Osteoarthritis in 2007

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Abstract

Osteoarthritis (OA) is often a progressive and disabling disease resulting from a combination of risk factors, including age, genetics, trauma, and knee alignment, as well as an imbalance of physiologic processes resulting in inflammatory cascades on a molecular level. The synovium, bone, and cartilage are each involved in the pathophysiological mechanisms that lead to progressive joint degeneration, and, thus, also serve as targets for therapies. Efforts to identify disease-modifying osteoarthritis drugs (DMOADs) have been hampered by several factors, but the focus has now shifted toward the validation of chemical and imaging biomarkers that should aid in DMOAD development. In this review, we summarize current pathological mechanisms occurring in the individual but interconnected compartments of OA joints, as well as discuss related therapeutic interventions that are currently available or on the horizon.

Osteoarthritis (OA) is a degenerative joint disease that is the leading cause of physical disability and impaired quality of life in industrialized nations. The disease dramatically impacts health care usage and leads to total joint replacement in a half-million Americans each year. Such burdens on society are expected to soar in the coming decades as the population both ages and increases.

There are no current interventions proven to restore cartilage or curb the disease processes; therefore, OA often results in chronic pain, joint destruction, disability, depression, and social isolation. A host of etiologic risk factors and pathophysiologic processes all contribute to the progressive nature of the disease and serve as targets of behavioral and pharmacologic interventions. Some risk factors, such as age, gender, trauma, overuse, genetics, and obesity, lead to injury in all of the different components of the joint. The chemical processes affecting either the cartilage, bone, or synovium eventually intertwine and collectively damage all three components as well (Fig. 1). The effects on the three joint compartments manifest as articular cartilage breakdown, osteophyte formation, subchondral sclerosis, and alterations of the synovium on both morphologic and biochemical levels. Thus, the molecular and cytokine-based events that are paramount in rheumatoid arthritis (RA) and in the other inflammatory arthritides have gradually emerged as pathogenic paradigms highly relevant to the development of future OA therapeutics.

With increasing appreciation of the contribution of all three joint compartments to disease progression, current research in OA pathogenesis, biomarkers, and treatment has broadened immensely in recent years. This review will focus on emerging concepts that are likely to have an impact on the search for newer disease-modifying osteoarthritis drugs (DMOADs).

Cartilage Damage

The synovium, bone, and cartilage are each well-established sites affected by the pathophysiological mechanisms of OA that can lead to progressive joint degeneration. Yet the cartilage has traditionally received the most attention in the study of OA because of the gross damage found in imaging
studies and pathology, and the multitude of biochemical processes that are activated.

Some of the key aspects of cartilage pathogenesis in OA include metabolic signals and degradation that are driven by cytokine cascades and the production of inflammatory mediators. Chondrocytes of OA patients produce increased levels of inflammatory cytokines, such as IL-1β and TNF-α, which, in turn, decrease collagen synthesis and increase degradative proteases (including matrix metalloproteinases, or MMPs) and other inflammatory mediators, such as IL-8, IL-6, prostaglandin E2, and nitric oxide. In turn, nitric oxide plays multiple roles with respect to its effect on chondrocytes that promote cartilage degradation, including inhibition of collagen and proteoglycan synthesis, MMP activation, and increased susceptibility to other oxidant injury.

Two other key pathogenic events occurring in OA chondrocytes, which also appear to result from nitric oxide and other oxidative injury, are premature senescence and apoptosis; these contribute to the concept that OA is a disease of premature aging of the joint. Senescence, marked by shortened telomeres, increased levels of B-galactosidase, and decreased ATP production from mitochondrial dysfunction, has been demonstrated histologically in chondrocytes taken from OA patients. Studies suggest that oxidative stress causes the telomere shortening and reduced number and function of mitochondria in OA chondrocytes. Other work implicates nitric oxide as an important mediator in chondrocyte apoptosis, which is a common feature in progressive OA. Immunohistochemistry of joint tissue from OA patients co-localizes apoptosis with iNOS (inducible nitric oxide synthase) protein in articular cartilage cells, while canine and murine models have corroborated this link by reducing the progression of cartilage lesions when inhibiting nitric oxide. Thus, it should not come as much of a surprise that researchers are showing interest in resveratrol, an antioxidant found in red wine, as a resource to limit this chondrocyte damage. Resveratrol, which protects against atherosclerosis and enhances the longevity of yeasts, worms, flies, and mice, also inhibits the production of nitric oxide, lengths telomeres, and restores mitochondrial function, thereby increasing ATP levels. The findings of premature senescence and apoptotic acceleration in OA substantiate that the disease is age dependent, mechanically driven, and chemically mediated.

More Than a Disease of Cartilage

Synovium

The classification of OA as a noninflammatory arthritis is, in part, due to the synovial fluid leukocyte count that is typically less than 2000 cells/mm³. Yet the clinical presentation in OA joints (such as swelling, effusions, and stiffness) clearly reflects synovial inflammation, as a low-grade contribution to disease pathogenesis. This synovitis occurs even in early OA and can be subclinical, as arthroscopic studies suggest that localized proliferative and inflammatory changes of the synovium occur in up to 50% of OA patients (many of whom do not appear to have active inflammation). Synovial histological changes include synovial hypertrophy and hyperplasia, with an increased number of lining cells, often accompanied by infiltration of the sublining tissue, with scattered foci of lymphocytes. In contrast to RA, synovial inflammation in OA is mostly confined to areas adjacent to pathologically damaged cartilage and bone. This activated synovium can release proteinases and cytokines that may accelerate destruction of nearby cartilage.

The synovium produces some of the chemokines and metalloproteinases that degrade cartilage, even though the cartilage itself produces most of these destructive molecules.
in a vicious autocrine and paracrine fashion. In turn, cartilage breakdown products, resulting from mechanical or enzymatic destruction, can provoke the release of collagenase and other hydrolytic enzymes from synovial cells and lead to vascular hyperplasia in OA synovial membranes. This cascade sequentially results in the induction of synovial IL-1β and TNF-α, which further the inflammatory outcome.

This cytokine storm may be more likely to occur in earlier stages of the disease before end-stage damage, as shown by a recent study of 10 patients with early OA (arthroscopic specimens) and 15 patients undergoing total knee arthroplasty; synovial tissues from early OA had higher levels of IL-1β and TNF-α and increased mononuclear cell infiltration compared to late OA. In contrast, IL-1 and TNF induce iNOS in bone cells, and nitric oxide (NO) derived from this pathway potentiates bone loss. In vitro studies from diseased human OA tissue have implicated MMP-10 expression in synovial fibroblasts, as well as in OA synovial fluid and chondrocytes stimulated with catabolic IL-1 and oncostatin M.

Bone
Pathology specimens and imaging studies clearly demonstrate the osteophytes and thickening of subchondral bone that are characteristic of OA (Fig. 3), but the inflammatory mediators involved with OA bone are less well understood than those produced by cartilage and synovium. Nitric oxide is known to contribute to bone cell function, which could have implications for OA by resulting in subchondral bone changes. The endothelial isoform endothelial cell nitric oxide synthase (ecNOS) is constitutively expressed in bone, likely regulating osteoblast activity and bone formation and mediating the effects of mechanical loading on the skeleton. ecNOS appears to act along with prostaglandins to promote bone formation and suppress bone resorption.

Erosive OA likely represents a more inflammatory process, as evidenced by higher proteinase and cytokine levels. One study of rapidly destructive hip OA demonstrated MMP-3 and -9 levels that were especially elevated, not only in patients' synovial cells but also in their synovial fluid, plasma, and sera. In vitro studies from diseased human OA tissue have implicated MMP-10 expression in synovial fibroblasts, as well as in OA synovial fluid and chondrocytes stimulated with catabolic IL-1 and oncostatin M.

Biomarkers: A Tool to Improve Upon Current Treatment Options?
At present, we lack any approved DMOADs to target the mechanisms described above. Current medical therapies for OA are focused upon symptomatic relief, using analgesics such as acetaminophen and nonsteroidal antiinflammatory drugs (NSAIDs), as well as intra-articular injections of corticosteroids and the hyaluronans. Furthermore, controversy exists around the cardiovascular safety of traditional NSAIDs and cyclooxygenase 2 (COX-2) selective inhibitors. Additional nonpharmaceutical, or nutraceutical agents, including glucosamine and chondroitin, may provide symptomatic benefit in selected patients.

The search for suitable DMOADs has spurred great interest in finding reliable markers—clinical, imaging and biochemical—that can be used to track improvement, stabilization, or even progression of OA with the use of new therapeutic agents. We have advanced beyond radiographic images that are insensitive to early change within cartilage...
and bone and do not reflect synovial pathology. Traditional MRI is now being studied for quantitative assessment of hyaline cartilage thickness and volume, synovial hypertrophy, and bone marrow edema, while functional MRI studies, such as dGEMRIC and T1ro, which detect biochemical changes in cartilage, may demonstrate in the short term that treatment restores normal chondrocyte metabolism. Biochemical markers that are under investigation include serum COMP, urinary CTX-II, and serum hyaluronic acid.

Overall, the development of sensitive and specific biomarkers can guide patient selection, reduce the number needed to treat, and strengthen the power of DMOAD studies, while also indicating efficacy of response. The Osteoarthritis Biomarkers Network, a consortium of five NIH (National Institutes of Health) designated sites, recently proposed a classification scheme for biomarkers for OA (whether they are clinical, imaging, or biochemical). With the acronym BIPED, this system proposes to aid in the study of all aspects of OA, from basic science research to clinical trials: Burden of disease, Investigative, Prognostic, Efficacy of intervention, and Diagnostic. While an ideal DMOAD would both control symptoms and provide structure modification, the reality may be that effective therapies will only target one or some of these outcomes or categories, and that patients may need to take combinations of treatments for successful disease control. In the next section we will outline some of the current DMOAD candidates.

Early Data from Potential Structure Modifying Agents

**IL-1β blockade**

Of the cytokines thought to be involved in the pathogenesis of OA, IL-1β has attracted the most interest as a target for disease modification. The addition of IL-1 antagonists, such as IL-1 receptor antagonist (IL-1Ra), to OA explants inhibits inflammatory mediator and MMP production, while significantly increasing type II collagen and aggrecan synthesis. In animal models of OA, delivering IL-1Ra either intra-articularly or by gene transfer significantly reduces osteophyte formation and the severity of cartilage lesions. Studies of extended haplotype analysis and linkage disequilibrium analysis show that a common haplotype in the IL-1A–IL-1B–IL-1RN gene cluster confers a four-fold higher risk of OA in these individuals. These studies raise the possibility that IL-1 gene polymorphisms could contribute to increased IL-1 expression in selected patients.

Thus, IL-1β has attracted significant interest as a target for disease modification in OA in humans though the results thus far are inconclusive at best. One 12-week open-label study seemed promising and showed benefit of intra-articular IL-1Ra injection for symptomatic knee OA, but a follow-up controlled trial done by the same authors found no statistical improvement over placebo after one month. Trials with diacerein, which inhibits IL-1β production from synovial tissue and cartilage, failed to show a significant symptom-
In a cross-sectional analysis of elderly females with knee OA, Carbone and coworkers reported that females treated with alendronate and estrogen had decreased prevalence of subchondral bone lesions, compared with those reporting no use of these medications. Alendronate use was also associated with a reduction in knee pain according to the Western Ontario and McMaster Universities Osteoarthritis Index measurements.

**Doxycycline**
Tetracyclines inhibit collagenase levels and nitric oxide production in vitro, thereby decreasing chondrocyte MMP activity and increasing proteoglycan synthesis, attenuating OA in animal models. In 2005, Brandt and associates conducted a randomized, placebo-controlled, double-blind trial in which they examined the effect on JSN of doxycycline 100 mg BID versus placebo for 30 months in more than 400 obese, middle-aged females. Doxycycline reduced the mean loss of joint space width (JSW) in the OA knee by approximately 30% at 30 months; however, the mean progression of JSN in both groups was limited. It is unknown whether a statistically significant slowing of radiographic progression is clinically significant and can predict an improved clinical outcome. Moreover, doxycycline did not significantly prevent the onset of progressive JSN in the contralateral knee, and did not improve measures of pain or function in this study.

**Inducible Nitric Oxide Synthase**
Several compounds that inhibit iNOS are under investigation for potential DMOADs, as this enzyme is upregulated in OA cartilage and can produce NO, which can be catabolic. Among its deleterious actions, NO increases MMP activity, inhibits cartilage matrix synthesis, and induces apoptosis in chondrocytes by reducing mitochondrial potential, ATP generation, and by increasing caspase activity. iNOS deficient knockout mice do not develop experimental OA, and dogs given L-NIL, a selective inhibitor of iNOS, have attenuated progression of experimental OA.

**Glucosamine and Chondroitin**
Clinical studies of these two agents, given either in combination or separately, have yielded variable results with regard to reducing both symptoms and progression of JSN. This may be, in part, due to mostly small numbers of patients enrolled and methodological differences, as well as different commercial sources (and therefore bioavailability) of the glucosamine preparations. It has been noted that positive studies have been sponsored by industry, but there is no evidence to indicate that this can plausibly explain the results of blinded studies of radiographic outcome. A recent Cochrane review, which analyzed 20 glucosamine studies in which there were over 2500 patients, concluded that glucosamine taken for 2 to 3 months neither improves pain nor WOMAC (Western Ontario and McMaster Osteoarthritis Index) function. Two 3-year RCTs, using a particular manufacturer-sponsored glucosamine preparation, found that glucosamine significantly prevented radiographic progression in knee OA, as compared with placebo. Criticism of both of these trials has focused on the fact that JSW was assessed using standing anteroposterior knee radiographs, and a change in knee pain may affect the ability to extend the knee and thereby alter apparent JSW. The NIH-sponsored Glucosamine/Chondroitin Arthritis Intervention Trial (GAIT), which enrolled 1583 patients with painful knee OA, failed to reveal an effect of glucosamine or chondroitin alone or in combination when compared to placebo. It must be noted that the study utilized glucosamine hydrochloride, while European studies have used glucosamine sulfate. Moreover, the study’s high placebo response rate (60%) may have hampered the ability to show a difference, and current subgroup analyses and evaluation of imaging outcomes from this study may further clarify their potential efficacy as DMOADs.

**Calcitonin**
There has been recent interest in calcitonin as a potential treatment for OA, based on its metabolic activities in both cartilage and bone turnover. In vitro and ex vivo studies have found that calcitonin has both anti-catabolic and anabolic effects in cartilage, by attenuating proteoglycan and collagen type II degradation as well as by inducing their syntheses. A small phase II randomized, double-blind, placebo-controlled trial assessing the efficacy of oral salmon calcitonin in knee OA was recently published. Results showed an improvement in Lequesne’s function scores as well as a reduction of certain biomarker levels such as urinary CTX-II, MMP-3 and 13, and serum hyaluronan. While this study was not analyzed as an intention to treat endeavor and the sample size was not adequately powered to draw efficacy conclusions, its promising results will hopefully lead to further, larger trials.

**Conclusion**
OA is, by far, the most common type of arthritis encountered worldwide, yet the development of effective disease-modifying treatments has lagged behind that of other arthritides. Current challenges that will need to be met include improving identification of patients at risk for progression by using growing knowledge of the epidemiological, genetic, biochemical, and imaging findings that predict clinically meaningful progression. As the pathogenesis of OA is further elucidated, and the discovery of improved biomarkers continues, we hope to see true DMOADs emerge in the near future.

**Disclosure Statement**
Svetlana Krasnokutsky, M.D., and Jonathan Samuels, M.D., do not have a financial or proprietary interest in the subject matter or materials discussed in the manuscript, includ-
References


