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# Aging Processes and the Development of Osteoarthritis

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## Abstract

**Purpose of review—**Aging is a primary risk factor for the development of osteoarthritis (OA) and the understanding of how aging processes contribute to the development of OA is an important area of active research. The most recent literature in this area was reviewed in order update investigators on the status of the field.

**Recent findings—**The field is beginning to move beyond a cartilage focus to include other joint tissues relevant to OA such as ligaments, meniscus, and bone. Synovitis also appears to play a role in OA but has not been a focus of aging studies. Studies in small animals, including mice and rats, demonstrate age-related changes that can contribute to OA and show that animal age is a key factor to be considered in interpreting the results of studies using surgically-induced models of OA. There is accumulating evidence that cellular processes such as damage-induced cell senescence contribute to OA and a growing body of literature on the role of epigenetic regulation of gene expression in aging and OA.

**Summary—**Not all OA is due to aging processes in joint tissues but the age-related changes being discovered certainly could play a major contributing role.

### Keywords

aging; osteoarthritis; ligament; articular cartilage; meniscus; bone

## Introduction

It is well accepted that increased age is a key risk factor for osteoarthritis (OA) in the joints typically affected including hands, hips, knees, and spine. The rare cases of OA diagnosed in people under the age of 25–30 years are almost always due to mutations in matrix genes that cause significant structural abnormalities and/or joint deformities. OA is a prototypic “degenerative” condition of aging that in the past had been attributed to an accumulation of “wear and tear” type damage to joint tissues. As both general aging research and OA specific research have progressed, it has become increasingly clear that conditions associated with aging, such as OA, are much more complex than an accumulation of damage over time and that the term degenerative disease is a vast oversimplification. This review focuses on research published over the past 18 months in the field of aging and OA which has contributed to the advancement in our knowledge of this complex and multifactorial disease. Although intervertebral disc aging likely contributes to OA in the spine, this area of research is not covered here.

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OA in humans usually becomes symptomatic after the age of about 50 years which is also when the radiographic changes of OA become more common. Although radiographic signs of OA, such as osteophytes and joint space narrowing, do not always correlate well with symptoms, epidemiologic studies of large cohorts commonly depend on radiographs to define OA. A recent report from the Chingford Women's study, which is a community-based cohort living in the UK, showed that at baseline, when the median age was 53 years, 13.7% of the subjects had radiographic knee OA [1•]. Over the 14 subsequent years of the study the annual cumulative incidence was 2.3%. The affect of age was apparent when the annual rate between baseline and year 5 (2.3%) was compared to the rate between years 10 and 15 (3.3%). Demonstrating that age is not the only risk factor for OA, just over half of the entire cohort (52.2%) remained free of radiographic knee OA over the 14 years of follow-up when the median age had reached 68 years but obese subjects had an almost 20% higher cumulative incidence of knee OA compared to both normal and overweight categories.

Atherosclerosis is another common age-related multi-factorial disease. In the Rotterdam population of men and women aged 55 years and older, radiographic OA and atherosclerosis (measured as carotid intima media thickness or plaque) were associated, particularly for hand OA in the distal interphalangeal joints and carotid plaque in women (OR 1.4, CI 1.19–1.65) [2]. The risk for hand OA has been thought to be more associated with systemic or metabolic factors than knee OA, which has a greater association with joint injury. Systemic inflammation, which is associated with aging, could play a role in both diseases. Previous studies have associated systemic markers of inflammation, such as high sensitivity c-reactive protein with radiographic OA and atherosclerosis, and a recent study of subjects reported an association of serum levels of high sensitivity CRP, as well as TNFα, with worsening knee pain [3•].

Because articular cartilage lacks a nerve supply, joint pain is thought to be due to OA-related changes in the synovium, the bone (including osteophytes), the joint capsule, the ligaments, and, in the knee, the meniscus[4]. Age-related processes in these tissues and their role in the development of OA have been less well studied than in the articular cartilage. However, as will be reviewed below, recent studies demonstrate age-related changes in these tissues that may be important to the development of OA. Most of this work is at the histological level while recent studies of aging in cartilage have focused more on cellular changes which will be reviewed as well.

## Aging changes in tissues other than cartilage which may contribute to OA

Injury to the meniscus is an important risk factor for knee OA. MRI studies have shown that meniscal lesions are common in people with knee OA, even without a known history of joint injury [5•] and meniscal lesions are associated with knee pain [6]. A pathological study of menisci from deceased human tissue donors by Pauli et al[7••], revealed age-related changes including increased Safranin-O staining, decreased cell density with associated appearance of acellular zones, mucoid degeneration, and loss of collagen fiber organization. These changes are similar to those seen in other tissues with aging, such as articular cartilage. The exception is the increased Safranin O staining. Increased staining would suggest a focal increase in proteoglycans which would be difficult to explain unless cells in the aged meniscus were producing more proteoglycans. An alternative is that loss of some other matrix protein, such as collagen, allowed for increased dye binding. As expected, menisci taken from knees that exhibited significant cartilage pathology showed more severe matrix disruption, areas of calcification, and large areas of cell loss accompanied by focal areas of cell clusters, similar to the clusters seen in OA cartilage.

A study that compared normal bovine meniscus obtained from fetal, juvenile and adult animals demonstrated developmental changes that result in increased size of the meniscus and maturation of the mechanical properties of the tissue but also found the repair capacity of the tissue, when studied *in vitro* after full-thickness defects were created, was reduced with age [8]. In a human study, expression of a panel of pro-inflammatory and matrix degrading genes was evaluated using RNA from meniscal tissue obtained during partial meniscectomy in patients with either an isolated meniscal tear or one accompanying an ACL tear[9•]. An age-related difference in gene expression was noted such that samples from patients under the age of 40 years exhibited higher IL-1β, ADAMTS-5, MMP-1, MMP-9, MMP-13, and NFκB2. This finding suggests that younger patients exhibit a greater inflammatory and catabolic response after injury which would seem to contradict the notion that aging promotes a more pro-inflammatory state. However, an active response to acute injury could be important to the body's attempt at wound repair and aging may be more associated with a chronic low grade pro-inflammatory state that contributes to degenerative type meniscal tears.

In addition to aging studies in the human meniscus, the anterior [10••] and posterior[11] cruciate ligaments (ACL and PCL respectively) have also been studied. Similar to the meniscus work noted above by Pauli et al[7••], the same group used human donor tissue and compared changes in the ACL and PCL to those in cartilage from the same joints. Even though the subjects did not have a known history of joint trauma, ligamentous changes were common in older adults and included ACL rupture in 10% of the knees but no ruptures of the PCL. The correlations between histologic scores of degeneration in the ligaments and cartilage were also much stronger for the ACL than the PCL and, unlike the ACL, the PCL changes were not significantly correlated with donor age. A difference from the meniscus study, where inflammatory cell infiltration was not apparent, was the finding of ligament sheath inflammation which was much more common in the ACL than PCL and increased with age. These studies suggest that aging changes, particularly in the ACL, likely contribute to age-related OA.

In addition to the soft-tissues discussed above, bone is affected in OA with osteophyte formation, subchondral plate thickening, and focal areas of necrosis and remodeling that appear as bone marrow lesions on MRI in areas of greatest mechanical stress (reviewed in[4]). The bone lesions could be attributed to aging processes in the osteocytes which are important regulators of the bone remodeling that occurs in response to mechanical stress. An autopsy study using normal human femoral bone from 32 tissue donors with ages in a range between the 1$^{st}$ and 9$^{th}$ decade noted an age-dependent decrease in total osteocyte lacunar number and hypermineralization of the osteocyte lacunae that were present which has been called micropetrosis [12]. These changes could reduce the capacity of bone to respond to mechanical stress and make the bone more brittle. Consistent with a role in OA, similar findings of a reduction in osteocyte lacunar number and an increase in micropetrosis were noted in a study of bone from patients with hip OA [13•].

## Rodent models of aging and OA

Because of the difficulties studying cellular and molecular processes in human joint tissue *in vivo*, animal models are necessary. A comprehensive histological study of knee joint tissues from male C57BL/6 mice demonstrated that lesions induced by a commonly used surgical procedure (destabilized medial meniscus or DMM model) were similar to those that developed naturally with age [14]. This study supported previous work demonstrating the importance of chondrocyte death with both aging and OA as well as an age-related decline in cartilage thickness. The lesions were most prominent in the medial tibial plateau, which is also the most common site for human OA. The findings were consistent with a histological

study of young and old male Wistar rats which also had a reduction in cell number and in non-calcified cartilage thickness in the medial plateau [15].

In a study that compared the severity of histologic OA and changes in gene expression between young adult (12 week-old) and middle-aged (older) adult (12 month-old) male C57BL/6 mice, the articular cartilage lesions developing after DMM surgery in the older animals were twice as severe as those in the young [16•]. Significant differences in the patterns of gene expression were noted when RNA isolated from the joint organ (cartilage, subchondral bone, meniscus, and joint capsule with synovium) was analyzed by microarray. More genes were upregulated in the older mice relative to the young and differentially expressed genes included muscle structure and development, and immunoglobulin domain genes. In order to study which genes changed with age, independent of the DMM surgery to induce OA, the sham control joints were compared. This revealed an age-related decrease in matrix gene expression and an increase in immune and defense response genes. Of interest was that many of the genes in these categories that went down with age were found to be re-expressed in the older DMM joints.

Reports using transgenic and knock-out mice continue to provide information on specific genes that may play a role in the OA process[17]. Most commonly, investigators induce OA in very young animals around the ages of 8 to 12 weeks. The differences in gene expression between 12 week-old and 12 month-old mice noted above suggest that caution will be needed when interpreting studies only done in young mice which are the equivalent of a teen-aged human. However, two recent studies have examined both naturally occurring OA with age and surgically induced OA and found results that were similar in the two models. The role of glycosphingolipid synthesis in OA was investigated by studying the effect of knocking out a key enzyme required for glycosphingolipid synthesis and then examining the development of both naturally occurring OA in aged animals as well as surgically-induced OA in young animals [18]. They showed worse OA developed in the knock-outs in both models. Another study examined conditional deletion of the fibroblast growth factor receptor 1 (FGFR1) in both aging-associated spontaneous OA at 12 months of age and in the DMM model with surgery performed on 10 week old animals [19•]. They noted proteoglycan loss at 12 months of age was less severe in the FGFR1 knock-outs as were cartilage lesions at 8 weeks after surgery in the DMM model using younger mice. This study contrasts with a previous study where FGFR3 knockout mice were found to develop more severe OA with age [20]. Together these studies suggest an anabolic/joint protective function for FRGFR3 and a catabolic/joint destructive function for FGFR1.

Dual functions for a growth factor in cartilage homeostasis and age-related OA that depend on differences in signals generated by specific receptors has also been suggested by studies of the activin receptor-like kinases (ALKs) activated by TGF-β. ALK5 activation has been shown to be pro-anabolic and ALK1 activation is pro-catabolic [21]. With aging and in OA, the ratio of ALK1 to ALK5 is increased promoting the development of OA and similar changes may occur with the ratio of FGFR1 to FGFR3 [22].

## Epigenetics

There has been a growing interest in the aging field about the role epigenetics plays in age-related conditions including OA. Epigenetic regulation of gene expression includes DNA methylation, histone acetylation and methylation, and micro-RNA (mi-RNA). Sirtuins are a family of NAD+ dependent deacetylases which have been linked to aging and more recently shown to be involved in OA through regulation of cellular energy and metabolism [23]. The sirtuin SirT1 promotes chondrocyte survival and matrix gene expression. TNFα was found to cleave and inactivate SirT1 and thereby contribute to reduced matrix gene expression

[24]. Heterozygous SirT1 (+/−) mice with a significant decrease in SirT1 were found to develop premature OA-like changes at 9 months of age that was associated with increased chondrocyte apoptosis [25•].

Recent evidence for altered DNA methylation in OA was provided by study which found a site within the matrix metalloproteinase 13 (MMP-13) promoter was demethylated in OA chondrocytes resulting in increased MMP-13 expression mediated by cAMP response-element binding (CREB) at the demethylated site [26•]. Histone methylation has been implicated in the age-dependent expression of the transcription factor nuclear factor of activated T cells 1 (Nfat1) which promotes cartilage homeostasis [27]. Finally, several studies have recently reported on the role of miRNAs including work showing changes with age. In one study, miR-199a-3p and miR-193b were up-regulated with age while miR-320c was decreased [28]. The two up-regulated miRNAs were found to reduce collagen and aggrecan expression *in vitro* suggesting they may be anti-anabolic and involved in the age-related decrease in matrix gene expression.

## Chondrocyte senescence

The study of cell senescence continues to be an active area in OA and aging research. Telomere shortening and/or telomere damage have been noted to occur with aging and have been suggested to contribute to OA. Rose et al [29•] compared normal cartilage from autopsy specimens and OA cartilage from knee replacements but did not find evidence of telomere shortening. However, another study of human OA knee cartilage that used a unique assay for ultra-short single telomeres found increased numbers of ultra-short telomers per cell in OA cartilage lesions but without a reduction in mean telomere length [30]. In another study, passaged human bone marrow mesenchymal stem cells were shown to exhibit replicative senescence with telomere shorting that was prevented by culturing in the presence of estrogen [31]. This work, if replicated, could be relevant to the use of mesenchymal cells for cartilage repair which may be limited by the age of the donor.

The study by Rose et al [29•] was successful in demonstrating DNA damage in OA cartilage and that agents which cause oxidative stress or genotoxic stress can promote DNA damage and senescence-associated β-galactosidase activity *in vitro*. They also used immunostaining for two proteins that should be found in most chondrocytes, vimentin and S-100 protein, and found heterogeneity in cells double-labeled for both proteins in OA cartilage and in normal chondrocytes with induced DNA damage. They concluded that these findings are consistent with stress-induced senescence resulting in a chaotic gene activation pattern. Stress-induced senescence, as opposed to replicative senescence, does seem more likely in a tissue such as articular cartilage where cell division is rare. More studies with additional genes will be needed to support the concept that this leads to discoordinated or chaotic gene expression.

One of the genetic conditions that results in premature aging is Hutchinson-Gilford progeria syndrome resulting from mutations in lamin A. Patients with this syndrome have premature osteoporosis but OA has not been well documented [32]. However, Attur et al [33] found increased expression of lamin A in OA chondrocytes relative to normal and when overexpressed in chondrocytes *in vitro,* lamin A promoted expression of the senescence marker $p21^{WAF1}$ but not $p16^{INK4A}$. The latter makes the significance of the association between lamin A and chondrocyte senescence unclear. However, overexpression of lamin A did increase caspase-3 activation and TUNEL staining for apoptosis which could be relevant to cell death in OA.

An important feature of cell senescence that could contribute to joint tissue destruction in OA is the development of the senescence-associated secretory phenotype (SASP). The SASP is characterized by increased production of pro-inflammatory mediators and matrix

degrading enzymes [34]. The “secretome” of cartilage has been studied using a proteomics approach [35,36] but studies to date have not focused on age-related differences. With aging, there is evidence for increased MMP-mediated cartilage matrix damage and recently both collagenases and cathepsin K have been implicated [37]. Because of the central role of matrix degrading enzymes in joint tissue destruction in OA, future studies should determine if cell senescence contributes to an increased release of these factors and determine the mechanisms involved.

## Conclusions

Aging changes in the cartilage matrix and chondrocyte senescence are key contributors to the aging processes that promote age-associated OA. However, recent work has begun to elucidate aging changes in the other joint tissues involved in OA, including meniscus, ligaments, bone, and perhaps synovium. Studies in these tissues are mainly at the descriptive level but mechanistic studies should be forthcoming. Because aging is a systemic process, it is likely that mechanisms can be found which apply to most, if not all, the joint tissues. Discovery of the common mechanisms will lead to novel interventions to slow the aging process and thus slow the development of OA.

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**Key Points**

- Aging processes that contribute to OA occur not only in the articular cartilage but also in the meniscus, ligaments, bone and perhaps synovium.
- Mice and rats develop spontaneous age-related OA at ages comparable to humans. It is important to consider animal age when designing a study to model a condition that first appears in middle-aged to older adult humans.
- Aging is associated with alterations in histone acetylation, histone and DNA methylation, and micro-RNA (mi-RNA) expression that can contribute to OA.
- In the mechanical environment of the joint, cell senescence, mostly studied in chondrocytes so far, is most likely due to stress- or damage-induced senescence rather than replicative senescence.