

Research Article

Autophagy-mediated chondrocyte homeostasis: Research progress of hydrogel carriers in the treatment of osteoarthritis

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Abstract

Osteoarthritis (OA) is a common chronic degenerative joint disease in older adults, characterized by joint pain, stiffness, swelling, and functional limitation. Increasing evidence suggests that OA progression is closely associated with disruption of the joint microenvironment, chondrocyte inflammation, oxidative stress, cellular senescence, and impaired autophagy. The PI3K-Akt-mTOR pathway is a key signaling axis that regulates cellular metabolism, survival, and autophagy, and may contribute to chondrocyte autophagy inhibition, extracellular matrix degradation, and amplification of inflammatory responses. This review summarizes the pathological basis of age-related OA, chondrocyte autophagy dysfunction, PI3K-Akt-mTOR pathway regulation, and hydrogel-based local delivery strategies. We focus on hydrogel material categories, fabrication approaches, deliverable cargos, release mechanisms, and targeted, lubricating, and stimuli-responsive designs, and further discuss current evidence for EGFR inhibitors, PI3K inhibitors, mTOR inhibitors, dual PI3K/mTOR inhibitors, natural compounds, and active ingredients of traditional Chinese medicine. Hydrogels may prolong intra-articular drug retention, enable sustained release, and reduce systemic exposure, thereby providing a local delivery platform for pathway-targeted agents. However, hydrogel delivery does not replace the need for rigorous validation of drug efficacy and safety. Most available evidence remains based on cell experiments, small animal models, or non-OA disease models; long-term drug safety, standardized autophagic flux assessment, age-appropriate OA models, and translational evaluation of hydrogel systems require further investigation.

Keywords: PI3K-Akt-mTOR pathway, osteoarthritis, autophagy, hydrogel, older adults

INTRODUCTION

Disease burden and therapeutic challenges of age-related osteoarthritis

Osteoarthritis (OA) is a heterogeneous, degenerative joint disease characterized primarily by articular cartilage degeneration, osteophyte formation, and joint dysfunction. It remains one of the leading global causes of pain and disability, imposing a substantial socioeconomic burden and significantly compromising patients' quality of life^[1-2]. In China, the prevalence of OA among the elderly represents a pressing concern, with rates continuing to rise in parallel with the accelerating process of population aging^[3]. The hallmark pathological features of OA include articular cartilage degeneration and destruction, osteophyte formation, synovitis, and joint space narrowing. During OA progression, the hyaline cartilage, synovial capsule, and subchondral bone are progressively affected^[4-6]. The thinning, fissuring, and eventual erosion of cartilage subsequently precipitate joint pain, functional limitation, and persistent inflammatory responses. The disease predominantly manifests in weight-bearing or highly mobile joints, including the knee, hip, spine, ankle, and hand joints^[7-11].

Current clinical management of OA primarily focuses on the objectives of pain relief, functional improvement, and the deceleration of disease progression^[12-13]. Standard therapeutic modalities include the administration of non-steroidal anti-inflammatory drugs (NSAIDs) for analgesia, intra-articular injections (e.g., hyaluronic acid) to enhance joint lubrication, exercise therapy, weight management, and surgical intervention for end-stage cases^[14-15]. While oral NSAIDs exert anti-inflammatory and analgesic effects by inhibiting prostaglandin synthesis, their efficacy is largely limited to symptomatic relief, with negligible capacity to reverse established cartilage degeneration and structural joint damage^[16]. Furthermore, exercise therapy and weight management have demonstrated therapeutic benefits for OA. Studies indicate that exercise therapy, regardless of intensity, alleviates symptoms associated with knee OA^[17], whereas obesity represents a definitive, modifiable risk factor for the disease^[2]. Nevertheless, these conventional approaches primarily prioritize symptom control and functional restoration, offering limited disease-modifying effects on underlying

pathological processes such as cartilage matrix degradation, synovitis, and dysregulation of the joint microenvironment [Figure 1].

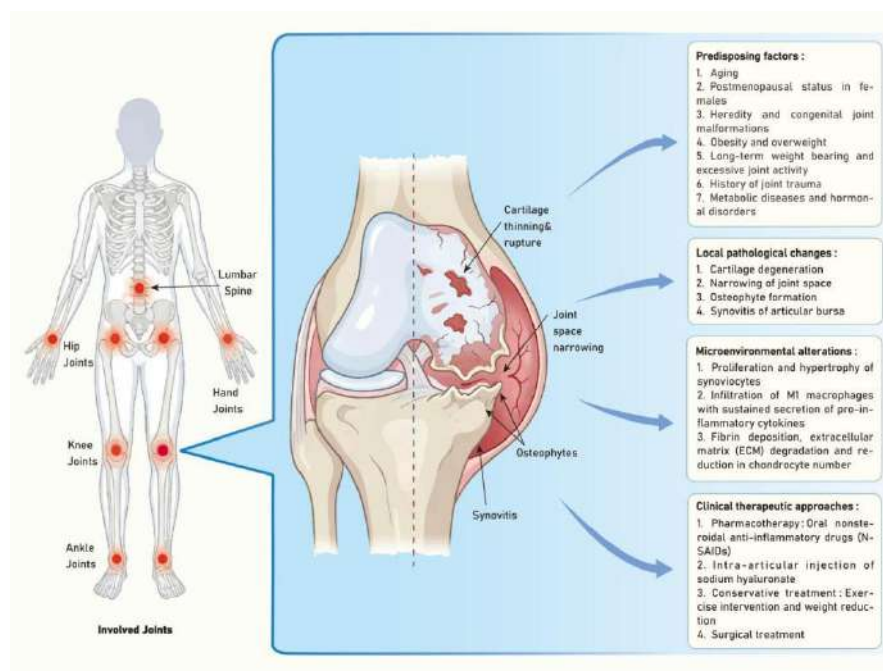


Figure 1. Risk factors, potential influencing factors, and their interaction mechanisms in osteoarthritis.

Necessity of local delivery therapies

Elderly patients with OA frequently present with multiple comorbidities, such as cardiovascular diseases, gastrointestinal disorders, renal function decline, and glucose metabolism abnormalities, coupled with long-term, multi-drug combination regimens. Therefore, the safety and tolerability of systemic pharmacological treatments are of particular concern in the elderly population. Although NSAIDs alleviate pain and inflammation by inhibiting the production of inflammatory mediators, their distribution lacks specific targeting to diseased joints. Long-term application may increase the risk of gastrointestinal, cardiovascular, and renal adverse reactions, thereby limiting their sustained use in elderly OA patients^[18]. Furthermore, while intra-articular injections such as sodium hyaluronate can improve joint lubrication and pain symptoms to a certain extent, they predominantly offer short- or medium-term symptomatic relief, with limited disease-modifying effects on pathological processes such as cartilage matrix

degradation, synovitis, and subchondral bone remodeling. For patients with end-stage disease, surgery can ameliorate pain and functional impairment, but the associated trauma, perioperative risks, and postoperative rehabilitation requirements render it poorly tolerated by some advanced-age or comorbid patients.

Against this backdrop, intra-articular (IA) administration provides a crucial rationale for local intervention in elderly OA. Compared with systemic administration, IA delivery enables therapeutic agents to act more directly on the affected joints, enhancing the bioavailability of drugs at the target site while reducing systemic exposure, systemic side effects, and treatment costs^[19]. This characteristic is particularly suitable for elderly OA patients who require long-term management and face high risks from systemic medication. However, conventional intra-articular injections of free drugs still exhibit distinct limitations: drugs are susceptible to synovial fluid dilution, lymphatic clearance, and joint motion shear forces, leading to a short local retention time, large fluctuations in drug concentration, and limited effective action duration, potentially necessitating repeated injections to maintain efficacy^[20].

Therefore, local treatment for elderly OA requires not only “injecting drugs into the joint cavity”, but also constructing delivery systems capable of prolonging local drug retention, achieving controlled release, and reducing the risk of repeated administration. Based on this, the key issue in local delivery therapy has shifted from merely increasing intra-articular drug concentration to achieving long-term, safe, and controlled release of drugs within the diseased joint.

Focus of this review

In recent years, the pathogenesis of OA has been increasingly recognized as being closely associated with joint microenvironment imbalance, chondrocyte inflammation, oxidative stress, cellular senescence, and autophagy dysfunction. Among them, the PI3K-Akt-mTOR pathway, serving as a vital signaling axis regulating cellular metabolism, survival, and autophagy, may be implicated in processes such as

chondrocyte autophagy inhibition, matrix metabolism imbalance, and inflammatory response amplification^[21-22]. Local intervention targeting this pathway is expected to provide novel research insights for the treatment of elderly OA.

Based on the above background, this review centers on the main thread of “pathological microenvironment of elderly OA—chondrocyte autophagy dysfunction—PI3K-Akt-mTOR pathway regulation—hydrogel-based local delivery strategies”. First, we summarize the pathological basis and autophagy dysfunction of elderly OA, followed by elaborating the role of the PI3K-Akt-mTOR pathway in chondrocyte autophagy regulation. Next, we discuss the material types, fabrication approaches, deliverable cargos, and responsive designs of hydrogels as platforms for intra-articular local delivery and cartilage functional replacement. Finally, we summarize the research status and limitations of intervention strategies such as EGFR inhibitors, PI3K inhibitors, mTOR inhibitors, dual PI3K/mTOR inhibitors, natural compounds, and active ingredients of traditional Chinese medicine, thereby providing a reference for the subsequent development of safer, more durable, and more precise local therapeutic regimens for elderly OA.

PATHOLOGICAL BASIS AND AUTOPHAGY DYSFUNCTION IN AGE-RELATED OSTEOARTHRITIS

OA is not simply caused by mechanical wear of articular cartilage, but is a whole-joint organ disease involving articular cartilage, synovium, subchondral bone, and surrounding tissues. Its occurrence and development are accompanied by multiple pathological alterations such as chronic low-grade inflammation, oxidative stress, mitochondrial dysfunction, cellular senescence, and intercellular communication abnormalities, which jointly disrupt intra-articular homeostasis and form a persistent degenerative microenvironment^[23-24]. In elderly OA, the adaptive capacity of chondrocytes to inflammation and oxidative stress declines, and cellular homeostasis maintenance mechanisms such as autophagy are impaired, making it difficult to timely clear damaged organelles and abnormal proteins, which further aggravates cartilage

matrix degradation and joint structural destruction. Therefore, understanding the relationship among inflammation, oxidative stress, cellular senescence, and autophagy dysfunction in elderly OA serves as an important foundation for elucidating the interventional value of the PI3K-Akt-mTOR pathway [Figure 2].

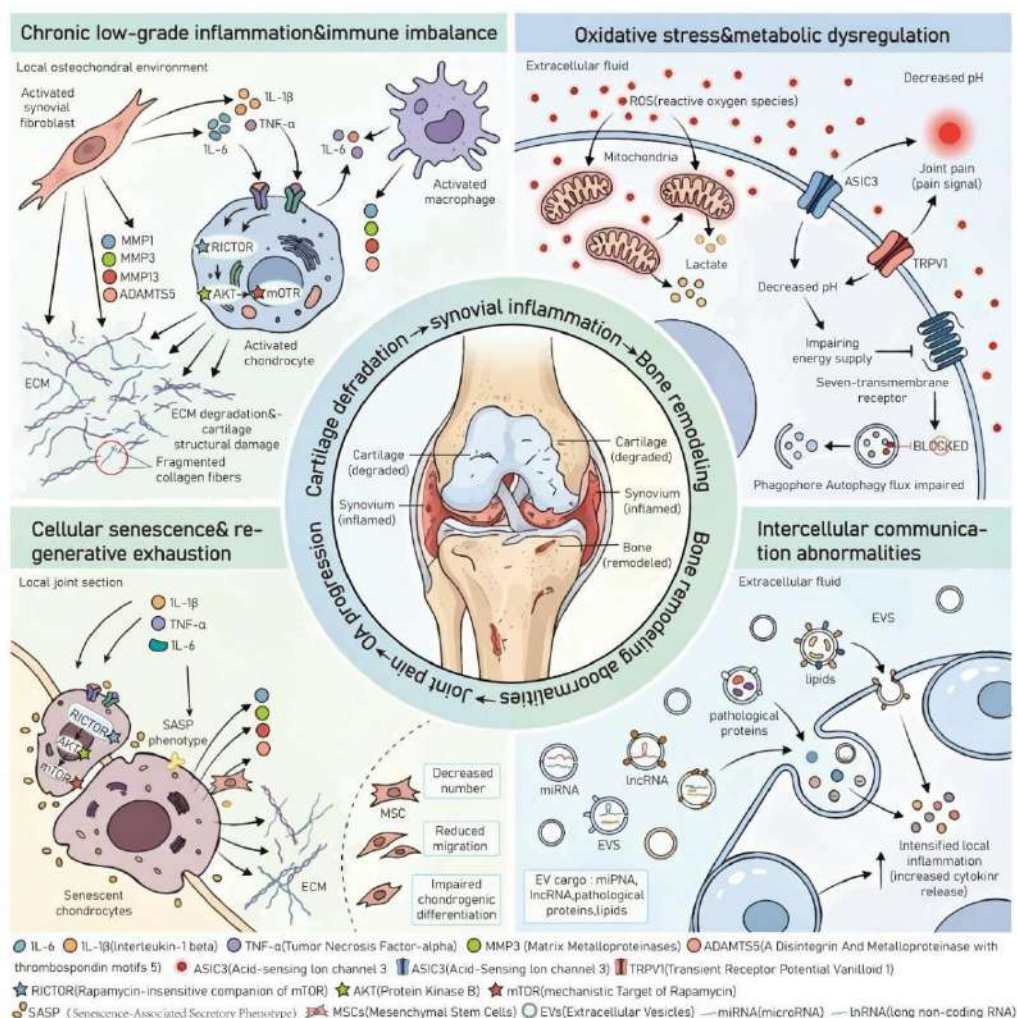


Figure 2. Pathological basis of osteoarthritis regarding inflammation, oxidative stress, cellular senescence, and autophagy dysfunction.

Chronic low-grade inflammation and cartilage matrix degradation

OA was traditionally considered a “non-inflammatory” degenerative joint disease; however, accumulating evidence indicates that chronic low-grade inflammation permeates the entire process of OA occurrence and development^[25-26]. Within the OA joint microenvironment, synovial cells, chondrocytes, and infiltrating immune

cells—particularly macrophages—can be persistently activated by aberrant mechanical stimuli, damage-associated molecular patterns, and matrix degradation products, subsequently releasing large amounts of pro-inflammatory cytokines and catabolism-related mediators. Elevated levels of pro-inflammatory cytokines such as IL-1 β , IL-6, and TNF- α , as well as matrix-degrading enzymes such as MMP13 and ADAMTS5, serve as critical manifestations of the inflammatory microenvironment and cartilage matrix destruction in OA^[27].

Inflammatory cytokines such as IL-1 β and TNF- α are frequently overexpressed in the synovial fluid, synovium, cartilage, and subchondral bone tissues of patients with OA^[28-29]. These inflammatory cytokines can activate signaling pathways such as NF- κ B, p38 MAPK, and c-Jun N-terminal kinase, promoting the expression of various cytokines, adhesion molecules, inflammatory mediators, and catabolic enzymes, thereby disrupting the metabolic homeostasis between chondrocytes and the extracellular matrix^[30-33]. Among them, enzymes such as MMP1, MMP3, MMP13, and ADAMTS5 can directly degrade cartilage matrix components including type II collagen and aggrecan, leading to decreased cartilage tissue elasticity, impaired structural integrity, and compromised joint function.

More importantly, the inflammatory response not only directly promotes cartilage matrix degradation but also further accelerates OA progression by impairing chondrocyte autophagy. Sustained stimulation by IL-1 β and TNF- α can induce elevated RICTOR expression and further activate the AKT/mTOR signaling pathway, thereby inhibiting the chondrocyte autophagy process^[34]. Following autophagy suppression, the capacity of chondrocytes to clear damaged organelles, abnormal proteins, and inflammation-associated damage components declines, leading to the further amplification of oxidative stress and inflammatory responses, thereby forming a vicious cycle of “inflammation-autophagy impairment-matrix degradation”. Therefore, chronic low-grade inflammation is not only a major driving factor of OA cartilage degeneration

but also a critical pathological link connecting the PI3K-Akt-mTOR pathway, autophagy dysfunction, and cartilage matrix destruction.

Oxidative stress, mitochondrial damage, and cellular senescence

In addition to chronic low-grade inflammation, oxidative stress and cellular metabolic disorders are also important factors driving the progression of age-related OA. The overproduction of reactive oxygen species (ROS) can directly damage chondrocytes and the extracellular matrix, acting as signaling molecules to further amplify inflammatory responses and disrupt the redox homeostasis within chondrocytes^[35-37]. In the OA microenvironment, the energy metabolism pattern of chondrocytes can gradually shift from relatively steady oxidative phosphorylation to enhanced glycolysis, leading to the accumulation of metabolites such as lactate^[38]. The local acidic environment can not only activate pain-related receptors such as ASIC3 and TRPV1 to aggravate joint pain, but also induce chondrocyte stress responses, disrupt autophagic flux, and promote cellular senescence and apoptosis^[39-40].

Mitochondria are the core organelles for ROS generation and cellular energy metabolism regulation, as well as vital targets prone to damage in age-related OA. The sustained accumulation of inflammatory cytokines and ROS can lead to decreased mitochondrial membrane potential, reduced ATP generation, and mitochondrial dysfunction. Concurrently, the diminished autophagy and mitophagy capacities of senescent chondrocytes make it difficult to clear damaged mitochondria in a timely manner, further exacerbating ROS generation and cellular stress responses, thereby forming a positive feedback loop of “mitochondrial damage-oxidative stress-autophagy impairment”^[41]. This process not only promotes chondrocyte apoptosis and a decline in matrix synthesis capacity but also enhances the expression of pro-inflammatory cytokines and matrix-degrading enzymes, thereby accelerating cartilage degeneration.

Cellular senescence is an important pathological foundation distinguishing age-related OA from general degenerative injuries. With increasing age, chondrocytes, synovial

cells, and other intra-articular cells gradually exhibit a senescence phenotype, manifested as cell cycle arrest, decreased stress tolerance, and attenuated repair capacity. Senescent cells in the OA microenvironment frequently present a senescence-associated secretory phenotype (SASP), continuously releasing pro-inflammatory and pro-catabolic factors such as IL-6, IL-1 β , TNF- α , chemokines, and matrix-degrading enzymes^[26,28]. These SASP factors can not only directly destroy the surrounding cartilage matrix but also further impair the autophagy function of adjacent normal cells, maintaining a local state of chronic inflammation and catabolism^[42].

Furthermore, mesenchymal stem cells (MSCs) possessing tissue repair potential in age-related OA may also exhibit functional decline such as reduced numbers, decreased migration capacity, and impaired chondrogenic differentiation, leading to an insufficient repair response of joint tissues following injury^[43]. Therefore, oxidative stress, mitochondrial damage, and cellular senescence are not mutually independent pathological events, but jointly constitute an important foundation for persistent cartilage degeneration in age-related OA. Their combined result is the attenuation of the chondrocyte's ability to maintain homeostasis and clear damaged components, providing a pathological background for subsequent autophagy dysfunction and aberrant activation of the PI3K-Akt-mTOR pathway.

Intercellular communication is another important component of the OA microenvironment. Extracellular vesicles, particularly exosomes, can transfer miRNAs, lncRNAs, proteins, and lipids among chondrocytes, synovial cells, subchondral bone cells, and immune cells, thereby influencing cell proliferation, apoptosis, inflammatory responses, and autophagy^[44-45]. In this review, extracellular vesicles are considered primarily as mediators of disease-microenvironment communication rather than as a core hydrogel cargo, thereby maintaining the focus on PI3K-Akt-mTOR-directed pharmacological delivery.

Chondrocyte autophagy dysfunction

Autophagy is an essential protective mechanism for chondrocytes to maintain internal environment homeostasis, primarily helping cells adapt to complex microenvironments such as low nutrition, hypoxia, and mechanical loads by clearing damaged organelles, misfolded proteins, and metabolic waste. Due to the absence of blood vessels, nerves, and lymphatic structures in mature articular cartilage, chondrocytes reside in a relatively hypoxic and nutrient-deprived environment for extended periods, and their ability to maintain cellular homeostasis and matrix metabolic balance is highly dependent on cellular protection mechanisms such as autophagy. Therefore, when autophagy function declines, the tolerance of chondrocytes to inflammatory stimuli, oxidative stress, and mechanical injury decreases, rendering them susceptible to apoptosis, senescence, and attenuated matrix synthesis capacity.

In age-related OA, chondrocyte autophagy dysfunction is generally not an isolated event, but the result of the combined action of chronic inflammation, oxidative stress, mitochondrial damage, and cellular senescence. Pro-inflammatory cytokines such as IL-1 β and TNF- α can inhibit the chondrocyte autophagy process by inducing RICTOR expression and activating the AKT/mTOR signaling pathway^[34]. Concurrently, ROS overaccumulation and the local acidic metabolic environment can interfere with normal autophagic flux, promoting cellular stress, senescence, and apoptosis^[39-40]. When mitochondrial damage persists and mitophagy is insufficient, damaged mitochondria cannot be cleared in a timely manner, further increasing ROS production and amplifying the inflammatory response, thereby forming a positive feedback loop of “oxidative stress-mitochondrial damage-autophagy impairment”^[41]. In addition, SASP factors released by senescent cells can also continuously maintain the local pro-inflammatory and pro-catabolic microenvironment, further impairing the autophagy function of adjacent cells^[42].

Chondrocyte autophagy dysfunction directly affects extracellular matrix homeostasis. On the one hand, insufficient autophagy reduces the capacity of chondrocytes to clear damaged components and maintain energy metabolism balance, leading to decreased

cellular activity and reduced matrix synthesis; on the other hand, autophagy impairment can enhance the sustained activation of inflammation-related signals such as NF- κ B and MAPK, promoting elevated expression of matrix-degrading enzymes such as MMP13 and ADAMTS5, thereby accelerating the degradation of type II collagen and aggrecan. Consequently, cartilage tissue progressively exhibits matrix loss, structural integrity destruction, and mechanical property decline, driving the further development of OA.

It should be noted that autophagy is not simply “the stronger, the better”. At different disease stages and in different cellular states, autophagy may be protective or may reflect a compensatory response following cellular stress or injury. Previous studies suggest a complex relationship between autophagy and chondrocyte fate. In early OA, moderate enhancement of autophagy can help clear damaged organelles, alleviate inflammation and oxidative stress, thereby combating chondrocyte apoptosis^[46]; however, when autophagy is severely impaired or aberrantly activated, it may also be associated with cell death modalities such as autophagy-dependent ferroptosis^[47]. Furthermore, the relationship between autophagy and cellular senescence is not unidirectional, and certain autophagy abnormalities in OA can be related to SASP formation and the chondrocyte senescence phenotype^[48-49]. Chondrocyte autophagy is equally important for cartilage development, joint formation, and matrix homeostasis; relevant models show that impaired autophagic flux or aberrant autophagy-related signaling can affect chondrocyte maturation, cartilage matrix formation, and joint homeostasis maintenance^[50-51]. Therefore, when evaluating the chondrocyte autophagy state, one should not solely rely on the expression changes of a single indicator such as LC3, Beclin-1, ATG5, or p62, but should comprehensively judge by combining autophagic flux, lysosomal function, and functional outcomes such as cell survival, matrix synthesis, and inflammation levels. For age-related OA, the truly therapeutically meaningful goal is not simply to elevate a specific autophagy marker, but to restore a moderate, effective, and sustainable autophagic homeostasis of chondrocytes within the diseased joint microenvironment.

In summary, chronic inflammation, oxidative stress, mitochondrial damage, and cellular senescence jointly weaken chondrocyte autophagy function in age-related OA, while reduced autophagy further aggravates inflammation amplification, cellular damage, and cartilage matrix degradation. As a vital signaling axis regulating cellular metabolism, survival, and autophagy, the PI3K-Akt-mTOR pathway occupies a key intersection position in the aforementioned pathological network. Therefore, elucidating the role of this pathway in chondrocyte autophagy regulation is an important prerequisite for understanding hydrogel-delivered drug interventions in age-related OA.

REGULATORY ROLE OF THE PI3K-Akt-mTOR PATHWAY IN CHONDROCYTE AUTOPHAGY

The PI3K-Akt-mTOR pathway is an essential signaling pathway regulating cell growth, proliferation, metabolism, survival, and autophagy. During the occurrence and development of OA, chondrocytes are chronically stimulated by inflammatory cytokines, oxidative stress, abnormal mechanical loads, and metabolic disorders, resulting in a progressive decline in their cellular homeostasis maintenance capacity. As a critical pathway connecting external stimuli with intracellular metabolic, autophagic, and matrix metabolic responses, the PI3K-Akt-mTOR signaling axis plays an important role in chondrocyte injury, inflammation amplification, extracellular matrix degradation, and autophagy dysfunction. Therefore, elucidating the role of this pathway in chondrocyte autophagy regulation serves as the basis for understanding subsequent drug interventions and hydrogel-based local delivery strategies.

Overview of the PI3K-Akt-mTOR pathway

The PI3K-Akt-mTOR pathway can be activated by growth factors, insulin, and signals related to certain receptor tyrosine kinases or G protein-coupled receptors. Activated PI3K phosphorylates PIP2 (phosphatidylinositol 4,5-bisphosphate) to generate PIP3 (phosphatidylinositol 3,4,5-trisphosphate), whereas PTEN antagonizes this signaling by dephosphorylating PIP3 back to PIP2. PIP3 then serves as a membrane-associated second messenger that facilitates AKT activation; activated AKT phosphorylates and

inhibits TSC2, thereby promoting Rheb-dependent mTORC1 activation. Activated mTORC1 suppresses the ULK1 complex and consequently inhibits autophagy initiation^[52].

Under conditions of nutrient deprivation (e.g., amino acid deficiency), energy insufficiency (increased AMP/ATP ratio), or stress, mTORC1 activity is suppressed, releasing the inhibition on the ULK1 complex and thereby initiating autophagy ^[53]. Under starvation and malnutrition conditions, LKB1 binds to upstream kinase-active AMPK to act on the mTORC1 complex, causing the complex to lose activity, and the ULK1 complex dissociates from the mTORC1 complex to form pre-autophagosomal vesicles (the initial form of autophagosomes) through a series of complex mechanisms; concurrently, to induce autophagy, the PI3KC3 complex I recruits the ATG12L1 complex and LC3-I to form lipidated LC3-II, which possesses lipophilic properties and can insert into the vesicle membrane. LC3-II carries ubiquitinated P62 and waste to the vicinity of the autophagic vesicles, and under the action of WIPI2, the vesicles continuously grow to form autophagosomes. Autophagosomes mature under the action of Pacer and UVRAG, and the matured autophagosomes fuse with lysosomes to form autolysosomes, digesting and decomposing intracellular metabolic waste. mTOR is primarily composed of two complexes, mTORC1 and mTORC2, among which mTORC1 is most directly related to nutrient sensing and autophagy regulation, whereas mTORC2 is more involved in the regulation of Akt activation, the cytoskeleton, and cell survival [Figure 3].

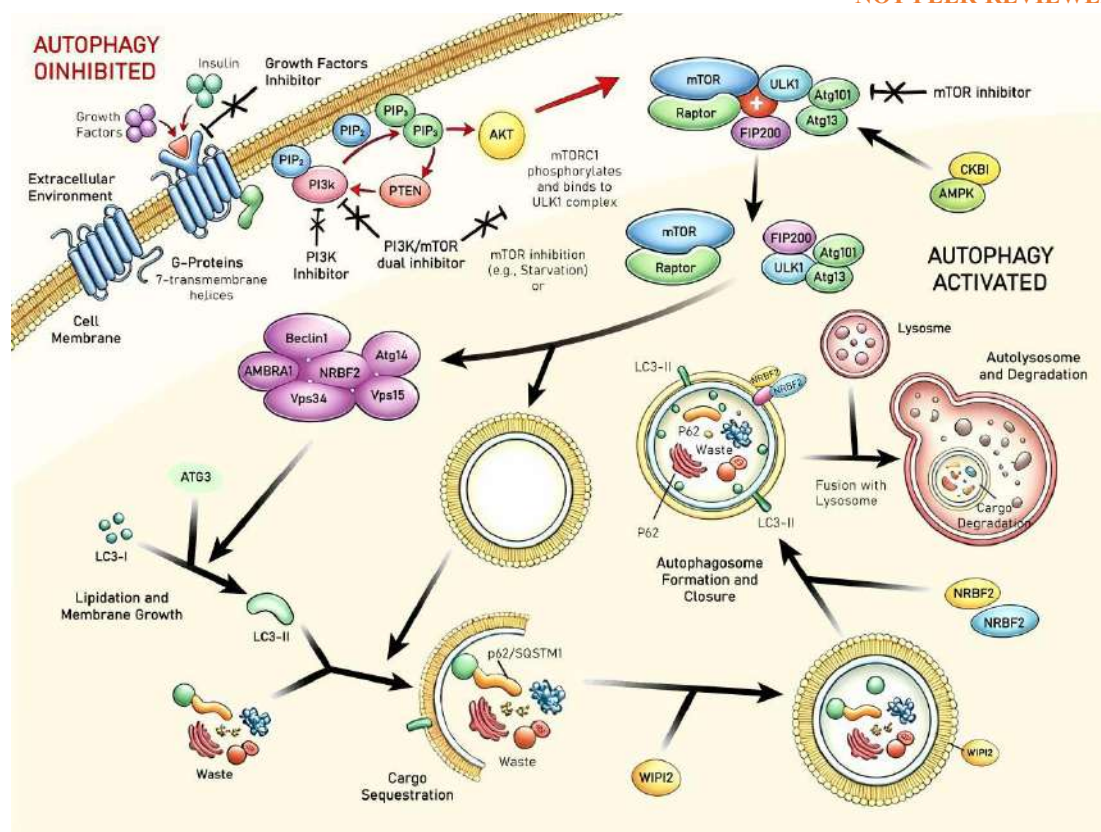


Figure 3. Under physiological conditions, autophagy occurs via intrinsic regulation and contributes to normal cellular processes. During the development of OA, the autophagic system is significantly suppressed, impeding the timely clearance of intracellular metabolic waste. Therapeutic agents, including growth factor inhibitors, PI3K inhibitors, dual PI3K/mTOR inhibitors, mTOR inhibitors, specific natural compounds, and certain traditional Chinese medicine ingredients, can effectively modulate the PI3K/Akt/mTOR signaling pathway and reactivate autophagy.

The PI3K-Akt-mTOR pathway and autophagy inhibition

Autophagy serves as a crucial protective mechanism for chondrocytes to clear damaged organelles, abnormal proteins, and metabolic waste. In canonical autophagy regulation, mTORC1 acts as a primary suppressor of autophagy initiation. Persistent activation of PI3K-Akt signaling further enhances mTORC1 activity, thereby inhibiting ULK1 complex-mediated autophagy and diminishing cellular capacity to clear damage-induced stimuli^[52-53]. Conversely, inhibition of mTORC1 activity reactivates

the autophagic process, enhancing chondrocyte capacity to clear damaged mitochondria and abnormal proteins, thus contributing to the restoration of cellular homeostasis.

Within the OA microenvironment, inflammatory cytokines, oxidative stress, and metabolic dysregulation can disrupt the equilibrium between the PI3K-Akt-mTOR pathway and autophagy. Pro-inflammatory cytokines, such as IL-1 β and TNF- α , not only directly promote cartilage matrix degradation but also induce RICTOR expression, leading to the activation of the AKT/mTOR signaling pathway and subsequent suppression of chondrocyte autophagy^[34]. Following autophagy inhibition, the impaired clearance of damaged mitochondria and oxidative damage components leads to the further accumulation of ROS, which in turn upregulates inflammatory signaling and matrix-degrading enzymes, creating a vicious cycle of “inflammation-autophagy impairment-matrix degradation”.

Studies on the mTOR inhibitor rapamycin provide supporting evidence for this mechanism. As a classic mTOR inhibitor, rapamycin primarily suppresses mTORC1 activity via binding to FKBP12, thereby lifting the mTORC1-mediated inhibition of autophagy^[54-55]. Relevant studies have shown that mTORC1 inhibition correlates with increased levels of autophagy markers (e.g., LC3B, ATG5) and decreased MMP13 expression^[56]; however, these findings require further validation via autophagic flux assays and long-term functional assessments, rather than relying solely on the upregulation of individual markers to indicate full restoration of autophagic function.

The role of this pathway in OA

The role of the PI3K-Akt-mTOR pathway in OA extends beyond autophagy regulation and is intimately linked to chondrocyte inflammation, apoptosis, metabolic reprogramming, and extracellular matrix (ECM) metabolism^[22]. Persistent exposure to IL-1 β , TNF- α , ROS, and abnormal mechanical stimulation within the OA joint microenvironment modulates PI3K-Akt-mTOR signaling through various upstream pathways, thereby altering chondrocyte responses to injurious stimuli. Recent research

suggests that GPRC5B participates in regulating OA cartilage homeostasis via AKT-mTOR-autophagy signaling; its deletion exacerbates DMM-induced OA phenotypes, whereas its overexpression attenuates cartilage degeneration and regulates the balance between matrix synthesis and catabolism^[12]. These findings imply that the AKT-mTOR-autophagy axis is not merely a downstream response to cartilage injury but may constitute a critical mechanistic link for certain protective therapeutic targets. Aberrant activation of this pathway, leading to mTOR-mediated autophagy inhibition, may result in the accumulation of damaged organelles and abnormal proteins, rendering chondrocytes more susceptible to apoptosis, senescence, and reduced matrix synthesis capacity.

Moreover, the PI3K-Akt-mTOR pathway may modulate the expression of molecules associated with cartilage matrix degradation. Under inflammatory stimuli, chondrocytes and synovial cells produce catabolic factors such as MMP13 and ADAMTS5, which facilitate the degradation of type II collagen and aggrecan. Impaired autophagy leads to the persistent amplification of cellular stress and inflammatory signals, further exacerbating ECM metabolic imbalance. Thus, a reciprocal promoting relationship exists between aberrant PI3K-Akt-mTOR activation, autophagy dysfunction, and cartilage matrix degradation.

However, the PI3K-Akt-mTOR pathway is not a unidirectional “pathogenic switch” in OA. Emerging research indicates that PI3K/Akt signaling may also contribute to cell survival, anti-apoptotic pathways, and repair processes under specific conditions. Consequently, the role of this pathway in OA may be modulated by cell type, disease stage, stimulus intensity, and the timing of therapeutic intervention. For chondrocytes, sustained mTORC1 activation may be detrimental to autophagy maintenance; however, in synovial cells, immune cells, or subchondral bone cells, variations in PI3K-Akt-mTOR signaling may exert distinct or even opposing effects. Therefore, targeting this pathway for OA therapy should not be perceived merely as

“pan-inhibition”, but should emphasize precise regulation within specific cell populations, disease stages, and therapeutic dosage windows.

Limitations of this pathway as a therapeutic target

Despite being a crucial target for regulating chondrocyte autophagy and matrix metabolism, the PI3K-Akt-mTOR pathway presents distinct limitations as a therapeutic target for OA. Firstly, this pathway is ubiquitously involved in fundamental biological processes such as cell growth, metabolism, immune regulation, and tissue repair; excessive or prolonged inhibition may impair normal cellular functions or interfere with cartilage repair and tissue homeostasis. Thus, pharmacological interventions targeting this pathway necessitate clearly defined dosage windows, treatment durations, and local safety profiles.

Secondly, OA is a whole-joint organ disease involving chondrocytes, synovial cells, subchondral bone cells, and immune cells, all of which contribute to disease progression. The functional role of the PI3K-Akt-mTOR pathway varies among these cell types. Taking the PI3K inhibitor LY294002 as an example, *in vitro* studies suggest it attenuates TNF- α -induced overexpression of Cadherin-11 in OA fibroblast-like synoviocytes and reduces their invasive capacity^[57-59], while also modulating glycolysis and pro-inflammatory cytokine secretion^[60]. However, in collagenase-induced OA mouse models, systemic administration of LY294002, while reducing Cadherin-11 expression in the synovium, failed to significantly ameliorate synovitis or cartilage injury^[57]. This result suggests that protective phenotypes observed via *in vitro* pathway inhibition do not necessarily translate into clinical improvement *in vivo*.

Thirdly, autophagy regulation itself exhibits stage-specificity and duality. In early OA, moderate restoration of chondrocyte autophagy may facilitate the clearance of damaged organelles, mitigate oxidative stress, and maintain matrix metabolism. However, in late-stage disease, characterized by severe cartilage structural destruction, subchondral bone remodeling, and persistent synovitis, autophagy modulation alone may be

insufficient to reverse complex joint structural damage. Moreover, current studies often infer autophagy levels based on the expression changes of markers such as LC3B, ATG5, Beclin-1, or p62, which do not fully represent the actual restoration of autophagic flux. Therefore, future studies should integrate autophagic flux assays, indicators of cartilage matrix synthesis and degradation, histological scoring, and joint function evaluations to comprehensively assess the real-world efficacy of PI3K-Akt-mTOR targeted interventions.

Finally, systemic inhibition of the PI3K-Akt-mTOR pathway may trigger off-target effects and systemic adverse reactions, which is a major driver for the growing interest in local delivery strategies. Intra-articular delivery platforms, such as hydrogels, hold promise for improving the feasibility of localized application for these pathway-modulating drugs by prolonging drug retention, minimizing systemic exposure, and enabling sustained release. Nevertheless, hydrogel-based delivery does not inherently resolve the safety and efficacy concerns of the drugs themselves; further investigations into drug release kinetics, intra-articular distribution, chondrotoxicity, and long-term therapeutic outcomes remain essential.

HYDROGELS AS PLATFORMS FOR INTRA-ARTICULAR DELIVERY AND CARTILAGE FUNCTIONAL REPLACEMENT

Intra-articular administration can enhance local drug exposure in diseased joints; however, free drugs are prone to synovial fluid dilution, lymphatic clearance, the cartilage ECM barrier, and joint motion-induced shear forces, resulting in short retention times, significant fluctuations in local drug concentration, and a necessity for frequent re-administration^[20,61]. Consequently, the key to local OA therapy lies not merely in “injecting drugs into the joint”, but in constructing delivery platforms that prolong intra-articular retention, achieve controlled release, improve surface lubrication, and minimize systemic exposure. Due to their high water content, ECM-mimetic structure, excellent biocompatibility, injectable gelation, and tunable release properties, hydrogels possess significant potential for local intra-articular treatment of OA^[62]. For

drugs targeting the PI3K-Akt-mTOR pathway, hydrogels can serve as local drug reservoirs, minimizing systemic exposure and providing a more stable environment for modulating chondrocyte autophagy [Table 1].

Table 1. Primary categories and characteristics of hydrogels for intra-articular OA delivery and cartilage functional replacement.

Category	Representative Materials/Systems	Gelation or Release Characteristics	Main Cargos or Applications	Evidence Boundaries and Limitations
Natural biodegradable hydrogels	HA, gelatin/GelMA, collagen, chitosan, alginate	Physical/chemical crosslinking, ionic crosslinking, photocrosslinking	Anti-inflammatory drugs, natural compounds, rapamycin, etc	Exhibit superior biocompatibility and ECM-mimetic features; however, mechanical strength, batch-to-batch variability, and degradation rates require further optimization ^[62] .
Synthetic/Composite injectable hydrogels	PEG, PLGA-PEG-PGA, PNIPAAm, Pluronic F127, mPEG-polypeptide	Thermosensitive gelation, in situ drug depot, tunable release	Glucocorticoids, quercetin, etanercept, etc.	Gelation kinetics and release behavior are tunable; however, attention must be paid to initial burst release, drug stability, and long-term local safety ^[65,67,71-72] .
Nanoparticle-hydrogels	Liposomes, micelles,	Hierarchical release,	Rapamycin, siRNA/meta	Effectively reduce burst release and

l composite systems	polymer nanoparticles/ microspheres- hydrogel	mitigated burst release, enhanced drug stability	bolic regulatory agents, etc.	enhance drug stability; however, complex structures demand high batch-to-batch consistency and clinical fabrication standards ^[4,56,62-63,73] . Integrate cartilage targeting with interfacial lubrication; however, long-term wear resistance, deep cartilage penetration, and the safety of repeated injections require validation ^[56,63,74] . Potential for pathological signal-triggered on-demand release; however, the matching of response thresholds with authentic OA joint signals, stability, and reproducibility necessitate further
Targeted/L ubricating hydrogels	Cationic liposome-HA microspheres, self-renewing hydration layer microspheres	Cartilage electrostatic targeting, rolling lubrication, hydration layer reconstruction	mTOR inhibitors and tribological lubrication	
Stimuli-res ponsive hydrogels	ROS-, pH-, or MMP/enzyme -responsive systems	Pathological signal-triggered release, on-demand drug delivery	Anti-inflam matory, antioxidant, and autophagy-r egulating agents	

validation^[3,63,65].

Suitable for long-term

load-bearing,

lubrication, or

functional

replacement

for

end-stage

OA or

exploration

of delaying

surgical

intervention

long-term follow-up

remain core

concerns^[76-78].

Fundamental requirements for intra-articular delivery systems

The OA joint microenvironment imposes multiple requirements on delivery systems. Primarily, the system must exhibit excellent injectability and in situ gelation capabilities to allow minimally invasive administration and adaptation to irregular joint spaces. Secondly, the material must maintain structural stability under synovial fluid flow and joint motion-induced shear forces to prevent rapid drug clearance. Thirdly, the delivery system should be capable of adjusting release kinetics according to drug properties, thereby mitigating initial burst release and local toxicity while maintaining a sufficiently long therapeutic window. Furthermore, the dense, negatively charged ECM of cartilage limits drug penetration and retention; thus, parameters such as particle size, surface charge, cartilage adhesiveness, and tissue penetration capabilities are critical determinants of therapeutic efficacy^[63-64].

Ideal hydrogels for intra-articular use should also balance biocompatibility, low immunogenicity, predictable degradation profiles, and reproducible fabrication

techniques. In elderly OA patients, the joint microenvironment is often characterized by chronic inflammation, oxidative stress, chondrocyte senescence, and reduced repair capacity; the material itself should not exacerbate synovitis or induce chronic foreign body responses. Therefore, the evaluation of hydrogels should extend beyond “gelation capacity” and “sustained-release capability” to include functional metrics such as intra-articular retention time, drug release kinetics, cartilage/synovial safety, histological outcomes, and measures of pain and gait [Figure 4].

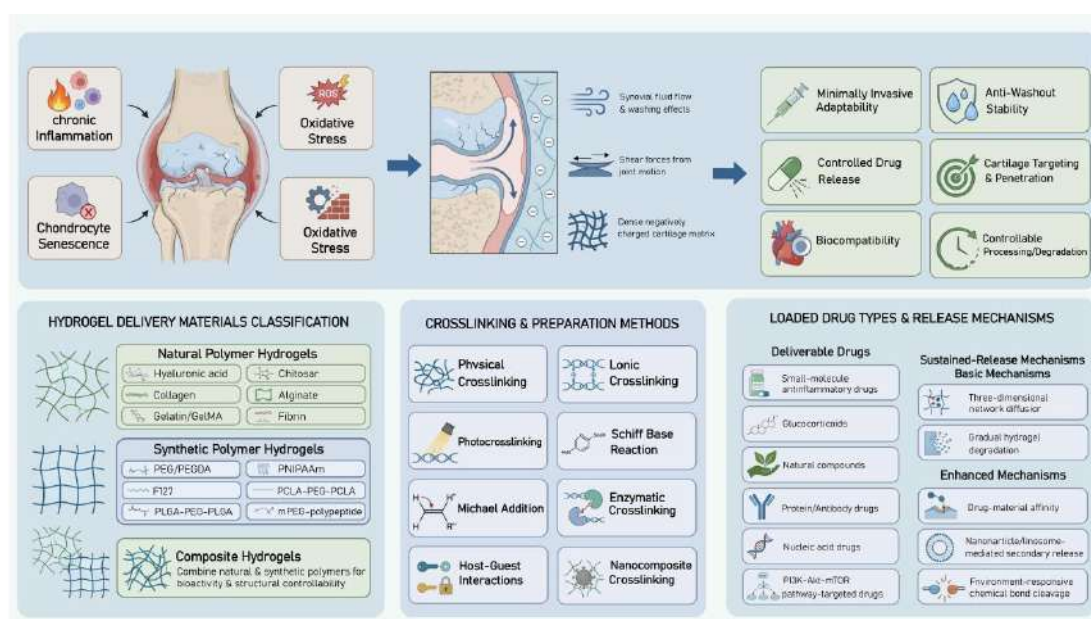


Figure 4. Overview of design requirements, material systems, and drug release mechanisms of intra-articular injectable hydrogel delivery systems for age-related OA.

Material categories and fabrication methods of injectable and biodegradable hydrogels

Injectable hydrogels utilized for intra-articular OA drug delivery can be broadly classified into natural polymers, synthetic polymers, and composite hydrogels. Natural polymer materials—including hyaluronic acid (HA), collagen, gelatin or gelatin methacryloyl (GelMA), chitosan, alginate, and fibrin—typically exhibit superior biocompatibility and ECM-mimetic characteristics. HA is intrinsically a major constituent of synovial fluid, playing an essential role in joint lubrication and cartilage surface protection; meanwhile, gelatin, collagen, and GelMA provide cell-adhesive

motifs, rendering them well-suited for constructing delivery microenvironments with high bioactivity. Synthetic polymer materials, such as PEG/PEGDA, PLGA-PEG-PLGA, PNIPAAm, Pluronic F127, PCLA-PEG-PCLA, and mPEG-polypeptides, offer prominent advantages including high structural designability, tunable gelation kinetics, and controllable degradation rates^[62,65].

From the perspective of fabrication strategies, hydrogels can be formed via physical crosslinking, ionic crosslinking, thermosensitive gelation, photocrosslinking, Schiff-base reactions, Michael additions, enzymatic crosslinking, host-guest interactions, and nanocomposite/microsphere incorporation. Thermosensitive hydrogels represent a widely utilized class of systems in intra-articular OA delivery; their precursor solutions maintain fluidity at room temperature and undergo a sol-to-gel transition at physiological body temperature post-injection to form an in situ drug depot, thereby prolonging intra-articular retention and reducing administration frequency^[65-66]. For instance, a thermosensitive injectable hydrogel composed of chitosan, Pluronic F127, and β -glycerophosphate has been utilized for the delivery of the TNF- α inhibitor etanercept, demonstrating the feasibility of natural/synthetic composite systems for the localized delivery of anti-inflammatory biologics^[67].

Deliverable cargos and drug release mechanisms of hydrogels

Cargos deliverable via hydrogels encompass small-molecule anti-inflammatory drugs, glucocorticoids, natural compounds, protein or antibody therapeutics, nucleic acid drugs, and candidate molecules targeting the PI3K-Akt-mTOR-related pathways. Drug release is primarily governed by mechanisms including passive diffusion through the three-dimensional network, progressive matrix degradation, drug-matrix affinity interactions, secondary sustained release from encapsulated nanoparticles or liposomes, and stimuli-responsive bond cleavage^[62,65]. Given the substantial disparities among diverse therapeutics in terms of molecular weight, hydrophilicity/hydrophobicity, stability, and therapeutic window, key hydrogel parameters—including pore size, crosslinking density, degradation rate, encapsulation strategy, and surface charge—must

be tailored to match the specific cargo. More broadly, hydrogel platforms have been employed for controlled delivery of anticancer agents, growth factors, and nanoparticle-based therapeutics in other biomedical settings^[68-70]. These studies illustrate the formulation versatility of hydrogel networks but should not be interpreted as direct evidence of efficacy in OA.

Regarding conventional anti-inflammatory drug delivery, a poly(organophosphazene)-based thermosensitive nanoparticle hydrogel successfully encapsulated triamcinolone acetonide to form a synovial-like 3D gel depot at body temperature, achieving sustained *in vitro* release for approximately 6 weeks and demonstrating long-term anti-inflammatory and chondroprotective efficacy following a single intra-articular injection in early-stage OA rat models^[71]. Natural compounds such as quercetin can likewise achieve sustained release via mPEG-polypeptide thermosensitive hydrogels; studies demonstrated that quercetin release persisted for over 28 days, significantly improving gait parameters and OARSI scores in post-traumatic OA rat models^[72]. These findings collectively indicate that hydrogels can overcome the inherent limitations of "rapid clearance and short-lived efficacy" associated with small molecules or natural compounds within the joint cavity by extending local drug exposure.

For autophagy-modulating agents more directly aligned with the core focus of this review, hydrogel-mediated delivery of rapamycin serves as a prototypical paradigm. Early studies engineered rapamycin-micelle-loaded gelatin hydrogels for controlled intra-articular release; in murine OA models, this system increased the proportion of autophagy-marker-positive chondrocytes, improved histological scores, and downregulated OA-associated catabolic genes^[73]. Subsequently, rapamycin-liposome-loaded hyaluronic acid hydrogel microspheres further integrated sustained drug release, cartilage targeting, and lubrication functionalities: the positively charged liposomes targeted the negatively charged cartilage matrix via electrostatic interactions to release rapamycin for chondrocyte autophagy enhancement, while the

hydrogel microspheres improved joint lubrication via a ball-bearing mechanism and a self-renewing hydration layer^[56].

Nanoparticle-hydrogel composite systems represent another noteworthy delivery modality. Therapeutics can be pre-encapsulated into liposomes, polymeric nanoparticles, micelles, or microspheres before being embedded into the hydrogel network, establishing a “nanocarrier-in-hydrogel” hierarchical release architecture that minimizes burst release, enhances drug stability, and augments tissue targeting^[62-63]. For instance, targeted lipid nanoparticles dispersed within a self-assembling peptide nanofiber hydrogel modulated chondrocyte cholesterol metabolism and recruited endogenous synovial mesenchymal stem cells in OA models, thereby remodeling the inflammatory microenvironment and facilitating cartilage repair^[4]. These studies highlight that hydrogels are not merely passive entrapment matrices, but function as sophisticated engineering platforms for the sustained spatial localization and controlled release of nanotherapeutics within the articular cavity.

Targeted, lubricating, and stimuli-responsive hydrogels

To enhance intra-articular delivery efficiency, hydrogel design is evolving from conventional sustained-release matrices toward multifunctional targeted, lubricating, and stimuli-responsive platforms. Targeted designs predominantly focus on cartilage adhesion, tissue penetration, and lesion recognition—for example, by tuning surface charges, conjugating cartilage-homing peptides or antibodies, or incorporating motifs with high affinity for ECM components—to selectively concentrate therapeutics within cartilaginous or synovial lesion sites. Because the dense collagen network and negatively charged proteoglycans of the cartilage ECM physically restrict drug penetration into deep zones, targeted delivery implies not merely “proximity to the joint”, but fundamentally overcoming dense tissue barriers and achieving precise lesion localization^[63,74].

Lubricating hydrogels emphasize the simultaneous improvement of the frictional

microenvironment at the articular surface alongside therapeutic cargo delivery. Due to their excellent injectability and biocompatibility, HA-based hydrogel microspheres can act as “ball bearings” to significantly reduce friction at sliding articular interfaces. By encapsulating rapamycin-loaded liposomes within methacrylated hyaluronic acid microspheres (RAPA@Lipo@HMs), the microspheres continuously expose liposomes during frictional wear to reconstruct the hydration layer, achieving self-renewing lubrication; concurrently, the released rapamycin liposomes enhance chondrocyte autophagy and retard OA progression^[56]. This design elegantly exemplifies a multifunctional synergy of “mechanical lubrication + sustained drug release + cellular homeostasis regulation” [Figure 5].

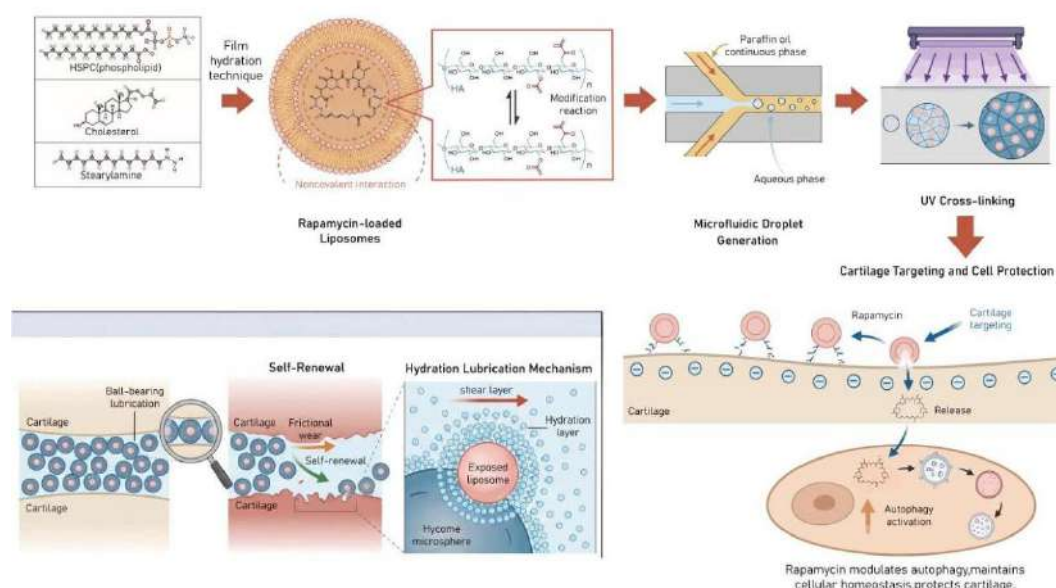


Figure 5. Preparation process and therapeutic principle of rapamycin-loaded hydrogels. Stimuli-responsive hydrogels leverage the pathological microenvironment of OA—characterized by elevated ROS levels, pH fluctuations, increased MMP/enzymatic activity, and aberrant mechanical loading—to achieve on-demand drug release. ROS-responsive systems facilitate the release of antioxidants or anti-inflammatory agents in environments characterized by high oxidative stress. pH-responsive systems utilize localized acidification resulting from inflammation and lactate accumulation to modulate therapeutic release. MMP- or other enzyme-responsive systems are engineered to release drugs specifically at lesion sites where matrix-degrading enzymes

are overexpressed^[3,65]. However, the conceptual superiority of stimuli-responsive hydrogels does not directly translate to *in vivo* efficacy. Rigorous validation is required to ensure that their response thresholds are accurately matched to the pathophysiological signaling within the authentic OA joint microenvironment, and that the release profiles remain stable, predictable, and reproducible [Figure 6].

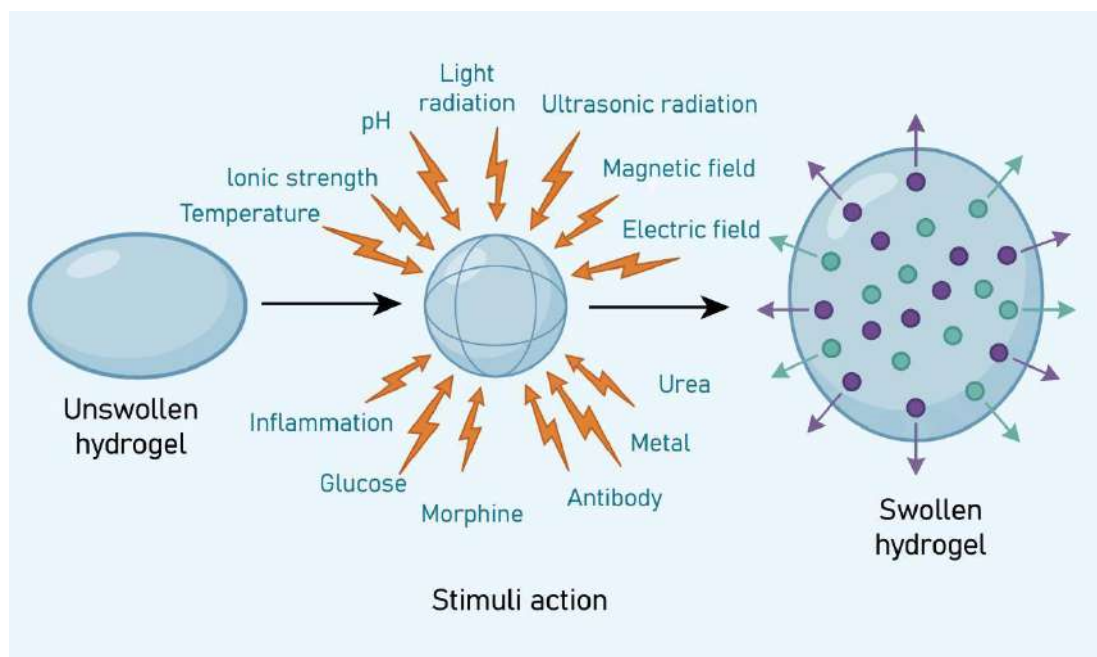


Figure 6. Diverse stimuli-responsive factors employed in hydrogel design.

Andrographolide-loaded hydrogels provide a recent paradigm for integrating natural compound delivery with the modulation of autophagy. The 4-arm PEG-Mix-Hydrogel/PF system effectively encapsulates the hydrophobic agent andrographolide, achieving sustained release for approximately 24 days. Research indicates that andrographolide enhances chondrocyte autophagy via PRKCA/EGFR-related signaling, thereby attenuating inflammation, matrix degradation, and apoptosis; furthermore, a single intra-articular injection significantly ameliorated joint degeneration and gait abnormalities in OA mouse models^[75]. Although these findings support the feasibility of hydrogel-based delivery of natural compounds, the direct causal linkage between this mechanism and the PI3K-Akt-mTOR signaling axis warrants further investigation [Figure 7].

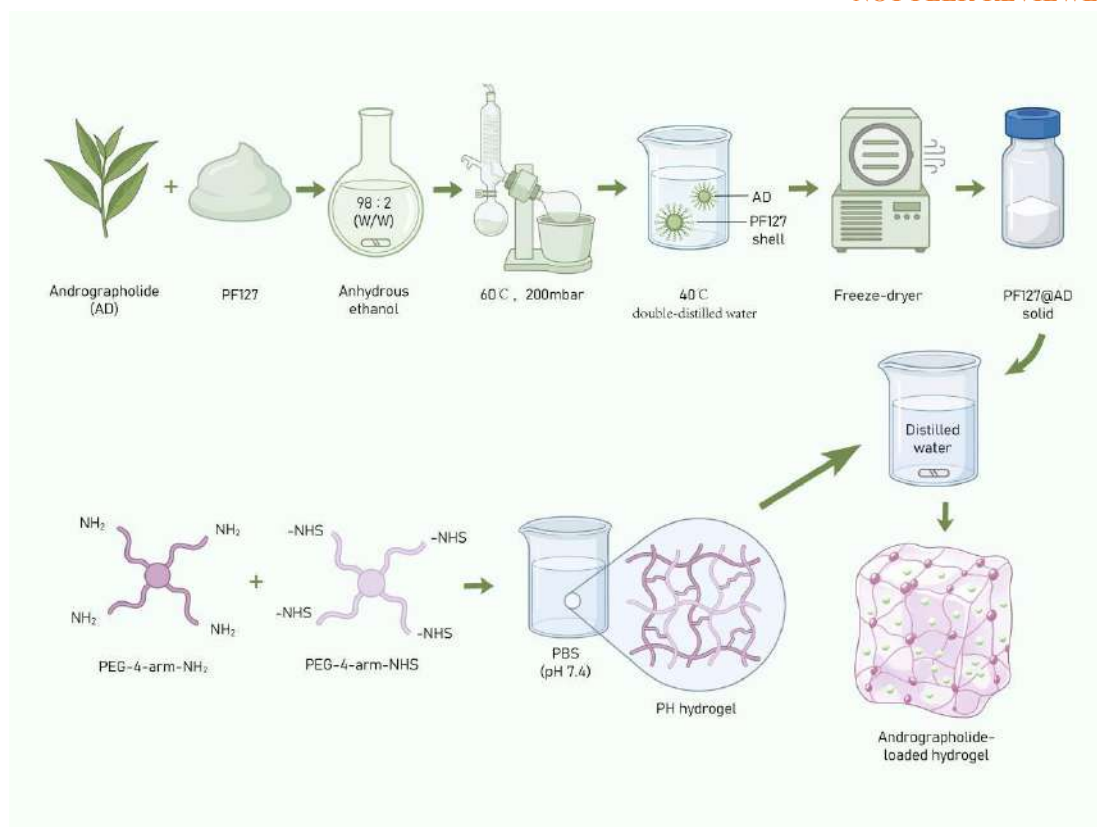


Figure 7. Fabrication workflow of andrographolide-loaded hydrogels.

Non-degradable hydrogels and functional replacement for end-stage OA: Potentials and limitations

Distinct from biodegradable drug-delivery hydrogels, non-degradable or slowly degradable hydrogels primarily aim to provide long-term load-bearing support, friction reduction, and functional replacement of the cartilage interface. High-strength double-network, nanocomposite, and polyvinyl alcohol (PVA)-based hydrogels can enhance fatigue resistance, compressive load-bearing capacity, and tribological performance through multi-network energy dissipation, crystalline phase reinforcement, or the design of surface hydration layers. Certain artificial cartilage-like hydrogels exhibit lubrication and deformation recovery properties comparable to those of native cartilage under cyclic loading and elevated contact pressures^[76-78]. While these materials provide a foundational basis for artificial cartilage implants or joint surface coatings, their material properties should not be directly equated with long-term clinical benefits in patients with end-stage OA [Figure 8].

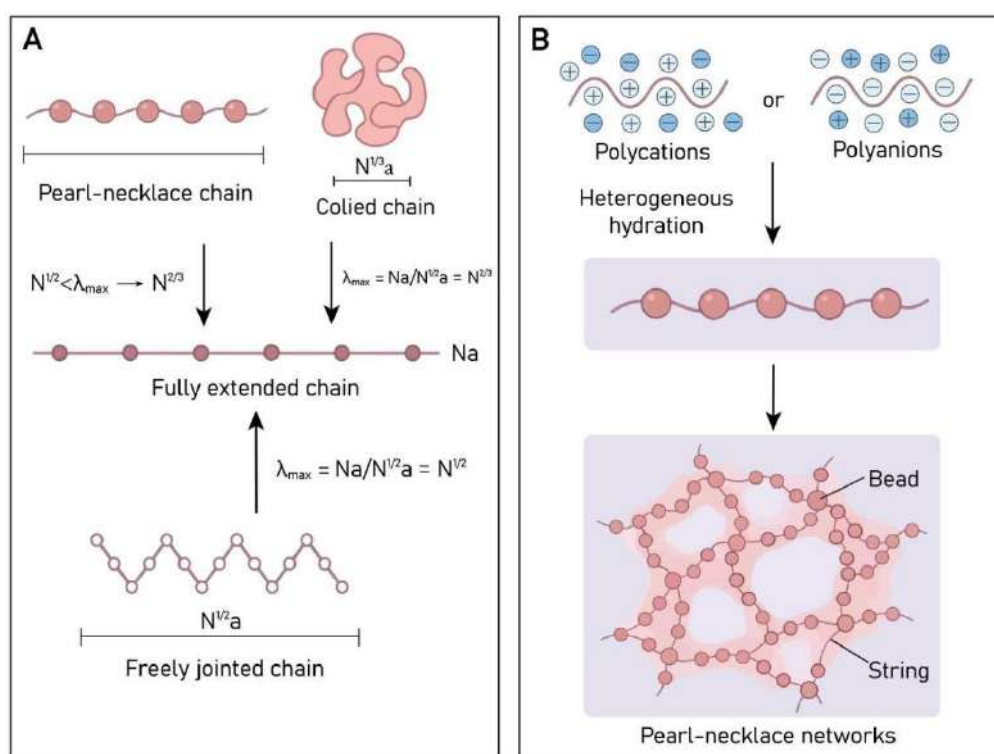


Figure 8. Fabrication process and working principle of non-degradable hydrogels.

For patients unable to tolerate joint arthroplasty or those seeking to delay surgical intervention, non-degradable or slowly degradable hydrogels represent an exploratory avenue for local friction reduction, partial joint surface reconstruction, or cartilage functional replacement; however, they should not be characterized as established alternatives to joint arthroplasty^[77-78]. Their clinical translation must still address critical challenges, including implant fixation, cartilage-material interface matching, wear debris, foreign body responses, synovial irritation, mechanical fatigue, and insufficient long-term follow-up data. Drug loading may serve as an extended application for these materials; however, this necessitates independent verification of long-term release controllability, material stability, and histocompatibility.

THERAPEUTIC AGENTS TARGETING THE PI3K-Akt-mTOR PATHWAY AND HYDROGEL-BASED DELIVERY STRATEGIES

Given the regulatory role of the PI3K-Akt-mTOR pathway in chondrocyte autophagy,

inflammatory responses, and matrix metabolism, pharmacological intervention targeting various nodes of this pathway has emerged as a significant frontier in OA research^[22]. Theoretically, EGFR inhibitors, PI3K inhibitors, mTOR inhibitors, dual PI3K/mTOR inhibitors, as well as select natural compounds and active ingredients from traditional Chinese medicine, may regulate chondrocyte autophagy and ECM metabolism by modulating this signaling axis. Concurrently, hydrogel-based delivery systems provide a robust foundation for the local application of these agents in elderly OA patients by prolonging intra-articular retention, achieving sustained release, and minimizing systemic exposure.

However, it is imperative to acknowledge that the strength of evidence for these diverse pharmacological agents remains inconsistent. Currently, relatively direct evidence is predominantly concentrated on mTOR inhibitors and specific hydrogel delivery systems; in contrast, the evidence supporting EGFR inhibitors, PI3K inhibitors, and dual PI3K/mTOR inhibitors in OA is complicated by model-dependent discrepancies, inconsistencies between *in vitro* and *in vivo* findings, or extrapolations from non-OA disease models. Accordingly, the focus of this chapter is not merely to catalogue these agents, but to systematically delineate their mechanistic foundations, existing evidence, and the feasibility boundaries of hydrogel-based delivery according to their specific sites of action [Table 2].

Table 2. Representative agents targeting the PI3K-Akt-mTOR pathway, relevant autophagic research advances, and evidentiary boundaries.

Drug and Target	Research Progress	References
Gefitinib (EGFR Inhibitor)	As an EGFR inhibitor, gefitinib effectively reverses the degenerative phenotype of chondrocytes <i>in vitro</i> and promotes matrix synthesis. When combined with advanced	[82]

	thermosensitive injectable hydrogel delivery systems, it enables localized sustained release and long-term therapeutic effects in animal models, effectively delaying intervertebral disc degeneration.	
LY294002 (PI3K Inhibitor)	LY294002 attenuates TNF- α -induced overexpression of Cadherin-11 in OA fibroblast-like synoviocytes and reduces their invasive capacity, though it shows limited efficacy in ameliorating synovitis and cartilage injury <i>in vivo</i> .	[57-59]
Rapamycin (mTOR Inhibitor)	By inhibiting mTORC1, rapamycin lifts the suppression of autophagy initiation. Hydrogel-based local delivery increases autophagy-related markers and improves histological outcomes and matrix metabolism in experimental OA models, although assessments of autophagic flux and long-term safety remain necessary.	[56,73,85]
BEZ235 (Dual PI3K/mTOR Inhibitor)	As a dual PI3K/mTOR inhibitor, preclinical studies demonstrated its radiosensitizing efficacy in colorectal cancer; however, Phase Ib clinical trials in advanced renal cell carcinoma revealed significant toxicity and a lack of objective therapeutic benefit, leading	[88-89]

	to the termination of its development.	
	GNE-947 acts as a dual PI3K/mTOR	
GNE-947 (Dual PI3K/mTOR Inhibitor)	inhibitor with documented anti-angiogenic activity in laser-induced rat choroidal neovascularization models, characterized by an extended half-life.	[90]
Neolymphostin A (Dual PI3K/mTOR Inhibitor)	Neolymphostin A exhibits high selectivity for PI3K and mTOR, alongside favorable cell permeability and functional activity, blocking AKT phosphorylation with nanomolar IC50 values in living cells; however, its synthesis remains challenging.	[91-92]
Eupatorin (Natural Compound)	Eupatorin targets key molecules such as MMP9, EGFR, and PTGS2. It modulates the PI3K/AKT and estrogen-related signaling pathways, thereby inhibiting inflammation and ECM degradation while facilitating the restoration of autophagy.	[99]
Puerarin (Natural Compound)	Puerarin exhibits multi-target regulatory characteristics, manifesting anti-inflammatory, anti-apoptotic, and pro-ECM synthetic effects, potentially mediated by the activation of the PI3K-AKT pathway.	[100]
Digoxin (Natural Compound)	Digoxin stimulates chondrocyte differentiation and anabolic	[102-103]

metabolism to counteract cartilage degradation; it suppresses M1 polarization of synovial macrophages to alleviate synovitis, and downregulates miR-146b-5p in M1-derived exosomes to modulate the inflammatory microenvironment via Usp3 and Sox5.

Quercetin (Natural Compound/TCM) While quercetin possesses anti-inflammatory and antioxidant activities (with evidence of PI3K/Akt/mTOR-mediated autophagy regulation primarily from diabetes, oncology, or fibrosis models), its application in OA—via mPEG-polypeptide thermosensitive hydrogels—has demonstrated gait improvement and enhanced OARSI scores. Its pathway-specific mechanism and localized delivery efficacy in OA require independent evaluation. [72,106-109,111-113]

Andrographolide (Natural Compound/TCM) A 4-arm PEG-Mix-Hydrogel/PF system enables approximately 24-day sustained release of andrographolide. This agent may enhance chondrocyte autophagy via PRKCA/EGFR-related mechanisms, ameliorating inflammation, matrix degradation, and apoptosis. The direct causal linkage to [75,114]

the PI3K-Akt-mTOR axis requires
further validation.

EGFR inhibitors

The Epidermal Growth Factor Receptor (EGFR) is a member of the HER/ErbB receptor tyrosine kinase family^[79-81]. Its activation initiates the downstream PI3K-Akt-mTOR pathway and may potentially modulate autophagic processes via mTOR-dependent signaling. Gefitinib, a classical small-molecule EGFR inhibitor, has been investigated in models of intervertebral disc degeneration (IVDD). These studies demonstrate that gefitinib can attenuate the degenerative phenotype of chondrocyte-like cells *in vitro* and promote the synthesis of extracellular matrix (ECM). When integrated with a thermosensitive injectable hydrogel delivery system, it achieves local sustained release in puncture-induced rat IVDD models, and by persistently blocking EGFR activity, it enhances matrix production, activates autophagy, and suppresses matrix degradation^[82] [Figure 9].

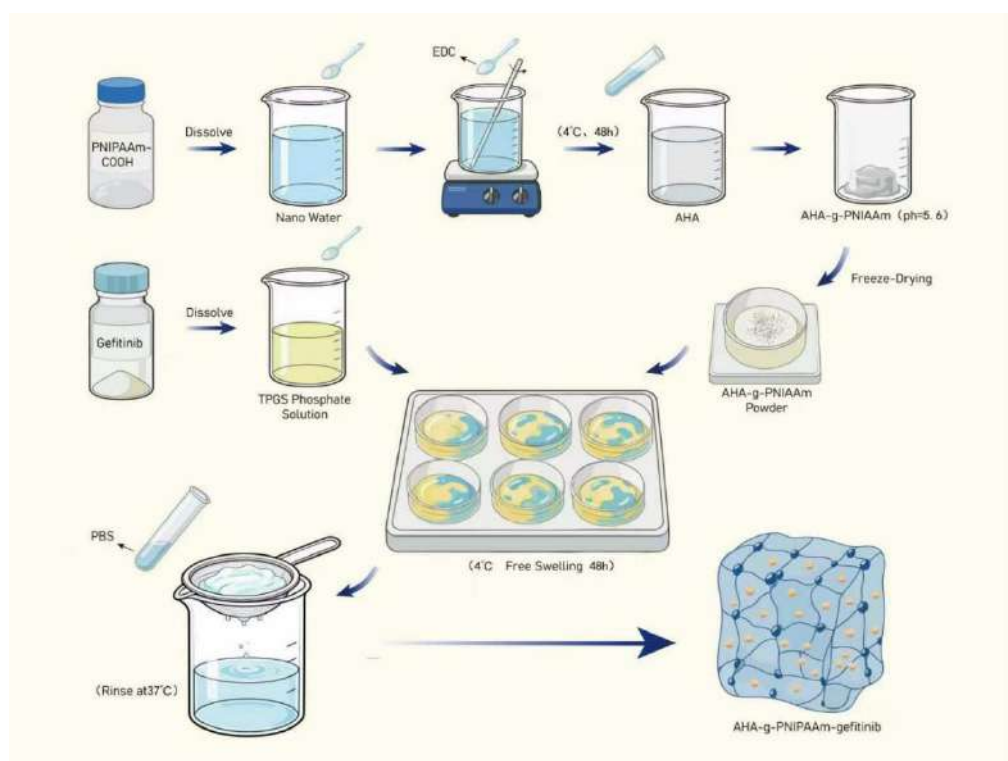


Figure 9. Fabrication workflow of gefitinib-loaded hydrogels.

These findings suggest that the combination of EGFR inhibitors and injectable hydrogels holds the potential to modulate matrix metabolism and autophagic processes via local delivery. However, it should be noted that the aforementioned evidence is primarily derived from intervertebral disc degeneration models rather than prototypical OA models. Given the distinct differences between intervertebral disc tissue and articular cartilage regarding mechanical environments, cellular composition, nutritional conditions, and pathological progression, these results cannot be directly extrapolated to the treatment of age-related OA. For OA, intra-articular injection of gefitinib-encapsulated hydrogels remains a candidate strategy; its efficacy necessitates further validation across OA-related chondrocytes, synoviocytes, subchondral bone microenvironments, and aged animal models.

From a delivery perspective, the potential value of hydrogel systems lies in minimizing systemic exposure to gefitinib while maintaining relatively stable local drug concentrations within the lesion site. Future OA-related research should prioritize evaluating intra-articular retention time, release profiles, safety profiles regarding chondrocytes and synoviocytes, impacts on autophagic flux, and long-term effects on cartilage structural preservation. At this stage, EGFR inhibitors should not be characterized as a mature therapeutic regimen for OA but rather positioned as a potential research avenue for upstream pathway modulation.

PI3K inhibitors

The PI3K/Akt signaling pathway plays a pivotal role in cell survival, metabolic regulation, inflammatory responses, and autophagy, serving as a critical midstream node within the PI3K-Akt-mTOR axis. LY294002 is a commonly utilized PI3K inhibitor that has been extensively investigated in both *in vitro* and animal models. Studies have demonstrated that LY294002 attenuates TNF- α -induced Cadherin-11 overexpression and invasive capacity in OA fibroblast-like synoviocytes^[57-59]; it also inhibits glycolysis and pro-inflammatory cytokine secretion^[60], while enhancing the pro-survival,

anti-apoptotic, and pro-matrix synthetic effects of certain protective factors on chondrocytes^[83].

However, the *in vivo* effects of PI3K inhibitors do not fully correspond to *in vitro* experimental results. It has been observed that in collagenase-induced OA (CIOA) mouse models, intraperitoneal injection of LY294002 reduces Cadherin-11 protein expression in the synovium but fails to significantly ameliorate synovitis or cartilage injury. In contrast, intra-articular intervention targeting specific downstream molecules—such as the application of Cadherin-11 antibodies—in the same model exhibits more pronounced efficacy in alleviating synovitis and cartilage damage^[57]. These findings imply that systemic inhibition of the PI3K/Akt pathway may not adequately replicate the protective effects observed *in vitro*, as therapeutic outcomes may be modulated by cell type, administration route, drug distribution, off-target effects, and systemic feedback regulation.

Consequently, PI3K inhibitors are better positioned as candidates for early-stage OA inflammatory modulation and autophagic intervention, rather than as an established therapeutic regimen. Should LY294002 or other PI3K inhibitors be integrated with hydrogel delivery systems, research emphasis should shift toward local dosage windows, release kinetics, chondrocyte and synoviocyte toxicity, impacts on autophagic flux, and long-term effects on synovitis and cartilage injury. While hydrogel-based delivery may minimize systemic exposure and prolong local residency time, it does not intrinsically resolve the instability of PI3K inhibitor efficacy *in vivo*.

mTOR inhibitors

mTOR is the central regulatory node within the PI3K-Akt-mTOR pathway; as a serine/threonine protein kinase, it regulates cell growth, metabolism, survival, and autophagy via two distinct complexes, mTORC1 and mTORC2^[54,84]. Among these, mTORC1 is most closely associated with the initiation of autophagy and is a canonical negative regulator of the autophagic process. Rapamycin is the most representative

mTOR inhibitor, primarily suppressing mTORC1 activity through binding to FKBP12, though its inhibitory effect on mTORC2 remains relatively weak^[54-55].

Among current candidate drugs targeting the PI3K-Akt-mTOR pathway, mTOR inhibitors demonstrate the most direct logical link to chondrocyte autophagy modulation. *In vitro* studies indicate that rapamycin-mediated mTORC1 inhibition reduces sGAG release from chondrocytes under inflammatory conditions, enhances the expression of chondrogenic markers such as SOX9, COL2A1, and ACAN, and mitigates cell death and inflammatory processes, suggesting that mTORC1 inhibition may contribute to maintaining chondrocyte phenotype and ECM homeostasis^[85]. At the delivery level, gelatin hydrogels loaded with rapamycin-micelles enable controlled intra-articular release; in murine OA models, this system increases the number of autophagy-marker-positive chondrocytes, improves histological scores, and downregulates OA-associated mediators^[73].

Subsequent research on hydrogel microspheres further integrated rapamycin-loaded liposomes, hyaluronic acid hydrogel microspheres, and self-renewing hydration-based lubrication layers. This system demonstrated elevated expression of autophagy-related proteins such as LC3B and ATG5, alongside decreased MMP13 expression. Furthermore, it achieved local enrichment via electrostatic interactions between cationic liposomes and the negatively charged cartilage matrix, while simultaneously improving joint interface lubrication^[56]. Compared with free drugs, the advantage of rapamycin-loaded hydrogels lies in the simultaneous improvement of local retention, lubricative protection, and sustained drug release, providing a more stable intra-articular microenvironment for mTORC1-mediated autophagic regulation. However, these findings must be interpreted with caution. Upregulation of LC3B and ATG5 indicates changes in autophagy-related protein expression but cannot be equated to the restoration of autophagic flux; the decrease in MMP13 largely reflects a reduction in matrix degradation trends, necessitating further validation through autophagic flux assays, histological scores, long-term joint function assessments, and aged OA models. Future

progression of this strategy toward preclinical translation requires further clarification of the local rapamycin dosage window, release kinetics, long-term chondrotoxicity, synovial responses, and risks associated with repeated administration.

Furthermore, multiple generations of mTOR inhibitors have emerged, such as the second-generation inhibitor PP242 and the third-generation inhibitor RapaLink-1. While second-generation agents simultaneously suppress both mTORC1 and mTORC2, third-generation inhibitors exhibit increased potency and the capacity to overcome certain resistance mutations^[54]. However, these agents are primarily utilized in oncological contexts, and there is currently a paucity of direct evidence regarding their efficacy, safety, and the feasibility of hydrogel-based delivery within the intra-articular environment. Consequently, these should be viewed as future expansion directions rather than immediate candidates for the treatment of age-related OA.

Dual PI3K/mTOR inhibitors

Dual PI3K/mTOR inhibitors simultaneously target both key nodes; mechanistically, they may more comprehensively block the PI3K-Akt-mTOR signaling axis and, to some extent, circumvent feedback activation resulting from single-target inhibition^[86]. Pharmacological inhibition of the PI3K/AKT/mTOR axis has been extensively investigated in oncology, providing a mechanistic and drug-development framework for these inhibitors^[87]. However, direct evidence for these agents in OA autophagy regulation and intra-articular hydrogel delivery remains strictly limited, with existing inferences primarily derived from oncology, ophthalmology, or other disease models. Accordingly, this section positions dual PI3K/mTOR inhibitors as prospective candidates rather than validated therapeutic strategies for OA.

BEZ235 is among the most extensively studied dual PI3K/mTOR inhibitors; preclinical research demonstrated its potential to enhance radiosensitivity in colorectal cancer^[88]. Nevertheless, in Phase Ib clinical trials for advanced renal cell carcinoma, it manifested significant toxicity, including fatigue, rash, nausea, vomiting, diarrhea, and mucositis,

alongside a lack of objective clinical benefit, leading to the termination of its development^[89]. These findings imply that while dual inhibition of PI3K and mTOR offers theoretical advantages in pathway blockade, the associated systemic toxicity and the narrow therapeutic window are critical concerns. Given the higher safety standards required for chronic non-lethal conditions such as OA, potent pathway inhibitors established in oncology cannot be simply extrapolated to intra-articular applications.

GNE-947 has demonstrated anti-angiogenic activity in laser-induced rat choroidal neovascularization models, and when administered via intravitreal injection as a suspension, it exhibits an extended half-life in rabbit eyes, offering a pharmacokinetic reference for long-acting local exposure^[90]. However, significant disparities exist between intraocular and intra-articular environments; the latter involves unique factors such as synovial fluid dilution, mechanical shear forces, the cartilaginous barrier, and synovial reactions. Consequently, the long-acting exposure characteristics of GNE-947 merely suggest its potential utility in local sustained-release designs, rather than definitively supporting its suitability for intra-articular delivery in OA.

Neolymphostin A, a covalent dual inhibitor derived from the bacterium *Salinispora arenicola*, facilitates irreversible binding to the Lys802 residue of PI3K α via a vinyllogous ester moiety, exhibiting potent PI3K/mTOR inhibitory activity in living cells^[91]. However, the chemical synthesis of this agent is highly complex, and evidence regarding its utility in OA models or local intra-articular administration is currently lacking^[92]. Other novel inhibitors—such as VDC597, PKI-179, imidazo[1,2-a]pyridine-based compounds, SHR8443, and ZDQ-0620—are similarly confined to research contexts such as osteosarcoma, colorectal cancer, or other oncological investigations^[93-97]. Therefore, these agents are more appropriately positioned as a library of candidate molecules for future screening in local OA pathway modulation; their intra-articular adaptability, chondrotoxicity, release characteristics, and therapeutic window for chronic disease management warrant dedicated investigation rather than immediate adoption as standard care for elderly OA.

Natural compounds and active ingredients of traditional chinese medicine

Natural compounds and active ingredients derived from traditional Chinese medicine have garnered significant attention in OA intervention research due to their multi-target and multi-pathway regulatory characteristics^[98]. Compared with single-target small-molecule inhibitors, these agents may simultaneously modulate inflammatory responses, oxidative stress, apoptosis, ECM metabolism, and autophagic processes. However, their complex composition, multifarious molecular targets, pharmacokinetic instability, and the challenges in elucidating their precise mechanisms necessitate a cautious evaluation of their evidentiary strength. For the scope of this review, only those natural compounds that concurrently implicate OA, the PI3K-Akt-mTOR pathway, and autophagy or ECM metabolism are deemed suitable for focused discussion.

Eupatorin and Puerarin serve as representative natural compounds in this context. Eupatorin potentially acts on key targets such as MMP9, EGFR, and PTGS2, inhibiting inflammation and ECM degradation while modulating autophagic processes via the PI3K/AKT and estrogen-related signaling pathways^[99]. Puerarin exhibits multi-target regulatory properties, exerting anti-inflammatory, anti-apoptotic, and pro-matrix synthetic effects, which may partially be mediated by the PI3K-AKT pathway^[100]. These studies suggest that natural compounds may participate in OA intervention by influencing PI3K-Akt-mTOR signaling; however, the majority of evidence remains confined to cellular or animal studies, lacking systematic evaluation when integrated with hydrogel-based delivery systems.

Evidence regarding digoxigenin/digoxin-related compounds must be interpreted with caution. In hepatocellular carcinoma cells, digoxigenin has been reported to activate autophagy through regulation of the PI3K/AKT/mTOR pathway^[101]. By contrast, OA-specific studies on digoxin indicate that it targets low-density lipoprotein receptor-related protein 4 (LRP4) and exerts chondroprotective effects^[102], while additional work suggests that digoxin can ameliorate the joint inflammatory

microenvironment by suppressing M1-like synovial macrophage polarization and the exosomal miR-146b-5p/Usp3&Sox5 axis^[103]. These findings arise from different compounds and disease contexts and should not be merged into a single mechanistic claim. Accordingly, their precise relevance to PI3K-Akt-mTOR-directed intra-articular therapy in age-related OA remains to be established.

Traditional Chinese medicine and its active components have established a preliminary experimental foundation in OA research, with some formulations or TCM-based interventions demonstrating potential in alleviating pain, inflammation, and cartilage injury in OA animal models^[104-105]. Regarding specific active components, quercetin and andrographolide are common representatives in this research domain. It should be noted that quercetin is a widely distributed polyphenolic flavonoid in plants and should not be oversimplified as a “proprietary Chinese medicine”. Studies have indicated that the diverse biological effects of quercetin are linked to the regulation of the PI3K/Akt/mTOR pathway^[106-109]. Quercetin has also been reported to regulate autophagy through the PI3K/Akt/mTOR pathway in a non-OA viral infection model^[110]. In diabetic GK rat models, quercetin promotes protective autophagy by inhibiting the PI3K/Akt/mTOR pathway, thereby mitigating hepatic, splenic, and renal injury^[111]; in Burkitt lymphoma, it suppresses the PI3K/Akt/mTOR pathway, induces intact autophagic flux, and facilitates the degradation of mutant c-Myc proteins^[112]; in epidural fibrosis models, it modulates fibroblast proliferation via PI3K/Akt/mTOR-dependent autophagy regulation^[113]. However, these findings are primarily drawn from diabetes, oncology, or fibrosis models and cannot be directly extrapolated to age-related OA.

Andrographolide is a bioactive plant-derived component extracted from *Andrographis paniculata*. Research has established a 4-arm PEG-Mix-Hydrogel/PF injectable system for the sustained release of andrographolide (approximately 24 days). In OA models, a single injection ameliorated joint degeneration, rectified gait abnormalities, and restored chondrocyte autophagy, while concurrently reducing inflammation, matrix degradation,

and apoptosis^[75]. Mechanistically, the effects of andrographolide on chondrocyte autophagy may involve the regulation of PRKCA/EGFR signaling, an inhibition mechanism supported by prior studies on PRKCA-mediated EGFR suppression^[114]. However, further clarification regarding the long-term safety, release kinetics, and the direct causal connection with the PI3K-Akt-mTOR pathway is requisite for this strategy.

Consequently, for natural compounds and active ingredients of TCM, it is more appropriate to adopt the expression of “prospective candidates with mechanisms awaiting further verification”. Future integrations with hydrogel delivery systems should prioritize the evaluation of active ingredient stability, encapsulation efficiency, release profiles, local intra-articular safety, the genuine impact on autophagic flux and ECM metabolism, and compatibility with the pathological microenvironment of age-related OA. Network pharmacology and molecular docking analyses are useful for hypothesizing candidate mechanisms but cannot serve as substitutes for cellular, animal, or preclinical validation.

CURRENT CHALLENGES AND FUTURE DIRECTIONS

Although targeting the PI3K-Akt-mTOR pathway to modulate chondrocyte autophagy, combined with hydrogel-based intra-articular delivery, provides novel therapeutic insights for age-related OA, this strategy still faces multifaceted limitations prior to clinical application. Current research is predominantly focused on *in vitro* studies, small animal models, or non-OA disease models; evidence concurrently demonstrating “pathway modulation, autophagy restoration, chondroprotection, and the efficacy of hydrogel delivery” remains limited. Therefore, future studies must be refined through mechanistic validation, standardized detection protocols, material safety assessments, and preclinical translation.

Insufficient mechanistic evidence

While studies on PI3K-Akt-mTOR pathway-mediated OA progression suggest its association with chondrocyte autophagy, inflammation, apoptosis, and ECM metabolism, the precise underlying mechanisms remain incompletely understood. Firstly, the PI3K-Akt-mTOR pathway is not a monolithic pathogenic switch. It is broadly involved in cell growth, metabolism, survival, and immune regulation, potentially exerting divergent effects depending on cell type and disease stage. In chondrocytes, constitutive mTORC1 activation may suppress protective autophagy and exacerbate cellular damage; whereas in synovial cells, immune cells, and subchondral bone cells, alterations in this pathway may elicit distinct or even opposing biological effects. Consequently, “inhibiting the PI3K-Akt-mTOR pathway” cannot be equated with “treating OA”.

Secondly, the evidentiary sources for many candidate drugs do not fully align with the research context of OA. Primary evidence for the EGFR inhibitor gefitinib is derived from models of intervertebral disc degeneration, while the bulk of data concerning dual PI3K/mTOR inhibitors stems from oncological or ophthalmic models; furthermore, evidence for certain natural compounds and active ingredients of traditional Chinese medicine relies heavily on network pharmacology, molecular docking, or non-OA disease models. While such studies may provide insights for OA drug screening, they do not directly confirm definitive therapeutic efficacy for age-related OA. Future research should prioritize the use of OA-relevant cellular models, cartilage-synovium co-culture systems, aged animal models, and large animal models to systematically validate the comprehensive effects of diverse agents on chondrocyte autophagy, synovitis, subchondral bone remodeling, and joint function.

Furthermore, most studies currently emphasize single pathway nodes or individual agents, failing to fully account for the multifactorial crosstalk within the complex OA microenvironment. Age-related OA involves multiple concurrent pathological processes, including inflammation, oxidative stress, mitochondrial damage, cellular senescence, abnormal mechanical loading, and metabolic dysregulation. The PI3K-Akt-mTOR

pathway may represent merely one critical intersection point within this network, rather than the sole determinant of disease progression. Future investigations must further elucidate the reciprocal regulation between this pathway and other signaling axes, such as NF- κ B, MAPK, AMPK, SIRT1, and Nrf2, to avoid oversimplifying complex disease processes into single-pathway modulation.

Lack of standardized autophagy detection

Autophagy is a dynamic process; therefore, its assessment cannot rely solely on the expression changes of individual markers such as LC3B, Beclin-1, ATG5, or p62. In some studies, elevated expression of LC3B or ATG5 is interpreted as enhanced autophagy; however, in the absence of autophagic flux assays, such changes may instead reflect autophagosome accumulation or impaired lysosomal degradation, rather than the restoration of complete autophagic function.

This issue is of particular significance within OA research. The aged OA microenvironment is characterized by inflammation, ROS overaccumulation, mitochondrial damage, and lysosomal dysfunction—factors that collectively disrupt the formation and degradation processes of autophagosomes. Consequently, relying solely on the observation of expression changes in autophagy-related proteins is insufficient to determine whether chondrocytes have truly regained effective damage clearance capacity. Future studies should incorporate autophagic flux assays to distinguish among distinct states, such as enhanced autophagy initiation, autophagosome accumulation, and completed autophagic degradation^[115].

Furthermore, the assessment of autophagy should be integrated with functional outcomes. For OA therapy, the primary objective is not merely the upregulation of specific autophagy markers, but rather the restoration of chondrocyte homeostasis, the reduction of catabolic enzymes such as MMP13 and ADAMTS5, the improvement of matrix synthesis indicators such as COL2A1 and Aggrecan, and the achievement of long-term improvements in histological scores, joint pain, and motor function.

Consequently, future studies should establish an integrated evaluation framework combining “autophagic flux assessment, matrix metabolism evaluation, histological outcomes, and functional endpoints” to enhance the reliability of result interpretation.

Barriers to clinical translation of hydrogels

As intra-articular delivery platforms, hydrogels can partially extend drug retention, enable sustained release, and reduce systemic exposure; however, their clinical translation encounters multiple hurdles. Firstly, the physicochemical properties of hydrogels must be highly compatible with the intra-articular environment. The OA joint cavity is characterized by synovial fluid flow, mechanical shear, repetitive loading, and fluctuating inflammatory microenvironments. Excessive degradation rates may preclude the maintenance of therapeutic drug concentrations, while insufficient degradation may increase risks of foreign body responses, synovial irritation, or restricted joint mobility. Therefore, parameters such as gelation time, mechanical properties, degradation rates, release kinetics, and intra-articular retention time require systematic optimization^[20].

Secondly, the long-term safety of hydrogel delivery systems warrants thorough validation. Agents targeting the PI3K-Akt-mTOR pathway are intrinsically involved in fundamental processes including cell growth, metabolism, and immune regulation; thus, even with minimized systemic exposure via local delivery, their long-term effects on chondrocytes, synoviocytes, subchondral bone cells, and immune cells must be rigorously evaluated. Particularly in elderly OA patients, where the microenvironment is already marked by cellular senescence and diminished repair capacity, over-inhibition of the PI3K-Akt-mTOR pathway may compromise tissue homeostasis and repair responses. Consequently, hydrogel-based delivery does not obviate the necessity for drug safety validation.

Thirdly, the standardization of material fabrication and clinical application remains a critical challenge. Batch-to-batch consistency, sterilization methods, drug encapsulation efficiency, release reproducibility, storage stability, and the controllability of injection

procedures all significantly influence clinical translation. For stimuli-responsive hydrogels, it is essential to demonstrate a definitive correlation between the triggering signals and the OA pathological microenvironment. For example, the stability, predictability, and reproducibility of drug release from ROS-, pH-, or MMP-responsive systems within the authentic joint microenvironment necessitate further confirmation via animal studies and preclinical research.

Future research directions

Future research should prioritize the establishment and application of relevant models for age-related OA. Currently, many animal studies in OA utilize young subjects or acute injury models, which fail to fully recapitulate the pathological hallmarks of age-related OA, such as cellular senescence, chronic low-grade inflammation, mitochondrial dysfunction, and diminished repair capacity. Consequently, studies should increasingly utilize natural aging models, surgically induced OA in aged animals, or composite models incorporating metabolic abnormalities to enhance the translational value for elderly patients.

Secondly, focus should shift from single-pathway intervention toward spatiotemporal precision regulation. The role of the PI3K-Akt-mTOR pathway may vary across distinct disease stages and cell types in OA; therefore, future efforts should avoid a simplistic pursuit of “potent” or “sustained” inhibition, instead focusing on designing rational release kinetics and dosing windows tailored to specific disease stages, target cell populations, and local microenvironmental states. In early-stage OA, therapeutic strategies may require prioritizing the suppression of inflammation and the restoration of protective autophagy, whereas mid-to-late-stage OA may necessitate a multifactorial approach encompassing chondroprotection, subchondral bone remodeling, synovitis management, and pain control.

Thirdly, hydrogel design should evolve from conventional sustained-release matrices toward intelligent responsive and multifunctional synergistic platforms. An ideal

delivery system should integrate injectability, appropriate degradation kinetics, cartilage adhesiveness, lubrication properties, and pathological microenvironment responsiveness, enabling on-demand release triggered by inflammatory, ROS, MMP, or pH signals. For agents targeting the PI3K-Akt-mTOR pathway, emphasis should be placed on optimizing drug encapsulation efficiency, release kinetics, and local safety profiles to circumvent potential risks associated with burst release or prolonged over-inhibition.

Finally, future research necessitates the establishment of evaluation frameworks more proximal to clinical translation. Beyond monitoring molecular markers such as LC3B, ATG5, p62, and MMP13, evaluation should incorporate assessments of autophagic flux, histological scores, cartilage thickness, subchondral bone alterations, synovitis, pain-related behaviors, gait analysis, and long-term safety profiles. For hydrogel-based systems exhibiting translational potential, further investigations into large animal models, repeat-dose studies, immunotoxicity assessments, and pharmacokinetic analyses are imperative. Only after systematic validation of mechanistic evidence, material performance, and preclinical safety can hydrogel-based strategies targeting the PI3K-Akt-mTOR pathway truly progress toward clinical translation for age-related OA. Furthermore, while exosome delivery, 3D-printed osteochondral scaffolds, and piezoelectric/piezoresistive materials represent potential long-term extensions of the hydrogel platform^[116-127], these fields entail independent challenges regarding source quality control, structural reconstruction, or electro-stimulation. Given the requirement for deeper mechanistic integration with the core theme of PI3K-Akt-mTOR/autophagy-based intra-articular delivery, these are not presented as primary strategies herein [Figure 10].

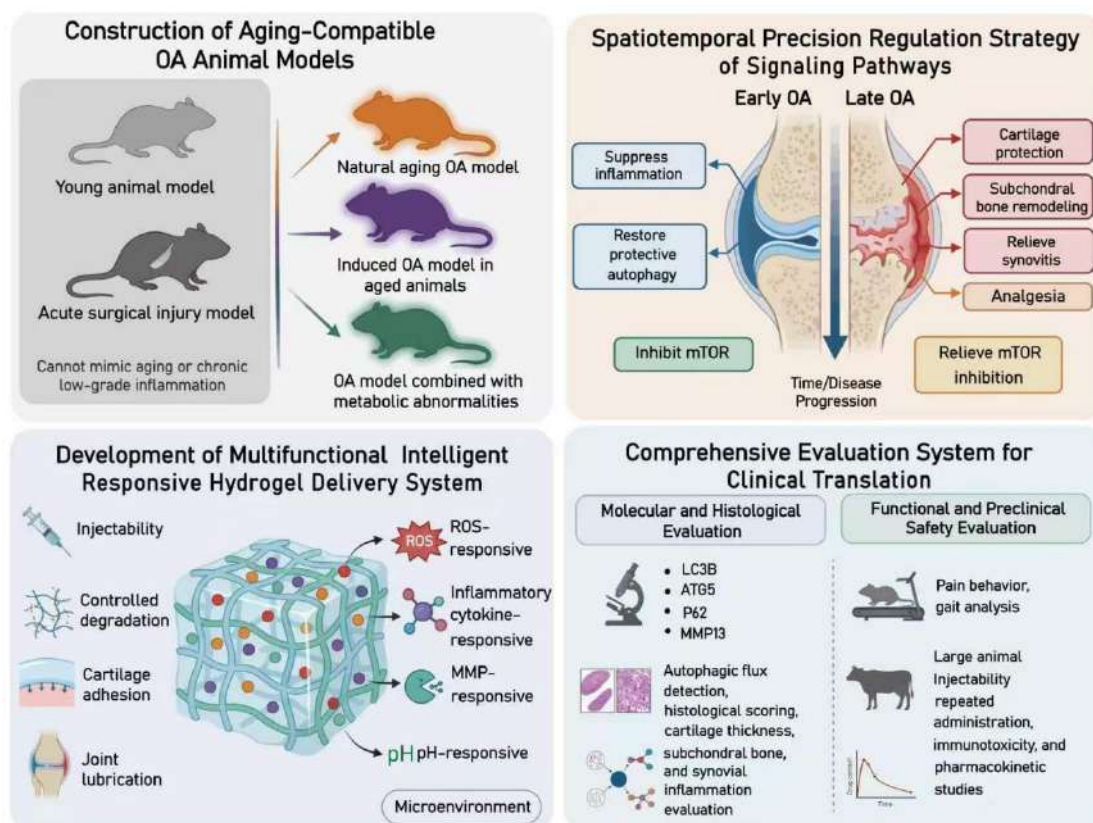


Figure 10. Recommendations for hydrogels applied to articular joints.

CONCLUSION

Age-related osteoarthritis (OA) is a degenerative joint disease driven by the synergistic effects of chronic low-grade inflammation, oxidative stress, mitochondrial dysfunction, cellular senescence, and extracellular matrix metabolic imbalance. Diminished chondrocyte autophagy is a critical consequence of these intersecting pathological factors, further impairing the cellular capacity to clear damaged organelles and aberrant proteins, thereby accelerating inflammation amplification, cellular senescence, and extracellular matrix degradation. Consequently, targeting chondrocyte autophagy provides a significant entry point for exploring disease-modifying therapeutic strategies for age-related OA.

As a central signaling axis regulating cellular metabolism, survival, and autophagy, the PI3K-Akt-mTOR pathway plays a pivotal role in chondrocyte injury, inflammatory responses, and matrix degradation during OA progression. Current evidence suggests

that EGFR inhibitors, PI3K inhibitors, mTOR inhibitors, dual PI3K/mTOR inhibitors, as well as certain natural compounds and active traditional Chinese medicine ingredients, may modulate the PI3K-Akt-mTOR pathway and downstream autophagic processes via distinct nodes. Among these, the mechanistic linkage between mTOR inhibitors and autophagy regulation is relatively direct, and strategies such as hydrogel-mediated rapamycin delivery provide a prototypical foundation for local modulation of the OA microenvironment. However, the strength of evidence varies significantly across these agents, and some candidates primarily derived from non-OA models, *in vitro* assays, or mechanistic predictions cannot be directly extrapolated into established therapeutic regimens for age-related OA.

As platforms for intra-articular delivery and cartilage functional replacement, hydrogels provide a robust foundation for PI3K-Akt-mTOR-targeted therapeutics by extending drug retention, enabling sustained release, minimizing systemic exposure, enhancing local lubrication, and facilitating cartilage-specific targeting. Injectable biodegradable hydrogels are particularly suited for establishing drug reservoirs and controlled release, whereas nanoparticle-hydrogel composite systems, lubricating hydrogel microspheres, and stimuli-responsive hydrogels further enhance local residency and on-demand release capabilities; conversely, non-degradable or slowly degradable hydrogels predominantly represent exploratory avenues for functional replacement or load-bearing support in end-stage OA. Particularly for elderly OA patients, local delivery strategies serve to mitigate systemic medication risks and improve the stability of therapeutic efficacy within the diseased joint. However, hydrogels cannot supersede the necessity for rigorous validation of drug efficacy and safety; their composition, degradation behavior, release kinetics, intra-articular retention time, immunogenicity, and long-term safety profile necessitate systematic evaluation.

In summary, targeting the PI3K-Akt-mTOR pathway to modulate chondrocyte autophagy, integrated with hydrogel-based intra-articular local delivery, represents a highly promising avenue in therapeutic research for age-related OA. Future research

should focus on clarifying the cell-type-specific and stage-specific roles of this pathway under various microenvironmental conditions, standardizing autophagic flux detection, establishing animal models that more faithfully recapitulate the characteristics of age-related OA, and conducting comprehensive long-term safety, large animal, and preclinical translational assessments. Only through the robust validation of mechanistic evidence, therapeutic efficacy, material safety, and functional outcomes can this strategy provide a reliable theoretical and experimental basis for precision local intervention in age-related OA.

DECLARATIONS

Authors' contributions

Writing – original draft, Methodology: Liu SY, Mi ZW, Liang SJ, and Jiao ZH;

Formal analysis, Data curation: Liang H, Gao XY;

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Availability of data and materials

Not applicable.

AI and AI-assisted tools statement

During the preparation of this review, artificial- intelligence- assisted tools were adopted to improve work efficiency. ChatGPT was used for literature calibration, sorting of reference order, translation assistance, and optimization of English grammar and sentence patterns. Citexs was applied to generate preliminary sketches for literature- related figures. All outputs generated by the above- mentioned AI tools were manually reviewed, revised and verified by the author. The research perspectives, logical framework, argumentation, core viewpoints and conclusions of this review are

independently completed by the author. No core scientific findings were directly produced by artificial intelligence. The author takes full responsibility for the academic integrity of this manuscript.

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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