Osteoarthritis
A Tale of Three Tissues

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Abstract

While research in osteoarthritis has focused on the events that lead to the destruction of articular cartilage, recent evidence suggests that two other components of the joints—bone and synovium—also play key roles in pathogenesis. All three tissues undergo alterations in concert at the structural levels in response to mechanical stress and joint malalignment. Advanced imaging studies such as MRI support this interdependence, revealing the classical changes of joint space narrowing and cartilage degeneration as well as the more recently appreciated bone marrow lesions and synovitis that may correlate with clinical symptoms. Molecular evidence also points to a coordinated release of cytokines and other inflammatory mediators from each of the three tissues together in progression of disease, although we are still in search of biochemical signatures that will predict the subset of patients who progress more quickly—and who will provide key clues to successful molecular targets in future therapies. At this time we lack definitive evidence pointing to which, if any, of the three tissues should serve as the main target for disease modification or structure protection, although most efforts have focused on cartilage. Thus current therapies focus on controlling symptoms, while research efforts search for reliable imaging and molecular biomarkers to help guide future trials of potential disease-modifying agents.

The prevalence and unchecked progression of osteoarthritis (OA) represents the most widespread cause of physical morbidity and impaired quality of life throughout the industrialized world. While many disease-modifying therapies are available for the more aggressive and inflammatory arthritis syndromes, such as rheumatoid arthritis, physicians treating OA are limited to taking care of patients symptomatically and supportively—with little ability to alter its disease course, short of surgery. Thus OA, which “sends” a half-million Americans to total joint replacement surgeries each year, will continue to burden our society’s aging and expanding population in increasing numbers, unless we are able to identify targets that will slow down or halt disease progression.

Numerous risk factors likely contribute to the pathogenesis of this disease, including both mechanical stresses, such as obesity, misalignment, joint trauma and surgery, and biochemical abnormalities, such as genetic predisposition and other metabolic disorders. While these risk factors have been known for years, what has changed in OA research efforts is our broadened knowledge that the pathophysiology involves not only the breakdown of articular cartilage, but changes in the bone and synovium as well (Fig. 1). We also boast a better understanding of the morphologic and molecular evidence of destruction in each of these tissues and suspect that OA involves crosstalk between tissues on the cellular and cytokine levels, at least in some subgroups or phenotypes. Furthermore, we are in search of clues that will explain why some patients’ joints worsen and undergo rapid destruction, while others progress at a more gradual pace. Ongoing and future efforts in developing the first true disease-modifying therapies in OA will need to keep these subgroups at the forefront, and question if we should target any of the three intertwined tissues more than the other two.

In this review, our objective is to address the crosstalk...
between the three different tissues in OA, on both macro and micro levels, and the efforts to predict among patients whose arthritis may worsen more rapidly, as these two emerging directions are keys in the search for the first disease-modifying medications. We will also outline the current treatment paradigm that tries to limit symptoms and maintain function, as we look forward to eventually being able to preserve joint structure and halt disease.

**Mechanical and Structural Clues**

Many studies through the years have identified physical risk factors that are associated with an increased likelihood of progressive knee OA, exemplified by one report that predicted radiographic worsening over a 2 to 5 year period. This study cited an 11-fold increase in progressive OA from obesity and an odds ratio of 5 for valgus or varus misalignment. Prior knee surgery was associated with a 2.6-fold increase for progressive disease, although more recent research suggests an even higher percentage of OA in patients who suffered meniscal or ligament tears. The OA resulting from these mechanical stresses was long heralded as a disease primarily of the articular cartilage, resulting in the radiographic joint space narrowing seen and reported for years in the literature. However, imaging techniques have become more sophisticated, especially in the last few years, with extensive MRI evaluation. As a result, we are now aware that certain anatomically-based subregions of the tibial and central weightbearing femoral cartilage are more prone to these defects of cartilage thickness. MRI and other imaging techniques are increasingly able to detect early cartilage fibrillation and defects not seen on conventional radiography, providing more avenues of investigation with this tissue type to determine which patients develop incident and more progressive OA. In addition, study of the topography of OA articular cartilage has shown that destruction of the cartilage—shown by inducible nitric oxide staining for the catabolic nitric oxide—occurs in the superficial zones, where the proteoglycan is lost. This activity is absent in the deep zones; thus, it is far away from the subchondral bone, reinforcing the fact that the cartilage itself should at least continue to be a target for intervention.

At the same time, morphologic detection of disease in the bone and synovium has increased as a result of MRI, supporting the emerging notion that OA is a disease of multiple compartments that emerge in concert. Radiographic studies and pathology specimens have long demonstrated the osteophytes and subchondral bone sclerosis that are characteristic of OA. With advances in imaging technology, we now observe additional abnormal findings relating to bone structure that may play important roles in this disease. Among the most important discoveries was that of bone marrow lesions, which are associated with knee pain and the risk of disease progression; they were first described as bone marrow “edema” by David Felson. Investigators, including those at our institution, are working to elucidate the patterns of progression and regression of these lesions. The focus of these studies is to determine whether bone marrow lesions will be useful in identifying patients at risk for disease progression and whether regression of these lesions can be used as a “biomarker” of response to disease modifying OA drug (DMOAD) therapy. The results of such studies should improve treatment strategies and facilitate clinical studies of future DMOADs, which depend upon enrollment of a sufficient number of disease “progressors.”

Synovial involvement, namely inflammation and proliferation, has re-emerged over the last 5 years as yet another key component of OA and a potential predictor of worsening disease. We know that in end-stage OA, synovitis is commonly...
Radiograph demonstrating joint space narrowing, osteophyte and subchondral sclerosis, and an intra-operative view of associated synovitis in an osteoarthritic knee resembling rheumatoid pannus.

seen at joint replacement surgery and even has been described to resemble rheumatoid arthritis pannus, with new blood vessel formation (Fig. 2). Synovitis also appears to be important at earlier stages of disease when patients present with pain, as demonstrated with arthroscopy by Ayral and colleagues. This study reported thickening, often localized, in almost half of such patients, and these patients were more likely to have progression of cartilage lesions on repeat arthroscopy 1 year later. More recently, synovial thickening has been reported with ultrasound images (both gray scale and power Doppler) and MRIs (particularly when enhanced by gadolinium contrast). Our group has identified and quantified this synovitis, using gadolinium in a cohort of OA patients, reporting that higher synovial volumes correlate with other measures of worsening OA, including KL score, joint space narrowing, and even bone marrow lesions. It is not clear that any one of these three affected tissues represents primary disease, or if, as is more likely, they are each a manifestation of the “failing” OA joint, with the potential for each failing compartment to exacerbate disease in the adjoining tissues.

Cellularly and Molecularly Mediated Progression

While time and age may have some effect on all people, the “right” genetic background will lead to OA at earlier ages. The genetics combine with mechanical forces to stress cartilage, synovial tissue, and bone to lead to the release of injurious mediators. Clearly, genetic factors play a role in both the incidence and, very likely, the progression of OA. The genetic contribution to progression is evidenced by the clinical observation that the presence of Heberden’s nodes confer a six-fold increased risk of progression of knee OA. While genetic factors influence the incidence and progression of OA, the damage incurred by joint tissues is mediated by a variety of cytokines, growth factors, proteases, and inflammatory mediators, such as prostaglandins and nitric oxide. There is active investigation of the relationship between specific genetic polymorphisms, for example, of the IL-1, TNF-α, or cyclo-oxygenase genes, in an effort to link a genetic disposition to OA and the known pathophysiological and biochemical disease processes.

In the cartilage, chondrocytes (like osteocytes in bone) act as mechanical sensors that respond to pressure. Under normal circumstances, they respond by making extracellular matrix, such as aggrecan and type II collagen. However, abnormal mechanical stress, as occurs in OA, has been shown to alter chondrocyte metabolism and induce the production of proteases and such inflammatory mediators. These processes also lead to elevated levels of 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. In particular, an important study by Fermor and coworkers of porcine cartilage explants examined iNOS expression following mechanical compression. In these studies, the classical chemical stimuli for nitric oxide production, interferon, and endotoxin, induced iNOS to the same extent as did mechanical compression, further promoting the relationship between bad biomechanics and the inflammatory mediators. Other histology-proven chondrocytic processes involving oxidative injury contribute to the concept that OA is a disease of premature aging: senescence and apoptosis. Studies suggest that oxidative stress causes senescence by shortening telomeres and decreasing the number and function of mitochondria—thus, decreasing ATP production from mitochondrial dysfunction, while nitric oxide has also been implicated as a direct cause of apoptosis in progressive OA. Therapeutically, this could lead to future disease-modifying therapy as canine and murine models have corroborated the importance of nitric oxide by reducing the progression of cartilage lesions when inhibiting this molecule. In addition, resveratrol, an antioxidant found in red wine, has gained interest relative to telomere lengthening, and in our studies restored mitochondrial function and attenuated apoptosis following exposure to IL-1.

We are gradually gaining a better understanding of the inflammatory mediators involved with bone in OA, beyond the resorption and remodeling functions of osteoblasts and osteoclasts that have suggested that anti-resorptive agents slow OA progression. It is still unclear if the cytokines from bone are a driving force in OA, or rather a concomitant response to mechanical forces or molecular events from the 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 (eNOS) 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.\textsuperscript{16} In contrast, IL-1 and TNF induce iNOS in bone cells, and nitrous oxide derived from this pathway potentiates bone loss.\textsuperscript{17} Local production of anabolic growth factors, such as insulin-like growth factor-1 (IGF-1) and TGF-β, which are highly expressed in osteophytes of the femoral head in OA patients, contribute to osteophyte formation and subchondral bone remodeling.\textsuperscript{18} More recently, there is evidence that production of vascular endothelial growth factor (VEGF) and other endothelial markers promote penetration of new vessels into the tidemark to the subchondral bone—and that this osteochondral angiogenesis is independent of that of the synovial processes.\textsuperscript{19} Still, while subchondral bone is abnormal on a molecular level, it is not yet clear that targeting this bony abnormality will be a strategy for modifying disease progression.

Of the three tissues in osteoarthritic joints, the one that is most inflammatory on the molecular level is the synovium, and it is this tissue that provides the best evidence that all three tissues are involved in a coordinated biochemical process. In contrast to rheumatoid arthritis, 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. Even in early OA or subclinical disease that does not appear to have active inflammation, immunostaining of proliferative OA synovitis for chemokines, stromelysin, and collagenase reveals active degradative enzymes that abut articular cartilage. 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.

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.\textsuperscript{17} 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 MMP-9 levels that were especially elevated, not only in patients’ synovial cells but also in their synovial fluid, plasma, and sera.\textsuperscript{20,21} 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.\textsuperscript{22}

### Bridging the Gap Between Current Treatment Options and Disease-Modifying Agents

#### 1. 2007 OARSI Treatment Guidelines

Despite our progress in understanding OA pathophysiology, we have yet to target the mechanisms described above with

<table>
<thead>
<tr>
<th>Pharmacologic Modalities of Treatment</th>
<th>Level of Evidence</th>
<th>SOR% (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen (up to 4g/day)</td>
<td>Ia (knee)</td>
<td>92 (88-99)</td>
</tr>
<tr>
<td>IV (hip)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSAIDs/COXibs (with caveats for gastroprotection and CV risk)</td>
<td>Ia</td>
<td>93 (88-99)</td>
</tr>
<tr>
<td>Topical NSAIDs/Capsaicain</td>
<td>Ia</td>
<td>85 (75-95)</td>
</tr>
<tr>
<td>IA Corticosteroids</td>
<td>Ia (knee)</td>
<td>78 (61-95)</td>
</tr>
<tr>
<td>IB (hip)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IA Hyaluronate</td>
<td>Ia (knee)</td>
<td>64 (43-85)</td>
</tr>
<tr>
<td>IB (hip)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucosamine and/or (for symptoms)</td>
<td>Ia</td>
<td>63 (44-82)</td>
</tr>
<tr>
<td>Chondroitin sulphate</td>
<td>Ia</td>
<td></td>
</tr>
<tr>
<td>Glucosamine sulphate (possible structure-modification)</td>
<td>Ib (knee)</td>
<td>41 (20-62)</td>
</tr>
<tr>
<td>Chondroitin sulphate</td>
<td>Ib (hip)</td>
<td></td>
</tr>
<tr>
<td>Diacerein</td>
<td>Ib</td>
<td></td>
</tr>
<tr>
<td>Opioids and narcotic analgesics</td>
<td>Ia (weak opioids)</td>
<td>82 (74-90)</td>
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<tr>
<td>IV (strong opioids)</td>
<td></td>
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<tr>
<td>IV (others)</td>
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any treatments that slow or stop joint destruction. Unlike treatments for the more aggressive arthritides, OA regimens provide mainly symptomatic relief, from the long-standing analgesics, such as acetaminophen, to traditional NSAIDs, and cyclooxygenase 2 (COX-2) selective inhibitors, as well as corticosteroid and hyaluronic injections into the joints. Just last year, a group of 20 experts in OA convened under the auspices of the Osteoarthritis Research Society International (OARSI) and published updated pharmacological guidelines for hip and knee OA (Table 1).23 After reviewing the literature for all treatments and performing a year-long evidence-based analysis, these researchers together commented on the level of evidence supporting each of the treatment modalities: oral (including glucosamine and narcotic agents), topical, and intra-articular regimens. Their report went one step further to score the strength of recommendation (SOR)—to suggest, for example, that even if one treatment might appear to be accepted from a meta-analysis of randomized controlled trials, that would not necessarily mean that “they” believed it was, in fact, a good treatment. In sum, the group reported generally good data for acetaminophen, despite relatively few randomized clinical trials against placebo, and good trials for NSAIDs and COX-2 inhibitors, and even some meta-analyses of the topical agents. They endorsed the positive findings for acetaminophen and NSAIDs, with SOR scores exceeding 90%, but they showed tempered enthusiasm for topical creams and for intra-articular steroids, and even less for glucosamine (especially in terms of structure modification) and injectable hyaluronates. This group’s summation of treatment options underscores the notion that we often identify problems with the heterogeneity of published randomized trials and question their validity, whether the outcomes are positive or negative.

2. Continued Search for Helpful Biomarkers
As is evidenced in the OARSI guidelines, clinical data regarding the use of analgesics in OA reveals that the currently available drugs have, at best, modest effect size (less than 35%), and concerns over the long-term safety data for the more effective NSAIDs has constrained their use. Treatment options are further limited by the lack of DMOADs. The development of these agents is hampered by the absence of reliable and consensus-based markers of disease that could be used as benchmarks of improvement. In fact, there is concern that, even if we possibly had a good candidate drug thus far, our efforts may have missed it or not proven it because of inadequate biomarker tools—clinical, imaging, or biochemical—to track improvement, stabilization, or even progression of OA. As mentioned earlier, we have advanced to the use of MRI in studies, beyond radiographic images that are insensitive to early changes. But experts now debate if early cartilage lesions, bone marrow lesions, or synovial thickening are helpful markers of disease, or simply reactive sequelae. The same questions arise from functional MRI studies, for example, of dGEMRIC and T1ro. These investigations detect biochemical changes in cartilage, which may demonstrate, in the short term, that treatment restores normal chondrocyte metabolism. We still lack validation of biochemical markers, such as serum COMP, urinary CTX-II, and serum hyaluronic acid. Overall, the eventual identification of sensitive and specific biomarkers can guide patient selection, reduce the number requiring treatment, and strengthen the power of DMOAD studies, while also indicating efficacy of response.

3. Pursuing Agents for Structure Preservation, Beyond Symptom Control
Identifying reliable biomarkers is less than half the battle in the search for the first DMOAD, as the industry’s drug development pathway is especially difficult relative to this disease. Once a molecular target has been validated in vitro and in animal studies, a drug must pass phase I safety trials in humans before embarking on a 12-week randomized clinical trial of several thousand patients in phase II and III studies. Most DMOAD development strategies at the present time prefer demonstration of efficacy for the treatment of signs and symptoms before longer (2 year) structure-modification studies are initiated for FDA (Food and Drug Administration, Rockville, Maryland) approval as a DMOAD. The challenges for companies are daunting. The benefit of a drug that might work to slow progression (e.g., an MMP inhibitor), but have no symptomatic benefit in the first 2 years of treatment, may need to be measured as a decreased likelihood of joint replacement. Therefore, absent reliable biomarkers that predict long-term symptomatic efficacy of DMOADs, many drugs are delayed in development because of the high cost of bringing them to clinical trials.

As a result, there is a lot of interest in OA biomarkers that might tell us whether a patient will progress rapidly (because only 15% to 20% of people with OA worsen significantly over 2 years), and whether biomarker measurement over 3 months will be predictive of patients who would benefit from the drug after two years. These kinds of changes in blood, urine, and imaging studies might serve as surrogates for structure modification, and then allow a company to do a “proof of mechanism” or “proof of concept” study based on such biomarkers.

While none of the proposed DMOADs to date have proven effective in published trials, a host of current candidates are still under clinical investigation following encouraging basic and animal results (which will not be addressed here). Early trials with IL-1β antagonists have produced mixed results with intra-articular antagonists,24,25 while other studies with inhibitors of production from synovial tissue and cartilage26 failed to show significant symptomatic or radiographic improvement.27,28 Several groups have looked at direct inhibition of MMPs in both OA and RA, and these agents have been associated with adverse musculoskeletal events, such as bursitis and fibrosing contractures, when used in oncology trials29; still, there is hope that more focused
MMP inhibitors that are specific for MMP-13 and ADAMTS will be more successful. Bisphosphonates have been considered as mentioned earlier, but imaging data have not been convincing; for example, risedronate did not halt structural progression of OA, despite improvement of symptoms and reduced cartilage degradation markers (such as CTX-II) in both a 1-year study and a 2-year multinational phase III trial of 2400 knee OA patients. Several compounds that inhibit iNOS are under investigation for potential DMOADs, including a phase II study conducted by one of the pharmaceutical companies, as this catabolic enzyme exerts many deleterious actions described earlier in this review. Others are pursuing calcitonin for use in OA based on its dual anti-catabolic and anabolic effects in cartilage, by synthesizing and attenuating the breakdown of proteoglycan and collagen type II. One underpowered phase II trial using oral salmon calcitonin for knee OA reported 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. Finally, the much discussed glucosamine and chondroitin sulfate have been studied by many groups, but with conflicting results both symptomatically and radiographically; questions raised include the small number of patients enrolled, methodological differences, high placebo response rates, and even different commercial preparations that may affect bioavailability and clinical efficacy.

Conclusion
Research efforts continue to focus on identifying the first disease modifying drug for OA, which remains the most common type of arthritis. While both biochemical and imaging studies have shown us that OA manifests in bone and synovium as well as cartilage, it is still unclear which of these three tissues—if any of them—should serve as the key biomarker or target, as the pathophysiologic processes are, in many respects, intertwined. Thus, we need to view OA as a disease of the entire joint as we apply our various potential biomarker techniques to identify those patients at risk for accelerated progression, and to ensure better success in clinical trials of emerging DMOAD candidates.

Disclosure Statement
Steven B. Abramson, MD, serves as a consultant to Novartis Pharmaceuticals Corp., Merck & Co., Inc., Pfizer, Inc., Schering-Plough, CombinatoRx, and Amgen.

References
20. Masuhara K, Nakai T, Yamaguchi K, et al. Significant increases in serum and plasma concentrations of matrix metalloproteinases 3 and 9 in patients with rapidly destructive osteoarthritis...