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Is osteoarthritis a disease involving only cartilage or other articular tissues?

Osteoartrit sadece kıkırdak ya da diğer artiküler dokuları içeren bir hastalık mıdır?

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Osteoarthritis (OA) is a progressive and disabling disease resulting from a combination of risk factors, including advancing age, genetics, trauma, knee malalignment, increased biomechanical loading of joints through obesity, augmented bone density and an imbalance in physiological processes resulting in catabolic cascades on a molecular level. This review will highlight the involvement early in the disease process of not only the cartilage but also the synovial membrane and subchondral bone and the pathophysiological mechanisms of each of these tissues that lead to joint degeneration. We will summarize the current pathological mechanisms that occur in the abovementioned articular tissues, and briefly discuss their interconnections during OA.

Key words: C-reactive protein; magnetic resonance imaging; osteoarthritis; subchondral cyst; synovial membrane.

Osteoartrit (OA) ilerleyen yaş, genetik travma, diz malalignmenti, obezlikten kaynaklanan artan biyomekanik eklem yüklemesi, artırılmış kemik yoğunluğu, ve moleküler düzeydeki katabolik kaskadlara neden olan fizyolojik süreçteki dengesizliği içeren risk faktörlerinin kombinasyonu sonucu ortaya çıkan engelleyici ve progresif bir hastalıktır. Bu yazıda sadece kıkırdağın erken hastalık sürecindeki tutulumu değil, ayrıca eklem dejenerasyonuna neden olan sinovyal membran, subkondral kemik ve patofizyolojik mekanizmaların her bir dokusundaki tutulumları da vurgulandı. Biz yukarıda bahsedilen artiküler dokularda meydana gelen güncel patolojik mekanizmayı özetleyecek ve kısaca OA boyunca olan bağlantılarını tartışacağız.

Anahtar sözcükler: C-reaktif protein; manyetik rezonans görüntüleme; osteoartrit; subkondral kist; sinovyal membran.

Osteoarthritis (OA) is the most common form of arthritis. Although the hallmark of the disease is the progressive degeneration of articular cartilage and subsequent joint space narrowing, OA leads to pain, loss of motion, instability, and physical disability, thus impairing quality of life. The joints most commonly affected by OA are the base of the thumb, the end or middle joints of the fingers, the hips, the knees and the base of the big toe, though the neck (cervical spine) and the lower back (lumbar spine) can also be affected. At present, there are no therapies proven to arrest or curb the disease process, and therefore in many individuals OA still leads to hip or knee joint replacement.

It has long been believed that the morphological changes seen early in OA are only age-related. We now know that, even if changes associated with aging and OA appear similar in the early stages, at a certain point they can be discriminated. However, these processes are not mutually exclusive, as the changes that occur with aging could lead to OA.

The etiology of OA remains to be completely understood, but the course of joint degeneration is well known to be variable. Although some risk factors for OA are the same for men and women, including age, genetics, previous injury, knee malalignment and obesity, others could lead

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to differential risk according to the gender and the state of articular tissues. For example, a higher bone density is associated with an increased incidence of radiographic knee OA in women,[1] but this relationship has not been seen to the same degree in men, nor for OA of the hands.[2,3]

Osteoarthritis results from a complex system of interacting mechanical, biological, biochemical, molecular and enzymatic feedback loops. The final common pathway is joint tissue destruction resulting from the failure of cells to maintain a homeostatic balance between matrix synthesis and degradation. As the disease advances, the degradative process eventually exceeds the anabolic process, leading to progressive joint tissue lesions. This appears to occur when the physiological balance between the synthesis and degradation of the extracellular matrix favours catabolism.

Osteoarthritis of the knee is a heterogeneous chronic disease involving the entire organ, including the articular cartilage, subchondral bone, menisci, and periarticular soft tissues such as synovial membrane. In this disease, the occurrence of alterations in cartilage metabolism is well established, and data suggest that the changes are primarily the result of a disturbance in the remodelling process of this tissue. Moreover, in this disease, the participation and role of synovial inflammation are now widely accepted. Synovitis appears to result from the synthesis and release of many factors and is considered to be secondary to the changes in the cartilage. Yet, findings indicate that synovial inflammation could be a component of the early events leading to the clinical stage of OA. In addition, emerging evidence suggests that changes in subchondral bone and menisci are closely involved in the disease progression. Data even suggest that the subchondral bone alterations may precede cartilage changes. In brief, subchondral bone is suggested to be the site of the causally most significant pathophysiological events occurring in cartilage.

CARTILAGE

Articular cartilage is a specialized avascular and neural connective tissue that provides covering for the osseous components of diarthrodial joints. It serves as a load-bearing material, absorbs impact and is capable of sustaining shearing forces. The unique properties of this tissue are related to the composition and structure of its extracellular matrix, which is composed mainly of a high concentration of proteoglycans (aggrecans) entangled in a dense network of collagen fibres and a large amount of water. This tissue allows the frictionless motion of the joint in which it absorbs and dissipates load.

The articular cartilage is composed of a sparse population of cells called chondrocytes, which are responsible for the synthesis and maintenance of the extracellular matrix. The chondrocytes are embedded within the negatively charged extracellular matrix and are subjected to mechanical and osmotic stresses. Data showed that chondrocytes also act as mechano- and osmo-sensors that could alter their metabolism by responding to local physicochemical changes in the microenvironment.[4,5] Therefore, perpetuation of OA could be, at least in part, mediated by biochemical pathways, as changes in gene expression and production of catabolic factors occur in response to mechanical stress.

In brief, during the disease development, joint tissue degradation results from several distinct biological processes operating spatially and temporally not only in the cartilage but also in other joint tissues, and include changes in the cell metabolism of these tissues.

Cartilage macromolecules

The cartilage matrix consists of macromolecules of which collagen and proteoglycans (aggrecans) are the main representatives. These components are highly ordered from the cartilage surface to the deepest layers. Cartilage is divided into four zones with different functions: the superficial, middle or transitional, deep or radial, and calcified cartilage zones, without a sharp boundary between the first three zones.

During OA, an enhanced degradation process occurs in the macromolecular components of cartilage. Aggrecans are probably among the first cartilage matrix constituents to be affected, as they are progressively depleted in parallel with the severity of the disease.

In OA cartilage, chondrocytes synthesize proteases that cleave the proteoglycan monomer releasing fragments which rapidly diffuse from cartilage into the synovial fluid, leaving behind normal proteoglycan still capable of

aggregation. New aggrecan synthesis does occur in OA cartilage, presumably in an attempt by the chondrocytes to initiate repair. The newly synthesized aggrecan forms proteoglycan aggregates that are retained in the cartilage during the early stages of OA, but in later stages they are also lost to the synovial fluid.[6] The newly synthesized aggrecan has a composition more similar to juvenile cartilage than adult cartilage.[7] At a certain stage in the evolution of OA, the chondrocytes appear unable to compensate fully for proteoglycan loss even in the presence of its increased synthesis, resulting in a net loss of matrix. The rate at which proteoglycan synthesis and degradation occur may vary in different regions of the cartilage, due to differences in the mechanical stress to which it is subjected.

The other major macromolecule of articular cartilage is type II collagen. The triple helical region of the type II collagen molecule is resistant to degradation by most proteases, but can be cleaved by the action of collagenases.[8] Mammalian collagenases act consecutively at a single site in each of the three alpha (α)-chains to yield fragments that are about three quarters and one quarter the length of the intact molecule.

SYNOVIAL MEMBRANE

The synovial membrane is the joint capsule lining and all structures within the joint, except the cartilage, are covered by synovium. This tissue is well vascularized and innervated and its surface is folded into villi. The synovial membrane consists of two layers: a lining layer directly next to the joint space named the intima, and the subsynovial or sub-intima. The outer portion of the subsynovial tissue merges with the fibrous capsule of the joint. The synovial cells consist mostly of two main types, named type A and type B, of which type A are macrophage-like and type B are the synovial fibroblasts. The synovial membrane secretes synovial fluid.

Synovial inflammation

The progress made in the understanding of the pathophysiological pathways of this disease clearly demonstrated that synovial inflammation occurs in early OA and can be subclinical. However, synovitis is evident at the clinical stage of the disease[9,10] and could be the cause for a patient to see a physician. In OA, synovial histological changes include synovial hypertrophy and hyperplasia, with an increased number of lining cells, often accompanied by infiltration of the sublining tissue. Synovitis is believed to be induced at first by the cartilage matrix proteolytic degradation products that produce wear particles and soluble cartilage-specific neo-antigens, as well as other factors including microcrystals and abnormal mechanical stress. These components are released into the synovial fluid and are phagocyted by synovial lining macrophages, perpetuating the inflammation of the synovial membrane through the synthesis of mediators. In turn, these mediators diffuse through the synovial fluid into the cartilage, and create a vicious circle, with increased cartilage degradation, and subsequently produce more inflammation. In the synovial membrane, inflammatory mediators are synthesized by different cell populations: synovial lining cells and infiltrated inflammatory cells.

Knee OA patients showing synovitis also showed a more rapidly progressing disease.[11-13] Moreover, serum C-reactive protein, cartilage oligomeric protein, hyaluronic acid, glucosyl-galactosyl pyridinoline and serum type II collagen N-terminal propeptides, recognized as biomarkers of synovial inflammation or joint destruction, have been associated with the development/progression of OA.[14-19] There are also increased numbers of immune cells, such as activated B cells and T lymphocytes, including antigen-driven B-cell.[20,21]

In addition to its contribution to joint inflammation and cartilage degradation, it is believed that synovitis contributes significantly to the development of pain.

SUBCHONDRAL BONE AND MENISCUS

The degeneration and erosion of cartilage has recently been challenged as the primary pathological mechanism of OA and the subchondral bone is suggested to play a key role. The subchondral bone plate is in direct contact with the cartilage and could therefore influence its degradation. Evidence from humans and animal models has shown that subchondral bone alterations may precede cartilage degradation. The subchondral bone is an active component in the initiation/progression of OA by providing catabolic factors to the overlying cartilage and promoting abnormal cartilage metabolism. The subchondral bone is

richly vascularized whereas the hyalin cartilage is not, hence the nutrition of the articular cartilage is provided in part by the vascular bed of the subchondral bone in addition to the synovial fluid. Moreover, any loss of vascular tone in the subchondral bone could potentially affect the cartilage. In this respect, the observation of early microvascular damage affecting the venous circulation in the bony tissue in OA is important to consider. Whether these vascular changes are secondary to bony changes or whether they prompt them, still remains an open question.

Moreover, the concept that the subchondral bone and cartilage should be considered an interdependent functional unit is gaining strong support and a biochemical investigation of the serum levels of some factors released from cartilage and bone during the early stage of OA in humans is indicative that the pathological processes in cartilage and subchondral bone coincide.[22]

Bone matrix

Bone is a specialized connective tissue made up of several components including the specific cells osteoblasts, osteocytes and osteoclasts, inorganic non-collagenic substances such as proteoglycans, and a collagenic component of which type I collagen is the major constituent. Bone remodelling occurs through osteoblast activity in bone formation via the synthesis of bone matrix, and through osteoclast activity in the degradation of bone matrix. The equilibrium between the activities of these two cells maintains the mineral homeostasis via the release of calcium and phosphorous into the circulation. The bone remodelling cycle includes several distinct phases, the main ones being activation, resorption, reversal and formation. Physiological events such as mechanical force and stress induce bone remodelling, in which osteoclast precursors and mature osteoclasts are recruited from the circulation to the bone remodelling unit, thereby initiating the resorption of the mineralized matrix. Following this process, the osteoclasts undergo apoptosis, leaving an opening for osteoblasts to deposit newly synthesized matrix.

Subchondral bone remodelling and the OA process

There is increasing evidence that bone marrow lesions (BMLs) and bone cysts have an important role in the pathogenesis of knee OA.[23-27] Bone marrow lesions consist of a number of heterogenous histologic abnormalities including bone marrow necrosis, trabecula abnormalities, bone marrow fibrosis and edema.[28] Bone marrow lesions may originally correspond to an acute inflammatory response, edema, contusion and/or necrosis, which over time is replaced by more permanent bone marrow remodelling such as fibrosis and myxomatous connective tissue.[29] Histologic findings of bone cysts reveal necrotic bone fragments with dead denuclearized cells surrounded by a nonepithelial fibrous wall.[26] In OA patients, BMLs and bone cysts appear to be inter-related in that subchondral bone cysts develop in the pre-existing regions of BML-like signals in OA patients.[30] In established OA, BMLs are associated with radiological progression of knee OA[31] and enlargement of BMLs is strongly associated with increased cartilage loss whereas reduction of the extent of BMLs is associated with a decrease in cartilage loss.[25,27] Moreover, the presence of BMLs could predict higher risk for disease progression in patients with knee OA.[27,31] It is suggested that factors contributing to the development of BMLs result in impairment of the supply of nutrients to the overlying cartilage in addition to reducing the strength of the bony support of the cartilage.[30]

Moreover, although BMLs have been associated with knee pain,[32,33] cysts which were also found to be associated with OA and cartilage loss, did not appear in knee OA to be associated with the disease symptoms.[34]

In support of a disturbed subchondral bone cell metabolism early in the OA process is that osteocalcin (a marker of bone formation) in synovial fluid and serum osteopontin (a bone specific matrix protein) were significantly higher in patients with knee scan abnormalities.[35] Since serum osteopontin levels increase shortly after trauma, this implies that alterations in bone cell activity may occur quite early in disease. This was supported by in vitro studies in which human OA subchondral bone osteoblasts demonstrated abnormal metabolism including elevated alkaline phosphatase activity and increased release of osteocalcin.[36] Other factors such as transforming growth factor (TGF)-β1, insulin-like growth factor-1 (IGF-1), the urokinase-type plasminogen activator (uPA)/plasmin system, interleukin (IL)-6 and IL-1β have also been found at abnormal levels in OA subchondral bone.[37-40]

Further data show that although at a later stage of OA there is sclerosis of the subchondral bone, this occurs without a concomitant increase in bone mineralization pattern. Subchondral bone sclerosis in OA results from an increased stiffness and an increase in material density, but not an actual increase in bone mineral density. In fact, OA subchondral bone demonstrates an increased osteoid collagen matrix and an abnormal mineralization resulting in a hypomineralization of this tissue.[41,42] This could explain the data showing that one response of the OA knee to increased load is for the tibial plateau to expand,[43] which may redistribute the mechanical load and perturb the mechanical competence of the bone. Consequently, a more compliant bone due to inhomogeneities in density or stiffness will deform the articular cartilage. Such deformation can then stretch the articular cartilage at the edge of the joint contact area, generating tensile and shear stresses. Although the subchondral bone tissue is hypomineralized in OA, the increase in trabecular number and volume compensates for this situation, thus providing an apparent stiffer structure.

Hence, although type I collagen is elevated in OA subchondral bone, an abnormal collagen content is present and leads to abnormal mineralization.[44-46] Type I collagen is composed of a heterotrimer of α1 and α2 chains at an average ratio of 2.4:1 in normal bone; however, this ratio varied between 4:1 and 17:1 in OA bone tissue,[47] and this appears to be responsible for the abnormal mineralization pattern found in OA subchondral bone. A reduction in α2 chains may lead to a tighter packing of collagen fibers and, coupled with the reduction in cross-links observed in OA bone tissue[45] and the over-hydroxylation of lysine in collagen fibrils,[47] may explain the reduction in bone mineralization. Further data revealed that elevated TGF-β1 levels in OA subchondral bone osteoblasts are responsible, at least in part, for abnormal ratio of collagen α1 to α2 chains, thus for the abnormal production of native type I collagen.[46] Interestingly, such a disturbance in the type I collagen α chains was shown in a mouse model to cause a 50% reduction in bone strength.[48]

Subchondral bone also experiences phases of resorption, which appear to be a very important event in the remodelling of this tissue and the progression of OA. Some clinical studies in OA patients have suggested that the indices of bone resorption are increased early in the disease process.[49] This concurs with the in vivo findings on animal models of OA allowing the chronological analysis of the disease progression. In one of these studies,[50] there was the presence at an early stage of the disease process of an increase in subchondral bone loss with a reduction in the surface and the trabecular thickness, an increased number of osteoclasts, as well as production of proteases involved in resorption activity, including cathepsin K and matrix metalloprotease (MMP)-13.

Menisci and the OA process

The meniscus is an integral part of the biomechanical system of the knee. It is essential for the distribution of axial forces on the knee and absorption of shock. Meniscal extrusion may simulate a condition similar to complete meniscectomy and result in alteration of meniscal function, modifying the pattern of load distribution and contributing to compartmental instability.[51] As a result, this tissue's impact on the femoral and tibial bone surfaces is likely to increase the susceptibility of the subchondral bone to trauma during dynamic movements of the knee.

Meniscal extrusion occurs frequently in knees with established OA[52] and is associated with articular changes such as joint space narrowing,[53,54] cartilage loss,[24,25,52,55] and chondral lesions.[56] Interestingly, in a non-OA cohort,[55] associations were found between meniscal extrusion and the prevalence of subchondral BMLs and cysts cross-sectionally, and the change in both longitudinally, as well as loss of cartilage.[55] The changed biomechanical environment of the knee due to meniscal extrusion would lead to the development or progression of BMLs, bone cysts, and subchondral bone expansion, all of which have been shown to be associated with cartilage loss and disease progression. Thus, the subchondral bone changes could be an early consequence of meniscal extrusion and reflect the biomechanical changes resulting from meniscal extrusion.

FACTORS INVOLVED IN OA TISSUES

Cartilage catabolic factors

Metalloproteases

Multiple members of the MMP family acting in unison are responsible for the degradation of the

cartilage matrix macromolecules, which results in the irreversible fibrillation of the articular cartilage in the OA joint. Generally, all the MMPs involved in cartilage can be expressed by the chondrocytes.

Proteolytic damage to the collagen fibrils during the initial phase of OA probably contributes to the hypertrophy and increased hydration of the articular cartilage, as the weakened collagen fibril network may not adequately resist the swelling properties of the entrapped proteoglycan. In OA, the expression and synthesis of the three collagenases, MMP-1, MMP-8, and MMP-13 were found at higher levels in OA.[57,58] Although all three collagenases are active on collagen fibrils, the specificity between them for a specific collagen type differs as does their topographical location, suggesting a selective involvement of each during the disease process. In brief, in the early stages of OA, MMP-13 is predominantly expressed in the lower intermediate and deep layers of cartilage,[59,60] and was suggested to be responsible for the remodelling process that occurs in this layer. Matrix metalloprotease-1 appears to be involved during the inflammatory phase. A specific role of MMP-8 in OA progression remains to be documented.

Two gelatinases have been found in articular tissues: MMP-9 and MMP-2. Matrix metalloprotease-9 is reported to be expressed and synthesized in OA, but not in normal cartilage.[61] The fact that MMP-9 is selectively expressed in OA fibrillated cartilage is consistent with the possibility that this enzyme could be responsible for progressive articular cartilage degradation in this disease. Matrix metalloprotease-2 expression was also shown to be increased in OA cartilage.[62] In OA, collagen is first degraded by the collagenase, and the collagen fragments may denature allowing further cleavage by proteases such as MMP-2 and MMP-9.

It had long been thought that the predominant protease degrading the proteoglycan during OA was the stromelysin or MMP-3. However, in cartilage, although MMP-3 is present in this normal tissue and upregulated in early OA, it is downregulated in the late stages.[62] At present MMP-3 is considered to be the crucial enzyme in matrix turnover/homeostasis. Analysis of aggrecan fragments in OA tissues showed a proteolytic cleavage of the Glu373-Ala374 bond of the interglobular domain of the proteoglycan,[63] and the enzymes responsible for such cleavage belonged to a subgroup of the ADAM family, the ADAMTS, and were named aggrecanases. Two such enzymes have been reported to be present in cartilage, ADAMTS-4 and ADAMTS-5, and recent studies in ADAMTS-5 knock-out mice and ADAMTS-5-resistant aggrecan knock-in mice, demonstrated protection of the joint from OA.[64,65] However, in humans, these data have not yet been confirmed, suggesting rather that it may be ADAMTS-4 that is the most involved.

Other catabolic factors

Other catabolic factors could at one point act as amplifier/catalyst of the cartilage degenerative process and lead to the development of OA. Some of these include, in addition to the proteases, fibronectin, some neuromediators, and inflammatory mediators.

Cartilage anabolic factors

The capacity of OA cartilage to spontaneously heal is limited even though anabolic factors such as the growth factors are found in cartilage. In healthy adult cartilage, the levels of those factors are normally low and maintain optimal matrix quantity and quality. In OA, although the levels of many of the growth factors are generally increased, they obviously cannot compensate for the loss/degradation of the cartilage matrix macromolecules.

Growth factors known to play a role in cartilage formation and maintenance include TGF-β, bone morphogenic proteins (BMPs), cartilage-derived morphogenic proteins (CDMPs), IGFs, connective-tissue growth factor (CTGF), and fibroblast growth factor (FGF).

Because of their anabolic properties, some of them are being evaluated as therapeutic agents in the repair of damaged cartilage. However, their use in the treatment of OA is a challenging avenue of research with several problems still to be addressed. Among them, some play a dual (anabolic/catabolic) role in cartilage, or induce the formation of osteophytes, are non-responsive on older cells, or are incapable of counteracting the catabolic actions of pro-inflammatory molecules. It is still unknown whether their increase in OA cartilage is the result of repair attempts by the cells or of an upregulation due to the presence of catabolic factors. Regardless of the originating cause, the increased levels are not adequate to counteract the degradative process and repair the cartilage. Moreover, for some of the

growth factors, natural antagonists or inhibitors exist which could be up-regulated during the OA process, thus limiting their activities.

Cartilage and synovial membrane pro-inflammatory cytokines

Among the catabolic factors, the proinflammatory cytokines play an important role during the OA disease process and IL-1β production is a key event in the perpetuation of OA pathophysiology.[66] Tumor necrosis factor (TNF)-α is also an important inflammatory mediator in the catabolic process, but in OA this cytokine appears to be present at a late stage.

The association of IL-1β with tissue damage arises from its propensity to stimulate the proteolytic and catabolic pathways of extracellular matrix degradation and, at the same time, suppress the synthetic pathways. Hence, in addition to inducing proteolytic enzymes in OA tissues, IL-1β can either decrease the synthesis of matrix macromolecules, including type II collagen and proteoglycans, or increase collagen types not involved in normal cartilage, resulting in the tissue's loss of strength.[67] Indeed, in cartilage, IL-1β stimulates the production of types I and III collagen and decreases the synthesis of the major collagen type, type II collagen. Such changes result in inappropriate matrix repair that leads to further cartilage damage.

Other proinflammatory cytokines, such as TNF-α, IL-6, leukemia inhibitory factor (LIF), IL-17 and IL-18, as well as some chemokines such as IL-8, are also considered as potential contributing factors to the pathogenesis of OA. It has been shown that all of these cytokines are expressed in OA tissue. However, the exact role and importance of each in the OA process is not yet clearly established, and it is not yet known whether a functional hierarchy exists between them.

Other inflammatory factors

In addition to cytokines, other inflammatory mediators also play major roles in the OA pathological process. Among them are nitric oxide (NO) and some eicosanoids.

Nitric oxide

Osteoarthritic cartilage produces a large amount of NO (and reactive oxygen species), and a high level of nitrites/nitrates has been found in the synovial fluid and serum of arthritis patients.[68] This is attributable to an increased expression of inducible NO synthase (iNOS). Nitric oxide was shown to be involved in the promotion of cartilage catabolism in OA through a number of mechanisms, including the induction of synovial inflammation, the inhibition of the synthesis of cartilage matrix macromolecules, such as aggrecans, the enhanced MMP activity, and the reduced synthesis of IL-1 receptor antagonist (IL-1Ra) by chondrocytes. Nitric oxide also plays a role in chondrocyte apoptosis[69] and its induction of chondrocyte death in human OA is related to the production of prostaglandin E_2 (PGE_2) via the induction of cyclooxygenase (COX)-2.[70] Collectively, inducible NO acts by reducing the major anabolic processes and increasing the catabolic processes, making it a complete factor favoring joint destruction.

Eicosanoids

Other inflammatory factors involved in OA are eicosanoids, among which are the prostaglandins and leukotrienes. The literature on the effects of eicosanoid overproduction in arthritic diseases reveals a variety of both catabolic and anabolic activities. This is likely due to the fact that different eicosanoid end-products have been shown to exert divergent effects on the metabolism of joint tissue cells.

The critical role of PGE_2 in the pathology of arthritis was substantiated in animal models of arthritis and mice lacking COX-2 or PGE_2 receptors.[71,72] It is well known that increased synthesis of PGE_2 plays a role in exacerbating joint inflammation; PGE_2 can act on the synovial membrane lining cells and macrophages, chondrocytes, and bone cells. Prostaglandin E_2 affects articular tissue remodelling directly or functions indirectly as an autocrine regulatory factor. Moreover, in addition to exerting inflammatory effects on its own, PGE_2 can potentiate the effects of other mediators of inflammation. Besides its proinflammatory actions, PGE_2 may contribute to joint damage by promoting MMP production and other catabolic events.

Until recently, COX activity was considered the key step in prostaglandin synthesis. The metabolism of the substrate arachidonic acid by COX (COX-1 or COX-2) yields to the unstable intermediary PGH_2, which can be further metabolized into

PGE_2, PGD_2, $PGF_{2\alpha}$, PGI_2 (prostacyclin) or thromboxane A_2. However, the enzyme responsible for the isomerization of PGH_2 was little known until recent identification of PG synthase (PGS) as the terminal enzyme responsible for end products.

For PGE_2 at least three distinct PGES isoforms have been identified: cytosolic PGES (cPGES), microsomal PGES-1 (mPGES-1), and mPGES-2.[73-76] Cytosolic PGES is constitutively and ubiquitously expressed and is preferentially coupled with COX-1, promoting immediate production of PGE_2.[75,77] By contrast, mPGES-1 is markedly upregulated by proinflammatory stimuli and is functionally coupled with COX-2, promoting delayed PGE_2 synthesis.[78-80] Microsomal PGES-2 is ubiquitously expressed in diverse tissues and is functionally linked to both COX-1 and COX-2. However, the role of mPGES-2 in physiology and pathogenesis remains elusive. Studies from mPGES-1-deficient mice and animal models of inflammatory arthritis strongly suggest the role of mPGES-1 in inducible PGE_2 production and arthritis.[81]

The use of non-steroidal anti-inflammatory drugs (NSAIDs) or COX-2 selective inhibitors has shown that PGE_2 inhibition alone does not delay the natural history of progressive OA. This could be explained by the fact that PGE_2 synthesis is only one part of the arachidonic acid pathway which gives origin to many other lipid mediators, including leukotrienes, and that leukotrienes were shown to play a major role in the development and persistence of the inflammatory process. The literature has shown that prostaglandins and leukotrienes have complementary effects.

Leukotrienes are produced from the metabolism of arachidonic acid by the enzyme 5-lipoxygenase (5-LOX). Leukotriene A_4 (LTA_4) is the first to be synthesized and is then processed into LTB_4 or LTC_4, then LTD_4 and LTE_4, which are potent chemotactic and inflammatory factors. Levels of LTB_4 and LTC_4 are increased in OA articular tissues.[82,83] Studies also revealed that, on human OA synovial membrane, LTB_4 potently stimulated the release of proinflammatory cytokines such as IL-1β and TNF-α.[83-87] Thus, the failure of NSAIDs to impact OA progression was suggested to occur due to the fact that inhibiting only the COX pathways could lead to a shunt to leukotriene production in these tissues.[88-93] Based on this concept, it is hypothesized that blocking production of both leukotrienes and prostaglandins could have a synergistic effect in achieving optimal or a wider-spectrum of anti-inflammatory activity.

Subchondral bone catabolic factors

Among the cytokines and eicosanoids produced by bone cells, IL-1β, IL-6, PGE_2 and LTB_4 are the most important regulators of the extracellular matrix. Interleukin-1β and IL-6 can directly promote matrix degradation in both subchondral bone and cartilage due to their action on selective MMPs in these tissues.[38,94] Interestingly, OA subchondral bone osteoblasts showed opposite levels of PGE_2 and LTB_4.[38,90] Hence, as with the cartilage, inhibiting only PGE_2 could induce a shunt in LTB_4 levels, which would stimulate osteoclast differentiation and bone resorption, thus bone remodelling.[95]

Other factors such as some members of the TNF superfamily were also demonstrated to play major roles in regulating bone metabolism. On subchondral bone osteoblasts, two of them, OPG (osteoprotegerin) and RANKL (receptor activator of nuclear factor-κB) and more particularly the ratio of OPG: RANKL, which is considered to better reflect environmental signals, have been found highly implicated. Indeed, a high ratio of OPG: RANKL is indicative of promoting bone formation while a low ratio favours bone resorption. Such imbalance has been encountered in human OA subchondral bone osteoblasts, and data demonstrated abnormal OPG and RANKL levels and consequently an altered OPG: RANKL ratio.[96] The involvement of some osteotropic factors generally targeting RANKL with a differential modulation of the RANKL isoforms has also been shown in human OA subchondral bone.[97]

CONCLUSION

Research in recent years has shown that OA is a disease that is considerably more complex than previously thought. Indeed, it is now accepted that OA is not a single disease, but should rather be regarded as a common final stage of joint failure, the initial stages of which can be triggered by numerous causes and/or factors. Despite major progress, there is still a great deal to learn about the pathogenesis of this disease. The slowly progressive loss of cartilage, the multifactorial nature of the disease, and the cyclical course with periods

of active disease followed by remission have limited our comprehension of OA.

Although several cellular and molecular pathways have been identified, elucidation of the critical pathways at its beginning stages involves discrimination of the different facets of OA. However, the methods presently used (X-rays) to assess structural changes in articular tissues during OA lack sensitivity. This could explain why OA clinical trials have mainly focused on symptomatic OA patients, i.e. patients showing clinical parameters such as pain and joint function disability, a stage of the disease in which the structural changes are already advanced to severe.

Sensitive and accurate methods to assess structural changes at the onset of OA are therefore crucial to the discovery of the key players in the initiation and progression of the disease, to differentiate the disease subgroups, and to assess the therapeutic efficacy of new treatments. To this end, recently described new applications of magnetic resonance imaging allow precise visualization and quantification of joint tissues such as cartilage, bone, synovial membrane, synovial liquid, and menisci, at the onset of OA and of its progression over time, and enable the discrimination of OA subgroups.

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