Review

Developments in the scientific understanding of osteoarthritis

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Abstract

Osteoarthritis is often a progressive and disabling disease, which occurs in the setting of a variety of risk factors - such as advancing age, obesity, and trauma - that conspire to incite a cascade of pathophysiologic events within joint tissues. An important emerging theme in osteoarthritis is a broadening of focus from a disease of cartilage to one of the 'whole joint'. The synovium, bone, and cartilage are each involved in pathologic processes that lead to progressive joint degeneration. Additional themes that have emerged over the past decade are novel mechanisms of cartilage degradation and repair, the relationship between biomechanics and biochemical pathways, the importance of inflammation, and the role played by genetics. In this review we summarize current scientific understanding of osteoarthritis and examine the pathobiologic mechanisms that contribute to progressive disease.

Introduction

Osteoarthritis (OA) is characterized by a progressive loss of articular cartilage accompanied by new bone formation and, often, synovial proliferation that may culminate in pain, loss of joint function, and disability. A variety of etiologic risk factors and pathophysiologic processes contribute to the progressive nature of the disease and serve as targets of behavioral and pharmacologic interventions. Risk factors such as age, sex, trauma, overuse, genetics, and obesity can each make contributions to the process of injury in different compartments of the joint. Such risk factors can serve as initiators that promote abnormal biochemical processes involving the cartilage, bone, and synovium, which over a period of years result in the characteristic features of OA: degradation of articular cartilage, osteophyte formation, subchondral sclerosis, meniscal degeneration, bone marrow lesions, and synovial proliferation.

Risk factors for osteoarthritis

Genetic predisposition

A genetic disposition to OA has been clear since it was first reported by Kellgren and coworkers [1] that generalized nodal OA was twice as likely to occur in first-degree relatives as in control individuals. Twin pair and family risk studies have indicated that there is a significantly higher concordance for OA between monozygotic twins than between dizygotic twins, and that the hereditable component of OA may be in the order of 50% to 65% [2]. However, because of the prevalence of OA in the general population and extensive clinical heterogeneity, the precise genetic contribution to the pathogenesis of OA has been difficult to analyze. Moreover, it is clear that multiple genetic factors can contribute to the incidence and severity of OA, and that these may differ according to specific joint (hand, hip, knee, or spine), sex, and race. There is also evidence, given the variety of candidate genes that predispose to OA, that there may be an additive effect of individual genes in the development of disease [3].

Several candidate genes encoding proteins of the extracellular matrix of the articular cartilage have been associated with early-onset OA [4]. In addition to point mutations in type II collagen [5], inherited forms of OA may be caused by mutations in several other genes that are expressed in cartilage, including those encoding types IV, V, and VI collagens, as well as cartilage oligomeric matrix protein (COMP) [6].

Candidate genes for OA have also been identified that are not structural proteins. Among such candidates are the secreted frizzled-related protein 3, asporin, and von Willebrand factor genes [7,8]. In follow-up studies it has been reported that the asporin, frizzled-related protein 3, and von Willebrand factor genes have now been found not to replicate in large Caucasian meta-analyses and that the association with growth differentiation factor (GDF)-5 in Caucasians has been confirmed in larger meta-analyses [9-12]. Finally, evidence from mouse models indicates that genetic disorders affecting the architecture of subchondral bone can cause OA. Mice with a null mutation of the latent

ADAMTS = a disintegrin and metalloprotease with thrombospondin motifs; CCR = C-C chemokine receptor; COMP = cartilage oligomeric matrix protein; COX = cyclo-oxygenase; CTX-II = carboxyl-terminal cross-linking telopeptide of type II collagen; ICE = IL-1β-converting enzyme; IL = interleukin; iNOS = inducible nitric oxide synthase; MMP = matrix metalloproteinase; MRI = magnetic resonance imaging; OA = osteoarthritis; RANTES = regulated on activation, normal T-cell expressed and secreted; TACE = TNF-α-converting enzyme; TGF = transforming growth factor; TNF = tumor necrosis factor.

transforming growth factor (TGF)-β binding protein-3, which regulates the activation of TGF-β, developed both osteosclerosis and OA [13]. In addition, a recent report demonstrated that a genetic defect of type I collagen resulted in rapidly progressive OA in a mouse model [14].

In recent population studies, genome-wide linkage scans have highlighted several specific genes involved in disease risk [15]. Chromosome 2q was positive in several scans, suggesting that this chromosome is likely to harbor one or more susceptibility genes. Two IL-1 genes (*IL1α* and *IL1β*) and the gene encoding IL-1 receptor antagonist (*IL1RN*), located on chromosome 2q13 within a 430-kilobase genomic fragment, have been shown to associate with the development of primary knee, but not hip, OA [16]. *IL1RN* haplotype variants have also been shown to associate with radiographic severity of the OA [17]. Recently, a genome-wide association scan has identified a cyclo-oxygenase (COX)-2 variant involved in risk for knee OA [18]. These genetic associations of genes such as *IL1α*, *IL1β*, *IL1RN*, and *COX2* underscore the potential role of inflammatory pathways in the pathogenesis of knee OA.

Age

Age is the risk factor most strongly correlated with OA, and therefore understanding age-related changes is essential. Age-related mechanical stress on joint cartilage may arise from a number of factors, including altered gait, muscle weakness, changes in proprioception, and changes in body weight. In addition, age-related morphologic changes in articular cartilage are most likely due to a decrease in chondrocytes' ability to maintain and repair the tissue. This is because chondrocytes themselves undergo age-related decreases in mitotic and synthetic activity, exhibit decreased responsiveness to anabolic growth factors, and synthesize smaller and less uniform large aggregating proteoglycans and fewer functional link proteins [19]. Age also appears to be an independent factor that predisposes articular chondrocytes to apoptosis, because the expression levels of specific pro-apoptotic genes (those encoding Fas, Fas ligand, caspase-8, and p53) are higher in aged cartilage [20,21].

Obesity

Obesity is another important risk factor for OA [22]. An increase in mechanical forces across weight-bearing joints is probably the primary factor leading to joint degeneration. The majority of obese patients exhibit varus knee deformities, which result in increased joint reactive forces in the medial compartment of the knee, thereby accelerating the degenerative process [23]. Emerging data implicate a crucial role for adipocytes in regulation of cells present in bone, cartilage, and other tissues of the joint. The comparatively recently discovered protein leptin may have important involvement in the onset and progression of OA, and increase our understanding of the link between obesity and OA [24]. In addition, adipocyte-derived factors such as IL-6 and C-reactive protein appear to be pro-catabolic for chondrocytes. Further work is needed to determine whether leptin or other adipokines are important systemic or local factors in the link between obesity and OA.

Joint malalignment

Whether joint malalignment leads to the development of OA is a matter of debate [25]. However, the evidence does indicate that varus or valgus deformities are markers of disease severity and are associated with risk for progression of knee OA [26]. Indeed, there is evidence to suggest that much of the effect of obesity on the severity of medial compartment knee OA can be explained by varus malalignment [27]. Hunter and colleagues [28] have reported that enlarging or new bone marrow lesions occurred mostly in malaligned limbs, on the side of the malalignment. With regard to mechanisms, altered joint geometry may interfere with nutrition of the cartilage, or it may alter load distribution, either of which may result in altered biochemical composition of the cartilage [29].

Sex

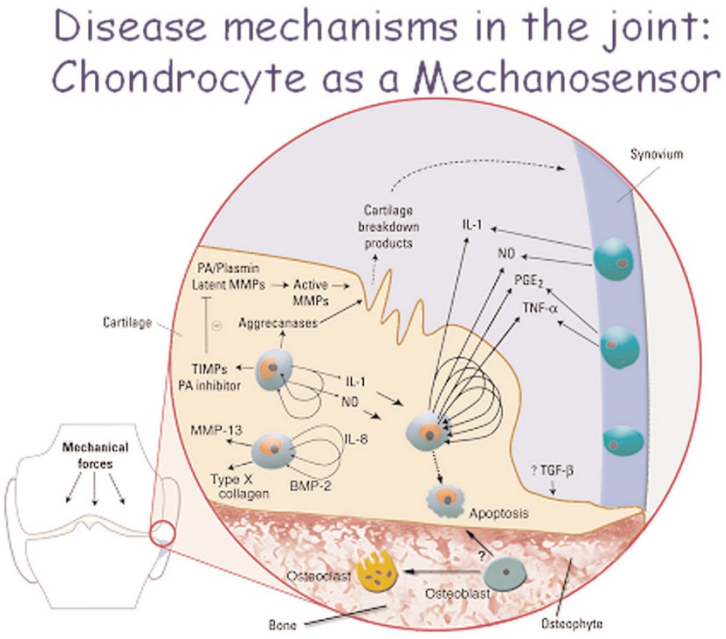
Although hip OA is slightly more common in men, there is a marked increase in prevalence among women after the age of 50 years, particularly in the knee, and the cause of this increase - which has been ascribed to estrogen insufficiency - is poorly understood [30]. Articular chondrocytes possess functional estrogen receptors, and there is evidence that estrogen can upregulate proteoglycan synthesis [31]. In support of a role for estrogens in OA, there are human and animal studies indicating that estrogen replacement therapy reduces the incidence of OA [32,33], although prospective randomized trials to confirm these observations, particularly with respect to structure modification, have not been performed. It should be noted, however, that the evidence for a relation between estrogen deficiency and OA in women is inconsistent, and one 4-year study showed no effect of estrogen plus progestin versus placebo on symptoms or disability in postmenopausal women [34].

The pathobiology of osteoarthritis

Biomechanics and loading: chondrocytes as mechano-sensors

Chondrocytes embedded within the negatively charged cartilaginous extracellular matrix are subjected to mechanical and osmotic stresses [35-37]. One of the most exciting emerging areas is that chondrocytes, like osteocytes in bone, serve as mechano-sensors and osmo-sensors, altering their metabolism in response to local physicochemical changes in the microenvironment. Therefore, while obesity and joint misalignment are risk factors for OA in specific joints, the mechanism by which these risk factors initiate and perpetuate OA is largely mediated by biochemical pathways. Several groups have identified osmo-sensors and mechano-sensors in chondrocytes in the form of several ion channels, sulfate transporters and integrins [35-37]. In response to mechanical

Figure 1



Molecular and cellular mechanisms that perpetuate osteoarthritis. BMP, bone morphogenetic protein; MMP, matrix metalloproteinase; NO, nitric oxide; PA, plasminogen activator; PG, prostaglandin; TGF, transforming growth factor; TIMP, tissue inhibitor of MMP; TNF, tumor necrosis factor. Adapted from Abramson and coworkers [79].

stress, changes in gene expression and an increase in production of inflammatory cytokines and matrix-degrading enzymes have been noted (Figure 1) [38]. The recognition that chondrocytes act as mechano-sensors and osmo-sensors has opened up the possibility that these proteins could serve as novel targets for disease-modifying OA drugs.

Degeneration of articular cartilage in osteoarthritis: cartilage degradation

OA is characterized by a loss of articular cartilage matrix, which is the result of the action of proteolytic enzymes that degrade both proteoglycans (aggrecanases) and collagen (collagenases). Native collagen has been shown to be cleaved by matrix metalloproteinase (MMP)-1, MMP-8, and MMP-13. Of the three major MMPs that degrade native collagen, MMP-13 may be the most important in OA because it preferentially degrades type II collagen [39] and it has also been shown that expression of MMP-13 greatly increases in OA [40]. Among the characteristic changes in OA cartilage is the development of the hypertrophic chondrocyte phenotype, characterized by increased production of MMP-13, type X collagen, and alkaline phosphatase. Kawaguchi [41] has provided evidence that the induction of the transcriptional activator Runx2 (runt-related transcription factor 2) under mechanical stress in turn induces the hypertrophic phenotype, which leads to type II collagen degradation (MMP-13 production), endochondral ossification, and chondrocyte apoptosis.

The aggrecanases belong to a family of extracellular proteases known as the ADAMTS (a disintegrin and metalloprotease with thrombospondin motifs) [39]. Two aggrecanases, ADAMTS-4 and ADAMTS-5, appear to be major enzymes in cartilage degradation in OA [40]. Recently, an ADAMTS-5 knock-out mouse and ADAMTS-5-resistant aggrecan knock-in mouse, both of which show protection from OA, have validated ADAMTS-5 as a target for OA [42,43].

IL-1 stimulates the synthesis and secretion of many degradative enzymes in cartilage, including latent collagenase, latent stromelysin, latent gelatinase, and tissue plasminogen activator [44]. The balance of active and latent enzymes is regulated by at least two enzyme inhibitors: tissue inhibitor of metalloproteinases and plasminogen activator inhibitor-1 [45]. These enzyme inhibitors are synthesized in increased amounts under the regulation of TGF-β.

Degeneration of articular cartilage in osteoarthritis: cartilage synthesis

The metabolic imbalance in OA includes both an increase in cartilage degradation and an insufficient reparative or anabolic response. The identification of anabolic agents that can be utilized to restore cartilage is an area of significant investigation. Molecules of interest include cartilage anabolic factors such as bone morphogenetic proteins, insulin-like growth factor-I, TGF-β, and fibroblast growth factors. Growth factors such as bone morphogenetic proteins have the ability

to reverse catabolic responses by IL-1 [46]. Conversely, normal chondrocytes exposed to IL-1 or chondrocytes from OA patients exhibit decreased responsiveness to growth factors [47]. An understanding of the interaction between catabolic cytokines and anabolic growth factors could lead to the identification of molecules that restore the responsiveness of diseased chondrocytes to anabolic growth factors or inhibitors of inflammatory cytokines.

Degeneration of articular cartilage in osteoarthritis: inflammation

The role played by inflammatory cytokines and mediators produced by joint tissues in the pathogenesis of OA is attracting increased attention. Among the many biochemical pathways that are activated within joint tissues during the course of OA are mediators classically associated with inflammation, notably IL-1β and tumor necrosis factor (TNF)-α. These cytokines, in an autocrine/paracrine manner, stimulate their own production and induce chondrocytes to produce proteases, chemokines, nitric oxide, and eicosanoids such as prostaglandins and leukotrienes. The action of these inflammatory mediators within cartilage is predominantly to drive catabolic pathways, inhibit matrix synthesis, and promote cellular apoptosis. Thus, although OA is not conventionally considered an inflammatory arthritis, that concept - based historically on the numbers of leukocytes in synovial fluid - should be reconsidered. Indeed, 'inflammatory' mediators perpetuate disease progression and therefore represent potential targets for disease modification.

Cytokines and chemokines

As noted above, a characteristic feature of established OA is increased production of pro-inflammatory cytokines, such as IL-1β and TNF-α, by articular chondrocytes. Both IL-1β and TNF-α exert comparable catabolic effects on chondrocyte metabolism, decreasing proteoglycan collagen synthesis and increasing aggrecan release via the induction of degradative proteases [48]. IL-1β and TNF-α also induce chondrocytes and synovial cells to produce other inflammatory mediators, such as IL-8, IL-6, nitric oxide, and prostaglandin E_2. The actions of both cytokines are in part mediated by activation of the transcription factor nuclear factor-κB, which further increases their own expression and that of other catabolic proteins such as inducible nitric oxide synthase (iNOS) and COX-2, thus creating an autocatalytic cascade that promotes self-destruction of articular cartilage [49].

IL-1β and TNF-α are both synthesized intracellularly as precursors, converted through proteolytic cleavage to their mature forms by caspases - membrane-bound IL-1β-converting enzyme (ICE) and TNF-α-converting enzyme (TACE) - and released extracellularly in their active forms. The expression of both ICE and TACE has been shown to be upregulated in OA cartilage [50]. Inhibitors of both ICE and TACE are of interest as future therapeutic small-molecule antagonists of downstream IL-1β and TNF-α expression, respectively; studies with an ICE inhibitor are now underway in two murine models.

Osteoarthritic cartilage is also the site of increased production of both C-X-C and C-C chemokines. These include IL-8, monocyte chemoattractant protein-1, and RANTES (regulated on activation, normal T-cell expressed and secreted; also known as C-C chemokine ligand-5), as well as the receptors C-C chemokine receptor (CCR)-2 and CCR-5 [51]. RANTES induces expression of its own receptor, CCR-5, which suggests an autocrine/paracrine pathway of the chemokine within the cartilage. Monocyte chemoattractant protein-1 and RANTES promote chondrocyte catabolic activities, including induction of nitric oxide synthase, increased MMP-3 expression, inhibition of proteoglycan synthesis, and enhancement of proteoglycan release.

Prostaglandins

Chondrocytes from human OA cartilage explants express COX-2 and spontaneously produce prostaglandin E_2 [52]. We have recently reported that prostaglandin E_2 produced by OA cartilage explants decreases proteoglycan synthesis and enhances the degradation of both aggrecan and type II collagen. These effects are associated with downregulation of MMP-1 and upregulation of MMP-13 and ADAMTS-5, and are mediated via engagement of the prostaglandin E receptor 4 (EP4) [53]. How the divergent synthesis of MMP-1 and MMP-13 is regulated remains unknown, but we previously reported that upregulation of the nuclear orphan receptor NURR1 (NR4A2) in OA cartilage causes similar divergent effects. This suggests that the effect of prostaglandin E_2 on MMP-1 and MMP-13 may be a result of NURR1 activation (NR4A2) [54]. In their interesting recent report of a genome-wide scan, Valdes and coworkers [18] identified a COX-2 variant that was associated with increased risk for knee OA - a finding that underscores the possible importance of this signaling pathway in the pathogenesis of knee OA.

Reactive oxygen species

Among the inflammatory mediators that are of interest in the pathogenesis of OA are both oxygen and nitrogen-derived free radicals. Reactive oxygen species such as superoxide anion, hydrogen peroxide, and hydroxyl radicals directly promote chondrocyte apoptosis, most probably via mitochondrial dysfunction [55,56].

Nitric oxide

Nitric oxide, produced by the inducible isoform of nitric oxide synthase (iNOS), is a major catabolic factor produced by chondrocytes in response to pro-inflammatory cytokines such as IL-1β and TNF-α [57]. Considerable evidence indicates that the overproduction of nitric oxide by chondrocytes plays a role in the perpetuation of cartilage destruction in OA. Although normal cartilage does not express iNOS or produce nitric oxide without stimulation by cytokines such as IL-1, OA cartilage explants spontaneously produce large amounts of nitric oxide [58].

Nitric oxide exerts multiple effects on chondrocytes that promote articular cartilage degradation [57]. These include

inhibition of collagen and proteoglycan synthesis; activation of metalloproteinases; increased susceptibility to injury by other oxidants (for example, hydrogen peroxide); and apoptosis. Several studies have implicated nitric oxide as an important mediator in chondrocyte apoptosis, a feature that is common in progressive OA. There is evidence that apoptosis results from the formation of peroxynitrite, a toxic free radical produced by the reaction of nitric oxide and superoxide anion [59].

Nitric oxide and its derivatives may also play protective roles, however, because protease activity and proteoglycan degradation are enhanced when nitric oxide production is blocked [60]. In murine models the development of surgically induced OA can be accelerated in mice that are knocked out for IL-1β, IL-1-converting enzyme, or iNOS. This suggests that a certain level of these molecules may be necessary to maintain a healthy joint and that complete pharmacologic suppression may be detrimental [61]. The protective roles played by nitric oxide in multiple cell types may reflect differing properties of the redox form of the molecule produced in the microenvironment [62].

Abnormalities of bone

Osteophyte formation and sclerosis of subchondral bone are hallmarks of OA. It has been theorized that osteophytes occur as a result of penetration of blood vessels into the basal layers of degenerating cartilage, or as a result of abnormal healing of stress fractures in the subchondral trabeculae near the joint margins [63]. TGF-β, when introduced into the joint in experimental animals, induces osteophyte formation, and TGF-β expression is observed in osteophytes in patients with OA [64,65].

With regard to subchondral bone sclerosis, it has been suggested that excessive loads may cause microfractures of subchondral trabeculae that heal via callus formation and remodeling. Whether subchondral sclerosis precedes the onset of OA or is a change that occurs but is not required for cartilage degeneration is not known. However, strategies targeted at bone disorders such as osteoporosis, and molecular targets that alter osteoclast and/or osteoblast function may represent opportunities to modulate pathologic subchondral changes in OA, and are therefore under consideration in efforts to develop disease-modifying treatments.

Bone marrow lesions

Felson and coworkers [66] reported that medial bone marrow lesions observed on magnetic resonance imaging (MRI) are associated with both knee pain and the risk for disease progression. However, it should be noted that, depending on size and location, the significance of bone marrow lesions in the individual patient might vary. The presence of bone marrow lesions and their relation to progression has been explained in part by an association with limb alignment [66]. The histopathologic nature of bone marrow lesions in OA is not yet clear, and it is probable that a number of tissue abnormalities such as microfractures, cysts, and avascular necrosis may contribute to the MRI findings.

Synovial proliferation and inflammation

It is increasingly appreciated that some degree of synovitis may be observed even in early OA [67]. Synovial histologic 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 [68]. Synovitis is often localized and may be asymptomatic. Arthroscopic studies suggest that localized proliferative and inflammatory changes of the synovium occur in up to 50% of OA patients, and the activated synovium may produce proteases and cytokines that accelerate progression of disease [69]. Cartilage breakdown products, derived from the articular surface as a result of mechanical or enzymatic destruction of the cartilage, can provoke the release of collagenase and other hydrolytic enzymes from synovial cells and macrophages. Cartilage breakdown products are also believed to result in mononuclear cell infiltration and vascular hyperplasia in the synovial membrane in OA. A consequence of these low-grade inflammatory processes is the induction of synovial IL-1β and TNF-α, which are probable contributors to the degradative cascade**.** There are also reports of increased numbers of immune cells in synovial tissue, such as activated B cells and T lymphocytes, including evidence for a clonally expanded, antigen-driven B-cell response that may contribute to the development or progression of the disease [70].

Biomarkers

Among the more exciting advances in our understanding of OA has come from the study of imaging and chemical biomarkers, which have revealed new aspects about the pathogenesis and progression of the disease.

Imaging biomarkers

Although conventional radiography is useful for the diagnosis of established disease, it has shortcomings with respect to the assessment of progressive disease. For example radiographic images are insensitive to early change within cartilage and bone and do not reveal synovial or meniscal pathology. They also lack correlation with severity of symptoms and are nonspecific measures of disease progression. The potential value of MRI as a 'biomarker' has been illustrated by studies that indicate that the presence of either bone marrow lesions [66] or meniscal disease [71] predict patients with knee OA at higher risk for disease progression. 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 [66,72]. In addition, functional MRI studies (delayed gadolinium-enhanced MRI of cartilage or sodium MRI), which detect biochemical changes of extracellular matrix proteins in cartilage, have attracted great interest as 'proof of mechanism' biomarkers that might demonstrate in

Table 1

Biomarkers of bone, cartilage and synovial turnover, and the BIPED classification

Tissue	Molecule	Markers of synthesis	Markers of degradation	BIPED classification
Bone	Type I collagen		PYD[a]	B
			NTX-I[a,b]	D
			CTX-I[a,b]	P
	Noncollagenous proteins	Osteocalcin[b]		P
Cartilage	Type II collagen	PIIANP[b]		P
		Total PIINP		D
		PIICP[b,c]		D, P
			CTX-II[a,c]	D, B, P, E
			HELIX-IIa	P
			Coll 2-1[a,b]	P
			Coll 2-1 NO_2[a,b]	P
			C2C[a,b]	P, E
			1,2C[a,b]	P, E
	Aggrecan	Epitope 846 (cartilage content[c])		E
	Nonaggrecan and noncollagenous proteins		COMP[b,c]	D, B, P
			Pentosidine[a,b]	P
	Proteases and their inhibitors		MMPs[b]	B, P, E
			TIMPs[b]	B, P
Synovium	Type III collagen		Glc-Gal-PYD[a]	E
	Noncolagenous proteins	YKL-40[b,c]		B, E
		Hayluronic acid[b]		B, P

[a]Urine. [b]Serum. [c]Synovial fluid. BIPED, B (burden of disease), I (investigative), P (prognostic), E (efficacy of intervention), D (diagnostic); C1,2C, assay that detects COL2-¾C (short) epitope; C2C, assay that detects COL2-¾C (long) epitope; Coll 2-1, 9-amino-acid peptide of type II collagen; Coll 2-1 NO_2, nitrated form of Coll 2-1; COMP, cartilage oligomeric protein; CTX-I, carboxyl-terminal cross-linked telopeptide of type I collagen; CTX-II, C-terminal cross-linked telopeptide of type II collagen; Glc-Gal-PYD, glucosyl-galactosyl-pyridinoline; HELIX-II, helical type II collagen; MMP, matrix metalloproteinase; NTX-I, N-terminal cross-linked telopeptide of type I collagen; PIIANP, N-propeptide IIA of collagen type II; PIICP, C-propeptide of collagen type II; PIINP, N-propeptide II of collagen type II; PYD, pyridinoline; TIMP, tissue inhibitor of matrix metalloproteinase; YKL-40, cartilage glycoprotein 39. Reproduced with permission from Rouseeau and Delmas [80].

the short term (4 to 6 weeks) that a treatment restores normal chondrocyte metabolism.

Biochemical markers

It is likely that biochemical markers will be used in conjunction with imaging in order to establish stage of disease, predict progression, and assess disease activity and progression in OA. The Osteoarthritis Biomarkers Network, a consortium of five National Institutes of Health-designated sites, has recently proposed a classification scheme of biomarkers for OA [73]. Five categories of biomarkers (captured in the acronym BIPED) were proposed to aid the study of all aspects of OA, from basic science research to clinical trials (Table 1): burden of disease, investigative, prognostic, efficacy of intervention, and diagnostic.

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 COMP, urinary carboxyl-terminal cross-linking telopeptide of type II collagen (CTX-II), and serum hyaluronan [74]. Candidate prognostic markers include serum COMP, urinary CTX-II, serum hyaluronic acid [75], and pentosidine, an advanced glycation end-product [76]. The available data suggest that urinary CTX-II is of particular interest. Elevated levels of CTX-II have also been found to predict progression of joint space narrowing in both knee and hip OA. Moreover, Garnero and coworkers [77] found that bone marrow abnormalities on MRI significantly correlated with 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. Finally, 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.

It should be noted, however, the predictive value of these markers in clinical trials has yet to be proven and, as such,

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there remains a need to validate these and other new biomarkers. Indeed, caution regarding the predictive value of drug-induced declines in CTX-II has been raised by Bingham and coworkers [78], who reported that risedronate decreases biochemical markers of cartilage degradation but does not decrease symptoms or slow radiographic progression in patients with medial compartment OA of the knee.

Conclusion

During the past decade there have been significant developments in the scientific understanding of OA. Aided by advances in imaging technology, we have come to appreciate that OA is a disease of the 'whole joint', which involves a complex series of molecular changes at the cell, matrix, and tissue levels and complex interactions between the tissues that make up the joint. We are beginning to understand better the mechanisms by which genetic, mechanical, and metabolic risk factors initiate and perpetuate the biochemical changes that lead to progressive failure of the joint. We are also gaining a better appreciation of the processes of aging and senescence that underlie disease mechanisms. These discoveries have opened opportunities for the identification of targets for therapeutic intervention, which hopefully will lead to effective therapies that reduce the symptoms and slow the progression of OA.

Competing interests

The authors declare that they have no competing interests.

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