Biomarkers in Osteoarthritis

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Abstract

Osteoarthritis (OA) can be a progressive disabling disease, which results from the pathological imbalance of degradative and reparative processes, with concomitant inflammatory changes. The synovium, bone, and cartilage are each well established sites involved in the pathophysiological mechanisms that lead to progressive joint degeneration. The search for disease-modifying osteoarthritis drugs, DMOADs, has been hampered by several factors, including the variable progression of disease, the lack of specificity and sensitivity of standard radiography, and the fact that the slowing of radiographic progression may not result in corresponding improvement in pain and function. As a result, there is general agreement that development of DMOADs will be facilitated by advances in imaging and the validation of chemical biomarkers. Such biomarkers should be useful tools that will identify patients at risk for disease progression and predict responses to candidate structure-modifying drugs.

Osteoarthritis (OA) can be a progressive disabling disease, leading to diminished quality of life and, for over 500,000 individuals annually in the United States, total joint replacement. It is estimated that over 20 million people in the United States are affected by OA. In the elderly, the impact on disability attributable just to knee OA is similar to that of cardiovascular disease.

The etiology of OA varies among individuals, with possible roles for systemic factors, such as genetics and obesity, as well as for local biomechanical factors, such as muscle weakness, joint laxity, and traumatic injury. Joint deterioration occurs over extended periods of time, and the diverse molecular mechanisms that mediate pathogenic events of early, mid, and late disease are not yet fully understood. In OA, the synovium, bone, and cartilage are each well established as sites that can be involved in the pathophysiological mechanisms that can lead to progressive joint degeneration.

Various disease-modifying treatments have been studied for OA, and, to date, no drugs have achieved US Food and Drug Administration (FDA) approval as disease-modifying osteoarthritis drugs (DMOADs). At present, the development of DMOADs requires demonstration of slowing of radiographic joint space narrowing (JSN) that is “clinically meaningful”—that is, will be associated with improvement in symptoms or function. Given the slow rate of progression of JSN in many patients, the lack of specificity and sensitivity of standard radiography, and the fact that a candidate DMOAD may slow JSN but not improve symptoms, DMOAD development has been a very difficult task for industry. Before significant progress can be made, key elements along the pathway to DMOAD development will need to be addressed. First, disease mechanisms of OA will need to be better understood in order to identify the best targets for preclinical and clinical trials. The heterogeneous etiology of OA and the pathophysiological events that may be stage-specific, and perhaps site-specific, can delay our advancement toward this information. Second, patients have variable progression of disease, so we need a better understanding of who will progress over time and whether they have distinguishing features based on clinical, radiological, or laboratory assessments. Finally, once potentially disease-modifying treatments are available, determining the efficacy of intervention will be important.

It is widely agreed that the validation of improved imaging and chemical biomarkers will facilitate the process of DMOAD development. In particular, biomarkers that
Pathogenic Mechanisms in OA

In OA, the entire joint structure is affected. The cartilage, synovium, and bone can all be major sites for production of cytokines, growth factors, chemokines, and mediators classically associated with inflammation, which eventually promote progressive joint destruction. These catabolic molecules, in each of the joint compartments, can be considered targets for disease modification. Most interest in DMOAD development has focused on molecular events within articular cartilage (Fig. 1). These include not only the production of metalloproteinases, collagenases, and aggrecanases that lead to cartilage breakdown in chondrocytes, but also the production of cytokines, such as interleukin-1 (IL-1), tumor necrosis factor (TNF), IL-6, IL-8, and nitric oxide (NO). These act on other chondrocytes to cause this catabolic state, creating a positive amplification loop leading to more protease production. Eventually, many of these cells, via NO and other oxygen species production, undergo apoptosis and die.

The synovial compartment is also regarded as important in OA. Some patients undergo acute episodes of synovitis, and at surgery and arthroscopy one can find synovial proliferation and inflammatory changes. Activated synovium can release proteases and cytokines that may accelerate deterioration of adjacent cartilage lesions. Synovitis in end-stage OA can even resemble the pannus seen in RA, with neoangiogenesis, fibroblasts, and macrophage infiltration seen on pathology.

The role of bone in OA is least well understood but is an area of great interest and investigation. Subchondral bone remodeling is increased early in the course of the disease, especially in areas that underlie damaged cartilage. Biomechanical and biochemical factors seem to influence the remodeling process, but the underlying pathogenesis is not yet identified. Osteophyte formation, also an early feature of OA, appears to result from local production of anabolic factors such as transforming growth factor beta (TGF-β) and insulin-like growth factor (IGF-1). The increase in bone turnover can be measured by biomarkers such as urinary N-terminal crosslinking telopeptide of type I collagen (NTx) which is a marker of bone resorption.

Imaging as a “Biomarker”

The many measurable outcomes in OA include pain, function, synovitis, and serum and urine biomarkers or imaging biomarkers. Currently, radiographic outcomes are used to establish diagnosis and follow structural progression of the disease. While current radiographic techniques (x-rays) are useful for the diagnosis of established disease, they have shortcomings with respect to the assessment of progressive disease. For example x-ray images are insensitive to early change within cartilage and bone and do not report synovial pathology. They also lack correlation with severity of symptoms and are nonspecific measures of disease progression. There has been significant debate regarding the best technique to track progression of OA on plain radiographs, although now the gold standard is semiflexed, fluoroscopic positioning. Moreover, radiographic measures of joint space width (JSW) report not only decreased volume of articular cartilage, but also meniscal cartilage lesions and meniscal extrusion. Techniques for the quantitative and functional assessment of cartilage, synovium, and bone by MRI are advancing, making it likely that MRI will eventually replace conventional radiology as a more sensitive and specific measure of disease progression. Work done by Davidelson and coworkers has demonstrated that subchondral bone marrow edema is a potent risk factor predicting structural joint deterioration in knee OA. Positive uptake on bone scintigraphy, as shown by Dieppe and colleagues, may also predict patients at risk for disease progression, as defined by requirement for total joint replacement. Most recently, functional MRI studies (dGEMRIC, NaMRI, or T1ro), which detect biochemical changes of extracellular matrix proteins in cartilage, have attracted great interest as “proof of mechanism” biomarkers that might demonstrate in short term (i.e., 4-6 weeks) that a treatment restores normal chondrocyte metabolism.

Biochemical Markers

It is also likely that biochemical markers will be used in conjunction with imaging in order to establish stage of disease, predict progression, and assess improvement in
the setting of clinical trials. The Osteoarthritis Biomarkers Network, a consortium of five NIH designated sites, has recently proposed a classification scheme of biomarkers for OA.\textsuperscript{11} Five categories of biomarkers are proposed to aid in the study of all aspects of OA, from basic science research to clinical trials. The acronym BIPED represents the five categories: Burden of disease, Investigative, Prognostic, Efficacy of intervention, and Diagnostic (Table 1). The current classification of OA severity is the Kellgren-Lawrence grade of the radiograph, but, as previously discussed, this will likely be replaced by more sensitive and specific modalities. Burden of disease markers denote severity or extent of disease in one or multiple joints. Some examples that are elevated in populations of patients with hip or knee OA include serum cartilage oligomeric matrix protein (COMP), urinary C-terminal cross-linking telopeptide of type II collagen (CTX-II), and serum hyaluronan.\textsuperscript{11} Prognostic markers also include serum COMP, urinary CTX-II, and serum hyaluronic acid.\textsuperscript{12,13} In 2002, Garnero et al measured markers of Type II collagen synthesis and degradation: N-propeptide of type IIA procollagen (PIIANP) and urine CTX-II, respectively, and correlated them to findings on radiographs and arthroscopy. They found that patients with low serum levels of PIIANP and high urine levels of CTX-II (thus those who had an uncoupling between collagen synthesis and degradation) had relative risks of progression of 2.9 by radiography and 9.3 by arthroscopy.\textsuperscript{14} Elevated levels of CTX-II have also been found to predict progression of JSN in hip OA.\textsuperscript{15} Garnero and coworkers recently demonstrated that bone marrow abnormalities on MRI significantly correlated to urine CTX-II and that patients with highest baseline urinary CTX-II levels were more likely to have worsening bone marrow abnormalities at 3 months.\textsuperscript{16} A caveat to keep in mind when studying urine and serum biomarkers is that they may be affected by age, gender, race, and physical activity. Urinary CTX-II increases after menopause, consistent with the acceleration of OA in postmenopausal women and raising an intriguing question about the protective effect of estrogens in OA.

**Clinical “Markers” of Disease Progression**

Clinical endpoints can also serve as markers of disease progression. For example, synovitis has been shown to track with knee OA progression. Dougados and colleagues performed arthroscopies in patients with knee pain and K-L grades 2 to 3; 50% of patients were found to have localized synovial proliferation.\textsuperscript{7} At 1 year fol-

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**Table 1** Summary of “BIPED” Biomarker Classification for Osteoarthritis (OA)*

<table>
<thead>
<tr>
<th>Definition</th>
<th>Burden of Disease</th>
<th>Investigative</th>
<th>Prognostic</th>
<th>Efficacy of Intervention</th>
<th>Diagnostic</th>
</tr>
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<tbody>
<tr>
<td>Biomarker</td>
<td>Biomarker not yet meeting criteria for another category of OA</td>
<td>Biomarker not yet meeting criteria for another category of OA</td>
<td>Predicts onset or progression</td>
<td>Indicative or predictive of treatment efficacy</td>
<td>Differentiates diseased from nondiseased</td>
</tr>
<tr>
<td>Type of Biomarker Subjects</td>
<td>Variant only</td>
<td>Variant or invariant</td>
<td>Variant or invariant</td>
<td>Variant or invariant</td>
<td>Variant or invariant</td>
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<tr>
<td>Design</td>
<td>Cross-sectional, case-control</td>
<td>NA</td>
<td>NA</td>
<td>Controlled trial</td>
<td>Cross-sectional or case-control</td>
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<tr>
<td>Outcomes</td>
<td>Extent or severity of OA</td>
<td>NA</td>
<td>NA</td>
<td>New or worsening OA</td>
<td>New or worsening OA</td>
</tr>
<tr>
<td>Analysis</td>
<td>Sensitivity, specificity, likelihood ratio, AUC</td>
<td>NA</td>
<td>NA</td>
<td>Risk or odds ratio with 95% CI</td>
<td>Risk or odds ratio with 95% CI among treated</td>
</tr>
<tr>
<td>Criteria</td>
<td>Significant association between marker and extent or severity of OA</td>
<td>NA</td>
<td>NA</td>
<td>Significant association between marker and onset or progression of OA</td>
<td>Significant association between marker and OA diagnosis</td>
</tr>
</tbody>
</table>

* AUC indicates area under the curve; NA, not applicable.

The validation of reliable surrogate biomarkers may facilitate the development of structure-modifying drugs.

Traditional, often nonmodifiable, risk factors such as age, gender, body mass index (BMI), injury, and genetic influences can also be considered predictors of disease progression. First degree relatives of patients with generalized OA have a two-fold risk of developing the disease compared to the general population. Investigations into the IL-1 gene cluster, by extended haplotype analysis and linkage disequilibrium analysis, demonstrated a common haplotype in the IL-1A–IL-1B–IL-1RN gene complex that confers a four-fold higher risk of OA in these individuals.17

Use of Biomarkers in Drug Development

Currently, regulatory agencies such as the FDA in the United States and the European Medicines Agency in Europe have created guidelines for the development and approval of structure-modifying OA drugs by industry. The drug must be shown to slow joint space narrowing by a “clinically relevant” amount at 1 year. Unfortunately, a candidate DMOAD that does not have intrinsic analgesic properties (e.g., a metalloproteinase inhibitor) may slow radiographic progression at 1 year but not show symptomatic benefit over that time frame. Evidence of clinical efficacy, such as fewer joint replacements and less disability, could require a longer time to show clinical benefit. Therefore, interest is great in finding markers (either in the blood or by imaging), the improvement of which in the short-term would predict both structural and ultimately clinical benefit to the patient (Fig. 2). Biomarkers should function to shorten the course of such a clinical development program and reduce its expense. In the future, in addition, predictive biomarkers will guide the selection of patients who are likely to progress, thereby reducing the number needed to treat and strengthening the power of the DMOAD study. Thus, given the obstacles to DMOAD development there is great anticipation that the validation of new imaging and chemical biomarkers, particularly those that are prognostic or act as surrogate markers indicating efficacy of response, will facilitate the development of future DMOAD treatments.

References