Aging and the development of Osteoarthritis: Not Just Wear and Tear

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INTRODUCTION

Osteoarthritis (OA) is a chronic disabling condition of the articular joints characterized by degradation and loss of the articular cartilage, osteophyte formation, subchondral sclerosis, synovial inflammation (of some degree), meniscal degeneration, and thickening of the joint capsule. It has been noted to occur in almost every animal species from dinosaurs to man. OA can be thought of as "joint failure" that is due to multifactorial process involving altered biomechanics and altered metabolism of joint tissues. Although considered to be a "non-inflammatory" form of arthritis, OA is characterized by inflammation on a molecular level (role of cytokines, chemokines, adipokines, and growth factors) rather than classic cellular inflammation (influx of inflammatory cells into the joint such as seen in rheumatoid arthritis). OA should no longer be considered as a "degenerative disease" or "wear and tear arthritis" that results merely from longstanding joint overuse or abuse but rather as a true "itis" at the molecular level. Molecular inflammation may be driven, at least in part, by biomechanical processes that act to damage and destroy the joint tissues through activation of catabolic pathways.

ROLE OF SYNOVIAL INFLAMMATION IN OA

The degree of synovial inflammation in OA is certainly less than that seen in the classic forms of inflammatory arthritis such as RA. But even in early stages of the disease (knee pain and cartilage damage without significant radiographic disease) some degree of synovial inflammation can be seen in at least 50%. In more advanced OA, about one third have evidence of mild synovial inflammation, one third are moderate and one third are severe (almost pannus like tissue more similar to RA). There is evidence that synovial involvement may be a risk factor for progression of joint destruction. Current OA therapies (such as NSAIDs) do not directly target the mediators of synovial inflammation and it is not yet clear if the "biologics" used to treat RA (such as anti-TNF or IL-1RA) would be useful in OA.

ROLE OF BONE IN OA

The structural changes of OA which appear on plain x-rays are joint space narrowing due to cartilage loss, bony spurs or osteophytes at the joint margins, and bony sclerosis just underneath the articular cartilage. Thus, much of what is apparent radiographically in OA is bone involvement and at the histologic level it is unusual to find evidence of cartilage lesions without also finding changes in the bone. Bone activity in OA was noted years ago on technicium scans and recently MRI studies have noted bone lesions in OA subjects that were initially called bone marrow edema lesions but later found to be fibrotic/remodeling areas. These bone changes have been correlated with pain, with malalignment and with local progression (for example medial lesions in varus knees associated with medial joint space progression).

The driving force behind the deeper bone lesions is not clear (purely mechanical, biological or both) but recent work has implicated TGF-beta as a primary mediator of osteophyte formation in OA. Other growth factors and cytokines have been shown to be released from OA bone which could impact metabolism of the neighboring articular cartilage. The extensive bone involvement in OA has led some investigators to argue that OA may be a primary disease of bone rather than cartilage. Bone is currently being examined as a therapeutic target. Bisphosphonates in animal studies looked promising but initial trials in humans have been disappointing.

INVOLVEMENT OF THE ARTICULAR CARTILAGE IN OA

The articular cartilage provides a surface with very low friction that facilitates the normal smooth gliding motion of the joint. When the articular cartilage fails, joint motion is compromised and pain ensues. Since cartilage lacks a nerve supply, pain is likely due to associated damage to local joint tissues including neighboring bone, synovium, menisci, the joint capsule and other soft tissues. Because progressive cartilage destruction is characteristic of osteoarthritis and considered to be a central feature of the condition, it has received the most research attention in the OA world.

The chondrocytes are the only cell type present within cartilage and are responsible for both synthesis and degradation of the very abundant extracellular matrix which they must maintain for the lifetime of an individual. Very little cell division occurs in normal cartilage and if a chondrocyte is lost due to cell death it is unlikely to be replaced. Chondrocytes are responsive to mechanical stimuli, which under normal loading conditions help to maintain tissue homeostasis. When normal mechanics are altered and abnormal joint loading occurs, the chondrocyte can respond in such a way that matrix catabolism is favored over repair.

Chondrocyte metabolic activity is controlled by the local production of anabolic growth factors and catabolic cytokines which work in concert with mechanical stimuli. Anabolic factors active in cartilage include IGF-I, OP-1 (BMP-7), TGF-beta, IL-4, BMP-2, and CDMPs. Catabolic factors include IL-1, IL-6, IL-8, TNF-alpha, NO and reactive oxygen species, IL-17, IL-18, LIF, Oncostatin M, Endothelin 1 and bFGF. During the development of OA, an increase in both anabolic and catabolic activity has been observed in early disease but eventually catabolic activity overwhelms the anabolic side resulting in matrix destruction and loss. The increase in catabolic signaling results in increased expression and release of enzymes which degrade type II collagen and a large proteoglycan called aggrecan, the major matrix proteins in cartilage. These enzymes include several of the metalloproteinases, such as MMP-1 and MMP-13 that degrade collagen, and enzymes called aggrecanases which degrade aggrecan. The excessive enzymatic activity in OA results in degradation and loss of cartilage matrix. Matrix loss is accompanied by both cell death and by chondrocyte proliferation, the latter thought to be an attempt of the chondrocyte to repair the damaged matrix.

IMPORTANCE OF AGING IN THE DEVELOPMENT OF OA

Although multiple factors such as obesity, previous joint injury, and genetics can lead to the development of OA, the primary risk factor is age and so any discussion of the biology of OA needs to consider how aging plays a role in the development of the disease. Current research suggests that OA is not an inevitable consequence of aging but rather aging changes within joint tissues that affect repair and remodeling processes predispose the joint to failure when other factors (obesity, joint injury, altered mechanics…) are also present.

It appears that age-related changes in the extracellular matrix of cartilage result in a tissue that is less able to handle mechanical stress. Perhaps the most striking age-related change in articular cartilage is the accumulation of advanced glycation end-products (AGEs), likely promoted by the very low turnover rate of cartilage matrix proteins. AGEs such as pentosidine, which can cross-link collagen molecules, may make the tissue more "brittle." The prevalence of cartilage calcification (chondrocalcinosis) also increases with age and calcification is found in advanced OA, although its exact role in the development of the disease is not clear.

Like matrix changes, aging changes in chondrocyte function can occur over many years due to the normally low turnover of chondrocytes. The ability of the chondrocyte to maintain cartilage homeostasis declines with aging. This appears to be primarily due to decreased anabolic activity although recent studies have also shown an increase in catabolic responsiveness with age. The mechanism responsible for an age-related decline in growth factor response is not clear but recent work supports a role for altered cell signaling.

It is possible that other age-related changes in the ECM could feedback to affect chondrocyte function. As noted above, probably the strongest association with the aging ECM is the accumulation of AGEs (advanced

glycation end-products). The best characterized AGE receptor is called RAGE (receptor for advanced glycation end-products). RAGE signaling has been shown to induce oxidative stress and activate MAP kinase signaling leading downstream to increased NFÎB activity. Recent studies have shown that chondrocytes express RAGE and that RAGE signaling can stimulate production of MMP-13, a potent enzyme that degrades type II collagen.

Oxidative stress may be one mechanism to explain the connection between aging and the development of OA. The free radical theory of aging suggests that the chronic production of endogenous reactive oxygen species (ROS) and subsequent cellular damage from these species could mediate many of the changes that are associated with cellular aging. Perhaps more importantly, changes in the cellular redox status alter the activity of cell signaling networks. Current studies are determining if this signaling alteration might contribute to the imbalance in anabolic and catabolic activity in cartilage.

CONCLUSION

We have come a long way in our understanding of the biology of OA but still have much to learn before this knowledge may be effectively translated into new therapies to halt or reverse disease (structural) progression. Clearly OA involves the entire joint (not just the articular cartilage) and it may be necessary to target more than one joint tissue. OA is characterized by increased activity of multiple inflammatory pathways at a molecular level. Aging plays a key role in the development of OA, perhaps through dysregulated cell signaling resulting from age-related oxidative stress that contributes to a pro-inflammatory state. As we begin to better understand the biology of OA and develop novel therapies, an additional challenge will be determining how to detect disease at a stage where an intervention will work and how to determine which patient population to target with a specific intervention.

FURTHER READING

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