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Current opinion: where are we in our understanding and treatment of osteoarthritis?

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Summary

There has been important recent progress in our understanding of the molecular pathology of osteoarthritis (OA) and how it might be treated. New technologies have been developed and others refined to identify patients for recruitment in clinical trials who exhibit measurable progression. Combined with the ability to determine more effectively short-term efficacy of treatment, significant obstacles are being removed that have negated or led to the failure of earlier trials. The future for disease-modifying osteoarthritis drug (DMOAD) development and more effective pain control is therefore much more encouraging. But it is extremely important that these new therapeutic and clinical trial opportunities receive timely recognition and support from regulatory authorities. The importance and clearly demonstrated value of the coordination of clinical research and private/public initiatives, such as the OA Initiative and the European APPROACH project, and involvement of informed patients in research and policy decision making cannot be over emphasised.

Key words: *osteoarthritis; molecular pathology; joints; MRI; biomarkers; pain; clinical trials*

Introduction

Osteoarthritis (OA) frequently has no known cause. It is a debilitating condition that can affect almost any diarthrodial joint in the body. It commonly develops in joints such as the knee and hip, within the hand and in facet joints of the spine to mention but some sites. It is mainly a disease associated with ageing, probably developing over a period of 20 to 30 years before becoming symptomatic. It also presents with symptoms within 10 to 15 years following injury to a joint, such anterior cruciate ligament (ACL) damage and meniscal tears in the much studied knee. This is known as post-traumatic OA and is the type of experimental OA most commonly studied today, especially murine models, where the ability to manipulate gene expression and hence metabolism of specific tissues such as hyaline cartilage make them the animal of choice in research and drug development. Injury can immediately change joint biomechanics and with it change gene expression in joint tissues. This creates early degenerative changes that can be detected within a few weeks in experimental models, according to the species and surgery employed. Permanent changes in human knee metabolism can appear within a day or two, if not hours, and are reflected by alterations in levels in synovial fluid of molecular biomarkers of joint metabolism.

More common in women, it is the pain that generally results in OA detection, often accompanied by early focal articular cartilage pathology, now usually detected by MRI; this may progress to radiographic OA [1, 2]. In contrast, onset of such early focal degenerative changes during natural ageing in mice may be observed at or after 10 months according to the strain, whose lifetimes vary from 1.3 to 3 years.

OA is at least ten times more common than rheumatoid arthritis, affecting more than 10% to 12% of the population. Yet for years it was neglected by many researchers, being viewed more as a mystical black box of hidden pathology. The same was the case with osteoporosis until a major research effort, mainly in the USA, led to its successful treatment with a variety of very effective disease-modifying therapies. In great contrast, there is no disease-modifying osteoarthritis drug (DMOAD) available today. The main reason that osteoporosis is now treatable is that a precise technology was developed whereby bone mineral density could be measured accurately and the effectiveness of therapy in clinical trials could be determined. No such gold standard technique with which to accurately measure disease progression in clinical trials has thus far been approved for OA. Even today, radiological measurements, such as of joint space narrowing (an indirect measure of articular cartilage loss), continue to be mandated by regulatory agencies as a measure of joint degeneration in the conduct of clinical trials of potential new DMOADs. Such measures are fraught with inaccuracies [3] because of the lack of precision of radiological measurements of joint damage. This is in contrast to the ability to analyse pathology and its progression in soft tissues made possible by advances in magnetic resonance imaging (MRI).

Because of this reliance on inaccurate and insensitive radiology, clinical trials require many hundreds of patients over periods of at least 2 years. Moreover, during this period a large majority of patients (often 75–85%) usually exhibit little if any detectable evidence of disease progression

since cartilage loss (loss of joint space) and osteophytes are used as key radiological indicators of disease activity. Even use of MRI over a 3-year period in patients with radiological OA has revealed that only 25% of patients exhibit progression [2]. Since a majority of patients do not exhibit measurable progression within this time period (evidence indicates that OA is phasic) one cannot identify efficacy of treatment within cohorts even if it is there. Consequently, phase II and III OA trials are not only extremely expensive but are skewed to failure, enough to deter most companies from committing to developing new therapies at this point in time. Thus no DMOADs exist today although the needs are clearly identifiable. Recently, spurred on by these considerable demands, the research and regulatory communities have been working in a more collaborative way to identify new drug targets and to identify and develop new technologies to meet these needs. In future the regulatory process and the guidance it offers, which is developed in consultation with the research community, must offer timelier implementation of new advances in technology and our knowledge of OA to make it possible to conduct clinical trials that are hopefully more effective and less costly.

Pain control in OA also leaves much to be desired, especially since, until the early 2000s, so little research was being done on arthritis-related pain. When rofecoxib (Vioxx®) was introduced many patients felt significant symptomatic benefits. Yet when it was withdrawn as a result of cardiovascular side effects, patients were never consulted. In Canada, they (Consumer Advisory Council unpublished report, Canadian Arthritis Network [CAN]) expressed their desire to be allowed to make their own decisions as to whether they continue with this medication and live with the potential side effects; for them there was no other effective alternative joint pain relief available.

In pain research, as well as our understanding of joint pathology in OA, much new knowledge has been gained in recent years. As with osteoporosis, this has again resulted from a major increase in research of both a basic and clinical nature and, importantly, of a more integrated kind that we strove to develop in CAN, a Canadian government funded centre of excellence funded for 14 years. Fortunately, research has broadened from the focus on cartilage to one that looks at all joint and associated tissues. This has greatly benefited our understanding of OA.

In this paper space limitations permit us only to look mainly at some of the more recent highlights of all this research activity, focused mainly on knee OA or, experimentally, OA of the stifle joint. These findings will probably apply to other joints.

Overview of the osteoarthritic joint versus the healthy diarthrodial joint

OA is now known to involve pathological changes in most, if not all, tissues within the joint. In the knee this would also involve: synovial inflammation, especially in established and advanced disease; extensive subchondral bone remodelling occurring alongside articular cartilage degeneration, initially observed at the articular surface [4]; ligament and meniscal degeneration and extrusion of the latter; remodelling of entheses and proinflammatory changes in the infrapatellar fat pad, a repository of stem cells and generator of adipokines that influence cellular metabolism. Whether meniscal and cruciate ligament degeneration precede or accompany cartilage degeneration is still open to debate, but subchondral bone changes, such as the so-called bone marrow lesions (sites of focal inflammation), clearly often accompany focal degenerative changes in the adjacent overlying articular cartilage.

The earliest lesions seen in knee articular cartilages, with MRI, with arthroscopy or at autopsy, are generally focal in nature. Such early lesions in the absence of overt joint inflammation would best fit the concept of osteoarthrosis. Although they exhibit the molecular changes seen in OA [5], it is unclear whether such lesions enlarge in size and progress to overt OA. Nor do we know if such early lesions are reversible with appropriate treatments. Only careful longitudinal studies will clarify this. As OA becomes established and joint damage worsens, synovial and capsular inflammation develops, with accompanying effusions. The latter condition is best referred to as osteoarthritis (OA), where the suffix “itis” draws attention to the presence of inflammation. It is my personal belief, based on our studies of molecular and cellular changes in human articular cartilages, that most osteoarthrosic changes, which may be therapeutically reversible, will progress over time to overt irreversible osteoarthritis. The use of such terms to describe OA and possibly pre-OA provides a more realistic basis for staging joint degeneration. Inflammation is particularly a component of established and advanced OA, the latter often approaching the need for joint replacement.

In the absence of convincing evidence for the adaptive/auto-immunity that is a fundamental component of the pathology of rheumatoid arthritis, inflammation in OA is considered to be driven in part by innate immunity. This, combined with biomechanical alterations within the joint influencing how chondrocytes respond to their environment, serves to create much of the pathology. There is active generation of proinflammatory and destructive cytokines such as tumour necrosis factor-alpha (TNFα), interleukin-1beta (IL-1β) and interleukin-17 (IL-17), adipokines, complement activation and other inflammatory mediators [6]. Such immunity involves both activated type A synovial cells (macrophage lineage) and infiltrating activated macrophages. Chondrocytes are also involved, and the perceived activation of chondrocytes by such synovium-/capsule-derived “exogenous” cytokines, which occurs in rheumatoid arthritis, has been much studied *in vitro* yet not convincingly demonstrated *in vivo* in OA to my knowledge. Activated macrophages probably account for most of this inflammation in OA [7].

The articular cartilages, together with the synovial fluid, normally create an almost frictionless articulation [8]. Without their presence joint function would be lost. Therefore, research continues on preserving these cartilages by identifying the reason for the destruction of the extensive extracellular matrix of cartilage so that it can be arrested.

Joint pathology and potential clinical targets

Maintaining structural integrity

Articular cartilage

Maintaining the integrity of articular cartilage and its ability to function is an essential component in preserving joint function. Some critics have tended to dismiss the continuing emphasis on articular cartilage. That cartilage loss may be driven by changes in other tissues, particularly early changes that result in alterations in the compressive and shear forces to which cartilage is subjected, is indisputable. I personally view the subchondral bone changes as being mainly driven by responses to early changes in biomechanical loading resulting from degeneration of the overlying articular cartilages. In some cases, bone changes may precede cartilage pathology and cause the onset of changes in the overlying cartilages [9]. The much researched opinion that patients with osteoporosis often fail to exhibit OA [10] may, if some consensus is finally reached, provide insight into whether bone has a primary role in the pathogenesis of OA.

Yet if we are unable to identify and arrest the mechanisms that drive cartilage resorption, I feel that we shall be unable to adequately control joint degeneration in view of the critical importance of this tissue in joint function. In more advanced knee OA synovial inflammation is probably the main contributory factor to disease progression, generating proinflammatory cytokines that negatively impact cartilage and directly or indirectly influence bone metabolism and other joint tissues.

With ageing, and as the risk of OA grows, there is emerging evidence for a loss of mechanisms that ordinarily keep articular cartilages healthy. The evidence has come mainly from studies of murine, bovine and, most importantly, human tissues. Here the transforming growth factor-beta (TGF-β) superfamily plays a crucial role. Its protective effects are lost in age and its signalling mechanisms change with the involvement of other chondrocyte receptors. The Smad2/3 pathway decreases with age and these changes favour expression of the degradative collagenase MMP-13 [11]. Human OA genotyping has also revealed that a short nucleotide polymorphism (SNP) in Smad3 is significantly associated with joint space narrowing and the degree of joint degeneration [12].

Cartilage degeneration involves progressive depletion of the extensive extracellular matrix of articular cartilage. *In vivo*, wherever we observe proteoglycan depletion (such as loss of aggrecan staining by safranin O) we also see excessive cleavage and denaturation of type II collagen, even in the earliest pathology [4, 5]. The increased IL-1β and TNα expression by chondrocytes, as well as of other cells such as synovial and capsular, results in an overproduction by chondrocytes of fibrillar collagen degrading collagenases [13], especially matrix metalloproteinase (MMP)-13 [14], and proteoglycan-digesting MMPs and ADAMTS-5 (A Disintegrin And Metalloproteinase with ThromboSpondin motifs) [15] leading to the loss of cartilage matrix, originally produced by the same chondrocytes. The excessive proteolysis of the fibrillar collagen component of the matrix is closely associated with hypertrophic differentiation of chondrocytes [16], something that we normally only observe in endochondral bone formation in the growth plates of bones [17] and in fracture callous. But unlike in OA, here it is carefully controlled and physiological. Chondrocyte hypertrophy is commonly observed in early OA cartilages where it is an uncontrolled pro-degradative phenotype that results in cell death by apoptosis and with it a loss of cellularity [18] and any capacity for repair as cartilage is avascular.

Apoptosis also results from a lack of autophagy in adult tissues, including cartilage. Autophagy, a natural cell survival mechanism, is regulated by mechanistic target of rapamycin (mTOR) signalling. Over expression of mTOR in articular cartilages, which occurs in human and experimental OA, is associated with increased chondrocyte cell death by apoptosis. Cartilage-specific ablation of mTOR results in significant protection from experimental OA [19]. As articular cartilage ages, so autophagy decreases followed by the onset of chondrocyte apoptosis, cartilage degeneration and structural loss [20]. Autophagy is defective in type 2 diabetes, a risk factor for OA. Insulin, which is elevated in this condition, downregulates autophagy in chondrocytes resulting in increased matrix degradation and MMP-13 and IL-1β expression [21]. These and other studies reveal the critical importance of autophagy in maintaining cartilage health as cartilage ages.

In research the unexpected observation can offer new insights. That cartilage-specific ablation of nuclear factor of activated T cells (Nfatc1) in Nfatc2$^{-/-}$ mice leads to early onset of OA in multiple joints is an intriguing discovery, especially so since in human OA lesions NFATC1 expression is down-regulated compared with normal [22]. These observations point to these molecules as natural suppressors of OA, an improved understanding of which offers a therapeutic opportunity.

The accumulation of lipids in chondrocytes and its relevance to pathology has been hardly studied. It is now known that Hedgehog (Hh) signalling regulates genes that govern cholesterol homeostasis and influence cholesterol metabolism in chondrocytes [23]. Experimental activation of Hh causes elevated Gli-mediated transcriptional activation involving accumulation of intracellular cholesterol with OA onset and increased severity. The fact that a reduction in Hh signalling reverses cholesterol accumulation and that statin treatment attenuates cartilage degeneration offers potential therapeutic insights [23]. Experimental studies have also shown that dietary fatty acid content can influence onset and mitigate OA severity [24]. Such studies are now being actively pursued.

The importance of the canonical Wnt/β-catenin pathway in chondrocyte-mediated cartilage degeneration, as well as in cartilage and bone development, is well established. Therefore the observation that overexpression of DKK1, an antagonist of this pathway, can inhibit experimental OA was important [25]. Since growth differentiation factor 5 (GDF5) C genotype and CC allele are protective against OA development [26], it is noteworthy that GDF5 can induce DKK1, as well as another Wnt pathway antagonist FRZB, and that DKK1 is capable of suppressing the expression of the chondrocyte collagenase MMP-13 [27]. In

a screen of drugs approved by the US Food and Drug Administration (FDA) that induce FRZB expression and suppress Wnt/β-catenin signalling in human OA chondrocytes, verapamil was identified. It also enhances expression of aggrecan and type II collagen, key components of cartilage matrix, inhibits chondrocyte hypertrophy, and suppresses experimental OA [28].

Recent confirmation that the small molecule kartogenin, which can stimulate chondrogenesis, has the capacity to delay experimental OA [29] offers an alternative approach to therapy.

Synovium and synovial fluid

The principal lubricants present in synovial fluid are hyaluronic acid (HA) and lubricin, a mucin-like glycoprotein and proteoglycan also known as PRG4. Both are synthesised and secreted by synovial cells, cells encasing ligaments and meniscal cells, as well the superficial cells of articular cartilage. Lubricin is a boundary lubricant essential for joint function. Human and experimental genetic deficiencies result in elevated joint friction and accelerated cartilage damage involving chondrocyte apoptosis [30]. It binds to HA and fibrillar collagen [31] providing a very low coefficient of friction [32].

In vivo, long term expression of lubricin protects against age-related OA in mice and also in post-traumatic experimental OA, inhibiting the transcriptional programmes that promote cartilage catabolism and chondrocyte hypertrophy [33]. It also binds toll-like receptors 2 and 4, exhibiting an anti-inflammatory role [34]. Studies of mixtures of lubricin and HA have revealed that the boundary lubricating ability of these mixtures is dependent upon the concentration of high molecular weight HA and lubricin concentration. When lubricin is added to cross-linked HA, as a viscosupplement, friction is reduced; this is not seen with native HA [35]. These observations point to intra-articular therapeutic opportunities. As lubricin is susceptible to enzymatic degradation, mimetics are now being prepared [36].

Controlling joint pain

Joint pain was largely neglected for many years although, as we have already noted, it is the most common concern of patients and their main reason for seeking the help of a specialist. Its neglect was a sad sign of the lack of patient input in planning national research programmes that was corrected by CAN. Recently, it has received much more attention, especially the origins and nature of the pain, since more effective therapies are much needed. We must be able to treat both disease activity causing joint damage and control the attendant pain. We now know that early cartilage damage, subchondral bone marrow lesions, meniscal tears and body mass index (BMI) are all associated with pain symptoms [1, 37]; that ultrasound-detected knee effusions correlate with pain scores upon walking and stair climbing; that suprapatellar synovitis has the highest pain score on sitting and that meniscal protrusions are associated with pain on stair climbing [38]. In obese patients with OA (mainly women) a clear association was also noted between the severity of knee pain and inflammation of the infrapatellar fat pad [39].

The strong link between joint pain and inflammation in knee OA is demonstrated by treatments targeting TNFα. Systemic adalimumab over 12 weeks alleviated OA knee pain [40]. A single intraarticular injection of etanercept also reduced joint pain [41]. These observations highlight the role of TNFα: IL-6, TNFα and IL-17 all cause mechanical hyperalgesia, a feature of OA [42].

Damaged joint tissues, including articular cartilages, produce nerve growth factor (NGF) [43, 44]. In mice experiencing experimentally induced onset of stifle joint pain, upregulation of NGF and bradykinin receptors B1 and B2, as well as tachykinin and its receptor, occurs in articular cartilage [44]. Clinical trials show that a monoclonal antibody to NGF effectively treats OA pain in knees [45] and hips [46]. FDA-regulated trials that were halted due to adverse effects, requiring joint replacement [47], are now ongoing following reapproval.

The study of the genomics of OA joint pain is still in its infancy. Genes are being identified that relate to the pain [48]. It is important to study patients who are painless yet have advanced OA, such as in larger joints, often so damaged that the need for joint replacement is imminent. They may have a genetically determined greater ability to generate analgesic molecules. Why women ordinarily perceive pain more frequently and more severely than men [49] needs to be understood. Analyses of gene expression in synovia and capsules may be helpful in revealing gender differences and providing explanations. There are many such questions to be answered.

Early detection and assessment of disease activity, progression and responses to treatment

One of the major challenges that we face is early OA detection. Are those small focal lesions in articular cartilage that we see at autopsy [5] and with MRI [1, 2] early OA lesions? This needs to be established by longitudinal imaging. Early detection of OA is important since our experience with rheumatoid arthritis has indicated that, in general, the earlier and more aggressively you treat, such as with anti-TNF biologics, the more effective the result. The same is true for many chronic diseases. Although at present we have no DMOADs, they will come. So we need the requisite tools at the ready to enable the most effective use of DMOADS when they are available.

To promote the identification of existing technology and creation of new tools research partnerships involving academia and industry were created. With the all-important financing, solutions could then be sought for DMOAD development. This public/private consortium is called the OA Initiative [50]. Very detailed and comprehensive longitudinal studies were planned, based on three position papers (clinical, imaging and biomarkers), one of which, on molecular biomarkers, I was invited to create. Clinical analyses, imaging and biospecimen collection have been conducted over a 7-year period. Data analysis from this prospective study is examining knee OA onset and progression in 4800 patients. Monitoring involves 3 Tesla MRI, radiographic and DNA analyses and the analysis of molecular (biochemical) biomarkers in synovial fluid, serum

and urine. Funded and jointly managed by public/private interests, the initiative for this came from the National Institutes of Arthritis and Musculoskeletal and Skin Diseases / National Institutes of Health (NIH), in partnership with academia and industry.

More recently, the project has benefited from the involvement of the Foundation for NIH. This has driven such projects as an independent critical assessment of potential molecular biomarkers. The wealth of information generated by this clinical initiative, available for analysis by all investigators, has already resulted in creation of much invaluable new knowledge, especially in the field of molecular and imaging biomarkers. The initiative continues with continuing partnerships with the pharmaceutical and biotechnology industries which, with patients first and foremost, all stand to gain from this important and extremely productive international partnership. Some important findings emerging from this study will be described below. A similar private-public partnership was established in 2015 in Europe [51]. The APPROACH (Applied Public-Private Research enabling OsteoArthritis Clinical Headway) project aims to develop a set of guidelines that allow for the selection of patients to support clinical trials, with medication that is specifically designed for subsets of OA patients.

Promising new ways whereby early detection of OA is becoming possible include genetic and molecular biomarkers and joint imaging biomarkers. With MRI one can image articular cartilages, menisci, ligaments, synovia, fat pads and synovial fluid, all the tissues that we cannot image with routine radiology. With advances in instrumentation, use of dynamic contrast enhanced MRI, image capture and analysis, much improved interpretation has been achieved as to what images represent at the molecular level. Importantly, MRI can detect early joint tissue degeneration prior to structural change. Sodium based MRI is another example where early changes in joint tissues, such as cartilage, can be viewed and followed over time. This is because the abundant negatively charged glycosaminoglycan components of proteoglycans in cartilage matrix bind sodium. Thus, when these molecules are lost in OA, the sodium content diminishes and this can be detected [52]. But patient access to MRI must be much improved by substantially reducing cost barriers that can act as deterrents to its more common use in clinical trials and in the clinic.

Biomarkers of disease onset, activity and progression

Studies involving the extensive and fully accessible data set generated in the OA Initiative, as well as independent studies of other cohorts, are leading to new ways to identify patients who are likely to develop OA or have early OA, and who may exhibit disease progression in a clinical trial. Patients with early pre-radiographic OA and cartilage, meniscal and ligament degeneration can be identified and molecular biomarkers of disease activity can be developed and used to help set dosages of potential DMOADs in clinical trials and provide improved measures of pain.

Genetic biomarkers of patient heterogeneity and disease activity

Findings from a variety of studies are starting to provide a genetic basis for the heterogeneity of OA patient populations. Multiple genes appear to be involved in the development of OA. Mitochondrial haplotypes have revealed some of the most interesting findings. For example, of the many biomarkers of proteases and cartilage matrix molecules that were examined in haplotypes H and J, only serum collagenase MMP-13 exhibited an elevation over that of healthy controls. Type II collagen biomarkers were elevated only in patients with the H haplotype [53]. In a 4-year study of knee OA progression, haplotype T showed the least progression, measured as joint space narrowing and cartilage volume loss [54]. Patients belonging to the cluster TJ also exhibit less radiographic progression than seen in patients in the KU cluster. Those in the more common haplogroup H, where MMP-13 is elevated, are more likely to need total joint replacement than non-H patients [55]. This fits with the known close association of collagenase activity, especially MMP-13, with cartilage degeneration [14, 56].

These and other haplogroup differences may be caused by differences in the cellular use of glycolysis versus oxidative phosphorylation [57]. Most recently a combination of eight nucleotide polymorphisms showed promise in predicting knee OA progression [58]. These important observations provide not only important insights into new ways to predict OA progression, but also into how progression is determined and, therefore, how it can be prevented.

A potentially rich source of study for those working on the genetic determinants of OA are those patients in their 70s and older who have no significant joint pain. Many aging people never show any signs of OA, particularly evident at autopsy. By asking what genetic differences distinguish these individuals from those with OA of the same gender and age could be very revealing.

Molecular biomarkers of disease onset, inflammation, tissue involvement and progression

It is the serum and urine biomarkers of collagen turnover, be they biomarkers of cartilage or bone resorption, that so far provide the best opportunities to detect early onset of knee OA, as well as its progression. As a part of the OA Initiative (OAI), a guidance document for molecular/biochemical biomarker use in clinical trials was prepared for the FDA [3]. Twelve biomarkers with promise were identified. Together with other promising new candidates, they were then independently evaluated in a large number of knee OA patients from the OA Initiative. Results of the study of predictors of knee OA progression have just been released [59]. Of the 18 biomarkers examined, 2 baseline biomarkers of cartilage type II collagen degradation, urine CTXII and urine C2C-HUSA, each predicted subsequent pain worsening and joint space loss and their combination. Baseline biomarkers of type I collagen cleavage reflecting bone resorption, serum CTXI and NTXI, together with hyaluronan, a biomarker of joint synovial inflammation, also provided similar indications.

Another very recent study of a community-based cohort showed that analysis of baseline urine with C2C-HUSA™, an assay designed to detect a specific fragment of type II collagen generated in part by collagenase activity, can predict disease progression over 3 years and help identify early and late knee cartilage damage [2]. Increases in collagenase activity in such early [5] and late [14, 56] cartilage le-

sions were first observed when analysed at autopsy. An assay closely related to C2C-HUSA, which detects the same cleavage product(s), has been successfully used to monitor effective therapy with an inhibitor of the collagenase MMP-13 in an experimental dog model of OA [60].

These are important observations. They reveal the value of genetic biomarkers and markers of tissue-specific degradative events involving measurement of selective fragments of structural collagen molecules. They also identify the value of biomarkers of joint inflammation. Together they reveal the importance of these events in the pathology of knee OA and serve as an important research tool with which to study these events *in vivo* and in the recruitment of patients for clinical trials. The involvement of bone biomarkers highlights the earlier described remodelling of subchondral bone and osteophyte formation [61] that occur side-by-side with cartilage resorption, and indicates that these events are all fundamental components of the pathology.

Hyaluronan is a well-established and valued indicator of synovitis in arthritis. Its elevation in serum was first recognised in rheumatoid arthritis where synovitis is pronounced [62]. It is not specific for synovitis in that it is elevated in patients with liver cirrhosis [63] (it is naturally removed by the liver endothelial cells), general inflammation and sepsis [64]. Thus it is important to rule out such comorbidities in OA patients. The involvement of synovial inflammation in the pathogenesis of knee OA is indicated particularly in advanced knee disease [65] but also in hand OA [66]. In the latter case the number of joints involved, or burden of OA, correlate with serum levels. A recent study of hyaluronan also showed its value in predicting knee OA progression [67].

That joint inflammation in OA involves the influx of activated macrophages into the synovium and underlying joint capsule is revealed by a study of their analysis in joints and the release into plasma of the macrophage marker CD14, levels of which are associated with joint effusions, self-reported knee pain and joint space narrowing [7].

MRI as a biomarker of early and advanced joint pathology

Significant advances are being made in instrumentation, image capture and interpretation of what images represent at the molecular level. The use of dynamic contrast-enhanced MRI, such as dGEMRIC, enables detection of early cartilage degeneration prior to detection of structural change [68] and joint inflammation [39]. Sodium-based MRI, with 3 Tesla imaging employing fluid attenuation by T1 weighting, can distinguish knee OA from healthy controls [69]. A combination of joint imaging and tissue analyses has revealed that T1ρ and T2 images both correlate with the degree of cartilage degeneration and proteoglycan glycosaminoglycan content [70]. MRI imaging of cartilage composition has clearly progressed [71]. These advances enable the detection and interpretation of pre-radiographic changes. But access to this technology for patients needs much improvement as the much increased costs of MRI act as a deterrent to its more common use, and improved detection and treatment of OA.

MRI is proving of value in identifying patients at risk of OA onset. Baseline T2 values of articular cartilages in patients without any radiographically detectable OA (Kellgren-Lawrence grade 0; KL0) are significantly higher, especially in the superficial layers, in patients subsequently developing radiological OA within a 4-year period [72]. These KL0 symptomatic patients exhibit early lesions involving cartilage damage (76%), closely associated subchondral bone marrow lesions (61%), the presence of meniscal tears (21%) and meniscal extrusions (14%) [37]. The three-dimensional bone shape of the knee, captured with MRI, can predict future OA onset [73]. Fat accumulation in quadriceps muscle observed with MRI correlates with knee joint space, suggesting a direct relationship of quadriceps function to joint mechanics and thus pathology [74].

The application of the various biomarkers described above to improved identification of OA and disease activity is summarised in table 1.

There is one area where care must be taken in interpreting MRI measurements of early increases in articular cartilage thickness following ACL damage, the so-called cartilage hypertrophy. This is thought by some to reflect a reparative response in human studies. Cartilage hypertrophy, as opposed to chondrocyte hypertrophy, was well documented, first by Bywaters in 1937 and subsequently confirmed in human studies and various animal models of OA, such as following ACL section in dogs and rabbits, and ACL damage in humans [75, 76]. Considerable evidence from experimental and human studies now indicates that this is, in fact, swelling of articular cartilage, especially the superficial zone, accompanied by an increase in water content. There is a consensus among experts in matrix biology and biomechanics that the swelling results from cleavage and denaturation of the extensive extracellular collagen fibrillar network, permitting increased hydration of the proteoglycan aggrecan as it imbibes water and swells: it is no longer fully restricted to partial hydration by the fibrillar network. Such observations continue to be made, often by authors unaware of earlier work in this area. A recent MRI study of patients 2 to 3 years after surgery for ruptured ACL observed such an increase in thickness in reconstructed compared with control knees [77].

Conclusions

We have yet to witness the successful treatment of osteoarthritis, both in terms of disease modification and symptom relief. But considerable progress has been made in identifying new therapeutic targets, as well as the development of tools with which to conduct clinical trials in a manner that will favour success. These advances have been greatly helped by public/private partnerships such as the OA Initiative. With continuing proactive involvement of industry and a more timely involvement of regulatory agencies, the immediate future will hold much promise. OA is an extremely challenging nut to crack. But creation of an even stronger collaborative environment will favour more productive partnerships with industry and regulatory authorities as a new way forward is better defined and progressively improved.

Table 1: Summary of biomaker usage to detect and study osteoarthritis disease activity.

Biomarker	Indication	Reference
Genetic		
Mitochondrial haplotypes	Disease activity	53
	Structural progression	54, 55, 58
Molecular		
Type I (bone: CTXI, NTXI) and type II (cartilage: C2C-HUSA; CTXII) cleavage products in urine	Structural progression and pain outcomes	2, 59
Hyaluronan in serum	Synovitis	65, 66
	Structural progression	67
MRI		
dGEMRIC	Early degeneration prior to structural change	68
Sodium MRI	Early degeneration	69
T2 MRI	Prediction of radiographic OA onset	72
Three-dimensional bone shape	Prediction of OA onset	73

MRI = magnetic resonance imaging; OA = osteoarthritis

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