Age-Related Changes in the Musculoskeletal System and the Development of Osteoarthritis

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KEYWORDS

• Aging • Osteoarthritis • Articular cartilage
• Elderly • Cell senescence • Oxidative stress

The prevalence of osteoarthritis (OA) increases with age such that 30% to 50% of adults older than 65 years suffer from this condition.[1,2] Radiographic changes of OA, in particular the presence of osteophytes, are even more common such that radiographic surveys of multiple joints (hands, spine, hips, and knees) reveal OA in at least one joint in over 80% of older adults.[3] However, only about half of people with radiographic OA experience significant symptoms. Likewise, not all older adults with symptoms of joint pain have radiographic evidence OA in the painful joint. In a study of 480 adults older than 65 years who reported chronic knee pain, only about 50% had radiographic evidence of knee OA.[4]

Although OA is most common in the hands, involvement of the knees and hips is usually much more disabling. Radiographic involvement of the distal interphalangeal joints in the hand was present in more than half of men older than 65 and more than half of women older than 55 years,[5] but only 13% of men and 26% of women older than 70 were found to have symptomatic hand OA.[6] The prevalence of radiographic knee osteoarthritis in subjects aged 60 years and older increased with each decade of life from 33% among those 60 to 70 years to 43.7% among those older

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than 80 years, while the prevalence of symptomatic knee OA in these subjects was 9.5%, and increased with age in women but not men.[7] In the Johnson Country Osteoarthritis cohort, the prevalence of radiographic knee OA rose from 26.2% in the 55- to 64-year range to nearly half of participants in the 75+ group, and the prevalence of symptomatic knee OA likewise increased from 16.3% to 32.8% between these age groups.[8] Symptomatic hip OA in this cohort was reported as 5.9% in the 45- to 54-year age group, increasing to 17% in the 75+ age group.[9]

The relationship between aging and OA is well known but the mechanisms for how aging predisposes the joint to developing OA are still not fully understood. Changes intrinsic to the joint as well as those extrinsic (such as sarcopenia, altered bone remodeling, and reduced proprioception) contribute to the development of OA. The concept that aging contributes to, but does not directly cause OA, is consistent with the multifactorial nature of this condition and the disparity in which joints are most commonly affected. In this article, current concepts of the biology of OA are reviewed and the relationship between aging and the development of OA considered.

THE PATHOBIOLOGY OF OSTEOARTHRITIS

OA is a multifactorial condition, but the pathologic changes seen in osteoarthritic joints have common features no matter what the cause(s) of the condition in a given individual. These features include degradation of the articular cartilage starting at the joint surface and progressing to full thickness loss, thickening of the subchondral bone with accumulation of poorly mineralized matrix, osteophyte formation at the margins of joint surfaces, variable degrees of synovial inflammation with limited pannus formation, degeneration of ligaments and in the knee the menisci, with eventual ligamentous rupture and meniscal extrusion, and hypertrophy of the joint capsule contributing to joint enlargement (**Fig. 1**). In some individuals, increased subchondral bone remodeling results in bone marrow lesions detected on magnetic resonance imaging (MRI) and, in many older adults, calcification in the articular cartilage and/or the menisci is seen on plain radiographs. In the articular cartilage, the earliest changes at the joint surface occur in the areas that receive the greatest mechanical forces.

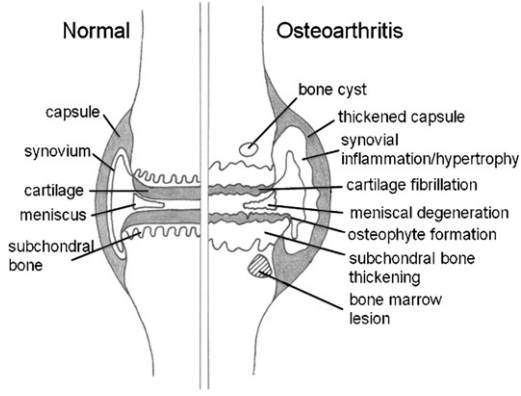

Fig. 1. Pathology of osteoarthritis. The osteoarthritic joint is characterized by degradation and loss of the articular cartilage, thickening of the subchondral bone accompanied by formation of bone marrow lesions and cysts, osteophytes at the joint margins, variable degrees of synovitis with synovial hypertrophy, meniscal degeneration (knee), and thickening of the joint capsule.

As OA progresses, the loss of the articular cartilage affects joint movement because of the loss of a smooth lubricated surface responsible for the normal gliding motion of the joint. The pathologic changes noted in the other joint tissues also contribute to the loss of normal joint function and, because unlike the cartilage they contain pain fibers, these tissues are responsible for the pain experienced by people with OA.

There are reasons to believe that although OA has common pathologic features seen once the disease becomes advanced, it may start with selected features that are dependent on the initiating factors in a given individual. For example, in an individual with posttraumatic OA resulting from rupture of the anterior cruciate ligament, the condition likely started with a period of acute joint inflammation with synovitis and cartilage matrix destruction followed later by development of bony changes, whereas in an individual with OA related to obesity it may have started with increased bone formation followed by articular cartilage matrix destruction and secondary synovial inflammation stimulated by release of cartilage matrix fragments. The early stages of OA have been difficult to study. Most people do not develop symptoms until significant joint damage has occurred, commonly after age 50 to 60 years, but there is radiographic evidence for OA in a significant percentage of women beginning in the early forties.[10] Researchers are attempting to develop biomarkers and advanced imaging techniques that could detect early-stage disease but, given the slowly progressive nature of OA, it will be some time before sufficient information is available to determine the predictive power of these techniques.

At the cell and tissue level, cartilage in OA is characterized by an imbalance in matrix synthesis and matrix degradation. The chondrocyte is the only cell type present in articular cartilage and therefore is responsible for both the synthesis and breakdown of the cartilaginous extracellular matrix.[11] Signals generated by cytokines, growth factors, and the matrix regulate chondrocyte metabolic activity. In the early stages of OA, there is evidence of increased matrix synthesis, although not all the matrix proteins produced are the same as those made by normal adult articular chondrocytes. There is increased expression of the fetal form of type II collagen (type IIA)[12] and of type III collagen and fibronectin,[13,14] as well as proteoglycans with altered sulfation patterns.[15] Excessive matrix degradation progressively overwhelms matrix synthesis, and this appears to be caused by inflammatory and catabolic signals that are present in excess of the anti-inflammatory and anabolic signals (**Fig. 2**). Proinflammatory cytokines found in OA cartilage include interleukin (IL)-1, IL-6, IL-7, IL-8, and tumor necrosis factor (TNF)-α, to name just a few. The presence of a large number of inflammatory mediators within the articular cartilage indicates that OA is much more inflammatory than previously thought. The excess of inflammatory signals inhibits matrix synthesis and promotes increased production of matrix degrading enzymes, including matrix metalloproteinases (MMPs), aggrecanases, and other proteases that degrade the cartilage matrix. As OA develops, chondrocytes can assume a hypertrophic phenotype characterized by production of type X collagen, alkaline phosphatase, and MMP-13 (collagenase-3).[13]

Chondrocyte death has been observed during the development of OA, but whether this is an early or late event is not clear.[16,17] Because cartilage lacks an abundant supply of stem or progenitor cells, the loss of chondrocytes to cell death results in a decline in cell numbers. This decline is most apparent in the superficial region of the articular cartilage. Although normally adult articular chondrocytes rarely divide, there is evidence for cell proliferation during the development of OA, resulting in clusters of chondrocytes being present. However, these cells are unable to maintain the matrix, which may be due at least in part to a reduced ability to respond to growth factor stimulation further contributing to an imbalance in matrix synthesis and degradation.

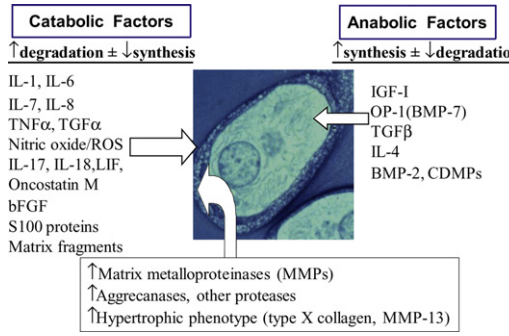

Fig. 2. Catabolic and anabolic factors that regulate chondrocyte function. A host of factors, produced locally by articular chondrocytes, regulate matrix synthesis and degradation in articular cartilage. As osteoarthritis develops, catabolic activators overwhelm anabolic factors resulting in an imbalance in matrix synthesis and degradation. Matrix degradation is mediated by MMPs, aggrecanase, and other proteases produced by the chondrocyte in response to the catabolic factors. A change in the chondrocyte phenotype to a hypertrophic phenotype also occurs, likely in response to one or more of the catabolic factors. BMP, bone morphogenetic protein; CDMP, cartilage-derived morphogenetic protein; FGF, fibroblast growth factor; IGF, insulin-like growth factor; IL, interleukin; OP, osteogenic protein; TGF, transforming growth factor; TNF, tumor necrosis factor.

In contrast to matrix loss in the articular cartilage, the subchondral bone undergoes increased matrix production, resulting in a thickening of this region. Older theories of OA suggested that the increased subchondral bone resulted in increased stiffness that contributed to the degradation of the overlying cartilage by increasing local stresses.[18,19] However, later studies found that the subchondral bone in OA was poorly mineralized and perhaps less stiff than normal bone.[18–20] More recently, studies have focused on inflammatory mediators produced by subchondral bone cells that could diffuse through the calcified cartilage zone or enter through cracks in the calcified cartilage to negatively affect the overlying articular cartilage.[21] The presence of localized areas of increased bone remodeling detected by bone scans or MRI has been noted in areas of cartilage loss, and is associated with pain in OA.[22] The correlation of these lesions in the knee with the location of excessive loading, that is, medial bone lesions in association with varus alignment and lateral lesions with valgus alignment, suggest they are mechanically mediated.[23]

The degree of synovitis present in OA is variable. In people with OA severe enough to require knee replacement, about one-third of patients had marked synovitis, one-third moderate synovitis, and one-third little to no synovitis,[24] which suggests that synovitis may be important in a subset of people with OA but that it is not required to progress to end-stage disease. However, an arthroscopic study of people with early OA did find an association between the presence of synovitis and progression of cartilage lesions measured a year later.[25] Studies of OA synovial fluid have revealed the presence of inflammatory cytokines that could be involved in stimulating cartilage destruction as well as destruction of other joint tissues such as the meniscus and ligaments. The growth factor transforming growth factor (TGF)-β, although an important contributor to cartilage matrix production, may be responsible for the stimulation of synovial hypertrophy as well as osteophyte formation.[26]

Although the synovium is involved in OA, the extent of inflammation is usually less than that found in rheumatoid arthritis (RA), where pannus formation is much more extensive and appears to be directly responsible for joint tissue destruction.

The extent of synovial inflammation as well as higher systemic levels of inflammatory mediators has been used to classify RA as inflammatory arthritis and OA as ''noninflammatory.'' However, as noted earlier, inflammatory mediators are responsible for joint tissue destruction in OA and elevated serum levels of C-reactive protein,[27] and cytokines including IL-6[28] in people with OA indicate that inflammation plays a role in OA as well as RA.

RISK FACTORS FOR DEVELOPMENT OF OSTEOARTHRITIS IN THE ELDERLY

Besides age, the common risk factors for OA include obesity, previous joint injury, genetics, and anatomic factors including joint shape and alignment.[29] Additional factors include gender, race, and nutritional factors, such as vitamin D deficiency.[30,31] These risk factors appear to interact with age to determine which joints are affected by OA and how severe the condition will be (**Fig. 3**). A joint injury earlier in life predisposes that particular joint to OA later in life.[32] There is also evidence to suggest that an older adult will develop OA faster than a younger adult after an acute joint injury such as an anterior cruciate ligament tear.[33] Other age-related factors that contribute to the development of OA include a decline in muscle strength, loss of proprioception, degenerative changes in the meniscus and joint ligaments, increased bone turnover, and calcification of joint tissues.[29,34,35]

In terms of knee OA, recent MRI studies have revealed the important role of the meniscus. Incidental meniscal damage on MRI is quite common in the elderly, ranging from a prevalence of 19% in women aged 50 to 59 years to 56% in men in the 70- to 90-year-old age group.[36] The prevalence increased to 63% in symptomatic subjects with at least moderate radiographic OA measured by plain films. In a longitudinal study, symptomatic subjects with significant meniscal damage had an odds ratio of

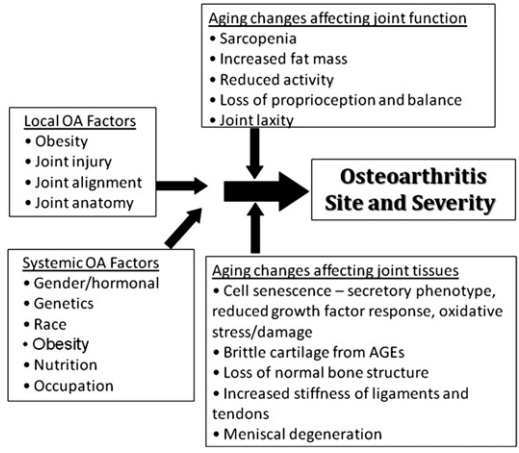

Fig. 3. Relationship between osteoarthritis risk factors and aging changes that interact to promote the development of osteoarthritis. OA is a multifactorial condition that is not simply the direct result of aging. Rather, aging changes increase the susceptibility to the development of OA when OA risk factors are also present. The OA factors are both local and systemic. Obesity can have local effects due to increased joint loading and systemic effects due to the production of adipokines and cytokines by adipose tissue that may contribute to the development of OA. The various aging and OA factors interact to influence the site and severity of the disease.

7.4 for the development of radiographic knee OA.[37] These studies suggest that age-related changes in the meniscus may contribute to meniscal degeneration that in turn may contribute to the development and progression of knee OA.

Recent MRI studies have also shown that anterior cruciate ligament (ACL) disruption is common in older adults with knee OA, even without a known history of trauma.[38] A well-known risk factor for the development of posttraumatic knee OA, age-related changes in the ACL may predispose the ligament to spontaneous rupture or rupture after minimal trauma. Changes that occur in aging ligaments such as increased stiffness from collagen cross-linking combined with decreasing fibril diameter may increase the risk for ACL tears.[39] Studies are needed to better characterize aging changes in joint ligaments and to determine if the mechanisms are similar to those occurring in other soft tissues in the joint such as the cartilage and meniscus.

As detailed earlier, the subchondral bone is clearly involved in the development of OA, and knowledge is being gained on the mechanisms that seem related to increased bone remodeling and the laying down of an abnormal matrix, processes that are potentially affected by aging.[19,40] Bone marrow lesions detected by MRI in people with OA are associated with pain and disease progression.[22,23,41] First thought to represent edema because of their bright appearance on T2-weighted MRI, these areas most likely represent areas of localized remodeling.[42] The association of bone marrow lesions with malalignment suggests excessive loading may play a role in their development. Increasing age has been shown to be a risk factor for the development of bone marrow lesions in asymptomatic individuals.[43] This is another area where future research may help elucidate how aging changes in a tissue outside of cartilage contributes to the risk of OA progression in older adults.

Finally, calcification and crystal formation within joint tissues are common findings in older adults that may play a role in OA progression. The association between calcium pyrophosphate deposition disease (CPPD) and the presence of radiographic osteoarthritis has been well established[35,44]; however, the role of calcium crystals in the progression of OA has been debated. Some believe that OA and CPPD are common but separate age-related conditions and others believe that the two are closely connected.[35,45,46] Because OA and calcium pyrophosphate are equally associated with osteophyte formation, it has been suggested that mechanical stress may induce release of chemokines that encourage both proliferative bone changes and calcium pyrophosphate formation.[47,48] Crystals within the articular cartilage or in the synovium could stimulate toll-like receptors on chondrocytes and synovial cells, resulting in production of inflammatory mediators.[49] Crystals may play a role in erosive OA, a more destructive form of OA seen most commonly in the distal digits of the hands in elderly women in which inflammation is a prominent component.[50,51]

THE CONTRIBUTION OF AGING IN CELLS AND TISSUES TO THE DEVELOPMENT OF OSTEOARTHRITIS

Cell Senescence

Most of the work to date on the relationship between aging changes at the cellular level and the development of OA has focused on the articular cartilage. Given the similarities between chondrocytes and meniscal cells these studies probably also relate to aging in the meniscus, but more studies need to be done in that specific tissue. Normally there is little to no cell turnover in adult articular cartilage[52] and so chondrocytes are thought to be long-lived cells and, as such, can accumulate age-related changes over many years. In many tissues, senescent cells can be replaced by differentiation of cells from a local pool of progenitor cells, but in adult articular

cartilage it is not clear if such a pool exists. Recent studies have challenged the notion that cartilage does not contain progenitor cells, but these studies were performed with either bovine tissue from very young animals[53] or OA tissue,[54] the latter of which might have included cells from other tissues such as the synovium or bone marrow that can make their way to the cartilage when it is severely damaged. Even if there is a local pool of progenitor cells, they do not appear to be capable of replacing senescent, damaged, or dead cells in the articular cartilage.

There does appear to be an age-related reduction in the number of chondrocytes in cartilage and a further loss of cells in OA cartilage, but the extent of cell death is debated.[16,17,55] A 30% decrease in cell density between the ages of 30 and 70 years has been described in human hip specimens.[56] However, a study of human knees found less than 5% cell loss with aging.[52] Although many studies have reported apoptotic chondrocytes in OA cartilage,[17] few have examined apoptosis in cartilage with normal aging with the exception of a study in rat cartilage that found evidence of increased apoptosis with aging.[57] An age-related decline in levels of the high-mobility group box (HMGB) protein 2, which is expressed in the superficial zone of cartilage, might contribute to an increase in chondrocyte death.[58] HMGB2 is a nonhistone chromatin protein that can serve as a transcriptional regulator. Deletion of HMGB2 in transgenic mice was found to cause an early onset of OA-like changes in the superficial zone of cartilage that were associated with an increase in susceptibility of chondrocytes to cell death.

Chondrocytes have been shown to exhibit telomere shortening,[59] a classic feature of cell senescence, but because chondrocytes rarely divide it is unlikely that the shortened telomeres represent replicative senescence. Classic replicative senescence requires more than 30 to 40 population doublings,[60] which would be unlikely to occur in adult cartilage. Telomere shortening can also occur from extrinsic or ''stress-induced'' senescence that results from the chronic effects of oxidative damage, activated oncogenes, and inflammation.[61,62] This form of cell senescence is much more likely in cartilage, where oxidative stress and chronic inflammation could be factors.[63]

The concept of cell senescence has developed beyond classic replicative senescence, which refers to the inability of senescent cells to undergo further cell division. There is mounting evidence that cell senescence can also result in a phenotypic alteration of cells called the senescent secretory phenotype.[62,64] This phenotype is characterized by the increased production of cytokines including IL-1, IL-6, and IL-8, MMPs, and growth factors such as epidermal growth factor. The accumulation of cells expressing the senescent secretory phenotype can contribute to tissue aging and given the increased production of cytokines and MMPs in OA cartilage, may directly link aging to the development of OA (**Table 1**). There is evidence for increased MMP-3 and MMP-13 in cartilage with aging[65] as well as an age-related accumulation of collagen neoepitopes representing denatured or cleaved collagen.[66,67] Cleavage of type II collagen by MMPs has been noted in cartilage from hip joints of older individuals[66] as well as in ''normal-appearing'' knee cartilage taken at autopsy.[65] However, because these joints are commonly affected by OA, it is not clear if the collagen damage represents aging changes, early OA, or a continuum from aging to OA.

Cell senescence in cartilage has been associated with a decline in the ability of chondrocytes to respond to growth factors, and this could be an important contributing factor to the change in the balance of anabolic and catabolic activity seen in OA. Key matrix stimulating growth factors in cartilage include insulin-like growth factor (IGF)-I, osteogenic protein (OP)-1 (bone morphogenetic protein [BMP]-7), and TGF-β. There is substantial evidence for a decline in the chondrocyte response to IGF-I with aging[68–70] and in chondrocytes isolated from OA cartilage.[69,71] There is evidence that

Table 1
Aging changes in joint tissues and the contribution of aging to the development of OA

Aging Change	Contribution to OA
Accumulation of cells exhibiting the senescent secretory phenotype	Increased cytokine and MMP production stimulates matrix degradation
Oxidative stress/damage	Increased susceptibility to cell death and reduced matrix synthesis
Decreased levels of growth factors and decreased growth factor responsiveness	Reduced matrix synthesis and repair
Increased AGE formation	Brittle tissue with increased fatigue failure
Reduced aggrecan size and cartilage hydration and increased collagen cleavage	Reduced resiliency and tensile strength
Increased matrix calcification	Altered mechanical properties and potential activation of inflammatory signaling

Abbreviations: AGE, advanced glycation end-products; MMP, matrix metalloproteinases.
Reproduced from Anderson AS, Loeser RF. Why is osteoarthritis an age-related disease? Best Pract Res Clin Rheumatol 2010;24:15–26; with permission.

the decline in IGF-I response (or IGF-I resistance) is due to altered cell signaling. A reduced ability of IGF-I to activate cell signaling was noted in aging rat cartilage[70] and in aged equine chondrocytes.[72,73] Because IGF-I is an important autocrine survival factor in cartilage[74] the age-related decline in IGF-I signaling may play a role in age-related cell death. The expression and amount of OP-1 present in cartilage declines with age,[75] which may be related to increased DNA methylation at the OP-1 promoter.[76] Likewise, levels of TGF-β2 and TGF-β3 (but not TGF-β1) decline with age as does the level of the TGF-β receptors I and II.[77] Similar to IGF-I, age-related alterations in the TGF-β signaling pathway have been described, and these may also contribute to the development of OA.[78]

Aging in the Cartilage Matrix

Age-related changes that occur in the cartilage matrix can also contribute to the development of OA. There is evidence from knee MRI studies that cartilage thins with aging, particularly at the femoral side of the joint[79] and at the patella,[80] suggesting a gradual loss of cartilage matrix with aging. This loss could be due to a loss of cells and the reduced growth factor activity discussed above, but could also be due to something as simple as reduced water content. Articular cartilage is about 70% to 80% water. The water content in cartilage is controlled to a large extent by the presence of aggrecan, a large ''aggregating'' proteoglycan found in the cartilage matrix. Aggrecan contains highly sulfated glycosaminoglycan chains that are negatively charged and therefore very hydrophilic, and are responsible for the resiliency in cartilage. Age-related changes in the size, structure, and sulfation of aggrecan have been reported,[81–84] which reduce cartilage resiliency and hydration.[85]

Perhaps the best studied aging-related matrix protein modification in cartilage is the accumulation of advanced glycation end-products (AGEs). AGEs are produced by the spontaneous nonenzymatic glycation of proteins that occurs when reducing sugars including glucose, fructose, or ribose react with lysine or arginine residues.[86] Because the articular cartilage has a relatively low turnover rate, it is particularly susceptible to AGE formation that in other tissues occurs most commonly in diabetics with chronically elevated glucose levels. Type II collagen, the most abundant matrix protein in cartilage, has a half-life that has been calculated to be longer than 100 years.[87]

The accumulation of AGEs in knee cartilage has been suggested to play a role in the development of OA.[86,88] Modification of collagen by AGE formation results in increased cross-linking of collagen molecules. The most common AGE-related cross link is pentosidine, which has been found to be present in cartilage in increasing amounts with age.[87,89,90] Formation of excessive collagen cross-links affects the biomechanical properties of cartilage leading to increased stiffness, making the cartilage more brittle[91] and increasing the susceptibility of the tissue to fatigue failure.[89] Increased levels of AGEs in cartilage have also been associated with a decline in anabolic activity.[92] Although reported in a small study that used tissue removed at the time of joint replacement, amyloid has been detected in meniscal tissue from older adults,[93] suggesting additional age-related matrix changes may play a role in the development of OA.

The Role of Age-Related Oxidative Stress and Oxidative Damage in OA

The theory that aging changes in tissues are the result of oxidative damage from the chronic production of endogenous reactive oxygen species (ROS) or ''free radicals'' was proposed in the 1950s[94] and is still relevant to aging in joint tissues such as the articular cartilage. Human articular chondrocytes actively produce several different forms of ROS including superoxide, hydroxyl radical, hydrogen peroxide, as well as reactive nitrogen species, most notably nitric oxide.[95–97] Increased levels of intracellular ROS were recently detected in cartilage from old rats when compared with young adult rats.[98] Normally the levels of ROS are controlled by the balance of ROS production and the presence of various antioxidants. Glutathione is an important intracellular antioxidant, and when levels of ROS are in excess the ratio of oxidized to reduced glutathione is changed. Previous studies have detected an increase in oxidized glutathione with age in chondrocytes isolated from normal ankle tissue.[99] There is also evidence that levels of antioxidant enzymes, including catalase and superoxide dismutase, are present at lower levels with aging[98,100] and in OA cartilage.[101]

Because of the slow turnover of cells and matrix in cartilage, it is likely that damage from excessive ROS would accumulate over time. Evidence for oxidative damage in articular cartilage was provided by a study showing increased nitrotyrosine (a measure of oxidative damage to proteins) with aging, as well as with OA.[102] Increased levels of ROS can result in DNA damage, which has been noted in OA cartilage[103] including in mitochondrial DNA.[104] This damage can affect cell viability and matrix production. Oxidative stress can also contribute to the senescent phenotype of chondrocytes.[105] The resistance to IGF-I noted in aging and OA chondrocytes may also be related to excessive levels of ROS that have been shown to interfere with normal IGF-I signaling, resulting in reduced matrix production.[106] This situation could also occur indirectly by the production of oxidized low-density lipoproteins in cartilage, which can in turn contribute to chondrocyte senescence and reduced chondrocyte signaling.[107]

An aging-related increase in ROS levels could play an important role in the development of OA.[108] The various inflammatory mediators found to be increased in OA, including IL-1, IL-6, IL-8, TNF-α, and other cytokines, can all stimulate the further production of ROS, and ROS in turn can be involved in the increased production of MMPs.[109] In support of a role for ROS in the development of OA, the use of several antioxidant vitamins along with selenium (a glutathione peroxidase cofactor) was shown to reduce the development of OA in a mouse model,[110] *N*-Acetylcysteine (NAC) reduced cartilage destruction and chondrocyte apoptosis in a rat OA model[111] and in impact-loaded osteochondral explants,[112] and low intake of antioxidant vitamins has been associated with OA progression in humans.[113] However, we still have much to learn about ROS and oxidative stress in aging and OA in order to define

more specific targets. In human clinical trials of chronic age-related diseases, the use of general antioxidants or antioxidant vitamins has had modest or no benefit. Defining the specific mechanisms by which ROS act, including their role in the regulation of cell signaling, should provide novel and more specific targets for therapies that would represent an advance over nondirected treatment with general antioxidants.

SUMMARY

Age is a primary risk factor for the development of OA, likely due to aging changes in cells and tissues that make the joint more susceptible to damage and less able to maintain homeostasis. OA is characterized by an imbalance between catabolic and anabolic activity driven by local production of inflammatory mediators in the cartilage and surrounding joint tissues. The senescent secretory phenotype likely contributes to this imbalance through the increased production of cytokines and MMPs and a reduced response to growth factors. More information is needed to better understand how aging changes in the bone, meniscus, and ligaments contribute to the development of OA. Oxidative stress appears to play an important role in the link between aging and OA. Understanding the basic mechanisms by which excessive ROS affect cell function at the molecular level may provide the knowledge needed to develop novel preventative treatments for OA.

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