Published version of the article can be found at:
https://doi.org/10.1016/j.joca.2023.06.005 - Osteoarthritis and Cartilage

Foundations of Osteoarthritis: An initiative of *Osteoarthritis and Cartilage*:

Inflammatory mediators in Osteoarthritis

Astrid De Roover[1*] and Ana Escribano-Núñez[1*], Silvia Monteagudo[1], Rik Lories[1,2]

[1]Laboratory of Tissue Homeostasis and Disease, Skeletal Biology and Engineering Research Center, Department of Development and Regeneration, KU Leuven, 3000 Leuven, Belgium.

[2]Division of Rheumatology, University Hospitals Leuven, 3000 Leuven, Belgium.

*These authors contributed equally to this work.

Abstract

Objectives

As more has become known of the pathophysiology of osteoarthritis (OA), evidence that inflammation plays a critical role in its development and progression has accumulated. Here, we aim to review current knowledge of the complex inflammatory network in the OA joint.

Design

This narrative review is presented in three main sections: local inflammation, systemic inflammation, and therapeutic implications. We focused on inflammatory mediators and their link to OA structural changes in the joint.

Results

OA is characterized by chronic and low-grade inflammation mediated mostly by the innate immune system, which results in cartilage degradation, bone remodeling and synovial changes.

Synovitis is regarded as an OA characteristic and associated with increased severity of symptoms and joint dysfunction. However, the articular cartilage and the subchondral bone also produce several pro-inflammatory mediators thus establishing a complex interplay between the different tissues of the joint. In addition, systemic low-grade inflammation induced by aging, obesity and metabolic syndrome can contribute to OA development and progression. The main inflammatory mediators associated with OA include cytokines, chemokines, growth factors, adipokines, and neuropeptides.

Conclusions

Future research is needed to deeper understand the molecular pathways mediating the inflammation in OA to provide new therapeutics that target these pathways, or to repurpose existing drugs.

Keywords: Osteoarthritis, Inflammation, Synovium, Cartilage, Cytokines, Adipokines

Introduction

Osteoarthritis (OA) is no longer viewed as a prototypical degenerative disease resulting from wear and tear, but rather as a complex multifactorial disorder of the whole joint. The pathophysiology and underlying mechanisms of OA are becoming better known and increasing evidence supports the concept that low-grade, chronic inflammation has an important role in OA. This multifactorial and complex inflammatory process arises early during OA and can affect the entire joint contributing to joint pain and damage. Further unravelling the inflammatory pathophysiology of OA is important to provide new therapeutic approaches that can potentially modify the progression of OA.

This review aims to provide an overview of effector molecules, cells, and cytokines in both local and systemic OA-associated inflammation, and their association to structural changes in the joint that develop in the disease course. In addition, we explore potential therapeutic strategies that target this low-grade inflammation in the treatment of OA. Due to the broad scope of this review, we do not intend to give detailed insights into the underlying pathways of the mentioned players or to more deeply address other features of disease to which inflammation can strongly contribute, such as pain, which was extensively reviewed by Conaghan, et al[1].

Local inflammation

Chronic synovial hypertrophy and low-grade inflammation of the synovium are well-established hallmarks of OA. In addition, chondrocytes and osteoblasts in the cartilage and subchondral bone can express a multitude of inflammatory mediators and receptors. The local inflammation that may be present in all tissues of the joint results in a complex pathology process causing more pain and tissue damage.

Synovium

The synovium is a thin loose connective tissue that lines the joint cavity in synovial joints. It consists of two layers: the outer sub-lining layer or subintima, composed of loose connective tissue, and the inner lining layer that mainly contains tissue resident macrophages and synovial fibroblasts. These cells produce synovial fluid that delivers nutrients and oxygen to the joint and removes metabolites and products of matrix degradation[2, 3]. In OA patients, the synovium can display signs of hypertrophy, hyperplasia, inflammatory cell infiltration, increased thickness, fibrosis and neoangiogenesis[2-4]. In several studies, an association between synovitis and increased severity of OA symptoms and progression was observed although causality cannot be inferred [5-8]. C-reactive protein (CRP) could be a potential biological marker of OA synovitis, as CRP level positively correlates with joint inflammation, clinical severity, pain, and number of affected joints[9-11]. Synovial inflammation is often apparent in the onset and progression of OA[12]. However, the onset of synovial inflammation and precise triggers in OA remain unknown. A more extensive discussion on the role of synovial inflammation in OA progression can be found in a recent review by Sanchez-Lopez *et al*.[13]

Cells in the inflamed synovium

Even though T cells (mainly of the CD4+ helper type) are found in the OA synovium, the involvement of the adaptive immune system is still uncertain and mainly cells from the innate immune system, also known as non-specific immune system, are thought to be involved in the pathogenesis of the disease[14]. The most frequently found immune cells in the inflamed synovium are macrophages and T cells, followed by mast cells, B cells and plasma cells, although the latter two in lower amounts. Neutrophils are seldom found [15]. Macrophages, located in the lining layer of the synovium, play a critical role in the maintenance of tissue homeostasis and, consequently, are involved in the pathogenesis of OA once dysregulated.

Synovial macrophages are an important source of pro-inflammatory molecules, including matrix-degrading enzymes, alarmins and cytokines such as interleukin-1 (IL-1) and tumor necrosis factor (TNF)[16]. In agreement, depletion of macrophages from OA synovial cells *in-vitro* resulted in a strong reduction of cytokines such as IL-1β, TNF, IL-8 and IL-6, and of tissue-destructive enzymes matrix metalloproteinases (MMP)-1 and 3[17]. Synovial macrophages have also been associated with osteophyte formation in OA. Of note, depletion of synovial macrophages using clodronate liposomes in a collagenase-induced OA mice model and in mice intra-articularly injected with transforming growth factor-β (TGF-β) resulted in reduced osteophyte formation, fibrosis and synovial activation[18, 19]. Macrophages have also been found in the synovial fluid of OA joints and their presence positively correlates with pain and joint stiffness[20, 21].

A detailed study revealed the composition, origin and differentiation of subsets of macrophages within healthy and inflamed joints[22]. Pro-inflammatory macrophages are derived from blood monocytes but certain subsets of macrophages populate organs during early development and subsequently self-sustain their numbers in a monocyte-independent manner. Culemann *et al.* showed that joint resident synovial macrophages can be subdivided into CX_3C motif chemokine receptor 1 (CX_3CR1)+ cells and CX_3CR1- interstitial macrophages. CX_3CR1+ macrophages display features typical of epithelial cells, forming a compact immunological barrier that isolates the joint from the surrounding synovium and controls the onset of inflammation thereby protecting intra-articular structures. The authors further demonstrated that CX_3CR1+ cells express immunomodulatory markers characteristic of an anti-inflammatory M2-like phenotype, like Trem2 and Axl. Interestingly, locally proliferating CX_3CR1- macrophages repopulate and maintain the numbers of the CX_3CR1+ cells[22].

Thus, macrophages are important mediators of OA-associated inflammation and modulating these cells could potentially be a promising strategy against OA development.

Molecules in the inflamed synovium

Cytokines are involved in the pathogenesis of OA[23, 24]. IL-1β and TNF can induce their own production in an autocrine manner[25, 26] as well as stimulate the expression of other pro-inflammatory cytokines (IL-6 and IL-8)[27, 28], reactive oxygen species (ROS)[29], nitric oxide and prostaglandin E2[30]. In addition, these catabolic molecules can increase the expression and activity of matrix-degrading enzymes and inhibit the production of collagen 2 and aggrecan, both essential components of the cartilage extracellular matrix (ECM)[31-34]. Moreover, nerve growth factor (NGF), an important regulator of OA pain, can be induced by IL-1β and TNF among other factors[35]. However, despite the detrimental effects of IL-1β and TNF, approaches targeting these pro-inflammatory cytokines have not been successful[1].

The circulating levels of IL-17 are significantly higher in OA patients compared to non-OA patients and two IL-17 polymorphisms are associated with OA susceptibility[36]. IL-17 can stimulate OA synovial fibroblasts to produce proangiogenic factors[37]. In a recent study, Faust *et al*. demonstrated that intra-articular injection of an IL-17-neutralizing antibody in mice reduced joint degeneration and decreased expression of the senescence marker Cdkn1a, putting forward that IL-17 could be a specific therapeutic target[38].

High levels of IL-6, IL-8, IL-15 and IL-18 are also found in plasma or synovial fluid from OA patients compared to non-OA patients, and positively correlate with cartilage damage[39-42]. The elevated levels of IL-8 and IL-18 might be associated with the pathogenesis of OA via the activation of MMP-3[41]. Other cytokines and chemokines involved in OA pathogenesis were reviewed by Molnar *et al*.[43] and Jrad *et al.*[44]

Adipokines can also be found in the OA synovium and are classically released by adipose tissue, like the infrapatellar fat pad. However, adipokines can also be synthesized by other joint cells

such as synoviocytes. These molecules might also be key players in the pathophysiology of OA-associated inflammation, senescence and cartilage degradation[45-47].

Bradykinin, NGF and neuropeptides like Substance P are also present in the OA synovium, which contains nociceptive fibers, as opposed to articular cartilage[35, 48]. Bradykinin is involved in OA inflammation and in the excitation and sensitization of sensory nerve fibers, thus producing pain. Bradykinin B2 receptor antagonists (Icatibant and Fasitibant) present analgesic effects and reduce the release of pro-inflammatory cytokines, representing a potential approach to slow down OA development[49].

Together, these molecules create a complex functional network of inflammatory factors in the synovium, and apart from the individual functions described here, it is becoming increasingly evident that there is significant crosstalk among the pathways and that the overall effect depends on the balance of multiple molecules. Elucidation of the exact connections between these pathways will lead to a better understanding of the pathogenesis of OA inflammation.

Cartilage

Articular cartilage is a highly specialized structure that covers the bone ends within the joint to allow low-friction movement. The articular cartilage is composed of an ECM and contains a unique cell-type called the articular chondrocytes. These specialized chondrocytes play a crucial role in the development, maintenance, and repair of the ECM that mainly consists of type 2 collagen fibers and proteoglycan aggrecan. Progressive damage to the articular cartilage is a major event in the pathogenesis of OA. Articular cartilage appears to have a specific type of inflammatory response upon damage despite its avascular structure and absence of a resident macrophage population.

Articular chondrocytes are normally quiescent cells. However, during OA, the cells are driven into a pro-inflammatory state that contributes to joint inflammation. Articular chondrocytes can

respond directly to mechanical injury in a number of ways, including by release of matrix-sequestered growth factors such as FGF2, TGFβ[50] and activation of cell surface ion channels like PIEZO1 and TRPV4[51]. Mechanical injury or abnormal loading, can also activate a cascade of molecular events by a process named "mechanoflammation".

Mechanoflammation involves the activation of the TGFβ-activated kinase 1 (TAK1), which can stimulate mitogen-activated protein kinases (MAPK) and, nuclear factor kappa B (NF-κB), resulting in regulation of ECM degrading enzymes and molecules important in pain such as NGF [52]. Following degradation, cartilage damage may also lead to the release of intracellular alarmins such as S100A8/9, HMGB1 or matrix fragments that have inflammatory actions within the cartilage and elsewhere in the joint[14, 53]. These so-called damage associated molecular patterns (DAMPs), can trigger the innate immune response via pattern-recognition receptors (PRRs), such as toll-like receptors (TLRs)[54]. Examples of specific DAMPs include fibronectin[54, 55], tenascin C[56], biglycan[57] and hyaluronic acid[58]. Strong in vivo support, in non-inflammatory models of OA, for this hypothesis has not been demonstrated. Finally, chondrocytes can produce and respond to several pro-inflammatory cytokines and chemokines leading to ECM degradation[59]. As stated above, TNF, IL-1β and IL-6 are the main inflammatory mediators in OA cartilage and can also be actively produced by OA chondrocytes[43]. TNF and IL-1β are synergistic pro-inflammatory cytokines that both exert their effects primarily through MAPK, NF-κB and activator protein 1 (AP-1) pathways[60-62]. In chondrocytes, TNF-α and IL-1β block the synthesis of ECM components such as type 2 collagen and proteoglycans[63, 64]. They also induce matrix degrading enzymes including MMP-1, MMP-3, MMP-13, ADAMTS-4 and ADAMTS-5[34, 62, 64]. Furthermore, they promote the synthesis of each other and other pro-inflammatory cytokines and chemokines such as IL-6 and IL-8[65]. In addition, TNF can promote apoptosis and cell death[66]. Of note, these concepts are largely built on in vitro and in vivo model

data while it has been challenging to find corroborating evidence in clinical trials or specific cohort studies.

In contrast, IL-6's exact role in OA remains difficult to define, as it has both beneficial and detrimental effects[67, 68]. On the one hand, numerous studies have shown that higher blood levels of IL-6 are associated with mobility impairment and disability in older adults[69] as well as with an increased risk of knee OA progression[70]. However, knockout of IL-6 in male mice resulted in more severe OA upon aging[71]. This controversy may be explained by IL-6's complex signaling pathway. IL-6 binds to either membrane-bound (mbIL-6R) or soluble (sIL-6R) specific IL-6 receptors. Binding of IL-6 to mbIL-6R forms a complex that activates the "classic" signaling pathway which results in an anti-inflammatory response[72]. On the other hand, binding of IL-6 to sIL-6R forms a complex that associates with gp130 protein and activates "trans" signaling responsible for the pro-inflammatory properties of IL-6[72]. Thus, both signaling pathways require further study to elucidate the exact role of IL-6 in OA.

Subchondral bone

The subchondral bone is the zone of epiphyseal bone underneath the articular cartilage. It can be divided into two different regions, the subchondral bone plate and the underlying trabecular bone. The presence of channels and pores allow cross talk between the subchondral bone and cartilage. The subchondral bone is a very dynamic structure that adapts to mechanical forces to provide support and shock-absorbance in the joint. This dynamic remodeling involves osteoblasts and osteoclasts. Osteoclasts are responsible for bone resorption while osteoblasts produce new bone. During OA, there is a dysregulation of subchondral bone remodeling. Osteoblasts isolated from OA subchondral bone demonstrate an altered phenotype. They secrete TGF-β and IL-6, molecules involved in the structural changes of OA synovium and cartilage[73]. IL-1β and IL-6 are suggested to be responsible for this altered phenotype in OA

osteoblast[73]. In addition, synovitis is positively associated with osteophyte formation especially since new bone formation is stimulated by TGF-β secreted from macrophages during synovial inflammation[13].

Systemic inflammation

Apart from local inflammation, OA has also been associated with low-grade systemic inflammatory states.

Aging

Aging is one of the most important risk factors contributing to the development of OA. The responsible mechanisms appear to be multifactorial and may include an age-related pro-inflammatory state, often referred to as "inflammaging", which can be both systemic and local[70]. The efficiency of the innate immune system decreases with aging and becomes chronically activated to a low-grade extent, contributing to the development and progression of age-related diseases such as OA[14].

Systemic inflammation can be in part promoted by aging-associated changes in tissues that result in increased and sustained production of the pro-inflammatory cytokines IL-6, TNF and CRP[11, 74, 75]. Interestingly, another study reported a robust increase in the expression of the alarmins S100A9 and S100A8 with aging which can also contribute to the development of chronic inflammation[76] and joint destruction[77, 78]. The role of the "geriatric" cytokine IL-6 in OA is not well understood as described above in this review.

The inflammasome is a key driver of the innate immune response seen in aging, therefore contributing to the process of "inflammaging". The best characterized member is NLRP3, which is highly expressed in chondrocytes, macrophages, synoviocytes, and osteoblasts. NLRP3 has been implicated in the pathogenesis of several arthritic disorders, participating in

the processing and maturation of IL-1β and IL-18[79]. Clavijo *et al.* showed that NLRP3 protein expression is 5.4-fold increased in the synovium of patients with knee OA and that it correlated with expression of xanthine oxidase, an enzyme responsible for the generation of ROS[80]. There is accumulating evidence for the participation of the NLRP3 inflammasome in OA onset and progression, therefore it is proposed as a potential biomarker for OA diagnosis and patient classification[81].

Another mechanism by which aging promotes chronic inflammation that could be important in OA is through cell senescence and in particular chondrocyte senescence. Cell senescence is characterized by growth arrest (replicative senescence) and the induction of a distinctive secretory phenotype called senescence-associated secretory phenotype (SASP). Senescence also has physiological functions. For instance, it contributes to tissue development during embryogenesis and suppresses tumor formation by preventing the propagation of damaged cells. However, accumulation of excessive senescent cells are implicated in the pathophysiology of many diseases associated with aging like OA, where senescent cells accumulate in cartilage and synovium thereby increasing the secretion of pro-inflammatory mediators and matrix-degrading enzymes[70]. Interestingly, local clearance of senescent chondrocytes attenuated the development of joint destruction during experimental post-traumatic OA and created a pro-regenerative environment[82]. Age-related changes of joint tissues are critical in the development of OA and strategies targeting the underlying mechanisms are promising approaches to OA therapy.

Obesity

Obesity is a well-recognized risk factor for OA incidence and progression. It affects both weight-bearing and non-weight-bearing joints because of excessive joint loading and systemic low-grade inflammation[83]. This systemic inflammation is induced by pro-inflammatory

adipokines secreted by the adipose tissues, such as the infrapatellar fat pads and other joint cells[47, 84]. The main adipokines that have been studied in association with OA are leptin, adiponectin, visfatin, and resistin. Obese individuals have higher levels of leptin, adiponectin and resistin in their synovial fluid, which are positively correlated with OA pain and progression[47, 84-87]. Visfatin is especially present inside OA osteophytes and is mainly secreted by the OA chondrocytes within the joint[86]. Mechanistically, these adipokines have been shown to support cartilage damage via increasing the expression of several cytokines such as IL-1β and IL-6, and MMPs in articular chondrocytes[88-92]. Furthermore, patients with obesity have a higher prevalence and severity of synovial inflammation[93]. They present with synovial fibrosis, increased macrophage infiltration and elevated TLR4 expression[94]. Although obesity evidently facilitates synovitis, there appears to be no improvement of synovial inflammation after weight loss[95, 96]. Indeed, improved knee pain in obese OA patients after weight loss was not mediated by a decrease in synovitis but rather by improvement in pressure pain threshold and mental health[97]. The reason why obesity, but not weight loss, has an effect on synovitis still remains unclear. Obesity could potentially cause long-lasting epigenetic or structural changes, which contribute to OA even after weight loss. Obesity-associated diet might also play a role in OA. Indeed, a higher diet inflammatory index score is associated with a higher prevalence of radiographic and symptomatic knee OA, independent of patient weight[98]. In addition, a western diet was associated with progression of OA[99]. Therefore, diet and gut microbiome involvement are gaining interest in OA research.

Type 2 diabetes

Studies demonstrate that patients with type 2 diabetes mellitus (T2DM) have a higher prevalence of OA[100, 101]. In contrast, other reports show no correlation between T2DM and OA prevalence[102, 103]. Yet, high glucose levels have been shown to induce vascular endothelial

growth factor (VEGF) secretion and ROS in OA synovial fibroblasts thereby inducing angiogenesis, tissue damage and inflammation[104]. Hyperglycemia is also directly associated with the accumulation of advanced glycation end-products (AGEs), which result from a reaction between α-ketoaldehydes and proteins[105]. AGEs are able to bind receptors of AGEs (RAGE) and TLRs on the chondrocyte cell surface thereby inducing a pro-inflammatory response[106]. Glyoxalase-1, the main enzyme responsible for the removal of AGE precursors, is downregulated by IL-1β in OA chondrocytes, which further contributes to AGE accumulation[107]. In addition, the onset of insulin resistance within the joint undermines the anti-inflammatory and chondroprotective effects of insulin[108-110]. The exact role of T2DM on OA independent of aging and obesity requires further study.

Metabolic syndrome

Metabolic syndrome (MetS) is characterized by a combination of hyperglycemia, abdominal obesity, hyperlipidemia, hypertension, and low serum high-density lipoprotein (HDL). It significantly increases the risk for a number of chronic disorders such as stroke, coronary heart disease, T2DM and also OA[111, 112]. The occurrence and progression of OA were strongly correlated with the number of components of MetS present in OA patients[113]. Mechanistically, MetS may increase the risk of OA by impairing the regulation of metabolic and inflammatory pathways[114]. Obesity- and T2DM-associated inflammation were previously discussed in this review. In addition, hypertension and other vascular components may lead to subchondral ischemia, which could compromise the nutrient supply to the articular cartilage and trigger subchondral bone remodeling[115, 116]. Indeed, in a recent meta-analysis patients with hypertension had a 2-fold and 1.5-fold increase in the risk for radiographic and symptomatic knee osteoarthritis, respectively[117]. Similarly, hypertensive rats spontaneously developed more subchondral bone damage compared to normotensive rats[118]. Dyslipidemia has also been

associated with osteoarthritis[119, 120]. Ectopic lipid deposition in chondrocytes induced by dyslipidemia may contribute to OA development, which is aggravated by deregulated cellular lipid metabolism in OA joint tissues[121]. Elevated levels of free fatty acids (FFAs) due to hyperlipidemia can also increase the expression of cytokines IL-6 and IL-8 in chondrocytes[122]. Furthermore, MetS is associated with a sedentary lifestyle and with limited physical exercise, which can increase the incidence of OA[112, 123]. Taken together, the potential underlying mechanisms are complex and involve a combination of different MetS components and pathways.

Therapeutic implications

There are currently no effective drugs to stop or reverse OA, although many advances have been made in understanding the pathophysiological processes of the disease, including inflammation. Classical non-targeted strategies for OA therapy, such as the use of non-steroideal-anti-inflammatory (NSAIDs) drugs and intra-articular injections of steroids, can reduce synovial inflammation and pain in OA. Chondroitin sulfate also modulates the inflammatory activity of synovitis by reducing the nuclear translocation of the transcription factor NF-κB in synoviocytes and macrophages[124]. However, NSAIDs can lead to a number of adverse effects and its use is contraindicated in some cases. In addition, intra-articular injections of steroids have only a short-term effect on knee pain and function, and treatments with more sustained efficacy are needed[125]. Also, a number of biological agents, mainly targeting TNF and IL-1β showed promising results in pilot studies but did not deliver successful results in clinical trials[126, 127]. However, post hoc analyses from the CANTOS trial showed that canakinumab treatment over 3 years led to a reduction in the rate of total knee or hip replacement compared with placebo, which suggests that long-term IL-1β inhibition could be

protective for the joints[128]. Therefore, this exploratory analysis supports further investigation of IL-1β for treatment of OA.

Beyond IL-1β and TNF, other cytokines are being investigated as potential treatment targets in OA, including IL-6 and IL-17. While studies investigating the role of IL-6 in OA are controversial[42, 71], targeting IL-17 seems promising[38]. The NLRP3 inflammasome is also an attractive target due to its involvement in the pathogenesis of OA. However, it is necessary to further elucidate the mechanisms behind NLRP3 activation and regulation[81].

Another emerging approach is to specifically remove senescent cells to avoid detrimental secretion of SASP-related factors. Selective deletion of senescent chondrocytes from OA patients shows promise[129]. In addition, several senolytics have been identified. For instance, the senolytic molecule ABT-263, a specific inhibitor of the anti-apoptotic proteins BCL-2 and BCL-xL, counteracts the anti-apoptotic functions of senescent cells, allowing them to initiate apoptosis thereby ameliorating OA in a rat model[130, 131]. Currently, senolytic drug Fisetin is in Phase I/II clinical trail for knee OA[132]. However, a previous Phase II study failed to demonstrate efficacy of senolytic molecule UBX0101 in knee OA[133]. SIRT6 depletion can induce chondrocyte senescence[134], while overexpression of this histone deacetylase could alleviate OA and inhibit synovial inflammation[135] putting forward that SIRT6 could be a novel therapeutic target in OA.

Of central importance for the initiation of innate immune responses is TLR signaling, which lead to cell stress and tissue damage. Therefore, inhibiting TLRs or their ligands might be promising options for OA therapy. Indeed, inhibiting TLR4 signaling by linarin, a natural flavonoid glycoside, appears to prevent the inflammatory response in OA[136].

Conclusions

Inflammation is an important part of the complex pathophysiology of OA and is characterized by a complex interplay between different tissues and between molecular pathways. All tissues of the joint can produce pro-inflammatory mediators thereby contributing to OA-associated low-grade inflammation. In addition, systemic inflammatory mediators due to aging, obesity, T2DM and MetS can also contribute to inflammation in the joint. The main inflammatory mediators associated with OA include cytokines, chemokines, growth factors, adipokines, and neuropeptides. OA-associated inflammation has a deleterious effect on cartilage, bone and synovium, leading to more pro-inflammatory mediators and resulting in a vicious cycle. Deciphering the complex interplay and the inflammatory pathways involved in OA is critical for the discovery of new therapies or to repurpose existing drugs.

Author contributions

All authors participated in the conception of the chapter, drafted the article, revised it, and approved the final version to be published. ADR and AEN contributed equally to this review.

Conflict of interest

Leuven Research and Development, the technology transfer office of KU Leuven, has received consultancy and speaker fees and research grants on behalf of R.J.L. from Abbvie, Boehringer-Ingelheim, Amgen (formerly Celgene), Eli-Lilly, Galapagos, Janssen, Fresenius Kabi, MSD, Novartis, Pfizer, Biosplice Therapeutics (formerly Samumed) and UCB The other authors declare that they have no competing financial interests.

Acknowledgements

ADR and AEN are recipients of a strategic basic and a fundamental research PhD fellowship, respectively, from Flanders Research Foundation (FWO-Vlaanderen) (1S35622N and

11L1822N). R.L. is the recipient of a senior clinical investigator fellowship (18B2122N) from FWO-Vlaanderen. Work on osteoarthritis in the Tissue Homeostasis and Disease laboratory is supported by grants from FWO-Vlaanderen (G097118N, G0B2120N, G099922N, G056822N and G059223N) and from KU Leuven (C14/20/117).

Figures

Figure 1

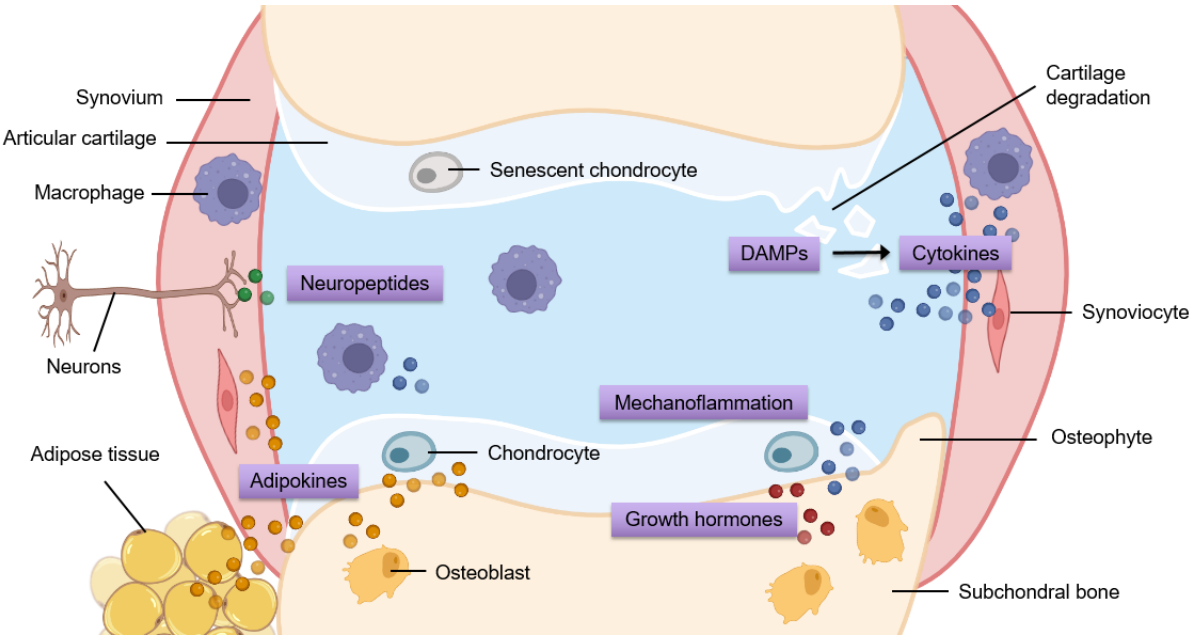

Figure 1 Overview of the inflammatory mediators in OA. The interplay between the different pro-inflammatory mediators and mechanisms in the different tissues of the OA joint. DAMPs: disease-associated molecular patterns.

References

1. Conaghan PG, Cook AD, Hamilton JA, Tak PP. Therapeutic options for targeting inflammatory osteoarthritis pain. Nat Rev Rheumatol 2019; 15: 355-363.
2. Mathiessen A, Conaghan PG. Synovitis in osteoarthritis: current understanding with therapeutic implications. Arthritis Res Ther 2017; 19: 18.
3. Sellam J, Berenbaum F. The role of synovitis in pathophysiology and clinical symptoms of osteoarthritis. Nat Rev Rheumatol 2010; 6: 625-635.
4. Scanzello CR, Goldring SR. The role of synovitis in osteoarthritis pathogenesis. Bone 2012; 51: 249-257.
5. Ayral X, Pickering EH, Woodworth TG, Mackillop N, Dougados M. Synovitis: a potential predictive factor of structural progression of medial tibiofemoral knee osteoarthritis -- results of a 1 year longitudinal arthroscopic study in 422 patients. Osteoarthritis Cartilage 2005; 13: 361-367.
6. Hill CL, Hunter DJ, Niu J, Clancy M, Guermazi A, Genant H, et al. Synovitis detected on magnetic resonance imaging and its relation to pain and cartilage loss in knee osteoarthritis. Ann Rheum Dis 2007; 66: 1599-1603.
7. Kortekaas MC, Kwok WY, Reijnierse M, Stijnen T, Kloppenburg M. Brief Report: Association of Inflammation With Development of Erosions in Patients With Hand Osteoarthritis: A Prospective Ultrasonography Study. Arthritis Rheumatol 2016; 68: 392-397.
8. Roemer FW, Guermazi A, Felson DT, Niu J, Nevitt MC, Crema MD, et al. Presence of MRI-detected joint effusion and synovitis increases the risk of cartilage loss in knees without osteoarthritis at 30-month follow-up: the MOST study. Ann Rheum Dis 2011; 70: 1804-1809.
9. Pearle AD, Scanzello CR, George S, Mandl LA, DiCarlo EF, Peterson M, et al. Elevated high-sensitivity C-reactive protein levels are associated with local inflammatory findings in patients with osteoarthritis. Osteoarthritis Cartilage 2007; 15: 516-523.
10. Stürmer T, Brenner H, Koenig W, Günther KP. Severity and extent of osteoarthritis and low grade systemic inflammation as assessed by high sensitivity C reactive protein. Ann Rheum Dis 2004; 63: 200-205.
11. Spector TD, Hart DJ, Nandra D, Doyle DV, Mackillop N, Gallimore JR, et al. Low-level increases in serum C-reactive protein are present in early osteoarthritis of the knee and predict progressive disease. Arthritis Rheum 1997; 40: 723-727.
12. Sokolove J, Lepus CM. Role of inflammation in the pathogenesis of osteoarthritis: latest findings and interpretations. Ther Adv Musculoskelet Dis 2013; 5: 77-94.
13. Sanchez-Lopez E, Coras R, Torres A, Lane NE, Guma M. Synovial inflammation in osteoarthritis progression. Nat Rev Rheumatol 2022.
14. van den Bosch MHJ, van Lent P, van der Kraan PM. Identifying effector molecules, cells, and cytokines of innate immunity in OA. Osteoarthritis Cartilage 2020; 28: 532-543.
15. de Lange-Brokaar BJ, Ioan-Facsinay A, van Osch GJ, Zuurmond AM, Schoones J, Toes RE, et al. Synovial inflammation, immune cells and their cytokines in osteoarthritis: a review. Osteoarthritis Cartilage 2012; 20: 1484-1499.
16. Wu CL, Harasymowicz NS, Klimak MA, Collins KH, Guilak F. The role of macrophages in osteoarthritis and cartilage repair. Osteoarthritis Cartilage 2020; 28: 544-554.
17. Bondeson J, Wainwright SD, Lauder S, Amos N, Hughes CE. The role of synovial macrophages and macrophage-produced cytokines in driving aggrecanases, matrix

metalloproteinases, and other destructive and inflammatory responses in osteoarthritis. Arthritis Res Ther 2006; 8: R187.
18. Blom AB, van Lent PL, Holthuysen AE, van der Kraan PM, Roth J, van Rooijen N, et al. Synovial lining macrophages mediate osteophyte formation during experimental osteoarthritis. Osteoarthritis Cartilage 2004; 12: 627-635.
19. van Lent PL, Blom AB, van der Kraan P, Holthuysen AE, Vitters E, van Rooijen N, et al. Crucial role of synovial lining macrophages in the promotion of transforming growth factor beta-mediated osteophyte formation. Arthritis Rheum 2004; 50: 103-111.
20. Sakurai Y, Fujita M, Kawasaki S, Sanaki T, Yoshioka T, Higashino K, et al. Contribution of synovial macrophages to rat advanced osteoarthritis pain resistant to cyclooxygenase inhibitors. Pain 2019; 160: 895-907.
21. Gómez-Aristizábal A, Gandhi R, Mahomed NN, Marshall KW, Viswanathan S. Synovial fluid monocyte/macrophage subsets and their correlation to patient-reported outcomes in osteoarthritic patients: a cohort study. Arthritis Res Ther 2019; 21: 26.
22. Culemann S, Grüneboom A, Nicolás-Ávila J, Weidner D, Lämmle KF, Rothe T, et al. Locally renewing resident synovial macrophages provide a protective barrier for the joint. Nature 2019; 572: 670-675.
23. Martel-Pelletier J, Alaaeddine N, Pelletier JP. Cytokines and their role in the pathophysiology of osteoarthritis. Front Biosci 1999; 4: D694-703.
24. Farahat MN, Yanni G, Poston R, Panayi GS. Cytokine expression in synovial membranes of patients with rheumatoid arthritis and osteoarthritis. Ann Rheum Dis 1993; 52: 870-875.
25. Sadouk MB, Pelletier JP, Tardif G, Kiansa K, Cloutier JM, Martel-Pelletier J. Human synovial fibroblasts coexpress IL-1 receptor type I and type II mRNA. The increased level of the IL-1 receptor in osteoarthritic cells is related to an increased level of the type I receptor. Lab Invest 1995; 73: 347-355.
26. Alaaeddine N, DiBattista JA, Pelletier JP, Cloutier JM, Kiansa K, Dupuis M, et al. Osteoarthritic synovial fibroblasts possess an increased level of tumor necrosis factor-receptor 55 (TNF-R55) that mediates biological activation by TNF-alpha. J Rheumatol 1997; 24: 1985-1994.
27. Guerne PA, Carson DA, Lotz M. IL-6 production by human articular chondrocytes. Modulation of its synthesis by cytokines, growth factors, and hormones in vitro. J Immunol 1990; 144: 499-505.
28. Lotz M, Terkeltaub R, Villiger PM. Cartilage and joint inflammation. Regulation of IL-8 expression by human articular chondrocytes. J Immunol 1992; 148: 466-473.
29. Yasuhara R, Miyamoto Y, Akaike T, Akuta T, Nakamura M, Takami M, et al. Interleukin-1beta induces death in chondrocyte-like ATDC5 cells through mitochondrial dysfunction and energy depletion in a reactive nitrogen and oxygen species-dependent manner. Biochem J 2005; 389: 315-323.
30. El Mansouri FE, Chabane N, Zayed N, Kapoor M, Benderdour M, Martel-Pelletier J, et al. Contribution of H3K4 methylation by SET-1A to interleukin-1-induced cyclooxygenase 2 and inducible nitric oxide synthase expression in human osteoarthritis chondrocytes. Arthritis Rheum 2011; 63: 168-179.
31. Xiang X, Zhou Y, Sun H, Tan S, Lu Z, Huang L, et al. Ivabradine abrogates TNF-α-induced degradation of articular cartilage matrix. Int Immunopharmacol 2019; 66: 347-353.
32. Goldring MB, Birkhead J, Sandell LJ, Kimura T, Krane SM. Interleukin 1 suppresses expression of cartilage-specific types II and IX collagens and increases types I and III collagens in human chondrocytes. J Clin Invest 1988; 82: 2026-2037.

33. Raymond L, Eck S, Mollmark J, Hays E, Tomek I, Kantor S, et al. Interleukin-1 beta induction of matrix metalloproteinase-1 transcription in chondrocytes requires ERK-dependent activation of CCAAT enhancer-binding protein-beta. J Cell Physiol 2006; 207: 683-688.
34. Xue J, Wang J, Liu Q, Luo A. Tumor necrosis factor-α induces ADAMTS-4 expression in human osteoarthritis chondrocytes. Mol Med Rep 2013; 8: 1755-1760.
35. Manni L, Lundeberg T, Fiorito S, Bonini S, Vigneti E, Aloe L. Nerve growth factor release by human synovial fibroblasts prior to and following exposure to tumor necrosis factor-alpha, interleukin-1 beta and cholecystokinin-8: the possible role of NGF in the inflammatory response. Clin Exp Rheumatol 2003; 21: 617-624.
36. Lee YH, Song GG. Association between IL-17 gene polymorphisms and circulating IL-17 levels in osteoarthritis: a meta-analysis. Z Rheumatol 2020; 79: 482-490.
37. Honorati MC, Neri S, Cattini L, Facchini A. Interleukin-17, a regulator of angiogenic factor release by synovial fibroblasts. Osteoarthritis Cartilage 2006; 14: 345-352.
38. Faust HJ, Zhang H, Han J, Wolf MT, Jeon OH, Sadtler K, et al. IL-17 and immunologically induced senescence regulate response to injury in osteoarthritis. J Clin Invest 2020; 130: 5493-5507.
39. Scanzello CR, Umoh E, Pessler F, Diaz-Torne C, Miles T, Dicarlo E, et al. Local cytokine profiles in knee osteoarthritis: elevated synovial fluid interleukin-15 differentiates early from end-stage disease. Osteoarthritis Cartilage 2009; 17: 1040-1048.
40. Meehan RT, Regan EA, Hoffman ED, Wolf ML, Gill MT, Crooks JL, et al. Synovial Fluid Cytokines, Chemokines and MMP Levels in Osteoarthritis Patients with Knee Pain Display a Profile Similar to Many Rheumatoid Arthritis Patients. J Clin Med 2021; 10.
41. Koh SM, Chan CK, Teo SH, Singh S, Merican A, Ng WM, et al. Elevated plasma and synovial fluid interleukin-8 and interleukin-18 may be associated with the pathogenesis of knee osteoarthritis. Knee 2020; 27: 26-35.
42. Doss F, Menard J, Hauschild M, Kreutzer HJ, Mittlmeier T, Müller-Steinhardt M, et al. Elevated IL-6 levels in the synovial fluid of osteoarthritis patients stem from plasma cells. Scand J Rheumatol 2007; 36: 136-139.
43. 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.
44. Jrad AIS, Trad M, Bzeih W, El Hasbani G, Uthman I. Role of pro-inflammatory interleukins in osteoarthritis: a narrative review. Connect Tissue Res 2022: 1-10.
45. Francisco V, Pino J, Gonzalez-Gay MA, Mera A, Lago F, Gómez R, et al. Adipokines and inflammation: is it a question of weight? Br J Pharmacol 2018; 175: 1569-1579.
46. Xie C, Chen Q. Adipokines: New Therapeutic Target for Osteoarthritis? Curr Rheumatol Rep 2019; 21: 71.
47. Presle N, Pottie P, Dumond H, Guillaume C, Lapicque F, Pallu S, et al. Differential distribution of adipokines between serum and synovial fluid in patients with osteoarthritis. Contribution of joint tissues to their articular production. Osteoarthritis Cartilage 2006; 14: 690-695.
48. Sutton S, Clutterbuck A, Harris P, Gent T, Freeman S, Foster N, et al. The contribution of the synovium, synovial derived inflammatory cytokines and neuropeptides to the pathogenesis of osteoarthritis. Vet J 2009; 179: 10-24.
49. De Falco L, Fioravanti A, Galeazzi M, Tenti S. Bradykinin and its role in osteoarthritis. Reumatismo 2013; 65: 97-104.
50. Vincent TL. Targeting mechanotransduction pathways in osteoarthritis: a focus on the pericellular matrix. Curr Opin Pharmacol 2013; 13: 449-454.

51. Zhang M, Meng N, Wang X, Chen W, Zhang Q. TRPV4 and PIEZO Channels Mediate the Mechanosensing of Chondrocytes to the Biomechanical Microenvironment. Membranes (Basel) 2022; 12.
52. Vincent TL. Mechanoflammation in osteoarthritis pathogenesis. Semin Arthritis Rheum 2019; 49: S36-s38.
53. Berenbaum F. Osteoarthritis as an inflammatory disease (osteoarthritis is not osteoarthrosis!). Osteoarthritis Cartilage 2013; 21: 16-21.
54. Robinson WH, Lepus CM, Wang Q, Raghu H, Mao R, Lindstrom TM, et al. Low-grade inflammation as a key mediator of the pathogenesis of osteoarthritis. Nat Rev Rheumatol 2016; 12: 580-592.
55. Homandberg GA, Meyers R, Xie DL. Fibronectin fragments cause chondrolysis of bovine articular cartilage slices in culture. J Biol Chem 1992; 267: 3597-3604.
56. Midwood K, Sacre S, Piccinini AM, Inglis J, Trebaul A, Chan E, et al. Tenascin-C is an endogenous activator of Toll-like receptor 4 that is essential for maintaining inflammation in arthritic joint disease. Nat Med 2009; 15: 774-780.
57. Melrose J, Fuller ES, Roughley PJ, Smith MM, Kerr B, Hughes CE, et al. Fragmentation of decorin, biglycan, lumican and keratocan is elevated in degenerate human meniscus, knee and hip articular cartilages compared with age-matched macroscopically normal and control tissues. Arthritis Res Ther 2008; 10: R79.
58. Liu-Bryan R, Terkeltaub R. Chondrocyte innate immune myeloid differentiation factor 88-dependent signaling drives procatabolic effects of the endogenous Toll-like receptor 2/Toll-like receptor 4 ligands low molecular weight hyaluronan and high mobility group box chromosomal protein 1 in mice. Arthritis Rheum 2010; 62: 2004-2012.
59. Goldring MB, Otero M. Inflammation in osteoarthritis. Curr Opin Rheumatol 2011; 23: 471-478.
60. Henderson B, Pettipher ER. Arthritogenic actions of recombinant IL-1 and tumour necrosis factor alpha in the rabbit: evidence for synergistic interactions between cytokines in vivo. Clin Exp Immunol 1989; 75: 306-310.
61. Jenei-Lanzl Z, Meurer A, Zaucke F. Interleukin-1β signaling in osteoarthritis - chondrocytes in focus. Cell Signal 2019; 53: 212-223.
62. Choi MC, Jo J, Park J, Kang HK, Park Y. NF-κB Signaling Pathways in Osteoarthritic Cartilage Destruction. Cells 2019; 8.
63. Séguin CA, Bernier SM. TNFalpha suppresses link protein and type II collagen expression in chondrocytes: Role of MEK1/2 and NF-kappaB signaling pathways. J Cell Physiol 2003; 197: 356-369.
64. Wang X, Li F, Fan C, Wang C, Ruan H. Effects and relationship of ERK1 and ERK2 in interleukin-1β-induced alterations in MMP3, MMP13, type II collagen and aggrecan expression in human chondrocytes. Int J Mol Med 2011; 27: 583-589.
65. 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.
66. Wojdasiewicz P, Poniatowski Ł A, Szukiewicz D. The role of inflammatory and anti-inflammatory cytokines in the pathogenesis of osteoarthritis. Mediators Inflamm 2014; 2014: 561459.
67. Porée B, Kypriotou M, Chadjichristos C, Beauchef G, Renard E, Legendre F, et al. Interleukin-6 (IL-6) and/or soluble IL-6 receptor down-regulation of human type II collagen gene expression in articular chondrocytes requires a decrease of Sp1.Sp3 ratio and of the binding activity of both factors to the COL2A1 promoter. J Biol Chem 2008; 283: 4850-4865.

68. van de Loo FA, Kuiper S, van Enckevort FH, Arntz OJ, van den Berg WB. Interleukin-6 reduces cartilage destruction during experimental arthritis. A study in interleukin-6-deficient mice. Am J Pathol 1997; 151: 177-191.
69. Singh T, Newman AB. Inflammatory markers in population studies of aging. Ageing Res Rev 2011; 10: 319-329.
70. Greene MA, Loeser RF. Aging-related inflammation in osteoarthritis. Osteoarthritis Cartilage 2015; 23: 1966-1971.
71. de Hooge AS, van de Loo FA, Bennink MB, Arntz OJ, de Hooge P, van den Berg WB. Male IL-6 gene knock out mice developed more advanced osteoarthritis upon aging. Osteoarthritis Cartilage 2005; 13: 66-73.
72. Scheller J, Chalaris A, Schmidt-Arras D, Rose-John S. The pro- and anti-inflammatory properties of the cytokine interleukin-6. Biochim Biophys Acta 2011; 1813: 878-888.
73. Sanchez C, Deberg MA, Piccardi N, Msika P, Reginster JY, Henrotin YE. Osteoblasts from the sclerotic subchondral bone downregulate aggrecan but upregulate metalloproteinases expression by chondrocytes. This effect is mimicked by interleukin-6, -1beta and oncostatin M pre-treated non-sclerotic osteoblasts. Osteoarthritis Cartilage 2005; 13: 979-987.
74. Ershler WB. Interleukin-6: a cytokine for gerontologists. J Am Geriatr Soc 1993; 41: 176-181.
75. Paolisso G, Rizzo MR, Mazziotti G, Tagliamonte MR, Gambardella A, Rotondi M, et al. Advancing age and insulin resistance: role of plasma tumor necrosis factor-alpha. Am J Physiol 1998; 275: E294-299.
76. Swindell WR, Johnston A, Xing X, Little A, Robichaud P, Voorhees JJ, et al. Robust shifts in S100a9 expression with aging: a novel mechanism for chronic inflammation. Sci Rep 2013; 3: 1215.
77. van Lent PL, Blom AB, Schelbergen RF, Slöetjes A, Lafeber FP, Lems WF, et al. Active involvement of alarmins S100A8 and S100A9 in the regulation of synovial activation and joint destruction during mouse and human osteoarthritis. Arthritis Rheum 2012; 64: 1466-1476.
78. Schelbergen RF, de Munter W, van den Bosch MH, Lafeber FP, Sloetjes A, Vogl T, et al. Alarmins S100A8/S100A9 aggravate osteophyte formation in experimental osteoarthritis and predict osteophyte progression in early human symptomatic osteoarthritis. Ann Rheum Dis 2016; 75: 218-225.
79. Sanchez-Lopez E, Coras R, Torres A, Lane NE, Guma M. Synovial inflammation in osteoarthritis progression. Nat Rev Rheumatol 2022; 18: 258-275.
80. Clavijo-Cornejo D, Martínez-Flores K, Silva-Luna K, Martínez-Nava GA, Fernández-Torres J, Zamudio-Cuevas Y, et al. The Overexpression of NALP3 Inflammasome in Knee Osteoarthritis Is Associated with Synovial Membrane Prolidase and NADPH Oxidase 2. Oxid Med Cell Longev 2016; 2016: 1472567.
81. McAllister MJ, Chemaly M, Eakin AJ, Gibson DS, McGilligan VE. NLRP3 as a potentially novel biomarker for the management of osteoarthritis. Osteoarthritis Cartilage 2018; 26: 612-619.
82. Jeon OH, Kim C, Laberge R-M, Demaria M, Rathod S, Vasserot AP, et al. Local clearance of senescent cells attenuates the development of post-traumatic osteoarthritis and creates a pro-regenerative environment. Nature Medicine 2017; 23: 775-781.
83. Berenbaum F, Wallace IJ, Lieberman DE, Felson DT. Modern-day environmental factors in the pathogenesis of osteoarthritis. Nat Rev Rheumatol 2018; 14: 674-681.
84. Gegout PP, Francin PJ, Mainard D, Presle N. Adipokines in osteoarthritis: friends or foes of cartilage homeostasis? Joint Bone Spine 2008; 75: 669-671.

85. Duan L, Ma Y, Wang Y, Liu J, Tan Z, Wu Q, et al. Infrapatellar fat pads participate in the development of knee osteoarthritis in obese patients via the activation of the NF-κB signaling pathway. Int J Mol Med 2020; 46: 2260-2270.
86. Tu C, He J, Wu B, Wang W, Li Z. An extensive review regarding the adipokines in the pathogenesis and progression of osteoarthritis. Cytokine 2019; 113: 1-12.
87. Van Spil WE, Welsing PM, Kloppenburg M, Bierma-Zeinstra SM, Bijlsma JW, Mastbergen SC, et al. Cross-sectional and predictive associations between plasma adipokines and radiographic signs of early-stage knee osteoarthritis: data from CHECK. Osteoarthritis Cartilage 2012; 20: 1278-1285.
88. 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: R231.
89. Zhang Z, Xing X, Hensley G, Chang LW, Liao W, Abu-Amer Y, et al. Resistin induces expression of proinflammatory cytokines and chemokines in human articular chondrocytes via transcription and messenger RNA stabilization. Arthritis Rheum 2010; 62: 1993-2003.
90. Vuolteenaho K, Koskinen A, Kukkonen M, Nieminen R, Päivärinta U, Moilanen T, et al. Leptin enhances synthesis of proinflammatory mediators in human osteoarthritic cartilage--mediator role of NO in leptin-induced PGE2, IL-6, and IL-8 production. Mediators Inflamm 2009; 2009: 345838.
91. Lago R, Gomez R, Otero M, Lago F, Gallego R, Dieguez C, et al. A new player in cartilage homeostasis: adiponectin induces nitric oxide synthase type II and pro-inflammatory cytokines in chondrocytes. Osteoarthritis Cartilage 2008; 16: 1101-1109.
92. Laiguillon M-C, Houard X, Bougault C, Gosset M, Nourissat G, Sautet A, et al. Expression and function of visfatin (Nampt), an adipokine-enzyme involved in inflammatory pathways of osteoarthritis. Arthritis Research & Therapy 2014; 16: R38.
93. Kanthawang T, Bodden J, Joseph GB, Lane NE, Nevitt M, McCulloch CE, et al. Obese and overweight individuals have greater knee synovial inflammation and associated structural and cartilage compositional degeneration: data from the osteoarthritis initiative. Skeletal Radiol 2021; 50: 217-229.
94. Harasymowicz NS, Clement ND, Azfer A, Burnett R, Salter DM, Simpson A. Regional Differences Between Perisynovial and Infrapatellar Adipose Tissue Depots and Their Response to Class II and Class III Obesity in Patients With Osteoarthritis. Arthritis Rheumatol 2017; 69: 1396-1406.
95. Gudbergsen H, Boesen M, Christensen R, Bartels EM, Henriksen M, Danneskiold-Samsøe B, et al. Changes in bone marrow lesions in response to weight-loss in obese knee osteoarthritis patients: a prospective cohort study. BMC Musculoskelet Disord 2013; 14: 106.
96. Daugaard CL, Henriksen M, Riis RGC, Bandak E, Nybing JD, Hangaard S, et al. The impact of a significant weight loss on inflammation assessed on DCE-MRI and static MRI in knee osteoarthritis: a prospective cohort study. Osteoarthritis Cartilage 2020; 28: 766-773.
97. Jafarzadeh SR, Neogi T, Stefanik JJ, Li JS, Guermazi A, Apovian CM, et al. Mediating Role of Bone Marrow Lesions, Synovitis, Pain Sensitization, and Depressive Symptoms on Knee Pain Improvement Following Substantial Weight Loss. Arthritis Rheumatol 2020; 72: 420-427.
98. Veronese N, Shivappa N, Stubbs B, Smith T, Hébert JR, Cooper C, et al. The relationship between the dietary inflammatory index and prevalence of radiographic

symptomatic osteoarthritis: data from the Osteoarthritis Initiative. Eur J Nutr 2019; 58: 253-260.
99. Xu C, Marchand NE, Driban JB, McAlindon T, Eaton CB, Lu B. Dietary Patterns and Progression of Knee Osteoarthritis: Data from the Osteoarthritis Initiative. Am J Clin Nutr 2020; 111: 667-676.
100. Piva SR, Susko AM, Khoja SS, Josbeno DA, Fitzgerald GK, Toledo FG. Links between osteoarthritis and diabetes: implications for management from a physical activity perspective. Clin Geriatr Med 2015; 31: 67-87, viii.
101. Schett G, Kleyer A, Perricone C, Sahinbegovic E, Iagnocco A, Zwerina J, et al. Diabetes is an independent predictor for severe osteoarthritis: results from a longitudinal cohort study. Diabetes Care 2013; 36: 403-409.
102. Kuusalo L, Felson DT, Wang N, Lewis CE, Torner J, Nevitt MC, et al. Metabolic osteoarthritis - relation of diabetes and cardiovascular disease with knee osteoarthritis. Osteoarthritis Cartilage 2021; 29: 230-234.
103. Rogers-Soeder TS, Lane NE, Walimbe M, Schwartz AV, Tolstykh I, Felson DT, et al. Association of Diabetes Mellitus and Biomarkers of Abnormal Glucose Metabolism With Incident Radiographic Knee Osteoarthritis. Arthritis Care Res (Hoboken) 2020; 72: 98-106.
104. Tsai CH, Chiang YC, Chen HT, Huang PH, Hsu HC, Tang CH. High glucose induces vascular endothelial growth factor production in human synovial fibroblasts through reactive oxygen species generation. Biochim Biophys Acta 2013; 1830: 2649-2658.
105. Cannata F, Vadalà G, Ambrosio L, Napoli N, Papalia R, Denaro V, et al. Osteoarthritis and type 2 diabetes: From pathogenetic factors to therapeutic intervention. Diabetes Metab Res Rev 2020; 36: e3254.
106. Chen YJ, Sheu ML, Tsai KS, Yang RS, Liu SH. Advanced glycation end products induce peroxisome proliferator-activated receptor γ down-regulation-related inflammatory signals in human chondrocytes via Toll-like receptor-4 and receptor for advanced glycation end products. PLoS One 2013; 8: e66611.
107. Trellu S, Courties A, Jaisson S, Gorisse L, Gillery P, Kerdine-Römer S, et al. Impairment of glyoxalase-1, an advanced glycation end-product detoxifying enzyme, induced by inflammation in age-related osteoarthritis. Arthritis Res Ther 2019; 21: 18.
108. Courties A, Sellam J. Osteoarthritis and type 2 diabetes mellitus: What are the links? Diabetes Res Clin Pract 2016; 122: 198-206.
109. Hamada D, Maynard R, Schott E, Drinkwater CJ, Ketz JP, Kates SL, et al. Suppressive Effects of Insulin on Tumor Necrosis Factor-Dependent Early Osteoarthritic Changes Associated With Obesity and Type 2 Diabetes Mellitus. Arthritis Rheumatol 2016; 68: 1392-1402.
110. Rosa SC, Rufino AT, Judas F, Tenreiro C, Lopes MC, Mendes AF. Expression and function of the insulin receptor in normal and osteoarthritic human chondrocytes: modulation of anabolic gene expression, glucose transport and GLUT-1 content by insulin. Osteoarthritis Cartilage 2011; 19: 719-727.
111. Puenpatom RA, Victor TW. Increased prevalence of metabolic syndrome in individuals with osteoarthritis: an analysis of NHANES III data. Postgrad Med 2009; 121: 9-20.
112. Liu SY, Zhu WT, Chen BW, Chen YH, Ni GX. Bidirectional association between metabolic syndrome and osteoarthritis: a meta-analysis of observational studies. Diabetol Metab Syndr 2020; 12: 38.
113. Yoshimura N, Muraki S, Oka H, Tanaka S, Kawaguchi H, Nakamura K, et al. Accumulation of metabolic risk factors such as overweight, hypertension, dyslipidaemia, and impaired glucose tolerance raises the risk of occurrence and

progression of knee osteoarthritis: a 3-year follow-up of the ROAD study. Osteoarthritis Cartilage 2012; 20: 1217-1226.
114. Berenbaum F, Walker C. Osteoarthritis and inflammation: a serious disease with overlapping phenotypic patterns. Postgrad Med 2020; 132: 377-384.
115. Findlay DM. Vascular pathology and osteoarthritis. Rheumatology (Oxford) 2007; 46: 1763-1768.
116. Imhof H, Sulzbacher I, Grampp S, Czerny C, Youssefzadeh S, Kainberger F. Subchondral bone and cartilage disease: a rediscovered functional unit. Invest Radiol 2000; 35: 581-588.
117. Zhang YM, Wang J, Liu XG. Association between hypertension and risk of knee osteoarthritis: A meta-analysis of observational studies. Medicine (Baltimore) 2017; 96: e7584.
118. Chan PB, Wen C. Spontaneous hypertensive rat exhibits bone and meniscus phenotypes of osteoarthritis: is it an appropriate control for MetS-associated OA? Annals of the rheumatic diseases 2018; 77: e25.
119. Baudart P, Louati K, Marcelli C, Berenbaum F, Sellam J. Association between osteoarthritis and dyslipidaemia: a systematic literature review and meta-analysis. RMD Open 2017; 3: e000442.
120. Courties A, Berenbaum F, Sellam J. The Phenotypic Approach to Osteoarthritis: A Look at Metabolic Syndrome-Associated Osteoarthritis. Joint Bone Spine 2019; 86: 725-730.
121. Gao YH, Zhao CW, Liu B, Dong N, Ding L, Li YR, et al. An update on the association between metabolic syndrome and osteoarthritis and on the potential role of leptin in osteoarthritis. Cytokine 2020; 129: 155043.
122. Medina-Luna D, Santamaría-Olmedo MG, Zamudio-Cuevas Y, Martínez-Flores K, Fernández-Torres J, Martínez-Nava GA, et al. Hyperlipidemic microenvironment conditionates damage mechanisms in human chondrocytes by oxidative stress. Lipids in Health and Disease 2017; 16: 114.
123. Liu SH, Waring ME, Eaton CB, Lapane KL. Association of Objectively Measured Physical Activity and Metabolic Syndrome Among US Adults With Osteoarthritis. Arthritis Care Res (Hoboken) 2015; 67: 1371-1378.
124. Iovu M, Dumais G, du Souich P. Anti-inflammatory activity of chondroitin sulfate. Osteoarthritis Cartilage 2008; 16 Suppl 3: S14-18.
125. Jüni P, Hari R, Rutjes AW, Fischer R, Silletta MG, Reichenbach S, et al. Intra-articular corticosteroid for knee osteoarthritis. Cochrane Database Syst Rev 2015; 2015: Cd005328.
126. Oo WM, Yu SP, Daniel MS, Hunter DJ. Disease-modifying drugs in osteoarthritis: current understanding and future therapeutics. Expert Opin Emerg Drugs 2018; 23: 331-347.
127. Chevalier X, Eymard F. Anti-IL-1 for the treatment of OA: dead or alive? Nat Rev Rheumatol 2019; 15: 191-192.
128. Schieker M, Conaghan PG, Mindeholm L, Praestgaard J, Solomon DH, Scotti C, et al. Effects of Interleukin-1β Inhibition on Incident Hip and Knee Replacement : Exploratory Analyses From a Randomized, Double-Blind, Placebo-Controlled Trial. Ann Intern Med 2020; 173: 509-515.
129. Jeon OH, Kim C, Laberge RM, Demaria M, Rathod S, Vasserot AP, et al. Local clearance of senescent cells attenuates the development of post-traumatic osteoarthritis and creates a pro-regenerative environment. Nat Med 2017; 23: 775-781.

130. Chang J, Wang Y, Shao L, Laberge RM, Demaria M, Campisi J, et al. Clearance of senescent cells by ABT263 rejuvenates aged hematopoietic stem cells in mice. Nat Med 2016; 22: 78-83.
131. Yang H, Chen C, Chen H, Duan X, Li J, Zhou Y, et al. Navitoclax (ABT263) reduces inflammation and promotes chondrogenic phenotype by clearing senescent osteoarthritic chondrocytes in osteoarthritis. Aging (Albany NY) 2020; 12: 12750-12770.
132. Senolytic Drugs Attenuate Osteoarthritis-Related Articular Cartilage Degeneration: A Clinical Trial (NCT04210986). ClinicalTrials.gov: Steadman Philippon Research Institute 2022.
133. Tirumalaraju D. Unity's Phase II osteoarthritis study of UBX0101 misses primary goal. clinicaltrialsarena.com2020.
134. Nagai K, Matsushita T, Matsuzaki T, Takayama K, Matsumoto T, Kuroda R, et al. Depletion of SIRT6 causes cellular senescence, DNA damage, and telomere dysfunction in human chondrocytes. Osteoarthritis Cartilage 2015; 23: 1412-1420.
135. Chen J, Chen S, Cai D, Wang Q, Qin J. The role of Sirt6 in osteoarthritis and its effect on macrophage polarization. Bioengineered 2022; 13: 9677-9689.
136. Qi W, Chen Y, Sun S, Xu X, Zhan J, Yan Z, et al. Inhibiting TLR4 signaling by linarin for preventing inflammatory response in osteoarthritis. Aging (Albany NY) 2021; 13: 5369-5382.