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A review on various types of osteoarthritis induction and in-vivo animal models for articular cartilage regeneration study: osteoarthritis defects

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Abstract:

Reconstruction of articular cartilage degenerative diseases such as osteoarthritis is one of the most important challenges in musculoskeletal medicine. So far, a lot of research has been done on the repair of damaged articular cartilage in vivo. The study of in vivo animal models is essential to evaluate cartilage tissue engineering techniques. In this review, we study the articular cartilage structure and osteoarthritis disease features. Also, animal species that have been used in various studies as a model of articular cartilage damage and the advantages and disadvantages of any species models were studied.

Keywords: Articular cartilage; Animal models; Osteoarthritis**.**

1. Introduction

Articular cartilage (AC) is a specialized avascular and aneural type of connective tissue that covers the bony parts of diarthrodial joints [1, 2]. AC predominantly consist of chondrocytes differentiated from mesenchymal stem cells [3]. Structurally, it is divided into four zones: superficial, transitional, middle, and calcified. The superficial layer zone includes disc-shaped chondrocytes that produce extracellular matrix constituents. Also, there are a large amount of collagen II, a small amount of collagen I as well as lubricin and a low proteoglycan content [4, 5]. In the transitional layer, cellular density is reduced, chondrocytes are round-shaped, and proteoglycan content is increased [6]. In the middle zone, there are less proteoglycan content and lower spherical chondrocytes with a columnar arrangement [7]. The calcified zone has an extracellular matrix without proteoglycans surrounding the small number of round-shaped chondrocytes [8]. Physiologically, the AC distributes the loads to the underlying subchondral bone and minimizes the impact forces, resulting in smooth, low-friction, and sliding movements [9, 10]. Therefore, due

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to its major function, damage to AC often severely affects the daily life of patients [11].

Osteoarthritis (OA) is a chronic and debilitating disease that precipitates the gradual degradation of AC, mostly in the middle-aged and elderly population [12, 13]. The pathology mainly involves the AC of large joints, including knees, hips, cervical and lumbosacral spine, and ankle, but it can also affect the smaller joints such as distal, proximal inter-phalangeal, and carpometacarpal joints [14, 15]. The etiological factors of OA are different and include the female sex, aging, previous joint injuries, obesity, heredity, and mechanical pressure [16, 17]. This disease is categorized into primary or idiopathic such as a history of trauma, septic conditions, and systemic diseases as well as intense or incongruous work or sport activities [18, 19]. The changes in structural and biochemical characteristics of the AC increase the secretion of catabolic factors by the articular chondrocytes. Further breakdown causes apoptosis of the articular chondrocytes and decreases joint space resulting in friction between the bones and thereby may cause pain and limited mobility [20]. Symptoms include persistent and progressive pain, which is worsened with any activity, difficulty in waking up/after inactivity, and joint swelling [21, 22]. Due to its high disability rate, OA is considered to be the most common health problem worldwide [23]. Most data on OA is obtained from both preclinical and clinical researches. However, clinical studies present challenges because OA is a chronic disease and has variable symptom onset and rate of progression. In addition, obtaining human samples in the early stages of OA is difficult since patients mostly refer to the clinic once the disease has developed [24]. Hence, preclinical models of OA can provide invaluable tools for learning about and treating the disease. In this regard, there are various models which address different aspects of OA development and progression [25] as follows:

Spontaneous OA animal models are widely applied for the examination of primary OA and classified into naturally occurring and genetically modified models. The occurrence of gradual progression of OA in the mentioned models highly imitates the natural progression of human primary OA [26, 27]. Also, genetically modified models (i.e., knock-out and knock-in animal models) have been designed for the evaluation of OA development without intervention and provide the opportunity to assess the function of specific genes that contribute to OA pathophysiology [27, 28].

As mentioned earlier, although secondary OA occurs through different causes or risk factors such as congenital and metabolic defects and infections, OA due to injury, insult, or trauma (post-traumatic OA) is the most common subtype of the disease to study [29]. For secondary OA investigations, there are invasive and non-invasive models induced by direct or indirect injuries to the joints [30]. Invasive models are generally applied to examine post-traumatic OA pathogenesis and evaluate the effectiveness of therapeutic agents for the disease and can be subcategorized into the models induced by surgeries and chemicals. In surgically-induced models (e.g., anterior cruciate ligament transection, meniscectomy, medial meniscal tear, and ovariectomy) using aseptic techniques for OA induction in animals, the disruption of joint biomechanics, production of inflammation and instability of joint load-bearing occur, while with the administration of a toxic or inflammatory compound such as papain, sodium monoiodoacetate, quinolone and collagenase, joint homeostasis happens, resulting

in the histological and morphological damages [26]. In the last few years, it has also been described several non-invasive models of secondary OA, including intra-articular tibial plateau fracture, axial tibial loading model, cyclic AC tibial compression, and tibial compression overload which degenerate joints leading to external trauma via mechanical impact [31]. It is worth mentioning that each model for OA induction in animals has its advantages, and no individual model seems suitable for the investigation of this disease as a whole.

Because of the avascular and aneural characteristics of AC, it has a limited ability to repair itself after damage [32, 33]. While different options are available in the clinics such as exercise, physical therapy, lifestyle changes, pain medications, and surgery, they are only helpful to relieve OA symptoms and improve joint functional capacity and are sometimes associated with adverse side effects [34, 35]. Therefore, active research keeps going to explore new tools for more effective and useful therapies of this disease. In recent years, tissue engineering has emerged as an interdisciplinary field as it combines several therapeutic approaches considering cell and molecular biology, material science, and biomedical engineering to repair damaged tissue function [36]. In the technological process related to AC tissue engineering, after the expansion of cells in cultures, they are seeded in a three-dimension scaffold and produce a cell-scaffold construct. Then, the construct is inserted in the tissue defect, in which the scaffold is slowly degraded, and after a while, differentiated cells only remain [37]. As understood, AC tissue engineering generally uses scaffolds because they provide the proper environment for growth and differentiation of cells into chondrocytes and also allow a more constant distribution of cells and thereby avoid their scattering in the articular space [38]. Thus, AC tissue engineering has provided great hope to treat OA through induction of the repair and regeneration of damaged AC.

This review addresses globally experimental models examining cartilage regeneration in vivo which helps to choose one more appropriate model when designing future investigations and develop data transformation from experiments to clinics. Table 1 represents different osteoarthritis induction models.

2. Animal Models of OA

To establish OA models in animal species and to evaluate the success oftheraputic intervention on OA, different procedures inducing the pre-clinical OA model have introduced. As mentioned earlier, natural OA in humans involves various joint components as well as articular cartilage, subchondral bone, meniscus, ligaments, and joint capsules [39]. Selecting an effective method for induction of the OA model that creates a translatable animal model to natural human OA is still challenging. The existence of anatomical and physiological differences between animal species and humans are very critical issues in induction of preclinical models [40]. The ideal model for OA induction is a model that affects different joint structures similar to the progressive condition of OA in humans [27]. Different factors are involved in the variation of preclinical OA models such as causes of injury, affected tissues, stage of disease, and symptoms [41]. Knee joint is the most regular site to induce an animal model of OA [42], although, in some studies, horse metacarpophalangeal joint is introduced as the most similar joint to the human knee joint [43-45]. Extent of tissue damage in OA

Table 1. Different osteoarthritis induction models.

	Models	Advantages	Disadvantages	Methods	Species	Pathological evidences	Ref.
Primary osteoarthritis	**Spontaneous osteoarthritis**	No need for any intervention	Time consuming	-	Mouse, Guinea pig, Rabbit	Increasing ligament laxity, patella displacement, collagen turn over in anterior cruciate ligament, and oxidative stress leading to apoptosis of chondrocytes	(Sabatini et al., 2005), (Bendele, 2001, Mason et al., 2001), (Wendler & Wehling, 2010)
	Genetically modified osteoarthritis	Evaluation of the role of genetic factors in osteoarthritis progression	Cost and time consuming, incompatible with human clinical studies	Transgenic animal and knock out manipulation	Mouse	Cartilage degeneration in mouse due to knock out of a single gene, such as collagen IX, collagen type II alpha 1 chain, collagen type lX alpha 1 chain, aggrecan, alpha-1 integrin subunit, and A disintegrin and metalloproteinase with thrombospondin-like motifs	(Little & Hunter, 2013), (Miller, Lu, Tortorella, & Malfait, 2013), (Glasson, 2007)
Secondary osteoarthritis	**Chemically induced osteoarthritis**	Rapid and non-invasive, suitable for assessing the therapeutic efficacy of novel therapies	Incompatible with the degenerative form of human osteoarthritis	Monosodium iodoacetate (MIA)	Rat, Mouse, Rabbit	Inhibiting glyceraldehyde-3-phosphate dehydrogenase of the Krebs cycle leading to chondrocytes apoptosis and consequence articular cartilage degradation	(Lampropoulou-Adamidou et al., 2014), (Guzman, Evans, Bove, Morenko, & Kilgore, 2003)
				Papain	Rat, Mouse, Rabbit	Breaking down the matrix of AC through affecting the synthesis and structure of glycosaminoglycan and decreasing the basophilic staining of cartilage matrix	(Potter, McCluskey, Weissmann, & Thomas, 1960), (Havdrup, Henricson, & Telhag, 1982)
				Collagenase	Mouse	Breaking down peptide bonds in collagen type 1 and decreasing collagen matrix leading to joint instability	(van der Kraan, Vitters, van Beuningen, Van De Putte, & Van den Berg, 1990), (Kikuchi, Sakuta, & Yamaguchi, 1998)
		Rapid and reproducible, similar to the traumatic form of	Invasive, an increased risk for infection and not appropriate for	Anterior cruciate	Rat, Mouse, Rabbit,	Inducing anterior cruciate ligament injury leading to degradation of articular cartilage	(Proffen et al., 2012), (Piskin et al., 2007)

	Surgically induced osteoarthritis	human osteoarthritis	inducing the degenerative form of human osteoarthritis	ligament transection	Dog, Cat, Sheep, Goat		
				Total and partial meniscectomy	Rat, Mouse, Ewe, guinea pig, Dog	Inducing post-traumatic degradation of articular cartilage	(McDermott & Amis, 2006), (Karahan, Kincaid, Kammermann, & Wright, 2001)
				Medial meniscus tear	Rat, Guinea pig, Pig	Inducing focal cartilage lesions	(Bendele, 2001)
				Ovariectomy	Rat, Ewe	Inducing estrogen deficiency and weight gain leading to articular cartilage erosions	(Ham et al., 2002) & (Høegh-Andersen et al., 2004)
				Cartilage defect	Rat, Dog, Rabbit, Ewe, Horse, Sheep, Goat	Inducing focal trauma and consequent defects in the cartilage surface and subchondral bone	(Ahern et al., 2009) & (Wei & Messner, 1999)

models is classified as follows: 1) articular cartilage damage (proteoglycan depletion and chondrocyte apoptosis), 2) subchondral bone injuries (increased turnover), 3) joint capsule (fibrosis), 4) synovium and fat pad (fibrosis and infiltration of inflammatory cells) [46-48]. Due to the incompleteness of each OA induction model, it is essential to use more than one OA model to clarify the therapeutic efficacy of novel therapies [47].

Generally, there are two types of OA induction models in animal studies:

1- Primary OA: spontaneous and genetically modified OA models

2- Secondary OA: chemically and surgically induced OA models [49].

The studies showed secondary OA model is faster and cheaper than primary OA [49].

Primary OA: Natural or spontaneous OA models

It has been reported that OA naturally occurs in some species through aging, particularly in Dunkin-Hartley guinea pigs [50]. Also, besides, the occurrence of the spontaneous model of OA has been announced in other animals including mice, dogs, and rabbits [51]. Because of the slower progression and onset, spontaneous model is the most similar model to human OA [52]. Consequently, the obtained results of novel therapies from this model seem to be more reliable. Ligament laxity is enhanced via aging in guinea pigs leading to spontaneous OA [52]. In recent studies, this model has been disused because an increase of collagen turn over in anterior cruciate ligament (ACL) of guinea pigs plays an vital role in the etiology of spontaneous OA by causing laxity and joint instability [41]. Also, increment in reactive oxygen spices via aging can lead to oxidative stress, which augments apoptosis of chondrocytes in the articular cartilage of some animal species such as mice, rats, and rabbits [53]. It must not be forgotten that the availability of this OA model is limited and time-consuming. Another drawback of this model is the high cost of housing due to the need of a prolonged time for instance three months to develop OA in guinea pigs [41, 54].

Also, it has been reported that spontaneous OA develops after 3 to 5 months in knee joints of STR/ort mice [55, 56]. The primary etiology of OA in STR/ort mice is controversial but patella displacement has been proposed as potential damage inducing factor [57]. It has been reported that most of the STR/ort mice had OA complications in the medial tibial cartilage in 9 months age. Besides, spontaneous temporomandibular joint OA in STR/ort mice was reported in 40 to 50 weeks age [55].

Primary OA: Genetically modified OA models

These models are induced by transgenic or knock-out manipulations of specific genes related to the cartilage [58]. Genetically modified animals are usually used to highlight the role of genetic influences in OA [29]. Mouse is the most widely used animal to induce a genetically modified model of OA. Indeed, these models are mostly used to clarify the role of specific genes on the OA developments [49]. It is of note that polymorphisms or mutations in genes encoding extracellular matrix and signaling molecules cause OA model [59]. Therefore, KO a single gene, such as collagen IX, collagen type ll alpha 1 chain, collagen type lX alpha 1 chain, aggrecan, alpha-1 integrin subunit, and disintegrin and metalloproteinase with thrombospondin-like motifs (ADAMTS5) causes OA model in mice [60]. Generally, employing transgenic and KOs for structural genes is beneficial to indicate the pathophysiology of OA induction and progression in mice. Interestingly, it has been reported that more intensive genetically modified OA models are induced

in the interleukin 6 knock-out, TIMP-3 knockout and beta-1 Integrin knock-out and growth hormone transgenic mice [60].

Secondary OA: Chemically induced OA models

Different chemical substances like papain, monosodium iodoacetate (most common substance), quinolone and collagenase are used to induce OA, usually via intra-articular injection in different animal species [26]. These models are easily developed without surgery or other interventions. However, they cannot completely simulate the natural human OA due to extensive chondrocyte cell death [49]. Chemically induced models are mostly used for studying pain behavior related to OA [26].

Monosodium iodoacetate (MIA) blocks glyceraldehyde-3-phosphate dehydrogenase and leads to chondrocyte apoptosis and consequence articular cartilage degradation [61]. As mentioned before, MIA is the most common agent in chemically induced OA models, and Intra-articular injection of MIA leads to acute cartilage degeneration [62]. MIA-induced OA model is commonly used in mice and rats [63]. MIA administration into the articular joint is a well-established OA model particularly in rodents that can be used for assessing pain behavior and histopathological progression of OA similar to human OA [64]. It is of note that impossibility to use in larger animals and lack of similarity with slow progress of human OA are the two most important weaknesses of this model [65].

Collagenase is an enzyme that breaks down peptide bonds in collagen type I [66]. Administration of collagenase into the articular joint leads to a decrease of the collagen matrix and consequently leads to joint instability [67]. Inflammatory cytokines such as interleukin-1 and tumor necrosis factor stimulate the collagenase secretion. The OA onset and progression of intra-articular injection of collagenase is slower than MIA [68]. Intra-articular injection of collagenase in mice can analogize characteristics of spontaneous OA model [69]. Histopathological changes in this preclinical model in rabbits and rodents are similar to the human OA progression that is characterized by intensive cartilage lesions, remodeling subchondral bone and osteophyte formation [70]. It has been stated that the collagenase-induced OA model is a promising preclinical model to study pain in OA [71].

Papain is a proteolytic enzyme that can break down polypeptides [14]. Numerous studies have confirmed the biological and economic importance of papain in medical and industrial aspects [72]. Based on the available literature data, papain is one of the first chemical substance that is used for the induction of OA in preclinical animal models [73]. It has been reported that intra-articular injection of papain in the knee joints of different animal species leads to degenerative changes in articular cartilage almost after two days [74]. Indeed, papain breaks down the matrix of articular cartilage through affecting the synthesis and structure of glycosaminoglycan [49]. Besides, in another study, intravenous injection of papain led to a depletion of cartilage matrix which, was approved by decreasing the basophilic staining of cartilage matrix [75]. Recently, the use of papain to induce the OA model is less considered than other mentioned chemicals [76]. Histopathological alternations in papain-induced OA are approximately similar to human OA [77]. Instead, the disease onset in papain administration is very fast and intensive compared to human OA [74].

Secondary OA: Surgically induced OA models

Different surgical procedures have been proposed to induce the OA models such as anterior cruciate ligament (ACL) transection (most common model),

medial meniscal tear, meniscectomy, ovariectomy and, cartilage defects [49]. Although surgical models are very invasive and may be at increased risk for infection, they are very rapid and ideal for short-term studies [78].

Anterior cruciate ligaments transection (ACLT) is one of the frequent surgical induction methods particularly, in dogs, rabbits, sheep, and goats [78]. ACLT method is similar to the post-traumatic OA that is induced by an ACL injury. As mentioned earlier, this method can be used in several animal models, still sheep and goats are the two most suitable animals due to the larger size and anatomical similarities with humans [78, 79]. Similar to the ACLT, meniscectomy leads to degradation of articular cartilage, but in contrast to ACLT, meniscectomy develops more rapidly [80]. Total meniscectomy is more intensive than partial meniscectomy. A review of literature data has indicated that total meniscectomy was mostly applied in dogs [81]. Partial meniscectomy is induced in both meniscuses that vary based on animal species due to the load bearing; for example, partial meniscectomy is performed in lateral meniscus for rabbits and medial meniscus for guinea pigs [51]. Medial meniscus tear is another surgical method to induce OA that is performed via transection of the medial collateral ligament. This method is usually utilized in rats and guinea pigs and leads to focal cartilage lesions after 4 to 6 weeks [50, 51]. Ovariectomy of female animals, as an OA induction model, leads to estrogen deficiency, weight gain and, consequently, articular cartilage erosions in the knee joints [82]. This type of OA model is relevant to human post-menopausal osteoporotic OA. Ovariectomy is a convenient and more rapid model of OA, particularly in rats and ewes [83]. Urinary secretion of a collagen catabolism marker (CTX-II) was reported 4-6 weeks post-ovariectomy of animals that can be considered as a biomarker of OA [41].

Creating a cartilage defect is a conventional surgery to induce OA in different animal spices [84]. This model is relevant to the human OA that is caused by focal trauma and consequent damages in the cartilage surface and subchondral bone [84]. Cartilage defect model is employed in different animal spices such as rodents, sheep, goats, rabbits, horses and dogs. It has been reported that cartilage defects in goats and horses is more closely resemble humans, but working with smaller animals such as rabbits and rats is more applicable and affordable [85]. This model is very excellent for evaluating different articular cartilage reconstruction techniques such as stem cell therapy and tissue engineering [85]. In rabbits, defect size is usually 3-5 mm, and defects can be induced in the femoral trochlea, the lateral and medial femoral condyles [86]. In dogs, defect size is usually 2-10 mm and defects can be created without involving the subchondral bone in the femoral trochlea, the lateral and medial femoral condyles [87]. In horses, defect size is usually 8-15 mm, exactly similar to the human articular defects, and defect usually is created in lateral trochlea of the femur (most common region) [83].

3. Evaluating of disease outcome

In OA-induced models and human OA, different joint structures are affected; therefore, sampling, recognition and analysis of all the structures are needed via appropriate techniques such as histologic staining, immunohistochemistry, real-time PCR, pain scaling, biomarkers evaluation, and imaging techniques [40]. Magnetic resonance imaging (MRI) is the most reliable and convenient method to assess early lesions in humans and large animal models [69]. There are different histologic grading systems to indicate the severity of lesions and tissue damage, for

example Mankin scoring system [27]. Besides, biochemical markers can be used to predict the progression of OA and response to therapies in animal models of OA [88]. Undeniably, it is imperative to complement these markers with histopathological and imaging findings. Urinary C-telopeptide of type II collagen (CTX II) and serum cartilage oligomeric matrix protein (COMP) are the two most important biomarkers which are used in OA-induced studies [88, 89]. Pain is one of the most important hallmarks of OA. Therefore, introducing a successful treatment should be accompanied by evaluating its analgesic effects [90, 91]. Among the methods that are described, intra-articular injection of MIA and surgical procedures (e.g., ACLT and Meniscectomy) are frequently employed for induction of pain model of OA [92]. Motor and behavioral tests, including gait analysis, lameness, knee extension, mechanical and thermal sensitivities, are used to indicate the extent of pain [93].

4. Animals used as models for cartilage defects

Joint cartilage has attracted the attentions of recent studies due to its poor regenerative power. Relatively, most of these studies have been done in animal models of OA. OA animal model is aimed to achieve desired results of novel treatments from laboratory studies to human clinical studies [95]. The joint anatomy of selected animal species should be most similar to humans. The knee joint has been studied more than other joints.

Comparing joint anatomy in different species (e.g., cows, goats, sheep, dogs, rabbits and pigs) with human joints revealed that all of them have totally similarities with human join structures (AC, ligaments, and meniscus). However, there are some differences in the length and width of the ligaments and the size of the AC. Also, the range of extension and flexion varies according to their movements in different species [78]. Compared to body mass in mammalians, the articular surface area is increased in larger animals, but the AC thickness bears a negative allometric relationship to body mass, and the cell density is decreased. Besides, the articular surface is more compact in smaller animals [96].

The studies of animal models are varied regarding joint surfaces, subchondral bone, differentiation of implanted stem cells, animal size, availability and applicable for therapeutic measurements. Animal species for induction of OA model are generally divided into the following groups:

Mice

Mice have been used in many studies because of their availability, affordability and easy to breed and maintenance. Also, due to the availability of immunocompromised mice, this species is promising to transplant cells and tissues from other species [84]. As an AC model, mice have small and too thin AC, which only consists of a few cell layers; in addition, very small cartilage defects can be created in this model so data from these studies are not very reliable. Also, surgical operation is very difficult on these animals [95]. One of the similarities between mice and humans is the development of spontaneous OA that occurs in the knee joint of C57BL/6 mice [97]. This process is gradual and spontaneous, and the study of the new drug efficacy on this model is time-consuming; however, its pathology is similar to humans [98]. There are different strains in mice that make them possible for comparative studies. In the study of Ma et al., they reported that the regenerative power of AC in male and female mice is different, and found that the rate of repair in female mice is higher than males [99]. Fitzgerald et al. compared the AC regeneration in MRL/MpJ and C57BL/6 mice and

stated that MRL mice had better healing power [100]. Mak et al. examined the beneficial effects of synovial mesenchymal stem cell transplantation in a mouse cartilage defect model, although MRL-derived stem cells were accumulated at the defect site, the cartilage defect was not completely alleviated [101]. A comparison of the knee and ankle joints has shown that in both humans and mice, the ankle cartilage thickness is half of the knee joint, and the subchondral bone is more compact in the ankle joint. Also, the ankle joint is more resistant to OA in both humans and mice, so that these similarities can be used in comparative studies of the knee and ankle joints [97].

Due to the possibility of genetic manipulation in mice, they can be used to investigate the effect of different genes. Manas et al. investigated the role of a disintegrin and metalloproteinase with thrombospondin motifs-4 and a disintegrin and metalloproteinase with thrombospondin motifs-5 gens in the induction of OA in mice and suggested knock-outing these genes may ameliorate OA symptoms [102].

Rats

Rats like mice are economically viable and more applicable in chemical induction models of OA and suitable to study the effect of novel drugs in these models of OA [98]; also creating cartilage damage is more possible in them due to their larger size and scaffolds and biomaterials can be used in this animal model [103]. Surgical induction procedures are less common in rats. Also, their gait pattern and biomechanical loading environment are different compare to humans [104]. The AC thickness in rats is 166.5µm, in which the surface layer is composed of compressed chondrocytes [105]. Katagiri et al. investigated the role of surgical defect size on the cartilage healing and stated that defects less than 0.9 mm in diameter heal after four weeks but defects greater than 1.4 mm and a depth of 1 mm take longer time due to increase interleukin 1β, fibroblast growth factor 2 and inflammation in the AC [106]. Research has shown that three CIA (collagen-induced arthritis), AIA (adjuvant-induced arthritis), and SCW (streptococcal cell wall-induced arthritis) methods can be used to create rodent models of immune-mediated arthritis model in rats, while mice are resistant to the AIA and SCW models [107]. However, mice are preferred animal in genetic investigations. Hu et al. examined the effect of the CIA on the induction of arthritis in rats and its pathological effects on AC and subchondral bone and indicated that bony spur formation is a common pathological symptom in degenerative joint diseases [108].

Rabbits

Rabbits, like mice and rats, are widely used in preclinical models of OA, due to easier handling, low cost, and the possibility of genetic studies [95]. Rabbits have larger joint size and depth compared with rodents (221-341µm) [109], which allows creating cartilage defect with a diameter of 3-4 mm, and this species is more used in osteochondral defect models [110, 111]. The most common depth to create cartilage defect in rabbits is reported 3 mm, which due to the thinness of the AC, more defect is created in subchondral bone [111, 112]. Cartilage damage in rabbits can improve spontaneously that can affect the evaluation of treatment success, while this spontaneous improvement does not exist or is very weak in humans. Older rabbits have a lower chance of self-improvement [86]. One of the disadvantages of using rabbits compared to humans is the low weight of rabbits (2-4.5kg) and the low pressure on the AC [84]. However, the thickness of calcified cartilage and bone plate and the density of bone minerals in human

medial femoral condyle (MFC) are similar to rabbit trochlea [113]. Usually, an average of 6-210 rabbits has been used in studies that have been followed for a period of 2-76 weeks [114]. Rabbits are also more applicable in stem cell therapies in animal models, and the most widely used type of stem cells is fat-derived stem cells [115].

Dogs

There are similarities between dogs and humans, such as the inability to heal cartilage defects intrinsically and the incidence of cartilage problems like OA in them [109, 116]. The thickness of the AC in dogs (524-771µm) is greater than rabbits and other rodents, and we can induce cartilage defect of 4 mm diameters in these animals [84, 109, 116-119], therewith dogs are used to study of partial-thickness cartilage repair [120]. Human and dog stifle joint anatomy are partly different; there are a lateral long digital extensor tendon (LDET) and an extra intra-capsular tendon in dogs that their function is dorsiflexion of the foot during knee flexion. As well as LDET is seen in some quadrupeds [78]. The important advantage of the canine model compared to the rodent model is the conceivability of arthroscopic surgery in the tibiofemoral joint that allows macroscopic visualization and biopsies of defects. Also, dogs can be trained to use treadmill exercise and accept bandages, braces and slings [118]. Defects can be induced in the medial femoral condyle, femoral trochlea and both condyles. Almost 25 to 30 dogs have been used in OA studies which they were 18 to 72 months old and were followed for a period of 2 to 78 weeks [84].

Goats

Like humans and dogs, goats have a poor intrinsic ability to heal cartilage defects and have a larger joint compared to dogs [121]. Its femorotibial joint anatomy is like humans and its total cartilage thickness (calcified plus non-calcified cartilage) is 1510- 699 µm which is thicker than dogs and makes cartilage repair study feasible [108]. Also, in goats, subchondral bone consistency and trabecular structure are closer to humans than canines, sheep or small animals [121]. Goats are relatively inexpensive and easy to handle compared to other large animal models. Also, it is easy to create cartilage defects in goats because of the larger size of the joint compared to smaller animals. However, exercise protocols and protected weight-bearing are difficult to the appliance in goats [122]. The subchondral bone in the goat knee joint is softer compared to sheep and osteochondral defects can easily be induced by surgical techniques [123].

In a comparative study of the anatomy of the knee joint, the goats were more similar to the human compared to cows, dogs, sheep, pigs, and rabbits [78]. Also, the goat cartilage is thinner than human cartilage, but the elastic modulus and stiffness of the caprine cartilage are greater than human AC [124]. Almost 25 to 32 goats have been used in OA studies, which they were 18 to 72 months old. OA model in goats has usually been followed for a period of 2 to 104 weeks [84]. Goats are suitable species for evaluation of cells and scaffolds transplantation for the treatment of osteochondral defects [125]. Nam et al. reported the potential use of autologous BM-MSCs as a treatment for focal cartilage defect in goats. They used subchondral drilling as the method for marrow stimulation in caprine model and suggested that BM-MSCs transplantation as an adjunct therapy could improve cartilage defect [126]. Levingstone et al. implanted a multi-layered collagen-based scaffold surgically in the goat stifle joint, which consisted of three distinct layers and mimicked the stratified composition of native osteochondral tissue. The

mentioned scaffold increased the formation of subchondral trabecular bone and hyaline-like cartilage tissue [127].

Horses

Cartilage problems like OA and cartilage injury involve horses similar to dogs and humans. Also, veterinarians have tried to develop the treatments of cartilage injuries in horses because of the racing industry [128]. Horses have a low intrinsic capability to repair AC defects like humans and goats [129]. The cartilage thickness of the horse is 1761-2215 µm which is similar to human cartilage thickness (2.35mm) [108]. Also, the glycosaminoglycan content is increased over the first 600 mm from the surface in both the lateral and medial equine condyles and the same trend is observed for human cartilage tissue from both lateral and medial condyles [130]. So that cartilage defects and treatment methods can be utilized in horses and generalized to human cartilage injuries [131]. Other analogies between horses and humans are the thick and large dimensions of articular cartilage, and knee joints movements during gaiting [132]. Arthroscopic surgical techniques can be used in horses since it was shown that implantation of mesenchymal stem cells in these animals could significantly improve the healing of defects [127]. Also, implantation of autologous chondrocytes in horse cartilage defect models can meliorate defects [133]. The horses are the largest animal models for articular cartilage damage studies and have a hard subchondral bone due to their weight and physiology [134]. The costs of veterinary, caring and procuring of the animals, as well as access to appropriate facilities, are the most disadvantages of horse models [95]. 6 to 12 horses are used in each study that is 12 to 72 months old and is followed from 2 to 52 weeks [84].

Pigs

Pigs are similar to humans in joint size, cartilage thickness and weight-bearing requirements [135]. Cartilage thickness in the medial femoral condyle of pigs is 1.5-2 mm [136] and is very suitable for partial or full-thickness defects models. The Pig knee joint is feasible for arthroscopic evaluations [137], but it cannot be trained for exercise protocols.

Tomaszewski et al. made a cartilage defect in pigs and used two different scaffolds to ameliorate defects, 1) a scaffold which supplemented with bone marrow and growth plate chondrocytes and 2) a hyaluronic acid-based scaffold accompany with marrow stimulation and showed that growth plate chondrocytes seeded on a scaffold with bone marrow created more improvement in animals [138].

Like rabbits, spontaneous repair occurs in small cartilage defects of immature pigs [139], so that adult pigs are used in investigations to decrease the effect of spontaneous healing on clinical treatments. Almost 11 to 57 pigs are used in the studies and they are followed from 1 to 52 weeks and are 12 to 234 weeks old. Nevertheless, pigs are large animals hereon difficult to caring and housing so that they are not widely used for cartilage repair studies [140, 141]. But minipig strains can be used instead of pigs. Although mini-pigs have smaller joint compare to humans, but cartilage defects by 6–8 mm in diameter can be created in their femoral condyles and the trochlear groove [132]. Gotterbarm et al. created osteochondral and chondral defects in the mini-pig and did not find complete spontaneous healing; thereby they established the utility of this strain for AC damage studies [126]. Chul-won used human umbilical cord blood-derived mesenchymal stem cells on a hydrogel-based scaffold to evaluate its efficacy in a minipig cartilage injury model and showed that articular surface of the defect site in the

transplanted knee was relatively smooth, and similar to that of the surrounding normal cartilage [142]. In another study, Christensen et al. used either autologous bone graft (ABG) or autologous dual-tissue transplantation (ADTT) to repair knee cartilage defect in Gottingen mini-pigs. Histological and radiological outcomes exhibited similar healing characteristics by two grafts in cartilage defect groups [143].

Sheep

Sheep are also utilized in cartilage repair models due to their advantages such as availability, easy handling, and inexpensiveness and are suitable for arthroscopic surgery [144, 145]. Sheep stifle joint can be used in surgical operations because it has similar anatomy to human like LCL complex, cruciate ligament, popliteus tendon, menisci, and popliteofibular ligament [78]. The depth of calcified and non-calcified cartilage is 542-707 µm and 275-698 µm, respectively [108] which are thinner than normal human MFC [113]. Sheep has a very dense and hard subchondral bone that requires drilling to create osteochondral defects [146, 147]. Different anatomical sites of the sheep stifle joint have different responses to OA damage. Orth et al. created osteochondral defects in the medial femoral condyle and the lateral trochlear facet in sheep, and suggested that the trochlear facet had better healing ability as compared to the femoral condyle [148]. New regenerative medicine procedures such as stem cell therapy and biomaterial scaffolds are commonly used in sheep cartilage damage models. Manunta et al. created surgical defects in the femoral condyle of the sheep knee joint and injected embryonic stem-like (EsL) cells to generate new cartilage. They found that 24 months after surgery, EsL-M transplantation improved histological evidence of cartilage repair [149]. In another study, Hooper et al. used Peripheral blood mononuclear cells, and Zorzi et al. implanted a scaffold contained human adipose tissue mesenchymal stem cells to improve healing in a sheep cartilage injury model and suggested that these cells can promote cartilage repair in the ovine model. [150,151]. The average cartilage defect induced in the distal femoral condyle of sheep is 7.4 mm in diameter (range 2-15), and 4 to 40 sheep have been used in studies and have been followed for 2 to 78 weeks [84].

Table 2 summarizes different animals used for AC regeneration.

4. Conclusions

All of the mentioned OA induction models have their advantages and disadvantages; indeed, there is no accurate similar model to human OA. Today, the studies are still ongoing to reach a more satisfactory conclusion. The progression of OA in animal models is different based on animal species. As an example, the progress of OA in rodents (mice and rats) is faster compared to the large animals (sheep and goats) [39]. Undoubtedly, utilizing an OA induction method in large animals is more time consuming and expensive than rodents [84]. Scientists usually prefer to use a more rapid OA induction model due to speed up the approval process of suggested treatments. It should be noted that each preclinical model can just simulate limited features of OA. According to this point, considering the strategies of each novel therapy is entirely essential to select an appropriate OA model.

Table 2. Animals used for AC regeneration.

Animals	Authors	Year	Study design
Mice	Ma et al. (Ma et al., 2007)	2007	Comparing the regenerative power of articular cartilage in male and female mice
	Majumdar et al. (Majumdar et al., 2007)	2007	Investigating the role of a disintegrin and metalloproteinase with thrombospondin motifs-4 and a disintegrin and metalloproteinase with thrombospondin motifs-5 gens in the induction of osteoarthritis in mice
	Fitzgerald et al. (Fitzgerald et al., 2008)	2008	Comparing the AC regeneration in MRL/MpJ and C57BL/ 6 mice
	Mak et al. (Mak et al., 2016)	2016	Investigating the beneficial effects of synovial mesenchymal stem cell transplantation in a mouse cartilage defect model
	Chang et al. (Chang et al., 2016)	2016	Investigating pathophysiology and molecular characteristics of ankle OA in C57BL/6 mice and comparing with humans
Rats	Bendele et al. (Alison Bendele et al., 1999)	1999	Establishing methods for inducing OA in rats
	Ferretti et al. (Ferretti, Marra, Kobayashi, Defail, & Chu, 2006)	2006	Using Polyethylene glycol hydrogels as a biocompatible scaffold in rat osteochondral defects
	Kamisan et al. (Kamisan, Naveen, Ahmad, & Tunku, 2013)	2013	Investigating the relationship between chondrocyte densities, protein content, gene expressions and cartilage thickness in rats, rabbits, and goats
	Katagiri et al. (Katagiri, Mendes, & Luyten, 2017)	2017	Investigating the role of surgical defect size in the cartilage healing
	Hu et al. (Hu, Yang, & Luo, 2017)	2017	Investigating the effect of collagen induced arthritis on the induction of arthritis in rats
Rabbits	Wei et al. (Wei & Messner, 1999)	1997	Investigating the age-related healing of full-thickness cartilage defects in the rabbit medial femoral knee condyle
	Wei et al. (Wei & Messner, 1999)	1999	Comparing spontaneous healing of osteochondral defects in the knee joints in immature and adult rabbits
	Han et al. (Han et al., 2003)	2003	Using optical coherence tomography for evaluation of rabbit AC repair after chondrocyte implantation
	Buma et al. (Buma et al., 2003)	2003	Comparing implanted cross-linked type, I and II collagen matrices into full-thickness defects in the femoral trochlea of adolescent rabbits

	Frisbi et al. (Frisbie et al., 2006)	2006	Comparing the thickness of non-calcified and calcified cartilages and subchondral bone plate in human, horse, goat, dog, sheep, and rabbit stifle joints
	Malda et al. (Malda et al., 2013)	2013	Comparing the AC thickness between rodents and mammalians
	Chevrier et al. (Chevrier, Kouao, Picard, Hurtig, & Buschmann, 2015)	2015	Comparing rabbit subchondral bone properties with humans, horses, and sheep
	Tang et al. (Tang et al., 2019)	2019	Implanting autologous bone-derived mesenchymal stem cells scaffolds into the rabbit cartilage defects after bone marrow stimulation.
Dogs	Shortkroff et al. (Shortkroff et al., 1996)	1996	Investigation the role of cultured autologous chondrocytes in chondral and osteochondral defects healing in a dog model
	Cook et al. (Cook et al., 2003)	2003	Using recombinant human osteogenic protein-1 to elicit the repair of osteochondral defects in dogs
	Feczkó et al. (Feczkó et al., 2003)	2003	Using different biodegradable materials for increasing tissue formation on the surfaces of the harvested holes in the dog knee joint by arthroscopy procedure
	Lee et al. (Lee, Grodzinsky, Hsu, & Spector, 2003)	2003	Implanting an autologous articular chondrocyte-seeded type II collagen scaffold in a canine chondral defect model
	Frisbie et al. (Frisbie et al., 2006)	2006	Comparing AC thickness in the stifle joints between dogs and human, horse, goat, sheep, and rabbit.
Goats	Butnariu-Ephrat et al. (Butnariu-Ephrat, Robinson, Mendes, Halperin, & Nevo, 1996)	*1996*	Implanting bone marrow-derived chondrocytes in a goat articular defect model for the regeneration of new articular cartilage.
	Jackson et al. (Jackson, Lalor, Aberman, & Simon, 2001)	2001	Investigating the spontaneous repair of full-thickness defects (6 mm diameter and depth) of AC in a goat model
	Brehm et al. (Brehm et al., 2006)	2006	Implanting scaffold-free, autologous cartilage constructs within superficial osteochondral defects created in the stifle joints of adult goats
	Nam HY et al. (Nam et al., 2013)	2013	Implanting autologous bone marrow-derived mesenchymal stem cells as a treatment for focal cartilage defect in goats.
	Patil et al. (Patil, Steklov, Song, Bae, & D'Lima, 2014)	2014	Comparing biomechanical and anatomical characteristics of human and caprine knee AC
	Levingstone et al. (Levingstone et al., 2016)	2016	Implanting a multi-layered collagen-based scaffold in the goat stifle joint for evaluating regeneration of functional osteochondral tissue

Horses	Litzke et al. (Litzke et al., 2004)	2004	Using autologous chondrocyte transplantation for repair of cartilage defect in a horse model over a period of 2 years
	Nixon et al. (Nixon, Fortier, Goodrich, & Ducharme, 2004)	2004	Using resorbable polydioxanone pins for arthroscopic reattachment of osteochondritis dissecans lesions in horses
	Strauss et al. (Strauss, Goodrich, Chen, Hidaka, & Nixon, 2005)	2005	Investigating the response of AC adjacent to chondral defects for implantation of genetically modified or unmodified cells in an equine model
	Murray et al. (Murray et al., 2007)	2007	Investigating the effect of exercise on subchondral bone thickness, hardness, and remodeling in horses
	Wilke et al. (Hopper et al., 2015)	2007	Implanting mesenchymal stem in articular defects for increasing chondrogenesis
	Malda et al. (Malda et al., 2012)	2012	Comparing osteochondral tissue characteristics between equine and human stifle joint
Pigs/mini-pigs	Vasara et al. (Vasara et al., 2006)	2006	Investigating spontaneous healing in immature porcine knee cartilage lesions with or without autologous chondrocyte transplantation
	Gotterbarm et al. (Gotterbarm et al., 2008)	2008	Establishing the utility of chondral defects in 6.3mm diameter for AC damage studies in the Gottingen mini-pigs
	Ha C-W et al. (Ha, Park, Chung, & Park, 2015)	2015	Investigating the use of human umbilical cord blood-derived mesenchymal stem cells on a hydrogel-based scaffold in a minipig cartilage injury model
	Christensen et al. (Christensen et al., 2015)	2015	Investigating the use of either autologous bone graft or autologous dual-tissue transplantation to repair knee cartilage defect in Göttingen mini-pigs
	Tomaszewski et al. (Tomaszewski, Wiktor, & Gap, 2019)	2019	Comparing the effect of the scaffold which supplemented with bone marrow and growth plate chondrocytes with empty scaffold in cartilage defects
	Tang et al. (Tang et al., 2019)	2019	Implanting autologous bone marrow-derived mesenchymal stem cells scaffolds into the minipig cartilage defects after bone marrow stimulation.
	Lu et al. (Burks, Greis, Arnoczky, & Scher, 2006)	2000	Investigating the effect of monopolar radiofrequency energy on partial-thickness defects of AC in sheep
	Jelic et al. (Jelic et al., 2001)	2001	Investigating the effect of osteogenic protein-1 on the regeneration of AC by creating knee chondral defects in sheep

Sheep	Burks et al. (Burks, Greis, Arnoczky, & Scher, 2006)	2006	Comparing a small osteochondral autograft plug with an untreated or a bone-grafted defect in a sheep articular defect model
	Benazzo et al. (Benazzo et al., 2008)	2008	Investigating the effect of pulsed electromagnetic fields on the integration of osteochondral autografts in sheep
	Patrick Orth et al. (Orth et al., 2013)	2013	Comparing osteochondral defects in the medial femoral condyle and the lateral trochlear facet in sheep
	Hopper et al. (Hopper et al., 2015)	2015	Investigating the ability of peripheral blood mononuclear cells for the improvement of healing in a sheep cartilage defect model
	Zorzi et al. (Zorzi et al., 2015)	2015	Creating partial-thickness defect in the medial femoral condyle of sheep and implanting Human adipose tissue mesenchymal stem cells for regeneration of AC
	Manunta et al. (Manunta et al., 2016)	2016	Using male embryonic stem cells in the treatment of osteochondral defects of the knee in an ovine model

In brief, there is no general consensus that which model and species are the most related and similar to human OA, because of the complexity and different etiology of human OA. Moreover, each animal model has its advantageous and disadvantages. Taken together, it seems that the spontaneous model of OA is most relevant to human OA but it is very time consuming and challenging to create. Chemical and surgical induced models of OA are very cheap, fast and intensive, and they are relevant to the traumatic form of human OA and not to degenerative form. Due to the existence of multiple animal OA models and also the differences between each model, it is essential that investigations must be continued to reach the ultimate conclusions and gold standard models.

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