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Genetic Mouse Models for Osteoarthritis Research

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1. Introduction

Osteoarthritis (OA), a degenerative joint disease, increases in prevalence with age, and affects majority of individuals over the age of 65. OA frequently affects several joints including the hands, knees, hips and spine, and is a leading cause of impaired mobility in the elderly. The major clinical symptoms include chronic pain, joint instability, stiffness and radiographic joint space narrowing (Felson, 2006; Goldring & Goldring, 2007).

During OA development, articular chondrocytes undergo hypertrophy leading to extracellular matrix degradation, articular cartilage breakdown and osteophyte formation in the margins of the articular cartilage (Felson, 2006; Goldring & Goldring, 2007). The precise signaling pathways which are involved in the degradation of cartilage matrix and development of OA are poorly understood and there are currently no effective interventions to decelerate the progression of OA or retard the irreversible degradation of cartilage except for total joint replacement surgery (Krasnokutsky et al., 2007). In this chapter, we will summarize important molecular mechanisms related to OA pathogenesis and provide new insights into potential molecular targets for the prevention and treatment of OA.

2. Characteristics of articular cartilage

The skeleton is an organ composed of two distinct tissues: bone and cartilage. Bones are rigid mineralized organs formed in a variety of shapes. Normal articular cartilage, emerging during the postnatal stage as a permanent tissue distinct from the growth plate cartilage, is an extremely smooth, hard and white tissue that lines the surface of all the diarthrodial joints. Articular cartilage facilitates interactions between two bones in a joint with a low coefficient of friction. Water, type II collagen (Col2), and proteoglycans are the principle components of articular cartilage. Of the wet mass, 65%~80% of cartilage is water, 10%~20% is Col2, and 4%~7% is aggrecan. Other collagens and proteoglycans such as types V, VI, IX, X, XI, XII, XIV collagens (Eyre et al., 2002) and decorin, biglycan, fibromodulin, lumican, epiphygan, and

perlecan (Knudson & Knudson, 2001) also contribute a small part (less than 5%) of the normal cartilage composition. The articular chondrocyte is the only cell type in articular cartilage and as such is the major player in cartilage development and maintenance.

During articular cartilage development, articular chondrocytes establish the cartilage matrix by synthesizing and depositing collagens and proteoglycans. The collagen/proteoglycan matrix consists of a highly dense meshwork of collagen fibrils including the major collagen type II (Col2) and minor collagen types IX, and XI embedded in gel-like negatively-charged proteoglycans (Kannu et al., 2009). This hydrated architecture of the matrix provides the articular cartilage with tensile and resilient strength which allows joints to maintain proper biomechanical function (Iozzo, 2000).

As articular cartilage matures, articular chondrocytes maintain the cartilage by synthesizing matrix components (Col2 and proteoglycans) and matrix degrading enzymes with minimal turnover of cells and matrix. The existing collagen network becomes cross-linked, and articular cartilage matures into a permanent tissue with the ability to absorb and respond to mechanical stress (Verzijl et al., 2000). Under normal conditions, articular chondrocytes become arrested at a pre-hypertrophic stage of differentiation, thereby persisting throughout postnatal life to maintain normal articular cartilage structure (Pacifici et al., 2005).

3. Progression of osteoarthritis

Articular cartilage can be damaged by normal wear and tear or pathological processes such as abnormal mechanical loading or injury. Because articular cartilage is an avascular tissue, and chondrocytes possess little regenerative capacity and are arrested before terminal hypertrophic differentiation, articular cartilage has very limited capacity to repair after damage.

During the early stages of OA, the cartilage surface is still intact. The molecular composition and organization of the extracellular matrix is altered first (Glodring & Glodring, 2010). The articular chondrocytes, which possess little regenerative capacity and have a low metabolic activity in normal joints, exhibit a transient proliferative response and increase matrix synthesis (Col2, aggrecan etc.) attempting to initiate repair caused by pathological stimulation. This response is characterized by chondrocyte cloning to form clusters and hypertrophic differentiation, including expression of hypertrophic markers such as *Runx2*, *ColX*, and *Mmp13*. Changes in the composition and structure of the articular cartilage further stimulate chondrocytes to produce more catabolic factors involved in cartilage degradation. As proteoglycans and then the collagen network break down (Mort & Billington, 2001), cartilage integrity is disrupted. The articular chondrocytes will then undergo apoptosis and the articular cartilage will eventually be completely lost. The reduced joint space resulting from total loss of cartilage will cause friction between bones, leading to pain and limited joint mobility. Other signs of OA, including subchondral sclerosis, bone eburnation, osteophyte formation, as well as loosening and weakness of muscles and tendons will also appear.

4. Genetic contribution to osteoarthritis

The etiology of OA is multi-factorial, including obesity, joint mal-alignment, and prior joint injury or surgery. These factors can be segregated into categories such as mechanical

influences, the effects of aging and genetic factors. Meniscal injuries are among the most common causes of OA in younger populations. The meniscus is a C-shaped structure that functions as shock-absorbing, load bearing, stability enhancing, and lubricating cushion in the knee joint. Studies show that loss of intact meniscus function leads to OA in humans due to joint instability and abnormal mechanical loading (Ding et al., 2007; Hunter et al., 2006). Recently, the meniscal-ligamentous injury (MLI) induced-OA model is becoming a well-established mouse model which mimics clinical situation allowing us to study the development and progression of trauma-induced OA on defined genetic backgrounds (Clements et al., 2003; Sampson et al., 2011). In this model, the ligation of the medial collateral ligament coupled with disruption of the meniscus from its anterior-medial attachment can reproducibly induce OA over a 3 month time period.

There are rare cases of OA involving mutations of *types II, IX and XI collagen* (Li et al., 2007; Kannu et al., 2009). In addition, OA progression is also affected by pro-inflammatory factors such as prostaglandins, TNF- α , interleukin-1, interleukin-6 and nitric oxide. However, there is no evidence supporting a critical role for these factors in the development of severe OA (Kawaguchi, 2009). As articular chondrocytes inappropriately undergo endochondral ossification-like maturation in the context of OA, however, several genetic mouse models have been developed and demonstrated potential roles of affected genes in OA pathogenesis.

4.1 TGF- β signaling

Chondrocyte differentiation and maturation during endochondral ossification are tightly regulated by several key growth factors and transcription factors, including members of the transforming growth factor β (TGF- β) super family, fibroblast growth factors (FGFs), indian hedgehog (Ihh), parathyroid hormone-related protein (PTHrP), and Wnt signaling proteins (Blaney Davidson et al., 2007; Kolpakova & Olsen, 2005; Komori, 2003; Kronenberg, 2003; Ornitz, 2005). The inhibition of TGF- β signaling represents a potential mechanism in the development of OA because TGF- β inhibits chondrocyte hypertrophy and maturation (Blaney Davidson et al., 2007). There are three isoforms of TGF- β , TGF- β 1, 2 and 3, which can bind to the type II receptor to activate the canonical TGF- β /Smad signaling cascade. In the canonical pathway, TGF- β binds to the type II receptor which then phosphorylates type I transmembrane serine/threonine kinase receptors. The type I receptor subsequently phosphorylates Smads 2 and 3 (R-Smad) at a conserved SSXS motif at the C-terminus of Smads 2 and 3. The activated R-Smads thus dissociate from the receptor complex and form a heteromeric complex with the common Smad, Smad4. This heteromeric Smad complex then enters the nucleus and associates with other DNA binding proteins to regulate target gene transcription (Miyazawa et al., 2002).

Deletion of any TGF- β isoform gene could result in embryonic lethality and loss of TGF- β 2 or TGF- β 3 results in defects in bone development affecting the forelimbs, hindlimbs and craniofacial bones, suggesting that TGF- β plays an important role in skeletogenesis (Nicole & Kerstin, 2000). Recent genetic manipulation of TGF- β signaling members also demonstrated that TGF- β signaling plays a critical role during OA development. Transgenic mice that over-express the dominant-negative type II TGF- β receptor (*dnTgfr2*) in skeletal tissue exhibit articular chondrocyte hypertrophy with increased type X collagen expression, cartilage disorganization and progressive degradation (Serra et al., 1997). Consistent with these findings, Smad3 knockout mice show progressive articular cartilage degradation

resembling human OA (Yang et al., 2001). In order to overcome embryonic lethality and redundancy, we generated chondrocyte-specific *Tgfb2* conditional knockout mice (*Tgfb2* cKO or *Tgfb2*^{Col2CreER} mice) in which deletion of the *Tgfb2* gene is mediated by Cre recombinase driven by the chondrocyte-specific Col2a1 promoter in a tamoxifen (TM)-inducible manner (Chen et al, 2007; Zhu et al, 2008, 2009). These mice exhibit typical clinical features of OA, including cell cloning, chondrocyte hypertrophy, cartilage surface fibrillation, vertical clefts and severe articular cartilage damage as well as the formation of chondrophytes and osteophytes (Shen et al., unpublished data). In addition, the relationship between TGF- β signaling and OA is strengthened by the discovery that a single nucleotide polymorphism (SNP) in the human Smad3 gene is linked to the incidence of hip and knee OA in a 527 patient cohort (Valdes et al., 2010).

4.2 Wnt/ β -catenin signaling

The canonical Wnt/ β -catenin signaling pathway, which controls multiple developmental processes in skeletal and joint patterning, may also be involved in the progression of OA. *In vitro* studies show that over-expression of constitutively active β -catenin leads to loss of the chondrocyte phenotype including reduced Sox9 and Col2 expression in chick chondrocytes (Yang, 2003). When Wnt binds its receptor Frizzled and the co-receptor protein LRP5/6, the signaling protein Dishevelled (Dsh) is activated, leading to inactivation of the serine/threonine kinase GSK-3 β , thus inhibiting the ubiquitination and degradation of β -catenin. β -catenin then accumulates in the nucleus and binds LEF-1/TCF to regulate the expression of Wnt target genes. In the absence of the Wnt ligand, cytosolic β -catenin binds the APC-Axin-GSK-3 β degradation complex, and GSK-3 β in this complex phosphorylates β -catenin to induce its proteosomal degradation. The degradation of β -catenin represses the expression of Wnt responsive genes, allowing binding of the corepressor Groucho to the transcription factors LEF-1/TCF.

Genome-wide scans, candidate gene association analyses and single nucleotide polymorphism (SNP) studies have demonstrated the association of hip OA with the Arg324Gly substitution mutation in the sFRP3 protein that antagonizes the binding of Wnt ligands to the Frizzled receptors. The mutation of sFRP3 causes increased levels of active β -catenin, promoting aberrant articular chondrocyte hypertrophy and thereby leading to hip and knee OA in patients (Loughlin et al., 2004; Lane et al., 2006; Loughlin et al., 2000; Min et al., 2005). Consistent with this finding, *Frzb* knockout mice are more sensitive to chemical-induced OA (Lories et al., 2007).

Since human genetic association studies suggest that Wnt/ β -catenin signaling may play a critical role in the pathogenesis of OA, we have generated chondrocyte-specific β -catenin conditional activation (cAct) mice. These mice show high expression of β -catenin in articular chondrocytes leading to abnormal articular chondrocyte maturation and progressive loss of the articular cartilage surface in 5- and 8-month old mice (Zhu et al., 2009). The role of Wnt/ β -catenin signaling in cartilage degeneration is further demonstrated in other animal models. Chondrocyte-specific Col2a1-Smurf2 transgenic mice develop an OA-like phenotype due to up-regulation of β -catenin caused by Smurf2-induced ubiquitination and degradation of GSK-3 β (Wu et al., 2009). Furthermore, over-expression of Wnt-induced signaling protein 1 (WISP-1) in the mouse knee joint also leads to cartilage destruction (Blom et al., 2009). Consistent with these findings, it has been reported that a panel of Wnt signaling-related genes, including WISP-1 and β -catenin, were significantly

up-regulated in knee joints and disc samples from patients with OA and disc degenerative disease (DDD) (Blom et al., 2009; Tang et al., unpublished data).

4.3 Indian hedgehog (Ihh) signaling

The Indian hedgehog (Ihh)/parathyroid hormone-related protein (PTHrP) negative-feedback loop is critical for chondrocyte differentiation during endochondral bone formation. Articular chondrocytes undergo cellular changes reminiscent of terminal growth plate chondrocyte differentiation during OA (Kronenberg, 2003). These observations suggest a pivotal role for Ihh signaling in OA development. Ihh is a major Hh ligand in chondrocytes, which binds with the Patched-1 (PTCH1) receptor to release its inhibition on Smoothed (SMO). SMO can then activate the glioma-associated oncogene homolog (Gli) family of transcription factors to initiate transcription of specific downstream target genes, including Hh signaling pathway members *Gli1*, *Ptch1* and hedgehog-interacting protein (HHIP).

Immunohistochemical studies demonstrated that Ihh signaling activation positively correlates with the severity of OA in human OA knee joint tissues and high expression of GLI1, PTCH and HHIP was found in surgically induced murine OA articular cartilage. Activation of Ihh signaling in mice with chondrocyte-specific over-expression of the *Gli2* or *Smo* genes induced a spontaneous OA-like phenotype with high MMP-13, ADAMTS5 and ColX expression. In contrast, deletion of the *Smo* gene or treatment with a pharmacological inhibitor of Ihh attenuated the severity of OA induced by MLI injury (Lin et al., 2009).

4.4 HIF-2 α

The HIF proteins, including HIF-1, 2 and 3, are the basic helix-loop-helix transcription factors which function differently under normoxic and hypoxic conditions (Semenza, 2000; Lando et al., 2002; Bracken et al., 2003; Schofield and Ratcliffe, 2004). HIF-1 α , in the articular cartilage, acts as an anabolic signal by stimulating specific extracellular matrix synthesis (Pfander et al., 2003; Duval et al., 2009). In contrast, HIF-2 α (encoded by *EPAS1*) is a potential catabolic regulator of articular cartilage and induces articular cartilage degeneration (Saito et al., 2010; Yang et al., 2010). Promoter assays suggest that NF- κ B signaling could significantly induce HIF-2 α expression and then HIF-2 α specifically regulate transcription of several catabolic genes such as *Mmp13* (Saito et al., 2010). Genetic screen using the human osteoarthritic cartilage UniGene library suggests that HIF-2 α is a potential catabolic regulator of articular cartilage (Yang et al., 2010). Based on the Japanese population ROAD study, a functional SNP in human *EPAS1* proximal promoter region was associated with knee osteoarthritis in a 397 patient cohort (Muraki et al., 2009; Saito et al., 2010). Consistent with this finding, HIF-2 α expression was markedly increased in OA patients with degenerative cartilage (Saito et al., 2010; Yang et al., 2010). Chondrocyte-specific *Epas1* transgenic mice could spontaneously develop osteoarthritis phenotype with increased MMP-13 and ColX expression in articular cartilage. In addition, *Epas1* heterozygous deficient mice showed resistance to cartilage degeneration induced by meniscus surgery (Saito et al., 2010; Yang et al., 2010). Therefore, HIF-2 α may be a critical transcription factor that targets several genes for osteoarthritis development.

4.5 Insulin-like growth factor (IGF)

The progressive nature of OA is characterized by a growing imbalance between anabolism and catabolism in articular cartilage. The three above-mentioned signaling pathways are

mainly involved in regulation of articular chondrocyte catabolism. In contrast, insulin-like growth factor (IGF) is the most likely candidate affecting cartilage matrix synthesis (Guenther et al., 1982; McQuillan et al., 1986). The most important ligand in IGF signaling is IGF-1 which interacts with specific IGF membrane receptors as well as with the insulin receptor to activate their cytoplasmic tyrosine kinase domains and initiate the MAPK cascade and promote cell proliferation and differentiation. The action of IGF signaling on cellular anabolism is governed at different levels, including IGF ligand, receptors and IGF binding proteins (IGFBP) which modify the interaction of IGF with its receptor (Martel-Pelletier et al., 1998). In cartilage, IGF-1 is believed to stimulate synthesis of extracellular matrix proteins in chondrocytes (Schoenle et al., 1982; Trippel et al., 1989). The local production of IGF-1 is significantly increased in human OA synovial fluid, due to attempting to repair the damaged cartilage. However, the diseased cells are hyporesponsive to IGF-1 stimulation since highly-expressed IGFBP3 on the cell membrane interferes with the binding of IGF-1 to its receptor (Doré et al., 1994; Tardif et al., 1996). Moreover, the highly expressed IGF-1 may contribute to the subchondral bone sclerosis and osteophyte formation (Martel-Pelletier et al., 1998).

5. Cartilage degradation during OA

Articular chondrocytes, the only cell type in cartilage, are sensitive to altered mechanical loading pattern induced by obesity, injury and aging (Goldring & Goldring, 2007). Chondrocytes have receptors responding to mechanical stimulation, including integrins which serve as receptors for extracellular matrix components such as fibronectin (FN) and type II collagen fragments (Millward-Sadler & Salter, 2004). In addition to these receptors, several signaling pathways mentioned above are mechano-responsive in chondrocytes as well, including TGF- β , Wnt and Ihh signaling (Blaney Davidson et al., 2006; Komm & Bex, 2006; Ng et al., 2006; Robinson et al., 2009). Activation of these signaling pathways induces the expression of matrix-degrading proteinases. Studies of large scale gene expression profiling from tissue samples of OA patients revealed two principle enzyme families responsible for cartilage degeneration during OA development: the matrix metalloproteinase (MMP) family members which target collagens and a disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS) family members which mediate aggrecan degeneration (Aigner et al., 2006).

5.1 Collagenase: Matrix metalloproteinase

MMP-13 is a substrate-specific enzyme that targets collagen for degradation. Compared to other MMPs, MMP-13 expression is more restricted to connective tissues (Borden & Heller, 1997; Mengshol et al., 2000; Vincenti et al., 1998; Vincenti, 2001). MMP-13 preferentially cleaves Col2, which is most abundant in articular cartilage and in the nucleus pulposus, inner anulus fibrosus and cartilage endplate of the intervertebral disc. It also targets the degradation of other proteins in cartilage, such as aggrecan, types IV and IX collagen, gelatin, osteonectin and perlecan (Shiomi et al., 2010). MMP-13 has a much higher catalytic velocity rate compared with other MMPs over Col2 and gelatin, making it the most potent peptidolytic enzyme among collagenases (Knäuper et al., 1996; Reboul et al., 1996).

Clinical investigations revealed that patients with articular cartilage destruction had high MMP-13 expression (Roach et al., 2005), suggesting increased MMP-13 may be the cause of

cartilage degradation. *Mmp13* deficient mice show no gross phenotypic abnormalities, and the only alteration is in growth plate architecture during early cartilage development (Inada et al., 2004; Stickens et al., 2004). However, transgenic mice with cartilage-specific *Mmp13*-overexpression develop spontaneous articular cartilage destruction characterized by excessive cleavage of Col2 and loss of aggrecan (Neuhold et al., 2001). In the above-mentioned *Tgfr2* cKO and β -catenin cAct mouse models, MMP-13 expression is significantly increased (Shen et al., unpublished data; Zhu et al., 2009). These findings suggest that MMP-13 deficiency does not affect articular cartilage function during the postnatal and adult stages but abnormal up-regulation of MMP-13 can lead to cartilage destruction. Moreover, deletion of the *Mmp13* gene prevents articular cartilage erosion induced by meniscal injury (Little et al., 2009). Deletion of the *Mmp13* gene at least partially rescues the OA-like phenotype observed in *Tgfr2* cKO and β -catenin cAct mice (Shen et al., unpublished data; Wang et al., unpublished data), suggesting that TGF- β /Smad3 and Wnt/ β -catenin signaling play a critical role in the development of OA through up-regulation of MMP-13 expression.

5.2 Aggrecanase: ADAMTS

The ADAMTS family consists of large family members and they share several distinct protein modules as well. Studies show that ADAMTS4 and 5 expression levels are significantly increased during OA development. Single knockout of the *Adamts5* gene or double knockout of the *Adamts4* and *Adamts5* genes prevents cartilage degradation in surgery-induced and chemical-induced murine knee OA models (Glasson et al., 2005; Majumdar et al., 2007; Stanton et al., 2005). Interestingly, in *Tgfr2* cKO, β -catenin and *Ihh* activation mouse models, ADAMTS5 was significantly increased in articular cartilage tissue, suggesting that maintaining proper ADAMTS5 levels are essential for normal articular cartilage function. Taken together, these findings indicate that catabolic enzymes play a significant role in OA progression and targeting these enzymes may be a viable therapeutic strategy to decelerate articular cartilage degradation.

6. Potential therapeutic approaches

MMP-13 and ADAMTS5 are two potentially attractive targets for OA therapy. The inhibition of these enzymes and their regulatory mechanisms have been extensively studied. Tissue inhibitors of metalloproteinases (TIMP) are specific inhibitors which directly bind MMPs and ADAMTS in chondrocytes to prevent the destruction of articular cartilage (Stetler-Stevenson & Seo, 2005). A specific small molecule MMP-13 inhibitor can attenuate the severity of OA in the MLI-induced injury model as well (Wang et al., unpublished data). In addition to proteinase inhibitors, the transcription factor Runt domain factor-2 (Runx2) appears to be another potential target to regulate MMP-13 and ADAMTS5 *in vivo*. DNA sequence analysis of *Mmp13* and *Adamts5* promoters identified putative Runx2 binding sites in the promoter regions of these genes. In addition, Runx2 has an overlapping expression pattern with MMP-13 and ADAMTS5, almost exclusively in the developing cartilage and bone, suggesting that Runx2 may be an important transcription factor regulating tissue-specific expression of *Mmp13* and *Adamts5* in articular chondrocytes (Ducy et al., 1997; Enomoto et al., 2000; Inada et al., 1999; Komori et al., 1997). *In vitro* studies confirmed that MMP-13 and ADAMTS5 expression dramatically increase after alterations in TGF- β /Smad3,

Wnt/ β -catenin and Ihh signaling pathways and concomitant up-regulation of Runx2 expression (Lin et al., 2009; Shen et al., unpublished data; Wang et al., unpublished data). Thus, manipulation of Runx2 expression *in vivo* could be an effective therapeutic strategy. During bone development, the temporal and spatial expression patterns of *Runx2* are regulated by cytokines and growth factors including TGF- β , BMP, and FGF (Kim et al., 2003; Takamoto et al., 2003; Tou et al., 2001; Zhou et al., 2000). In addition to gene expression, Runx2 protein levels are also regulated through post-translational mechanisms involving phosphorylation, ubiquitination and acetylation (Zhao et al., 2003, 2004; Jeon et al., 2006; Jonason et al., 2009; Shen et al., 2006a, 2006b; Shui et al., 2003; Zhang et al., 2009). We have recently found that cyclin D1 induces Runx2 ubiquitination and degradation in a phosphorylation-dependent manner leading to the inhibition of Runx2 transcriptional activity (Shen et al., 2006b). MicroRNA regulation is another important regulatory mechanism for protein translation. MicroRNA-140 (miR-140) is the first microRNA demonstrated to be involved in the pathogenesis of OA at least partially through regulation of ADAMTS5 mRNA expression. MiR-140 knockout mice are susceptible to age-related OA progression and conversely, over-expression of miR-140 in chondrocytes protects mice from OA development (Akhtar et al., 2010; Miyaki et al., 2009; Yamasaki et al., 2009).

7. Summary

Articular chondrocyte is the sensor of articular cartilage homeostasis, and plays a critical role in maintaining the normal physiological structure and function of articular cartilage. Recent studies demonstrate that articular chondrocyte homeostasis can be disrupted by multiple factors, including abnormal mechanical loading, and aging. Additionally, genetic alterations in TGF- β /Smad, Wnt/ β -catenin and Ihh signaling pathways can disrupt the balance between anabolic and catabolic activity in articular cartilage and result in irreversible degradation of the extracellular matrix. Thus far, most of the mouse models of osteoarthritis converge at the up-regulation of catabolic enzymes, such as MMP-13 and ADAMTS5, suggesting that these enzymes may serve as potential therapeutic targets in regulation of the progression of OA. In addition, manipulation of the above-mentioned signaling pathways in articular chondrocytes could also play a role in articular cartilage regeneration.

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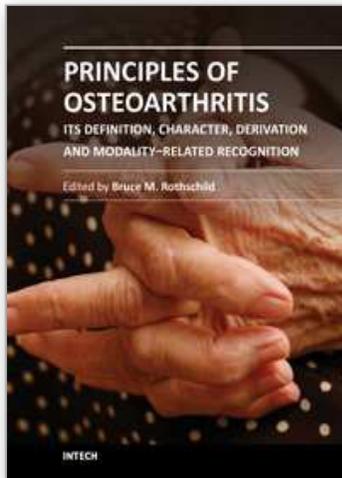
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This volume addresses the nature of the most common form of arthritis in humans. If osteoarthritis is inevitable (only premature death prevents all of us from being afflicted), it seems essential to facilitate its recognition, prevention, options, and indications for treatment. Progress in understanding this disease has occurred with recognition that it is not simply a degenerative joint disease. Causative factors, such as joint malalignment, ligamentous abnormalities, overuse, and biomechanical and metabolic factors have been recognized as amenable to intervention; genetic factors, less so; with metabolic diseases, intermediate. Its diagnosis is based on recognition of overgrowth of bone at joint margins. This contrasts with overgrowth of bone at vertebral margins, which is not a symptomatic phenomenon and has been renamed spondylosis deformans. Osteoarthritis describes an abnormality of joints, but the severity does not necessarily produce pain. The patient and his/her symptoms need to be treated, not the x-ray.

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