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Emerging Targets in Osteoarthritis Therapy

Mary B. Goldring, PhD[1] and **Francis Berenbaum**[2]

[1]Tissue Engineering, Regeneration and Repair Program, Hospital for Special Surgery; and Department of Cell and Developmental Biology, Weill Cornell Medical College, New York, New York, USA

[2]Department of Rheumatology, AP-HP Saint-Antoine Hospital, 75012 Paris, France

Abstract

Osteoarthritis (OA) is a destructive joint disease in which the initiation may be attributed to direct injury and mechanical disruption of joint tissues, but the progressive changes are dependent on active cell-mediated processes that can be observed or inferred during the generally long time-course of the disease. Based on clinical observations and experimental studies, it is now recognized a that it is possible for individual patients to exhibit common sets of symptoms and structural abnormalities due to distinct pathophysiological pathways that act independently or in combination. Recent research that has focused on the underlying mechanisms involving biochemical cross talk among the cartilage, synovium, bone, and other joint tissues within a background of poorly characterized genetic factors will be addressed in this review.

Introduction

Osteoarthritis (OA) is the most common joint disorder and is a leading cause of disability in the adult population. The disease manifestations in the joint are well characterized, including progressive loss of articular cartilage, cartilage calcification, osteophyte formation, subchondral bone remodeling, and mild to moderate inflammation of the synovial lining. Many therapeutic clinical trials have been conducted with designs based on subject selection related to the joint location or on whether the disease is primary or secondary to other types of arthritis [1–3]. Most trials, including those addressing targeted therapies, have evaluated patient-reported outcomes of function and pain at later stages of disease when there is radiographic evidence of damage, i.e., joint space narrowing and osteophytes. However,

Address correspondence to: Mary B. Goldring, PhD, Research Division, Hospital for Special Surgery, Caspary Research Building, 5th Floor, 535 East 70th Street, New York, NY 10021, Tel: 212-774-7564, Fax: 212-249-2373, goldringm@hss.edu.

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symptoms and disease progression do not necessarily correspond in an individual patient and there is significant patient-to-patient variability in the time course of progression. Furthermore, the disease multifactorial process is impacted by aging, genetic predisposition, abnormal biomechanics, obesity, and trauma and influenced by co-morbidities such as cardiovascular disease, metabolic syndrome, and diabetes. Recognition that it may be possible to classify OA patients according to these diverse etiologies could optimize patient cohort selection for trial design [4–7].

To date, no efficacious structure-modifying agent has been approved by any regulatory agency and available pain therapies are limited in efficacy and have associated toxicities [8]. Although there are promising candidates, there is a paucity of validated diagnostic and prognostic molecular biomarkers that could be used to evaluate efficacy in pre-symptomatic early-stage disease prior to irreversible joint damage [9–12]. Imaging biomarkers are also under intensive study [13]. Given the complexity of OA, a single therapy is not likely to be effective and therefore promising strategies should focus on how to address both symptoms and structural changes [14–17]. This review will focus on emerging strategies based on novel research findings that are undergoing validation and translation in pre-clinical models and have promise for development in proof-of-concept early phase trials and for informing the design of future definitive clinical trials.

Existing therapies and current research goals

Current guidelines consist of OA therapy in the following defined order: (1) behavioral interventions, (2) simple analgesic such as acetaminophen (paracetamol), (3) nonsteroidal anti-inflammatory drugs, including COX-2 inhibitors [18], (4) intraarticular injection of hyaluronic acid or corticosteroid, and finally (5) total joint replacement. Anti-pain drugs include opioids and centrally acting drugs such as duloxetine, which have adverse side effects. Since these current treatment options are lack efficacy for the majority of patients, there is a great, unmet medical need that has been exacerbated by the recent closure of research programs by pharmaceutical companies wary of investing in identifying complex OA treatments and proving their efficacy in clinical trials [8].

Despite the identification of pro-inflammatory cytokines such as interleukin (IL) 1, which is used in vitro to mimic the catabolic responses that occur in OA, as potential targets in pre-clinical animal models, anti-cytokine therapies that have been successful in other inflammatory and autoimmune diseases affecting joints have not proven to be effective against OA in clinical studies [19,20]. Preclinical studies indicate that MMP-13 is a critical target for blocking cartilage erosion in OA [21] and that a number of other molecular targets should be amenable to therapy [22–24]. However, therapies that directly inhibit catabolic enzymes or signaling pathways, have inadequate efficacy or unacceptable side effects, even with increased specificity. Thus, many clinical programs addressing such products as OA therapies have been discontinued. This has fostered renewed efforts in the academic community to find novel strategies.

Emerging strategies for structure modification

Current research goals are directed toward understanding the different etiologies in terms of the common and distinct molecular mechanisms that would be amenable for targeted therapies. One classification scheme proposes a continuum of potential phenotypes [4] involving post-traumatic, metabolic, and aging-related (including post-menopausal), changes that are most prominent at young, middle, and advanced ages, respectively, as well as a genetic phenotype, in which different mutations produce susceptibility across an age-associated continuum [25]. Any of these OA phenotypes may be associated with abnormal biomechanics and malalignment as part of a whole-joint organ failure that frequently involves episodes of inflammation [26].

Laboratory studies using cell-based assays, animal models, and human OA joint tissues have identified a number of molecular pathways that are induced by mechanical, inflammatory, and oxidative stresses in the resident cells. In the cartilage, these stresses result in the release of the chondrocytes from growth arrest, loss of homeostasis, and activation of aberrant cellular signal transduction and gene expression [27]. Among the early events is the disruption of the pericellular matrix, associated with abnormal activation of cell surface receptors [28,29]. The subsequent loss of surface lubrication is associated with proteoglycan loss and collagen erosion, while increased cartilage calcification and tidemark advancement or duplication are associated with vascular penetration from the subchondral bone. Since the damaged collagen network cannot be repaired to its original state, the challenge is to develop therapies that either prevent the destruction in the first place or promote repair to replicate the physiological and functional properties of the original cartilage.

Targeted therapies, however, have been elusive, since manipulation of any of the genes encoding potential targets by knockout or transgenic overexpression in mice can individually have profound effects on OA development [30,31]. For example, mice deficient in the critical aggrecan- and collagen-degrading genes, *Adamts5* and *Mmp13*, are protected against cartilage damage and other aspects of OA development. The mouse studies do not necessarily correspond with genome wide association studies (GWAS), which have identified genes that harbor OA susceptibility alleles, including *GDF5*, *SMAD3*, *DIO2*, *DIO3*, *RUNX2*, *PTHLH*, *CHST11*, *TP68*, *DOT1L*, *COL11A1*, *VEGF*, and *IGFBP3* [32–35]. Many of these, including GDF5, whose 143383 C to T SNP has been validated thus far as the strongest OA-related variant and which is regulated by DNA methylation [36,37], are skeletal developmental genes that could be associated with cartilage calcification, osteophyte formation, and subchondral bone changes in OA[38]. On the other hand, proteomic profiling of OA synovial fluid indicates that a major proportion of the knee OA proteome contains acute phase response, coagulation, and complement proteins generated from the synovium [39]. Gene profiling data will likely enable sub-setting of different OA populations into cohorts, but whether a single, one-drug-fits-all strategy will result is highly unlikely. Furthermore, profiling single patients to guide individualized OA therapy is a long-term future goal [12].

Inflammatory, mechanical, and oxidative stress

Inflammation can be observed at the macroscopic level as synovitis and synovial effusion during operative procedures such as arthroscopy or by MRI and is associated with more rapid progression to OA [40–43]. Recent studies, however, highlight a role for chronic low-grade inflammation, termed “microinflammation”, which is often associated with aging and can disrupt homeostasis in joint tissues and drive the degradative responses [44–47]. This is an important consideration in OA joints, since mechanical stress may induce similar signaling responses in the absence of overt inflammation.

Oxidative stress, resulting from increased levels of reactive oxygen species (ROS) relative to antioxidants, may act together with inflammatory and/or mechanical stress to accentuate catabolic processes, depending upon the availability of signals and the state of the tissue damage. Mechanical injury, inflammatory cytokines, and matrix fragments, such as fibronectin fragments via integrins can induce ROS, and the age-related decline in the responses of chondrocytes to anabolic growth factors may be attributable to altered cell signaling mediated by increased oxidative stress [48,49]. NF-κB signaling is an integrating mechanism underlying most responses to inflammatory, mechanical, and oxidative stresses [27,50–52]. Components of NF-κB signaling are found prominently among the different gene signatures in experimental OA models [53].

Genomic and proteomic analyses of synovial fluids and joint tissues collected at the time of arthroscopic or joint replacement surgery have indicated that there is a spectrum of cellular and molecular phenotypes from early through late-stage OA disease [39,54–56]. In patients with traumatic ACL or meniscal injury, but no radiographic evidence of OA, the synovium retrieved during arthroscopy is frequently inflamed and the inflammation scores are associated with increased pain and dysfunction, as well as unique cytokine and chemokine gene expression profiles [55] High expression of genes encoding cytokines, chemokines, proteinases, and NF-κB signaling molecules may also be observed in meniscus samples from patients with both meniscal and ACL tears[57]. Gene signatures associated with the immune response, inflammation, cell cycle, and cellular proliferation are increased with aging in the damaged meniscus, whereas genes associated with cartilage and skeletal development and extracellular matrix synthesis are repressed [58].

Cartilage is an avascular tissue, and as the normal environment for chondrocytes, hypoxia is important for the maintenance of homeostasis via hypoxia inducible factor (HIF)-1α. During oxidative stress, NF-κB signaling is required for the induction of HIF-2α, which regulates both endochondral ossification and OA-related cartilage destruction, in part, by directly targeting HREs within the MMP13 COL10A1, and VEGFA promoters [52,59] and by inducing proteinases and inflammatory genes in chondrocytes [60]. The down-regulation of HIF-1α and 2α target genes and up-regulation of HIF-3α appear to be part of the mechanism by which overexpression of PRG4, the gene encoding lubricin, prevents the induction of catabolic and hypertrophy-related responses and protects against aging-related or post-traumatic OA development in mice [••61]. Another novel pathway is the Zinc-ZIP8-MTF1 axis [••62]. ZIP8, a Zn2+ transporter, which is highly upregulated by IL-1β, induces MMP3,

9, 12, and 13 and ADAMTS5 gene expression via MTF1 (metal regulatory transcription factor-1), which is induced by hypoxia and oxidative stress [62].

The requirement of canonical NF-κB signaling for the induction of HIF2α [59] and other inflammation-inducible transcription factors such as Elf3[63] and the cooperation HIF2α with C/EBPβ and Runx2[64] suggest the importance of an integrated network converging on transcriptional regulation of MMP13 and other catabolic and inflammatory genes. In contrast, the non-canonical NF-κB signaling kinase, IKKα/CHUK, promotes the aberrant expression of genes involved in endochondral ossification, including Runx2, COL10A1, and VEGF, but not MMP13. The increased MMP-13 activity and collagen remodeling can be attributed to the increased gene expression of MMP-10, an activator of MMPs [••65].

Adaptive and innate immunity

Evidence for a role of adaptive immunity in OA is restricted to the initial interactions of T cells that can be activated in response to the damage associated molecular patterns (DAMPs), also known as alarmins, which can be released from degraded cartilage and other tissues [66] However, during the chronic phase, the innate immune system plays an important role in the initiation and perpetuation of the low-grade inflammation in OA [40,41,67–69] through cellular activation by DAMPs, including high mobility group box-1 (HMGB1), S100A8 (MRP8, calgranulin A) and S100A9 (MRP14, calgranulin B), serum amyloid A (SAA), collagen and proteoglycan constituents, and calcium pyrophosphate or hydroxyapatite crystals. These extracellular ligands interact with pattern recognition receptors (PRRs) such as toll-like receptors (TLR)-2 and -4 and the receptor for advanced glycation end-products (RAGE) to induce cellular inflammatory responses via NF-κB to drive synovitis and cartilage destruction [45,70]. DAMPs serve homeostatic functions eliciting sterile wound healing and tissue repair, but in OA it is not clearly defined where, when, and how the ligands are generated and whether these are initiating or amplifying events. Nevertheless, TLR4, which has been well studied in the context of LPS activation and for which many inhibitory compounds exist, has been proposed as a direct and specific target for candidate OA disease-modifying agents [71]. However, deficiency of TLR-1, 2, 4, or 6 or their shared signaling molecule MyD88 has no effect on OA development in mice with partial meniscectomy[72].

Complement proteins are additional candidates detected in synovial fluids of OA patients by proteomic analysis [39,54,73,74]. DAMPs, including COMP, fibromodulin, the collagen XI NC4 domain, and the C-type lectin of the aggrecan G3 domain, can activate complement pathways [75,76]. The classical, mannose-binding lectin, and alternative complement pathways all converge on C3 to activate the membrane attack complex (MAC) formed from the complement effector C5b-C9. Knockout of the C5 and C6 components or pharmacological treatment with CR2-fH attenuates joint damage in the medial meniscectomy mouse model, whereas knocking out the naturally occurring complement inhibitor CD49 or deficiency of carboxypeptidase increases degenerative changes [77,78].

Autophagy, cell survival, and bioenergetics

Chondrocytes are post-mitotic cartilage cells, and due to their virtually absent proliferative activity in adult articular cartilage, they use autophagy as a very efficient housekeeping program to maintain cellular function and homeostasis by removing damaged or malfunctioning cellular structures, eliminating exogenous cellular aggressors, and providing alternative sources of energy during ER stress, hypoxia, starvation, and other adverse events [79,80]. Three autophagy-related pathways have been described in mammalian cells based on cellular localization and markers, including Atg5, and Atg7 for microautophagy (MA), Hsc-70 and LAMP-2A for chaperone-mediated autophagy (CMA, and Hsc-70, Vps4 and Tsg101 for endosomal microautophagy (eCI) [79]. In all cases, LC3 is recruited to the nascent autophagosome and cleaved upon fusion between the autophagosome and the lysosome or endosome; its cleavage, termed LC3 flux, is used to assess the efficiency of fusion [81].

The loss of autophagy in articular cartilage under mechanical or inflammatory stress is linked to aging-related cell death and increasing OA severity [82,83]. LC3 and Beclin1 are upregulated in chondrocytes in OA cartilage and in response to inflammatory and nutritional stress in a manner dependent upon ATG5 [84]. Rapamycin, an inhibitor of mTOR that can increase the lifespan of middle-aged mice, reduces the severity of experimental murine osteoarthritis by inhibiting ribosomal protein S6 phosphorylation, a target of mTOR signaling. Rapamycin-induced activation of LC3 increases ULK1, beclin 1, and LC3, promotes chondrocyte survival, decreases synovitis and ADAMTS5 and IL-1β, and prevents glycosaminoglycan loss [85,86]. PPARγ, which has roles in obesity and inflammation, also maintains homeostasis, in part by regulating mTOR [87]

Compared to autophagy, which is lysosome- or endosome-mediated, the unfolded protein response (UPR) is a non-lysosomal pathway for ubiquitin/proteasome degradation of unfolded proteins eliminated from the endoplasmic reticulum (ER) [••47]. The UPR is important for the normal differentiation program in chondrocytes proceeding to hypertrophy and apoptosis during growth plate development. [88–90]. Inflammatory, mechanical, and oxidative stress can induce ER stress and the UPR in cartilage via C/EBP homologous protein (CHOP) and X-box protein 1 (XBP1) [••47], both of which potentiate IL-1β-induced oxidative stress and pro-catabolic responses [91]; however, XBP1 can promote chondrocyte survival under certain conditions [92].

Also related to autophagy are the classic cell survival signals, phosphatidylinositol-3 kinase (PI3K) and its downstream target serine-threonine kinase (AKT) [93–95]. A key negative regulator of the PI3K/AKT pathway is the tumor suppressor gene, phosphatase and tensin homolog deleted on chromosome ten (PTEN), which is elevated PTEN in OA chondrocytes [96].

How autophagy and ER stress could be targeted for alleviating cartilage damage or pain in OA is not clear. Global *Chop* knockout partially protects against chondrocyte apoptosis and cartilage degradation in a mouse OA model, but without detectable modification of ER stress [97]. Cartilage-specific knockout of mTOR also protects mice from OA by

upregulating autophagy [98]. However, since rapamycin, an mTOR inhibitor, has immunosuppressive side effects, nutrient supplementation with spermidine, polyamines, or ω-6 polyunsaturated fatty acids, which increase lifespan in lower organisms or treatments with activators of the ubiquitin-proteosome system could be considered, although more work would be required to prove safety, specificity, and efficacy [80]. Glucosamine can also activate autophagy in vitro and in vivo via a mechanism dependent on the Akt//Fox03/mTOR pathway [99].

Articular chondrocytes rely on long diffusion pathways to obtain oxygen and derive ATP for their bioenergy needs from high basal glycolysis. Mitochondrial oxidative phosphorylation (OXPHOS) accounts for up to one-fourth of the total steady-state ATP production within articular cartilage. The impairment of chondrocyte mitochondrial function has emerged as a mechanism involved in impaired autophagy and deregulated bioenergetics in OA [100]. The oxidative stress damages the mitochondrial respiratory chain protein complexes resulting in decreased chondrocyte mitochondrial ATP generation, loss of the chondrocyte energy reserve, impaired matrix synthetic function, and decreased chondrocyte viability [100]. Certain mitochondrial haplotypes predispose to OA [101] and depletion of the antioxidant SOD2 promotes mitochondrial dysfunction and increases ROS in chondrocytes [102]. Furthermore, mitochondrial dysfunction can amplify the stress responses through increased nitric oxide generation, ROS production and NF-κB activation [102–104].

The serine/threonine kinase, AMPK, and the nicotinamide adenine dinucleotide (NAD+)-dependent protein deacetylase, SIRT1, act together to balance energy metabolism and coordinate several housekeeping activities, including autophagy, in the resistance to cell stress and inflammation by normalizing mitochondrial function [105]. Upon its activation by AMPK through increased intracellular NAD+, SIRT1 deacetylates liver protein kinase B1 (LKB1, which in turn activates AMPK in a positive feedback loop [106]. They also limit NF-κB induction of catabolic and inflammatory responses by deacetylating the p65 NF-κB subunit and priming it for proteasomal degradation, promoting autophagy through repair of damaged mitochondria [80,106–109]. Studies in OA and aging models suggest protective roles for SIRT1 and AMPK in cartilage[107–114]. Pharmacologic SIRT1 activation with resveratrol exerts chondroprotective effects, suggesting a potential therapeutic strategy through normalizing bioenergetics [15].

Angiogenesis and cartilage/subchondral bone interactions

Angiogenesis and sensory nerve growth are closely integrated processes that are potentially linked to the elevated crosstalk between the bone and cartilage in OA. Articular cartilage is normally avascular and aneural and is separated from the subchondral bone by a zone of calcified cartilage, with the tidemark as the histologically interface between the articular and calcified cartilage. Microcracks produced by mechanical stress and exacerbation of naturally occurring pores in the subchondral bone plate provide conduits for vascular invasion into the calcified cartilage and enable cross-talk through diffusion of small molecules [115,116]. TGF-β-mediated angiogenesis, potentially among the earliest events driving OA [117], is followed by vascular invasion into the osteochondral junction [118,119]. Examination of OA mouse models by microCT shows early and temporal subchondral plate porosity and

increased perforation with enhanced biochemical and mechanical interactions among the subchondral trabeculae, bone marrow cells, and articular cartilage. The advancement of the calcified cartilage, associated with tidemark duplication, into the deep zones of the articular cartilage leads to local cartilage thinning, thereby compromising the mechanical function of the osteochondral unit [120].

The regions of vascular invasion are associated with localized bone marrow replacement by fibrovascular tissue containing cells that express VEGF, accompanied by increased osteoclast activity, infiltration of inflammatory cells into the marrow spaces, and increased endothelial cell proliferation and vascular density [121]. The invasive vascular elements in calcified cartilage and synovium may serve as conduits for nerve fibers and stimuli for nerve growth factor (NGF) [122]. VEGF is expressed by chondrocytes in proximity to the angiogenesis, suggesting that it is involved in recruiting vascular elements. Gene expression profiling identified STC1, a gene encoding stanniocalcin-1, which regulates angiogenic sprouting via the VEGF/VEGF receptor 2 pathway, as the most highly up-regulated gene in inflamed synovial membrane compared to non-inflamed synovium from the same OA patients [123]. A recent study shows that VEGF blockade with bevacizumab inhibits post-traumatic OA in a rabbit model with pain relief possibly associated with prevention of both synovitis and angiogenesis [124].

Cartilage anabolism and tissue engineering strategies

Since members of the TGF-β/BMP superfamily have roles in chondrogenesis and articular cartilage maintenance, they have been used as additive factors in tissue engineering strategies. However, TGF-β signaling can play both protective and deleterious roles in OA, explained in part by the alteration of signaling pathways in aging chondrocytes through decreased ALK5, the canonical receptor that activates Smad2/3 to inhibit chondrocyte hypertrophy, and increased ALK1, which signals through Smad1/5/8 to induce MMP-13 and cartilage catabolism [125] and NGF [126]. Disruption of the pericellular matrix by the TGF-β-induced serine proteinase, HTRA1, may be one of the earliest events in OA chondrocyte activation [28]. These aberrant chondrocyte responses may account for the off-target effects of TGF-β injections in joints that result in osteophyte formation and synovial fibrosis.

Recent studies have also identified aberrant TGF-β signaling in bone as a key pathway in OA [127]. In the ACL transection model of OA, high doses of a TGF-β inhibitor administered systemically promoted cartilage proteoglycan loss, whereas lower doses prevented the migration and/or localization of MSCs, osteoprogenitors, and osteoblasts in the subchondral bone of operated limbs and attenuated neovascularization and cartilage loss. Transgenic expression of active TGF-β in osteoblasts induced the formation of nestin-positive MSCs in clusters, whereas knockout of *Tgfbr2* in nestin-positive MSCs prevented MSC migration to the subchondral bone and normalized bone parameters, cartilage homeostasis, and limb function. Furthermore, implantation of a TGF-β-specific antibody in the subchondral bone attenuated the OA changes in both the cartilage and bone, suggesting that bone-targeted therapies may be useful in some forms of the disease [117].

The FGFs are generally considered homeostatic factors in joint tissues [128], but FGF-2, for example, can be chondroprotective through FGFR3 or promote cartilage destruction via FGFR1 [129]. Of the four receptors, FGFR1 and 3 are the most abundant, and the ratio of FGFR3 to FGFR1 is reduced in OA cartilage. FGF-18 via FGFR3 also protects against loading-induced damage in cartilage explants ex vivo [130] and intraarticular administration of FGF18 protects against cartilage damage in a rat model of injury-induced arthritis [131] Thus, there is considerable interest in the potential of anabolic factors such as FGF-18 for enhancing cartilage regeneration with tissue engineering approaches [132]. However a recent proof-of-concept trial with human recombinant FGF-18, sprifermin, showed statistically significant dose-dependent improvement in pre-specified secondary structural end points by MRI, radiographic joint space narrowing, and WOMAC pain scores [133].

Targeting the Wnt/β-catenin pathway, which plays a role in both cartilage and bone development and pathology [134,135], has been investigated in OA, but with contrasting results. The Wnt antagonists, dickkopf-related protein-1 (DKK-1) and secreted frizzled-related protein 1 (sFRP1), along with the BMP antagonist Gremlin1, can prevent these adverse effects on articular cartilage homeostasis by decreasing hypertrophic differentiation [136,137] and expression of proteinases [138] Genome wide association studies have identified unique polymorphisms associated with hip OA in the FRZB gene encoding sFRP1 [139], which may have a protective role in OA by inhibiting MMP induction in chondrocytes [140]. However, differential effects of DKK-1 may be observed on cartilage and bone depending on dosage and mode of delivery and a recent study suggests that the inhibition of cartilage degradation by DKK-1 is related to its capacity to inhibit VEGF production by osteocytes and osteoblasts [141].

Another Wnt antagonist, sclerostin (SOST) identified originally as an osteocyte-specific, is expressed in cartilage and found at low levels in osteochondral tissues, plasma, and synovial fluid in OA patients and/or animal models [142,143] Sclerostin inhibitors that increase bone formation have been developed [144], but neither sclerostin deficiency in mice nor pharmacological inhibition in a rat meniscal tear model appear to impact on cartilage remodeling [145].

These conflicting findings may be related to the availability of Wnt ligands in different tissues and their use of distinct, canonical versus non-canonical, pathways over the course of differentiation and during pathology [134]. Consistent with this notion are findings from gene expression profiling comparing articular chondrocytes with prominent expression of BMP and Wnt signaling antagonists and osteophytic chondrocytes expressing genes involved in endochondral ossification [146]. Canonical Wnt signaling induced by Wnt3a or WISP1 promotes the switch of TGF-β signaling towards ALK1 and Smad 1/5/8 [•137] and mechanical load-mediated suppression of sclerostin requires TGF-β [147]. Although lithium chloride stimulates β-catenin signaling via inhibition of GSK-3, it inhibits catabolic events in surgically induced OA in mice via NF-κB, p38, and Stat3 signaling [148].

The predominant research strategy aimed at engineering functional cartilage with the identical properties of the native tissue has been to increase the accumulation of a cartilaginous matrix by exposing cells to anabolic agents such as those discussed above,

either through exogenous addition of recombinant proteins or genetic manipulation of the cells to overexpress them. This work has led to development of scaffold materials, identification of viable cell sources and culture conditions, including growth factor delivery and mechanical stimulation, as well as approaches for delivering cells alone or in a scaffold to the injury site. However, we are far from achieving a construct with the mechanical stability and lubricating properties of native cartilage. Successful cartilage tissue engineering strategies must also include retention of key matrix components within the construct over an extended lifespan and under inflammatory conditions and integration with the host tissue. Among the cell sources are mesenchymal stem cells (MSCs), which can be obtained from autologous adipose tissue, bone marrow, or muscle and expanded ex vivo in conditions that promote chondrogenesis. Although articular chondrocytes have no intrinsic repair capacity, the potential of a small population of cartilage-derived stem or progenitor cells to be stimulated in situ is the subject of current investigations [••149].

Prospects for the future

Application of our knowledge regarding the anti-inflammatory, anti-catabolic, and pro-anabolic factors to developing new structure modifying therapies is a promising outcome of the future. Also, a number of established OA susceptibility loci have been determined in large population studies, but functional follow-up is needed and their use for establishing cohorts for clinical trials is a future goal. Although clinical trials are ongoing to assess agents that address some of these targets, OA in humans develops slowly with time and may not be symptomatic until significant joint damage occurs. Thus, it has been extremely difficult to develop disease-modifying drugs and prove their effectiveness in clinical trials due to the lack of biomarkers and sensitive techniques for identifying and assessing patients with early changes. In the meantime, research efforts are evaluating more specific inhibitors that target OA disease-specific mechanisms in preclinical animal models that reflect different OA phenotypes [30,31]. Some of the emerging targets are summarized in Table 1.

Emerging targets in neuroinflammation-driven chronic pain include many factors involved in structure modification in OA. Studies in mouse OA models show central roles of nociception during inflammation, neuropathy, and mechanosensitivity and have identified several promising targets that affect physical function and pain sensitivity [150–152], as indicated in Table 1. Emerging mediators and molecular therapies that ameliorate OA and in some cases can even promote regeneration in animal models are summarized in Table 2.

As in other complex diseases, analysis of the structure and dynamics of molecular networks could give system-level understanding of potential targets of therapy and improve the efficiency of drug discovery [153]. Our recent ability to profile unique patterns of epigenetic changes offers novel strategies for distinguishing diverse chondrocyte phenotypes that relate to chondrogenic programming, articular cartilage homeostasis, and OA disease progression, and for identifying novel biomarkers of early OA, such as circulating long non-coding RNAs and miRNAs [154,155]. Correlating DNA methylation, chromatin marks, and miRNA signatures in human OA disease with those found in well-defined OA animal models could allow us to define the different regulatory requirements for stress-related phenotypes of OA chondrocytes [156]. However, therapies that target DNA or histone

methylation or miRNAs have been considered for cancer, their use in a non-life-threatening disease such as OA will require better understanding of gene and target cell specificities to avoid cytotoxicity and off-target effects. The academic community remains hopeful that rational molecular therapies may be on the horizon if their findings in pre-clinical models can be translated to proof-of-principle clinical trials designed to provide clear outcomes.

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•• of outstanding interest

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Highlights

- Different OA etiologies present a challenge for developing a single targeted therapy.
- Common mechanisms occur in inflammatory, mechanical, and oxidative stress in OA.
- Microinflammation, loss of autophagy, and angiogenesis indicate new targets.

Table 1

Emerging targets in structure modification and neuroinflammation-driven chronic pain.

Biological Process	Targets (Downstream Effectors)	Potential Therapeutics
Cartilage degradation	DDR2 activated by TGFβ-induced	Tyrosine kinase inhibitors
	HTRA1 serine proteinase [••28]	Serine proteinase inhibitors MMP inhibitors [161] MMP inhibitors [161]
	ADAM17 (via activating TNFα and EGFR ligands, e.g., TGFα[157–159]	Neutriceuticals, e.g., green tea polyphenol [162]
	Cathepsin K [160]	CatK inhibitors
Mechanical, inflammatory, and oxidative stress	Canonical NF-κB signaling [163]	Curcumin, resveratrol, IKKβ inhibitor (SAR113945); proteasome inhibitor (bortezomib) [164]
	JAK/STAT signaling [7]	Tofacitinib [165];SOCS [166,167]
	Reactive oxygen species	Anti-oxidants, iNOS inhibitors; mitochondrial ROS scavengers [168]
	HIF-2α(proteinases & hypertrophy markers)[52,60] Zinc-ZIP8-MTF1 axis (MMPs, ADAMTS5) [••62]	Antioxidants
Innate immunity	TLRs[71,72]	6-shogaol; boswellic acid; kampferol; oleocanthal; quercetin
	Complement [77,78]	CR2-fH
Chondrocyte hypertrophy	Hedgehog signaling [169,170] IKKα (MMP10) [65] ADAM10 (Notch signaling via RBPjk) [171–173]	Small molecule inhibitors of Gli, Smo, etc.
Angiogenesis and synovitis	* VEGF [124]	Bevacizumab [124]
Subchondral bone	WNT/β-catenin [174]	Sclerostin, DKK-1
	Adenosine receptors [175]	A2AR antagonists
Pain	* Monocyte chemoattractant protein (MCP1)/CCR2 chemokine receptor [••150]	CCR2 receptor antagonist
	* Peripheral calcitonin gene-related peptide receptor (CGRP)	CGRP 8-37 receptor antagonist [151]
	* Transient receptor potential vanilloid ion channels (e.g., TRPV4)	TRPV4 agonist (GSK1016790A) [••152]
	* Adenosine and purinergic receptors (via TRPV channels) [176,177]	A3AR agonists; P2X and P2Y antagonists

* Both structure modification and pain relief have been demonstrated in animal models

Table 2

Emerging mediators and molecular therapies that ameliorate OA and in some cases can even promote regeneration.

Biological Process	Mediators	Potential Therapeutics*
Autophagy and cell survival	mTOR [85,98]; AKT/Fox03/ mTOR [99]; PPARγ [87,178,179]	Rapamycin, polyamines, ω-6 polyunsaturated fatty acids; glucosamine
	CXCR2 [•180]	Chemokine antagonists or blocking antibodies
Chondrogenesis and inhibition of endochondral ossification	Runx1	TD-198946 [181]; Kartogenin [182,183]
	PTH receptor	Recombinant human PTH(1-34) (teriparatide)[184]
	EGFR signaling	Mitogen-inducible gene 6 (MIG6) [185]
Calcification and crystals	NPP1 [186]; transglutaminase, inorganic pyrophosphate, TLRs, NLRP3	Phosphocitrates, TLR and NLRP3 inhibition
Subchondral bone	WNT/β-catenin BMPs	Wnt antagonists (DKK1, SOST)
		BMP antagonists (Gremlin, follistatin) [136–138,141]
	BMP-7	Recombinant BMP-7 (Eptotermin) [187]
	TGF-β [117]	TGF-β-specific antibody
Cartilage anabolism	IGF-1	Humanized IGF-1-heparin-binding domain fusion protein. [190]
	FGF-18	Sprifermin [133]
	PRG4 [••61]	Oral or intraarticular calcitonin [191–193]
	NFATc2/c2[188]	
	Calcitonin [189]	
Circadian clock	Bmal1 [•194]	REV-ERB agonists [195]

*Both pre-clinical and clinical studies referred to without comment on efficacy