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□ Review Article □

Animal Model of Osteoarthritis

Hyun Ah Kim, Eun Jeong Cheon

Department of Internal Medicine, Hallym University Sacred Heart Hospital, Anyang, Korea

Osteoarthritis (OA) is the most common arthritis which leads to chronic disability. Because patients usually present at medical care at an advanced stage of disease, research on pathogenesis of OA using human subjects is difficult. Therefore, animal models of OA are used extensively in search of pathogenesis of degenerative joint disease and in search of potential disease modifying anti-OA drugs. For induction of OA, chemical and surgical methods have been employed widely due to several advantages, such as faster onset of disease and reproducible induction of arthritic change. Intra-articular injection of a chemical such as monosodium iodoacetate or collagenase can cause the degeneration of cartilage and the development of osteoarthritis by inhibition of the activity of glyceraldehyde-3-phosphate dehydrogenase in chondrocytes or by induction of synovial inflammation and degeneration of supporting structure and resultant instability, respectively. Surgical induction involves destabilizing the knee joint by transection of the cranial cruciate ligament, collateral ligaments, or meniscotibial ligament with or without removing all or part of the meniscus. Surgical models are used not only in small animals but also in larger animals such as rabbits, sheep and dogs. Additionally, genetically modified mouse models offer opportunities to look into a specific role of a molecule or signaling pathway in the joint degradation. On the other hand, whether these models, chemically or surgically induced, or genetically modified, properly represent human OA is a critical question. Except for a limited number of cases, most human OA develops insidiously over decades without significant antecedent knee injury. In this sense, spontaneous model which develops in mice and guinea pigs might more closely resemble human OA. In this review, widely used animal models of OA are presented, focusing on the methods of its induction, their use for determining the pathophysiology of OA, and advantages and limitations of its use.

Key Words. **Osteoarthritis, Animal model, Cartilage**

Introduction

Knee osteoarthritis (OA) is the most common form of arthritis that affects the elderly. It is a leading cause of disability and has a formidable societal and public health impact (1). The increasing prevalence of knee OA with age may present serious new health issues in any rapidly aging societies such as Korea. Although OA has been the subject of intense research in recent years, precise delineation of its pathogenesis remains elusive, possibly reflecting its heterogeneous etiology. This leads to hampering of the development of effective therapeutics. Degradation of extracelullar matrix in articular cartilage has been considered a central event leading to joint destruction in OA. In vitro studies focusing on chondrocytes responding to a variety of stimuli such as proinflammatory cytokines and mechanical loading by elaborating degradative enzymes and catabolic mediators still comprises the major portion in OA research. Recently however, the concept of "joint as an organ" has been put forward, with equal emphasis placed on the change in the subchondral bone, synovium, muscles, ligaments, and other periarticular structures. This change has also been reflected in the animal model of OA.

Animal models of OA are used extensively in search of pathogenesis of degenerative joint disease and in search of potential disease modifying anti-OA drugs, because patients usu-

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Corresponding to : Hyun Ah Kim, Division of Rheumatology, Hallym University Sacred Heart Hospital, 896, Pyeongchon-dong, Dongan-gu, Anyang 431-070, Korea. E-mail : kimha@hallym.ac.kr

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ally present at medical care at an advanced stage of disease, making the research of pathogenesis of OA using human subjects very challenging. Animal models, although imperfect, exhibit many of the pathologic features that characterize the human disease. Animal models of inflammatory arthritides, such as collagen induced arthritis in mice have been used to test the clinical efficacy of a candidate drug. However, this system of drug validation does not yet exist in OA, partly because no disease modifying anti-OA drugs have been proven for humans. In this review, widely used animal models of OA are presented, focusing on the methods of its induction, their use for determining the pathophysiology of OA, and advantages and limitations of its use. The review is confined to models of OA in knee joint, and the models are divided by the methods of induction rather than the animal species used.

Models of Spontaneous OA

Except for a limited number of cases, most human OA develops insidiously over decades without significant antecedent knee injury. In this sense, spontaneous model which develops in mice and guinea pigs might more closely resemble human OA (Table 1).

Large animals

Some breeds of dogs, including Labradors and beagles develop OA, but this is generally secondary to hip dysplasia (2). In the spontaneous canine models, early disease is characterized by a greater degree of synovitis and joint capsular fibrosis compared to human OA (3,4). Both rhesus (*Macaca mulatta*) and cynomolgus (*Macaca fascicularis*) macaques develop spontaneous OA, the pathology of which closely resemble that of human OA (5). Other features, such as the separation of aging and OA development (6), involvement of both cartilage metabolic changes and subchondral mineralization (7,8), and worsening of cartilage degeneration after oophorectomy in female animals (9), high incidence as well as adequate size of the joint permitting radiologic, histologic, and biochemical studies, makes this animal an optimal choice for the study of OA. However, studies may take long time due to the expanded life span of the animal species (18 to 30 years), and ethical and financial considerations are major obstacles.

Guinea pig

OA in the guinea pig occurs spontaneously, and also can be induced chemically and surgically. Outbred Dunkin-Hartley guinea pig is utilized most often. The advantages of the guinea pig as an OA model system is its histological similarity to the human disease. The development of OA in guinea pig is age-related and subject to a variety of well-known human OA risk factors such as obesity, mechanical overload, and high bone turnover (10). OA cartilage lesions are usually visible by 3 months of age, progressing to bilateral disease by 1 year of age, involving more than 50% of medial tibial cartilage. Lesions are more pronounced in the medial compartment, and

Table 1. Selected models of spontaneous OA

Species	Age	Findings
DBA/1 mice	0～6 months old	OA development at 4 months old only in males
STR/ORT mice	5～50 weeks	OA in 85% of all male mice; MMP and aggrecanase activity increase and colocalize with advancing OA; Chondrocyte apoptosis by TUNEL correlated with severity of OA lesions
C57BL/6 mice	18 months old±running	Increased incidence and severity of OA changes in mice run 1km/day, therefore running accelerated OA development; collagen degradation absent in areas of chondrocyte death
C57 mice	6 and 8～12 months old	Some heat shock proteins, interleukin-6, and interferon expression were upregulated
Hartley guinea pigs	2～30 months old	OA AC lesions visible by 3 months increasing to >50% of medial tibial AC bilaterally by 1 year old, with subchondral sclerosis; severity of OA lesions was reduced by 40% at 9 months, 56% at 18 months on restricted diet.
Rhesus macaque	5～25 years old	Young animals with OA had increased PG levels whereas old had decreased collagen correlated with age in both normal and OA but lower in OA AC. OA changes progressive through life with high prevalence.
Cynomolgus macaque	5～30 years old	High prevalence of OA lesions, subchondral bone changes common and severe, showing before AC changes; subchondral bone thickness of medial tibia correlated with severity of OA lesions and increasing weigh; prevalence and severity of OA lesions increased with age.

MMP: matrix metalloproteinase, AC: articular cartilage, PG: proteoglycan (Adapted from Moskowitz RW, Altman RD, Hochberg MC, Buckwalter JA, Goldberg VM. Osteorhitis. 4th ed. p110, Philadelphia, Lippincott Williams & Wilkins, 2007)

develops earlier in tibia than in femur (10). In addition to the pathological similarities with human disease, a variety of OA-related biomarkers, used to evaluate human OA, are detectable in guinea pig cartilage or body fluids (11). Joints are large enough for molecular analyses and biomechanical analyses.

Mouse

Some inbred strains of mice, such as STR/ort, BALB/c, DBA/1 and C57BL/6 develop spontaneous OA with age. However, the incidence of OA varies with strain and sex, and the morphologic changes arising from the aging process itself have not been addressed. STR/ort mouse develops spontaneous OA most consistently among mouse strains, especially among male strains, and develops OA at the medial tibial plateau between 12～20 weeks. The histopathological lesions are progressive and closely resemble those of human knee OA (12). Like in human disease, cartilage breakdown is effected by aggrecanases, collagenases and other matrix metalloproteinases (MMPs) (13). Like in STR/ort mice, OA in DBA/1 mice develop mostly in male mice. Although C57BL/6 mice are relatively resistant to the development of OA, running 1km/day increase the incidence and severity of OA changes in this mice (14).

Models of Chemical Injection

Intra-articular injections of diverse agents induce cartilage degeneration resembling OA, which include physiologic saline, corticosteroid, and estrogen. Selective degradation of cartilage extracellular matrix has been attempted by injecting proteolytic enzymes, such as papain, but the resultant pathology probably does not represent that of OA, because the injection is accompanied by acute inflammatory reaction.

Collagense injection model

Intra-articular injection of collagenase provokes joint instability by degrading the surrounding capsule and ligament, without inducing direct degradation of cartilage collagen. C57BL6 and C57BL10 are commonly used, with male (than female) and C57BL10 (than C57BL6) showing higher prevalence (15). Highly purified bacterial collagenase (5 μg) are injected into the knee joints twice on alternate days (16). Lesions develop after 1～4 weeks. Correlations between the degree of joint instability, the amount of cartilage degradation and the size of osteophytes are observed (17,18). Synovial activation is important for the induction of joint pathology, and like in human OA, macrophages are the predominant cell type in the inflamed synovium of mice with collagenase-induced OA, while no polymorphonuclear leukocytes are observed during the chronic phase of disease (16).

Monoiodoacetate injection model

A single injection of the irreversible NADPH inhibitor, sodium monoiodoacetate (MIA), which inhibit cellular glysolysis, has been used to induce the painful and structural components of OA in mice, rats, chickens, guinea pigs, rabbits, and horses. The usual rodent doses are 1, 2 or 3 mg, with the model usually assessed up to 14 days post-induction, with some studies extending observation further to 30, 56 or 68 days (19). MIA injection induces many features of human OA including synovial proliferation, loss of cartilage, and osteophytes. The model shows inflammatory change in the early phase of the disease as well as the induction of cartilage degrading enzymes. Despite being a convenient model (consistency in the induction of cartilage damage, rapidity, ease of application), whether this model represent human OA well enough to permit screening of therapeutic agents is debatable.

Models of Surgical Induction

Various damages leading to knee OA in human have been introduced to animals to induce OA. The cartilage damage induced by this maneuver resembles human knee OA, so this model has been used for evaluation of treatment, including analgesics and structure-modifying agents. The limitations of this approach include the fact that the observations are usually confined to knee joints, and that the use of small animals such as rodents can be technically challenging.

Anterior cruciate ligament transaction (Table 2, 3)

Rupture of the anterior cruciate ligament (ACL) is a major risk factors for the development of human OA, and is commonly observed in OA patients with significant association with knee pain (20). The ACL transection model of OA was first established in mature beagle dogs by transection of the ligament with a 2-mm stab incision through the capsule without damaging adjacent peri-articular structures (21). In this model, loss of cartilage proteoglycan staining, chondrocyte cloning, and increased surface fibrillation are observed. Cartilage shows evidence of stiffening of collagen network, which occurs even in the absence of surface erosion (22). This was the first animal model to evaluate the efficacy of various OA therapeutics. In time, ACL transection was attempted in various other breeds of dogs, including F0x-hound, and mongrel dogs. The weight and age of the animal used influence the rate of disease progression, with heavy breeds possibly more prone to the development of OA. Open procedure,

Table 2. Selected models of anterior cruciate ligament transection (ACLT) in dogs

Species	Post-ACLT duration and treatment	Age or body weight	Findings
Dog			Open unilateral
Mongrel dog	4, 10, and 32 weeks		Aggrecan mRNA up at 10 and 32 weeks; collagen type II mRNA up at all time points-signals for transcription must be different
	10 and 39 weeks	16～28 kg	Micro MRI and polarized light microscopy can detect changes in AC collagen fiber orientation at 12 weeks
	36 and 72 weeks	Adult	Significant trabecular bone loss with architectural adaptation by 36 weeks, less obvious at 72 weeks
Fox-hound	2 years	2 years old	AC change in expression of decorin and fibromodulin different in ACLT dogs to dogs with spontaneous OA
	2～24 months±running	2～3 years old	AC change occurred early; decreased severity in longterm AC damage is associated with increased osteophyte formation and less severe medial meniscus damage
Dog			Closed unilateral
Mongrel dog	12 weeks	2～3 years old (20～25 kg)	Chondrocyte apoptosis, caspase 3 and Bcl-2 markedly increased in AC
	8 weeks	20～25 kg	Expression of MMP-13, cathepsin K, ADAMTS-4, ADAMTS-5, 5-lipoxygenase increased in OA cartilage; decreased bone thickness with increased osteoclast staining of MMP-13 cathepsin K
Fox-hound	2, 10, and 18 weeks	19.0～8.5 kg	Synovial fluid prostaglandin E_2 correlated with clinical gait changes and may indicate lameness
Beagle	6, 12, 24, and 48 weeks	15～22 kg	Early stable elevation of collagen I and II expression by chondrocytes; MMP-13 not elevated until 24 weeks and aggrecan and tenascin C until 48 weeks

MMP: matrix metalloproteinase, AC: articular cartilage, ADAMTS: A disintegrin and metalloproteinase with thrombospondin motifs (Adapted from Moskowitz RW, Altman RD, Hochberg MC, Buckwalter JA, Goldberg VM. Osteorhitis. 4th ed. p113, Philadelphia, Lippincott Williams & Wilkins, 2007)

Table 3. Selected models using anterior cruciate ligament transection (ACLT) in small animals

Species	Post-ACLT duration and treatment	Age or body weight	Findings
Rabbit			Open unilateral
Rabbit	9 weeks	1 year old	Menisci from ACLT knees contained high numbers of apoptotic cells and nitrotyrosine immunoreactivity
	2, 4, and 9 weeks	9～10 months old	MMP-1, -3, and -13 gene expression in AC and meniscus increased rapidly in OA, whereas expression of aggrecanases remained stable
	4, 9, and 12 weeks	12 months old	Osteophyte formation associated with expression of vascular endothelial growth factor (VEGF) in chondrocytes
	3, 6, and 12 weeks	4 kg	Increased expression of hyaluronan receptor CD44v6 over time course of OA development
Other			Closed unilateral
Rat	2, 4, and 8 weeks	220～240 g	AC degeneration starts at the AC surface and is associated with localized expression of collagen type II degradation products
	2 and 4 weeks±exercise	8 weeks old	Beneficial effect of slight and moderate but not intense exercise on AC lesions, heat shock protein 70 expression, and chondrocyte apoptosis
Guinea pig	1～8 months	40 days old	ACLT progressively increases OA histopathological changes; osteophytes first visible at 3 months

AC: articular cartilage (Adapted from Moskowitz RW, Altman RD, Hochberg MC, Buckwalter JA, Goldberg VM. Osteorhitis. 4th ed. p114, Philadelphia, Lippincott Williams & Wilkins 2007)

which subsequently replaced the original stab incision method diminished synovial inflammation resulting from intraarticular bleeding due to rupture of vessels serving the ACL. This model has the advantage of a fairly slow natural history of OA, since full-thickness loss of articular cartilage does not develop until about 4～5 years after ACLT. The resulting degenerative changes in cartilage and synovial tissue thus closely resemble those in natural canine OA and human OA (23). In small animals, such as rabbits, guinea pigs, rats and mice, cartilage lesion and synovitis develops much rapidly than in the dogs. In these species, ACLT also induces anatomical and biochemical changes resembling human OA, too, eg. changes in both the cartilage and subchondral bones, upregulation of MMP, and loss of aggrecan and collagen.

Meniscectomy and meniscal destabilization model (Table 4)

The menisci are two crescent-shaped fibrocartilaginous wedges positioned between the femoral condyles and tibial plateau of the knee joint. Each meniscus covers approximately two thirds of the corresponding articular surface of the tibia, and provides shock absorption and load transmission during dynamic knee joint movement and static loading (24). Mechanical failure or removal of all or part of the meniscus leads to abnormally high focal stresses under static loading and results in the development of OA. The induction of OA in animals using meniscectomy first attempted by Moskowitz by partially excising the anterior horn of the medial meniscus in rabbits (25). Cartilage changes are observed from 2 weeks after surgery including loss of proteoglycan and surface fibrillation. Meniscectomy is also used to induce OA in guinea pigs, rats and mice. In guinea pigs, unilateral partial medial meniscectomy leads to rapid degradation of cartilage with moderate to severe cartilage lesion visible by 1 week (26). In rats, meniscectomy was found to induce significant tactile al-

Table 4. Models ofmeniscectomy (MX) and meniscal destabilization (MD) models of OA

Species	Mx method	Post-Mx duration	Age or body weight	Findings
Rabbit	Unilateral partial medial Mx	2, 4, 8, and 10 weeks	8 weeks (2.0～2.5 kg)	Increase in AC thickness from 4 weeks; AC eburnation, erosion, and osteophytes from 6 weeks
		8 and 52 weeks	2.5～3.5 kg	Parathyroid hormone-related protein increased in late OA AC in proliferating chondrocyte clones
	Unilateral total medial Mx	2～52 weeks	Various	Mx caused decreased tibial bone mineral density as well as typical AC OA lesions.
Guinea pig	Unilateral partial medial Mx	1～42 weeks	0.6～0.8 kg	Moderate to severe AC focal lesions by week 1; the contralateral joint was affected by 12 weeks. AC lesions first on medial tibial plateau then medial femoral condyle then lateral compartment.
Rat	Partial Mx	20 and 45 days	150 g	Disruption of Golgi complex in chondrocytes increases with time and OA
	Medial meniscal transection	Up to 32 days	Adult	Pain assessment over 28 days showed little hyperalgesia but increasing tactile allodynia
Mouse	Medial MD	4 and 8 weeks	10 weeks	No reduction of severity of AC destruction in ADAMTS-4 knockout mice compared to wild type but significant reduction of severity of AC destruction in ADAMTS-5 knockout mice
Grey hounds	Bilateral total medial Mx	6 months±exercise	Adult	AC degeneration in all Mx joints; lower glycosaminoglycan levels and more extractible PGs in AC from mobile contralateral Mx joints than in Mx or control joints.
Mongrel dogs	Unilateral total medial Mx	12 weeks	25～35 kg	AC tensile modulus decreased with no change in water or PG content. Reliable degenerative changes occurred Synovial fluid biomarkers altered with different acute and medium-term responses eg. cartilage oligomeric matrix protein (COMP)
Sheep	Unilateral total medial Mx	6 months±exercise	2 years old	PG content down at 6 months in passive and active Mx group
	Unilateral total lateral Mx			Lateral Mx induced higher PG loss from AC and lower PG synthesis rates than medial Mx.

AC: articular cartilage, PG: proteoglycan, ADAMTS: A disintegrin and metalloproteinase with thrombospondin motifs (Adapted from Moskowitz RW, Altman RD, Hochberg MC, Buckwalter JA, Goldberg VM. Osteorhitis. 4th ed. p115, Philadelphia, Lippincott Williams & Wilkins 2007)

lodynia over 4 weeks (27). Large animals, such as dogs, were also used with the degree of cartilage damage proportional to the amount of meniscus removed. Merino sheep show slow progression of cartilage damage spanning 3 to 24 months after meniscectomy. The rate of damage progression could be accelerated by regular weight-bearing exercise (28).

Other approaches

Combinations of ligament transection with or without meniscectomy are used to induce OA. Medial collateral ligament and posterior cruciate ligament are most often breached. Recently, a surgical technique that induces a more slowly progressive course of joint degeneration in mice was described, which uses transection of the medial meniscotibial ligament resulting in instability of the medial meniscus (29). Adult male C57BL/6 mice ages 10～12 weeks are used. A longitudinal incision medial to the patellar ligament is made, the joint capsule is opened, and the meniscotibial ligament, anchoring the medial meniscus to the tibial plateau, is identified and transected (30). Cartilage lesions are discernible 4 weeks after surgery.

Models of Genetic Modification

Transgenic or knockout mouse models with changes in the expression of transcription factors, MMPs, angiogenic factors, or ECM proteins have provided insight into the mechanisms that control cartilage development and, in some cases, OA pathology (Table 5) (31). While homozygous deficiency of

Table 5. Transgenic and knockout mouse models and susceptibility to OA

Gene	Gene defect or modification	Features
Extracellular matrix		
Col2a1	Heterozygous knockout or mutation	OA-like changes during aging
Col9a1	Transgenic truncation	Mild chondrodysplasia; OA
Col9a1	Knockout	Early onset OA
Col11a1	*Cho*/+; spontaneous deletion	OA-like changes during aging
Aggrecan	Cmd/+; spontaneous deletion	OA-like changes during aging
Fibromodulin	Knockout	Tendon mineralization; OA
Fibromodulin/biglycan	Double knockout	Ectopic mineralization; early-onset OA
Matrilin-3	Knockout	OA-like changes with aging
Proteinases and inhibitors		
Mmp9	Knockout	Exacerbation of surgically induced OA
Mmp13	Postnatal transgenic	Increased susceptibility to OA
Adamts5	Knockout	Decreased susceptibility to OA
Timp3	Knockout	Increased susceptibility to OA
Cytokines and related molecules		
IL-1 β	Knockout	Exacerbates OA in STR/ORT mice; protects against surgically induced OA
IL-6	Knockout	Severe spontaneous OA with subchondral bone sclerosis in aging males but not in females
ICE	Knockout	Exacerbates OA in STR/ORT mice
MK2	Knockout	More severe in surgically induced OA
NOS2	Knockout	Reduced proteoglycan depletion and restoration of IGF-1 responsiveness
Growth factor signaling		
Bmpr1a	Postnatal conditional knockout	OA-like cartilage degeneration
Tgf β RII	Transgenic dominant-negative truncation	Enhanced chondrocyte hypertrophy and progressive skeletal degeneration with OA
Smad3	Targeted disruption	Enhanced chondrocyte hypertrophy and OA-like cartilage erosion
Ank	*ank/ank* homozygous truncation mutation	Early onset OA associated with crystal deposition
Npp1	Knockout	OA associated with crystal deposition
α 1 integrin	Knockout	Accelerated cartilage degradation
Runx2	Conditional knockout	Enhance cartilage loss and increased osteophyte formation in surgical OA
Hif-2 α	Knockout	Accelerated cartilage degradation in surgical OA
miR-104	Knockout	Age-related OA-like changes

Adapted from Goldring Goldring MB, Goldring SR. Osteoarthritis. Journal of Cellular Physiology 2007;213:626-34

Col2a1, Col19a1, Col11a1, or aggrecan leads to embryonic lethality, heterozygous deficiency results in degenerative cartilage changes in the adult mice as well as developmental deficiencies. The single knockout of several members of the small, leucin-rich proteoglycan family results in anomalies of collagen fibre diameter, leading to growth failure, osteoporosis, tendon laxity and OA (32). Double knock-out of biglycan and fibromodulin leads to severe OA with features reminiscent of human disease, such as gait abnormality (33). The absence of signaling molecules, such as mitogen-inducible gene 6 and a receptor for bone morphogenetic proteins (BMP), also induce a propensity to develop OA (34,35). To induce OA lesion more rapidly, surgical instability have also been employed in genetically modified mice. While genetically modified mice are very useful for elucidation of the role of specific molecule or pathways in the pathogenesis of OA, single gene defects do not model human OA perfectly, and their use for screening of OA therapeutics is questionable.

General Recommendation

Human OA is a disease of the aged, and growing animals, like children, probably have a better capacity at repairing joint damage. Thus, to obtain the most meaningful insights into human OA, it is essential to use skeletally mature animals whenever possible (10). Minimum age for OA studies are 10 weeks for mice, 3 months for rats, 6 months for guinea pigs, 8～9 months for rabbits, and 2 years for sheep and horses (Table 6). Genetically modified mice should ordinarily be studied at 9～12 months when natural OA lesions start to appear in wild type mice (10). The anatomical differences between to humans and animals should also be considered. In rats and mice, some growth plates do not close completely, even though longitudinal long bone growth has ceased. Mouse knee joints are characterized by its extremely small size, with the cartilage thickness of only 30 μm (36). The layer of calcified cartilage is nearly as thick as the non-calcified cartilage (or even thicker in some joint regions), which is in stark contrast to the thin calcified cartilage layers seen in larger animals and humans (37). The cartilage is only several cell layers thick and does not have clearly distinguishable superficial, transitional and radial zones (37). Non-calcified cartilage loss tends to be an all-or-none phenomenon, with the pathology of cartilage degeneration rapidly progressing to full-depth fibrillation. Adult rabbit articular cartilage has a cell density ten-fold of that in adult humans (38). Because OA is considered an organ failure, histologic analysis encompassing not only cartilage but also all of joint structure should be performed.

Assessment of Pain

Knee pain derived from OA is a key symptom influencing the decision to seek medical attention, and it has been consistently reported that radiographic OA changes are often poorly correlated with pain (39). It is therefore important that OA animal models exhibit pain as well as joint damage. Over the past decades, progress has been made in objectively assessing pain in animals, which can be employed as surrogates of human pain, discomfort, and fatigue (10). It is important to assess pain on multiple occasions because pathogenetic mechanism of pain may change over time in models. Although spontaneous OA models may better represent pain than other models, meniscectomy models may also be relevant to studies of OA pain, because of the presence of nerve end-

Table 6. Maturation age, maximal non-calcified cartilage thickness and chondrocyte volume density (distal femoral cartilage) for the species for OA animal model and humans

	Maturation age	Thickness of distal femoral or tibial cartilage (animal age)	Chondrocyte volume density
Human	15～20 years	2.2 mm	2%
Rabbit	8 m	0.2～0.4 mm (femur)	2～12%
Rat	7～8 weeks	0.17 mm (femur)	10～25%
Sheep	＞2 years	Femur: 0.6～1 mm Tibia: 0.5～1.5 mm (2～3-year old castrated male)	5～10% (2～4-year-old castrated male)
Dog	10～18 months depending on breed	0.6～1.3 mm	2～12%
Goat	＞2 years	0.6～1.7 mm	6～7%
Horse	2 years	2 mm	1.5～6%
Mouse	7～8 weeks	0.030 mm (femur)	15～40%
Guinea pig	7 months (femur) and 12～18 months (tibia) of age	0.3 mm at 6 months of age (tibia)	15%

Adapted from Aigner T, Cook JL, Gerwin N, Glasson SS, Laverty S, Little CB, et al. Histopathologyatlasofanimal modelsystems-overview of guiding principles. Osteoarthritis Cartilage 2010;18 Suppl 3:S2-6

ings in the peripheral portion of the meniscus, which is prone to damage in idiopathic human OA. Although MIA injection model may not represent typical pathology of human OA, it is considered a clinically relevant model of arthritis pain. For analysis of pain, gait pattern may be utilized as a surrogate pain measure. The emotional component of pain should be measured using a behavioral output. Different pain manifestations may be evaluated by electrophysiologic studies.

Conclusion

Experimental animal studies of OA have been performed in many species in an attempt to increase our knowledge on the pathogenesis and treatment of osteoarthritis (OA). Although excellent models for establishing proof-of-principle and for examining the efficacy of therapeutic agents exist, no experimental animal model reflects human disease perfectly. In addition, standardization of the scoring systems should be established to reduce discrepancies between studies using the same models.

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