The Effects of Aging on the Development of Osteoarthritis

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Introduction

Osteoarthritis (OA) and aging are closely related; however, aging alone does not cause OA, but rather promotes the development of OA when other risk factors are present. Despite the strong association between aging and OA, we have an incomplete understanding of the basic mechanisms by which aging contributes to the development of OA. Aging at the systemic level as well as at the level of joint tissues and the cells that create and maintain them could play a role.

Physiology of Aging and OA

Systemic changes that occur with aging and may contribute to OA include sarcopenia, increased fat mass [3], a low-grade pro-inflammatory state, a decline in production of growth hormone and sex steroids, decreased bone mass and quality, and a decrease in proprioception and balance. How these systemic factors might contribute to OA is shown in Fig. 1.

The connection between some of these systemic factors and the development of OA was suggested by a study of a cohort of 90-year-olds living in the city of Leiden in the Netherlands that examined factors associated with the absence of OA [7]. The investigators found that only 16% of people in this aged population were free of radiographic disease. The absence of OA was associated with male sex (less knee OA than women, possibly due to hormonal factors), a normal BMI (lower fat mass), a history of heavy occupational work (increased physical activity), family history of nodal OA in the hands (less hand and hip OA related to genetics), and, in a

second study, lower production of IL-1 β and IL-6 when whole blood samples were stimulated with lipopolysaccharide (lower pro-inflammatory state) [8].

Studies on basic mechanisms of aging in tissues outside of the joint may help shed some light on the relationship between aging and OA. Evidence exists that the “aging stress response” contributes to the development of disease [9]. This response includes a role for excessive reactive oxygen species (ROS), mitochondrial dysfunction, protein misfolding and aggregation, and DNA damage; all of which promote a pro-inflammatory state and activation of genes related to cell senescence. Work in the aging field has provided evidence for a senescence-associated secretory phenotype (SASP) [5] that has many of the characteristics of an OA chondrocyte in terms of the cytokines, chemokines, and MMPs that are produced. Because chondrocytes rarely replicate, the mode of cell senescence in cartilage is most likely from “stress-induced senescence,” which could be promoted by years of excessive mechanical loading, oxidative stress, and mitochondrial dysfunction. Recent studies showed that mitochondrial ROS can act as signaling molecules and promote expression of pro-inflammatory cytokines [11]. The role of mitochondrial ROS as mediators of cytokine expression in joint tissues has not been well studied, but is an important area to explore.

Evidence exists for a number of changes in cartilage related to aging that could contribute to OA at the cell and tissue level. In addition to the possible role of the SASP and oxidative stress/damage, other changes occur: an accumulation of advanced glycation end-products that make the tissue more brittle; a reduction in the size of aggrecan with resultant decreased hydration that would reduce cartilage resiliency; an increase in collagen cleavage that would reduce tensile strength; increased matrix calcification that would alter mechanical properties and activate inflammatory pathways; and a reduced response to growth factors, including insulin-like growth factor 1 (IGF-1) and transforming growth factor- β (TGF- β) that would reduce repair [10]. The altered response to TGF- β appears to occur at the receptor level due to changes in the ratio of ALK1 to ALK5 promoting more catabolic relative to anabolic activity [1, 14], and for IGF-1, an altered balance of MAP kinase and Akt signaling due to ROS may be playing a

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Fig. 1. Systemic aging changes that may relate to the development of OA

role [15]. Other findings on OA chondrocytes that also might be linked to aging include reduced levels of Sirt1, a potential positive regulator of cartilage matrix gene expression [4, 6], and a decline in AMPK activity, which could also promote a pro-catabolic state [13].

Chondrocyte survival is reduced with aging, and death of chondrocytes appears to play a role in OA. Several factors promote chondrocyte survival, including IGF-1, and so an age-related loss in the response to IGF-1 could play a role in increased cell death. Recent studies suggested that the high-mobility group box protein HMGB2 is another factor that may be an important regulator of chondrocyte survival [12]. HMGB2 is expressed in superficial zone chondrocytes, and levels decline with aging. Mice deficient in HMGB2 by gene deletion develop premature OA [12].

Another important area of recent interest in cartilage biology that may relate aging and cell survival to OA are studies on autophagy. Autophagy is a mechanism by which cells protect themselves when stressed by degrading and recycling dysfunctional proteins and other macromolecules that can also be used as an alternative energy source [9]. Autophagy tends to decline with age in many cells and tissues including articular cartilage where autophagy markers are decreased in OA chondrocytes [2]. A loss in autophagy was associated with an increased cell death in articular cartilage.

Table 1 Where should we go from here to better understand aging and OA?

- More studies of the healthy elderly who do not have OA
- Better define how aging-related changes in muscle (sarcopenia), fat (increased fat mass), bone (increased turnover and loss), and other systemic changes (increased pro-inflammatory state and decreased endocrine function) contribute to OA
- Determine the role in OA of:
 - Senescence-associated secretory phenotype
 - Mitochondrial dysfunction and oxidative stress
 - Loss of stem cells

Summary

We are making progress in understanding the connection between aging and OA, but clearly more work is needed. Suggestions for future studies are provided in Table 1.

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