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Perspective Article

Hylonome

Cellular, molecular, and matrix changes in cartilage during aging and osteoarthritis

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Several anecdotal statements have commonly been used to describe the relationship between aging and degenerative cartilage disease or osteoarthritis (OA). For example, it is commonly stated that there are two fundamental mechanisms that lead to OA; either abnormal loading on normal cartilage or normal loading on abnormal cartilage. The first case refers to relatively young individuals who have damage to a joint that causes structural instability and almost inevitably leads to OA. The second case refers to older individuals who have likely experienced changes in cartilage associated with aging that render the cartilage unable to support relatively normal loading. Another relationship frequently observed is that "OA" does not equal "old age". This statement summarizes the finding that changes in cartilage with age are likely universal, however development of OA, while common, is not universal. While these are concepts that are generalizations, there is a basis in the research literature to support them[1]. This review will deal with a comparison of changes that take place in cartilage with normal aging and during the pathogenesis of osteoarthritis. The focus will be on alterations in chondrocyte homeostasis including changes in viability, proliferation and gene expression. The consequences of these changes on the composition of the matrix will be discussed. Finally, data will be presented on the importance of endoplasmic reticulum stress in chondrocyte biology and its possible occurrence in human OA.

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Age-associated changes in articular cartilage

The basic role of articular cartilage is to adequately transmit forces across diarhrodial joints and maintain a relatively friction-free surface to support limb movement. Numerous studies have described changes in articular cartilage that are relatively consistent and inevitable consequences of aging. These include mild fibrillation (fraying) and softening of the articular surface, a decrease in the average size of the proteoglycan monomers along with a decrease in the aggregation capacity of these molecules, and overall loss of matrix tensile strength and stiffness. These types of changes may be related to the proposed age-related shift in the chondrocyte phenotype[2] rendering the remaining resident cells less capable of maintaining cartilage homeostasis and setting the stage for overt degenerative cartilage disease.

Mechanical injury and secondary osteoarthritis

Mechanical injury to a joint is a major risk factor for developing OA. The pathogenic mechanism linking mechanical injury to OA may or may not be the same as what operates to link aging to primary OA. However, since there are clear and defined cellular and tissue responses in cartilage following mechanical injury[3], it is useful to determine how chondrocytes handle loss of homeostasis in this particular situation. Mechanical injury results in cartilage swelling and decreased compressive and shear stiffness of the tissue. These changes are likely due to damage to the collagen network. Chondrocyte cell death occurs following mechanical injury and the remaining resident cells appear to have a diminished capacity for biosynthesis and/or response to physiological signals such as loading or trophic factors. There is a loss of the proteoglycan component of cartilage following injury and there is increased expression of matrix degrading enzymes.

Changes in articular cartilage during the pathogenesis of primary osteoarthritis

Several recent articles have reviewed the changes observed during the progression of OA[4,5]. The most prominent macroscopic changes in the cartilage with advancing OA are softening (chondromalacia), fibrillation, and erosions (ulceration). At the microscopic level there is evidence of both degenerative changes and attempts at repair including cartilage clefts, loss of metachromasia, chondrocyte cell death, chondrocyte cloning, and duplication of the tidemark. Underlying these structural changes are biochemical changes such as decreased proteoglycan content and altered proteoglycan structure. Specifically, there is a higher percentage of non-aggregated proteoglycan with less of the monomers bound to hyaluronic acid. This change in composition of proteoglycan likely results from proteolytic cleavage of the native molecules. The change in the amount and form of the proteoglycan has profound consequences for the hydration profile of the cartilage. Although there is an overall increase in water content (swelling), the water is not as fixed to the negative charge of the glycosaminoglycan side chains resulting in a decrease in the hydrostatic pressure of the cartilage.

The changes in the proteoglycan component of the cartilage appear to precede the changes in the collagen during OA progression. Eventually the collagen network is disrupted resulting in a decrease in the tensile stiffness and strength of the cartilage. The actual breakdown of matrix components is mediated by the expression of matrix metalloproteinases either directly resulting from mechanical stresses or indirectly due to the expression of inflammatory cytokines such as interleukin-1 and/or tumor necrosis factor[6]. It is also important to point out that certain cytokines will have an anabolic effect on chondrocytes[6]. Clearly the chondrocytes are the central players in the whole spectrum of changes that occur either during normal aging or in primary or secondary osteoarthritis.

Molecular changes in aging and osteoarthritis

Chondrocytes are required to regulate the balance of matrix turnover and matrix synthesis. In general the extraceullular matrix proteins of cartilage, particularly collagen, have relatively long half-lives. In addition, chondrocytes in homeostasis normally have a low metabolic rate, remain viable but non-proliferative, and display a stable differentiated phenotype (pattern of gene expression). Protein kinases such as the mitogen-activated protein kinases and receptor-tyrosine kinases play a role in maintaining chondrocyte homeostasis and are targets for both age-associated and disease-associated modifications[7]. Another aspect of molecular regulation involves the inhibition of terminal differentiation in articular chondrocytes compared to growth plate chondrocytes[8]. There are reported data to suggest that this block

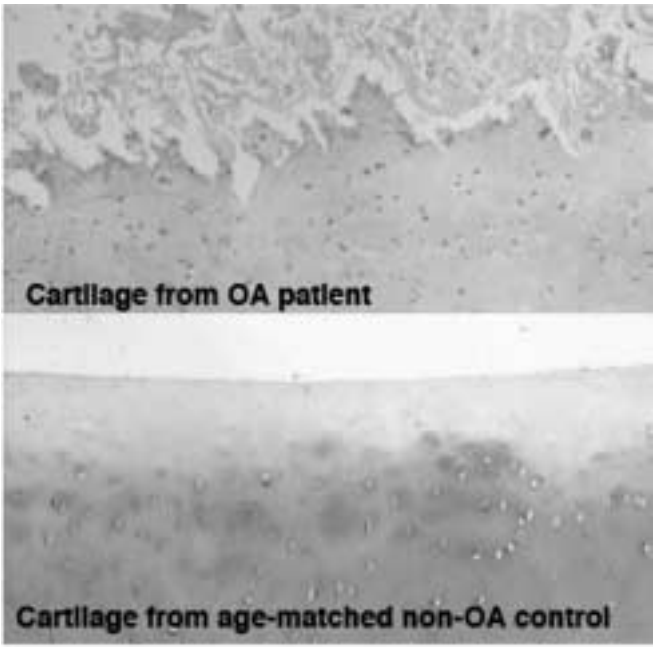

Figure 1. Expression of GRP-78, a marker for ER stress is upregulated in chondrocytes residing in cartilage from a patient with OA compared to an age-matched control.

or inhibition is released in OA resulting in more chondrocytes undergoing terminal differentiation accompanied by altered matrix synthesis, proliferation, and expression of markers for the hypertrophic phenotype[9]. Other research has demonstrated that the pattern of gene expression is different even in chondrocytes residing in minimally involved versus more degenerated cartilage from the same patient[10].

The chondrocyte in aging and osteoarthritis

Although it has always been clear that age was a risk factor for developing OA, the role of aging has not been precisely determined. The most prevalent theory for many years was that OA develops from continual mechanical wear and tear over time. Alternatively, theories related to programmed changes in the chondrocyte that require time to manifest have gained acceptance. For example, loss of functional chondrocytes due to apoptosis or other forms of programmed cell death would render aging cartilage more vulnerable to degenerative disease initiated by relatively normal loading. There is evidence that aging prior to overt disease involves increased apoptosis in articular cartilage[11] along with decreased expression of anti-apoptotic proteins[12]. There are also numerous reports of increased chondrocyte cell death associated with osteoarthritis in animals and humans[13]. Perhaps related would be the shift from a "youthful" to a senescent phenotype by a relatively greater proportion of the chondrocyte population resulting in altered

matrix synthesis, response to growth factors, proliferative activity, energy metabolism and ability to handle cell stress[14]. The fundamental pathogenic progression in OA is characterized by an imbalance between anabolic (matrix biosynthesis) and catabolic (matrix degradation) pathways that converge on the articular cartilage to alter its load-bearing properties. The overall pathogenic mechanism also involves tissues outside the articular cartilage such as the synovium as a potential site of cytokine production and the subchondral bone[15] as a region that either responds to or drives the breakdown of articular cartilage.

Endoplasmic reticulum (ER) stress and chondrocyte biology

Proteins destined for transport out of the cell are formed on the ER surface and move to the lumen of the ER where they are modified; for example, by glycosylation and/or the addition of disulfide bonds. Alterations in calcium homeostasis and accumulation of unfolded proteins in the ER can cause ER stress. ER stress in chondrocytes is not well studied. This is surprising since chondrocytes are highly specialized to secrete complex matrix proteins and it has been documented that abnormally modified matrix proteins accumulating in the ER and Golgi of chondrocytes can lead to cartilage malformations. There are models that suggest that ER stress may be a link between oxidative damage of proteins and the aging process[16,17]. Also, there is direct evidence that gadd153 expression is elevated in the liver with aging and this sensitizes cells to oxidative stress[18,19]. Recently published work has demonstrated that both physiological signals such as glucose withdrawal as well as pharmacological agents can induce ER stress in chondrocytes resulting in decreased proliferation, inhibition of collagen II expression and eventually apoptosis[20]. We also have preliminary data suggesting that chondrocytes residing in cartilage isolated from patients undergoing joint replacement therapy are experiencing ER stress (Figure 1).

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