Aberrant anabolism hinders constructive metabolism of chondrocytes by pharmacotherapy in osteoarthritis

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Osteoarthritis (OA) is a highly prevalent and disabling disease with an unmet therapeutic need. The characteristic cartilage loss and alteration of other joint structures result from a complex interaction of multiple risk factors, with mechanical overload consistently playing a central role. This overload generates an inflammatory response in the cartilage due to the activation of the innate immune response in chondrocytes, which occurs through various cellular mechanisms. Moreover, risk factors associated with obesity, being overweight, and metabolic syndrome enhance the inflammatory response both locally and systemically. OA chondrocytes, the only cells present in articular cartilage, are therefore inflamed and initiate an anabolic process in an attempt to repair the damaged tissue, which ultimately results in an aberrant and dysfunctional process. Under these circumstances, where the cartilage continues to be subjected to chronic mechanical stress, proposing a treatment that stimulates the chondrocytes' anabolic response to restore tissue structure does not appear to be a therapeutic target with a high likelihood of success. In fact, anabolic drugs proposed for the treatment of OA have yet to demonstrate efficacy. By contrast, multiple therapeutic strategies focused on pharmacologically managing the inflammatory component, both at the joint and systemic levels, have shown promise. Therefore, prioritizing the control of chronic innate pro-inflammatory pathways presents the most viable and promising therapeutic strategy for the effective management of OA. As research continues, this approach may offer the best opportunity to alleviate the burden of this incapacitating disease.

Article focus

- OA is a mechanically induced disease with a sustained chondrocyte inflammatory response.
- Inflammation leads to an aberrant anabolic chondrocyte phenotype in an attempt to repair tissue damage.
- Beyond treatments targeting overload and systemic risk factors, there is potential for pharmacological strategies to address inflammation and enhance anabolism.

Key messages

- Alongside standard therapeutic measures, anti-inflammatory treatment could be prioritized.
- The removal of hypertrophic-like phenomena in inflamed chondrocytes does not modify the course of OA, reflecting the failure of the reparative response in this context.
- Clinical trial results with anabolic agents have not yet demonstrated improved efficacy in OA patients.

Introduction

Osteoarthritis (OA) is the most prevalent chronic musculoskeletal disease in developed countries, and it is one of the leading causes of pain and disability in adults, placing a significant burden on global healthcare systems. With population growth and ageing, it is estimated that this disease will become the leading global cause of disability in a few years, affecting more than one-third of the global population.[1] However, despite enormous financial efforts in clinical research and drug development, treatment options for these patients have barely progressed in decades, failing to incorporate new therapies capable of altering the course of the disease, which often progresses to a loss of function,

eventually making surgical joint arthroplasty necessary.[2]

Classically described as a primary wear-and-tear disease of the articular cartilage, OA is now recognized as a condition with a substantial inflammatory component that affects not only the cartilage but also the synovial membrane, subchondral bone, and other joint structures.[3-5] In the search for new drugs, particularly in the identification of suitable therapeutic targets, it is crucial to analyze the complex pathogenic mechanisms involved in the disease, involving a close interaction between mechanical overload experienced by the joint, the pro-inflammatory response associated, and the pro-anabolic attempt to repair and regenerate tissue. In this work, our intention is not to systematically review the current pharmacological proposals for OA – there are excellent recently published works in this regard.[6,7] In this narrative review, we instead provide an overview on this complex pathophysiology of the disease, with special emphasis on the distinctive response of the cartilage to the different stimuli and how the various targeted therapeutic proposals could modulate this response, as well as that of the other joint tissues. Avoiding targeting inappropriate pathways could save considerable human and economic costs in this area.

Mechanical overload in an inflammatory context

OA is primarily associated with mechanical overload of the joint, which is the only factor consistently present in the onset and development of the disease.[8] Risk factors include malalignment, obesity, or repetitive stress due to certain occupations. These can lead to increased strain on otherwise healthy cartilage, contributing to the development and progression of OA. Alternatively, even a normal load on a joint that has lost its inherent structural properties can lead to injury.[8,9] This last scenario is particularly relevant for the elderly, or for joints with more fragile tissues due to genetic or metabolic factors. In such cases, the load is not excessive by normal standards, but is too much for a compromised structure to handle.[9,10] Thus, it may be considered a relative overload.

As a decisive factor in its pathogenesis, relief of mechanical overload alone leads to a slower progression of the disease. In this regard, joint distraction surgery has demonstrated promising outcomes in patients with knee OA. Jansen et al[11] reported that applying controlled mechanical stress to the affected joint stimulates cartilage regeneration, reduces inflammation, and enhances overall joint function, particularly in young adults with advanced OA. It is worth noting that these patients did not experience a complete cessation of loading, which could be detrimental to the cartilage, as observed in different in vitro and in vivo studies,[10] as they maintained synovial fluid pressure oscillation while walking.

Mechanical overload can induce joint damage through different mechanisms. Damage-associated molecular patterns (DAMPs) that arise from mechanically injured cartilage and other joint tissues, such as small fragments derived from extracellular matrix (ECM) disintegration, or released from apoptotic or damaged cells, are endogenous signals able to activate different Toll-like receptors (TLRs) (Figure 1).[12,13]

In addition, other evidence shows that mechanical overload per se does not solely cause the progressive wear of cartilage, but activates mechanosensors in this tissue specifically designed to respond to variations in load intensity. Various cellular mechanisms capable of translating physical signals into biochemical signals that activate cellular responses are present in cartilage.[14,15] Nociceptive and mechanosensitive mechanisms, particularly integrins, ion channels involved in Ca^{2+} influx such as Piezo1/2 and transient receptor potential channels of the vanilloid (TRPV) subfamily, TRPV1 and TRPV4, are expressed in chondrocytes, where they can transduce hyper-physiological mechanical stress into the activation of oxidative, proinflammatory, and chondrogenic pathways (Figure 1).[14,15] Interestingly, TLR4 activation could directly mediate mechanosensing pathways jointly modulating the activation of proinflammatory mediators, as has been described in innate immune cells.[16]

Therefore, mechanical stress not only directly causes physical deterioration of the ECM and the chondrocytes, but also triggers an inflammatory response through the activation of innate immune mechanisms, eventually leading to the activation of different nuclear factors (NFs), especially NFκB, via mechanisms dependent on the activation of mitogen-activated protein kinases (MAPKs), as depicted in Figure 1.[8,17,18] This ultimately induces the synthesis of pro-inflammatory mediators and catabolic enzymes responsible for cartilage degradation.[17-19] In contrast, and in line with the results from van Helvoort et al,[20] a physiological load induces an anti-inflammatory response in chondrocytes, mediated by the synthesis of cytokines such as IL-10 or IL-4. Collectively, these results indicate that chondrocytes are capable of regenerating cartilage when they are not subjected to intense mechanical loading.

Another aspect to consider is the complex effect of obesity and being overweight on OA outcomes. Substantial weight loss is associated with pain relief and a reduced rate of cartilage deterioration in OA patients,[4,21] while weight gain may exacerbate radiological and symptomatic OA.[22] However, it is essential to recognize that mechanical overload is just one aspect of the relationship between obesity and OA. The role of metabolic health in maintaining overall and joint wellbeing is critical. Poor nutrition, which can lead to immunosuppression, might contribute to conditions like muscle weakness, thereby posing an additional risk factor for OA. Additionally, overnutrition leads to chronic inflammation, which also adversely affects cartilage.[23,24] Different adipokines released by both intra-articular and extra-articular obese fat tissue have a pro-inflammatory effect on joint cells.[25-27] Specifically, leptin, adiponectin, resistin, and visfatin levels are locally dysregulated in OA joints, frequently in correlation with cartilage structural alteration, where these mediators mainly induce pro-inflammatory and pro-catabolic pathways.[28,29] In addition, the increased levels of specific nutrients would be able to structurally weaken the tissue. Different data show that elevated concentrations of specific fatty acids, glucose, and microcrystals – common occurrences in OA joints – are able to stimulate the chondrocyte release of pro-inflammatory enzymes and cytokines, as well as metalloproteases, which ultimately contribute to tissue damage.[26,30-35] Once again, the mechanism associated with the induction of the inflammatory response by these factors is the activation of the innate immune response, primarily through TLR2/4 and NOD-like receptor family pyrin domain containing 3 inflammasome (NLRP3) (Figure 1).[12,36]

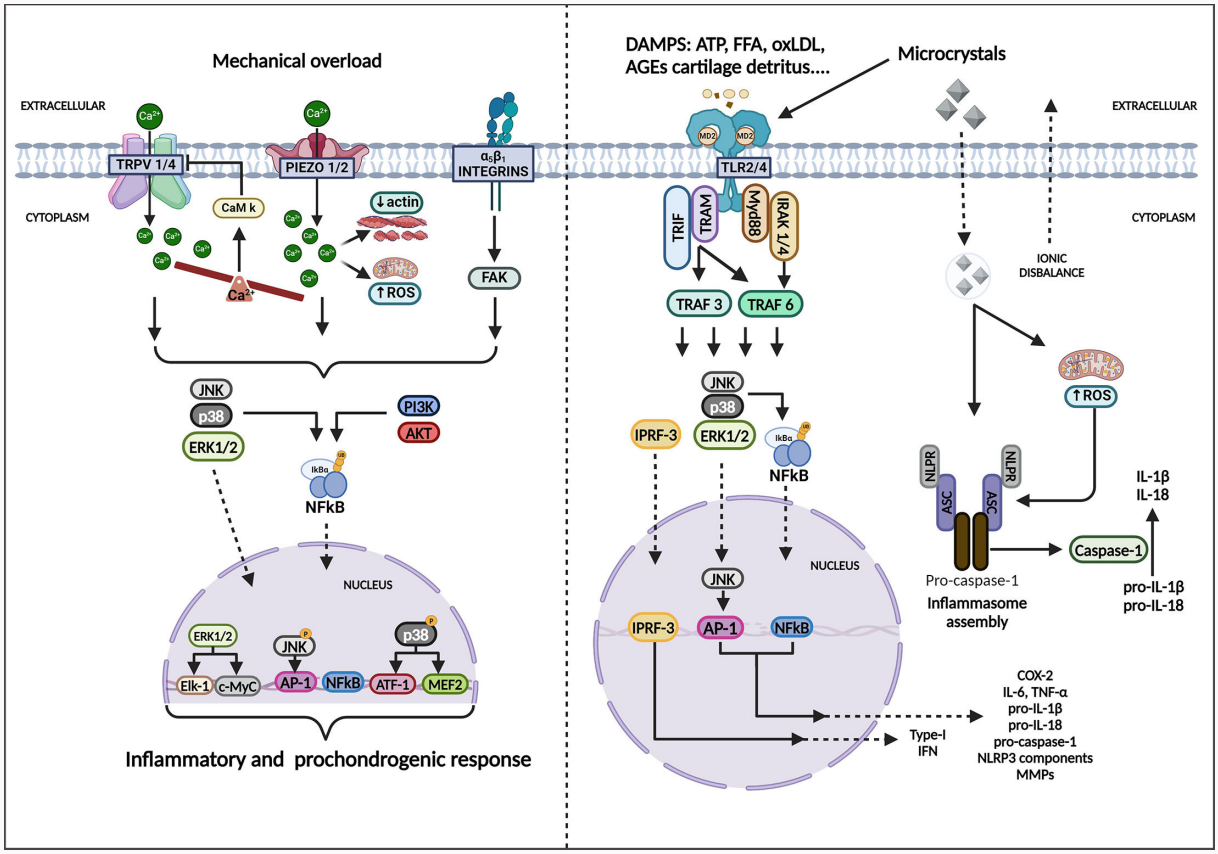

Fig. 1

Cellular mechanisms activating the innate immune response in osteoarthritic chondrocytes. Both direct mechanical overload and the presence of various damage-associated molecular patterns (DAMPs) can activate a pro-inflammatory and prochondrogenic response in osteoarthritic chondrocytes. Physical signals are detected and transduced by different cellular mechanisms, particularly integrins and ion channels involved in Ca^{2+} influx, such as Piezo1/2 and the transient receptor potential vanilloid (TRPV) subfamily. TRPV1/4 and Piezo1/2 channels are opened in response to mechanical overload, leading to a large influx of Ca^{2+} into the cytoplasm. Integrins act as mechanoreceptors through their interaction with the extracellular matrix (ECM), disrupting the cytoskeleton and activating the phosphorylation of focal adhesion kinases (FAKs). Dysregulation of the mitogen-activated protein kinase (MAPK) and phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K/AKT) pathways is ultimately responsible for activating pro-inflammatory and prochondrogenic pathways in osteoarthritis (OA) chondrocytes through the modulation of various nuclear factors. At the same time, direct activation of TLR2/4 receptors, which are overexpressed in OA chondrocytes, along with the assembly of the NOD-like receptor pyrin domain-containing-3 (NLRP3) inflammasome by microcrystals and other DAMPs, also activates pro-inflammatory mediators. All these mechanisms dysregulate MAPK, leading to the activation of nuclear factors such as NFκB, which increases the release of tissue-damaging enzymes and pro-inflammatory cytokines. AGEs, advanced glycation end products; AKT, protein kinase B; AP-1, activator protein-1; ASC, apoptosis-associated Speck-like protein; CaM K, calcium/calmodulin-dependent protein kinase; COX-2, cyclooxygenase-2; ERK, extracellular signal-regulated kinase; FFA, free fatty acid; IL, interleukin; IκBα, inhibitor of kappa B; IRAK, interleukin-1 receptor-associated kinase; JNK, c-Jun N-terminal Kinase; oxLDL, oxidized low-density lipoprotein; ROS, reactive oxygen species; TLR, Toll-like receptors; TRAM, TRIF-related adaptor molecule; TRIF, TIR-domain-containing adapter-inducing interferon-β. Created with BioRender.com.

Therefore, both mechanical overload and additional factors associated with obesity/being overweight are mechanisms that activate the innate immune response in cartilage, where they are capable of inducing pro-inflammatory and pro-catabolic mechanisms.

In general, the activation of the innate immune response is a mechanism designed for the self-defense of the organism against injury to any tissue, and it functions to fully resolve inflammation and facilitate tissue repair.[37] However, when the aggression persists and the mechanisms for the resolution of inflammation prove to be ineffective, inflammation can become chronic, presenting with the classic granulomatous appearance as seen in chronic skin ulcers, due to the development of extensive angiogenesis and cell infiltration. By contrast, cartilage is an avascular tissue, lacking the blood vessels typically involved in the inflammatory response. Pathological or relative chronic overloading can lead to a unique form of destruction specific to this tissue, which in turn hinders the proliferative phase inherent to the inflammatory response.[38] From this perspective, OA can be viewed as a chronic cartilage injury resulting from continuous mechanical stress without the involvement of classical tissue repair mechanisms.[36] However, the joint is composed of more structures that are also affected in OA, such as the synovium and the subchondral bone.[38] Hence, OA is a condition with a mechanical origin that leads to chronic inflammation of both the cartilage and synovium through the activation of the innate immune system.[12]

Aberrant anabolism

Although OA cartilage lacks classic inflammatory features such as neoangiogenesis and immune cell infiltration, it undergoes a chronic inflammatory process mediated by the release of proinflammatory cytokines, prostaglandins, oxidative stress

mediators, and DAMPs (Figure 2). As has been described, these cells exhibit an abnormal anabolic response, reactivating signalling pathways which operate during endochondral ossification in the growth plate during limb development.[39-41] As depicted in Figure 2, the hypertrophic-like phenotype is characterized by an increased gene expression of Runt-related transcription factor 2 (RUNX2), the hedgehog (HH) pathway, type X collagen, active metalloproteinase (MMP)-13, alkaline phosphatase, and others, while the expression of type II collagen or aggrecan decreases.[39-41] This phenotype manifests not only as altered gene expression but also as a hypertrophic morphological phenotype, evidenced by larger chondrocyte size compared to healthy counterparts (Figure 2). Importantly, this increase in cell size positively correlates with cartilage degeneration in both human and animal models of OA.[42] It is also important to note that both hypertrophic and inflammatory markers can be expressed simultaneously in OA chondrocytes.[42] This finding challenges the view that OA chondrocytes differentiate into either inflamed or hypertrophic states, suggesting instead a complex, multifunctional role in OA pathology whereby individual cells concurrently undergo inflammation and become embroiled in an ECM remodelling programme. However, the characteristics of these aberrant anabolic responses and those of hypertrophic-like chondrocytes are not yet fully understood. Recently, an experimental model of OA in genetically modified animals in which chondrocyte hypertrophy was knocked out in skeletally mature mice was employed to delve deeper into this issue. In this model, chondrocyte hypertrophy was specifically inhibited in skeletally mature mice. In these animals, induction of OA by joint instability did not activate the HH pathway in the articular cartilage.[39] In comparison with OA animals that were not genetically manipulated, no increase in the presence of RUNX-2 or collagen X was observed in the cartilage of the genetically modified OA mice. As hypertrophy was genetically inhibited, OA did not lead to an increase in chondrocyte size in these animals, in contrast to the non-modified animals, where chondrocyte enlargement was evident. Furthermore, hypertrophy blockade significantly reduced the levels of matrix metalloproteinase (MMP)-13 and MMP-3 compared to wild-type OA mice. However, the genetic manipulation which impeded the hypertrophic-like phenotype was not able to modify the cartilage damage observed in the OA animals.[39]

These data suggest that activation of the hypertrophic pathway in chondrocytes is not a primary pathogenic event, but rather a phenomenon that occurs as a result of the set of stimuli perceived by chondrocytes. These stimuli lead them to remodel the ECM, shifting towards a hypertrophic phenotype, characterized by decreased type II collagen and proteoglycans, increased type X collagen, and elevated levels of matrix-degrading enzymes. It becomes evident that the hypertrophic anabolic response fails in its reparative attempt in the context of OA. In line with this idea, it is therefore understandable that blocking the hypertrophic process in the mouse experimental OA model, as mentioned above, led to the persistence of the cartilage damage and the progression of its deterioration. The pathological attempt at chondrocyte repair, instead of restoring the cartilage, may contribute to the disease progression due to an inadequate and maladaptive response of the hypertrophic chondrocytes. Considering the aberrant anabolic transformation of chondrocytes, would it be reasonable to propose a pro-anabolic treatment in OA with the aim of restoring cartilage tissue while pathological overload continues to damage the tissue?

Targeting anabolic pathways in inflamed chondrocytes

With the rationale of enhancing the chondrogenic potential of cartilage and increasing ECM synthesis, various treatments have been proposed as potential disease-modifying OA drugs (DMOADs). Fibroblast growth factor (FGF)-18 is an essential regulator of chondrogenesis, and stimulates articular cartilage chondrocyte proliferation and the synthesis of ECM in cells in culture and cartilage explants.[43-45] Pre-clinical data have indicated that intra-articular administration of FGF-18 shows therapeutic efficacy in mouse models of spontaneous and surgically induced OA.[46] However, the administration of sprifermin, a truncated product of recombinant human FGF-18 with greater affinity to the FGF-18 receptor FGFR3, to knee OA patients with Kellgren-Lawrence grade 2/3, did not demonstrate any clinically significant effect on medial tibiofemoral cartilage thickness after a two-year evaluation using quantitative MRI. More recent post-hoc analyses conducted at longer timepoints have also failed to yield clinically relevant results.[47]

Transforming growth factor (TGF)-β has also been investigated as a DMOAD. TGF-β generally regulates ECM synthesis, but its effects can vary between different joint tissues, yielding contradictory results.[48] Dysregulation of TGF-β signalling occurs in ageing and OA chondrocytes, characterized by increased pro-catabolic signalling and a decrease in pro-anabolic effects.[49] However, it appears to contribute to osteophyte formation and synovial fibrosis in OA joints.[50]

In different clinical trials, intra-articular administration of allogenic chondrocytes, along with chondrocytes engineered to overexpress TGF-β, has been tested specifically in the hope of improving cartilage structure.[51] Although no safety issues were reported, and some studies indicated a possible improvement in OA symptoms, results from phase 2 and phase 3 clinical trials in recent years have not proven to be compelling enough for approval by regulatory agencies.[52] New phase 3 trials to determine effectiveness and efficacy are currently on hold.

In an attempt to target the increased Wnt pathway activity observed in chondrocytes, synovium, and subchondral bone, the administration of Wnt signalling inhibitors has been proposed as a form of OA treatment.[53,54] The inhibition of intranuclear kinases CLK2 and DYRK1A has shown promise in enhancing chondrogenesis and inhibiting joint destruction in preclinical OA models treated with Lorecivivint.[55] However, different phase 2 clinical trials analyzing the effect of intra-articular Lorecivivint administration during 24- and 52-week periods did not demonstrate significant effects on joint space width in comparison to placebo.[56-58] Long-term studies are currently being conducted.

In 2022, it was reported that the C-terminal portion of angiopoietin-like 3 had pro-chondrogenic effects. This derivative acted as a potent inducer of chondrogenesis in human mesenchymal stem cells. Moreover, it was shown to enhance cartilage matrix synthesis and regenerate cartilage in preclinical models of OA.[59] However, the cellular mechanisms by which these effects occur are yet to be clarified.[60] Phase 1 studies with this peptide do not show evidence of its efficacy in patients, although the treatment does appear

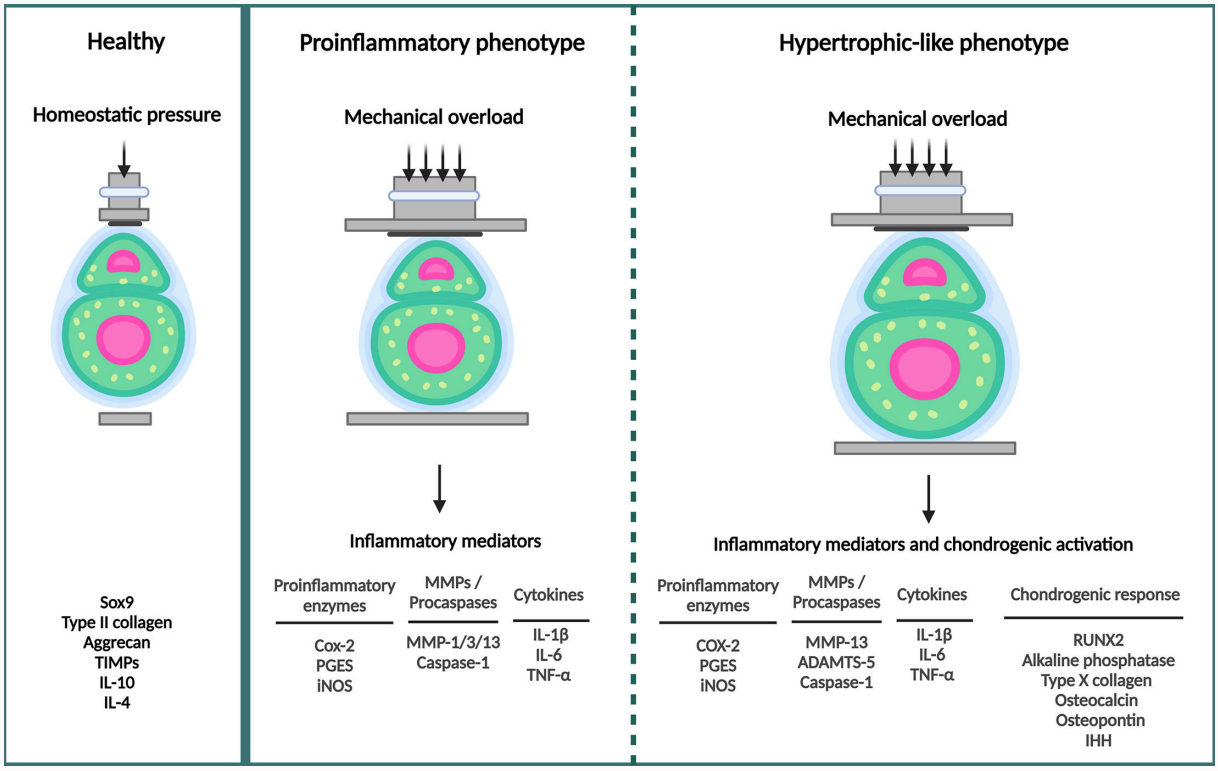

Fig. 2
Chronic mechanical overload induces chondrocyte phenotype transformation. Physiological load induces an anti-inflammatory response in chondrocytes, mediated by the synthesis of cytokines such as interleukin (IL)-10 or IL-4. In contrast, mechanical overload triggers an inflammatory response through the activation of innate immune mechanisms, which induces the synthesis and release of pro-inflammatory and catabolic mediators including procaspases, metalloproteases, and chondrogenic mediators. The persistence of the innate immune response activation generates a pro-anabolic response characterized by the recapitulation of expression patterns of hypertrophic chondrocytes in the growth plate, which fails to repair the tissue and results in a dysfunctional cartilage. ADAMTS-5, a disintegrin and metalloproteinase with thrombospondin motifs 5; COX-2, cyclooxygenase-2; IHH, Indian hedgehog; IL, interleukin; MMP, matrix metalloproteinases; TNF, tumour necrosis factor; TIMP, tissue inhibitor of metalloproteinase. Created with BioRender.com.

to have partially reverted the OA transcriptome signature in human cartilage.[59] This drug is currently in a phase 2b trial in patients with knee OA (NCT04864392).

Multiple clinical trials have been initiated in the last decade using mesenchymal stromal cells (MSCs) from different sources for the treatment of OA, as these cells have the potential to differentiate into chondrocytes capable of forming a cartilaginous matrix. However, the source, preparation for administration, route of administration, and placement within the joint lack standardization. Moreover, only a limited percentage of studies are placebo-controlled.[61] In any case, there is currently no evidence of DMOAD activity for these treatments.[62]

Anti-inflammatory pharmacology approach

As a result, anabolic drugs do not appear to be a promising strategy for treating OA. Instead, our approach should remain focused on the established strategy of eliminating risk factors that slowly erode cartilage integrity, rather than seeking a single definitive drug solution. From a pharmacological perspective, the objective could involve exploring drugs that moderately reduce the inflammatory response triggered by the activation of innate immunity.[12,25,63] In OA joints, various tissues are inflamed, including not only cartilage but also the synovium, both activated by the same inducers.[12,64] These factors stimulate the innate immune response mainly through TLR activation. These receptors are present in chondrocytes, synovial fibroblasts, and, critically, in macrophages.[13,65] TLR2 and TLR4 can be activated by mechanical overload, but also by different mediators released during ECM destruction, such as biglycan, fibronectin, low molecular weight hyaluronan, or cell damage such as alarmins HMGB1 and S100 family.[5,13,66-68] An inflammatory response is evident in synovial tissue, although it differs from more aggressive synovitis conditions such as rheumatoid arthritis (RA).[69] It features a discreet proliferation of lining cells, a significant increase in angiogenesis with distinct thicker-walled concentric vessels, and, notably, frequent perivascular oedema.[70] This oedema has been recently attributed to direct mechanical overloading effects, as it is observed in individuals with gait alterations in the early stages of the disease.[70] Macrophage infiltration is also characteristic, although overall cellular infiltration is not as extensive as in RA. Additionally, the contribution of a low-grade, chronic systemic inflammation to joint damage has been recognized, mainly associated with metabolic alterations such as obesity or type 2 diabetes.[71]

With the pharmacological goal of controlling the inflammatory component at both the joint and systemic levels, several therapeutic approaches have been explored.[2,72] The use of non-steroidal anti-inflammatory drugs (NSAIDs), inhibitors of cyclooxygenase (COX)1/2, are in fact the most commonly employed pharmacological therapy in the

treatment of OA, with a proven analgesic effect in multiple studies.[73,74] Moreover, some of these drugs have been shown to modulate the synthesis of certain pro-inflammatory mediators in the cartilage and synovial membrane of OA patients.[75-77] However, their effect on cartilage structure has been highly debated, not only in OA patients but also in different chronic inflammatory joint diseases.[78] Additionally, their side effects are recognized as a considerable limitation to their use, especially with continuous administration.[73,74]

Pro-inflammatory cytokine antagonists have been tested for the treatment of OA. However, various clinical trials failed to demonstrate protective effects on the OA joint in patients treated with IL-1 blockers or TNF antagonists over a duration of six to 12 months.[79–81] Nevertheless, a multitude of new clinical trials utilizing these drugs in different formulations for OA treatment are now underway.[72] The rationale for these trials is rooted in the outcomes of the CANTOS trial, where the administration of canakinumab, an IL-1β antagonist, to patients with a history of cardiovascular disease was shown to reduce the recurrence of new cardiovascular events.[82] In an exploratory analysis of these patients, it was revealed that canakinumab also reduced the need for hip/knee arthroplasties in OA patients.[83] However, while the CANTOS trial had a large sample size and long-term follow-up, it was not primarily designed to investigate the efficacy of canakinumab in OA, and many relevant outcomes were not initially assessed, necessitating further confirmatory studies.

It is interesting to note that intracellular pro-inflammatory pathways are redundant in OA chondrocytes. For example, the induction of the TNF pathway shares the activation of the TRAF6 factor with the TLR2/4 pathway.[12] Similarly, the activation of the IL-1β pathway increases the middosome complex formation, as in the TLR pathway.[84] This is probably why treatments that only block one of these mediators, such as anti-TNF or IL-1 blockers, have not been successful for OA treatment.[13] It is possible that the use of inhibitors of master-regulators of inflammation, such as regulators of MAPK phosphorylation or nuclear factor activity, could have a greater disease-modifying capacity.

Several hydrophobic small molecules, including quercetin, 6-gingerol, curcumin, resveratrol, berberine, and others, exhibit a TLR4 inhibitory profile, making them promising candidates for OA treatment.[85–87] Along these lines, we have tested the effect of 6-shogaol, a ginger derivative that was shown to block the activation of the innate immune response in chondrocytes.[88] Docking studies confirmed that this small molecule can specifically bind to TLR4 structure.[89] Natural ligands such as LPS bind inside the hydrophobic pocket of MD-2, the co-receptor, allowing the conformational change that transmits the signal.[90] Specifically, phenylalanine 126 moves towards the inner region of MD2, adopting what is known as agonist conformation, which favours signal transmission. 6-shogaol can bind to the hydrophobic pocket in MD-2 with predicted favourable binding energies. A dynamic study has corroborated that 6-shogaol binding retains the phenylalanine residue outside the structure, in an antagonist conformation. Therefore, 6-shogaol serves as an effective ligand for the TLR4/MD-2 complex, mimicking the action of certain small molecules known to inhibit or block TLR4 activity.[89] Furthermore, when administered orally, 6-shogaol has been shown to ameliorate knee OA in a mouse model of the disease, decreasing COX-2 and MMP13 expression in different joint tissues.[89]

The activation of the innate immune response in chondrocytes also alters the regulation of the phosphoinositide 3-kinase/protein kinase B (PI3K/AKT) pathway and increases oxidative stress in these cells.[91,92] In fact, the PI3K/AKT pathway is significantly inactivated in articular cartilage of OA patients compared to healthy individuals.[92] The decrease in autophagy in OA chondrocytes results from the dysregulation of various downstream mediators of this pathway, particularly hypoxia-inducible factor (HIF)-1α. In this context, various molecules have been proposed as potential treatments for OA in the hope of activating the PI3K/AKT pathway, restoring chondrocyte autophagy, increasing HIF-1α levels, and inhibiting the senescent phenotype in these cells.[93] Among them, studies involving metformin are noteworthy, as it has been shown to activate AMP-activated protein kinase (AMPK) and exert a chondroprotective effect by decelerating OA development and progression in mouse OA models.[94] Recent studies have suggested that metformin use may have a beneficial effect in obese or type 2 diabetic OA patients.[95,96] For this reason, several clinical studies are underway to establish whether metformin possesses DMOAD properties in these patients.[6]

Conclusion

In summary, the OA joint essentially functions as an inflamed organ wherein cartilage and synovium are highly sensitive not only to mechanical overload, but also to alterations in nutrient concentration and the presence of tissue debris resulting from joint degradation. These factors collectively trigger the activation of the innate immune response within these tissues. This immune response, regulated by MAP kinases, eventually activates nuclear factors, primarily NFκB, leading to the release of pro-inflammatory factors and catabolic enzymes. This response is further amplified by the released cytokines, creating a feedback loop that perpetuates inflammation and generates an aberrant pro-chondrogenic response in the cartilage, which fails to repair the damaged tissue. Treatment with agents aimed at stimulating the anabolic process in this context of dysfunctional anabolism does not seem likely to succeed. It is likely that early mitigation of the inflammatory burden could prevent the feedback loop and reduce the detrimental catabolic effects on the tissue. Therefore, the primary objective in OA treatment is to block pro-inflammatory and catabolic pathways. Targeting the chronic innate pro-inflammatory pathways represents the most promising approach for managing OA.

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