chondrocyte dysfunction, and cartilage matrix imbalance. Mechanistically, visfatin and resistin induce chondrolysis and synovial inflammation via the NF-κB and MAPK pathways, respectively. Saturated fatty acids promote apoptosis and matrix degradation through endoplasmic reticulum stress, autophagy inhibition, and STING pathway activation, whereas ox-LDL and cholesterol accelerate joint degeneration through LOX-1, Ras/ERK, and mitochondrial dysfunction-related pathways. In addition, adipose tissue-derived extracellular vesicles, including Ad-EVs carrying miR-3074-5p, may mediate remote intercellular communication and further drive OA progression. Created with https://www.biorender.com.

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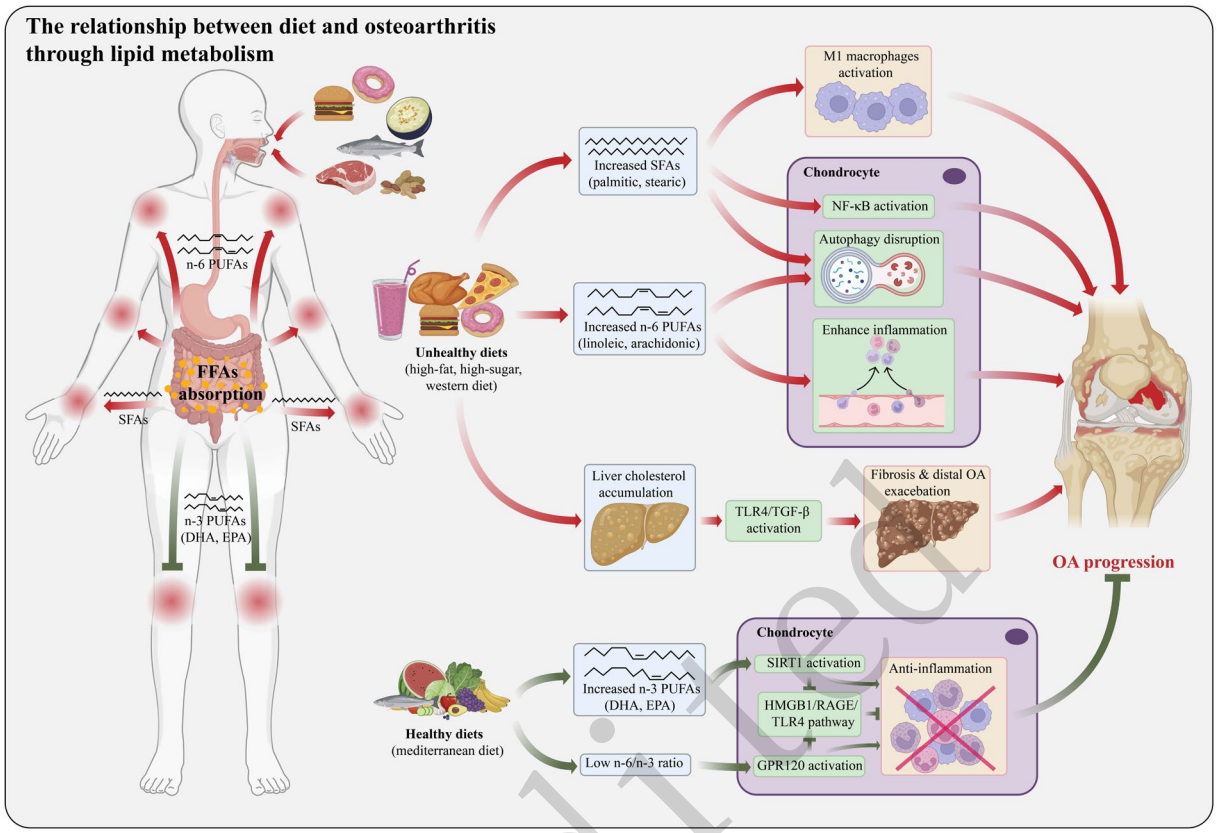


Fig.2 Role and mechanisms of dietary patterns in OA development. Unhealthy dietary patterns, especially high-fat and high-sugar diets, promote OA development by disturbing lipid metabolism and enhancing systemic and local inflammatory responses. Elevated levels of circulating free fatty acids and triglycerides may infiltrate the joint microenvironment, where they contribute to cartilage damage and synovial inflammation, thereby accelerating OA progression. Different fatty acid species have distinct effects on OA. Saturated fatty acids are predominantly pro-inflammatory and exacerbate cartilage injury, whereas the effects of unsaturated fatty acids vary by subtype. Among them, n-6 PUFAs may facilitate OA progression, while n-3 PUFAs, including DHA and EPA, exert protective effects on cartilage. Moreover, the dietary n-6/n-3 PUFA ratio appears to influence OA severity, with lower ratios being associated with reduced symptoms. High-sugar diets may also aggravate OA by driving lipid metabolic abnormalities through a pathological process characterized by hepatic free cholesterol accumulation, inflammation, and fibrosis. Created with https://www.biorender.com.

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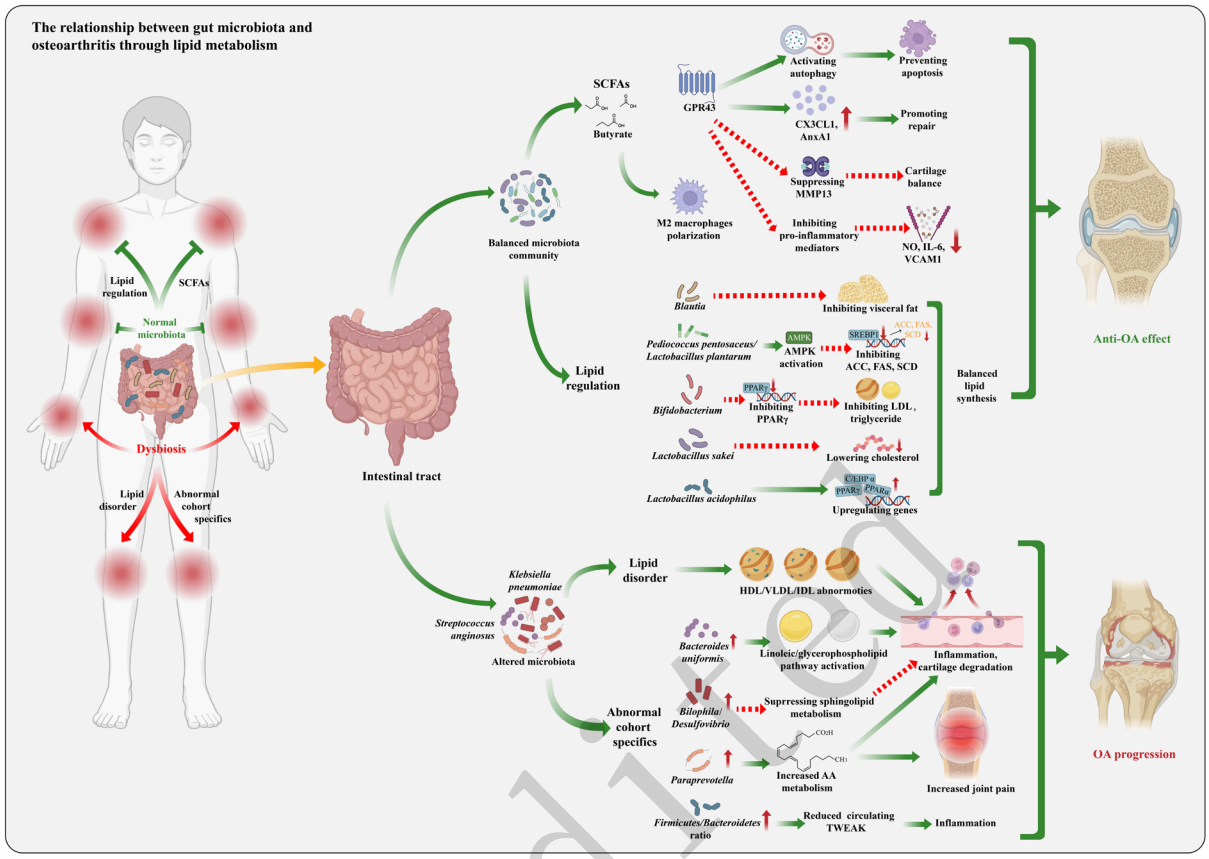


Fig.3 Microbiota–lipid–joint axis in OA. The gut microbiota modulates OA progression through SCFA production and regulation of lipid metabolism. Under normal conditions, microbiota-derived SCFAs, especially butyrate, protect cartilage by enhancing gut barrier function, suppressing inflammatory pathways, reducing catabolic mediators, restoring autophagy, and preserving extracellular matrix homeostasis. Beneficial microbes also support systemic lipid balance and anti-inflammatory immune responses. In contrast, gut dysbiosis promotes OA by disrupting circulating lipid profiles and driving pro-inflammatory metabolic changes, including abnormalities in cholesterol, triglyceride, sphingolipid, linoleic acid, and glycerophospholipid metabolism, thereby contributing to synovial inflammation, cartilage degeneration, and persistent pain. Created with https://www.biorender.com.

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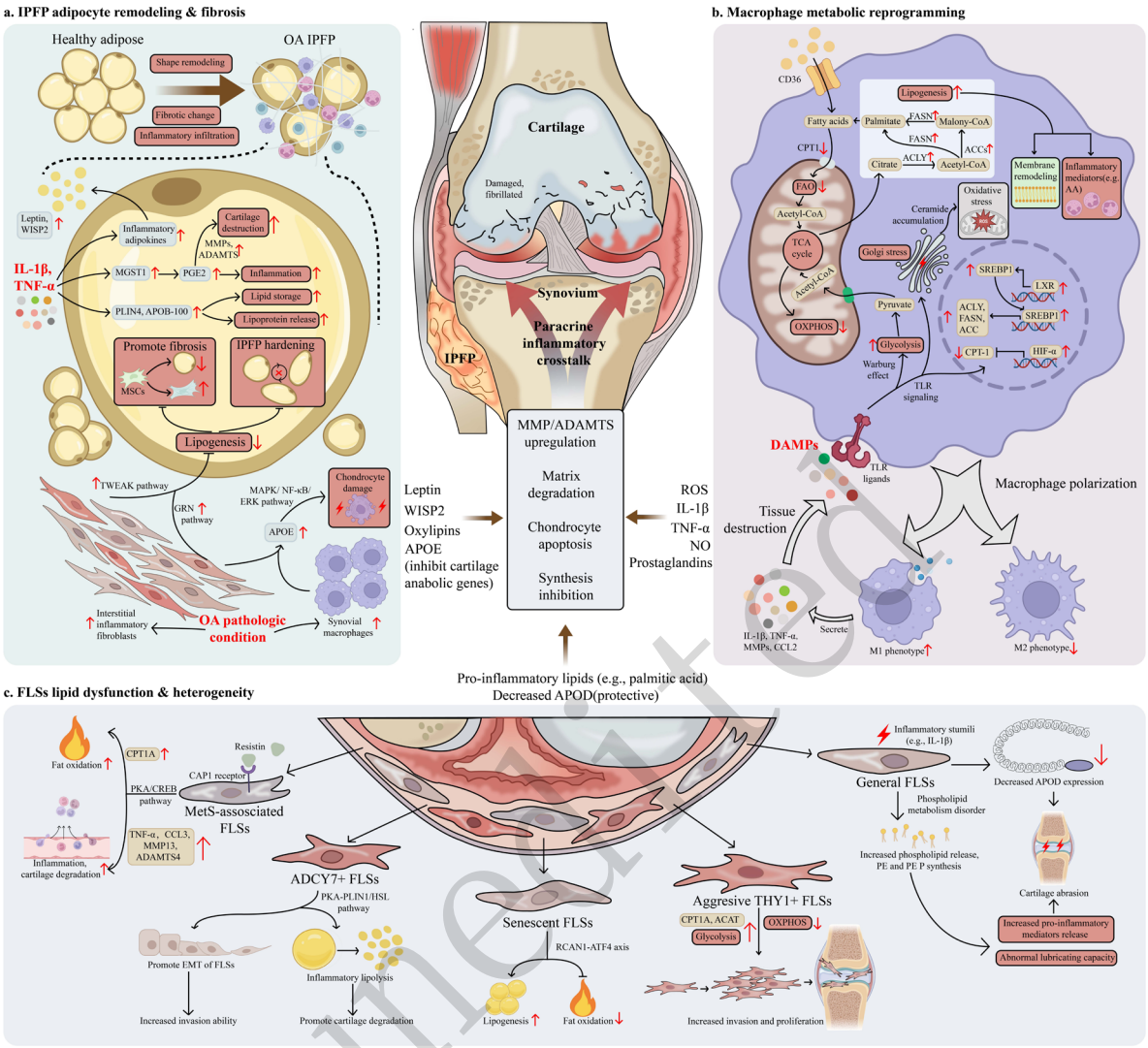


Fig. 4 Impact of local tissue lipid metabolism alterations on cartilage degeneration in OA. (a) In OA, the IPFP undergoes inflammatory, fibrotic, and metabolic remodeling, characterized by immune cell infiltration, impaired adipogenesis, reduced fatty acid synthesis, accumulation of pro-inflammatory lipids, and oxidative imbalance. These changes promote the release of adipokines and inflammatory mediators, thereby driving cartilage inflammation, matrix degradation, and apoptosis.

(b) OA-associated macrophages exhibit disrupted M1/M2 polarization accompanied by lipid metabolic reprogramming. M1 macrophages show reduced FAO and enhanced FAS, supported by increased glycolysis, metabolite accumulation, and activation of lipid synthesis regulators, while suppression of CPT-1-mediated FAO helps maintain the pro-inflammatory state.

(c) OA-FLSs show marked heterogeneity and lipid metabolic dysregulation, including increased glycolysis, altered cholesterol and fatty acid metabolism, increased lipolysis, and phospholipid imbalance. These changes promote synovial inflammation, invasiveness, impaired lubrication, and pathological crosstalk with chondrocytes, ultimately accelerating cartilage degeneration.

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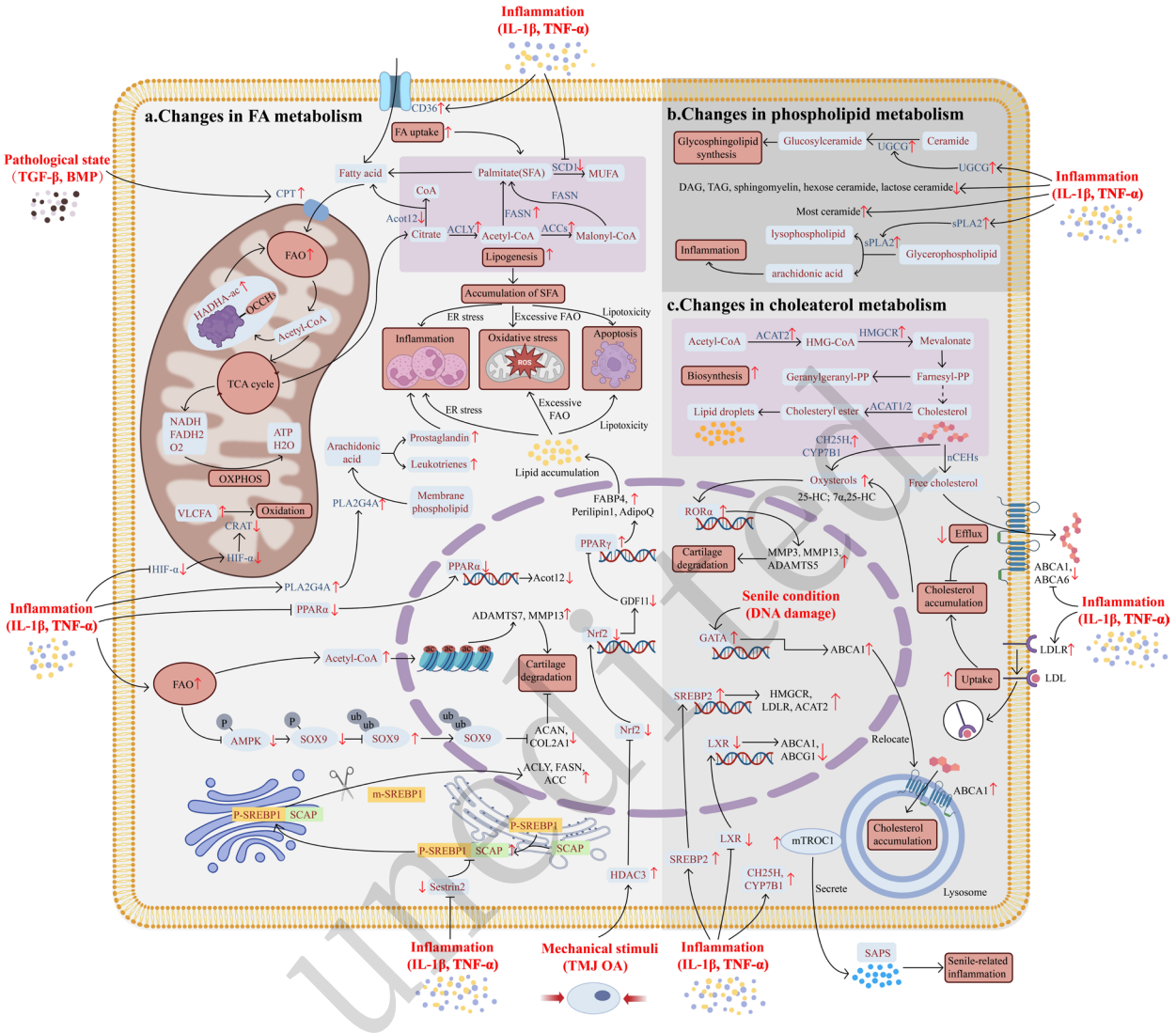


Fig. 5 Altered lipid metabolism in chondrocytes promotes cartilage degeneration in osteoarthritis.

(a) In OA, chondrocytes undergo marked fatty acid metabolic reprogramming, characterized by increased fatty acid synthesis and uptake, reduced protective lipid remodeling, and excessive fatty acid β-oxidation. These changes promote lipid accumulation, oxidative stress, mitochondrial dysfunction, inflammatory and catabolic activation, and apoptosis, thereby accelerating cartilage degeneration.

(b) Phospholipid metabolism is also altered in OA chondrocytes, as reflected by abnormal phospholipid remodeling, ceramide accumulation, disrupted lipid transport, and increased phospholipase-mediated degradation. These abnormalities impair membrane and organelle integrity, promote inflammatory lipid mediator release, and exacerbate matrix degradation and cartilage destruction.

(c) Cholesterol homeostasis is profoundly disrupted in OA chondrocytes, with increased choles-

terol uptake and synthesis, impaired efflux, and excessive oxysterol production. Cholesterol overload enhances catabolic signaling, cellular senescence, and persistent inflammation, thereby contributing to progressive cartilage matrix degradation. Created with https://www.biorender.com.

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