Anterior Cruciate Transection/Disruption Models of Post-Traumatic Arthritis

6

Kelly A. Kimmerling and Farshid Guilak

Introduction

The study of injuries of the anterior cruciate ligament (ACL) makes up a large body of research into the etiology of PTA in both an animal and clinical setting. Currently, animal models using ACL transection (ACL-T) include dogs, sheep, cats, rabbits, guinea pigs, rats, and mice [1–3]. The first reported ACL-T model was developed using a stab incision in a canine model by Pond and Nuki [4]. Subsequent studies in dogs and other animals have examined the effects of ACL-T on articular cartilage, synovium, gene expression, biomarkers, and pain, and have been used in a variety of settings to test various therapeutic interventions. This section focuses on the use of ACL-T animal models as a method for studying PTA, with the advantages, disadvantages, and relevant studies for each animal described below.

K.A. Kimmerling, M.Eng.
Departments of Orthopedic Surgery and Biomedical Engineering, Duke University Medical Center, 375 MSRB, Box 3093, Durham, NC 27710 USA
e-mail: kelly.kimmerling@duke.edu

F. Guilak, Ph.D. (✉)
Department of Orthopedic Surgery, Duke University Medical Center, 375 MSRB, Box 3093, Durham, NC 27710, USA
e-mail: guilak@duke.edu

Dog Model

The canine model has been used extensively for studying the effects of ACL-T, and there are a variety of advantages to using dogs for osteoarthritis (OA) research. For instance, they have a slow disease progression after injury, allowing for long-term observation of changes that occur as a result of PTA. Dogs also have thick articular cartilage, have larger joints, are trainable, and have well-documented outcomes to injury models, with a pathology that mimics naturally occurring arthritis. However, the high cost and public perception of using dogs are drawbacks to this model [1–3]. The first use of dogs for an ACL-T model was reported by Pond and Nuki in 1973, which utilized a stab incision into the knee joint to induce ACL-T [4]. Subsequent studies followed using the stab incision model, focusing on areas such as osteophyte formation [5], biochemical changes and gene expression [6–9], mechanical properties [10], and imaging techniques [11]. Therapeutic studies examined the effect of inhibiting nitric oxide (NO) [12] or delivering licofelone [9, 13] as a chondroprotective agent. A summary of the studies utilizing the stab incision model are given in Table 6.1.

After the introduction of the Pond-Nuki transection model (stab incision), other methods of ACL-T were studied. Brandt published a review validating the use of the canine ACL-T model for the study of arthritis [16], and open induction

S.A. Olson and F. Guilak (eds.), *Post-Traumatic Arthritis: Pathogenesis, Diagnosis and Management*,
DOI 10.1007/978-1-4899-7606-2_6,

Table 6.1 Canine ACL-T models (closed induction)

Strain	ACL-T type	Surgery age	Exp. time	Results	Reference
Unknown	Stab incision	Unknown	1–26 weeks	OA changes in articular cartilage (fibrillation, loss of cells in superficial layer); synovitis subsides within 1 week	[4]
Varies	Stab incision	Adult	1–48 weeks	Periarticular osteophytes seen weeks 3–48 in marginal zone	[5]
Varies	Stab incision	2 years	3, 6, 9, 48 weeks	Thicker cartilage observed; chondrocytes synthesize GAGs with more chondroitin sulfate vs. keratin sulfate than normal	[8]
Foxhounds, Collies, Alsatians	Stab incision	2 years	1–48 weeks	Experimental, biochemical, morphological changes observed	[7]
Greyhounds	Stab incision	2–3 years	6, 12 weeks	Significant ↓ in tension, compression, shear; significant ↑ in hydraulic permeability, hydration of cartilage matrix	[10]
Mongrel dog	Stab incision	2–3 years	12 weeks	↑ chondrocyte apoptosis, caspase 3, and Bcl-2 in articular cartilage; L-NIL (NO inhibitor) group showed ↓ apoptosis, caspase 3 after ACL-T	[12]
Mongrel dog	Stab incision	2–3 years	12 weeks	↑ IL-1-converting enzyme (ICE), IL-18 in articular cartilage; ↓ PI-9; ICE not regulated by NO	[6]
Mongrel dog	Stab incision	2–3 years	8 weeks	↑ gene expression of MMP-13, cathepsin K, ADAMTS-4, ADAMTS-5, 5-lipoxygenase in OA; ↑ bone loss and osteoclast staining of MMP-13, cathepsin K; licofelone ↓ OA changes	[9, 13]
Mongrel dog	Stab incision	2–3 years	8, 12 weeks	↑ osteocalcin week 8; ↑ MMP, PGE_2 at week 12; ↓ NO levels in trabecular bone at week 12	[14]
Beagle	Stab incision	1 year	6, 12, 24, 48 weeks	Subchondral bone edema in tibia by week 6; articular cartilage erosion by week 12; menisci degeneration by week 24; osteophytes by week 48	[11]
Beagle	Stab incision	1–2 years	6, 12, 24, 48 weeks	Elevation of collagen I, II early; ↑ MMP-13 week 24; ↑ aggrecan, tenascin C week 48	[15]

models were implemented, where the ACL was visualized and transected either through an arthrotomy or arthroscopically. A wide range of studies followed, looking at aspects of open-induction ACL-T such as biochemical changes and gene expression [17–24], bone morphological changes [25–28], biomarkers [29–31], and imaging techniques [32, 33]. O'Connor and coworkers published two studies looking at the combined effect of nerve removal and ACL-T on the development of PTA [34, 35]. Two therapeutic studies used the open-induction ACL-T model, including a doxycycline therapy study [36] and an MMP inhibitor study [37]. Doom and coworkers published a review of immunopathological mechanisms that result from the ACL-T model, leading to PTA [38]. A summary of the studies using the open-induction canine ACL-T model are listed in Table 6.2 below.

Sheep Model

The use of sheep has not been widely utilized for the study of PTA; however, sheep may provide advantages because of their large joint size, which allows for the analysis of biochemical and biomechanical measures that may not be able to be performed in human subjects [39–41]. As with other large animals, sheep can readily undergo arthroscopic surgery and MRI observation, allowing for more direct translation of studies to the clinic. However, there are limited reagents and antibodies available, and until recently, a limited mapped genome for sheep, making it difficult for genetic studies [1–3]. Furthermore, their large size is a disadvantage in testing novel pharmacologic interventions. Most studies utilizing the ACL-T model in sheep have focused on radiographic tracking and kinematics of PTA. O'Brien and coworkers examined the effects of immediate reconstruction of the transected ACL on cartilage degeneration and osteophyte formation [41], while Atarod and coworkers examined the kinematic loads placed on soft tissue after ACL-T in the sheep [39]. A summary of the use of ovine ACL-T models is in Table 6.3 below.

Cat Model

Neuromuscular control has been extensively studied in cats, as well as muscle mechanics and locomotion [42]. Logically, cats would be well suited to study interventions towards musculoskeletal diseases, such as PTA that results from an ACL-T injury. Cats are advantageous to use because of their large size and known genome. However, like dogs, cats can be costly to house during experiments, and public perception and their role as companion animals discourage the use of cats for research [1–3].

Herzog and coworkers first studied the effect of ACL-T in cats on hindlimb loading and changes in articular cartilage [42]. Khalsa and coworkers studied the effect of severing the nerves associated with the joint capsule after ACL-T [43]. Herzog and coworkers monitored cats for a year, using force testing plates and radiographs to track kinematic and radiographic changes due to OA [44, 45]. Boyd and coworkers studied the changes to the periarticular bone as a result of ACL-T, while Clark and coworkers studied the adaptive response of cartilage after ACL-T [46, 47]. A summary of the studies utilizing feline ACL-T models follow in Table 6.4.

Rabbit Model

Rabbits have been a popular model for use with both ACL-T and meniscus injury models because of their low spontaneous joint degeneration, large joint size, and ease in use for testing new therapeutic agents. Rabbits preferentially load their lateral side, unlike rodents, and have the capability to spontaneous regenerate transected menisci with fibrous tissue, which can cause disadvantages for some studies. Similarly, rabbits have altered joint biomechanics, potentially resulting in a change in disease pathology compared to what may be expected in other animals. However, rabbits have been widely used as a model for OA because they form lesions similar to those seen in clinical OA [1–3].

The ACL-T model has been used in rabbits to study many aspects of PTA development. Studies

Table 6.2 Canine ACL-T model (open induction)

Strain	ACL-T type	Surgery age	Exp. time	Results	Reference
Varies	Arthrotomy	Adult	45, 54 months	Articular cartilage thicker at month 36, focal loss at month 45; osteophyte formation; ulceration of articular cartilage on medial side; fibrous thickening of capsule	[27, 28]
Varies	Not specified	Adult	Unknown	Neurectomy + ACL-T resulted in significantly higher OA scores than neurectomy without ACL-T, ACL-T	[35]
Varies	Not specified	Adult	72 weeks	Dorsal root ganglionectomy (DRG) + ACL-T after results in significantly severe OA compared to ACL-T, ACL-T + DRG, DRG	[34]
Beagles	Arthroscopic	Adult	16 weeks	Loss of tensile properties and remodeling of collagen network in surface zone of articular cartilage	[18]
Mixed breeds	Cranial transection	2–7 years	4, 10, 32 weeks	Aggrecan mRNA ↑ weeks 10, 32; collagen type II mRNA ↑ at all time points; transcription mechanisms must differ	[20]
Mongrel dog	Lateral arthrotomy	1–3 years	3, 12 weeks	Structural changes in trabeculae in cancellous bone at 3 weeks, more prominent at 12 weeks; ↓ anisotropy-accompanied changes	[25]
Mixed breeds	Lateral arthrotomy	2–7 years	3, 12 weeks	20–38-fold ↑ collagen type I, VI at 3 weeks; 11–19-fold ↑ at 12 weeks; higher concentrations in medial menisci versus lateral	[24]
Varies	Naturally occurring	1–13 years	N/A	MMP-3, TIMP-1 ↑ in SF of arthritic groups; KS ↑ in SF after ACL rupture	[29]
Mixed breeds	Lateral arthrotomy	Adult	3, 12 weeks	↑ aggrecan, collagen type II mRNA in cartilage; amount of collagen type II > aggrecan for OA	[21]
Foxhound	Medial arthrotomy	2 years	2 years	Cartilage changes of decorin, fibromodulin, aggrecan differ in models	[19]
Mongrel dog	Cranial transection	Adult	12 weeks	Significant changes from μMRI: depth of maximum T_2, ↓ SF zone thickness, ↑ total cartilage thickness; PLM confirmed	[32]
Mixed breeds	Cranial transection	Adult	3, 12 weeks	Collagen type II markers ↑ in SF; collagen type II, aggrecan markers ↑ in serum; collagen type II markers ↑ in urine	[30]
Mixed breed	Lateral arthrotomy	Adult	36, 72 weeks	Mechanical changes in ACL-T group at 36 weeks less noticeable in both ACL-T and ACL-T + Dox group; Dox therapy limited bone loss at week 72	[36]
Walker hounds	Arthroscopic	Adult	2, 10, 18 weeks	PGE_2 levels ↑ through study; correlated with gait, pain	[31]
Foxhound	Not specified	2–3 years	2 years	Minor/severe articular cartilage damage in medial compartment; joint space significantly ↑ for minor group, no change for severe group; minor group had 73 % of observed osteophytes; severity of damage of menisci and cartilage related	[33]
Varies	Naturally occurring	Adult	N/A	↑ cathepsin-K+ cells in CCL-ruptured group; TRAP+ cell levels correlate with inflammation	[17]
Varies	Naturally occurring	3–8 years	N/A	Treatment of CCL-explant cells with COL-3 (MMP inhibitor) led to ↓ collagen fragment generation	[37]
Varies	Naturally occurring	Adult	N/A	↑ Cathepsin-KMMP-9, TRAP in SF of OA group; TRAP ↑ OA versus other arthritis groups; matrix turnover/immune response genes ↑ in OA	[23]
Varies	Naturally occurring	Adult	N/A	CD4+, CD8+, CD3 + CD4-CD8-lymphocytes ↑ in CCL-ruptured dogs; CD3 + CD4-CD8-lymphocyte levels in SF inversely correlated to radiographic OA	[22]

Table 6.3 Ovine ACL-T models

Strain	ACL-T type	Surgery age	Exp. time	Results	Reference
Suffolk-cross	Arthrotomy + reconstruction	3–4 months	4, 20 weeks	ACL-R group had ↑ cartilage + osteophyte scores compared to controls; some OA development	[41]
Suffolk-cross	Arthroscopic	3 years	20 weeks	Load redistribution after ACL-T led to a significant ↓ in both PCL and LCL loads; no change in MCL loads	[39]

Table 6.4 Feline ACL-T models

Strain	ACL-T type	Surgery age	Exp. time	Results	Reference
Outbred	Anterior capsulotomy	1–3 years	4, 12, 35 weeks	↓ in muscle mass in ACL-T knee; ↑ in cell density, hexuronic acid in articular cartilage at weeks 12 and 35	[42]
Outbred	Lateral arthrotomy	Adult	0 days	Mechanoreceptor neurons in joint capsule are not affected by ACL-T	[43]
Outbred	Arthroscopic	Adult	16 weeks	Significant ↑ in articular cartilage thickness, significant ↓ in stiffness in ACL-T knee	[44]
Outbred	Arthroscopic	Adult	Ongoing (1 year)	↑ in knee instability, osteophyte formation, articular cartilage thickness, joint degeneration	[45]
Outbred	Anterior capsulotomy	Adult	16 weeks, 60 months	Significant ↓ in cancellous bone mass, subchondral bone thickness at 60 months; ACL-T intensified bone changes compared to control	[46]
Outbred	Anterior capsulotomy	Adult	16 weeks	↑ patellar articular cartilage, larger chondrocytes, more chondrocyte clusters, larger chondrocyte volume fraction; no femoral groove cartilage adaptation	[47]

have examined articular cartilage and meniscus properties [48–50], gene expression and surface receptors [51–53], osteophytes [54], bone properties [55, 56], and imaging techniques [57, 58]. The rabbit ACL-T model has also been used to test out therapeutics, such as HA therapy [59] and oral glucosamine supplements [60]. Furthermore, one study compared surgically induced ACL-T versus a blunt trauma ACL-T, which closely resembles clinical ACL-T in humans [61]. Studies using rabbit models of ACL-T are summarized in Table 6.5.

Guinea Pig Model

Guinea pigs have been used to study OA because the Hartley strain, among others, develops spontaneous OA beginning at 3 months of age [1, 62–65]. Other advantages of using guinea pigs for the study of PTA include the fact that their histopathology is very similar to humans and that they are easy to manage during long studies. Disadvantages for their use include the fact that they preferentially load the medial side of the

Table 6.5 Rabbit ACL-T models

Strain	ACL-T type	Surgery age	Exp. time	Results	Reference
New Zealand	Medial arthrotomy	8–12 months	9 weeks	[Articular cartilage] Significant ↓ modulus (18 %); ↓ in GAG density; significant ↑ water content	[50]
New Zealand	Medial arthrotomy	12 months	9 weeks	Menisci from ACL-T knees had degenerative changes; high # of apoptotic cells on medial side of menisci; ↑ nitrotyrosine reactivity	[48]
New Zealand	Medial arthrotomy	9–10 months	2, 4, 9 weeks	Rapid ↑in MMP-1, -3, -13 gene expression in articular cartilage; aggrecanase-1, -2 levels stable	[51]
New Zealand	Anterolateral capsulotomy	12 months	3, 8 weeks	Matrix deterioration; medial menisci showed cell-depleted areas, cell clusters, altered cell distribution; ↑ collagen type I, III staining lat/med; ↑ collagen type II staining on med side only	[49]
New Zealand	Anterolateral capsulotomy	12 months	3, 8 weeks	Significant ↑ RNA yield from med menisci only; significant ↓ DNA yield from med menisci week 8; significant ↑ collagen type I, TIMP-1; significant ↓ decorin, TNF-α, IGF-2; more mRNA changes by medial/lateral side	[52]
New Zealand	Medial arthrotomy	12 months	4, 9, 12 weeks	Osteophytes present in femur and tibia compartments by week 12; hypertrophic chondrocytes in osteophytes produce VEGF; NO production/ chondrocyte death during osteophyte formation	[54]
New Zealand	Medial arthrotomy	Adult	2, 8 weeks	Can detect synovial effusion, menisci/ligament lesions, and osteophytes accurately using MRI	[57]
New Zealand	Medial arthrotomy	2.5 years	4, 8, 12 weeks	Bone loss 4 and 8 weeks after, but returns to baseline by week 12; osteophyte volume significantly ↑ at weeks 8 and 12; damage to cartilage correlates to MRI values	[56]
New Zealand	Medial arthrotomy	2.5 years	4, 8, 12 weeks	MRI and μCT can be used to detect changes in articular cartilage, joint space, BMD, calcified tissue associated with OA	[55]
New Zealand	Medial arthrotomy	Adult	9 weeks	Apoptosis ↑ with ACL-T; treatment with HA ↓ apoptosis	[59]
New Zealand	Medial arthrotomy	Adult	3, 6, 12 weeks	Linear correlation between post-surgery time and OA scores; CD44v6 correlated with histology and macroscopic grades	[53]
New Zealand	Medial arthrotomy	9 months	11 weeks	Glucosamine group had significant ↓ in loss of GAG in lateral tibial plateau, ↓ in loss of GAG in lateral femoral condyle in ACL-T; glucosamine had a site-specific, partial disease-modifying effect	[60]
Flemish Giant	Blunt force OR medial arthrotomy	Adult	12 weeks	Blunt force caused tears in lateral menisci; both models had chronic degradation and meniscal tears, but blunt force was more severe	[61]
New Zealand	Medial arthrotomy	24 weeks	13 weeks	T2 values significantly ↑ in ACL-T; cartilage lesion levels significantly ↑ at 6 and 12 weeks in ACL-T; T2 correlated with histology grading	[58]

Table 6.6 Guinea pig ACL-T models

Strain	ACL-T type	Surgery age	Exp. time	Results	Reference
Hartley	Medial arthrotomy	40 days	1–8 months	Osteophytes visible at 3 months; Mankin score significant at 4–8 months compared to 1 month	[66]
Hartley	Lateral arthrotomy	3 months	3, 12 months	Coefficient of friction of cartilage significantly greater in ACL-T knees; lubricin levels significantly less in ACL-T knees	[67]
Hartley	Lateral arthrotomy	3 months	9 months	Lubricin significantly ↓; C2C, GAG, IL-1β, MMP-13, SDF-1 ↑ in ACL-T knees	[68]

knee joint, are mainly sedentary animals, and are too small to allow for use of arthroscopic techniques for injury induction and observation [1–3].

Recently, guinea pigs have been used to study the effects of PTA as well as spontaneous OA by looking at the effects of ACL-T such as osteophytes and histopathologic changes [66], coefficient of cartilage [67], levels of lubricin in the joint [67, 68], and levels of biomarkers in synovial fluid including C2C, GAG, IL-1β, MMP-13, and SDF-1 [68]. The use of guinea pig ACL-T models in PTA studies is summarized in Table 6.6.

Rat Model

Rats have been increasingly used for ACL-T studies due to their small size, rapid speed of OA symptom onset, ability for pharmacological testing, translational potential to human PTA, and low spontaneous degeneration of their knee joints [1, 3, 69–71]. Rats also have thick enough cartilage to allow for both partial and full cartilage defects, which allows for a low-cost defect model for OA research. Disadvantages include their small size for injury induction, and the rapid onset of disease [1–3].

Rats have been used to examine a variety of different PTA outcomes. One group of studies focused on the articular cartilage destruction, subchondral bone changes, and osteophyte production after ACL-T [71–73]. Another group introduced exercise as a therapy for reducing the symptoms of PTA after ACL-T [74]. Three other studies focused on the addition of supplements or inhibitors, including alendronate, which inhibits bone resorption, lubricin, hyaluronic acid (HA), and etanercept, an inhibitor of tumor necrosis factor alpha [75–77]. Finally, one group examined gene expression of different groups of OA progression markers, including matrix degradation, chondrocyte differentiation, and osteoclastic bone markers as a way to track disease progression [69]. Studies utilizing rat ACL-T models are summarized in Table 6.7 below.

Mouse Model

Mice provide a number of important advantages for studying OA and PTA. They are relatively inexpensive and easy to manage during studies, can incorporate genetic modifications, and are easy to use for pharmacological studies because of the low dosage required for efficacy [1–3]. However, relatively few murine models have been developed using ACL-T, likely due to small size and difficulty of the surgical approach. Mice also have fairly rapid onset of severe OA changes

Table 6.7 Rat ACL-T models

Strain	ACL-T type	Surgery age	Exp. time	Results	Reference
Wistar	Medial arthrotomy	10 weeks	2, 7, 14, 21, 28, 70 days	Cartilage destruction (margins) weeks 1–3; ↑ fibrillation of central cartilage weeks 3–4; ↑ denatured collagen type II staining present	[73]
Wistar	Medial arthrotomy	Unknown	2, 7, 14, 28, 70 days	Superficial zone cartilage changes (chondrocyte death/swelling, ↑ fibrillation); ↑ denatured collagen type II staining in fibrillated areas	[71]
Wistar	Medial arthrotomy	8 weeks	7, 14, 28 days	Mankin score lower for slight and moderate exercise at day 14; ↓ lesions in slight and moderate groups at day 28	[74]
Sprague-Dawley	Medial arthrotomy	20 weeks	2, 10 weeks	Alendronate (ALN) prevented ↑ bone formation, reduced area and instance of osteophytes, blocked osteoclast recruitment, ↓ local TGF-β release	[76]
Sprague-Dawley	Medial arthrotomy	10 weeks	1, 2, 4, 6, 10 weeks	Cartilage surface damage and GAG loss at week 1; subchondral bone loss weeks 2–10; osteophyte formation by week 10 in ACL-T	[72]
Lewis	Lateral arthrotomy	7–8 weeks	1, 4 weeks	Gene expression of lubricin ↓ in injured joints; ↑ TNF-α, IL-1β in synovial fluid of injured joints; TNF-α inhibition = ↑ of cartilage-bound lubricin, ↓ sGAG release	[75]
Lewis	Medial arthrotomy	3 months	6 weeks	Lubricin and lubricin + HA groups had ↓ in radiographic/histologic scores of cartilage damage; oral lubricin ↓ cartilage damage	[77]
Sprague-Dawley	Medial arthrotomy	10 weeks	1, 2, 4, 6, 10 weeks	↑ aggrecanase-1, MMP-13 weeks 1–10; ↑ collagen type IIA, Sox-9, VEGF, CD31 weeks 2–4 with ↓ later; ↑ cathepsin K, TRAP week 2; ↑ Runx-2, osterix weeks 4–6	[69]

after surgery [1, 78]. Mice also have thin articular cartilage, which has limited the use of certain techniques, such as MRI or gene expression studies, to study PTA.

One example of the use of surgical ACL-T for the study of PTA was in a study published by Glasson and coworkers. When they compared the effects of ACL-T and destabilization of the medial meniscus (DMM) on the development of OA, the DMM model resulted in a slower and less severe progression of OA. However, as an alternative to surgical ACL-T, recent studies have examined the effect of cyclic loading [79] or a single loading cycle [80–82] to induce ACL-T in mice. The use of murine ACL-T models in studies is summarized in Table 6.8. A more detailed description of the single loading cycle to create ACL transection in a mouse is presented in the next chapter.

Conclusions

In summary, transection or rupture of the ACL provides a reproducible model of PTA. This procedure can be performed surgically or noninvasively and has been demonstrated in a variety of different animals that range in size from the mouse to the sheep. The changes occurring in the joint appear to parallel the degenerative changes that occur in clinical PTA, and appear to affect all of the joint tissues including the cartilage, meniscus, bone, and synovium.

Table 6.8 Murine ACL-T models

Strain	ACL-T type	Surgery age	Exp. time	Results	Reference
129S6/SvEv	Medial arthrotomy	Unknown	4, 8 weeks	Severe OA compared to DMM model; subchondral bone erosion of the tibial plateau; chondrogenesis of joint capsule	[78]
C57BL/6N	Tibial compression	10 weeks	1, 3, 7, 14, 28, 56 days	Rapid trabecular bone loss by 7 days; mild OA detected by day 56	[80]
C57BL/6N	Tibial compression	10 weeks	0, 10 days; 12, 16 weeks	Loss of trabecular bone by 10 days; bone loss ↓ in ACL-T compared to avulsion fracture	[81]
FVB	Cyclic axial loading	3 months	1, 8 weeks	ACL-T had significant articular cartilage degeneration score; synovitis present at 1 week; osteophytes present at 8 weeks	[79]
C57BL/6	Tibial compression	8 weeks	5, 9, 14 days	Chondrocyte apoptosis, cartilage matrix degradation, disruption of cartilage collagen fibril arrangement, ↑ serum COMP, ↑ synovitis	[82]

Acknowledgments Supported in part by grants from the Arthritis Foundation, Department of Defense, and National Institutes of Health grants AR50245, AR48852, AR48182, AG15768, and AG46927.

References

1. Bendele AM. Animal models of osteoarthritis. J Musculoskelet Neuronal Interact. 2001;1(4):363–76.
2. Gregory MH, et al. A review of translational animal models for knee osteoarthritis. Arthritis. 2012;2012:764621.
3. Little CB, Smith MM. Animal models of osteoarthritis. Curr Rheumatol Rev. 2008;4(3):1–8.
4. Pond MJ. Avulsion of the extensor digitorum longus muscle in the dog: a report of four cases. J Small Anim Pract. 1973;14(12):785–96.
5. Gilbertson EM. Development of periarticular osteophytes in experimentally induced osteoarthritis in the dog. A study using microradiographic, microangiographic, and fluorescent bone-labelling techniques. Ann Rheum Dis. 1975;34(1):12–25.
6. Boileau C, et al. The in situ up-regulation of chondrocyte interleukin-1-converting enzyme and interleukin-18 levels in experimental osteoarthritis is mediated by nitric oxide. Arthritis Rheum. 2002;46(10):2637–47.
7. McDevitt C, Gilbertson E, Muir H. An experimental model of osteoarthritis; early morphological and biochemical changes. J Bone Joint Surg Br. 1977; 59(1):24–35.
8. McDevitt CA, Muir H. Biochemical changes in the cartilage of the knee in experimental and natural osteoarthritis in the dog. J Bone Joint Surg Br. 1976;58(1):94–101.
9. Pelletier JP, et al. The protective effect of licofelone on experimental osteoarthritis is correlated with the downregulation of gene expression and protein synthesis of several major cartilage catabolic factors: MMP-13, cathepsin K and aggrecanases. Arthritis Res Ther. 2005;7(5):R1091–102.
10. Setton LA, et al. Mechanical properties of canine articular cartilage are significantly altered following transection of the anterior cruciate ligament. J Orthop Res. 1994;12(4):451–63.
11. Libicher M, et al. Early changes in experimental osteoarthritis using the Pond-Nuki dog model: technical procedure and initial results of in vivo MR imaging. Eur Radiol. 2005;15(2):390–4.
12. Pelletier JP, et al. Selective inhibition of inducible nitric oxide synthase reduces progression of experimental osteoarthritis in vivo: possible link with the reduction in chondrocyte apoptosis and caspase 3 level. Arthritis Rheum. 2000;43(6):1290–9.
13. Pelletier JP, 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(3):527–38.
14. Lavigne P, et al. Subchondral and trabecular bone metabolism regulation in canine experimental knee osteoarthritis. Osteoarthritis Cartilage. 2005;13(4): 310–7.
15. Lorenz H, et al. Early and stable upregulation of collagen type II, collagen type I and YKL40 expression levels in cartilage during early experimental osteoarthritis occurs independent of joint location and histological grading. Arthritis Res Ther. 2005;7(1):R156–65.
16. Brandt KD. Transection of the anterior cruciate ligament in the dog: a model of osteoarthritis. Semin Arthritis Rheum. 1991;21(3 Suppl 2):22–32.

17. Barrett JG, et al. Inflammatory changes in ruptured canine cranial and human anterior cruciate ligaments. Am J Vet Res. 2005;66(12):2073–80.
18. Guilak F, et al. Mechanical and biochemical changes in the superficial zone of articular cartilage in canine experimental osteoarthritis. J Orthop Res. 1994;12(4): 474–84.
19. Liu W, et al. Spontaneous and experimental osteoarthritis in dog: similarities and differences in proteoglycan levels. J Orthop Res. 2003;21(4):730–7.
20. Matyas JR, et al. The early molecular natural history of experimental osteoarthritis. I Progressive discoordinate expression of aggrecan and type II procollagen messenger RNA in the articular cartilage of adult animals. Arthritis Rheum. 1999;42(5):993–1002.
21. Matyas JR, et al. Regional quantification of cartilage type II collagen and aggrecan messenger RNA in joints with early experimental osteoarthritis. Arthritis Rheum. 2002;46(6):1536–43.
22. Muir P, et al. Lymphocyte populations in joint tissues from dogs with inflammatory stifle arthritis and associated degenerative cranial cruciate ligament rupture. Vet Surg. 2011;40(6):753–61.
23. Muir P, et al. Expression of immune response genes in the stifle joint of dogs with oligoarthritis and degenerative cranial cruciate ligament rupture. Vet Immunol Immunopathol. 2007;119(3–4):214–21.
24. Wildey GM, et al. Absolute concentrations of mRNA for type I and type VI collagen in the canine meniscus in normal and ACL-deficient knee joints obtained by RNase protection assay. J Orthop Res. 2001;19(4): 650–8.
25. Boyd SK, et al. Early regional adaptation of periarticular bone mineral density after anterior cruciate ligament injury. J Appl Physiol (1985). 2000;89(6): 2359–64.
26. Boyd SK, et al. Early morphometric and anisotropic change in periarticular cancellous bone in a model of experimental knee osteoarthritis quantified using microcomputed tomography. Clin Biomech (Bristol, Avon). 2000;15(8):624–31.
27. Brandt KD, et al. Anterior (cranial) cruciate ligament transection in the dog: a bona fide model of osteoarthritis, not merely of cartilage injury and repair. J Rheumatol. 1991;18(3):436–46.
28. Brandt KD, et al. Osteoarthritic changes in canine articular cartilage, subchondral bone, and synovium fifty-four months after transection of the anterior cruciate ligament. Arthritis Rheum. 1991;34(12):1560–70.
29. Hegemann N, et al. Biomarkers of joint tissue metabolism in canine osteoarthritic and arthritic joint disorders. Osteoarthritis Cartilage. 2002;10(9):714–21.
30. Matyas JR, et al. Analysis of cartilage biomarkers in the early phases of canine experimental osteoarthritis. Arthritis Rheum. 2004;50(2):543–52.
31. Trumble TN, Billinghurst RC, McIlwraith CW. Correlation of prostaglandin E2 concentrations in synovial fluid with ground reaction forces and clinical variables for pain or inflammation in dogs with osteoarthritis induced by transection of the cranial cruciate ligament. Am J Vet Res. 2004;65(9): 1269–75.
32. Alhadlaq HA, et al. Detecting structural changes in early experimental osteoarthritis of tibial cartilage by microscopic magnetic resonance imaging and polarised light microscopy. Ann Rheum Dis. 2004;63(6): 709–17.
33. Anderst WJ, Les C, Tashman S. In vivo serial joint space measurements during dynamic loading in a canine model of osteoarthritis. Osteoarthritis Cartilage. 2005;13(9):808–16.
34. O'Connor BL, et al. Sensory nerves only temporarily protect the unstable canine knee joint from osteoarthritis. Evidence that sensory nerves reprogram the central nervous system after cruciate ligament transection. Arthritis Rheum. 1993;36(8):1154–63.
35. O'Connor BL, et al. Neurogenic acceleration of osteoarthrosis. The effects of previous neurectomy of the articular nerves on the development of osteoarthrosis after transection of the anterior cruciate ligament in dogs. J Bone Joint Surg Am. 1992;74(3): 367–76.
36. Pardy CK, Matyas JR, Zernicke RF. Doxycycline effects on mechanical and morphometrical properties of early- and late-stage osteoarthritic bone following anterior cruciate ligament injury. J Appl Physiol (1985). 2004;97(4):1254–60.
37. Muir P, Manley PA, Hao Z. COL-3 inhibition of collagen fragmentation in ruptured cranial cruciate ligament explants from dogs with stifle arthritis. Vet J. 2007;174(2):403–6.
38. Doom M, et al. Immunopathological mechanisms in dogs with rupture of the cranial cruciate ligament. Vet Immunol Immunopathol. 2008;125(1–2):143–61.
39. Atarod M, Frank CB, Shrive NG. Decreased posterior cruciate and altered collateral ligament loading following ACL transection: a longitudinal study in the ovine model. J Orthop Res. 2014;32(3):431–8.
40. Barton KI, et al. Characterization of proteoglycan 4 and hyaluronan composition and lubrication function of ovine synovial fluid following knee surgery. J Orthop Res. 2013;31(10):1549–54.
41. O'Brien EJ, et al. Osteoarthritis develops in the operated joint of an ovine model following ACL reconstruction with immediate anatomic reattachment of the native ACL. J Orthop Res. 2013;31(1):35–43.
42. Herzog W, et al. Hindlimb loading, morphology and biochemistry of articular cartilage in the ACL-deficient cat knee. Osteoarthritis Cartilage. 1993;1(4): 243–51.
43. Khalsa PS, Grigg P. Responses of mechanoreceptor neurons in the cat knee joint capsule before and after anterior cruciate ligament transection. J Orthop Res. 1996;14(1):114–22.
44. Herzog W, et al. Material and functional properties of articular cartilage and patellofemoral contact mechanics in an experimental model of osteoarthritis. J Biomech. 1998;31(12):1137–45.

45. Suter E, et al. One-year changes in hind limb kinematics, ground reaction forces and knee stability in an experimental model of osteoarthritis. J Biomech. 1998;31(6):511–7.
46. Boyd SK, et al. Long-term periarticular bone adaptation in a feline knee injury model for post-traumatic experimental osteoarthritis. Osteoarthritis Cartilage. 2005;13(3):235–42.
47. Clark AL, et al. Heterogeneity in patellofemoral cartilage adaptation to anterior cruciate ligament transection; chondrocyte shape and deformation with compression. Osteoarthritis Cartilage. 2006;14(2): 120–30.
48. Hashimoto S, et al. Nitric oxide production and apoptosis in cells of the meniscus during experimental osteoarthritis. Arthritis Rheum. 1999;42(10):2123–31.
49. Hellio Le Graverand MP, et al. Early changes in lapine menisci during osteoarthritis development: Part I: cellular and matrix alterations. Osteoarthritis Cartilage. 2001;9(1):56–64.
50. Sah RL, et al. Physical properties of rabbit articular cartilage after transection of the anterior cruciate ligament. J Orthop Res. 1997;15(2):197–203.
51. Bluteau G, et al. Matrix metalloproteinase-1, -3, -13 and aggrecanase-1 and -2 are differentially expressed in experimental osteoarthritis. Biochim Biophys Acta. 2001;1526(2):147–58.
52. Bluteau G, et al. Early changes in lapine menisci during osteoarthritis development: Part II: molecular alterations. Osteoarthritis Cartilage. 2001;9(1):65–72.
53. Tibesku CO, et al. Increase in the expression of the transmembrane surface receptor CD44v6 on chondrocytes in animals with osteoarthritis. Arthritis Rheum. 2005;52(3):810–7.
54. Hashimoto S, et al. Development and regulation of osteophyte formation during experimental osteoarthritis. Osteoarthritis Cartilage. 2002;10(3):180–7.
55. Batiste DL, et al. High-resolution MRI and micro-CT in an ex vivo rabbit anterior cruciate ligament transection model of osteoarthritis. Osteoarthritis Cartilage. 2004;12(8):614–26.
56. Batiste DL, et al. Ex vivo characterization of articular cartilage and bone lesions in a rabbit ACL transection model of osteoarthritis using MRI and micro-CT. Osteoarthritis Cartilage. 2004;12(12):986–96.
57. Wachsmuth L, et al. In vivo contrast-enhanced micro MR-imaging of experimental osteoarthritis in the rabbit knee joint at 7.1T1. Osteoarthritis Cartilage. 2003;11(12):891–902.
58. Wei ZM, et al. Quantitative T2 mapping evaluation for articular cartilage lesions in a rabbit model of anterior cruciate ligament transection osteoarthritis. Chin Med J (Engl). 2012;125(5):843–50.
59. Diaz-Gallego L, et al. Apoptosis and nitric oxide in an experimental model of osteoarthritis in rabbit after hyaluronic acid treatment. J Orthop Res. 2005;23(6): 1370–6.
60. Tiraloche G, et al. Effect of oral glucosamine on cartilage degradation in a rabbit model of osteoarthritis. Arthritis Rheum. 2005;52(4):1118–28.
61. Killian ML, et al. Traumatic anterior cruciate ligament tear and its implications on meniscal degradation: a preliminary novel lapine osteoarthritis model. J Surg Res. 2010;164(2):234–41.
62. Bendele AM, Hulman JF. Spontaneous cartilage degeneration in guinea pigs. Arthritis Rheum. 1988;31(4):561–5.
63. Bendele AM, White SL, Hulman JF. Osteoarthrosis in guinea pigs: histopathologic and scanning electron microscopic features. Lab Anim Sci. 1989;39(2): 115–21.
64. Jimenez PA, et al. Spontaneous osteoarthritis in Dunkin Hartley guinea pigs: histologic, radiologic, and biochemical changes. Lab Anim Sci. 1997;47(6):598–601.
65. Silverstein E, Sokoloff L. Natural history of degenerative joint disease in small laboratory animals. 5. Osteoarthritis in guinea pigs. Arthritis Rheum. 1958;1(1):82–6.
66. Jimenez PA, et al. Induction of osteoarthritis in guinea pigs by transection of the anterior cruciate ligament: radiographic and histopathological changes. Inflamm Res. 1995;44 Suppl 2:S129–30.
67. Teeple E, et al. Coefficients of friction, lubricin, and cartilage damage in the anterior cruciate ligament-deficient guinea pig knee. J Orthop Res. 2008;26(2): 231–7.
68. Wei L, et al. Comparison of differential biomarkers of osteoarthritis with and without posttraumatic injury in the Hartley guinea pig model. J Orthop Res. 2010;28(7):900–6.
69. Pickarski M, et al. Molecular changes in articular cartilage and subchondral bone in the rat anterior cruciate ligament transection and meniscectomized models of osteoarthritis. BMC Musculoskelet Disord. 2011;12:197.
70. Smale G, Bendele A, Horton Jr WE. Comparison of age-associated degeneration of articular cartilage in Wistar and Fischer 344 rats. Lab Anim Sci. 1995; 45(2):191–4.
71. Stoop R, et al. Type II collagen degradation in articular cartilage fibrillation after anterior cruciate ligament transection in rats. Osteoarthritis Cartilage. 2001;9(4):308–15.
72. Hayami T, et al. Characterization of articular cartilage and subchondral bone changes in the rat anterior cruciate ligament transection and meniscectomized models of osteoarthritis. Bone. 2006;38(2):234–43.
73. Stoop R, et al. Differences in type II collagen degradation between peripheral and central cartilage of rat stifle joints after cranial cruciate ligament transection. Arthritis Rheum. 2000;43(9):2121–31.
74. Galois L, et al. Dose-response relationship for exercise on severity of experimental osteoarthritis in rats: a pilot study. Osteoarthritis Cartilage. 2004;12(10): 779–86.
75. Elsaid KA, et al. The impact of anterior cruciate ligament injury on lubricin metabolism and the effect of inhibiting tumor necrosis factor alpha on chondroprotection in an animal model. Arthritis Rheum. 2009;60(10):2997–3006.

76. Hayami T, 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(4):1193–206.
77. Teeple E, et al. Effects of supplemental intra-articular lubricin and hyaluronic acid on the progression of posttraumatic arthritis in the anterior cruciate ligament-deficient rat knee. Am J Sports Med. 2011; 39(1):164–72.
78. Glasson SS, Blanchet TJ, Morris EA. The surgical destabilization of the medial meniscus (DMM) model of osteoarthritis in the 129/SvEv mouse. Osteoarthritis Cartilage. 2007;15(9):1061–9.
79. Onur TS, et al. Joint instability and cartilage compression in a mouse model of posttraumatic osteoarthritis. J Orthop Res. 2014;32(2):318–23.
80. Christiansen BA, et al. Musculoskeletal changes following non-invasive knee injury using a novel mouse model of post-traumatic osteoarthritis. Osteoarthritis Cartilage. 2012;20(7):773–82.
81. Lockwood KA, et al. Comparison of loading rate-dependent injury modes in a murine model of post-traumatic osteoarthritis. J Orthop Res. 2014;32(1): 79–88.
82. Wu P, et al. Early response of mouse joint tissue to noninvasive knee injury suggests treatment targets. Arthritis Rheumatol. 2014;66(5):1256–65.