

Molecular Mechanisms of Osteoarthritis and their Potential Clinical Applications

E. Carlos Rodríguez-Merchán¹

¹ Department of Orthopedic Surgery, La Paz University Hospital, Madrid, Spain.

Conflict-of-interest statement: The author(s) declare(s) that there is no conflict of interest regarding the publication of this paper.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Correspondence to: Dr. E. Carlos Rodríguez-Merchan, Department of Orthopedic Surgery, La Paz University Hospital, Paseo de la Castellana 261, 28046-Madrid, Spain.
Email: ecrmerchan@hotmail.com

Received: September 12, 2022

Revised: October 26, 2022

Accepted: October 30 2022

Published online: December 28, 2022

ABSTRACT

The main molecular mechanisms implicated in the appearance of osteoarthritis (OA) are revised in this article: metabolic pathways, long noncoding ribonucleic acids (RNAs), genes, microRNAs and pieces derived from transfer RNA (tRNA), cytokines and chemokines, ADAMTS5 (a disintegrin and metalloproteinase with thrombospondin type 1 motif 5), the osteochondral interface, and AMP-activated protein kinase (AMPK) signaling. Recent studies have shown that some drugs could be of great interest in the future for the treatment of OA. Among them, the following stand out: quercitrin, Xiao Huoluo Pills (XHLP), paroxetine, LINC00473 (long intergenic non-protein coding RNA 473), sprifermin, lorecivint, angelicin, T-2054 (obeticholic acid derivative), bromelain, magnolin and TDP-43. However, future research is required to confirm the effectiveness and usefulness of the aforementioned drugs from the clinical point of view in patients with OA.

Key words: Osteoarthritis; Molecular mechanisms; Pathways; Long noncoding RNAs; Genes; Cytokines; Chemokines; ADAMTS5

© 2022 The Author(s). Published by ACT Publishing Group Ltd. All rights reserved.

Rodríguez-Merchan EC. Molecular Mechanisms of Osteoarthritis and their Potential Clinical Applications. *International Journal of Orthopaedics* 2022; 9(5): 1689-1698 Available from: URL: <http://www.ghrnet.org/index.php/ijo/article/view/3356>

INTRODUCTION

Osteoarthritis (OA) is a greatly incapacitating musculoskeletal illness incapacitating millions of human beings all over the world. OA is depicted by advancing destruction and immutable morphological alterations of joint tissues and structure^[1]. OA is an inveterate degenerative disease of the articulation and its frequency and intensity is augmenting due to the old age of the people. OA is depicted by the degeneration of joint cartilaginous tissue and restoration of the supporting osseous tissue.

OA is a frequent degenerative disorder of the articulations that affects the knee, hands, hip, spine and feet. The prevalence of OA is augmenting due to obesity and lifestyle. Individuals with OA have limited daily activities and a greater risk of mortality^[2]. Age is the main factor for OA due to ageing, muscle weakness and thinning of cartilage. Besides, obesity is strongly associated with knee OA^[2]. Apart from that, genetics and diet also influence the risk of OA. To date, the management for OA involves pain alleviation using non-steroid anti-inflammatory drugs (NSAIDs) and analgesics to relieve the symptoms (2) and surgical treatment for end-stage OA patients^[2]. Nonetheless, surgical treatment is costly. Therefore, adequate therapeutic strategies are essential to overcome existing problems. To get such strategies it is paramount to comprehend the molecular mechanisms entailed in the pathophysiology of OA^[2].

It has been reported that OA is an irremediable articular illness impairing 240 million elderly people, and important unmet medical necessities exist for more advantageous therapeutic alternatives for OA^[3]. OA is the most ordinary inveterate articular illness worldwide, with a big personal burden for the patients and a considerable socio-economic repercussion. Contemporary treatments are mainly limited to pain alleviation and rehabilitation and exercise approaches. For

severe cases, total joint arthroplasty might be the only alternative. Therefore, there is a tremendous requirement for the development of efficacious and innocuous illness-modifying anti-OA medications^[4].

The aim of this review article has been to revise the molecular mechanisms of OA and their potential clinical applications.

MOLECULAR MECHANISMS OF OSTEOARTHRITIS

Several reports on the molecular mechanisms of OA have been published and are discussed below.

Metabolic pathways involved in OA development

Pseudolaric acid B meliorates swelling of the synovial membrane and creation of vessels by making PPAR γ to restrain NF- κ B signalling pathway: According to Lu et al polarization of the macrophages of the synovial membrane and swelling are paramount for OA progress, yet the molecular processes and regulation accountable for the pathogenesis are still badly comprehended^[5]. They reported that pseudolaric acid B (PAB) alleviated the degradation of joint cartilaginous tissue and also synovial swelling (synovitis) during OA. PAB, a diterpene acid, restrained nuclear factor κ B (NF- κ B) signalling and diminished the generation of pro-inflammatory cytokines, which farther reduced the polarization of M1 and the creation of vessels. They also found that PAB halted NF- κ B signalling by stabilizing peroxisome proliferator-activated receptor gamma (PPAR γ). Utilizing PPAR γ antagonist could eliminate anti-inflammatory impact of PAB and recover the triggering of NF- κ B signaling in the course of OA^[5].

Restraint of nuclear receptor RORalpha alleviates cartilaginous tissue impairment in OA by regulating IL-6/STAT3 pathway: Liang et al stated that retinoic acid receptor-related orphan receptor- α (ROR α) is essential in the growth cartilaginous tissue and pathogenesis of OA. They studied the function and molecular process of ROR α , a major component of the nuclear receptor family, in regulating the appearance of OA pathologic characteristics. The findings of this study indicated the crucial role of the ROR α /IL-6/STAT3 (interleukin-6/signal transducer and activator of transcription 3) axis in OA advancement and verified that ROR α blockade ameliorated the matrix catabolism in OA cartilage cells (chondrocytes). These findings might render a possible management goal in OA treatment^[6].

Hushing of Vangl2 alleviates the swelling stimulated by Wnt5a via MAPK and NF- κ B pathway in cartilage cells: According to Zhang et al the Wnt planar cell polarity (PCP) pathway is involved in OA. Van Gogh-like 2 (Vangl2) is an essential PCP protein that is needed for the correct positioning of cartilage cells in the growth plate. Nevertheless, its roles in OA still endure indeterminate. Therefore they examined the consequences of Vangl2 on OA cartilage cells in vitro and farther clarified the molecular process of hushing Vangl2 in Wnt5a-overexpressing OA cartilage cells. This study showed that Vangl2 is entailed in the OA mechanism. Vangl2 hushing is able to remarkably lessen OA advancement in vitro by restraining the expression of MMPs and augmenting the creation of the matrix of cartilaginous tissue and is able to restrain the proinflammatory consequences of Wnt5a via MAPK and NF- κ B pathway^[7].

Initial degradation of patellofemoral joint cartilaginous tissue in an experimental model of patellar instability is related to triggering of the NF- κ B signaling pathway: According to Lin et al instability of the patella (IP) frequently enhances the likelihood of

lateral patellar dislocation and initial patellofemoral (PF) OA. Lin et al investigated the association connecting the NF- κ B signaling pathway and the degradation of the PF articular cartilaginous tissue. The study showed that early PF articular cartilage degradation might be produced by IP, together with an important loss of subchondral osseous tissue. Besides, the degradation of joint cartilaginous tissue might be related to the triggering of the NF- κ B signaling pathway and may progressively deteriorate as a consequence of IP^[8]. Figure 1 shows the main pathways involved the molecular mechanisms of OA.

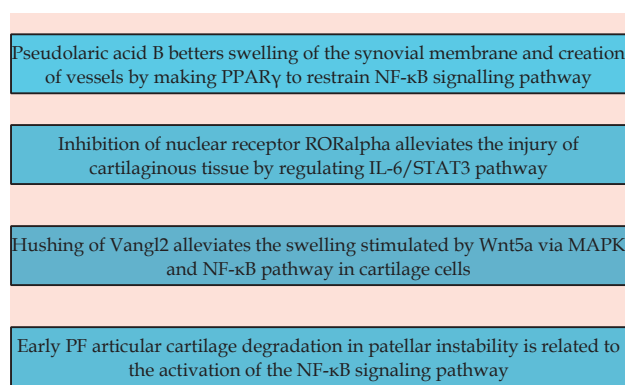


Figure 1 Main pathways involved in osteoarthritis (OA) development. PPAR γ , peroxisome proliferator- activated receptor gamma; NF- κ B, nuclear factor κ B; RORalpha, RAR-related orphan receptor alpha; RAR, retinoic acid receptor; IL-6/STAT3, interleukin-6/signal transducer and activator of transcription 3; Vangl2, vangl planar cell polarity protein 2; Wnt5a, a member of the Wntless/integrase 1 (WNT) family of secreted glycoproteins; MAPK, mitogen-activated protein kinase; PF, patellofemoral.

Long noncoding ribonucleic acids (RNAs)

Long noncoding RNA (LncRNA) THUMP3-AS1 augments the increase and inflammatory reaction of cartilage cells in OA: LncRNAs control the appearance and progress of OA, while the biological functions and processes of the lncRNA THUMP3-AS1 (THUMP3 antisense RNA 1) in OA persist still undefined. Wang et al reported the function and molecular process of lncRNA THUMP3-AS1 in controlling OA pathogenesis. The findings of this study highlighted the distinct consequences of lncRNA THUMP3-AS1 on cell death and inflammatory reaction, which augment the manifold roles of lncRNA epigenetics in OA pathogenesis^[9].

Favorable feedback cycle of lncRNA FAM201A/miR146a5p/POU2F1 controls IL1 β induced damage of cartilage cells in vitro: According to Gau et al many reports have previously showed that lncRNAs serve a significant regulatory function in OA. Specifically, the lncRNA family with sequence similarity 201 member A (FAM201A) was beforehand encountered to be downregulated in specimens of femoral head necrosis. Nevertheless, the function of FAM201A in IL1 β induced cartilage cell damage is still undefined. The hypothesis of Gau et al was that FAM201A might have a defensive role on IL1 β induced cartilage cell damage in OA by sponging microRNAs (miRNAs/miRs). The results of this research showed the protecting consequences of the FAM201A/miR146a5p/POU2F1 favorable feedback cycle on IL1 β induced cartilage cell damage and rendered a possible treatment goal for OA^[10].

PR11-364P22.2/ATF3 protein interplay moderates IL-1 β -induced catabolic consequences in articular cartilaginous tissue: Li et al explored the roles of the dysregulated lncRNAs in the pro-inflammatory cytokine IL-1 β -mediated catabolic consequences in

articular cartilaginous tissue. They recognized RP11-364P22.2 as dysregulated in OA patient-derived cartilaginous tissue and strongly sensitive to IL-1 β induction. This study highlighted the essential functions of lncRNAs in the pathologic process of OA and indicated the RP11-364P22.2/ATF3 regulatory axis as a possible treatment goal of swelling-induced OA^[11].

Long non-coding RNA PCAT-1 controls death of cartilage cells in OA by sponging miR-27b-3p: Zhou et al have analyzed the functions and associations of PCAT-1 (prostate cancer associated transcript 1) and miR-27-3p (microRNA-27b-3p) in the pathologic process of OA. They concluded that lncRNA PCAT-1 controlled the death of cartilage cells via sponging miR-27b-3p in OA. PCAT-1 has possible benefits to perform as an innovative treatment goal for people with OA^[12].

Knockdown of long non-coding RNA LINC00473 defends CHON-001 cells against interleukin-1 β -induced cell damage: Ou et al have reported that LINC00473 (long intergenic non-protein coding RNA 473) knockdown protected CHON-001 cells from IL-1 β induced cell damage via constraint of the methylation of LMP-1 (latent membrane protein 1). Therefore, LINC00473 may probably act as a new treatment goal for OA^[13]. **Figure 2** shows the main long non-coding RNAs involved in OA development.

LncRNA THUMP3-AS1 augments the inflammatory reaction of cartilage cells
Favorable feedback cycle of lncRNA FAM201A/miR-146a-5p/POU2F1 controls IL-1 β -induced cartilage cell damage
PR11-364P22.2/ATF3 protein interplay mediates IL-1 β -induced catabolic consequences in joint cartilaginous tissue
LncRNA PCAT-1 controls death of cartilage cells in OA via sponging miR-27b-3p
Knockdown of long non-coding RNA LINC00473 defends CHON-001 cells against interleukin-1 β -induced cell damage

Figure 2 A summary of the main long-noncoding ribonucleic acids (RNAs) involved in osteoarthritis (OA) development. LncRNA THUMP3-AS1, long non-coding RNA (lncRNA) THUMP3-AS1; IL1 β , interleukin 1 beta; PCAT-1, prostate cancer associated transcript 1; miR-27b-3p, microRNA-27b-3p; LINC00473, long intergenic non-protein coding RNA 473.

Genes involved in OA development

The function of TNFRSF11B in appearance of OA: According to Ruiz et al OA is an intricate genetic illness with distinct risk factors playing a part to its appearance. They studied the role of TNFRSF11B (tumor necrosis factor receptor superfamily member 11b) overexpression in development of OA. The findings of their study indicated that upregulation of gen TNFRSF11B in injured OA cartilage might act as a straight instigator for cartilage cells to osteoblast shift found in OA pathologic process. This shift did not seem to perform via the RANK/RANKL/OPG [receptor activator of nuclear factor- κ B (RANK)/RANK ligand (RANKL)/osteoprotegerin (OPG)] triad common in bone remodeling^[14].

Suppression of OA advancement by initiation of Nkx3.2 after birth: Oh et al observed an intense decrease of Nkx3.2 expression in three distinct experimental studies on OA. Besides, investigations of surgery-induced and age-related OA models showed that cartilage-specific initiation of Nkx3.2 after birth can halt OA advancement. The findings of this study suggested that Nkx3.2 is as a potential goal for OA medication progress^[5].

The role of microRNAs and pieces derived from transfer RNA (tRNA)

Little noncoding RNAs in knee OA: the function of microRNAs and pieces derived from tRNA

To comprehend the regulatory role of small non-coding RNAs (ncRNAs) on particular gene expression in OA of the knee, it is paramount to emphasize that cartilage cells represent about 1-5% of the whole amount of the articular cartilage^[15]. They create and maintain matrix cartilage, basically formed by collagen and proteoglycans. Chondrocytes render an equilibrium between anabolic and catabolic actions that guard the aggrecan configuration. OA begins with an augmented turnover of cartilage cells^[16]. Death, autophagy and necrosis play essential functions in the death of cartilage cells. Such aberrant apoptosis of cartilage cells not only diminishes their quantity, but also starts the degradation of the articular cartilaginous tissue^[17,18]. Absence of the cartilaginous matrix causes a lack of balance between the synthesis of cartilage and its resorption in the articulation^[19].

In the initial phases of OA, augmented formation of the extracellular matrix (ECM) constituents is surpassed by their degeneration, via an augmented formation and activity of proteases. Mechanical stress produces the upregulation of the cytokines. The principal cytokines that produce the degeneration in the synovial membrane are the interleukins: IL-1 β , IL-6, IL-17 and tumor necrosis factor-alpha (TNF- α)^[20,21].

IL-1 β is one of the most significant proinflammatory cytokines^[22,23]. Moreover, IL-1 β incites the creation of several cytokines and chemokines which make a contribution to the swelling. Experimental studies have demonstrated that IL-1 β plays essential functions in sensitivity to pain^[24].

According to Zacharjusz et al microRNAs (miRNAs) might procure an efficacious cellular path for the control of gene expression in the course of OA. The information of pieces derived from tRNA in OA is still scanty. Research on miRNAs and pieces derived from tRNA has started a novel field of their possible utilization: in the identification of OA as biomarkers. Extracellular miRNAs and pieces derived from tRNA are usually found in many tissues and liquids of the body^[25].

The role of cytokines and chemokines

According to Molnar et al OA impacts all articular tissues uniformly. The pathogenesis of OA is not fully known; nonetheless, a low-degree swelling leading to a lack of equilibrium between anabolic and catabolic activities is well understood. The intricate system of cytokines controlling these activities and cell communication has a crucial role in the appearance and advancement of OA. Amounts of both pro-swelling and anti-swelling cytokines have been encountered to be affected by the phase and activity of OA^[26].

Essential inflammatory mechanisms and facets in OA pathological process: The disrupted equilibrium of pro-swelling and anti-swelling cytokines (inclined toward pro-swelling cytokines) is accountable for the liberation of enzymes and other swelling molecules entailed in the pathological process of OA causing morphological alterations within the articulation such as cartilage degradation, bone spur (osteophyte) creation and other inflammatory alterations such as synovitis. Proinflammatory cytokines are the following: Interleukin 1- β (IL- β), interleukin (IL)-6, IL-15, IL-17, IL-18, IL-21, IL-22, and tumor necrosis factor α (TNF- α). Anti-inflammatory cytokines are the following: IL-4 and IL-10. Chemokines additionally make a contribution to swelling processes, arousing the chemotaxis of inflammatory cells that then

farther liberate proinflammatory cytokines. The main chemokines are the following: IL-8, C-C motif ligand 2 (CCL2), CCL3 and CCL5^[26].

IL-1 β role in OA pathological process: By binding to its receptor IL-1 receptor type I (IL-1RI), IL-1 β activates signaling pathways [NF- κ B (nuclear factor kappa-light-chain-enhancer of activated B cells) and MAPK (mitogen-activated protein kinase)] that, by raising the expression of enzymes [ADAMTS (a disintegrin-like and metalloproteinase with thrombospondin motif) and MMPs (matrix metalloproteinases)], cause catabolic responses, i.e., proteoglycan degeneration and collagen severance. Besides, by means of the same signaling pathways, IL-1 β restrains type II collagen formation via SRY-Box Transcription Factor 9 (SOX-9) suppression but also proteoglycan formation by augmenting the creation of COX-2-cyclooxygenase-2 (COX-2), prostaglandin E2 (PGE-2) and nitric oxide (NO). Besides, IL-1 β augments the expression of chemokines such as IL-8, CCL2 and CCL5, as well as the cytokines IL-6 and TNF- α , which entice inflammatory cells and produce swelling of the synovial membrane, apiece, causing even greater formation and liberation of IL-1 β ^[26].

IL-6 role in the pathological process of OA: IL-6 takes action by attaching membrane bound IL-6R or soluble IL-6 receptor (sIL-6R) that allies with glycoprotein130 (gp130). Gp130 starts intracellular signaling that controls the swelling and expression of enzymes, collagen and proteoglycans. sIL-6R is created via an alternate splicing of membrane-bound IL-6R. sgp130 is able to restrain IL-6 signaling. Via classic and trans-signaling, IL-6 stimulates the phosphoinositide 3-kinases (PI3K), JAK/STAT (Janus kinase/signal transducers and activators of transcription) and MAPK signaling pathways that regulate enzymes production [TIMP (tissue inhibitor of metalloproteinase), MMPs and ADAMTS] and type II collagen and proteoglycan formation. Therefore, IL-6 levels off between anti-swelling and pro-swelling consequences, but the last mentioned prevails, finally causing the advancement of OA^[26].

TNF- α function in OA pathogenesis: TNF- α can attach to a couple of receptors, tumor necrosis factor receptor 1 (TNRF-1) and TNRF-2. By clamping to TNRF-1, TNF- α is able to bring about two distinct signaling systems. System 1 stimulates cell endurance and the manifestation of NF- κ B, MAPK and activator protein 1 (AP-1), which causes proteoglycan degeneration, collagen severance and the constraint of proteoglycan and collagen formation. Besides, the stimulation of system 2 causes an avalanche of responses, which include the creation of Fas-associated death domain protein (FADD) and the stimulation of procaspase 8/10 and caspase 3, which subsequently causes cell death. In addition, the strapping of TNF- α to TNRF-2 stimulates NF- κ B and c-Jun N-terminal kinases (JNK). As a result, TNF- α causes degradation of cartilaginous tissue and other articular components, thus making a contribution to the initiation and advancement of OA^[26].

Chemokine C-C motif chemokine 22 (CCL22) causes pro-swelling alterations in fibroblast-like synoviocytes: According to Ren et al synovitis is frequent in people with OA and causes pain and illness advancement. They have beforehand shown that the chemokine C-C motif chemokine 22 (CCL22) causes cartilage cell death *in vitro*; nevertheless, the impact of CCL22 on the synovial membrane are still obscure. Consequently, they studied the impact of CCL22 on fibroblast-like synoviocytes (FLS). Management with CCL22 eliminated expression of IL-4 and IL-10 and stimulated expression of S100A12 in FLS. The reaction of FLS to CCL22 did not depend on the illness phase (e.g., normal versus OA). However it was associated with the amount of CCL22 in the synovial fluid

of the patient. Knockdown of CCR3 alleviated CCL22 induction of S100A12 in FLS. Thus, ligands of CCR3 (CCL7, CCL11) did not prompt the expression of S100A12^[27].

Cytokine-like protein 1 (Cyt11) may be involved in OA progression: Evidence suggests that cytokine-like protein 1 (Cyt11) may be involved in the regulation of OA advancement, gone along with the modulation of Sox9 and insulin-like growth factor 1 (IGF-1) expression. Besides, Cyt11 displays chemotactic and pro-angiogenic biological effects. In addition, CCR2 (C-C chemokine receptor type 2) has been recognized as a probable receptor for Cyt11, which mediates the ERK signalling pathway. Cyt11 also seems to mediate the TGF- β -Smad signalling pathway, which is theoretically unrelated to the CCR2 receptor. Establishing the molecular structure of Cyt11 and its function in OA pathological process will assist us to arrange therapies for Cyt11-associated diseases^[28]. **Figure 3** summarizes the main cytokines and chemokines implicated in OA appearance.

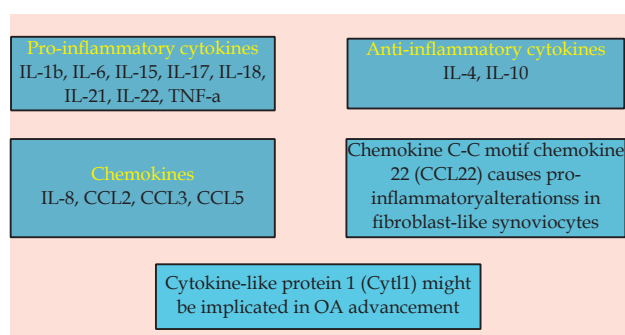


Figure 3 A summary of the main cytokines and chemokines involved in osteoarthritis (OA) development. IL, interleukin; CCL, chemokine C-C motif chemokine; TNF, tumor necrosis factor.

Other molecular mechanisms

ADAMTS5 in OA development: ADAMTS5 is implicated in the pathological process of OA. As the main aggrecanase-degrading joint cartilage matrix, ADAMTS5, has been considered a possible goal for OA management. Senility, heredity, swelling, and mechanical strain are implicated in the overactivation of ADAMTS5, making a contribution to the pathological process of OA. Numerous molecular signaling pathways have been encountered to modulate ADAMTS5 expression, particularly, Runx2 (Runt-related transcription factor 2), Fgf2 (fibroblast growth factor 2), Notch, Wnt, NF- κ B, YAP/TAZ [Yes-associated protein (YAP)/transcriptional coactivator with PDZ-binding motif (TAZ)], and the other inflammatory signaling pathways^[29].

Stimulation and decomposition system of ADAMTS5 *in vivo*: In healthy cartilaginous tissue, ADAMTS5 is prompted by the instigation of inflammatory molecules or decomposition products in the extracellular matrix (ECM) to the cartilaginous tissue. Following the dismissal of its pro-domain by furins, prompted ADAMTS5 splits the aggrecan core protein at its precise Glu-Xaa recognition motifs. ADAMTS5 can be restrained by tissue inhibitor of metalloproteinase (3TIMP3). ADAMTS5, in cooperation with TIMP3 is consequently endocytosed by cartilage cells via LRP-1 receptor and degenerated^[29].

Profile of signaling system in ADAMTS5 control in cartilage cells: In OA, mechanical stress, cell differentiation indicators, and swelling milieu are principal starters to ADAMTS5 overexpression. Some important signaling pathways are the following: Runx2 signaling, Notch signaling, Wnt/ β -catenin signaling, cytokine-mediated signaling pathways, YAP/TAZ signaling, and Sox4 signaling. Based on the comprehension of ADAMTS5 in OA pathological process,

monoclonal antibodies and small molecule inhibitors against ADAMTS5 have been produced and showed to be helpful in pre-clinical studies. Modern new RNA treatments showed possibilities in OA experimental studies. ADAMTS5 constraint and its signaling pathway-based modulations demonstrated excellent possibility in forthcoming therapeutic schemes for OA^[29].

The osteochondral interface in OA development: The osteochondral interface is an essential structure situated between hyaline cartilage and subchondral osseous tissue. The osteochondral interface experiences numerous pathological modifications in the course of OA^[30].

AMPK signaling in OA: According to Yi et al adenosine monophosphate (AMP)-activated protein kinase signaling (AMPK) mainly affects cartilage cell functions during OA appearance. The functions of AMPK in cartilage cells have been published since 2009. It began from comprehending the autophagy in cartilage cells. This may be associated with the beforehand knowledge that AMPK activation was stimulated by endoplasmic reticulum (ER) stress causing cartilage cell death^[31].

In experimental studies some authors have observed that cartilage cells expressed energy sensor AMPK-1, which stimulates cartilage cells autophagy related to Akt [or protein kinase B (PKB)] activation, mTOR (mammalian target of rapamycin) suppression, and HIF-1 (hypoxia inducible factor 1) expression^[32,33]. AMPK/FoxO3a pathway was encountered to be implicated in ASIC1a-mediated joint cartilage cell autophagy^[34-36].

Terkeltaub et al. suggested that AMPK inhibited matrix degeneration in cartilage cells in the presence of cytokines IL-1 β and TNF- α ^[37]. Zheng et al. demonstrated that stimulation of AMPK/Drp1 (dynamin-related protein 1) /mitochondrial fission pathway mediates cartilage cell apoptosis and migration damage^[38]. Furthermore, AMPK took part in cartilage cell dysfunction, hypertrophy, and fibrotic differentiation^[39,40].

Some authors have demonstrated that downregulation of AMPK signaling caused restraint of matrix catabolic responses in articular cartilage cell in the course of OA appearance^[41,42]. Ma et al. affirmed that SIRT1/AMPK/PGC-1 α signaling produces dysfunction in the mitochondria of cartilage cells with augmented oxidative stress and death, which might be the cause of OA. Albeit these reports suggested that AMPK takes part in the control of cartilage cell activity, more research is needed to farther understand the molecular processes of AMPK in the control of cartilage cell homeostasis^[43].

Although OA has been accepted as a low-degree inflammatory illness with elevations in systemic swelling markers, such as IL-1, IL-6, IL-10, and TNF- α , reports have suggested that OA is a metabolic illness too, where energy metabolic pathways are upregulated^[44,45].

Kang et al. encountered that in human OA cartilage cells adiponectin regulates matrix degeneration via AMPK and JNK pathways^[46]. Liu-Bryan et al. stated that in OA, swelling disturbs cellular energy equilibrium and increases cell stress via augmenting catabolic activities in degrading joint cartilage cells^[47]. Other authors showed that AMPK activity preserves articular homeostasis and OA appearance by augmenting IL-1 α -induced catabolic reaction^[48]. Some reports have shown that activation of AMPK phosphorylation suppresses NF- κ B and its downstream molecule p65, which is implicated in regulating OA cartilage in reply to IL-1 α -stimulated swelling^[49,50].

Kong et al. suggested that, in the presence of active vitamin D, AMPK-mTOR signaling pathway may diminish OA inflammation by means of activation of cartilage cell autophagy^[51]. Other authors observed that diminished phosphorylation of AMPKa at T172 in

cartilage cells worsened catabolic metabolism in reply to IL-1 β and TNF- α . And they also stated that AMPK and its downstream molecule SIRT1 could switch cartilage cell metabolic activities from oxidative phosphorylation to glycolysis together with an augmented production of catabolic factors. Mitochondrial, autophagy, and ER stress may also contribute to OA appearance via AMPK interacting with numerous signaling pathways^[50]. Yi et al suggested that AMPK could render energy for the inflammatory reactions to OA. However, its pathways and molecular processes need further investigation^[31].

Clusterin liberation is alleviated by the pro-swelling cytokines IL-1 β and TNF- α in models of degeneration of cartilaginous tissue:

The protein clusterin has been involved in the molecular changes that take place in joint cartilaginous tissue in the course of OA. There are two isoforms of Clusterin with opposing roles, and their functions in cartilaginous tissue have not been studied. The study of Matta et al implicated sCLU (secreted form of clusterin) in catabolic reactions of cartilage cells; however, farther research needed to assess its function in OA^[52].

Inflammation-activated CIC-3 activity controls PGE2 liberation in human OUMS-27 cartilage cells: Yamada et al suggested that CIC-3 is accountable for I_{Cl,swell} and regulatory volume reduction under the hypoosmotic milieu. It is possible that CIC-3 is related to the pathologic process of OA via PGE₂ release^[53].

Macrophage migration inhibitory factor (MIF) may has a defensive role in OA: Liu et al investigated the role of macrophage MIF in OA by studying MIF genotype, mRNA expression, and protein levels. Diminished MIF mRNA and protein expression in OA individuals suggested MIF may have a defensive function in OA and could be adequate as a biomarker to distinguish OA from other articular diseases^[54].

Fatty acid sensing GPCR (GPR84) signaling safeguards cartilage homeostasis and protects against OA: Wang et al showed that fatty acid sensing GPCR (Gpr84) signaling had a paramount function in OA pathological process, and activation of GPR84 or supplementation with MCFA [medium-chain free fatty acids (FFAs)] could halt the advancement of OA without serious side effects^[55].

The molecular structure and function of LECT2 or CHM-II in OA: Recently, leukocyte cell-derived chemotaxin-2 (LECT-2) was encountered to be associated with the appearance of OA, implicating the dysregulation of several types of cells in the osseous micromilieu: osteoclasts, mesenchymal stem cells (MSCs), osteoblasts, cartilage cells, and endothelial cells. However, it is necessary to fully comprehend the function of LECT2^[56].

Small extracellular vesicles from adipose derived MSCs alleviate in vitro the NF-kappaB dependent inflammatory/catabolic milieu: Cavallo et al investigated the impact of small extracellular vesicles (sEV) from adipose derived stromal cells (ADSC) on both cartilage cells and synoviocytes, with the aim of get a better comprehension of the processes regulating the inflammatory/catabolic OA milieu. Their report highlighted the possibility of ADSC derived sEV to impact gene expression and protein liberation of cartilage cells and synoviocytes, neutralizing IL-1 β incited swelling consequences, and rendered knowledge into their way of action. sEV uptake was quicker in synoviocytes, where it also prompted more robust consequences, particularly in terms of cytokine and chemokine regulation. The inflammatory/catabolic milieu mediated by NF- κ B pathway was alleviated by sEV, which could be a new approach to treat OA^[57].

It has been reported by Pelsma et al that variants of FOXO3 and RPA3 genes impacting IGF-1 degrees modify the risk of appearance of primary OA^[58]. The aforementioned authors analyzed the function

of IGF-1 degrees in primary OA pathologic process. Individuals from the Genetics osteoARthritis and Progression (GARP) Study with painful OA were compared to Leiden Longevity Study (LLS) controls. Individuals with primary OA had significantly greater IGF-1 degrees compared to controls. Furthermore, SNPs (single nucleotide polymorphisms) in the FOXO3 (forkhead box O3) and RPA3 (replication protein A3) genes were related to a modified risk of OA. Thus, modified IGF-1 degrees affected the appearance of OA, and were possibly the consequence of the pathologic process of OA^[58].

Expression of VEGF-A signaling pathway in cartilage ACLT-induced OA: The model of anterior cruciate ligament transection surgery (ACLT)-induced OA has been frequently utilized to study the molecular mechanism of knee OA. Quian et al investigated the pathological alterations following ACLT surgery and determined the expression characteristics of the VEGF-A/VEGFR2 signaling pathway^[59]. The expression of VEGF-A, VEGFR2, COX-2, and iNOS were greater than in control groups. The degenerative grade of joint cartilaginous tissue was time-dependent; formation of new vessels and swelling were significant pathological findings in the cartilaginous tissue. The expression of the VEGF-A/VEGFR2 signaling pathway was associated with the grade of knee OA^[59].

Synovium-synovial liquid axis in OA pathologic process: an essential regulator of cartilage degeneration: Ingale et al studied gene expressions in synovial-biopsies from distinct degrees OA individuals. They found a peak of IL-1 β , IL-15, PGE2 and NGF in early OA [Kellgren-Lawrence (KL) grade-I and II]; the greatest MMPs levels were encountered in advanced phases (KL degree-III and IV)^[60].

DNA damage caused by oxidative stress and repair in primary human OA cartilage cells: The IKKalpha and the deoxyribonucleic acid (DNA) mismatch repair system: Neri et al suggested an involvement of the DNA mismatch repair (MMR) system in the response to oxidative stress that is inclined to be more effective in I κ B kinase α (IKK α) knockdown cells^[61].

Molecular processes of OA mechano-pathology: Houtman et al recognized 156 genes differentially expressed between control and 65%MS (mechanical stress) human osteochondral explants. It was observed that IGFBP5 and MMP13 were the highest upregulated

genes, while IGFBP6 was the most downregulated gene. These findings represent transcriptomic broad effects of mechanical stress in human aged joint cartilage with MMP13, IGF binding proteins, and cellular senility as the most remarkable outcomes^[62]. **Figure 4** summarizes other processes involved in OA development.

Table 1 summarizes the main molecular mechanisms of OA and their potential clinical applications^[2-4,6,7,29,57,63-76].

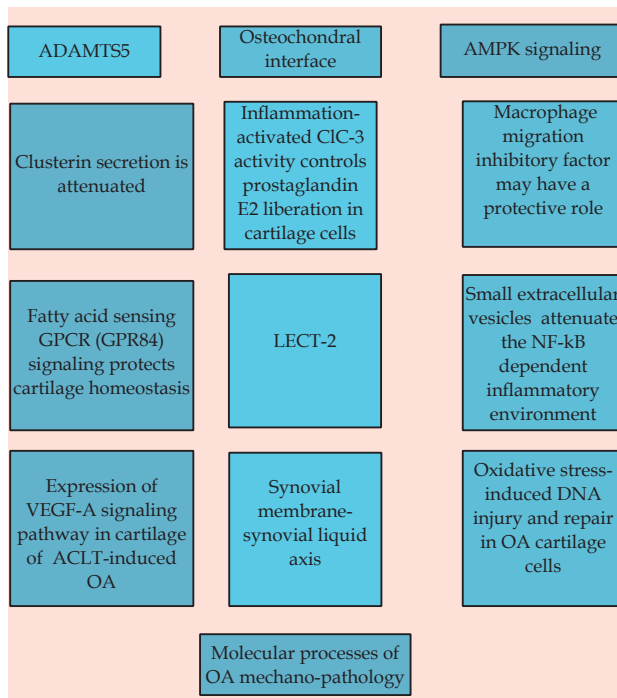


Figure 4 A summary of other molecular mechanisms involved in osteoarthritis (OA) development. ADAMTS5, a disintegrin and metalloproteinase with thrombospondin motifs; AMPK, Adenosine monophosphate (AMP)-activated protein kinase; GPCR, G-protein-coupled receptor; LECT2, Leukocyte cell-derived chemotaxin-2; NF κ B, nuclear factor κ B; VEGF-A, vascular endothelial growth factor A; ACLT, anterior cruciate ligament transection; DNA, deoxyribonucleic acid; IKK α , ikappaB kinase alpha.

Table 1 A summary of the main molecular mechanisms of osteoarthritis (OA) and their potential clinical applications.

AUTHORS	YEAR	MOLECULAR MECHANISM	POTENTIAL CLINICAL APPLICATION
Guo et al [63]	2020	Disruptions of extracellular matrix (ECM) degradation homeostasis. Matrix metalloproteinase 13 (MMP13) and collagen II are relevant elements of ECM.	Quercitrin may be a potential illness-modifying OA medication for prevention and treatment of early stage OA. Quercitrin could significantly decrease MMP13 gene expression and augment collagen II gene expression in IL-1 β -incited cartilage cells
Chen et al [64]	2021	Core target genes are implicated in signaling pathways related to cartilage degradation of knee OA.	This study provided theoretical basis and new management strategy for XHLP in the treatment of knee OA.
Mohd Noor et al [2]	2021	Extracellular vesicles (EV) have an essential function in intercellular communications and their concentration is increased in the articulations of OA individuals, although their way of action is not clear. Besides, mesenchymal stem cells (MSCs) have an important capacity in cartilage regeneration.	The possible role of MSC-derived EV in OA are reviewed in this study.
Oh et al [3]	2021	Nkx3.2 has a crucial function in OA pathologic process. Remarkable decrease of Nkx3.2 expression was found in three distinct experimental OA models.	This study suggested that Nkx3.2 is a promising target for OA medication development.
Carlson et al [65]	2021	This study stated that OA is driven by pathological chondrocyte hypertrophy (CH). It also analyzed the role of G protein-coupled receptor (GPCR)- G protein-coupled receptor kinase 2 (GRK2) pathway in OA.	The study confirmed the ability of paroxetine to lessen CH and cartilage degeneration. It was suggested that elevated GRK2 signaling in chondrocytes was a driver of CH in OA and recognized paroxetine as a illness-modifying medication for OA management.

Ou et al [66]	2021	LINC00473 knockdown defended CHON-001 cells from IL-1 β incited cell damage via restraint of the methylation of LMP-1.	LINC00473 might potentially act as a new therapeutic goal for OA.
Cherifi et al [4]	2021	Low levels of Wnt activity seemed essential to maintain chondrocyte viability but exaggerated activation was related to progressive articular injury.	This study stated some potential for the use of sprifermin and lorecivint.
Jiang et al [29]	2021	Senility, inheritance, swelling, and mechanical stress are implicated in the overactivation of ADAMTS5, making contributing to the pathologic process of OA. Numerous molecular signaling pathways were found to modulate ADAMTS5 expression, particularly, Runx2, Fgf2, Notch, Wnt, NF- κ B, YAP/TAZ.	ADAMTS5 inhibition and its signaling pathway-based modulations showed great potential in future therapeutic strategies for OA.
Cavallo et al [57]	2021	This study emphasized the possible impact of ADSC derived sEV (small Extracellular Vesicles) on gene expression and protein liberation of cartilage cells and synoviocytes, neutralizing IL-1 β induced inflammatory effects, and provided insights into their mechanisms of action. sEV uptake was quicker in synoviocytes, where it also provoked more robust effects, particularly in terms of cytokine and chemokine modulation.	The inflammatory/catabolic environment mediated by NF- κ B pathway was significantly attenuated by sEV, which could be a new therapeutic option in the future.
Tian et al [67]	2021	This study suggested that angelicin can attenuate the advancement of OA by regulating M1/M2 polarization via the STAT3/p-STAT3 pathway.	Angelicin may have a potential value in OA clinical management.
Guo et al [68]	2021	T-2054 effectively diminished the liberation of inflammatory mediators, as well as promoted ECM formation by means of the NF- κ B-signaling pathway.	The results of this study support the potential utilization of T-2054 as an efficacious therapeutic drug for the management of OA.
Pothacharoen et al [69]	2021	This study showed the chondroprotective value of bromelain on cartilage degeneration and the downregulation of inflammatory cytokine [tumor necrosis factor (TNF)- α , IL-1 β , IL-6, IL-8] expression in TNF- α -incited synovial fibroblasts by eliminating NF- κ B and MAPK signaling.	This study supported the anti-inflammatory and analgesic effects of bromelain in animal models and clinical studies of OA.
Xu et al [70]	2021	Magnolol showed important anti-swelling bioactivity on cartilage cells by halting the activation of NF- κ B pathway, which in turn displayed an important relief of OA.	Magnolol showed notable anti-swelling bioactivity on cartilage cells
Chang et al [71]	2021	This study indicated that TDP-43 maintains chondrocyte homeostasis under oxidative stress and alleviates degeneration of cartilaginous tissue in OA.	TDP-43 was identified as a potential target for the diagnosis and treatment of knee OA.
Liang et al [6]	2021	This study showed the crucial function of the retinoic acid receptor-related orphan receptor- α (ROR α) / IL-6 / STAT3 axis in OA advancement and proved that ROR α blockade ameliorated the matrix catabolism in OA cartilage cells.	These results may provide a potential treatment target in OA therapy.
Gan et al [72]	2021	This study showed the protective role of the FAM201A (lncRNA family with sequence similarity 201 member A) / miR146a5p/ POU2F1 favorable feedback loop on IL1 β incited cartilage cell injury.	The findings of this study provided a potential therapeutic target for OA
Dong et al [73]	2021	This study demonstrated that CDDO-Im (a synthetic triterpenoid CDDO-Im(1-[2-cyano-3,12-dioxooleana-1,9(11)-dien-28-oyl] imidazole) displays noticeable chondroprotective and anti-OA activities due to its Nrf2 activation and autophagy-enhancing characteristics.	The findings of this study might render new knowledge on the prevention and treatment of OA.
Zhang et al [7]	2021	This study found that Vangl2 (Van Gogh-like 2) was implicated in the OA pathologic process. Vangl2 silencing can attenuate OA advancement in vitro by restraining the expression of MMPs and increasing the formation of the cartilage matrix and can restrain the pro-swelling impact of Wnt5a via MAPK and NF- κ B pathway.	This study provided new insight into the mechanism of cartilage inflammation.
Han et al [74]	2021	This study suggested that β -Ecdysone functioned as a FOXO1 (nuclear forkhead box O1) activator to protect collagenase-incited damage of cartilaginous tissue.	FOXO1 might be a good option for the prevention and treatment of OA.
Collins et al [75]	2021	This study demonstrated that Sirtuin 6 (SIRT6) activity was changed with age and oxidative stress conditions related to aging. SIRT6 contributes to chondrocyte redox homeostasis by regulating specific members of the peroxiredoxin (Prx) catalytic cycle.	Targeted treatments aimed at averting the age-related decreased in SIRT6 activity may represent a new alternative to maintain redox equilibrium in joint tissues and reduce catabolic signaling events involved in OA.
Camargo Brindo da Cruz et al [76]	2021	This study found that the expression of type II collagen (Col II) was greater in rabbits with surgical-induced osteoarthritic joint cartilage.	Adipose-derived stem cells (ADSC) / type V collagen (Col V) may be a promising therapeutic goal for OA management.

CONCLUSIONS

OA is the most ordinary inveterate articular illness worldwide, with a big personal burden for the patients and a considerable socio-economic repercussion. Contemporary treatments are mainly limited to pain alleviation and rehabilitation and exercise approaches. For severe cases, total joint arthroplasty might be the only alternative.

Therefore, there is a tremendous requirement for the development of efficacious and innocuous illness-modifying anti-OA medications. In this article the molecular mechanisms of OA and their potential clinical applications have been reviewed: metabolic pathways, long noncoding RNAs, genes, cytokines and chemokines, ADAMTS5 (a disintegrin and metalloproteinase with thrombospondin type 1 motif 5), the osteochondral interface, and adenosine monophosphate

(AMP)-activated protein kinase (AMPK) signaling. Recent studies have shown that some drugs could be of great interest in the future for the treatment of OA. Among them, the following stand out: quercitrin, Xiao Huoluo Pills (XHLP), paroxetine, LINC00473 (long intergenic non-protein coding RNA 473), sprifermin, lorecivint, angelicin, T-2054 (obeticholic acid derivative), bromelain, magnolin and TDP-43. However, future research is required to confirm the effectiveness and usefulness of the aforementioned drugs from the clinical point of view in patients with OA.

REFERENCES

- De Palma A, Nalesso G. WNT signalling in osteoarthritis and its pharmacological targeting. *Handb Exp Pharmacol* 2021; **269**: 337-56. [PMID: 34510305]; [DOI: 10.1007/164_2021_525].
- Mohd Noor NA, Abdullah Nurul A, Ahmad Mohd Zain MR, Wan Nor Aduni WK, Azlan M. Extracellular vesicles from mesenchymal stem cells as potential treatments for osteoarthritis. *Cells*. 2021; **10(6)**: 1287. [PMID: 34067325]; [DOI: 10.3390/cells10061287].
- Oh HK, Park M, Choi SW, Jeong DU, Kim BJ, Kim JA, et al. Suppression of osteoarthritis progression by post-natal induction of Nkx3.2. *Biochem Biophys Res Commun*. 2021; **571**: 188-94. [PMID: 34330063]; [DOI: 10.1016/j.bbrc.2021.07.074].
- Cherifi C, Monteagudo S, Lories RJ. Promising targets for therapy of osteoarthritis: a review on the Wnt and TGF-beta signalling pathways. *Ther Adv Musculoskelet Dis*. 2021; **13**: 1759720X211006959. [PMID: 33948125]; [DOI: 10.1177/1759720X211006959].
- Lu J, Guan H, Wu D, Hu Z, Zhang H, Jiang H, et al. Pseudolaric acid B ameliorates synovial inflammation and vessel formation by stabilizing PPAR γ to inhibit NF- κ B signalling pathway. *J Cell Mol Med*. 2021; **25**: 6664-78. [PMID: 34117708]; [DOI: 10.1111/jcmm.16670].
- Liang T, Chen T, Qiu J, Gao W, Qiu X, Zhu Y, et al. Inhibition of nuclear receptor ROR α attenuates cartilage damage in osteoarthritis by modulating IL-6/STAT3 pathway. *Cell Death Dis*. 2021; **12(10)**: 886. [PMID: 34584074]; [DOI: 10.1038/s41419-021-04170-0].
- Zhang K, Li Z, Lu Y, Xiang L, Sun J, Zhang H. Silencing of Vangl2 attenuates the inflammation promoted by Wnt5a via MAPK and NF- κ B pathway in chondrocytes. *J Orthop Surg Res*. 2021; **16(1)**: 136. [PMID: 33588909]; [DOI: 10.1186/s13018-021-02268-x].
- Lin W, Kang H, Dai Y, Niu Y, Yang G, Niu J, et al. Early patellofemoral articular cartilage degeneration in a rat model of patellar instability is associated with activation of the NF- κ B signaling pathway. *BMC Musculoskelet Disord*. 2021; **22(1)**: 90. [PMID: 33461534]; [DOI: 10.1186/s12891-021-03965-8].
- Wang Y, Li T, Yang Q, Feng B, Xiang Y, Lv Z, et al. LncRNA THUMP3-AS1 enhances the proliferation and inflammatory response of chondrocytes in osteoarthritis. *Int Immunopharmacol*. 2021; **100**: 108138. [PMID: 34509934]; [DOI: 10.1016/j.intimp.2021.108138].
- Gau K, Wu W, Li J, Xu D, Liu Y, Bi M, et al. Positive feedback loop of lncRNA FAM201A/miR146a5p/POU2F1 regulates IL1 β induced chondrocyte injury in vitro. *Mol Med Rep*. 2022; **25(1)**: 20. [PMID: 34796909]; [DOI: 10.3892/mmr.2021.12536].
- Li X, Li Y, Yang X, Liao R, Chen L, Guo Q, et al. PR11-364P22.2/ATF3 protein interaction mediates IL-1 β -induced catabolic effects in cartilage tissue and chondrocytes. *J Cell Mol Med*. 2021; **25**: 6188-6202. [PMID: 34037306]; [DOI: 10.1111/jcmm.16561].
- Zhou L, Gu M, Ma X, Wen L, Zhang B, Lin Y, et al. Long non-coding RNA PCAT-1 regulates apoptosis of chondrocytes in osteoarthritis by sponging miR-27b-3p. *J Bone Miner Metab*. 2021; **39**: 139-47. [PMID: 32770398]; [DOI: 10.1007/s00774-020-01128-8].
- Ou D, Ding W, Tong C, Yi W. Knockdown of long non-coding RNA LINC00473 protects CHON-001 cells against interleukin-1 β -induced cell injury. *Biol Pharm Bull*. 2021; **44**: 232-7. [PMID: 33268698]; [DOI: 10.1248/bpb.b20-00688].
- Ruiz AR, Tuerlings M, Das A, de Almeida RC, Eka Suchiman H, Nelissen RGHH, et al. The role of TNFRSF11B in development of osteoarthritic cartilage. *Rheumatology (Oxford)* 2022; **61**: 856-64. [PMID: 33989379]; [DOI: 10.1093/rheumatology/keab440].
- Bhosale AM, Richardson JB. Articular cartilage: structure, injuries and review of management. *Br Med Bull*. 2008; **87**: 77-95. [PMID: 18676397]; [DOI: 10.1093/bmb/ldn025].
- Charlier E, Relic B, Deroyer C, Malaise O, Neuville S, Collée J, et al. Insights on molecular mechanisms of chondrocytes death in osteoarthritis. *Int J Mol Sci* 2016; **17(12)**: 2146. [PMID: 27999417]; [DOI: 10.3390/ijms17122146].
- Linkermann A, Green DR. Necroptosis. *N Engl J Med* 2014; **370**: 455-65. [PMID: 24476434]; [DOI: 10.1056/NEJMra1310050].
- Musumeci G, Castrogiovanni P, Trovato FM, Weinberg AM, Al-Wasiyah MK, Alqahtani MH, et al. Biomarkers of chondrocyte apoptosis and autophagy in osteoarthritis. *Int J Mol Sci* 2015; **16**: 20560-75. [PMID: 26334269]; [DOI: 10.3390/ijms160920560].
- Riegger J, Brenner RE. Pathomechanisms of posttraumatic osteoarthritis: chondrocyte behavior and fate in a precarious environment. *Int J Mol Sci* 2020; **21(5)**: 1560. [PMID: 32106481]; [DOI: 10.3390/ijms21051560].
- Martel-Pelletier J, Alaaeddine N, Pelletier JP. Cytokines and their role in the pathophysiology of osteoarthritis. *Front Biosci* 1999; **4**: D694-703. [PMID: 10525480]; [DOI: 10.2741/martel].
- Kapoor M, Martel-Pelletier J, Lajeunesse D, Pelletier JP, Fahmi H. Role of proinflammatory cytokines in the pathophysiology of osteoarthritis. *Nat Rev Rheumatol* 2011; **7**: 33-42. [PMID: 21119608]; [DOI: 10.1038/nrrheum.2010.196].
- Stöve J, Huch K, Günther KP, Scharf HP. Interleukin-1beta induces different gene expression of stromelysin, aggrecan and tumor-necrosis-factor-stimulated gene 6 in human osteoarthritic chondrocytes in vitro. *Pathobiology* 2000; **68**: 144-9. [PMID: 11174072]; [DOI: 10.1159/000055915].
- Chadjichristos C, Ghayor C, Kypriotou M, Martin G, Renard E, Ala-Kokko L, et al. Sp1 and Sp3 transcription factors mediate interleukin-1 beta down-regulation of human type II collagen gene expression in articular chondrocytes. *J Biol Chem* 2003; **278**: 39762-72. [PMID: 12888570]; [DOI: 10.1074/jbc.M303541200].
- Bowles RD., Mata BA, Bell RD, Mwangi TK, Huebner JL, Kraus VB, et al. In vivo luminescence imaging of NF- κ B activity and serum cytokine levels predict pain sensitivities in a rodent model of osteoarthritis. *Arthritis Rheumatol* 2014; **66**: 637-46. [PMID: 24574224]; [DOI: 10.1002/art.38279].
- Zacharjasz J, Mleczko AM, Bąkowski P, Piontek T, Bąkowska-Zywicka K. Small noncoding RNAs in knee osteoarthritis: the role of microRNAs and tRNA-derived fragments. *Int J Mol Sci*. 2021; **22(11)**: 5711. [PMID: 34071929]; [DOI: 10.3390/ijms22115711].
- Molnar V, Matišić V, Kodvanj I, Bjelica R, Jeleč Ž, Hudetz D, et al. Cytokines and chemokines involved in osteoarthritis pathogenesis. *Int J Mol Sci* 2021; **22(17)**: 9208. [PMID: 34502117]; [DOI: 10.3390/ijms22179208].
- Ren G, Al-Jezani N, Raitlon P, Powell JN, Krawetz RJ. CCL22 induces pro-inflammatory changes in fibroblast-like synoviocytes. *iScience*. 2020; **24(1)**: 101943. [PMID: 33490888]; [DOI: 10.1016/j.isci.2020.101943].
- Zhu S, Kuek V, Bennett S, Xu H, Rosen V, Xu J. Protein Cyt11: its role in chondrogenesis, cartilage homeostasis, and disease. *Cell Mol Life Sci* 2019; **76**: 3515-23. [PMID: 31089746]; [DOI: 10.1007/s00018-019-03137-x].
- Jiang L, Lin J, Zhao S, Wu J, Jin Y, Yu L, et al. ADAMTS5 in osteoarthritis: biological functions, regulatory network, and potential targeting therapies. *Front Mol Biosci* 2021; **8**: 703110. [PMID: 34434966]; [DOI: 10.3389/fmolb.2021.703110].

30. Fan X, Wu X, Crawford R, Xiao Y, Prasadam I. Macro, micro, and molecular. changes of the osteochondral interface in osteoarthritis development. *Front Cell Dev Biol* 2021; **9**: 659654. [PMID: 34041240]; [DOI: 10.3389/fcell.2021.659654].
31. Yi D, Yu H, Lu K, Ruan C, Ding C, Tong L, et al. AMPK signaling in energy control, cartilage biology, and osteoarthritis. *Front Cell Dev Biol* 2021; **9**: 696602. [PMID: 34239878]; [DOI: 10.3389/fcell.2021.696602].
32. Srinivas V, Bohensky J, Shapiro I.M. Autophagy: a new phase in the maturation of growth plate chondrocytes is regulated by HIF, mTOR and AMP kinase. *Cells Tissues Organs* 2009; **189**: 88-92. [PMID: 18703865]; [DOI: 10.1159/000151428].
33. Bohensky J, Leshinsky S, Srinivas V, Shapiro IM. Chondrocyte autophagy is stimulated by HIF-1 dependent AMPK activation and mTOR suppression. *Pediatr Nephrol* 2010; **25**: 633-42. [PMID: 19830459]; [DOI: 10.1007/s00467-009-1310-y].
34. Dai B, Zhu F, Chen Y, Zhou R, Wang Z, Xie Y, et al. ASIC1a promotes acid-induced autophagy in rat articular chondrocytes through the AMPK/FoxO3a pathway. *Int J Mol Sci* 2017; **18**(10): 2125. [PMID: 29019932]; [DOI: 10.3390/ijms18102125].
35. Zhao X, Li Y, Lin X, Wang J, Zhao X, Xie J, et al. Ozone induces autophagy in rat chondrocytes stimulated with IL-1beta through the AMPK/mTOR signaling pathway. *J Pain Res* 2018; **11**: 3003-17. [PMID: 30568481]; [DOI: 10.2147/JPR.S183594].
36. Ge Y, Zhou S, Li Y, Wang Z, Chen S, Xia T, et al. Estrogen prevents articular cartilage destruction in a mouse model of AMPK deficiency via ERK-mTOR pathway. *Ann Transl Med* 2019; **7**(4): 336. [PMID: 31475206]; [DOI: 10.21037/atm.2019.06.77].
37. Terkeltaub R, Yang B, Lotz M, Liu-Bryan R. Chondrocyte AMP activated protein kinase activity suppresses matrix degradation responses to proinflammatory cytokines interleukin-1beta and tumor necrosis factor alpha. *Arthritis Rheum* 2011; **63**: 1928-37. [PMID: 21400477]; [DOI: 10.1002/art.30333].
38. Zheng Z, Xiang S, Wang Y, Dong Y, Li Z, Xiang Y, et al. NR4A1 promotes TNFalpha-induced chondrocyte death and migration injury via activating the AMPK/Drp1/mitochondrial fission pathway. *Int J Mol Med* 2020; **45**: 151-61. [PMID: 31746366]; [DOI: 10.3892/ijmm.2019.4398].
39. Liu N, Fu D, Yang J, Liu P, Song X, Wang X, et al. Asiatic acid attenuates hypertrophic and fibrotic differentiation of articular chondrocytes via AMPK/PI3K/AKT signaling pathway. *Arthritis Res Ther* 2020; **22**(1): 112. [PMID: 32398124]; [DOI: 10.1186/s13075-020-02193-0].
40. Liu Z, Zhang H, Wang H, Wei L, Niu L. Magnolol alleviates IL-1beta-induced dysfunction of chondrocytes through repression of SIRT1/AMPK/PGC-1alpha signaling pathway. *J Interferon Cytokine Res* 2020; **40**: 145-51. [PMID: 31916911]; [DOI: 10.1089/jir.2019.0139].
41. Petrusson F, Husa M, June R, Lotz M, Terkeltaub R, Liu-Bryan R. Linked decreases in liver kinase B1 and AMP-activated protein kinase activity modulate matrix catabolic responses to biomechanical injury in chondrocytes. *Arthritis Res Ther* 2013; **15**(4): R77. [PMID: 23883619]; [DOI: 10.1186/ar4254].
42. Zhou S, Lu W, Chen L, Ge Q, Chen D, Xu Z, et al. AMPK deficiency in chondrocytes accelerated the progression of instability-induced and ageing-associated osteoarthritis in adult mice. *Sci Rep* 2017; **7**: 43245. [PMID: 28225087]; [DOI: 10.1038/srep43245].
43. Ma CH, Chiuva YC, Wu CHI, Jou M, Tu YK, Hung CH, et al. Homocysteine causes dysfunction of chondrocytes and oxidative stress through repression of SIRT1/AMPK pathway: a possible link between hyperhomocysteinemia and osteoarthritis. *Redox Biol* 2018; **15**: 504-12. [PMID: 29413962]; [DOI: 10.1016/j.redox.2018.01.010].
44. Zhuo Q, Yang W, Chen J, Wang Y. Metabolic syndrome meets osteoarthritis. *Nat Rev Rheumatol* 2012; **8**: 729-37. [PMID: 22907293]; [DOI: 10.1038/nrrheum.2012.135].
45. Zhai G. Alteration of metabolic pathways in osteoarthritis. *Me-tabolites* 2019; **9**(1): 11. [PMID: 30634493]; [DOI: 10.3390/metabo9010011].
46. Kang EH, Lee YJ, Kim TK, Chang CB., Chung JH., Shin K, et al. Adiponectin is a potential catabolic mediator in osteoarthritis cartilage. *Arthritis Res Ther* 2010; **12**(6): R231. [PMID: 21194467]; [DOI: 10.1186/ar3218].
47. Liu-Bryan R. Inflammation and intracellular metabolism: new targets in OA. *Osteoarthritis Cartilage* 2015; **23**: 1835-42. [PMID: 26521729]; [DOI: 10.1016/j.joca.2014.12.016].
48. Zhou S, Lu W, Chen L, Ge Q, Chen D, Xu Z, et al. AMPK deficiency in chondrocytes accelerated the progression of instability-induced and ageing-associated osteoarthritis in adult mice. *Sci Rep* 2017; **7**: 43245. [PMID: 28225087]; [DOI: 10.1038/srep43245].
49. Yang Y, Wang Y, Kong Y, Zhang X, Zhang H, Gang Y, et al. Mechanical stress protects against osteoarthritis via regulation of the AMPK/NF-kappaB signaling pathway. *J Cell Physiol* 2019; **234**: 9156-67. [PMID: 30311192]; [DOI: 10.1002/jcp.27592].
50. Wang J, Li J, Song D, Ni J, Ding M, Huang J, et al. AMPK implications in osteoarthritis and therapeutic targets. *Am J Transl Res* 2020; **12**: 7670-81. [PMID: 33437352]; [PMCID: PMC7791500].
51. Kong C, Wang C, Shi Y, Yan L, Xu J, Qi W. Active vitamin D activates chondrocyte autophagy to reduce osteoarthritis via mediating the AMPK-mTOR signaling pathway. *Biochem Cell Biol* 2020; **98**: 434-42. [PMID: 31815524]; [DOI: 10.1139/bcb-2019-0333].
52. Matta C, Fellows CR, Quasnicka H, Williams A, Jeremiase B, Allaway D, et al. Clusterin secretion is attenuated by the proinflammatory cytokines interleukin-1beta and tumor necrosis factor-alpha in models of cartilage degradation. *J Orthop Res*. 2021; **39**: 1017-29. [PMID: 32725904]; [DOI: 10.1002/jor.24814].
53. Yamada S, Suzuki Y, Bernotiene E, Giles WR, Imaizumi Y, Yamamura H. Swelling-activated CIC-3 activity regulates prostaglandin E2 release in human OUMS-27 chondrocytes. *Biochem Biophys Res Commun* 2021; **537**: 29-35. [PMID: 33383561]; [DOI: 10.1016/j.bbrc.2020.12.068].
54. Liu M, Xie Z, Sun G, Chen L, Qi D, Zhang H, et al. Macrophage migration inhibitory factor may play a protective role in osteoarthritis. *Arthritis Res Ther* 2021; **23**(1): 59. [PMID: 33610191]; [DOI: 10.1186/s13075-021-02442-w].
55. Wang F, Ma L, Ding Y, He L, Chang M, Shan Y, et al. Fatty acid sensing GPCR (GPR84) signaling safeguards cartilage homeostasis and protects against osteoarthritis. *Pharmacol Res* 2021; **164**: 105406. [PMID: 33359913]; [DOI: 10.1016/j.phrs.2020.105406].
56. Zhu S, Bennett S, Li Y, Liu M, Xu J. The molecular structure and role of LECT2 or CHM-II in arthritis, cancer, and other diseases. *J Cell Physiol* 2022; **237**: 480-8. [PMID: 34550600]; [DOI: 10.1002/jcp.30593].
57. Cavallo C, Merli G, Borzi RM, Zini N, D'Adamo S, Guescini M, et al. Small extracellular vesicles from adipose derived stromal cells significantly attenuate in vitro the NF-kappaB dependent inflammatory/catabolic environment of osteoarthritis. *Sci Rep* 2021; **11**(1): 1053. [PMID: 33441764]; [DOI: 10.1038/s41598-020-80032-7].
58. Pelsma ICM, Claessen, KMJA, Slagboom PE, van Heemst D, Pereira AM, Kroon HM, et al. Variants of FOXO3 and RPA3 genes affecting IGF-1 levels alter the risk of development of primary osteoarthritis. *Eur J Endocrinol*. 2021; **184**: 29-39. [PMID: 33112260]; [DOI: 10.1530/EJE-20-0904].
59. Qian JJ, Xu Q, Xu WM, Cai R, Huang GC. Expression of VEGF-A signaling pathway in cartilage of ACLT-induced osteoarthritis Mouse Model. *J Orthop Surg Res* 2021; **16**(1): 379. [PMID: 34127028]; [DOI: 10.1186/s13018-021-02528-w].
60. Ingale D, Kulkarni P, Electricwala A, Moghe A, Kamyab S, Jagtap S, et al. Synovium-synovial fluid axis in osteoarthritis pathology: a key regulator of the cartilage degradation process. *Genes (Basel)*. 2021; **12**(7): 989. [PMID: 34209473]; [DOI: 10.3390/genes12070989].

61. Neri S, Guidotti S, Bini C, Pelotti S, D'Adamo S, Minguzzi M, et al. Oxidative stress-induced DNA damage and repair in primary human osteoarthritis chondrocytes: focus on IKK α and the DNA Mismatch Repair System. *Free Radic Biol Med* 2021; **166**: 212-25. [PMID: 33636333]; [DOI: 10.1016/j.freeradbiomed.2021.02.020].
62. Houtman E, Tuerlings M, Riechelmann J, Suchiman EHED, van der Wal RJP, Nelissen RGHH, et al. Elucidating mechano-pathology of osteoarthritis: transcriptome-wide differences in mechanically stressed aged human cartilage explants. *Arthritis Res Ther* 2021; **23(1)**: 215. [PMID: 34399844]; [DOI: 10.1186/s13075-021-02595-8].
63. Guo H, Yin W, Zou Z, Zhang C, Sun M, Min L, et al. Quercitrin alleviates cartilage extracellular matrix degradation and delays ACLT rat osteoarthritis development: An in vivo and in vitro study. *J Adv Res* 2020; **28**: 255-67. [PMID: 33364061]; [DOI: 10.1016/j.jare.2020.06.020].
64. Chen W, Lin T, He O, Yang P, Zhang G, Huang F, et al. Study on the potential active components and molecular mechanism of Xiao Huoluo Pills in the treatment of cartilage degeneration of knee osteoarthritis based on bioinformatics analysis and molecular docking technology. *J Orthop Surg Res* 2021; **16(1)**: 460. [PMID: 34273999]; [DOI: 10.1186/s13018-021-02552-w].
65. Carlson EL, Karuppagounder V, Pinamont WJ, Yoshioka NK, Ahmad A, Schott EM, et al. Paroxetine-mediated GRK2 inhibition is a disease-modifying treatment for osteoarthritis. *Sci Transl Med* 2021; **13(580)**: eaa8491. [PMID: 33568523]; [DOI: 10.1126/scitranslmed.aau8491].
66. Ou D, Ding W, Tong C, Yi W. Knockdown of long non-coding RNA LINC00473 protects CHON-001 cells against interleukin-1 β -induced cell injury. *Biol Pharm Bull* 2021; **44**: 232-7. [PMID: 33268698]; [DOI: 10.1248/bpb.b20-00688].
67. Tian Z, Zeng F, Zhao C, Dong S. Angelicin alleviates post-trauma osteoarthritis progression by regulating macrophage polarization via STAT3 signaling pathway. *Front Pharmacol* 2021; **12**: 669213. [PMID: 34177582]; [DOI: 10.3389/fphar.2021.669213].
68. Guo D, He L, Gao Y, Jin C, Lin H, Zhang L, et al. Obeticholic acid derivative, T-2054 suppresses osteoarthritis via inhibiting NF- κ B-signaling pathway. *Int J Mol Sci* 2021; **22(8)**: 3807. [PMID: 33916928]; [DOI: 10.3390/ijms22083807].
69. Pothacharoen P, Chaiwongsa R, Chanmee T, Insuan O, Wongwichai T, Janchai P, et al. Bromelain extract exerts antiarthritic effects via chondroprotection and the suppression of TNF- α -induced NF- κ B and MAPK signaling. *Plants (Basel)* 2021; **10(11)**: 2273. [PMID: 34834636]; [DOI: 10.3390/plants10112273].
70. Xu K, Gao Y, Yang L, Liu Y, Wang C. Magnolin exhibits anti-inflammatory effects on chondrocytes via the NF- κ B pathway for attenuating anterior cruciate ligament transection-induced osteoarthritis. *Connect Tissue Res* 2021; **62**: 475-84. [PMID: 32602381]; [DOI: 10.1080/03008207.2020.1778679].
71. Chang L, Liu A, Xu J, Xu X, Dai J, Wu R, et al. TDP-43 maintains chondrocyte homeostasis and alleviates cartilage degradation in osteoarthritis. *Osteoarthritis Cartilage* 2021; **29**: 1036-47. [PMID: 33781898]; [DOI: 10.1016/j.joca.2021.03.015].
72. Gan K, Wu W, Li J, Xu D, Liu Y, Bi M, et al. Positive feedback loop of lncRNA FAM201A/miR-146a-5p/POU2F1 regulates IL-1 β -induced chondrocyte injury in vitro. *Mol Med Rep* 2022; **25(1)**: 20. [PMID: 34796909]; [DOI: 10.3892/mmr.2021.12536].
73. Dong J, Zhang KJ, Li GC, Chen XR, Lin JJ, Li JW, et al. CDDO-Im ameliorates osteoarthritis and inhibits chondrocyte apoptosis in mice via enhancing Nrf2-dependent autophagy. *Acta Pharmacol Sin* 2022; **43**: 1793-1802. [PMID: 34754093]; [DOI: 10.1038/s41401-021-00782-6].
74. Han J, Guan J, Zhu X. Beta-Ecdysone attenuates cartilage damage in a mouse model of collagenase-induced osteoarthritis via mediating FOXO1/ADAMTS-4/5 signaling axis. *Histol Histopathol* 2021; **36**: 785-94. [PMID: 33876419]; [DOI: 10.14670/HH-18-341].
75. Collins JA, Kapustina M, Bolduc JA, Pike JFW, Diekman BO, Mix K, et al. Sirtuin 6 (SIRT6) regulates redox homeostasis and signaling events in human articular chondrocytes. *Free Radic Biol Med* 2021; **166**: 90-103. [PMID: 33600943]; [DOI: 10.1016/j.freeradbiomed.2021.01.054].
76. Camargo Brindo da Cruz IC, Pereira Velosa AP, Carrasco S, Dos Santos Filho A, Tomaz de Miranda J, Pompeu E, et al. Post-adipose-derived stem cells (ADSC) stimulated by collagen type V (Col V) mitigate the progression of osteoarthritic rabbit articular cartilage. *Front Cell Dev Biol* 2021; **9**: 606890. [PMID: 33829012]; [DOI: 10.3389/fcell.2021.606890].