cohort study of patients with symptomatic hip OA to determine the relevant change in JSW (in mm) at the narrowest point needed to define radiological progression of hip OA[8,9]. The first analysis determined the relevant change based on the predictive validity for a subsequent decision to perform total hip arthroplasty, while the second analysis relied on consensus agreement by 2 experts about a clinically relevant change. In the first analysis, an absolute decrease in JSW ≥ 0.4 mm over 2 years had a sensitivity of 68% for a subsequent decision to perform hip arthroplasty and positive and negative predictive values of 50% and 80.5%, respectively[8]. In the second analysis, the best threshold was determined to be an absolute decrease in JSW ≥ 0.4 mm over 3 years, based on a sensitivity of 75% for patients with clinically relevant deterioration and a specificity of 75% for patients without clinically relevant deterioration[9]. Previous work by this group showed that the smallest detectable difference in JSW at the narrowest point, using the method of Bland and Altman, was 0.6 mm[10]. Hence, the recommended clinically relevant reduction in JSW appears to fall within the error of measurement of JSW. The implications for use of reduction in JSW as a surrogate outcome in clinical trials requires further discussion, particularly with regulatory agencies[11].

Finally, there is high interest in the development and validation of biomarkers for the identification of individuals at greater risk for progressive OA. In 2001, the Group for the Respect of Ethics and Excellence in Science published recommendations for use of biochemical markers in studies of OA[12]. Preliminary data from a small sample of patients with hip OA, based on analysis of paired radiographs obtained at a one-year interval and urine samples collected at the time of the second radiograph, suggest that patients with rapidly progressive hip OA have higher mean urinary concentrations of C-telopeptide of type II collagen (CTX-II) than those with slowly progressive hip OA. A direct relationship was noted between log transformed levels of urinary CTX-II and minimum JSW[13]. A recent post-hoc analysis of data from the ECHODIAH study showed that high baseline levels of urinary CTX-II and of serum hyaluronic acid were associated with a higher risk of radiographic progression in patients with hip OA[14].

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WHO GETS OSTEOARTHRITIS AND WHY? AN UPDATE

Eric L. Radin

What has happened since our presentation, "Who Gets Osteoarthritis and Why?", 2 years ago[1]? Are we heading for a cure?

A few recent articles shed some hope. Recent epidemiologic studies show a pattern of heightened incidence of OA in specific joints, in Beijing Chinese in comparison with Caucasians, associated with differences between the 2 groups with respect to mechanics of activities of daily living. Coupled with genomic investigation, the work recommends a genetic joint-by-joint approach, looking for OA susceptibility in genes that control movement[2]. In addition, this research team has found that the effect of body weight on the progression of knee OA is dependent on limb alignment[3].

The search for biomarkers of OA, telltale cartilage or bone molecules, seems to be dying out. Radiologic progres-

sion is still considered the most reliable marker[4], even though reproducibility remains a problem[5].

Mechanically induced death of chondrocytes in OA has rekindled speculation that senescence of chondrocytes limits cartilage repair in the older patient and could be a potentiating factor in the pressurized destruction of articular cartilage[6].

The past decade or more has seen a well-funded genetic "fishing expedition," sparked by the description of a rare inherited type II collagen defect that causes chondrodysplasia quite distinct from OA usually seen clinically[7]. A report from Australia suggests that OA is associated with genes that control bone mass, muscle strength, knee pain, and medial tibial bone area, but not cartilage volume[8]. It suggests that genetic predilection to OA may be musculoskeletal, involving anatomy, limb alignment, and/or motor control.

The original report associating bone mass and OA appeared in 1979[9]. Since then, most articles on this subject suggest that osteoporosis spares OA, but there have been reports that this is not always so. The explanation for this apparent discrepancy is that radiographic studies cannot distinguish between osteoporosis and osteomalacia, and women with late-life osteomalacia can develop OA[10].

Investigations of the relationship between load and articular cartilage metabolism continue. For example, it was shown that mechanically-induced gene transcription can be quantified[11], that sheer stress can modulate nitrous oxide release by chondrocytes[12], and that denaturation of type II collagen by cyclic loading is mechanically, and not enzymatically, induced[13]. Further, confirmation was obtained that the rate of impact loading affects changes in cartilage and underlying bone in rabbits[14].

Despite continued focus on articular cartilage as the keystone of OA pathophysiology, some papers have examined the role of bone[15]. There is confirmation that subchondral bone is stiffened in OA and that, because of its effect on the strain in the adjacent subchondral bone, this creates trabecular microfractures and a self-perpetuating radial stiffening of the subchondral bone[16]. In another study, magnetic resonance imaging was used to confirm a relationship between subchondral bone and articular cartilage structure in patients with varying degrees of OA severity[17].

Conclusion

In a recent review course for residents in orthopedic surgery given by internationally known experts, the residents were told that there was yet no good understanding of OA, that OA had multiple causes, and that no one had any idea of why some people who do hard work never get OA while some sedentary individuals do — and that, once cartilage is injured, the damage progresses. That's exactly what I was taught 50 years ago. I point out that the intervening literature contains a clear, workable definition of OA; that the continued focus in OA on cartilage and its cells to the exclusion of the rest of the joint is myopic; and that it isn't what you do to your joints but how you do it that provokes them to "wear out." Rather than understanding that inflammation in OA is secondary to joint debris, most OA research remains focused on inflammatory pathways, albeit at high power. Rather than looking at the genetics of motor control, bone density, and other deviations of the skeleton and joints, our focus has been on the categorization of genes in the widest variety of OA patients. When, in 1966, I began to try to understand the relationship between the various causes of OA, the field was going around in concentric circles. Sokoloff, in 1969[18], in a brilliant monograph, established that OA was not a process of senescence. Today, very competent scientists interested in OA still study the aging of articular cartilage and its cells. The reason there has been so little progress is that the OA research is still going around in circles.

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MESENCHYMAL STEM CELL DYSREGULATION IN HEREDITARY OSTEOARTHRITIS

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The availability of families with precocious hereditary OA provides a unique opportunity to characterize altered mechanisms involved in pathways related to articular cartilage degeneration and to define the effect on these pathways of mutations in matrix components (namely, COL2A1). The Arg^{519}-Cys mutation in COL2A1 has been well characterized in humans[1-3] and is known to result in severe precocious generalized OA. Preliminary data in our laboratory demonstrate a defect in the differentiation of mesenchymal stem cells (MSC) into chondrocytes in these individuals. Studies of this phenomenon may provide insight into the pathogenesis of inherited degenerative disorders.

Our laboratory first described precocious hereditary OA in a Michigan family[4]. Subsequently, this familial autosomal dominant condition was found to be genetically linked to COL2A1[5] and the specific point mutation was identified[6]. Numerous investigations in our laboratory have described the Arg^{519}-Cys mutation in COL2A1.

There is evidence to suggest that MSC numbers, proliferation rate, population-doubling potential, and predisposition to differentiate along various cell lineages may be altered in OA[7-10]. Additional data suggest that severely osteoarthritic individuals[9] have MSC that differ from those of normal individuals with respect to their growth response to cytokines and their bone-forming potential in response to osteogenic stimuli. This suggests the possibility that changes thought to manifest themselves primarily at the site of the injury, i.e., articular cartilage, may have origins in cell populations not presently residing in the degenerating tissue. In studies of advanced OA by Murphy and colleagues[9], populations of MSC from OA patients were compared with those from controls with respect to yield, proliferation, and capacity for differentiation. Results demonstrated that the proliferative capacity of MSC derived from patients with OA was significantly reduced. In a more recent study, Alsalameh and coworkers[11] demonstrated that the numbers of multipotential mesenchymal progenitor cells present in adult human articular cartilage were increased in cartilage from osteoarthritic joints.

In a preliminary investigation, we employed bone marrow-derived MSC to study *in vitro* chondrogenesis in patients with the COL2A2 mutation. These initial experiments were designed to investigate the ability of such MSC to proliferate, differentiate into chondrocyte-containing pellets[12], and express and synthesize mutated type II collagen. Our goal was to develop a method for isolation and purification of heterotrimers of mutated and wild-type type II collagen molecules as a means of investigating altered synthetic mechanisms associated with the Arg^{519}-Cys defect.

In these analyses, MSC were derived from bone marrow obtained at the time of hip replacement surgery. Both mutated and non-mutated pellets synthesized type I collagen. The absence of reducible material suggested type III collagen was not present. Western blot analysis of the material, using antibody against type II collagen (C4F6), showed the presence of type II collagen in the non-mutated, but not in the mutated, samples. It was noteworthy that the pellets derived from patients with the mutation were uniformly smaller than their wild-type counterparts: 15 of 15 mutant pellets were < 1 mm and 15 of 15 wild-type pellets were > 1 mm after 14 days' growth. Attempts to direct Arg^{519}-Cys-related pellets into the chondrogenic pathway by addition of fibroblast growth factor (FGF) to primary cultures and of bone morphogenetic protein-2 to pellets did not result in evidence of type II collagen synthesis.

Studies of Perichondrial Mesenchyme (Ring of La Croix) in Relation to Pathophysiology of OA

In a collaborative study with Robinson, *et al*[13] at Tel Aviv University, it was demonstrated that MSC from the perichondrial mesenchyme (ring of La Croix) selectively migrated to the physeal region of the growth plate when implanted either in the ring of La Croix or in the synovial space[13].

In further studies related to the perichondrial mesenchyme, we assessed stem cell and growth factor responses in relationship to osteophyte formation in the rabbit partial meniscectomy model of OA[14]. Specimens from knees of rabbits that were developing OA after partial medial meniscectomy were stained with anti-fibroblast growth factor-receptor 3 (FGF-R3) antibodies. An increase in FGF-R3 receptor was observed at the site of osteophyte formation at the confluence of the perichondrial, periosteal, and synovial attachment corresponding to the ring of La Croix at the medial tibial plateau. In serial analyses, the concentration of FGF-R3 receptor diminished as osteophytes matured. These findings suggest a relationship of FGF to the formation of osteophytes in this experimental model of OA.