Review

A metabolic aspect of osteoarthritis: lipid as a possible contributor to the pathogenesis of cartilage degradation

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ABSTRACT

Osteoarthritis (OA) is considered to be linked to obesity and body fat mass. Recent investigations, however, are aimed at clarifying the roles of adipose tissue-derived proteins and a wide variety of lipid mediators, including fatty acids, sphingolipids, and eicosanoids, in cartilage degradation in OA, in addition to the effects body weight itself. Here, we review recent progress in studies of OA, focusing on the potential role of lipid mediators in articular cartilage and introducing the concept that "OA is a metabolic disease" in which lipids essentially contribute to the pathophysiology of cartilage degradation.

Introduction

Osteoarthritis (OA) is considered to be a non-inflammatory, degenerative joint disease in which the aging process and repeated mechanical loading on the articular cartilage are major contributors. The results of recent investigations, however, aimed at clarifying the inflammatory, non age-related aspects of OA suggest that OA may be a systemic failure of cartilage structure maintenance, in which an array of lipids and lipid mediators (from fatty acids to complex lipids) have a key role. As discussed in a recent editorial in *Osteoarthritis and Cartilage,* a new concept that "OA is a metabolic disease in which all the components of the joint, including bone, muscles, synovia, and cartilage are generally affected by adipokine dysregulation or hyperactivity" (1) has emerged. In this review, we present current research progress on the pathogenesis of cartilage degradation in OA, focusing on the roles of lipids in the maintenance of articular chondrocytes.

Obesity and OA

Because articular cartilage serves as a load-bearing tissue in joints, excess body weight (*i.e.* mechanical overload to articular joints) is considered to be related to the pathophysiology of cartilage destruction in OA (reviewed in refs. 2 and 3). For example, articular chondrocytes express mechanoreceptors (*e.g.* integrin and CD44) that are sensitive to mechanical stress such as compression and stress and these stimuli induce the activation of a variety of signaling pathways leading to the production of inflammatory mediators (3). On the other hand, in addition to excess weight causing a mechanical overload, recent studies have revealed that adipose tissue-derived proteins, or adipokines, might also have a role in OA.

Adipose tissue is now accepted to be not only an energy reservoir, but also an endocrine organ that produces a variety of proteins, including cytokines and adipokines. Adipokines, which include adiponectin, resistin, and leptin, are expressed in and released from adipose tissue and share functional and structural properties with cytokines (4). Besides their essential roles in obesity and metabolic disorders, these adipokines are suggested to be involved in arthritic disorders. Adiponectin receptors are expressed in human and murine chondrocytes (5, 6). Adiponectin is found in both the sera and synovial fluid in OA patients; the level in the synovial fluid being lower than that in the sera (4, 5). Based on gel filtration chromatography studies, Chen *et al.* reported that adiponectin in the plasma from patients with OA is present in high molecular weight (HMW), hexamer, and trimer forms; however, in synovial fluid from OA patients, the percentage of HMW per total adiponectin is lower

than that in plasma, whereas the percentage of the hexamer form is similar between the two, and the trimer form is higher. Further, adiponectin upregulates mRNA expression of tissue inhibitor of metalloproteinase-2 and downregulates interleukin (IL)-1β-induced matrix metalloproteinase (MMP)-13, suggesting that adiponectin protects against the progression of OA (5). In contrast, Lago *et al*. recently reported that adiponectin induces the expression of an array of catabolic mediators, including nitric oxide synthase (NOS), IL-6, and MMP-3 in chondrocytes (6). Although the *in vivo* function of adiponectin requires further clarification, these findings suggest that an imbalance and/or multivalence of intraarticular adiponectin is involved in the pathogenesis and pathophysiology of OA.

Leptin, a 16-kDa product encoded by the obese (ob) gene, is also reported to have a role in cartilage homeostasis and OA (reviewed in refs. 1 and 3). For example, leptin regulates chondrocyte differentiation during endochondral ossification (7) and controls the activity of MMP-13 in chondrocytes through an epigenetic mechanism (8). In addition, the expression of leptin and the leptin receptor (Ob-Rb) is higher in advanced OA than in minimally affected OA (9), further supporting the idea that leptin contributes to the development of OA (9-12).

Together, these observations support the notion that adipokines are not only involved in the accumulation of body fat mass but are likely to be potent modulators of cartilage metabolism and matrix turnover in OA. Considering that adipose tissue secretes an array of adipokines and other mediators, the accumulation of adipose tissue in obese patients might partly contribute to cartilage degradation in the articular joints through systemic and/or local circulation of the mediators.

Body fat mass/metabolic syndrome and OA

Obesity is often accompanied by hyper(dys)lipidemia, and "metabolic syndrome" is characterized by "obesity, dyslipidemia, hypertension, and hyperinsulinemia (13)". However, the direct involvement of the metabolic abnormalities of obesity, including dyslipidemia in OA is currently under debate (reviewed in ref. 2). For example, in the Ulm OS study in 1998, Sturmer *et al*. assessed serum cholesterol levels in 809 patients with knee or hip joint replacement due to OA, and reported finding no association between hypercholesterolemia and bilateral OA (14). On the other hand, hypercholesterolemia and high serum cholesterol levels were associated with generalized OA, *i.e*. those in whom radiographic evidence of OA-related changes is observed in multiple joints, usually including finger joints (14). Toda *et al*. reported that decreasing body fat, but not body weight, correlates with symptomatic relief of knee OA in obese patients, although there was not necessarily a cause and effect relationship (15). These observations suggest that serum cholesterol and body fat, and not just body weight alone, have active roles in the degenerative process of articular cartilage in OA, at least in a subset of patients. In this regard, statins (HMG-CoA reductase inhibitors), widely used anti-hyperlipidemic agents, have an anti-inflammatory effect through the inhibition of MMPs and proinflammatory cytokines; nevertheless, it is controversial whether the use of statins might have a protective role against cartilage degradation (16-18).

Chondrocyte access to lipids

Besides providing a major source of energy, lipids form a hydrophobic barrier in the human body, and have an essential role in transducing signals between cells and within cells as a second messenger (19).

Articular cartilage is an avascular tissue that supports the articular structure with its extracellular matrix components, such as proteoglycan and collagen. Chondrocytes, the sole cellular component in cartilage, are scattered within the matrix under physiologic conditions, and nutrition and soluble factors, as well as mechanical signals, are transmitted to the cells from the synovial fluid through the matrix architecture.

Busso *et al*. reported that human synovial fluid from arthritic joints (including those with OA) contains apolipoprotein(a) [apo(a)] (as part of lipoprotein(a) [LP(a)]), cholesterol, triglycerides, and HDL-cholesterol (20). The authors demonstrated that Lp(a) in arthritic joints originates from the circulation, and is not synthesized locally (20). Also, lipids are stored in both the matrix and chondrocytes in adult articular cartilage, comprising 1% or less of the wet weight (21, 22). A study of the morphology of calcifying epiphyseal cartilage by Bonucci *et al*. revealed the presence of lipid in cartilage, particularly in the cytoplasmic dense bodies in chondrocytes, the pericellular space, and the calcifying cartilage matrix (23).

Arkill *et al*. analyzed the transport of fatty acids in the extracellular matrix of cartilage (24). In their study, albumin was labeled with rhodamine and lauric acid was labeled with nitrogenz-2-oxa-1,3-diazole; the albumin-bound lauric acid dissociated in the surface layer of the cartilage. The fatty acid then entered the cartilage matrix at a faster rate than albumin, and accumulated at the tidemark (24). Their findings suggested a possible role of dietary lipid transport in OA, although the rate of transport into the cartilage was low.

Together, these findings indicate that both the articular cartilage and chondrocytes are in a position to interact with lipids and lipid-derived mediators.

Fatty acids

Direct and indirect roles of fatty acids in the development of OA have been postulated, although this remains controversial (reviewed in ref. 24). For example, total fatty acid levels in cartilage specimens are markedly increased in association with the degree of lesion severity in OA cartilage (21).

Adkisson *et al*. demonstrated using capillary gas chromatography/mass spectrometry that cartilage has a unique fatty acid composition; that is, normal young cartilage contains unusually low levels of n-6 polyunsaturated fatty acids (PUFA;18:2 *cis*-$\Delta^{9,12}$ linoleic and 20:4 *cis*-$\Delta^{5,8,11,16}$ arachidonic acids), and high levels of an unusual n-9 fatty acid (20:3 *cis*-$\Delta^{5,8,11}$ [the Mead acid]) (25); in addition, they reported that the high levels of n-9 fatty acid in young cartilage are

progressively depleted during aging, accompanied by an increase in n-6 PUFA (26). Although the significance of the change in fatty acid composition in OA development is not fully known, the authors suggested that the 20:3 n-9 fatty acid, which lacks a double bond at C-14, cannot be a substrate for cyclooxygenase (COX), thus the cartilage is protected from prostaglandin (PG)-induced inflammatory responses (25).

In chicken hypertrophic chondrocytes, extracellular fatty acid binding protein (Ex-FABP), a 21-kD lipocalin identified by Cancedda *et al*. (27), is synthesized and secreted into the extracellular matrix, and is suggested to be involved in chondrogenesis (28-30). Ex-FABP selectively binds with long-chain fatty acids, particularly unsaturated fatty acids like oleic, linoleic, and arachidonic acid (27). Interestingly, although Ex-FABP is expressed during embryonic development, Ex-FABP synthesis is increased by inflammatory agents, and Ex-FABP expression also occurs in adult pathologic cartilage, similar to osteoarthritic chicken (28). Ex-FABP might also act as a survival protein or a stress protein in chondrocytes, because depletion of Ex-FABP in chondrocytes using antisense methods decreases cell viability and increases apoptotic cell death (31). Thus, although the corresponding human homologue of Ex-FABP has not been identified, such interactions between a protein and fatty acids under stress conditions are a potentially worthwhile target of further investigation.

Ceramide and sphingolipid

Sphingolipids are derivatives of sphingosine that comprise the lipid bilayer of the cellular membrane. Ceramide is a sphingolipid precursor, composed of sphingosine and a fatty acid, and is not only a structural component of the membrane but is also an important cellular signaling molecule, regulating cell growth, differentiation, and programmed cell death (32). Sabatini *et al*. reported that ceramide induces MMP-1, 3, and 13 mRNA expression, MMP activity, and MMP-3 production; and induces apoptosis in chondrocytes (33). The authors also reported that ceramide induces cartilage aggrecan degradation, mainly by increasing aggrecanase activation (34).

Sphingosine-1-phosphate (S1P) is a bioactive sphingolipid metabolite formed by the phosphorylation of sphingosine via the activation of sphingosine kinase (SPHK) (reviewed in ref. 35). Like ceramide, S1P exerts pleiotropic functions on cell growth, differentiation, and survival, and regulates immune functions (35, 36) through two distinct pathways: as an intracellular second messenger and through the activation of specific G protein-coupled receptors. The S1P receptors (S1PRs) include the family of Endothelial Differentiation lysophosphatidic acid G-protein-coupled receptors (EDG) (35), such as EDG1/S1P1, EDG5/S1P2, EDG3/S1P3, EDG6/S1P4, and EDG8/S1P5. S1P is released mainly from platelets, but other cell types, such as erythrocytes or mononuclear cells, also produce S1P (37). Human serum contains relatively high concentrations of S1P (*i.e*. in nanomolar to micromolar concentrations) (35, 38). S1P is detected at a higher concentration in the synovial fluid than in the sera of patients with rheumatoid arthritis (RA) and OA (39). Further, synovial tissues of patients with RA and OA express SPHK mRNA (40), suggesting local production in inflamed joints. Interestingly, although ceramide induces programmed cell death, S1P has an anti-apoptotic effect (41); in fact, Kim *et al*. reported that S1P stimulates the proliferation of rat chondrocytes (42). As for human cells, we previously reported that human articular chondrocytes express members of the EDG/S1PR receptor family, and that S1P-stimulated chondrocytes produce higher amounts of prostaglandin E_2 (PGE_2) than non-stimulated cells (43). Further, S1P-stimulated chondrocytes show reduced aggrecan release, suggesting a catabolic effect of S1P in human cartilage (43). More recently, Stradner *et al*. (44), using human and bovine chondrocytes, reported that S1P dose-dependently induces the proliferation of chondrocytes and reduces nitric oxide (NO) formation via suppressing inducible NO synthase (iNOS) expression. Further, they demonstrated an inhibitory role of S1P in IL-1-induced MMP-13 expression in chondrocytes. The overall effect of S1P in chondrocytes requires further investigation. Nevertheless, these observations imply that the sphingolipid balance might have an important role in determining the fates of cells (41) such as chondrocytes and in the pathogenesis of OA (42) and RA (39).

Eicosanoids

Arachidonic acid (ARA) is a widely distributed ω-6 fatty acid with 20 carbons (20:4) that is an important component of the cellular membrane lipid bilayer. It is digested by phospholipase A and released from the membrane when inflammatory signals such as IL or interferons stimulate the cellular membrane. The released ARA is then converted to PGH_2 by COX, or to 5-hydroxy-6,8,11,14-eicosatetraenoic acid, and further to leukotrienes by lipoxygenase. Prostaglandin analogues are derived from PGH_2 through the activation of each synthase, such as PGD synthase, or PGE synthase (PGES).

Human articular chondrocytes express phospholipase, COX, 5-lipoxygenase, and other PG synthases (45-47). In this context, microsomal PGES (mPGES)-1, an inducible enzyme whose expression is induced by inflammatory cytokines such as IL-1 or tumor necrosis factor-α, are detected in OA chondrocytes and cartilage, which supports the notion that inflammatory responses occur in OA (46, 48). In addition to the proinflammatory cytokines, Gosset *et al*. recently reported that mechanical compression induces the expression of mPGES-1, as well as of COX-2 and PGE_2, in cartilage explants (49). Thus, a prolonged mechanical overload is suggested to enhance inflammatory responses in load-bearing articular joints.

Among the PGs, PGE_2 has been focused on for its regulatory role in chondrogenesis and chondrocyte differentiation (50, 51), and also for its potentially catabolic effects on differentiated chondrocytes and chondrocytic cells (52, 53). It remains controversial, however, whether PGE_2 directly modulates cartilage degradation (54, 55) and thus the precise mechanisms by which PGE_2 contributes to the pathogenesis of OA are not fully clarified (56). One

explanation for the inconsistency is the different responses of chondrocytes to PGE_2 due to differences in receptor expression. Specifically, PGE_2 receptors (PGE receptors: EP) have at least four isoforms in humans (EP1, EP2, EP3, and EP4), which differ in their distribution as well as in their function. Accumulating evidence suggests that PGE_2 exerts different effects on chondrocytes through each EP (50, 51, 57). For example, Miyamoto *et al*. reported that simultaneous stimulation of EP2 and EP4 receptors is essential and sufficient to elicit the PGE_2 effect on chondrocyte differentiation in rat primary chondrocytes (51). On the other hand, using HCS-2/8 chondrocytic cells, Fushimi *et al*. showed that the inhibiting effect of PGE_2 on tumor necrosis factor -a-induced MMP-1 production is mimicked by a selective EP4 receptor agonist, but not by an EP-2 agonist (57). With regard to EP expression, Brochhausen *et al*. reported that EP expression in the growth plate differs depending on *in situ* and *in vitro* conditions, or chondrocyte differentiation status (58). Also, Alvaraz-Soria *et al*. demonstrated that EP1, EP4, and COX-2 expression are upregulated by IL-1 in articular chondrocytes (59). Taken together, it is conceivable that the expression pattern of EP as well as that of COX/mPGES and PGs in arthritic joints varies between patients or joints according to the degree of mechanical stress or the presence (or absence) of growth factors and/or cytokines, leading to a heterogeneous response of the chondrocytes to different PG levels.

Nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit COX activity. As PGs and leukotrienes are thought to be involved in symptoms such as swelling and pain, NSAIDs, or COX inhibitors, are often prescribed to arthritic patients. Recent studies, however, showed that NSAIDs also have disease-modifying effects in OA (60-66) and might induce, at least in part, a COX-independent effect (64, 66).

PPAR and chondrocytes

Peroxisome proliferator-activated receptors (PPAR) are a family of nuclear steroid hormone receptors that are ligand-responsive transcription factors. There are at least three PPAR isoforms, *i.e*. α, β, and γ. Each PPAR isoform has a unique distribution pattern in various tissues, and responds to natural PPAR ligands (including prostaglandin analogues) or synthetic ligands (*e.g*. fibrates). Activated PPAR is involved in regulating the expression of a variety of genes, including those involved in the metabolism of glucose and lipids.

PPAR activation is also involved in cartilage metabolism (67-73). For example, Francois *et al*. reported that activation of PPARγ or PPARα suppresses MMP-1 expression in chondrocytes *in vitro* (67, 69). Poleni *et al*. observed that a PPAR agonist inhibits transforming growth factor (TGF)-β to induce proteoglycan expression in cultured rat chondrocytes (70). In an *in vivo* analysis, Afif *et al*. showed that PPARγ expression is lower in OA cartilage than in normal human cartilage, suggesting a role for IL-1 in the reduced PPARγ expression (71). Further, Boileau *et al*. demonstrated that the oral administration of a PPARγ agonist, pioglitazone, suppresses the expression of MMP-1, ADAMTS (a disintegrin and metalloproteinase with thrombospondin motifs)-5, and iNOS in cartilage, and inhibits pathogenic deterioration of articular cartilage in an experimental OA animal model (68). In the latter study, pioglitazone treatment of dogs with OA (at a dosage of 15 mg/day or 30 mg/day) significantly reduced MMP-1, ADAMTS-5, and iNOS levels, and inhibited activation of the signaling pathways for mitogen activated protein (MAP) kinases ERK-1/2, p38, and nuclear factor kappa-B (NF-κB). Based on these findings, Boileau *et al*. speculated that PPARγ regulation might lead to a novel therapy against OA (68). In their study, however, the involvement of possible changes in lipid and/or glucose metabolism in the cartilage pathology of the treated animals was not fully evaluated.

Lipid peroxidation and cartilage

Several reports implicate the involvement of oxidative stress and reactive oxygen species in cartilage degradation in OA, although the clinical significance remains unclear (reviewed in ref. 74). Reactive oxygen species oxidize n-3 and n-6 PUFA of membrane phospholipids, and produce aldehydic end products such as 4-hydroxynonenal (HNE) and malonaldehyde (75). These products of lipid peroxidation and oxidized low-density lipoprotein (ox-LDL) are found in OA joints (76-79). Also, the expression of lectin-like ox-LDL receptor 1 is detected in OA cartilage at higher levels than in normal controls (78, 80).

As for the effects of the lipoxidation products on cartilage, Morquette *et al*. showed that HNE cleaves type II collagen and inhibits the expression of type II collagen and tissue inhibitor of metalloproteinase-1; HNE also induces the expression of MMP-13 through the activation of p38 MAPK (77). Furthermore, COX-2 expression is induced in OA chondrocytes by 4-HNE through activation of transcription factors ATF-2/CREB-1, whereas aldehyde inhibits iNOS expression via the inactivation of NF-κB signaling (81). Akagi *et al*. demonstrated that the expression level of ox-LDL and lectin-like oxidized LDL receptor 1 in cartilage significantly correlates with the modified Mankin score for OA severity, and further, that *in vitro* stimulation of chondrocytes with ox-LDL reduces cellular viability and proteoglycan synthesis (80).

Mesenchymal stem cells (MSCs)

Multipotential MSCs are derived from bone marrow and can differentiate into mesenchymal tissues such as bone, cartilage, muscle, tendon, ligament, adipose, and stroma (82-84). The direction of MSC differentiation is regulated by multiple factors. For example, MSCs isolated from adult bone marrow aspirates differentiate into adipocytes during cultivation in the presence of 1-methyl-3-isobutylxanthine, dexamethasone, insulin, and indomethacin; whereas chondrogenic differentiation is promoted by a pelletted micromass culture without serum and with TGF-β (82). In addition, a recent study demonstrated that bone morphogenetic protein-7 induces adipogenic, but not osteo-/chondrogenic development (85). Of note, in *in vitro* experiments, differentiated cells develop into other phenotypes within the progeny of the stromal

stem cells; that is, in fully differentiated MSCs, commitment and differentiation are not irreversible (83, 84). For example, the addition of serum that includes fatty acids changes an osteoblastic phenotype to an adipocytic phenotype (83). Moerman *et al*. demonstrated that aging alters the differentiation potential of the MSCs; more specifically, the authors observed that bone marrow cultured from old mice develops fewer osteoblastic colonies and more adipocytic colonies than marrow derived from adult animals (87). The expression of osteoblast-specific transcription factors and markers is decreased whereas that of adipocyte-specific factors is increased, suggesting roles for the PPARγ2 transcription factor and TGF-β/bone morphogenetic protein pathways in the age-related changes (86).

STR/Ort mice: an animal model of spontaneous OA?

Male STR/Ort strain mice are suggested to be an animal model of spontaneous OA (87, 88). During aging, the majority (~ 85%) of these mice develop osteoarthritic lesions in the knee joint, especially in the medial tibial condyle (88). In addition to degenerative changes in the cartilage, the mice are obese (89). A recent study by Watters *et al*. (89), in which microarray analysis was used to study gene expression in cartilage and subchondral bone in the tibial plateau of STR/Ort mice, demonstrated the upregulation of bone-patterning genes and a general downregulation of lipid metabolism genes. Genes involved in the modification of fatty acids were most significantly enriched and regulated during OA progression (89). Furthermore, the authors investigated the interaction networks formed by the multiple genes detected, and found that reduced signaling through PPARα and PPARγ is key to the progression of OA in the STR/Ort mice. Based on these findings, the authors hypothesized that a shift in MSC differentiation from adipogenesis towards osteogenesis in the subchondral region is an important component of the pathogenesis of spontaneous OA in STR/Ort mice.

Nevertheless, because the development of OA in this strain shows sexual dimorphism (male mice are likely to suffer OA, but females are not), there might be other important arthrogenic factors such as a different inflammatory milieu in articular joints between male and female mice, possibly induced by estrogen. Also, Jaeger recently conducted a genetic study of STR/Ort mice based on quantitative trait loci analyses, and concluded that obesity is not a cause or a consequence of OA, but rather an independent trait (90). Thus, further investigation is required to conclude that OA and obesity are related in the STR/Ort mice.

Dietary lipids and OA

Dietary lipids modify the fatty acid composition of articular cartilage. Xu *et al*. (91) reported that chickens fed menhaden oil plus corn oil have decreased levels of 20:4 n-6 PUFA in the cartilage. In addition, in an *in vitro* study at the cellular level, Nagao *et al*. (92) demonstrated that the fatty acid composition in articular chondrocytes is influenced by the amount of extracellular fatty acids. Thus, modulation of lipid levels in cartilage may be achieved by relatively simple and applicable procedures. Although further investigation is needed to determine whether therapy against dyslipidemia will lead to clinically significant chondroprotection, more detailed characterization of the lipid-mediated intracellular signaling, *e.g*. via PPAR, may open an avenue to establish a novel therapeutic strategy against OA cartilage pathology.

Concluding remarks: is OA a metabolic disease?

In the past, OA was generally accepted to be simply an age- or mechanical stress-related degenerative joint disease; however, recent findings indicate that this concept is no longer sufficient to explain the entire process. It is important to broaden the concept to include the idea that a dysregulation of lipid metabolism might underlie cartilage pathology in OA and other mesenchymal tissues derived from common mesenchymal precursors. More specifically, in aged or stressed articular joints, a plethora of catabolic signals, including repeated mechanical stress, altered oxygen tension, enriched inflammatory mediators, and dysregulated levels of lipids such as fatty acids, might collectively lead to a pathologic shift of the phenotypic change in MSCs, resulting in unbalanced turnover and degradation of the articular cartilage structure. An array of lipid-derived mediators such as PGs and ceramide further modulate the inflammatory reaction that occurs in the joint. Chondroprotection might be achieved in the future by modulating lipid metabolism *in vivo*.

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