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Aging and Osteoarthritis

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Abstract

Purpose of review—Osteoarthritis (OA) is strongly linked to aging but the mechanisms for this link are incompletely understood. The recent literature was reviewed to find studies providing new insights into the connection between aging and OA.

Recent findings—Basic aging studies in non-articular cells suggest that a cell stress or cell damage response contributes to chronic inflammation that promotes age-related diseases. This cellular response results in the senescence-associated secretory phenotype which has many of the characteristics of an OA chondrocyte in terms of the cytokines, chemokines, and proteases produced. Oxidative stress can promote cell senescence and studies have shown a role for oxidative stress in altering cell signaling pathways in chondrocytes that can disrupt the response to growth factors. Mitochondria are an important source of ROS and studies continue to support a role for the mitochondria in OA, including work suggesting changes in energy production. Cell death occurs in OA cartilage and recent studies suggest autophagy may play a role in determining if a cell lives or dies when stressed.

Summary—Continued progress is being made on characterizing aging-related changes in cartilage. Additional studies are needed that focus on the tissues outside of the articular cartilage that play a role in OA. Because OA occurs in older adults who also have age-related changes in muscle, bone, fat, and the nervous system, it is likely that a more general and systemic approach will be needed to better understand the link between aging and OA.

Keywords

aging; osteoarthritis; cartilage; bone; meniscus

Introduction

Osteoarthritis (OA) is the most common cause of chronic disability in older adults. However, aging alone does not cause OA but rather aging promotes the development of OA in conjunction with other risk factors. A recent meta-analysis of risk factors for incident knee OA in populations with a mean age of 50 years and older reported that, in addition to age, the most consistent risk factors for knee OA are obesity, previous knee injury, female gender, and the presence of hand OA[•1]. These OA risk factors have been recognized for quite some time but it is still unclear, at a more basic level, how they interact with the aging component of the disease process to result in OA in a given individual.

Two of the most common risk factors for OA are age and obesity. With the rapid rise in the number of older adults in the population combined with the epidemic of obesity, understanding the interaction of these two risk factors will be particularly important. As

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most people age they lose muscle mass and gain fat mass [2] which could contribute to progression of OA due to changes in joint loading. Importantly, a weight loss of 10% of body weight over 18 months in older adults has been shown to significantly reduce knee joint loads[•3]. In addition to affects on joint loading, there has been a growing interest in how adipose tissue may contribute to OA through local or systemic production of adipokines and other inflammatory mediators produced in fat that may negatively affect joint tissues. The infrapatellar fat pad in the knee may be a source of local production of these mediators[4] and one study, albeit in a small group of 15 knee OA subjects, found a positive association between age and the size of the infrapatellar fat pad measured by MRI[5].

It is unusual to find people over the age of 65–70 years without some radiographic changes of OA in one or more joints although these radiographic changes do not always correlate with symptomatic disease. A study that examined a cohort of 90-year-olds living in the city of Leiden in the Netherlands found that only 16% of people in that aged population were free of radiographic OA[•6]. Similar to previous studies in older adults, OA of the hand was most common followed by the knee and hip. Increased body mass index (BMI) was negatively associated with being free of OA in this older adult population, consistent with previous studies linking BMI to OA risk in younger populations. A finding contradictory to previous studies was that a history of heavy occupational work was associated with an absence of OA. A second study using this same cohort, found absence of OA was associated with a lower production of IL-1β and IL-6 when whole-blood samples were stimulated with lipopolysaccharide[•7]. It is not known if the participants with lower levels of cytokines measured when stimulated *ex vivo* would also have lower levels in their blood or locally in joint tissues. However, the findings are consistent with the concept that low-grade chronic systemic inflammation contributes to the pathogenesis of age-related conditions including OA.

This review will focus on recent basic research studies that are starting to shed light on the connection between aging changes in cells and tissues and the propensity for OA to occur in older adults. Aging research in general has continued to examine the role of cell senescence in age-related conditions but with a greater emphasis on how senescent cells may negatively affect their local environment. An example of this is the senescence-associated secretory phenotype (SASP)[•8]. This pro-inflammatory cellular phenotype, which can be induced by various senescence stimuli including DNA damage, may be quite relevant to the development of osteoarthritis. Cells such as fibroblasts exhibiting the SASP produce cytokines and matrix metalloproteinases (MMPs) which are very similar to those found in OA joint tissues, including IL-1β, IL-6, IL-8, MMP-3 and MMP-13[8]. The development of the SASP may be related to increased production of reactive oxygen species (ROS) from mitochondrial dysfunction and/or from activation of pro-inflammatory pathways induced as part of the “aging stress response” that include alterations in nutrient signaling pathways[9]. Research in these areas, as it relates to joint tissues affected by OA, will be discussed along with studies on altered growth factor signaling in OA and the potential role of autophagy. As in past years, most of the current research in this area continues to focus on the articular cartilage (Figure 1), despite the potential that age-related changes in other tissues in the joint likely play an important role in OA as well.

Mitochondrial Dysfunction, Reactive Oxygen Species, and Osteoarthritis

The mitochondria are an important source of ROS in cells and mitochondrial dysfunction is thought to play a role in age-related diseases including OA. There is evidence for mitochondrial DNA damage in OA and this may be promoted by inflammatory cytokines such as IL-1β and TNF-α and can contribute to chondrocyte death[•10]. Mechanical injury to cartilage results in increased ROS production which may come from a mitochondrial

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source and also promote chondrocyte death[11]. There is also some evidence that Kashin-Back disease, a rare form of endemic OA found primarily in China and Siberia, is associated with mitochondrial dysfunction and cell death[12]. In addition to a role for mitochondrial ROS inducing cell death, recent studies in other cell types have shown that mitochondrial ROS act as signaling molecules and promote expression of pro-inflammatory cytokines[13]. The role of mitochondrial ROS as mediators of cytokine expression in joint tissues has not been well studied but would be an important area to explore.

The Dunkin-Hartley guinea pig is often used as a model of spontaneous OA that increases in severity with age. A study of the expression of the superoxide dismutase (SOD) family of anti-oxidants demonstrated decreased expression of all three SOD isoforms, at the transcriptional level by real time PCR and protein level by immunohistochemistry[•14]. The decreased expression of mitochondrial SOD (SOD2), was associated with an increase in SOD2 promoter methylation suggesting epigenetic regulation of this anti-oxidant gene may be involved in the decreased expression. Although knock-down of SOD2 using siRNA resulted in increased mitochondrial ROS measured using a MitoSOX red stain, knock-down had the unexpected effect of reducing rather than increasing endogenous MMP-1 expression and IL-1 stimulated MMP-1 and MMP-13[•14]. It is not clear if knockdown of SOD2 might have caused some cell toxicity or what the effect was on other ROS such as H_2O_2 and so further work is needed to determine how anti-oxidant enzymes regulate MMP expression in chondrocytes.

Previous studies have suggested that certain mitochondrial DNA haplotypes may be associated with a decreased risk of OA while others increase the risk of OA progression[15]. A more recent study reported that people in Spain with mitochondrial DNA haplotype J, which is associated with a lower risk of OA, have lower serum levels of MMP-13 when compared to those with haplotype H, who also had higher levels of MMP-3[•16]. It is possible that the different haplotypes are associated with different levels of ROS production and perhaps different amounts of mitochondrial DNA damage although this has not been completely established. Of interest, a study examining a mouse model of premature aging that exhibits increased nuclear DNA damage due to deficiency of a repair enzyme found a significant increase in age-related bone loss but not in cartilage damage when the mice were compared to age-matched wild-type mice, suggesting nuclear DNA damage may not play an important role in OA[17]. Likewise, a study of a senescence-accelerated mouse strain did not find more severe degenerative changes at 58 weeks of age when compared to control mice although increased expression of the senescence marker p21 was noted in cartilage and associated with increased expression of a growth arrest and DNA damage response gene GADD45β[18].

Altered Growth Factor Signaling in Aging and OA

A hallmark of aging tissues is a reduced repair response which is due, at least in part, to the reduced ability of cells to respond properly to growth factor stimulation. It has been recognized for quite some time that chondrocytes found in aged and OA cartilage are less responsive to transforming growth factor-β (TGF-β) and insulin-like growth factor-1 (IGF-1). Altered TGF-β signaling appears to be occurring at the receptor level. TGF-β activation of the ALK5 receptor activates a Smad2/3 pathway that promotes matrix synthesis while activation of ALK1 activates Smad1/5/8 and promotes expression of MMP-13[19]. It appears that with aging and in OA there is a change in chondrocyte receptor expression such that the ratio of ALK1 to ALK5 increases resulting in more catabolic relative to anabolic activity of TGF-β[•19–20].

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Recent studies have provided evidence that a loss in responsiveness to IGF-1 may be due to oxidative stress and the resulting increased levels of ROS[21]. Oxidative stress can cause changes in chondrocytes that are consistent with cell senescence including evidence of DNA damage[22]. Excessive levels of ROS were found to inhibit activation of the IRS-1-PI-3 kinase-Akt signaling pathway, which normally promotes matrix synthesis, while at the same time ROS activated the ERK MAP kinase which suppresses chondrocyte aggrecan , type II collagen, and Sox-9 expression[21]. Sustained activation of ERK can contribute to cell senescence and a study using rat chondrosarcoma cells demonstrated that sustained ERK activation, mediated by FGFR3, promoted expression of markers of the senescent phenotype[23]. Extracellular ROS could also contribute to inhibition of the Akt pathway through oxidized low-density lipoprotein (LDL). Oxidized LDL binding to a cell surface receptor (LOX-1) was found to induce chondrocyte senescence which was associated with reduced levels of Akt phosphorylation after IGF-1 stimulation[24]. Oxidative stress induced by oxidized LDL has also been associated with promotion of the hypertrophic chondrocyte phenotype which has been described in OA cartilage[25].

The IGF-1 signaling pathway in chondrocytes has also been recently connected to the sirtuin family member SirT1. Sirt1 is an NAD-dependent histone deacetylase that was identified as a mediator of lifespan extension during caloric restriction[9]. Sirt1 has gained quite a bit of attention in the aging research field over the past few years. This is due in part because the compound resveratrol, which is found in grape skins and present in red wine, has been purported to have many beneficial health effects, including lifespan extension in yeast and flies, that have been attributed to activation of Sirt1. However, more careful biochemical studies have recently found that resveratrol does not directly activate Sirt1[••26]. Nevertheless, Sirt1 has been shown to be a positive regulator of cartilage matrix gene expression and levels of Sirt1 appear to be decreased in OA cartilage[27–28]. Expression of Sirt1 in chondrocytes increased the activity of the IGF-1 receptor and downstream PI-3 kinase-Akt survival signaling through repression of the protein phosphatase PTP1b[•29]. Another important energy regulator that may work in conjunction with Sirt1 is the AMP-activated protein kinase (AMPK). Similar to Sirt1, a recent study showed a decline in AMPK activity in OA cartilage and a loss of AMPK was shown to promote a pro-catabolic state[••30]. These recent studies on Sirt1 and AMPK in OA cartilage are pointing to a role for altered energy metabolism in OA which may be related to mitochondrial dysfunction and the aging-related stress response[9].

Autophagy, Cell Death and OA

An important mechanism by which cells protect themselves when stressed is through autophagy[9]. Autophagy (from the Greek auto-self and phagy-eat) is process used by the cell to degrade and recycle dysfunctional proteins and other macromolecules but it can also be used to provide cells with alternative energy sources when nutrients are scarce. Autophagy tends to decline with age in many cells and tissues including articular cartilage where autophagy markers were also found to be decreased in OA chondrocytes[••31]. A loss in autophagy was associated with increased cell death in articular cartilage. However, the role of autophagy in controlling chondrocyte death appears to be complex. Studies in the growth plate have suggested that increased chondrocyte death occurs when autophagy is sustained[32]. HIF-2α has been suggested to suppress autophagy in chondrocytes[33] but the effects of HIF-2α in articular cartilage might be detrimental since other studies have suggested that increased HIF-2α in OA cartilage promotes expression of catabolic factors and contributes to the development of OA[••34–35]. Further studies are needed in order to determine the precise role of autophagy in OA and how it is regulated.

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Another factor that may be an important regulator of chondrocyte survival is HMGB2. HMGB2 is a high-mobility group box protein that serves to regulate gene transcription through chromatin organization. There is evidence that HMGB2 is expressed in superficial zone chondrocytes and that levels of HMGB2 decline with aging[36]. The loss in HMGB2 was associated with increased chondrocyte death and mice deficient in HMGB2 by gene deletion were found to develop premature OA.

Conclusions

Significant advances continue to be made that are improving our understanding of how aging contributes to the etiopathogenesis of OA. Recent studies have focused on changes that occur with cell senescence in the articular cartilage. Mitochondrial dysfunction with increased production of ROS may be important and this may be related to changes in energy metabolism. Work in the area of cell signaling is beginning to better define how aging affects the response of chondrocytes to growth factor stimulation. Determining if aging results in joint tissue cells assuming the senescence-associated secretory phenotype will be important since this phenotype is quite similar to the phenotype of OA chondrocytes that produce increased amounts of cytokines, chemokines and MMPs. Studies of autophagy may reveal new mechanisms relevant to the cell's decision to live or die under conditions of stress.

What is still missing in the field of aging and OA research is a connection between what is happening at the level of the chondrocyte to changes occurring in the rest of the joint tissues and systemically in the older adult suffering from the disabling effects of pain and loss of function. Aging changes in cartilage and the other joint tissues are occurring in the context of aging changes in muscle (sarcopenia), bone (increased remodeling and bone loss), fat (increased depots), the nervous system (altered proprioception), that will all play a role in how a given older adult will develop OA and adapt to the resulting pain and loss of normal joint function. Given that OA is driven by biomechanical factors and accompanied by a low grade level of chronic local inflammation in joint tissues, new therapies will likely fail if both aspects of the disease are not considered along with the important systemic changes occurring in older adults.

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Key Points

- Chondrocyte senescence promoted by reactive oxygen species, DNA damage and mitochondrial dysfunction likely contributes to the development of OA in older adults.
- Autophagy is a new area of research that may be relevant to aging and OA including the determination of cell death in OA.
- Research needs to better define how age-related changes in cartilage, as well as other joint tissues, and systemic changes work together to promote OA in older adults.

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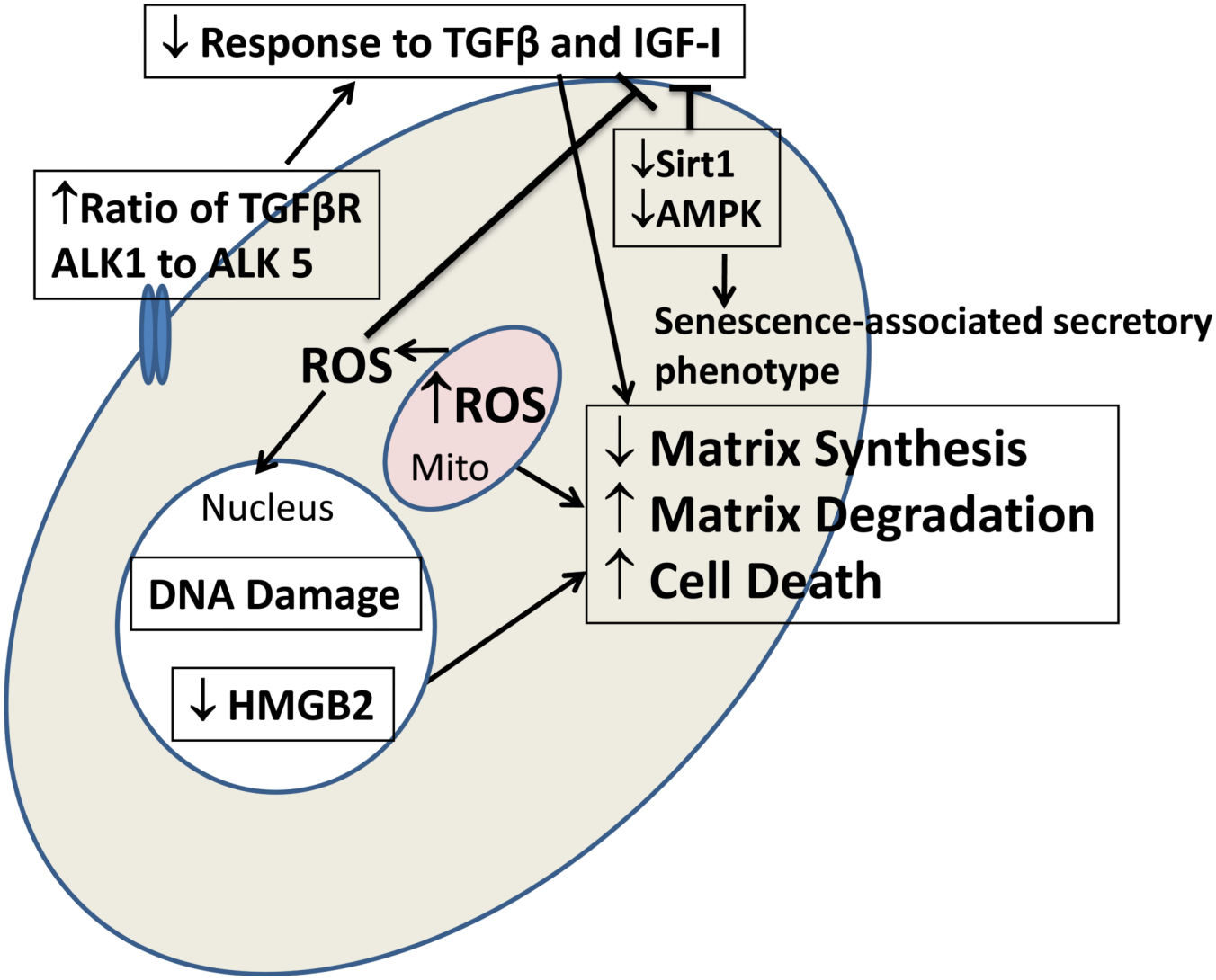

Figure 1.

The role of chondrocyte senescence in OA. Recent studies have demonstrated several age-related changes in chondrocytes that may contribute to the development of a senescence-associated secretory phenotype (SASP) characterized by increased production of inflammatory mediators and matrix degrading enzymes. These changes include an altered response to TGFβ due to an increase in the ratio of the ALK1 to ALK5 ratio and a reduced response to IGF-1 due to increased levels of reactive oxygen species (ROS) and a reduction in Sirt1. Decreased Sirt1 and AMPK may promote the catabolic pathways associated with the SASP. The mitochondria may serve as a source of increased ROS which can cause mitochondrial and nuclear DNA damage including telomere shortening. An increase in ROS as well as a reduction in the transcriptional regulator high-mobility group box protein 2 (HMGB2) may contribute to cell death.