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REVIEW

Animal models of osteoarthritis for the understanding of the bone contribution

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Osteoarthritis characterizes the joint disease that results in cartilage damage accompanied by bone lesions and synovial inflammation. Joint integrity results from physiological interactions between all these tissues. Local factors such as cytokines and growth factors regulate cartilage remodeling and metabolism as well as chondrocyte differentiation and survival. Tremendous progress has been made through the use of animal models and provided insight for the mechanism of cartilage loss and chondrocyte functions. Surgical, chemical or genetic models have been developed to investigate the role of molecules in the pathogenesis or treatment of osteoarthritis. Indeed, the animal models are helpful to investigate the cartilage changes in relation to changes in bone remodeling. Increased bone resorption occurs at early stage of the development of osteoarthritis, the inhibition of which prevents cartilage damage, confirming the role of bone factors in the crosstalk between both tissues. Among these numerous molecules, some participate in the imbalance in cartilage homeostasis and in the pathophysiology of osteoarthritis. These local factors are potential candidates for new drug targets.

Introduction

Cartilage loss is the hallmark of osteoarthritis (OA), but involves the whole joint tissues including bone, synovial tissues and ligaments. In humans, the characterization of each tissue lesion that leads to cartilage degradation in a longitudinal manner has been limited as samples are available only at the time of surgery. Recent data based on imaging provided useful information on the lesions developed in the joints at the early stages of OA.[1,2] Such evaluations have the advantage of providing the localization and the time-course of the tissue alterations such as cartilage, synovium, meniscus and bone. Indeed, synovial, meniscus and bone marrow lesions are good predictors of OA rapid progression at the knee.[3–7] However, this approach does not fully characterize the cellular and molecular changes that might occur early in the disease. Therefore, animal models are valuable tools to fully characterize the kinetics of the changes in the tissues and the activation/inhibition of implicated molecules. Moreover, animal models provide insight for the development of new molecules and their efficacy.

Animal Models in OA

The final goal of animal models is to reproduce human diseases. Given the heterogeneity of profiles in human OA, many models are needed. They are either spontaneous or induced. Spontaneous OA might occur naturally such as in Str-Ort mic or in genetically modified mice.[8] OA can also be induced by intra-articular injection of chemicals uch as mono-iodiacetate. Surgical models that are now widely used led to the description of several procedures, but they all target joint instability to induce OA.

Most of them focused in one factor that favors the development of OA such as aging, mechanical stress (surgery), chemical defect (enzyme) or in genetic factors. All of them differ in terms of severity, localization of lesions and pathogenesis. Hence, the choice of the model should be appropriate to the addressed question. For example, the choice should be focused on either the role of tissues or molecules that could trigger OA, the development under a specific genetic background or the use of drugs to prevent the occurrence of OA. Moreover, the necessity of animal models is driven by the need of preclinical studies in order to evaluate the safety, toxicity and effects of drugs.

The most widely used models are animals of small size such as mice, rats, guinea pigs and rabbits because of the easy access of animal facilities. Sheep, goats and horses are less used in relation of the financial burden they entail. For all of them, skeletally mature animals are suitable. Regardless of the techniques that are available to induce arthritis, histopathology scores are mandatory. The Mankin score has been used as

described for humans, and recently the OOCHAS score was developed in mice;[9] more recently, the OARSI scores have been established for each animal.[10] This initiative helped to standardize the lecture of the cartilage damages and in allowing the comparison across studies.

Different models are available to assess the effect of bone on cartilage. The most suitable model for assessing the influence of bone–cartilage interaction is the rat or the mouse, allowing the targeting of molecules through gene manipulation. Mechanically induced OA is widely used, related to the possibility of inducing lesions of various severities through procedures that include the combinations of ligament transection and menisectomy in the mouse knee joints. Four models of joint instability have been proposed that include the progressive removal of the structures. The mild model of OA consisted of the sectioning of the anterior cruciate ligament, the moderate model encompassed the removal of the medial meniscus in addition to anterior cruciate ligament (ACT) transaction, the medial model consisted of the sectioning of the medial meniscus and collateral ligament, whereas the severe model included the transection of the patellar ligament in addition to the sectioning of all these structures. Joint instability results in cartilage damage in a time-dependent manner and according to the number of joints structures that are removed or sectioned[11] (**Table 1**). Therefore, this model could be appropriate for identifying the early-stage changes in the whole joint tissues.

Subchondral Bone Lesions in OA

The role of the subchondral bone in the pathogenesis of OA was first suggested a long time ago on the basis of clinical evidence.[12,13] Negative correlations have been reported in the incidence of hip/knee OA and osteoporosis in the past,[14–16] but increased risk factures are observed in OA patients.[17,18] Moreover, subchondral bone changes in OA patients might trigger the initiation and promote the progression of cartilage lesions.[12,13,19] As subchondral bone transmits the mechanical strains applied to joints, cartilage lesions might be initiated when bone stiffness is high. It is hypothesized that zones with high mechanical loading lead to microfractures, which in turn

increases the subchondral bone remodeling in an attempt to repair the damage.[12,20,21] Therefore, bone features might result from joint repair as well as from an imbalance in the physiological interactions between the bone and the cartilage.[22] Subchondral bone is defined as the bone plate underlying the cartilage, although this often refers to the entire underlying trabecular network. The subchondral bone could be assessed in the epiphyseal region underlying the cartilage using microCT or histomorphometric methods that are applied for bone evaluation. The distribution and damping of mechanical loading depends on the quality of the subchondral bone,[12,20,21] and the mechanical competence of the cartilage is probably influenced by the mechanical properties of the bone plate and the trabecular network beneath. Bone remodeling leads to the apposition of new, less-mineralized bone and subsequently results in bone with a lower mineral content, which is more liable to deformation when loaded. Therefore, focal high bone remodeling could impair the mechanical properties of bone, which in turn would modify the transmission of mechanical strain and the response of the cartilage.

Increase in bone volume is characteristic of the later stages of OA in humans, and occurs when the cartilage has been degraded.[23,24] In advanced stages, the bone volume measured at the tibia plateau of OA patients is higher than that in controls; this is related to increased trabecular thickness, reflecting a high rate of bone formation.[25] In contrast, maintained trabecular separation suggests the absence of bone resorption. These features have been confirmed in severe OA.[26] Of note, data are mostly obtained from OA joints at the stage of joint replacement, which reflect the adaptive response of the bone to cartilage damage. Early changes are seldom reported in humans and some studies have shown that the trabecular network is poorly connected, indicating initial high bone remodeling might contribute to poor mechanical bone resistance.[27] Animal models provide evidence of high bone remodeling at various stages before cartilage matrix degradation occurs. In guinea pigs, which develop spontaneous knee OA, bone volume increases in parallel to cartilage wear followed by progressive thickening of the trabeculae at late stages. However, perforation of trabeculae is observed at early stages, indicating a high bone remodeling and decreased bone mineral density during the initial stage of OA.[28] The development of a mechanical model of OA induced by joint instability further confirms these observations. In dogs with a sectioned cruciate ligament, early-phase OA displays subchondral bone and trabecular thinning associated with increased bone resorption.[29] At later stages, decreased mineralization of subchondral bone occurs[30] while connectivity is restored.[31] This has been confirmed in rats with joint instability, in which osteoclastic activity and resorption markers are increased at early stages.[32] Interestingly, inhibiting bone resorption with alendronate alleviates cartilage degradation through a mechanism involving MMP13 expression.[33] In mice with joint instability induced by meniscectomy, subchondral bone thickening appears before cartilage degradation at 6–10 weeks.[11] Osteoclastic activity and structural changes precede cartilage lesions and can be prevented by osteoprotegerin, an inhibitor of bone resorption.[34] Moreover, inhibition of resorption in mice with high bone remodeling results in a reduction of cartilage lesions.[35,36] Interestingly, collagenase-induced OA results in changes in the trabecular network and promotes osteoclastogenesis,[37] confirming an early high bone

Table 1 Description of joint lesions in OA models

Models	Structures involved	Cartilage destruction	Osteophyte formation
Severe	Patellar ligament Medial collateral ligament Medial meniscus Anterior cruciate ligament Posteror cruciate ligament Lateral meniscus Lateral collateral meniscus	2 weeks	4 weeks
Medial	Medial collateral ligament Medial meniscus	8 weeks	12 weeks
Moderate	Medial meniscus Anterior cruciate ligament	4 weeks	4 weeks
Mild	Anterior cruciate ligament	8 weeks	8 weeks

resorption at early stages of OA regardless of whether the initial stress is mechanical or chemical. Altogether, the acceleration of bone remodeling might be an initial step, followed by the thickening of subchondral bone, which might be an adaptive response secondary to mechanical loading or an attempt to repair the cartilage.

As described above, animal models contribute to the understanding of cartilage remodeling, although they require heavy and time consuming experiments. The development of biochemical markers will improve the characterization of the kinetics of cartilage damage and the progression of the disease.

In conclusion, several animal models are available for the understanding of OA onset. They all mimic the phenotype of human OA but each of them is useful to integrate the pathophysiology and response to molecules. They have provided accumulating evidence that bone changes precede cartilage damage in OA and might favor the progression of OA along with cartilage damage. Therefore, targeting bone tissue is a possible approach to the prevention and treatment of OA.

Conflict of Interest

The authors declare no conflict of interest.

References

1. Crema MD, Roemer FW, Guermazi A. Magnetic resonance imaging in knee osteoarthritis research: semiquantitative and compositional assessment. *Magn Reson Imaging Clin N Am* 2011;**19**:295–321.
2. Guermazi A, Niu J, Hayashi D, Roemer FW, Englund M, Neogi T et al. Prevalence of abnormalities in knees detected by MRI in adults without knee osteoarthritis: population based observational study (Framingham Osteoarthritis Study). *BMJ* 2012;**345**:e5339.
3. Crema MD, Roemer FW, Zhu Y, Marra MD, Niu J, Zhang Y et al. Subchondral cystlike lesions develop longitudinally in areas of bone marrow edema-like lesions in patients with or at risk for knee osteoarthritis: detection with MR imaging—the MOST study. *Radiology* 2010;**256**:855–862.
4. Roemer F, Neogi T, Nevitt M, Felson D, Zhu Y, Zhang Y et al. Subchondral bone marrow lesions are highly associated with, and predict subchondral bone attrition longitudinally: the MOST study. *Osteoarthritis Cartilage* 2010;**18**:47–53.
5. Hunter DJ, Felson DT. Osteoarthritis. *BMJ* 2006;**332**:639–642.
6. Javaid MK, Lynch JA, Tolstykh I, Guermazi A, Roemer F, Aliabadi P et al. Pre-radiographic MRI findings are associated with onset of knee symptoms: the most study. *Osteoarthritis Cartilage* 2010;**18**:323–328.
7. Guermazi A, Roemer FW, Hayashi D, Crema MD, Niu J, Zhang Y et al. Assessment of synovitis with contrast-enhanced MRI using a whole-joint semiquantitative scoring system in people with, or at high risk of, knee osteoarthritis: the MOST study. *Ann Rheum Dis* 2011;**70**:805–811.
8. Lampropoulou-Adamidou K, Lelovas P, Karadimas E, Liakou C, Triantafillopoulos I, Dontas I et al. Useful animal models for the research of osteoarthritis. *Eur J Orthop Surg Traumatol* (e-pub ahead of print 13 March 2013; doi:10.1007/s00590-013-1205-2).
9. Pritzker K, Gay S, Jimenez S, Ostergaard K, Pelletier J, Revell P et al. Osteoarthritis cartilage histopathology: grading and staging. *Osteoarthritis Cartilage* 2006;**14**:13–29.
10. Aigner T, Cook JL, Gerwin N, Glasson SS, Laverty S, Little CB et al. Histopathology atlas of animal model systems - overview of guiding principles. *Osteoarthritis Cartilage* 2010;**18**(Suppl 3):S2–S6.
11. Kamekura S, Hoshi K, Shimoaka T, Chung U, Chikuda H, Yamada T et al. Osteoarthritis development in novel experimental mouse models induced by knee joint instability. *Osteoarthritis Cartilage* 2005;**13**:632–641.
12. Radin EL, Rose RM. Role of subchondral bone in the initiation and progression of cartilage damage. *Clin Orthop Relat Res.* 1986;**213**:34–40.
13. Radin EL, Paul IL, Tolkoff MJ. Subchondral bone changes in patients with early degenerative joint disease. *Arthritis Rheum* 1970;**13**:400–405.
14. Sambrook P, Naganathan V. What is the relationship between osteoarthritis and osteoporosis? *Baillieres Clin Rheumatol* 1997;**11**:695–710.
15. Dequeker J, Aerssens J, Luyten FP. Osteoarthritis and osteoporosis: clinical and research evidence of inverse relationship. *Aging Clin Exp Res* 2003;**15**:426–439.
16. Franklin J, Englund M, Ingvarsson T, Lohmander S. The association between hip fracture and hip osteoarthritis: a case-control study. *BMC Musculoskelet Disord* 2010;**11**:274.
17. Prieto-Alhambra D, Nogues X, Javaid MK, Wyman A, Arden NK, Azagra R et al. An increased rate of falling leads to a rise in fracture risk in postmenopausal women with self-reported osteoarthritis: a prospective multinational cohort study (GLOW). *Ann Rheum Dis* 2013;**72**:911–917.
18. Castano-Betancourt MC, Rivadeneira F, Bierma-Zeinstra S, Kerkhof HJ, Hofman A, Uitterlinden AG et al. Bone parameters across different types of hip osteoarthritis and their relationship to osteoporotic fracture risk. *Arthritis Rheum* 2013;**65**:693–700.
19. Brandt KD, Dieppe P, Radin E. Etiopathogenesis of osteoarthritis. *Med Clin North Am* 2009;**93**:1–24xv.
20. Burr DB. Anatomy and physiology of the mineralized tissues: role in the pathogenesis of osteoarthrosis. *Osteoarthritis Cartilage* 2004;**12**(Suppl A):S20–S30.
21. Brown TD, Radin EL, Martin RB, Burr DB. Finite element studies of some juxtarticular stress changes due to localized subchondral stiffening. *J Biomech* 1984;**17**:11–24.
22. Goldring MB, Goldring SR. Articular cartilage and subchondral bone in the pathogenesis of osteoarthritis. *Ann N Y Acad Sci* 2010;**1192**:230–237.
23. Beuf O, Ghosh S, Newitt DC, Link TM, Steinbach L, Ries M et al. Magnetic resonance imaging of normal and osteoarthritic trabecular bone structure in the human knee. *Arthritis Rheum* 2002;**46**:385–393.
24. Day JS, Ding M, van der Linden JC, Hvid I, Sumner DR, Weinans H. A decreased subchondral trabecular bone tissue elastic modulus is associated with pre-arthritic cartilage damage. *J Orthop Res* 2001;**19**:914–918.
25. Kamibayashi L, Wyss UP, Cooke TD, Zee B. Trabecular microstructure in the medial condyle of the proximal tibia of patients with knee osteoarthritis. *Bone* 1995;**17**:27–35.
26. Bobinac D, Spanjol J, Zoricic S, Maric I. Changes in articular cartilage and subchondral bone histomorphometry in osteoarthritic knee joints in humans. *Bone* 2003;**32**:284–290.
27. Ding M, Odgaard A, Hvid I. Changes in the three-dimensional microstructure of human tibial cancellous bone in early osteoarthritis. *J Bone Joint Surg Br* 2003;**85**:906–912.
28. Ding M, Danielsen CC, Hvid I. Age-related three-dimensional microarchitectural adaptations of subchondral bone tissues in guinea pig primary osteoarthrosis. *Calcif Tissue Int* 2006;**78**:113–122.
29. Pelletier JP, Boileau C, Brunet J, Boily M, Lajeunesse D, Reboul P et al. The inhibition of subchondral bone resorption in the early phase of experimental dog osteoarthritis by licofelone is associated with a reduction in the synthesis of MMP-13 and cathepsin K. *Bone* 2004;**34**:527–538.
30. Boyd SK, Matyas JR, Wohl GR, Kantzas A, Zernicke RF. Early regional adaptation of periarticular bone mineral density after anterior cruciate ligament injury. *J Appl Physiol* 2000;**89**:2359–2364.
31. Boyd SK, Muller R, Zernicke RF. Mechanical and architectural bone adaptation in early stage experimental osteoarthritis. *J Bone Miner Res* 2002;**17**:687–694.
32. Hayami T, Pickarski M, Wesolowski GA, McLane J, Bone A, Destefano J et al. The role of subchondral bone remodeling in osteoarthritis: reduction of cartilage degeneration and prevention of osteophyte formation by alendronate in the rat anterior cruciate ligament transection model. *Arthritis Rheum* 2004;**50**:1193–1206.
33. Hayami T, Pickarski M, Zhuo Y, Wesolowski GA, Rodan GA, Duong le T. Characterization of articular cartilage and subchondral bone changes in the rat anterior cruciate ligament transection and meniscectomized models of osteoarthritis. *Bone* 2006;**38**:234–243.
34. Kadri A, Ea H, Bazille C, Hannouche D, Lioté F, Cohen-Solal M. Osteoprotegerin inhibits cartilage degradation through an effect on trabecular bone in murine experimental osteoarthritis. *Arthritis Rheum* 2008;**58**:2379–2386.
35. Kadri A, Funck-Brentano T, Lin H, Ea HK, Hannouche D, Marty C et al. Inhibition of bone resorption blunts osteoarthritis in mice with high bone remodelling. *Ann Rheum Dis* **69**:1533–1538.
36. Funck-Brentano T, Lin H, Hay E, Ah Kioon MD, Schiltz C, Hannouche D et al. Targeting bone alleviates osteoarthritis in osteopenic mice and modulates cartilage catabolism. *PLoS One* 2012;**7**:e33543.
37. Botter SM, van Osch GJ, Waarsing JH, Day JS, Verhaar JA, Pols HA et al. Quantification of subchondral bone changes in a murine osteoarthritis model using micro-CT. *Biorheology* 2006;**43**:379–388.