

Review Article

The “skeletal muscle-cartilage unit” in knee osteoarthritis: from mechanical coupling to molecular mechanisms

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Abstract: Knee osteoarthritis (KOA) is a degenerative joint condition substantially influenced by the surrounding musculature. Skeletal muscle and articular cartilage form an integrated “skeletal muscle-cartilage unit” crucial for maintaining joint homeostasis. This review seeks to elucidate the biomechanical and molecular connections within the skeletal muscle-cartilage unit and their relevance to the development and management of KOA. Skeletal muscle failure, characterized by atrophy, compromises knee biomechanics. This atypical mechanical stress is transmitted by mechanosensitive ion channels (e.g., Piezo1, TRPV4) on chondrocytes, resulting in matrix degradation. At the same time, pathological skeletal muscle functions as an altered endocrine organ. Dysregulated myokine synthesis (elevated IL-6, less irisin) and the activation of shared pathways, such as NF-κB, substantially modify the local microenvironment. Conversely, restoring optimum muscle function can significantly reduce the generation of inflammatory mediators and protect cartilage integrity. Modifying this axis through evidence-based exercise treatment efficiently restores joint alignment, enhances physiological mechanical stress, and diminishes pro-inflammatory signals. Future research examining the relationship between exercise therapy, skeletal muscle secretion, and cartilage homeostasis holds significant promise for the enhancement of targeted KOA therapies.

Keywords: Knee osteoarthritis, skeletal muscle, biomechanics, mechanosensitive ion channels, myokines, exercise therapy

Introduction

Knee Osteoarthritis (KOA) is the most common chronic degenerative joint disorder seen globally, marked by the progressive deterioration of articular cartilage, remodeling of subchondral bone, synovial inflammation, and lesions in periarticular soft tissues, clinically presenting as chronic joint pain, stiffness, and functional limitations [1, 2]. KOA constitutes over 80% of the whole global burden of osteoarthritis. The rapid aging of the global population, coupled with the persistent increase in obesity rates,

has led to a rising prevalence, particularly among younger demographics. This trend not only significantly diminishes patients' quality of life but also places a substantial strain on global public health systems and socioeconomic development [3, 4]. Nonetheless, the present clinical management of KOA predominantly emphasizes symptomatic pain alleviation and functional enhancement, with no curative therapies available that can successfully postpone or reverse disease progression. The current therapeutic benefits significantly fall short of clinical expectations.

For an extended period, KOA research has predominantly adhered to the “cartilage-centric” paradigm, which perceives KOA as a solely degenerative condition of articular cartilage, emphasizing the molecular mechanisms behind cartilage degradation and specific therapeutic interventions. However, this conventional understanding fails to account for the pain and functional limitations seen in early-stage KOA patients prior to notable radiographic alterations in cartilage structure, nor does it adequately clarify the generally restricted clinical effectiveness of therapeutic approaches that focus solely on cartilage. In recent years, building upon the foundational concepts of the “muscle-bone unit” [5] and “osteochondral unit” [6], the academic community has introduced the innovative notion of the “skeletal muscle-cartilage unit” [7], a functional integrative unit that encompasses periarticular skeletal muscle (including tendons and myofascia), articular cartilage, synovium, and the mechanical conduction systems and molecular signaling networks among these components, regarded as an inseparable entity that is anatomically linked, functionally interdependent, and pathologically interconnected.

Skeletal muscle, as the fundamental driving element of the skeletal muscle-cartilage unit, is the largest organ system in the human body, essential for motor function, energy metabolism, and systemic homeostasis, while also serving as the principal regulator of joint dynamic stability [8]. Accumulating evidence indicates that skeletal muscle dysfunction precedes cartilage degeneration and is an established independent risk factor for the onset and progression of KOA [9-12]. Skeletal muscle, through active contraction, provides dynamic stability to joints, in contrast to the passive static stability offered by connective tissues like ligaments and joint capsules. It is crucial for preserving normal lower limb alignment and ensuring the precise movement trajectory of the knee joint. In daily activities, the knee joint may endure loads of 3-6 times the body weight, whereas the synchronized contraction of surrounding muscle groups, including the quadriceps and hamstrings, can mitigate about 50% of joint impact forces, thereby diminishing peak pressure and cumulative load on articular cartilage [13, 14]. The exact timing of skeletal muscle activation and the coordinated

contraction of opposing muscles govern the intricate movement patterns of the knee joint, such as flexion, extension, and rotation, thereby averting undue localized stress on the articular surface. Skeletal muscle atrophy, characterized by diminished muscle strength or neuromuscular control deficits, results in dynamic stability imbalance of the knee joint, misalignment of the lower limbs, and irregular joint load distribution, consequently hastening cartilage wear and degeneration. Moreover, as the predominant endocrine organ in the human body, skeletal muscle modulates the local joint microenvironment by the secretion of several myokines, which directly influence the metabolism, proliferation, and death of chondrocytes [15, 16]. Patients with KOA consistently exhibit distinct pathological alterations in periarticular skeletal muscle, characterized by diminished muscle mass, reduced muscle strength, and intramuscular fat infiltration. These anomalies further compromise joint stability and cartilage homeostasis.

This review posits that the fundamental academic perspective is that the homeostatic imbalance of the skeletal muscle-cartilage unit is the primary mechanism driving the start and progression of KOA, based on a systematic integration and critical review of available studies. In contrast to the conventional “cartilage-centric” theory, we contend that KOA is fundamentally a functional disorder of the skeletal muscle-cartilage unit: skeletal muscle dysfunction serves as the primary catalyst of the disease, disrupting cartilage homeostasis via the dual mechanisms of aberrant mechanical conduction and dysregulation of molecular signaling, thereby propelling the pathological progression of KOA (**Figure 1**). This perspective not only logically elucidates the clinical manifestations of early KOA and the constraints of conventional therapies but also offers an innovative theoretical framework for the prevention and management of KOA. This review systematically reviews the pathological characteristics of skeletal muscle in KOA from a functional integrative perspective of the skeletal muscle-cartilage unit, elucidates the mechanical and molecular mechanisms through which skeletal muscle abnormalities disrupt homeostasis in this unit, and evaluates prospective therapeutic strategies targeting skeletal muscle for KOA. The objective is to establish a novel theoretical

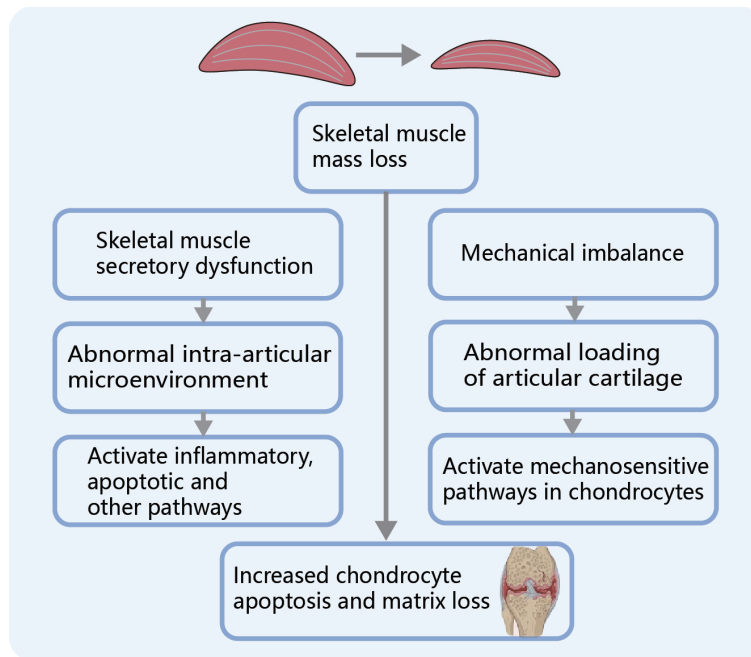


Figure 1. Skeletal muscle mass loss is the primary driver of skeletal muscle-cartilage Unit dysfunction. It drives cartilage degeneration through two parallel and synergistic pathways: (1) The molecular pathway: Skeletal muscle secretory dysfunction leads to abnormal intra-articular microenvironment, which activates inflammatory, apoptotic and other catabolic pathways in chondrocytes; (2) The biomechanical pathway: Skeletal muscle dysfunction causes joint mechanical imbalance and abnormal loading of articular cartilage, which activates mechanosensitive signaling pathways in chondrocytes. Both pathways converge to induce increased chondrocyte apoptosis and extracellular matrix loss, ultimately promoting the development and progression of KOA.

foundation and clinical understanding for the accurate prevention and management of KOA.

Biomechanical coupling between skeletal muscle and cartilage

Primary driver of articular mechanical Imbalance: skeletal muscle mass loss

Articular cartilage is devoid of blood vessels and nerves, and its homeostasis is mostly reliant on a suitable mechanical environment. Skeletal muscle, the principal tissue responsible for exerting and absorbing mechanical pressures, is essential for preserving the mechanical microenvironment of chondrocytes [17]. Muscle contraction produces the necessary force for movement, whereas joints and bones provide support to the skeletal muscles and facilitate force generation. Deviant skeletal muscle activity can disturb the biomechanical environment of the joints, thereby affecting

chondrocyte destiny via mechanosensitive pathways.

Contemporary medicine ascribes the pathological alterations linked to a reduction in skeletal muscle mass to muscle fiber atrophy, decreased fiber cross-sectional area, changes in fiber type, overall protein depletion, and histological fat infiltration, which are accompanied by reduced muscle strength, irregular muscle activation, and altered movement patterns, including gait abnormalities [18]. Skeletal muscle weakness is a critical factor in the initiation and advancement of KOA and correlates with a heightened risk of falls [19]. Cunha et al. [20] demonstrated in a rat model of KOA induced by anterior cruciate ligament transection (ACLT) that the cross-sectional area of muscle fibers in the quadriceps femoris and tibialis anterior muscles was significantly diminished in the KOA group, thereby confirming the presence of muscular atrophy

within the pathological framework of KOA. Yamauchi et al. [21] utilized magnetic resonance imaging (MRI) to assess the cross-sectional area of lower limb muscles in patients with KOA and observed a significant reduction in muscle volume in the lower limbs. The researchers determined that the ratio of the cross-sectional area of the adductor muscles in the mid-thigh to that of the quadriceps, along with the ratio of the cross-sectional area of the semimembranosus muscle to that of the hamstrings, are the most dependable indicators for evaluating thigh muscle atrophy in KOA. Additionally, certain researchers have observed that this atrophy is particularly significant in the adductor muscles [22]. Furthermore, adipose infiltration in the thigh musculature is typically more significant in individuals with knee osteoarthritis (KOA) than in those without the ailment [23]. AJ Teichtahl et al. [24] further found that reducing fat infiltration in the adductor muscles can markedly decrease the preva-

lence of KOA and is beneficial for affected patients.

The decline in physiological function ultimately leads to compensatory alterations in motor control patterns, including adjustments in muscle activation, joint range of motion, and gait patterns [25]. To mitigate the skeletal muscular weakness commonly observed in patients with KOA, the nervous system typically employs a “co-activation” strategy, which entails the simultaneous contraction of agonist and antagonist muscles to enhance joint rigidity and stability [26]. Co-activation enhances joint stability and alleviates pain from extreme postures, but it also increases contact pressure on the articular surfaces, thereby accelerating the mechanical deterioration of cartilage [27]. A study by Rutherford et al. demonstrated that systemic changes in certain knee muscle activation patterns correlate with the severity of the Kellgren-Lawrence (KL) grades system [28]. Haim et al. [29] noted that 60%-80% of the load is transmitted through the medial compartment of the knee during ambulation, leading to much more pressure in this area compared to the lateral compartment; hence, co-activation of the medial lower limb muscles is more common. The co-activation index of the vastus medialis and medial gastrocnemius (VM-MG) is advocated as an essential measure for evaluating the effectiveness of KOA rehabilitation [30].

Mechanotransduction bridge in articular chondrocytes: mechanosensitive ion channels

Skeletal muscle is crucial for maintaining joint stability by regulating the biomechanical environment of the joint and controlling movement. Decreased muscle strength or impaired coordination may lead to abnormal joint loading, hence promoting the start and progression of KOA. Chondrocytes perceive mechanical loads through mechanosensitive ion channels on their membranes, converting these stimuli into intracellular biological signals that regulate gene expression, metabolic activity, and cell fate, thereby aiding in the preservation of cartilage tissue homeostasis or the response to injury. Articular cartilage mostly comprises chondrocytes and an extracellular matrix abundant in type II collagen and sulfated proteoglycans. The extracellular matrix provides a micro-

environment for chondrocytes and, due to its viscoelastic properties, regulates the transmission and buffering of mechanical stimuli at both tissue and cellular levels, influencing cellular mechanosensitivity and signal transduction [31]. In optimal conditions, the magnitude and orientation of applied forces are crucial for maintaining cartilage health, whereas excessive or irregular mechanical stimuli accelerate cartilage degeneration [32]. Recent studies reveal that mechanosensitive ion channels, such as Piezo1 and Transient Receptor Potential Vanilloid 4 (TRPV4), function as the primary mechanoreceptors in chondrocytes. TRPV4 often transmits protective signals in response to physiological stress and changes in osmotic pressure, whereas Piezo1 commonly interacts with inflammatory pathways during abnormal mechanical loading conditions. Notwithstanding the distinct mechanical transmission processes of the two channels, they may have synergistic or complimentary effects through downstream signaling, collectively influencing disease onset and progression [33].

The Piezo channel protein family, discovered in 2010, represents a novel class of mechanosensitive ion channels. Multiple studies demonstrate that cells utilize Piezo1/2 ion channels to sense external environmental stimuli, converting mechanical impulses into biological signals (Ca^{2+} influx), hence influencing physiological and pathological processes such as cell proliferation, differentiation, and apoptosis [34]. In the unusual mechanical conditions caused by skeletal muscle atrophy, continuous activation of Piezo1 modulates the YAP pathway, increasing the synthesis of matrix metalloproteinases, which ultimately results in chondrocyte apoptosis and matrix degradation [35]. The Piezo1 pathway is closely associated with intra-articular inflammation; inflammatory mediators such as IL-1 β and TNF- α can increase Piezo1 expression, while excessive activation of Piezo1 intensifies the inflammatory response, establishing a “mechanical-inflammatory” positive feedback loop that accelerates cartilage degradation [36]. In vitro studies by Li et al. demonstrated that the application of fluid shear stress to chondrocytes increases Ca^{2+} levels and augments Piezo1 expression, resulting in elevated MMP-13 expression and subsequent matrix degradation; however, this effect is counteracted by the administration of

the inhibitor GsMTx4 [37]. Furthermore, Piezo1-mediated Ca^{2+} influx has been linked to endoplasmic reticulum stress (ERS); key molecules in the ERS signaling pathway, including as C/EBP homologs, have shown a positive correlation with cartilage degradation and apoptosis [38]. Thus, abnormal mechanical stimulation due to skeletal muscle dysfunction is the principal mechanism that triggers increased catabolic activity in cartilage via the Piezo1-mediated calcium signaling pathway.

TRPV4 is a member of the vanilloid receptor subfamily of the transient receptor potential ion channel family. It is a non-selective cation channel with moderate calcium ion permeability, widely distributed throughout the organs and tissues of various organisms. The TRPV4 ion channel operates as a multimodal receptor, activated by various inputs from internal and external environments, including as pH, mechanical force, temperature, and osmotic pressure, and is crucial for the regulation of normal physiological parameters [39]. TRPV4 is crucial for the proper growth and development of cartilage; moderate mechanical stimulation can promote chondrocyte proliferation and matrix formation through the TRPV4 and phosphatidylinositol 3-kinase/protein kinase B (PI3K/AKT) signaling pathways [40]. O'Connor et al. [39] found that without mechanical stimulation, the application of TRPV4 agonists to cells significantly increases matrix formation. The deletion of the TRPV4 gene accelerates the degenerative progression of osteoarthritis in aging and obese animal models [41]. Thus, TRPV4 is crucial for chondrocytes' perception of mechanical stimuli and for the synthesis and degradation of the cartilage matrix (**Figure 2**).

Through systematic integration and quantitative analysis of current clinical and fundamental research, a distinct mechanical coupling threshold effect has been identified between skeletal muscle function and cartilage health within the skeletal muscle-cartilage unit: a reduction in periarticular muscle strength exceeding 30% from baseline levels results in significant and largely irreversible deterioration of the joint mechanical environment. This threshold effect has been corroborated by numerous high-quality clinical research. A comprehensive meta-analysis conducted by Øiestad et al.,

encompassing 46,819 participants, revealed that people in the lowest tertile of knee extensor strength had a 1.85-fold increased risk of symptomatic KOA in women and a 1.43-fold increased risk in men, relative to those in the highest tertile [42]. Culvenor et al. [43] further corroborated that a $\geq 30\%$ decline in muscle strength is substantially linked to an elevated risk of structural development in KOA. A prospective cohort study conducted by Wang et al. revealed that a 1 cm^2 decrease in the cross-sectional area of the vastus medialis correlates with a $10.9 \mu\text{L}$ rise in medial tibial cartilage loss over two years and elevates the probability of joint replacement by 39% [44]. The molecular foundation of this threshold effect is intricately linked to the varied activation of mechanosensitive ion channels in chondrocytes. When skeletal muscle activity diminishes within the threshold range, the body preserves joint mechanical homeostasis via neuromuscular compensation mechanisms, including muscle co-activation. At this juncture, chondrocytes experience mechanical strain within the physiological range of 10%-15%, which mostly activates the TRPV4 channel-mediated protective signaling pathway [45]. When skeletal muscle performance deteriorates beyond this threshold, neuromuscular compensation mechanisms fail, resulting in significant malalignment of the lower leg and pronounced uneven distribution of joint loads. This exposes chondrocytes to mechanical strain over the pathogenic threshold of 20%, which consistently activates Piezo1 channels, resulting in calcium overload, inflammatory reactions, and chondrocyte apoptosis, thus commencing the irreversible process of cartilage degeneration [45]. The previously indicated threshold effect offers a distinct quantitative measure for the early stratified intervention of KOA. Interventions executed prior to the decrease of skeletal muscle function beyond the threshold can effectively rectify joint mechanical imbalance. Once the threshold is surpassed, the effectiveness of single muscle strength training diminishes, necessitating complete therapeutic measures, including alignment correction and anti-inflammatory therapy.

Skeletal muscle to cartilage signaling

Skeletal muscle functions as a source of mechanical stress and an essential endocrine

Skeletal muscle-cartilage crosstalk in knee osteoarthritis

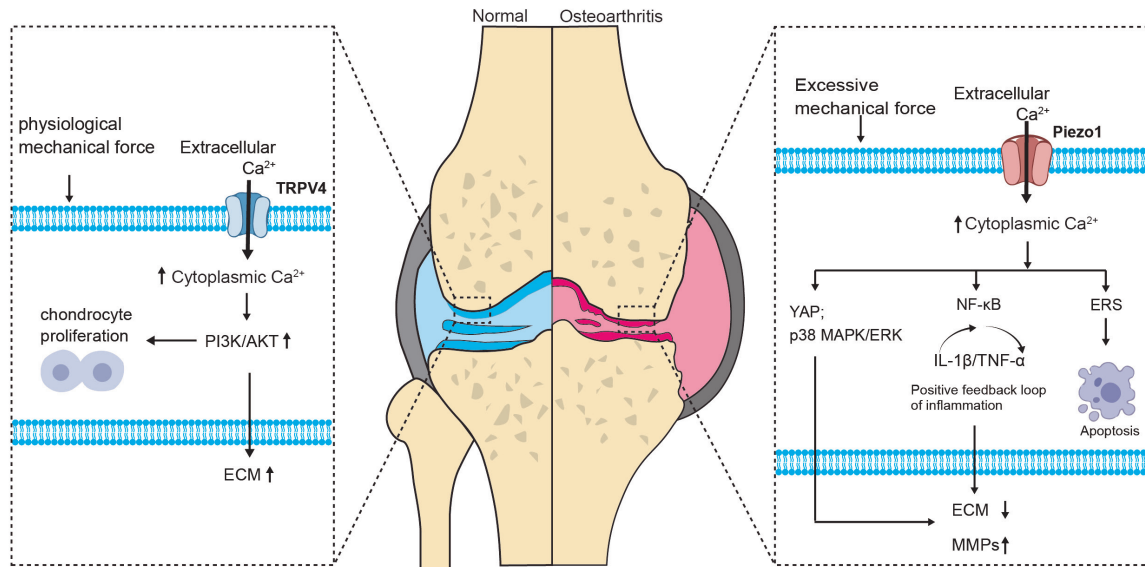


Figure 2. This schematic illustrates the distinct functions of TRPV4 and Piezo1 in mediating chondrocyte responses to mechanical stimuli under physiological and pathological conditions. Under normal conditions, physiological mechanical force activates TRPV4 channels, leading to moderate calcium influx and subsequent activation of the PI3K/AKT signaling pathway. This promotes chondrocyte proliferation and extracellular matrix (ECM) synthesis, thereby maintaining cartilage homeostasis. In contrast, in osteoarthritis (OA), excessive mechanical force activates Piezo1 channels, causing sustained cytoplasmic calcium overload. This triggers three major downstream pathogenic pathways: (1) Activation of YAP and p38 MAPK/ERK pathways, which upregulate matrix metalloproteinases (MMPs) and promote ECM degradation; (2) Activation of the NF- κ B pathway, which induces pro-inflammatory cytokine (IL-1 β , TNF- α) production and forms a positive feedback loop of inflammation; (3) Induction of endoplasmic reticulum stress (ERS), which leads to chondrocyte apoptosis. The combined effects of these pathways result in progressive cartilage degeneration.

organ. It engages in chemical communication with joint constituents, such as the synovium, cartilage, and bone, through the secretion of various cytokines and metabolites, hence playing a role in the regulation of joint homeostasis and inflammation [46]. This section analyzes potential molecular mediators linking skeletal muscle and cartilage, encompassing myokines, miRNAs, myogenic stem cells, and shared pathogenic pathways (**Figure 3**).

Myokines

Myokines are a class of cytokines or peptide molecules secreted by skeletal muscle during contraction, metabolic activities, or stress. They affect local or systemic tissues via autocrine, paracrine, and endocrine systems to regulate various physiological and pathological processes [47]. Myokines comprise IL-6, irisin, and various other bioactive peptides.

Research examining the molecular foundation of the association between skeletal muscle and cartilage in KOA identified inflammatory

cytokines as essential biological mediators. In the context of systemic or localized chronic inflammation, sustained elevated levels of IL-6 promote osteoclast activation and cartilage matrix degradation by activating signaling pathways such as Janus kinase/signal transducer and activator of transcription 3 (JAK/STAT3), mitogen-activated protein kinase (MAPK), and nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B), thereby accelerating bone resorption and joint degeneration [5, 48]. Levinger et al. [49] noted elevated skeletal muscle inflammation in KOA patients, marked by higher production of IL-6, p65 NF- κ B, STAT3, and JNK proteins compared to the control group. Furthermore, animal studies have shown that the activation of the IL-6 receptor and its downstream STAT3/ERK signaling in articular cartilage is associated with cartilage deterioration and discomfort. Conversely, the deletion of IL-6 or the suppression of its downstream signaling pathways can alleviate cartilage deterioration and pain hypersensitivity. Inflammatory responses in skeletal muscle may disrupt the

Skeletal muscle-cartilage crosstalk in knee osteoarthritis

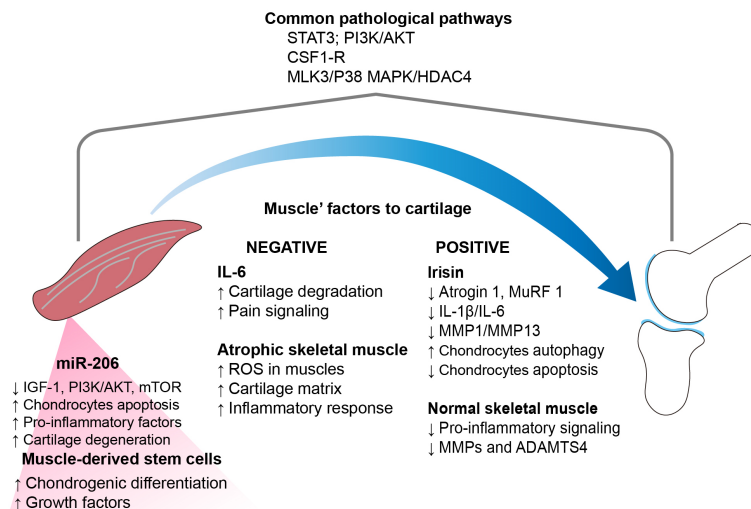


Figure 3. Molecular mechanisms of skeletal muscle-cartilage crosstalk. The diagram illustrates the bidirectional influence of skeletal muscle on articular cartilage homeostasis. Pathological factors (negative), including elevated IL-6, atrophied muscle secretions, and muscle-derived miR-206, drive cartilage degradation, reactive oxygen species (ROS) accumulation, and chondrocyte apoptosis by suppressing the IGF-1/PI3K/AKT/mTOR axis. Conversely, protective factors (positive) derived from healthy muscle, such as the myokine irisin and myogenic stem cells, mitigate joint damage by inhibiting pro-inflammatory signaling (IL-1 β , IL-6), downregulating matrix-degrading enzymes (MMPs, ADAMTS4), and promoting chondrogenic differentiation and autophagy. The crosstalk between these tissues is further mediated by shared common pathological pathways, including STAT3, PI3K/AKT, CSF1-R, and MLK3/P38 MAPK/HDAC4.

local inflammatory and metabolic balance in the joint through IL-6 and its downstream signaling pathways, hence promoting the progression of KOA [50]. In vitro co-culture studies reveal that secretions from healthy skeletal muscle can inhibit IL-1 β /TNF- α -induced chondroinflammation and cell death. The primary mechanism involves the suppression of pro-inflammatory signals, thereby diminishing the expression of matrix metalloproteinases (MMPs) and a disintegrin and metalloproteinase with thrombospondin motifs 4 (ADAMTS4) [51]. Conversely, atrophied skeletal muscle cells, coupled with elevated levels of reactive oxygen species (ROS), may stimulate the synovium to produce and release ROS into the joint cavity, resulting in cartilage matrix breakdown and exacerbating the inflammatory response [52].

Irisin is an anti-aging agent secreted by skeletal muscle during physical activity; it mitigates muscle atrophy, promotes osteoblast proliferation, and suppresses chondrocyte apoptosis [53]. The synthesis of irisin is closely linked to

peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1 α); muscular contraction and physical activity increase PGC-1 α expression, which in turn promotes the transcription of fibronectin type III domain-containing protein 5 (FNDC5) and, through proteolytic cleavage, releases irisin into the bloodstream [54]. Clinical and epidemiological studies demonstrate that serum and synovial fluid irisin concentrations are negatively related to the severity of KOA; notably, diminished irisin levels are often linked to increased C-reactive protein (CRP) levels and higher K-L grades [55]. Liu et al. [56] performed in vitro experiments showing that irisin can suppress muscle atrophy-related genes, stimulate osteoblast proliferation, enhance mitochondrial function, and protect chondrocytes by promoting autophagy and inhibiting apoptosis, thereby alleviating inflammation and tissue damage in KOA. Furthermore, an additional in vitro investigation using human chondrocytes demonstrated that irisin administration markedly elevated the ratio of collagen II to collagen I mRNA levels, suggesting that irisin can promote chondrogenic differentiation [57]. In animal models of post-traumatic osteoarthritis (PTOA) and ACLT, exercise or mechanical stress stimulates the PGC-1 α /irisin pathway, which reduces pro-inflammatory mediators such as IL-1 β and TNF- α in the joint cavity. Furthermore, exogenous irisin treatment suppresses IL-1 β /IL-6 production, downregulates MMP-1 and MMP-13, protects the extracellular matrix, and promotes chondrocyte proliferation, thereby delaying the progression of osteoarthritis [53].

miRNAs

Significant signaling pathways between skeletal muscle and cartilage encompass several microRNAs (miRNAs). Myogenic miRNAs are short non-coding RNAs predominantly found in skeletal muscle; they have a role in muscle

development, regeneration, and metabolic control, and can influence joint tissues through exosomes [58]. A recent study has elucidated the intricate functions of myogenic miRNAs in cartilage degradation. miR-206 is often down-regulated in cartilage tissue impacted by osteoarthritis. Inhibition of insulin-like growth factor-1 (IGF-1) and downregulation of the PI3K/AKT-mTOR signaling pathway result in heightened chondrocyte apoptosis and impaired autophagy, concurrently increasing pro-inflammatory cytokine levels (IL-6, IL-17, IL-18), thus facilitating cartilage degeneration [59]. Subsequent research has demonstrated that miRNAs can modulate the synthesis of critical elements in inflammatory pathways linked to extracellular matrix degradation, including as IL-1 β and MMP-13, hence affecting the advancement of KOA [60]. The regulating function of skeletal muscle-derived miRNAs in the pathophysiology of KOA necessitates further systematic validation.

Muscle-derived stem cells

Muscle-derived stem cells (MDSCs) demonstrate significant potential for chondrogenic differentiation [61]. Chan et al. [62] delivered MDSCs through intra-articular injection in a diabetes-induced osteoarthritis model, demonstrating that these cells enhanced anabolic processes in articular cartilage and mitigated pathological damage. The genetic modification of particular myogenic cell subpopulations can markedly improve therapeutic efficacy: the PP6 subpopulation transfected with bone morphogenetic protein (BMP4)/GFP demonstrated elevated survival rates and enhanced chondrogenic potential in vivo, thereby substantially facilitating high-quality cartilage regeneration [63]. Kuroda et al. [64] observed that the simultaneous treatment of BMP4+/sFlt-1-positive myogenic stem cells and a platelet-rich mixture significantly enhances cartilage regeneration in the knee joints of chemically generated immunodeficient rats suffering from osteoarthritis. A study conducted in vitro by Gao et al. shown that viral-mediated BMP2/GFP transduction significantly improves the chondrogenic differentiation capacity of human MDSCs [65]. A BMP2-releasing gel has demonstrated the ability to stimulate the differentiation of MDSCs into chondrocytes, hence facilitating cartilage regeneration and repair in

a monosodium iodoacetate (MIA)-induced osteoarthritis model. In conclusion, myogenic stem cells can efficiently facilitate the regeneration of impaired cartilage.

Common pathological pathways

Increasing evidence suggests that degenerative changes in skeletal muscle and cartilage may employ similar signaling mechanisms. Network pharmacology and animal studies indicate that curcumin can diminish myocyte apoptosis and promote cartilage regeneration via regulating the phosphorylation levels of the STAT3 and PI3K/AKT pathways [66]. Keeble et al. [67] found in a mouse model that the inhibition of the colony-stimulating factor-1 receptor (CSF1-R) could simultaneously reduce cartilage degradation and muscle atrophy. Wang et al. [68] demonstrated that the mixed lineage kinase 3/P38 MAPK/histone deacetylase 4 (MLK3/P38 MAPK/HDAC4) pathway represents a common pathological link between muscle injury and cartilage degeneration; the bioactive compound HBP-A can simultaneously inhibit both muscle and cartilage degeneration by regulating the MLK3/P38 MAPK/HDAC4 axis.

Recognizing mechanical imbalance and disrupted molecular communication as the two primary factors in KOA progression, research on knee preservation has shifted to investigating how clinical interventions - particularly exercise therapy-can restore the self-stabilizing mechanisms of the “skeletal muscle-cartilage functional unit”.

The potential role of exercise in skeletal muscle-cartilage crosstalk

An expanding collection of international guidelines uniformly advocates for exercise therapy as the first-line core treatment for KOA [69], encompassing modalities such as aerobic exercise, strength training, resistance training, aquatic exercise, and traditional mind-body practices like Tai Chi and Baduanjin [70-72]. Comprehensive clinical and fundamental research has substantiated that exercise therapy postpones the pathological progression of KOA via multidimensional and multitarget mechanisms [73]. Clinical studies indicate that regular exercise substantially alleviates pain, stiff-

ness, and functional limitations in patients; Ettinger et al. [71] discovered in a randomized single-blind trial that aerobic exercise significantly enhanced physical function in elderly KOA patients; Baker et al. [70] further corroborated that systematic strength training augmented knee extensor strength by 71% and diminished pain by 36%, thereby markedly enhancing patients' quality of life. Moreover, moderate-intensity aerobic exercise (30 minutes per session, three times weekly) is the predominant rehabilitation protocol in clinical settings, with research indicating a 30%-40% reduction in pain levels and a substantial enhancement in the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score [74]. Aquatic training utilizes the buoyancy, resistance, and temperature characteristics of water to rebuild muscle strength and joint flexibility, decrease joint loading, and has been demonstrated to alleviate pain and enhance knee function [75].

From a kinesiological standpoint, evidence-based exercise treatment mitigates cartilage deterioration caused by aberrant mechanical stress by enhancing lower limb alignment and optimizing load distribution [76]. The strength of periarticular muscles, especially the quadriceps, is essential for preserving joint function; increased muscular strength serves as a "biological shock absorber" for subchondral bone and menisci, efficiently dispersing joint impact stresses [77, 78]. Research demonstrates that sustained training exceeding 12 weeks can enhance quadriceps strength by 20%-30% [77]. Simultaneously, static stretching of the hamstrings and neuromuscular training that includes dynamic stability and coordination exercises augment the impact resistance of specific muscle groups, enhance joint stability and range of motion, thereby diminishing the risk of ligament and intra-articular injuries [79, 80].

At the molecular level, moderate exercise markedly enhances the local joint microenvironment: it facilitates blood circulation, accelerates the metabolism of inflammatory mediators, and substantially diminishes the levels of pro-inflammatory cytokines such as IL-1 β and TNF- α in synovial fluid; concurrently, it upregulates the expression of growth factors (e.g., IGF-1, TGF- β) and anti-inflammatory cytokines

(e.g., IL-4, IL-10), thereby inhibiting matrix degradation and promoting cartilage matrix synthesis [81, 82]. Aerobic exercise improves the anti-apoptotic and antioxidant stress capabilities of chondrocytes while decreasing levels of cartilage inflammatory markers [83]; optimal exercise intensity also promotes the expression of BMP family proteins (BMP2, BMP4, and BMP6) in superficial chondrocytes, thereby effectively postponing cartilage degeneration and osteophyte development.

Closing remarks and future directions

Skeletal muscle and articular cartilage are tightly coupled anatomically and functionally, constituting an inseparable skeletal muscle-cartilage functional unit (**Table 1**). Skeletal muscle dysfunction is a critical driving role in the intricate pathological progression of KOA: on the one hand, muscle atrophy and neuromuscular control abnormalities disturb lower limb biomechanical balance, inducing chondrocyte apoptosis and extracellular matrix degradation via mechanosensitive pathways such as Piezo1 and TRPV4; on the other hand, as a significant endocrine/paracrine organ, the pathological degeneration of skeletal muscle results in a dysregulated myokine secretion profile, modifying the local metabolic and inflammatory microenvironment of the joint. The synergistic effect of mechanical imbalance and abnormal molecular communication forms the core mechanism of KOA pathogenesis - the "skeletal muscle-cartilage unit". The newly discovered mechanical coupling threshold effect of the muscle-cartilage unit offers a quantitative foundation for early stratified intervention. Consequently, focusing on skeletal muscle as the core of KOA rehabilitation and treatment possesses substantial theoretical and clinical importance.

While current research has preliminarily elucidated the fundamental framework of skeletal muscle-cartilage interaction and established exercise therapy as the first-line core treatment for KOA, many critical scientific inquiries remain unresolved. Recent studies have primarily focused on improving joint biomechanics through exercise therapy, yet there remains insufficient evidence concerning the molecular mechanisms by which exercise therapy protects cartilage, especially the critical

Skeletal muscle-cartilage crosstalk in knee osteoarthritis

Table 1. Key mediators and mechanisms of skeletal muscle-cartilage crosstalk in knee osteoarthritis

Type of interaction	Critical Factors	Representative Evidence	Main Functions in Skeletal Muscle-Cartilage Crosstalk	References
Physical and biomechanical	Excessive mechanical force	Patients undergoing total knee arthroplasty (TKA)	Piezo1 ↑ → Inducing chondrocyte apoptosis via the YAP pathway	[35]
		Mouse model of OA/In vitro studies of chondrocytes	Piezo1 ↑ → Promoting Inflammatory Responses and the Progression of Osteoarthritis	[36]
		In vitro studies on chondrocytes	Piezo1 ↑ → MMP-13 expression increased, leading to matrix degradation; however, this phenomenon disappeared upon the addition of the inhibitor GsMTx4	[37]
		Rat model of OA	Piezo1 ↑ → Endoplasmic reticulum stress (ERS), apoptosis; GsMTx4 exerts a partial inhibitory effect	[38]
Molecular mechanisms	Physiological mechanical force	In vitro studies on chondrocytes	TRPV4 ↑ → Promotes chondrocyte proliferation and matrix synthesis	[39, 40]
	IL-6	Patients with osteoarthritis; Mouse model of OA	Expression of IL-6, p65 NF-κB, STAT3, and JNK proteins in skeletal muscle ↑; expression of the IL-6 receptor in articular cartilage ↑; however, knocking out the IL-6 gene or inhibiting downstream STAT3 and ERK reduces cartilage degradation and pain signaling	[49, 50]
	Normal skeletal muscle	Co-culture system with IL-1β/TNF-α-induced chondrocytes	Healthy skeletal muscle cells → pro-inflammatory signaling in chondrocytes (including NF-κB, ESE-1, COX-2, and GADD45-β) ↓ → MMPs and ADAMTS4 ↓	[51]
	Atrophic skeletal muscle	Mouse model of OA; co-culture system with chondrocytes	Atrophy of skeletal muscle cells → ROS ↑ → Synovial production and release of reactive oxygen species into the joint cavity → Loss of cartilage matrix and exacerbation of the inflammatory response; damage is exacerbated when osteoarthritic chondrocytes are co-cultured with atrophied muscle cells	[52]
	Irisin	Rabbit model of OA	PGC-1α/Irisin ↑ → Skeletal muscle IL-1β, TNF-α ↓ → Muscle atrophy-related genes: Muscle Atrophy F-box Protein (Atrogin1), muscle ring-finger protein-1 (MuRF1) ↓ → Intra-articular IL-1β, TNF-α, IL-6 ↓	[56]
	Irisin	Mouse model of OA; In vitro studies on chondrocytes	Irisin ↑ → Chondrocyte IL-1β, IL-6, TNF-α, COX2, iNOS ↓ → ECM degradation ↓; Intra-articular irisin injection attenuates murine OA progression	[53]
	miRNA	Rat model of OA; In vitro studies on chondrocytes	miR-206 is often downregulated in OA → targets IGF-1 and negatively regulates the PI3K/AKT and mTOR pathways → leading to abnormal autophagy, increased apoptosis, and elevated pro-inflammatory factors, thereby promoting degeneration	[59, 60]
	Muscle-derived stem cells	Rat model of OA; In vitro studies on chondrocytes	BMP2 and BMP4 induce chondrogenic differentiation; gene transfer or sustained release of growth factors can enhance chondrogenic efficiency	[62-65]
Common Pathological Pathways	STAT3; PI3K/AKT	Network pharmacology; rat model of OA	STAT3 ↓; PI3K/AKT pathway ↑ → inhibits myocyte apoptosis and promotes cartilage repair	[66]
	CSF1-R	Mouse model of OA	Blocking the colony-stimulating factor 1 receptor (CSF1-R) can simultaneously alleviate cartilage damage and muscle atrophy	[67]
	MLK3/P38 MAPK/HDAC4	Mouse model of OA	MLK3/P38 MAPK ↓; HDAC4 ↑, thereby achieving dual inhibition of muscle and cartilage degeneration	[68]

intermediate link of exercise in preserving cartilage homeostasis through the regulation of skeletal muscle's secretory function. Simultaneously, the dose-response relationship across various modalities (e.g., aquatic exercise, Tai Chi), individualized thresholds for distinct populations (e.g., elderly, obese, and rheumatoid arthritis patients with comorbid KOA), and the molecular basis of the time window effect remain inadequately clarified. Moreover, the bidirectional signaling mechanism between skeletal muscle and cartilage, the dynamic changes of the muscle-cartilage unit across various pathological stages, and the formulation of individualized precision exercise regimens based on disease progression and exercise dosage necessitate further comprehensive examination.

Future studies should concentrate on the novel regulatory pathway of "exercise therapy-skeletal muscle secretion-cartilage homeostasis", as shown by the existing research status. Initially, using multi-omics technologies such as single-cell sequencing, spatial transcriptomics, and metabolomics to systematically analyze the dynamic changes in the skeletal muscle secretome across various disease stages and exercise interventions will facilitate the identification of critical biomarkers associated with muscle atrophy and cartilage degeneration. Secondly, elucidating the roles of pivotal myokines, miRNAs, and exosomes in the interaction between skeletal muscle and cartilage would facilitate the development of a complete signaling regulation network for the muscle-cartilage unit. Third, large-sample multicenter clinical trials should be undertaken to confirm the optimal exercise dose parameters for various disease stages and demographics, as well as to delineate the molecular boundaries of the exercise intervention time window. Ultimately, the advancement of precision intervention strategies aimed at the "skeletal muscle-cartilage unit", encompassing intelligent biomechanical correction systems, personalized exercise prescription platforms, and novel drugs targeting myokines, will provide a new theoretical framework and intervention targets for clinical knee-preserving therapy for KOA.

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Disclosure of conflict of interest

None.

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