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Pathology and Risk Factors in Osteoarthritis

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Osteoarthritis is the most common disorder of the synovial joint. The pathological changes that occur in the osteoarthritic joints are well known and the molecular and cellular events that drive these are increasingly understood. The risk factors that predispose to the development of OA such as increasing age, obesity, genetics and mechanical loading have also been known for some time. As a consequence of population ageing and an increase in the rates of obesity the prevalence of OA is significantly increasing bringing more demands on health care systems. As such it is becoming additionally important to understand how these risk factors may individually and synergistically interact to contribute to disease susceptibility and pathogenesis. Such knowledge is accumulating and is beginning to indicate new routes by which OA may be prevented and managed in the clinic.

Key words: osteoarthritis (OA), ageing, pathogenesis

INTRODUCTION

Osteoarthritis (OA) is a disorder of diarthrodial or synovial joints. Although once thought of as a degenerative disease of articular cartilage, OA is now believed to be a disease of the diarthrodial joint as an organ. Pathological changes are seen in all joint tissues including cartilage, synovium, periarticular bone, menisci (when present), ligaments and fibrous capsule. OA may develop in any of the synovial joints but is most commonly seen in the joints of weight bearing joints such as the hip and knee or in the first metacarpal phalangeal joint of the hand and the distal interphalangeal joints of the fingers. Although OA may be associated with a slight increase in mortality its major effects are through a combination of pain and reduced joint function. As such the disorder is a significant burden on the individual through loss of quality of life and society as a whole through an increasing economic burden as a result of increased health care costs and loss of time at work. OA is a relatively common disease which is beginning to reach epidemic proportions globally Currently the lifetime risk of developing OA in one or more joints is in the region of 40-50% but this is expected to rise as the population ages and obesity becomes more widespread.

The pathological changes that occur in joints with OA are well recognised and the molecular and cellular mechanisms by which they arise are being increasingly understood. The risk factors that predispose to the development of OA such as increasing age, obesity, genetics and mechanical loading have also been known for some time. New insights into how increasing age, obesity and genetic variation may influence joint structure and function including the how mechanical loads are perceived and responded to by chondrocytes provide an opportunity to identify novel routes by which this debilitating disease can be treated or prevented.

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Pathological Features of Osteoarthritis

The osteoarthritic joint shows the result of both tissue loss and attempts at repair.

Articular cartilage

The loss of the protective function of the cartilage covering the articulating surfaces of the bones in the joint results in terminal joint failure. The progressive biochemical and histological changes in articular cartilage are well recognised. In early OA cartilage volume is increased due to increased water content and proteo-

glycan swelling which occurs secondary to physical or proteolytic disruption of the type II collagen network.[1-3] Subsequently, cartilage proteoglycan content decreases, a result of increased expression and activity of matrix metalloproteases (MMPs) and ADAMTS aggrecanases.[4] As OA progresses direct physical forces on the weakened cartilage cause matrix fibrillations, cracks in the superficial layer of the articular cartilage that run parallel to the surface. These cracks in time extend, following the tangential and vertical orientation of the collagen fibres in the mid and deep cartilage zones. Fissure branch and propagate as a result of ongoing mechanical trauma and this, in conjunction with continuing proteolytic activity leads to progressive cartilage loss.

In response to injury, chondrocytes the resident cartilage cells, either proliferate or under go cell death by apoptosis and necrosis leading to areas of hyper or hypocellularity. Proliferative activity is confined initially to the superficial zone. The increase in chondrocyte number is reflected in formation of small aggregates or clusters of cells. The size of these clusters and the number of constituent cells increases as the disease progresses. In areas of chondrocyte death the local tissue homeostasis is lost and absence of reparative activity enhances cartilage deterioration.

In contrast to reduction in the volume of non-calcified articular cartilage, the thickness of the calcified cartilage zone increases and is associated with duplication/multiplication and vascular invasion and innervation through the tidemark that separates calcified from non calcified cartilage.[5,6] Microcracks also appear in the calcified cartilage and may initiate bone remodelling.[7] The duplication / multiplication of the tidemark reflects episodes of tidemark advance which also contribute to cartilage thinning.[8]

Synovium and Meniscus

The synovium can be flat or demonstrate villous hyperplasia with increased numbers and size of surface synoviocytes, particularly macrophage-like type-A synoviocytes.[9] The synovial subintima is frequently hyperaemic and may be fibrotic or oedematous and contain a mild to marked chronic inflammatory cell infiltrate comprising macrophages, T and B lymphocytes.[10] Neutrophils are not common in uncomplicated disease. In rapidly progressive OA a granulomatous response with foreign body giant cells is seen. Traumatic meniscal injuries predispose to osteoarthritis. However in OA joints, even in the absence of a known previous of joint injurym menisci are rarely normal. They show a range of degenerative changes including macroscopic tears.[11] Histologically areas of mucoid degeneration, surface fibrillations and deeper fissures within the matrix are identified and are associated with hypo and hypercellularity and metaplasia to a more overt chondrogenic phenotype.

Bone

Pathological changes are seen in subchondral bone with changes in bone structure, cyst formation and radiologically recognised bone marrow lesions. At the margin of the joint osteophytes are formed.

In established OA increased thickening of the subchondral bone plate and changes in the architecture of subchondral bone trabeculae result in radiologically distinctive osteosclerosis. Subchondral bone sclerosis occurs as a re/modelling response[12] to the increased mechanical loads that are transmitted to the bone through as a consequence of altered biomechanics within the joint and cartilage loss. The trabecular bone volume increases by around twenty percent[13] due to an increase in trabecular bone number and reduced separation between trabeculae, rather than through thickening of the trabeculae. As the new bone formed is less mineralized than normal bone, although there is an increase in apparent density, the material density of the bone is significantly reduced.[12,14]

Subchondral bone cysts usually present deep to areas in which the overlying cartilage has been completely lost but this is not always the case. Subchondral bone cysts are histologically diverse consisting of pools of mucoid material or reparative mesenchymal tissue showing variable degrees of fibrous and fibrocartilaginous differentiation. There is usually evidence of new bone formation and remodelling at the periphery of the cysts but the cysts themselves do not normally contain bone – hence their radiolucency. Bone marrow lesions are areas of ill-defined bone marrow hyperintensities seen on T2W images in patients with osteoarthritis. Histological studies indicate that these are areas of localised bone and marrow necrosis with fibrosis and reparative changes.[15] They can be thought of as bone bruises. Some may progress to bone cysts.

Osteophytes arise at the periphery of the joint from perichondral / periosteal stem cells that are induced to proliferate and undergo chondrogenic differentiation under the influence of growth factors such as TGFbeta.[16] They are seen in load bearing and non-load bearing joints with both biomechanical and humoral factors being involved in their initiation.[17] Although they may be seen in joints where there is minimal or no cartilage damage the presence and size of osteophytes correlates with the ex-

tent of cartilage loss.[18]

Risk Factors and Osteoarthritis

Risk factors for the development of OA have been recognised for some time. These include increasing age, obesity, genetic predisposition and inappropriate mechanical loading. Racial/ethnic differences in the prevalence of OA and specific patterns of joint or compartment involvement have been noted. For instance, hand and hip OA appear to be less prevalent among Chinese than Caucasians[19] whilst lateral compartment knee OA is more common in this population.[20]

Osteoarthritis and Ageing

Age is a major risk factor for osteoarthritis. The relationship between increasing age and OA appears complex involving all tissues of the joint and supporting tissues such as skeletal muscle. A number of structural and functional changes occur with ageing that can influence development and progression of OA. Age-related decline in proprioception with a reduction in joint stability during locomotion may increase mechanical stresses within joints.[21] These may be compounded by the natural loss of muscle mass and strength seen with increasing age[22] that further compromise joint stability with movement.

Cellular and matrix changes are now recognised in cartilage with increasing age. Unlike most other tissue cells chondrocytes appear to have only limited replicative activity *in vivo*. As such with age there is relatively little renewal of the resident population of chondrocytes within articular cartilage. As individuals age their cartilage and chondrocytes age with them and chondrocytes from normal aged cartilage show a loss of the normal mitogenic response to growth factor stimulation.[23] Chondrocytes from cartilage of older individuals show shortened telomeres indicating senescence which is likely to be induced in response to accumulated exposure to oxidative stress and inflammatory mediators.[24-26] Chondrocyte senescence is associated with development of a secretory phenotype in which there is preferential production of pro-inflammatory cytokines and reduction of anabolic responses to growth factors such as IGF-1.[27,28]

Age-related changes also occur in cartilage matrix that may contribute to the development of OA. Proteins in cartilage of elderly individuals show increased levels of advanced glycation end-products (AGE), protein modification that occurs through spontaneous non-enzymatic glycation of proteins when reducing sugars such as glucose, fructose or ribose, react with lysine or arginine residues.[29,30] Accumulation of AGEs may adversely influence the biomechanical properties of the matrix through increasing collagen cross linking.[31]

Obesity and Osteoarthritis

Individuals who are obese have almost a three times risk of knee OA and the risk of OA increases with body mass index (BMI).[32,33] The effects of obesity, like that of other risk factors in OA are complex and multiple and include biomechanical, endocrine and metabolic factors. Increased weight results in excessive loading through weight bearing joints but in addition abnormal gait and joint malalignment may affect stresses within and across joints.

Obesity is however also associated with hand OA indicating that obesity has an effect on OA through mechanisms other than excessive or abnormal loading of joints. White adipose tissue is a rich source of endocrine molecules including pro-inflammatory cytokines such as IL-6, IL-1 and TNF-α, as well as adipokines, such as leptin, adiponectin, resistin, visfatin, chemerin, lipocalin, and serum amyloid A3 (SAA3).[34-36] As such obesity is now thought of as being a low grade chronic inflammatory condition and it has been proposed that the secretion of adipokines by white fat tissue may directly influence cartilage metabolism.[37] IL-6, leptin and adiponectin have each been linked with OA.[38-40] Leptin and its receptor Ob-R are increased in OA cartilage and synovial fluid. Leptin induces production of proinflammatory and catabolic factors known to be involved in cartilage degeneration supporting a role for this molecule as a pro-OA agent.[41,42] Similarly adiponectin has been shown to be pro-inflammatory and pro-catabolic when applied to chondrocytes in some studies, increasing IL-6, MMP-3, MMP-9, and MCP-1 production in the same cell type.[43] However the roles and effects of adiponectin appear complex. In some in vitro studies adiponectin has been shown to be anti-inflammatory, inhibiting the effects of IL1beta.[44] In addition not all clinical studies have confirmed a positive correlation between adiponectin levels and OA disease severity and indeed there is a suggested protective effect in hand OA.[45,46] Nevertheless increased production of adipokines from intra-articular sources such as the infrapatellar fat pad in the knee joint are likely to be important in the pathogenesis of certain forms of osteoarthritis.[47,48]

Genetics and Osteoarthritis

The heritable component of OA is estimated to be around 40-65%. Candidate gene studies[49] and more re-

cently genome wide association scans[50] are beginning to help identify key genetic factors that may influence susceptibility to onset and progression of OA. Genetic variation also partly explains ethnic and racial differences in OA.

From candidate gene studies genetic polymorphisms in a number of genes have been identified that appear to be associated with OA. These include ASPN, COMP, FRZB, COL2A1[51], GDF5[52] and IL4Ralpha.[53] Subsequent large scale studies and meta-analyses have often failed to support the initial findings but associations between OA and polymorphisms in GDF5[54] and ASPN[55] continue to be of interest. The gene for GDF5 codes for growth differentiation factor 5, is a member of the TGF-beta superfamily and is closely related to the bone morphogenetic protein (BMP) family. GDF5 has important roles in skeletal and joint development[56,57] and mutations result in a range of skeletal abnormalities. The rs143383 SNP causes a C to T transition which results in reduced GDF5 transcription in all joint tissues.[58] In vivo studies also support a role for decreased expression of GDF5 being associated with OA development.[59] ASPN encodes for asporin, a member of the sub family of small leucine-rich proteoglycans (SLRPs) that also includes decorin and biglycan.[60] Functionally, asporin binds to transforming growth factor-beta (TGF-beta), preventing its binding to the TGF-beta type II receptor and inhibiting TGF-beta-induced expression of anabolic cartilage molecules including aggrecan and type II collagen.[61] The effect on TGF-beta activity is allele-specific, with the D14 allele, which is associated with OA, causing a greater inhibition of TGF-beta activity than other alleles.[62]

Genome-wide association scans of OA provide the opportunity for discovery of unsuspected and unknown genes that are associated with OA. To this end, one such study has shown an association signal with a locus of high linkage disequilibrium on chromosome 7q22 stretching over 500kb that contains at least six genes PRKAR2B, HPB1, COG5, GPR22, DUS4L and BCAP29, none of which were obvious OA candidates.[50] The arcOGEN study has recently reported a GWAS on individuals with severe hip and knee OA, many of whom had undergone total joint replacement.[63] They identified polymorphisms in a number of loci and genes with genome wide significance. The most strongly associated locus straddled GLT8D1 and GNL3 on chromosome 3p21.1. GLT8D1 encodes the protein glycosyltransferase 8 domain containing 1, a member of the glycosyltransferase family that is of unknown function in cartiage. GNL3 encodes the guanine nucleotide binding protein-like 3, also known as nucleostemin. This molecule binds p53 and is involved in regulating differentiation and cell cycle transit. In vitro studies show that GNL-3 is present in the nuclei of OA chondrocytes and may be up-regulated in disease. Specific roles in cartilage are as yet unknown. Three other novel associated loci identified as being associated with OA were PTHLH, CHST11 and FTO. PTHLH codes for parathyroid hormone-like hormone that has roles in endochondral bone development. CHST11 codes for carbohydrate (chondroitin 4) sulfotransferase 11 and catalyzes the transfer of sulfate to position 4 of the N-acetylgalactosamine (GalNAc) residue of chondroitin during glycosaminoglycan synthesis. FTO (fat mass and obesity assocoiated gene) is strongly associated with fat mass, obesity and diabetes. These genes may have theoretical effects through actions on bone metabolism, cartilage matrix structure or white fat metabolic activity respectively but their function in regulation of joint tissue homeostasis remains to be elucidated.

Mechanical Loading and Osteoarthritis

Mechanical loading within a physiological range is necessary for maintaining joint tissues and cartilage in particular, in a healthy state. As such abnormalities of mechanical loading are central to the development of OA. OA arises when there is an imbalance between the mechanical forces within a joint and the ability of the cartilage to withstand these forces. This arises in two situations. In the first normal articular cartilage is exposed to abnormal mechanical loads whereas in the other the articular cartilage is fundamentally defective with biomaterial properties that are insufficient to withstand normal load bearing. Risk factors associated with development of OA may give have effects in either one or both of these scenarios. For instance some of the genetic predisposition to OA may be a result of subtle abnormalities of joint shape that result in abnormal loading through cartilage. The accumulation of AGEs in cartilage matrix with age results in a more brittle collagen network that is less able to withstand normal loads, again leading to cartilage degeneration.

Mechanical loading that is either below or in excess of the physiological range causes cartilage degeneration. The mechanisms are now beginning to be understood. Chondrocytes are able to recognise mechanical stimuli transmitted through the matrix. The mechanical forces are recognised by mechanoreceptors such as integrins.[64] Activation of these transmembrane molecules with associated proteins including CD47[65] results in stimulation

of a series of intracellular signal cascades that lead to expression of cartilage matrix molecules such as aggrecan and inhibition of matrix protease production.[66] As such an anabolic response is produced that maintains, and in some circumstances, improves cartilage structure and function. Mechanical signalling induces activation of a large number of intracellular molecules and cascades including FAK, PKC, JAK/STAT and MAP kinases.[67-69] The particular cascade stimulated will depend on the mechanoreceptor activated and the involvement of downstream autocrine and paracrine activity through release of locally acting mediators that include interleukin-4 and substance P.[70,71]

In contrast overloading induces molecular and biomechanical changes that shift the balance of tissue remodelling in favour of catabolic over anabolic activity. Although these events also appear to be integrin mediated, the molecules involved and pathways activated are different from that seen when cartilage is physiologically loaded. Stimulation of stress-induced intracellular pathways leads to the production of proinflammatory cytokines such as IL-1 and TNF-α which increase production of MMPs and aggrecanases.[72-75] Interestingly chondrocytes from OA cartilage show an altered responsiveness to mechanical loads as they fail to show an anabolic response to physiological loading but instead demonstrate a pro-inflammatory IL-1 beta dependent response.[76,77] This may further accelerate disease progression and attenuate cartilage repair.

CONCLUSION

OA is a disease of the diarthrodial joint with the gross and microscopic pathological changes being seen in all joint tissues although changes in articular cartilage are still believed to be paramount in the disease. The risk factors that predispose to the development of OA such as increasing age, obesity, genetics and mechanical loading have been known for some time. However it is only recently that we have begun to understand how these may influence normal joint function and response to injury. New insights into the effects of age, obesity and genetic variation on how mechanical loading is perceived and responded to by chondrocytes and other mechanosensitive cells within the joint environment may at last indicate novel routes by which this debilitating disease can be treated or prevented.

DISCLOSURE

The author declares that this study has no conflict of interest.

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