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Review Article

Current advances in animal model of meniscal injury: From meniscal injury to osteoarthritis

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ABSTRACT

Meniscal injury is a prevalent orthopedic practice that causes articular cartilage wear and degeneration due to tissue damage or loss, and may eventually result in the occurrence of knee osteoarthritis (KOA). Hence, investigating the structural regeneration and mechanical function restoration of the meniscus after injury is pivotal research topic for preventing KOA. Animal models are essential for investigating therapeutic strategies for meniscal injuries and their clinical translation, yet no current model can fully recapitulate the complexity of human meniscal injuries. This review aims to categorize the prevalent animal models of meniscal injury by their establishment methods, elucidate their principles and procedures, and discuss the suitability and limitations of each model. We delineate the pros and cons of different models in simulating the pathology and biomechanics of human meniscal injury. We also analyze different animal species regarding their meniscal structure, function, and repair potential, and their implications for model selection. We conclude that selecting an appropriate animal model requires a comprehensive consideration of various factors, such as research aims, anticipated outcomes, and feasibility. Furthermore, to translate novel therapeutic approaches to clinical applications more safely and effectively, future model development should emphasize aspects such as choosing animals of suitable age.

The Translational Potential of this Article: This review aims to categorize and discuss current animal models of meniscal injury by establishment methods and provides a comprehensive overview of the routinely employed experimental animals in each model to facilitate the clinical translation of OA-related research.

1. Introduction

The meniscus is a wedge-like fibrocartilage located between the tibial plateau and the articular surfaces of the femoral condyles [1]. As a smooth, lustrous, tough, and elastic fibrocartilage structure, it has superior load transfer and shock absorbing abilities, which alleviate the excessive stress on the articular cartilage [2]. Moreover, it contributes to limiting knee joint over-extension or over-flexion, promoting synovial circulation and lubrication of joints, and thus enhancing joint stability [2].

The meniscus plays such an important role in the joint function, partly because its constituents have unique physical and chemical properties that enable it to withstand various stresses generated by joint motion [2]. On the other hand, it is because its cells and extracellular matrix (ECM) are arranged in a specific way that allows optimal distribution of compressive stress, shear stress, circumferential stress, and hoop stress, thereby protecting the articular cartilage and bone [2,3]. For example, the inner region is mainly composed of glycosaminoglycans and type II collagen (COL-2), whereas circumferentially aligned type I collagen is predominantly located in the outer region [4]. Therefore, the inner two-thirds of the meniscus exhibits cartilage-like properties to resist compression, while the outer one-third allows the tissue to convert compressive stresses in the knee joint into circumferential hoop stresses, thereby preventing rupture or extrusion [4,5]. Consequently, the knee meniscus has anisotropic tensile properties, meaning that it exhibits different mechanical properties when tested in circumferential versus radial directions [6,7].

Given that the meniscus plays a crucial role in distributing stress and

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stabilizing the knee joint, it endures complex mechanical stresses during flexion, extension, rotation, and weight-bearing activities [8]. Especially in a flexed knee position, the meniscus is subject to significant shear and compressive forces, increasing the risk of injury [8]. The meniscus is thicker at the periphery and thinner at the inner edge, with a triangular cross-section. This structure makes the inner edge more susceptible to tears under load [9]. Additionally, the central portion of the meniscus (the white–white zone) lacks blood supply and relies on synovial fluid for nutrition, resulting in poor healing capacity. This vascular characteristic further increases the susceptibility of the central portion to injury. Furthermore, the medial meniscus is relatively more fixed and less mobile, making it more prone to stress and shear forces during knee joint movements, thereby increasing the risk of damage [9].

Meniscal injury is a common occurrence in orthopedic practice, and damage or loss of meniscal tissue can result in pain and knee joint dysfunction, often necessitating meniscectomy [10]. Although some studies have shown that partial or total meniscectomy can alleviate pain and eventually restore function, it also leads to increased joint loading and articular cartilage degeneration, resulting in osteoarthritic changes and long-term functional impairment in the knee joint [11,12]. The association between meniscal degeneration and cartilage histopathology suggests that osteoarthritis (OA) is a concomitant disease of both the cartilage and the meniscus in the context of meniscal injury [13](Fig. 1). At the cellular level, under the abnormal stress caused by meniscal injury, articular chondrocytes undergo aberrant maturation via a pathway similar to endochondral ossification, leading to the onset and progression of OA [14,15]. Inducing meniscal injury in animals under experimental conditions is a common method to establish experimental OA models, and some studies have observed human patients and found that meniscal tears or extrusion are also associated with OA progression [16,17].

There are multiple pathogenic factors related to OA, and most cases of OA are evidently associated with early joint injury [18]. Therefore, animal models of OA induced by meniscal damage are increasingly used for early OA research, which are characterized by mechanical alterations that cause joint instability, and thus potentially damage the articular cartilage surface by creating abnormal loads [6,18–21]. Each type of animal model has advantages and limitations in terms of cost, time, reproducibility, risk, and its reflection of human pathology [22,23]. Within this translational framework, both small and large animal models are essential alternatives for investigation [24]. However, there are significant differences in the metabolic processes between animals and humans, which may affect the time-dependent changes of tissue remodeling. Moreover, a controlled postoperative rehabilitation or relative limb immobilization cannot be performed in animal models, which can be done in human patients [25]. Therefore, the absolute values from animal studies cannot be directly translated to humans, and most people believe that large animal models are the next step for translation, but there is still no consensus on which large animal is the gold standard for meniscus research [26]. Although there is no perfect model yet, creating models that accurately and quantitatively mimic the human OA features is still an interesting research question.

Considering that there are many meniscal injury models currently used for research, but few researchers have classified and introduced them according to their establishment methods, this review will introduce and discuss the characteristics, establishment methods, and commonly used experimental animals of different models (Table 1). Overall, we will focus on the meniscal punch model, suitable for tissue-engineering studies; the meniscal resection model, used to explore post-meniscectomy regeneration strategies; and the meniscal longitudinal tear and tibiofemoral joint (TFJ) impact models, which simulate common clinical injuries. In summary, due to the close association between meniscal injuries and the onset and progression of KOA, this review aims to offer researchers valuable guidance in selecting appropriate animal models for studies focused on protecting joint cartilage through meniscal repair.

2. Meniscal punch model

2.1. Conventional punch model

The punch model disrupts the integrity of the meniscal tissue, both in the medial and lateral meniscus, resulting in meniscal damage due to abnormal mechanical stress on the knee joint, which increases the articular cartilage wear and risk of OA [20,27–31]. Many studies have shown that the lesioned part of the punch model is only partially filled with fibrous scar tissue or poorly filled, and tears can often be detected, which is similar to the clinical outcome after meniscal injury [28].

Tissue-engineered meniscus is currently regarded as a long-term therapeutic strategy to address meniscal regeneration, which aims to recapitulate the characteristics of native tissues and to enhance their survival in the biomechanical environment of natural knee joints [32]. Although the meniscal punch model lacks the intense mechanical challenges that occur in severe meniscal tear injuries, the defects in this model are completely surrounded by meniscal tissue and receive mechanical protection [20] (Fig. 2). Therefore, this model is particularly suitable for the regenerative repair of tissue-engineered meniscus, as it allows the quantitative assessment of defect bridging and the quality of the tissue within the defects [20]. Furthermore, since most current studies employ a single full-thickness punch model, this approach

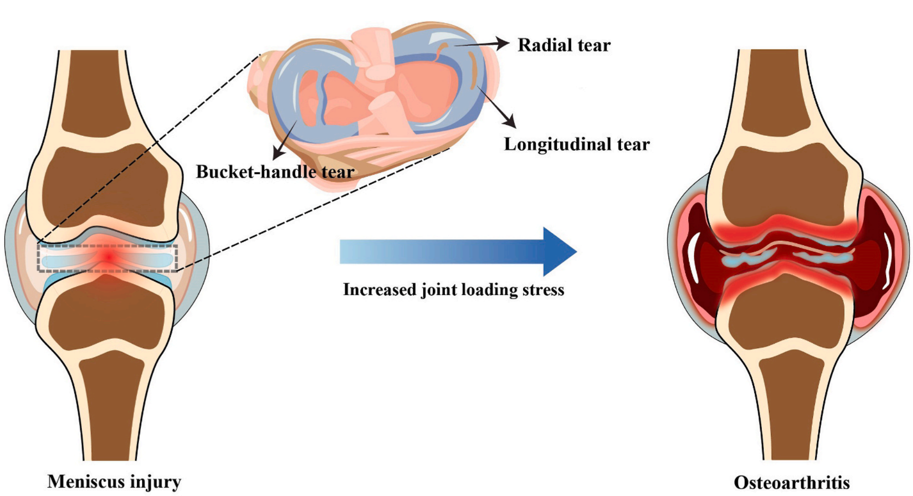

Fig. 1. Meniscal Injury and Osteoarthritis. Meniscus injury is a common occurrence in knee joint injury, and increased joint loading stress occurs after meniscus injury, which ultimately leads to the development of osteoarthritis.

Table 1
Summary of animal models.

Model	Site	Size	Animal
Meniscal punch model	Anterior horn of MM	1.5 mm in diameter	Japanese white rabbit [20], New Zealand White rabbit [30, 36]
	Anterior horn of MM	2 mm in diameter	Japanese white rabbit [25], New Zealand White rabbit [34]
	Anterior horn of MM	3 mm in diameter	New Zealand White rabbit [38]
	Anterior horn of LM	1.5 mm in diameter	New Zealand White rabbit [31]
	Body of LM	2 mm in diameter	New Zealand White rabbit [27–29]
Meniscal longitudinal tear model	Body of MM	4 mm in length	New Zealand White rabbit [174]
	Body of MM	5 mm in length	New Zealand White rabbit [37]
	Junction of the anterior horn and body in MM	4–5 mm in length	Minipig [13]
	Junction of the anterior horn and body in MM	15 mm in length	Merino sheep [95]
Meniscal resection model	Anterior third portion of MM	—	Japanese white rabbit [129]
	Anterior half of MM	—	Lewis rat [97,100–103], Japanese white rabbit [21], New Zealand White rabbit [130], Mexican hairless pig [98], Cynomolgus macaque [107]
	Posterior horn of MM	—	New Zealand White rabbit [132]
	Body of LM	—	New Zealand White rabbit [131]
	Total MM	—	New Zealand White rabbit [134,136], Dorset finn cross sheep [137], Bergamasca–Massese sheep [92,175]
	Total MM/ACL	—	SpragueeDawley rat [141], Siamese long tail sheep [144]
TFJ impact model	Posterior aspect of the medial femoral condyle	—	New Zealand White rabbit [132]
	Proximal tibia	—	Flemish giant rabbit [151]
	Distal femur	—	Flemish giant rabbit [19,59, 148]
Meniscal extrusion model	MM	—	Lewis rat [160]
Meniscal puncture model	Posterior half of MM	—	Microminipig [166]

Abbreviation: ACL: anterior cruciate ligament; LM: lateral meniscus; MM: medial meniscus; TFJ: tibiofemoral joint impact model.

generates stable and highly reproducible injuries while minimizing side-to-side differences and the confounding variables associated with suture regeneration attempts. Considering its standardization and good reproducibility, it has been used as a common model for creating meniscal injuries in some studies [20,27,28].

Mice and rats, as rodent models, are extensively used in biomedical research due to their fully sequenced genomes, which allow for various genetic engineering techniques to create conditional gene knockouts or overexpressions, thereby generating specific disease models. However, it must be acknowledged that their inherent regenerative potential may limit the direct translation of these research findings to clinical applications (Fig. 3). Large animal models, such as pigs and goats, which have physiological conditions and knee joint sizes similar to humans, are difficult to ensure sufficient sample size due to high surgical costs and complexity [33]. Although rabbit menisci are smaller than human menisci and have different loading cycles in their knee joints, rabbits have limited intrinsic regenerative potential of their menisci compared to small rodents, and their maintenance cost is much lower than that of large animals [34]. To improve the experimental reproducibility and comparability, as well as to enable quantitative and qualitative cross-comparison of the research outcomes from different teams, the use of rabbit meniscal punch can serve as a quantifiable and standardized injury model [35,36] (Fig. 3).

To minimize the harm to animals and to better mimic the clinical practice, the medial parapatellar approach is the most commonly chosen approach for establishing this model [20,30]. In order to expose the area to be punched, it is also necessary to dislocate the patella laterally [20, 30]. After sufficient exposure, a biopsy punch can be used to create the defect [20,30]. One point worth noting is that before punching, it is necessary to ensure that the meniscus has enough size to create the designed cylindrical defect, and to maintain the integrity of the meniscal rim at the same time. Although meniscal injuries are more common on the medial side in clinical settings, some surgeons also consider the less frequent lateral meniscal injuries, and thus they often choose to expose the lateral joint compartment by performing a lateral parapatellar arthrotomy, in order to perform a punch on the lateral meniscus (LM) [27–29]. Given that previous studies have reported that long-term inactivity has a detrimental effect on meniscal healing, most researchers do not impose any restriction on rabbits after modeling [37, 38].

Zellner et al. [27]created circular defects in the lateral menisci that were filled with fibrous tissue after 6 and 12 weeks, and some samples also showed tears oriented toward the meniscal rim. This confirmed the previous findings on meniscal defects, which showed that untreated injuries did not heal but rather resulted in pathological repair comparable to the human [28,29]. Additionally, Zellner et al. [29] found that the medial compartment of the knee joint showed early OA changes after 3 months of establishing the punch model, including cartilage wear, cartilage defects and surrounding cartilage softening, and osteophytes, which are a sign of early degenerative changes, were also mainly distributed in the medial compartment. In summary, these demanding early OA conditions in the model provide further evidence for the model's applicability in a clinical context, and therefore the animal model described here is considered suitable for evaluating the regenerative potential of therapeutic approaches after meniscal injury.

Notably, the limited size of small animal knee joints and the constraints of current imaging technologies make it challenging for rodents and rabbits to meet the requirements for quantitative assessment of meniscal degeneration and related chondral damage, as well as for validating the outcomes of meniscal implantation surgeries [39]. Rabbit meniscal cells are more abundant than human ones, thus it is not surprising that rabbit menisci have a greater spontaneous healing potential than human menisci [5]. Moreover, the small size and low weight of rabbits result in different surgical conditions and knee joint forces, which require consideration of interspecies differences when analyzing the experimental outcomes [5].

2.2. *Punch model of avascular zone*

Since meniscectomy increases the risk of knee OA (KOA), meniscal suture repair is recommended as the preferred surgery for meniscal tears, but only for the vascularized regions of the meniscus [40]. Capillaries from the lateral and medial geniculate arteries only penetrate 10–30 % and 10–25 % of the width of the medial and lateral menisci, respectively, so most of the meniscal regions cannot be sutured due to the lack or scarcity of blood vessels [40,41]. Given that most regions of the meniscus have limited or no capacity for spontaneous healing and cannot be sutured, the repair of avascular or minimally vascularized areas has long been a research focus. Compared to other models, such as

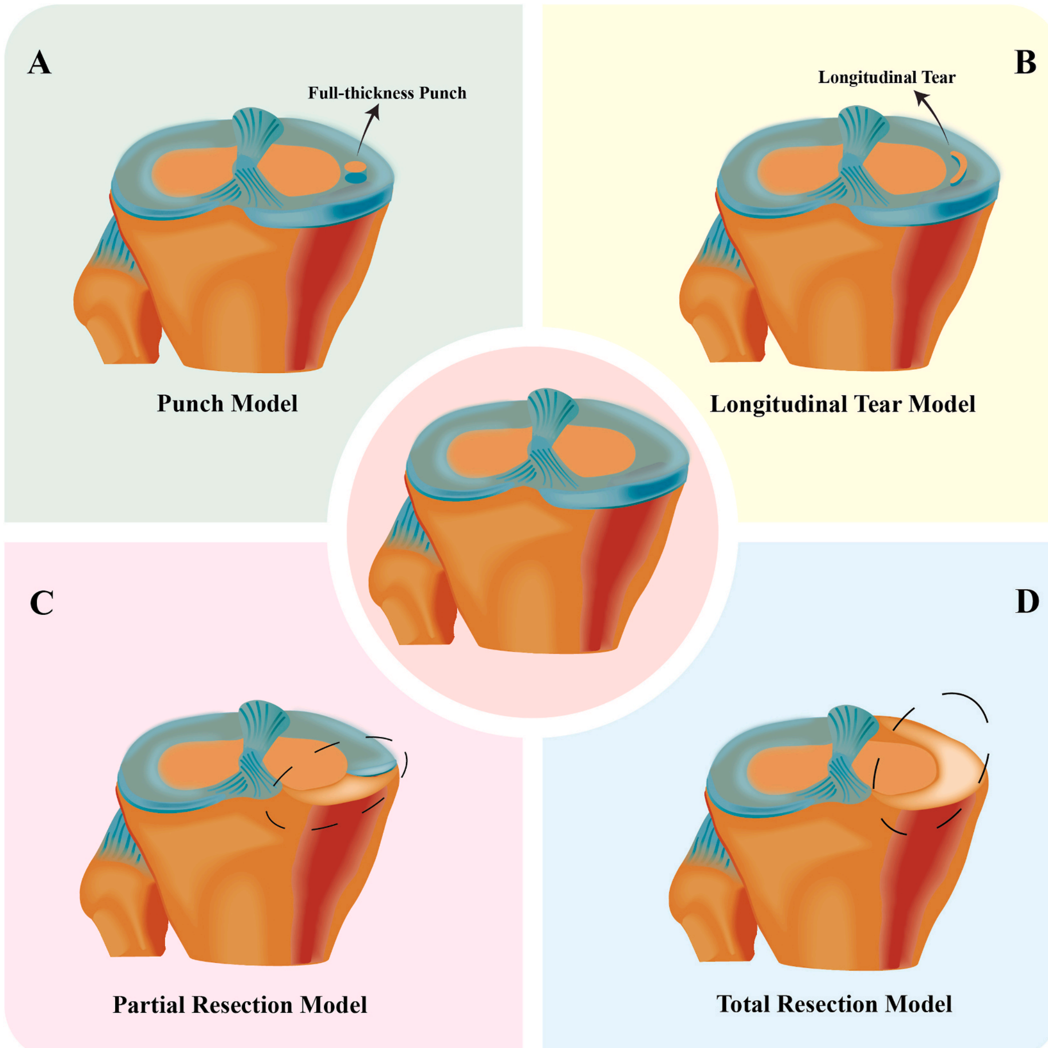

Fig. 2. Surgical modeling animal model. A. Meniscal punch model; B. Meniscal longitudinal tear model; C. Partial meniscal resection model; D. Total meniscal resection model.

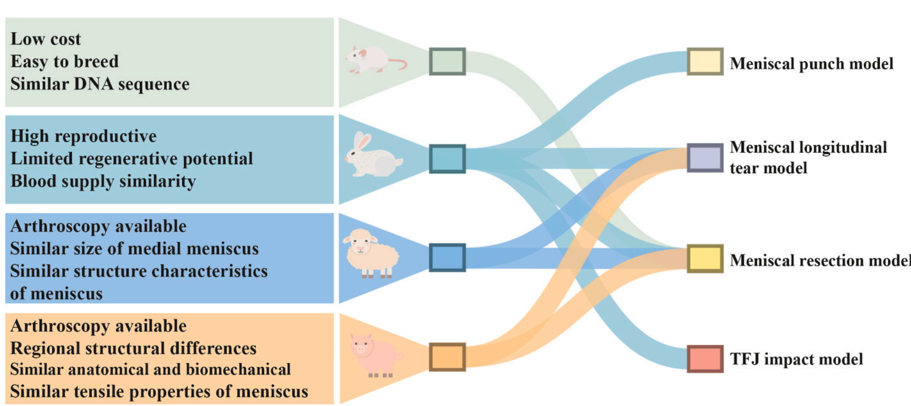

Fig. 3. Main advantages of animal used in meniscal injury model. The left side of the figure shows the main advantages of each animal, while the right side shows the common models corresponding to that animal. Abbreviation: TFJ: tibiofemoral joint impact model.

the meniscal resection model discussed later, the punch model offers a significant advantage: it allows precise control over the damage location within the avascular region. In contrast, other models inevitably cause damage to both vascular and avascular regions.

Abpeikar et al. [35] prepared a cylindrical full-thickness defect with a diameter of 2.0 mm in the avascular part of the anterior horn of the medial meniscus (MM) using a biopsy punch, after exposing the anterior horn of the MM completely by dislocating the patella and excising the medial collateral ligament, to explore the regeneration conditions of the meniscal avascular region [35]. Similarly, the punch model established by Zellner et al. [27] showed that, like untreated human menisci, untreated avascular defects did not exhibit any healing tendency. Moreover, the healing capacity of the anterior horn of the rabbit meniscus is lower than that of the posterior horn, which is consistent with the human meniscus [42,43]. Therefore, to better characterize the difference in meniscal healing capacity, most models design the damage location near the anterior horn [42,43]. In both New Zealand rabbits and humans, blood vessels penetrate the meniscal periphery from the joint capsule and ligaments, forming a network of penetrating vessels. Consequently, the inner edge of the meniscus has minimal blood supply and primarily relies on nutrients from the synovial fluid for metabolism. To reduce variability in experimental outcomes and better mimic clinical conditions, Deng et al. [42] excised the blood supply and synovium surrounding the meniscus in the knee joint. This approach aimed to minimize inflammatory responses and the influence of blood supply on the meniscal healing environment. Therefore, after establishing a full-thickness defect model of the avascular anterior horn of the lateral meniscus, they could better evaluate the movements after procedure by observing whether there were any gait abnormalities such as limping [42]. In summary, although there are structural differences between rabbit and human meniscus, the blood supply and structural characteristics of rabbit meniscus make their healing process after avascular damage similar to that of humans. Therefore, rabbit meniscus is also considered as a suitable model that can clearly reflect the impact of interventions in the avascular region of the meniscus on the intrinsic meniscal regeneration [42,43] (Fig. 3).

Although the meniscal punch model allows for precise control over the location and size of defects, it is undeniable that the injuries it induces in both avascular and vascular regions of the meniscus differ significantly from the irregular tears commonly seen in clinical settings. Therefore, the clinical relevance of this model is limited. However, based on its economic and controllable features, the meniscal punch model is beneficial for the development of tissue-engineered meniscus to prevent OA, as well as other studies related to promoting meniscal injury repair, as it facilitates comparison and validation among multiple studies.

3. Meniscal longitudinal tear model

One of the most common meniscal tears in individuals frequently engaged in sports or physical labor is the vertical longitudinal tear [44]. These vertical longitudinal tears extend parallel to the circumferential fibers of the meniscus, often resulting in a more stable tear pattern due to their partial retention of load transmission and shock absorption functions [45] (Fig. 2). The biomechanical changes and degenerative alterations induced by this pattern resemble the pathophysiological changes seen in early OA. In contrast, radial meniscal tears perpendicular to the circumferential fibers disrupt the integrity of the meniscus along its natural load-bearing direction, leading to more significant loss of function and stability. Indeed, many research groups have utilized the vertical longitudinal tear model in vitro and in large animal biocompatibility assessments, investigating various meniscal injury regeneration strategies based on scaffolds and surgical repair [46–49]. Clinically, longitudinal tears are more commonly associated with OA development, making this model particularly suitable for translational research. In summary, due to its biomechanical relevance, poor healing response, and clinical correlation with OA, the longitudinal tear model offers significant advantages for studies related to OA resulting from meniscal injury.

3.1. Meniscal longitudinal tear and load transmission

When the longitudinal tear injury is small, the resulting degenerative changes in the joint are very minor, and thus do not immediately affect the joint movement significantly. For example, Bansal et al. [13] found that the surgical-induced tear injury persisted for six months, but obvious degenerative changes such as macroscopic abrasion, meniscal Safranin-O content change, and cartilage tissue pathological change were observed only after six months. Therefore, these minor injuries do not require immediate repair in clinical practice, and they are less likely to progress to more complex bucket-handle tears [13,50]. However, over time, the initially minor injuries may expand, leading to larger and more complex tears or even complete tissue rupture, which will immediately alter the joint mechanics and cause pain and functional impairment [51,52]. Although longitudinal tears tend to have better clinical outcomes than other types of tears, they can also cause mechanical perturbations in the joint, especially when the tear is large. Regarding the peak contact pressure on the tibial plateau, the posterior horn with a small (<1.5 cm) longitudinal tear showed no change, but the large (>2.5 cm) longitudinal tear significantly increased the peak contact pressure [53,54]. In addition, a large longitudinal tear in the body of the meniscus also resulted in decreased strain in the anterior horn.

When more severe conditions occur, such as abnormal activities that cause a longitudinal tear to develop into a bucket-handle tear that may get stuck in the joint space, more serious cartilage damage will ensue [55]. In fact, it has been reported that longitudinal tears have little impact on contact mechanics, whereas bucket-handle tears have a greater impact, which also indicates that early vertical longitudinal tears do not immediately cause an unstable mechanical environment, but the damaged meniscus itself, including the fractured edge or subsequently formed free meniscal fragments, will cause secondary damage to the already degenerated cartilage [56,57]. Collectively, small meniscal longitudinal tears have little impact on the pathology and mechanics of the meniscus. However, they may lead to abnormal or increased load distribution in the meniscus, or both, if they are not treated timely or healed properly. Therefore, further studies are needed to explore the natural course of this injury type under controlled conditions and the related articular cartilage damage [13,45].

3.2. Longitudinal tear model of rabbit

As mentioned earlier, rabbits are widely used as experimental animals in the punch model, and they are also frequently used in the vertical tear model [28,58] (Fig. 3). Researchers exposed the knee joint in a rabbit model by performing a medial parapatellar arthrotomy and laterally dislocating the patella [37,58]. To ensure a clear view and minimize interference with the articular cartilage, they flexed the knee to approximately 90° and used micro forceps or a surgical hook to pull the meniscus anteriorly by about 5 mm, until the anterior edge of the meniscus was clearly exposed [37]. They then created a full-thickness longitudinal tear in the body of the MM, starting from the anterior horn and extending to the posterior horn. The tear was precisely located in the central portion of the meniscus, near the avascular zone, known for its poor healing capacity [9,58]. The length of the tear was approximately 5–6 mm, ensuring sufficient damage to evaluate the effectiveness of subsequent treatments [37,58].

Huang et al. [45] established a MM longitudinal tear (MMLT) model of approximately 2 cm in the MM body of rabbits to study the early degenerative changes of OA after meniscal injury. Their results showed that the MMLT model indeed exhibited early OA changes and that their severity increased in a time-dependent manner [45]. Specifically, MMLT resulted in significant cartilage fibrosis at 4 weeks after procedure, MM bucket-handle tear at 6 weeks, and full-thickness cartilage ulceration at 9 weeks, with some cases exhibiting free meniscal fragments [45]. Using a modified Mankin scoring system for quantitative histomorphological evaluation, Kurnaz et al. showed that the progression of lesions in the MMLT model was also time-dependent and similar to the macroscopic grading of degeneration [37,45]。

ACLT can alter joint kinematics by transecting the ACL, leading to meniscal and articular cartilage damage [59]. Previous studies have shown that animals with ACL rupture induced by TFJ impact have some meniscal lesions, among which complex longitudinal tears are the most common [59]. However, evidence suggests that the joint kinematic changes induced by ACLT play a minor role in the development of OA, compared with acute joint structural injuries such as meniscal tears, joint surface fractures or cartilage injures [45,60]. Compared with ACLT, the gross morphology after MMLT procedure showed large and long tears in the MM, as well as typical bucket-handle tears, and even partial detachment of the meniscus from the main body, resulting in free meniscal fragments [45]. As the damage progressed, MMLT procedure resulted in more severe cartilage degeneration in the medial femoral condyle (MFC) than ACLT, and exhibited higher levels of catabolic gene expression [45]. In addition, some studies have observed the loss of collagenous tissue and the decrease of cell density after longitudinal tear procedure, suggesting that longitudinal tear model can better reflect the clinical meniscal injury and induce reproducible degenerative joint changes within a reasonable time frame [59].

3.3. Meniscal longitudinal tear model of large animal

It is widely accepted that new technologies and surgical interventions for meniscal injury repair need to be evaluated in large animal in vivo systems before clinical trials [61]. These models have played a crucial role in advancing our understanding of the injury and disease processes, and can be used to optimize candidate therapeutic approaches and ensure the safety of these interventions before human clinical trials [62,63]. For example, in the field of articular cartilage repair, there are guidance documents that provide a standard to help researchers conduct best practice experimental studies using these large animal models and achieve better clinical translation [64]. Moreover, compared with small animal models, large animal models not only increase clinical translation by providing for increased spatial resolution, but also allow the creation of injuries using arthroscopic approaches, which reduce the detrimental effects of open surgery on the joint [65–67] (Fig. 3). Open surgery can lead to increased joint bleeding and inflammation, as well as excessive changes in the synovial environment, and may result in noticeable gait perturbation caused by open surgical trauma within a few weeks after surgery [68]. In contrast, interventions performed by arthroscopy are well tolerated, and thus can be performed bilaterally without compromising animal health (reducing animal numbers). Additionally, studies have found that open surgery can alter the homeostasis of the entire joint in cartilage biopsies, which also emphasizes the necessity of performing minimally invasive surgery as much as possible [69]. Therefore, minimally invasive large animal models created by arthroscopy are more clinically relevant, as they can better preserve the other normal tissues while reducing the joint homeostasis by altering the joint load transfer due to meniscal tears, and can more accurately study the cartilage degeneration under reduced confounding factors [13,66,67].

3.3.1. Longitudinal tear model of pig

Animals with meniscal tears usually have higher body weight, a finding that is closely related to the clinic and supported by a previous case–control study, which showed a significant association between increased body mass index and meniscal surgery in both men and women [70]. The prevalence and economic impact of meniscal longitudinal tear injuries have prompted researchers to create new regenerative solutions, and they must also extensively test these new technologies in large animal models prior to clinical trials. Previous studies have characterized the meniscus of human and farm pig, and have also attempted to fabricate tissue-engineered meniscus using cattle cells, but farm pigs and cattle may not be suitable for preclinical studies due to their large body weight differences from humans [71,72]. An emerging large animal model is the minipig, which has been proposed as a potential model that can be incorporated into future meniscus repair guidance documents [73] (Fig. 3). Among the minipig, the Yucatan breed is frequently used for biomedical research, and is becoming increasingly popular in orthopedic and musculoskeletal research [74,75].

A suitable animal model should have a similar physiological structure to humans and a docile temperament for postoperative care. First, minipigs are suitable for long-term studies, as they have a smaller body size compared with animals such as farm pigs, which reduces the requirements related to handling, surgery, anesthesia, and food [76]. Although pigs are quadrupeds, their knee joints have high anatomical and biomechanical similarity to humans, and have also been approved by the FDA as preclinical models for intra-articular ligament repair safety and efficacy studies [77–79]. Second, the physiology of the central nervous system physiology in minipig is quite similar to that of humans, particularly in studies involving neural regulation and pain perception [80,81]. This similarity allows researchers to more accurately assess the pain and functional impairment caused by meniscal injuries and OA, as well as to test corresponding treatments [80,81]. Third, the meniscus of adult pig has been shown to have similar cell density, collagen structure, and vascularization pattern to human [39,82]. Studies on the overall morphological characteristics of the minipig meniscus revealed that the regional width and peripheral height of the minipig meniscus were comparable to human [6]. Further studies on the biomechanical properties of the meniscus, which are essential for its function, found that the circumferential and radial tensile properties of the minipig and human menisci were also similar [6]. Moreover, human chondrocyte has higher similarity to pig than to sheep or horse chondrocyte in terms of cartilage structure and ECM synthesis [83]. Specifically, the joint cartilage of minipigs exhibits a layered structure similar to that of humans, including the superficial, transitional, deep, and calcified zones [84,85]. Additionally, when cultured in vitro, minipig chondrocytes demonstrate similar behavior to human chondrocytes in synthesizing and secreting matrix components, and they respond comparably to mechanical loading and inflammatory stimuli [83,85,86]. Therefore, many studies have suggested that minipig, such as the Yucatan breed, can serve as animal models for studying meniscus and articular cartilage injuries [5,80,87] (Fig. 3).

The posterior region of the MM is more prone to longitudinal tears in the clinic than the anterior region [88]. It has been suggested that this is because the posterior region of the human MM bears a greater load than the anterior region, thus experiencing higher radial stress, leading to longitudinal tears [88]. Previous studies have demonstrated regional variations in the mechanical properties of the meniscus in various species, such as cows, rabbits, and baboons [88,89]. Therefore, considering that the human meniscus also exhibits regional differences in its mechanical characteristics, Gonzalez-Leon et al. [6] investigated the regional variations in the mechanical properties of the minipig meniscus. It was found that the radial stiffness of the posterior region of the MM was significantly lower than that of the anterior region, indicating that the meniscus was more susceptible to injury in the posterior region [6]. The regional structural differences in the density or thickness of the radially oriented collagen fibers of the meniscus also supported the above mechanical data [6,88]. In summary, by analyzing the structure–function relationship of the minipig meniscus native tissue, it is found that compared with other regions of the MM, the posterior region has a higher degree of anisotropy, less cross-linked collagen, and lower radial tensile properties [6,88] (Fig. 3). Therefore, although there is currently no data on the occurrence of meniscal tears in minipig, existing data indicate that the posterior region of the meniscus has lower mechanical properties, and these findings are consistent with the reports of more damage in the posterior region of the human MM, suggesting that minipig as large animal models have clinical relevance [6,88].

Similar to rabbits, the knee joint of minipig requires a medial parapatellar arthrotomy to expose the entire MM by transecting the medial collateral ligament, allowing maximal flexion and external rotation of the knee joint [6,13,90]. Subsequently, a full-thickness longitudinal tear can be created at a designated location using tools such as a biopsy punch or a scalpel [6,13,90]. Benefiting from the use of a large animal model, a full-thickness defect can be ensured by inserting a right-angle probe into the lesion and piercing through the articular cartilage. A rigorous multi-scale (from macroscopic to tissue level) and multi-modal (histological, transmission electron microscopy, MRI, mechanical) quantitative analysis confirmed that the meniscus and cartilage of minipig underwent persistent degenerative changes after inducing a meniscal longitudinal tear [13,90]. In summary, considering the similarity of the mechanical properties and structure of the minipig meniscus to those of human, as well as the advantages of requiring less resources for surgery and handling, and changing less over a study's period, minipig has been widely used as large animal models to translate therapeutic strategies for meniscal injuries.

3.3.2. Longitudinal tear model of sheep

In studies of meniscal injury repair using larger and more expensive animals, dogs were a common animal model in the early days, but sheep seem to be a more accepted model in recent years [26,91,92]. A study that surveyed the large animal models widely used for meniscal repair found that the number of sheep used for meniscal injury repair research doubled from 2013 to 2017, while the use of dogs declined [26]. Some structural features of the human meniscus are crucial for meniscal repair, such as vascularization pattern, cell density and collagen ultrastructure, especially the vascularization pattern, which may fundamentally and significantly alter the meniscal healing process [93] (Fig. 3). The sheep meniscus has a high similarity to the human meniscus in terms of vascularization pattern, cell density, lamellar collagen structure and cross-sectional size [5]. Therefore, from the perspective of meniscal structural features, sheep has a significant advantage as animal model for meniscal repair, and this has practical implications for meniscal injury surgical model [5].

For sheep, a large animal, researchers usually choose a medial parapatellar incision extending from the distal femur to the distal end of the tibial tuberosity, and expose the knee joint by opening the joint capsule on the medial side of the incision [94]. After subluxating the patella laterally, the MM is fully exposed, and a defect can be created at a specific location [94–96]. Also benefiting from the larger size of the sheep knee joint, some specially developed instruments can be used to create full-thickness longitudinal tears, such as the one used by Duygulu et al. [94] with a 3 mm gap between a number 12 blade and a Kirschner wire. The final result showed that the tears created by this method were more regular, and the length and position were more consistent, thus reducing the experimental variability and improving the reproducibility and comparability of the experiments [94].

4. Meniscal resection model

The meniscal resection model is a common animal model for studying the conditions of meniscus regeneration after resection, such as the models established by partial meniscectomy in rat, rabbit and pig, which can demonstrate the effectiveness of treatment methods, such as promoting meniscus regeneration [21,97,98](Fig. 2). The current meniscal resection models mainly include partial and total resection, and the partial resection can be either anterior or posterior portion depending on the type of study [21,99–104].

Okuno et al. [97] established a MM resection model by resecting only the anterior half of the MM at the level of the medial collateral ligament and preserving the posterior half of the MM. Although the total resection model may be more popular, the meniscal injury model after total resection seems to have high invasiveness and complexity [105]. In the anterior half resection model of the MM, the medial collateral ligament can be preserved, which means that this model can be established with low invasiveness and high reproducibility [97,106,107]. However, since meniscal injuries often occur in the posterior portion, or the posterior third, it is necessary to establish a corresponding meniscal injury model for research. Previous studies have achieved the implantation of fascia tissue and exogenous fibrin clot in complex meniscal tear models [108]. Therefore, we believe that using Henning et al.'s posterior medial approach arthroscopic assisted technique can establish an animal model that is closer to the clinical situation of the posterior portion of the MM injury [108]. Moreover, the intrinsic healing capacity of human meniscus has been proven to be lacking in the inner third and very limited in the middle third, which is undoubtedly due to the vascular distribution of the meniscus. Although we emphasized earlier that the punch model can precisely create defects in the avascular zone of the meniscus, thus better studying the regeneration conditions of the meniscus avascular zone. Although we have emphasized that the punch model can precisely control the defect in the avascular region of the meniscus, which facilitates the study of the regeneration conditions of the avascular region of the meniscus, the meniscus is often damaged in both the avascular and vascular regions in clinical settings. Therefore, the meniscus resection model is required for exploring the healing conditions of this type of meniscal injury. In summary, although this model simulates the limited pathological conditions of meniscal lesions, many studies have demonstrated its effectiveness for investigating new therapeutic methods for meniscal regeneration after resection [21,99,106,109].

However, it is worth noting that although meniscal resection leads to some degenerative changes due to reduced absorption function, it cannot fully simulate the biomechanical environment of human PTOA, because most PTOA cases are caused by the combination of ACL rupture and meniscal tear [45,110,111]. Therefore, some researchers have suggested that this model is not suitable for studying PTOA [45,110,111]. However, clinical studies have shown that meniscal often occur as degenerative changes in patients over 60 years old, but in younger patients, they are more often traumatic [112]. Hence, the resection model has been proposed by some researchers as a more suitable approach to investigate the traumatic injuries in young patients [113]. When the knee joint suffers mild trauma, it may result in isolated meniscal injury without ligament damage. This population may not show clinical symptoms for a long time after the injury, but the meniscus function in load distribution, shock absorption and maintaining knee joint stability may be compromised due to the damage. When the meniscus loses its ability to absorb and distribute joint load over a long period, the surface contact area of the TFJ decreases, leading to increased stress on the femoral and tibial cartilage, which also causes PTOA. Thus, the resection model may also be relevant for some cases of PTOA resulting from mild trauma. Moreover, some studies have demonstrated that the pathological changes elicited by MM resection are milder than those induced by ACLT, which is consistent with the clinical finding that OA often arises from chronic wear leading to degenerative changes [45,114]. The use of this model may therefore highlight the importance of preventing joint degeneration and osteoarthritis.

However, the resection model also has some limitations. For example, in clinical situations, the knee joints of patients who have symptoms after meniscectomy usually lack sufficient space. This is mainly due to the contraction of the surrounding ligaments and muscles after meniscectomy, which narrows the joint cavity space. Consequently, the increased joint wear and pain result from the increased TFJ contact stress after meniscectomy. Nevertheless, in many studies related to the meniscal resection model, researchers often inject drugs or implant cell scaffolds for treatment into the joint cavity after resection, suggesting that the space of the meniscal resection is still maintained [98].

4.1. Meniscectomy and KOA

Despite its well-known adverse effects, total or partial meniscectomy is still the most common strategy for treating meniscal injuries, especially in the avascular region [115,116]. Subsequent studies have demonstrated that preserving as much meniscal tissue as possible significantly alleviates postoperative pain and maintains knee joint stability, thus recommending partial meniscectomy over total meniscectomy [117]. In fact, whether partial or total meniscectomy, the area of direct contact between the femur and tibia decreases and the pressure increases, resulting in a 2- to 7-fold higher risk of developing KOA [118, 119]. Biomechanical and clinical studies have shown that the knee joint contact area decreases by about 50 % after total meniscectomy, and under experimental conditions, removing 15%–34 % of the meniscus will increase the contact pressure by more than 3 times, and removing 10 % will cause cartilage damage [3,120]. Li et al. [12] utilized CT and MRI images to develop a three-dimensional finite element (FE) model to assess the compressive and shear stresses on bone tissue, cartilage, and the meniscus. The results indicated a significant increase in shear stress between the medial femur and tibia following meniscectomy [12,121]. Additionally, the stress nephogram showed that as meniscal tears progressively worsen, the shear stress on the articular cartilage gradually increases, peaking after meniscectomy. Interestingly, based on the stress values and meniscal displacement calculated through finite element simulations, the probability of developing osteoarthritis (OA) significantly increases after meniscectomy [12,25,122].

Meanwhile, although allogeneic meniscal transplantation is the mainstream choice for early joint pain and KOA after total meniscectomy, and has been performed for more than 20 years [123]. However, the use of meniscus allografts has several disadvantages, such as the risk of disease transmission (e.g., HIV, hepatitis), the alteration of graft structure, and the poor integration with host tissue [124]. Therefore, the development and evaluation of artificial meniscus replacement materials are essential for wider clinical application, but they require more robust data from further trials [57,125]. Collectively, how to promote meniscus regeneration after meniscectomy and maintain the natural characteristics of the meniscus as much as possible to reduce the occurrence of KOA have reached an overwhelming consensus [12].

4.2. Meniscal resection model of small animal

Frankly, rats may not be the most appropriate experimental animals for investigating meniscal injury regeneration [99,126]. This is largely because they exhibit a higher healing potential than humans, as previous studies have indicated that the meniscus in small animal is more cellular than that in human [106,127]. Consequently, many researchers contend that rat meniscus possesses an intrinsic regenerative capacity. Horie et al. [99] reported that there was no significant difference in the size of the meniscus between the experimental and control groups of rats eight weeks after meniscal resection, indicating that rat meniscus has a greater spontaneous healing potential, which limits the comparison of the effects of interventions on tissue regeneration. Moreover, because rat knee joints are more curved than human ones, the change in knee joint load after meniscal resection differs from that in humans, which may affect meniscal regeneration regardless of whether the anterior or posterior half of the meniscus is removed [102]. The small anatomical structures in rodent models also limit researchers' ability to precisely control injury and regeneration areas. For instance, accurately targeting and manipulating the meniscus during regeneration procedures becomes more complex, increasing the potential for experimental errors. Additionally, imaging techniques may lack sufficient resolution for such tiny structures, compromising the accuracy of postoperative assessments. Nevertheless, this model allows for the investigation of meniscal constructs with controlled size, type, and treatment in large cohorts with sufficient statistical power. It also enables the rapid evaluation of various treatment combinations, such as cell number, fibrin type or concentration, differentiation level in multipotent cell lines, and addition of growth factors or other biologics, in a controlled in vivo setting [67,94] (Fig. 3). More importantly, their fully sequenced genomes allow for a range of genetic engineering techniques to achieve conditional gene knockouts or overexpression, enabling the creation of specific disease models. Therefore, considering the economic and easy-to-model characteristics of rats, many researchers still use rats for their studies [102,126]. Moreover, rats have a high genetic similarity to humans, making them a suitable step between in vitro and larger scale in vivo work [102,126].

Most models use a technique that involves exposing the knee joint through a medial parapatellar incision after anesthesia, and then resecting the meniscus after subluxating it to the patellar side [102,113]. Considering that rat meniscus occasionally ossifies, ethylene diamine tetraacetic acid can be used to decalcify the tissue during processing, thus eliminating the detection of any significant ossification [101]. Furthermore, it is worth noting that many methods for treating meniscal injuries involve allogeneic or xenogeneic cells, and therefore, to reduce the immune response caused by using cells from other species, some researchers use nude rats for experiments to more accurately investigate the effects of the treatment methods [113,128].

Due to the limited intrinsic regenerative capacity of rabbit meniscus compared to smaller rodents, rabbit is a favorable animal model for evaluating meniscal regeneration techniques [36] (Fig. 3). Therefore, whether Japanese or New Zealand rabbit, a standardized method for anterior portion resection has been established, which involves subluxating and removing the meniscus after joint arthrotomy [129–131]. Qi et al. [130] performed anterior half resection of MM at the level of the medial collateral ligament. Histologically, they found more fibroblast-like tissue regeneration in the anterior part of the meniscus after 6 weeks of modeling, while fibrocartilage tissue regeneration was scarce [130]. After 12 weeks, the regenerated meniscus deteriorated, filled with fibroblasts but little ECM, which resembled the pathological repair after meniscal injury in the clinic [130]. For the resection of the posterior portion of the meniscus, an incision can be made on the midline of the posterior aspect of the knee joint, and the subcutaneous tissue can be cut along the medial side of the semimembranosus muscle and the medial head of the gastrocnemius muscle. After opening the joint capsule from the posterior side and fully exposing the joint, the posterior horn of the MM can be completely removed [132]. The advantage of this type of model is that the approach used does not damage the collateral and cruciate ligaments, and interestingly, some studies have suggested that radial transection of the posterior horn of the MM is biomechanically equivalent to total meniscectomy, and thus can be called functional MM total resection [126,132,133]. Considering that most clinically occurring injuries are in the posterior part of the MM, it is not difficult to understand such experimental results, which highlight the similarity of this type of model to the clinical situation [126,132].

As mentioned earlier, compared with partial meniscal resection, total meniscal resection may be a more popular model for studying meniscal regeneration in the previous period of time, in which most studies used a medial parapatellar incision, exposed the MM after cutting the medial collateral ligament, and performed total MM resection [134,135]. To investigate the feasibility and regeneration effect of a cortical bone matrix as a tissue-engineered meniscus graft, Mao et al. [136] used a more stable model of total meniscal resection, which involved entering the knee joint through a medial parapatellar incision, sharply resecting the meniscus along its lateral side, and preserving the medial collateral ligament, which is important for postoperative joint stability, while separating it from its anterior and posterior attachments [136]. This model could effectively restrict the valgus and external rotation of the knee joint, thereby protecting the meniscus and articular cartilage from excessive stress and damage [136].

4.3. Meniscal resection model of large animal

4.3.1. Meniscal resection model of sheep

Sheep is a common large animal model for studying meniscal injuries, owing to the morphological resemblance of its meniscus to human, and the similar healing response of its meniscus to injury as the human meniscus [96](Fig. 3). Hence, inducing a resection injury in sheep has clinical implications [96]. Although sheep has its limbs in an upright position when active, it is undeniable that its limbs are also in a flexed position for a long time like rabbit, which is different from human [5,137]. This may lead to the inability to reasonably verify the effectiveness of the tissue-engineered meniscus reimplanted after total or partial meniscal resection [137]. Patel et al. [137] showed that when the sheep knee joint is in a flexed position, the anterior region of the meniscus is relatively protected from high load, resulting in less loss of polymer fibers, while the posterior region suffers from severe fiber damage due to greater compressive and tensile stress. However, Chevrier et al. [5] assessed the suitability of sheep and rabbit as model for meniscal injury by comparing their meniscal structure with that of human. They observed that the adult sheep meniscus shared high structural similarity with the human meniscus in some key aspects of the regeneration process, thus conferring sheep an edge over rabbit as animal model for human meniscal regeneration [5].

Kon et al. performed a MM resection on skeletally mature adult sheep, and briefly, they incised the medial collateral ligament slightly above the joint line, and exposed the posterior and anterior horn of the meniscus by flexing, externally rotating and varus the knee joint, and finally detached the meniscus from its attachments and removed it from the joint capsule [92]. They evaluated the joint swelling and stability after euthanizing the sheep, followed by microbiological and inflammatory factor analysis of synovial fluid, and then performed a semi-quantitative systematic analysis of the implanted meniscus and the articular cartilage and subchondral bone of the femoral condyle and tibial plateau [92]. The results showed that except for the most severe changes occurring at the site closest to the main biomechanical obstacle (the MM resection site), the whole joint underwent gross and histological structural damage and proteoglycan loss, which was consistent with the clinical situation of impaired articular cartilage structure and function and the occurrence of KOA due to meniscal injury [91,92]. Patel et al. [137] also performed a complete MM resection on sheep by using a medial parapatellar arthrotomy, and the sheep were sent to a specialized farm for feeding about 2 weeks after surgery, and euthanized after 2 years of cultivation. A distinctive feature of their study was that the two-year research period allowed for a full demonstration of the degenerative joint changes caused by meniscal resection, and various forms of evaluation also indicated that a series of substantial pathological changes occurred within the entire joint [137]. Notably, due to the limited intra-articular space in sheep, performing partial or total meniscectomy requires dislocating the medial joint capsule and medial collateral ligament, which results in knee instability and can subsequently lead to excessive and abnormal osteophyte formation along the medial edges of the femoral condyle and tibial plateau [137].

4.3.2. *Combined meniscus resection and ACL injury of sheep*

The meniscus often suffers concomitant injury with the ACL, and non-contact injuries such as jumping landing, planting and pivoting movements may cause combined injury of the meniscus and ACL [138]. Moreover, studies have found that more than 80 % of ACL injury cases showed cartilage lesions in the posterior aspect of the tibia and anterior lateral aspect of the femoral condyle [139]. Therefore, the combined injury of the meniscus and ACL can alter the contact load on the articular cartilage, leading to further cartilage damage and osteophyte formation, which contribute to the degenerative changes of the joint [140,141]. Therefore, when the meniscus is injured along with the ACL, the risk of developing KOA increases from 6 % in the uninjured population to 70 % in the injured patients [142]. Previous studies have mostly focused on the isolated injury of the meniscus, but few have investigated the common combined injury of the meniscus and ACL at the initial stage of injury [143]. Therefore, Faqeh et al. [144] established a model of meniscus resection combined with ACL injury in sheep. They made a transverse skin incision along the direction of the tibial plateau, and after cutting the subcutaneous tissue and joint capsule, they exposed and removed the attachment point of the ACL, and performed a drawer test to ensure its complete removal [144]. Then they cut all the attachment points of the MM from the tail to the head, until the MM was completely removed [144]. Firstly, this model, as a large animal model, features knee joints of sufficient size to allow for the complete resection of MM and ACL while protecting the surrounding tissues [144]. Furthermore, in a study comparing various animal and human knee joints, it was found that compared with dog, rabbit and other animals, the size and proportion of the MM in sheep were most similar to those of humans, thus this model can well reflect the meniscus injury and verify the effectiveness of the treatment [77,144]. In summary, although there are differences in the activity of sheep limbs and human limbs, the MM resection model in sheep is suitable for studies on meniscus resection regeneration, regardless of whether the meniscus is injured alone or associated with ligament damage.

5. Tibiofemoral joint impact model

The meniscus, a crescent-shaped fibrocartilage within the knee joint, primarily functions to stabilize the knee and absorb impact during movement, thereby reducing joint wear [19]. Consequently, the meniscus is frequently injured during knee trauma, and such injuries are significantly associated with cartilage degeneration and the onset of PTOA [59,145,146]. Therefore, an animal model that simulates common clinical mechanisms of meniscal injury, rather than relying on specific surgical procedures, is needed to elucidate the relationship between meniscal injury and cartilage degeneration [147,148]. Therefore, the currently widely accepted approach is to use animal models that induce trauma to the closed joint by applying an impact force to explore the PTOA associated with meniscal damage, resulting in meniscal injury, and to investigate how to more effectively restore joint stability to prevent PTOA [149–151] (Fig. 4).

Considering the difficulty of controlling the conditions of in vivo closed TFJ impact using large animal, Flemish Giant (FG) rabbit, which has a larger body size than the common New Zealand white rabbit, is widely used for this type of model study, as it has larger tissue volumes that allow easier and more thorough analysis (Fig. 3). To establish a more human-like animal model of typical knee joint injury, Wei et al. [151] developed a traumatic ACL and meniscus injury model using FG rabbits. Similarly, Fischenich et al. [148] used a closed-joint in vivo TFJ impact model to study the macroscopic, mechanical, and histological changes of the articular cartilage and meniscus within 12 weeks after impact. Interestingly, they did not immediately assess the damage level of the joint tissues, but performed a preliminary MRI examination, because a previous study showed that the mechanical properties of the tissues did not change acutely after impact [152]. Although the closed-joint impact model can better simulate the real-life injury, it also causes some uncontrollable variations in the location and type of acute damage [148]. Therefore, to develop the most clinically translatable animal model, besides considering the animal species, it is also necessary to have an impact setting that can cause similar injury to the clinical one [148,151]. For this purpose, they exposed the proximal aspect of the knee joint and performed a TFJ impact using an improved traumatic impact test protocol [148,151]. To avoid fracture, they used a relatively low load rate to impact the tibia until it was compressed downward by 3.5 mm or soft tissue failure occurred, and then confirmed ACL rupture by drawer test [148,151]. Additionally, Isaac et al. [19] developed a model of traumatic ACL and meniscus rupture by applying compressive load to the TFJ and found that the optimal combination of joint flexion angle and impact energy to produce these injuries was 90° and 13 J, respectively, but further studies are needed to quantify the rotation and translation of the tibia [19]. In summary, when establishing a TFJ impact animal model, the impact force level needs to be high enough to cause ACL rupture and meniscus damage, which can induce degenerative changes in the articular cartilage and promote the development of PTOA, but also low enough to prevent fracture.

Within the knee joint, the medial hemi-joint is the most susceptible site for meniscus and cartilage damage and degeneration, where the central and posterior regions of the MM are the most common injury sites, and the proximal and distal parts of the MFC are the most affected cartilage areas (Fig. 4). Isaac et al. [19] reported results similar to the

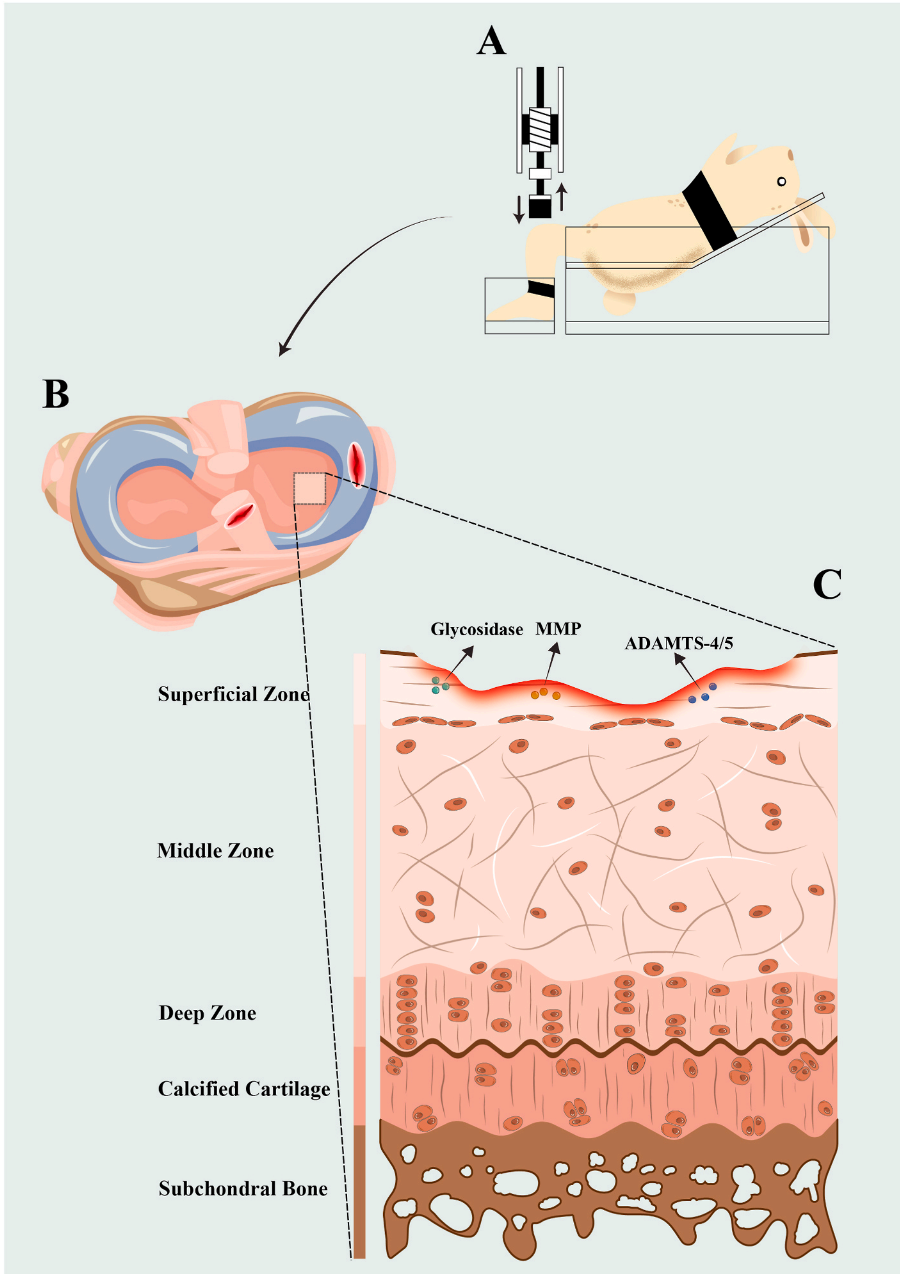

Fig. 4. Tibiofemoral joint impact model. A. The hind limb of rabbit is fixed at 90° and then an impact force is applied to the TFJ; B. Injuries to the medial meniscus and intra-articular ligaments often occur after impact force is applied to the TFJ; C. The superficial zone of articular cartilage can produce catabolic enzymes after injury, such as Glycosidase, MMP and ADAMTS-4/5. Abbreviation: TFJ: Tibiofemoral joint; MMP: Matrix Metalloproteinases; ADAMTS-4/5: A Disintegrin and Metalloproteinase-4/5.

clinical situation, as they found medial and lateral meniscus tears in about 30 % of the giant rabbit models, which all had radial and longitudinal components, and the cartilage damage of the MFC and the medial of tibial plateau was significantly more than lateral cartilage [19,151]. Fischenich et al. [148] also found that the medial hemi-joint had more delamination damage than the lateral hemi-joint, which was consistent with the clinical studies of OA patients, thus showing preliminary clinical relevance. Moreover, the main direction of meniscus tears was longitudinal vertical tears and they were more common in the posterior part of the meniscus, which also concurred with the injury outcomes in clinical practice [148,153]. It is speculated that the impact load increased the compressive load on the chondrocytes in the intermediate layer of the articular cartilage, resulting in increased wear and degradation enzyme production in the superficial layer [59,154] (Fig. 4). Further analysis of the morphology and properties of the articular cartilage related to OA pathology revealed that the medial tibial region exhibited more pronounced OA-associated changes (cartilage erosion, reduced fiber and matrix modulus, and increased tissue permeability) than the lateral region. This was consistent with the clinical observation that the most severe OA symptoms often occurred in the medial compartment of the knee joint, suggesting a close correlation between this model and PTOA in the clinic. Besides, mechanical data from the indentation relaxation test showed that the cartilage permeability increased and the matrix stiffness decreased in the impact joint, compared with the contralateral control joint [148]. In summary, this model can reveal the chronic damage of the joint, including evident meniscus injury and damage to the cartilage surface and its matrix, thus the TFJ impact model may help to understand more comprehensively the changes in the whole joint after blunt force injury.

6. Other meniscal lesion models

Studies have shown that meniscal extrusion frequently occurs after root tear, partial meniscectomy, and meniscal transplantation, and that meniscal extrusion is significantly associated with symptoms and joint space narrowing in patients with OA [155–159]. Therefore, to investigate meniscal extrusion, Ozeki et al. [160] developed a rat model of MM extrusion (MME). They combined previous studies and dislocated the patellar tendon laterally after skin incision, and then transected the anterior synovial capsule after transecting the MMTL at the tibial attachment site to induce MME [160]. Destabilization of the MM was confirmed by medially distracting it with forceps, and to quantify MME, we also defined the "meniscus extrusion ratio" and the "meniscus coverage ratio" [160,161]. Meniscal extrusion leads to further reduction of the contact area between the meniscus and the tibia, which is one of the strongest predictors of OA progression, resulting in rapid degeneration of the cartilage due to the increased peak load on the tibial plateau cartilage [44,162–164]. Ozeki et al. reported a study that was similar to the clinical situation, showing that MME significantly reduced the meniscal coverage of the tibial plateau, leading to poor distribution of joint load and the onset and progression of KOA [113,160]. However, due to the significant difference between the rat knee joint and the human knee joint, the rat model is not fully clinically relevant, especially in meniscus-related studies. Moreover, in clinical situations, the posterior portion of the MM is more involved in the pathological process related to extrusion than the anterior portion, but establishing an extrusion model of the posterior portion of MM by open surgery is highly invasive. Therefore, future studies need to use arthroscopy to establish a minimally invasive model in the posterior portion of MM in large animal models to further investigate the improvement methods for meniscal extrusion.

Clinically common meniscal tear injuries often show pathological changes of meniscal degeneration and disorganization, including decreased cell density, diffuse cell proliferation, and loss of collagenous matrix [165]. Therefore, some studies suggest that defects caused by scalpel or biopsy punch, as well as meniscal extrusion models, cannot well simulate the real pathological damage of meniscal tears [90,160,166]. Ozeki et al. [166] adopted a novel strategy to induce meniscal damage after exposing the entire MM. Specifically, they used a 23 G needle to puncture the posterior portion of the MM 200 times, which included 100 punctures in the vascularized region and 100 punctures in the avascular region, thus creating meniscal injury [166]. They also placed a spatula under the meniscus to avoid damaging the cartilage and to ensure complete puncturing of the meniscus from the femoral side to the tibial side [166]. Repeated puncturing resulted in significant histological and biochemical changes in the meniscus, characterized by decreased proteoglycan and COL-2 content, which resembled human meniscal degeneration [90]. Proton-weighted MRI images showed increased intensity of the entire meniscus, which indicated meniscal degeneration, and the extensive low birefringence areas observed in polarized light microscopy images also suggested disorganization of the meniscal collagenous matrix [90,166,167]. These results demonstrate that this model can effectively simulate the degenerative pathological changes after meniscal injury, providing a reliable animal model for investigating the mechanisms and treatments of meniscal degeneration. Moreover, it also suggests that the establishment of a meniscal injury model should consider not only the macroscopic degree of injury, but also the pathological changes at the time of injury, to enhance the clinical translatability of the animal model.

7. Conclusion and future perspectives

Meniscal injury is one of the most common injuries in sports medicine, which can cause knee pain, swelling, and functional impairment, and lead to abnormal load transmission and degeneration of articular cartilage. Although a few cases of injury can be treated conservatively or by suturing, the main treatment method is still partial or total meniscectomy, which significantly increases the risk of developing KOA [12]. Therefore, current research focuses more on how to promote the repair of meniscal injury and maintain the original structure and function as much as possible, and animal models are indispensable for discovering and developing methods and products that allow translation to humans. We have summarized several commonly used animal models of meniscus injury closely related to the occurrence and development of OA in current research, and classified them by establishing methods and clinical relevance. In essence, following a meniscal injury, the primary consideration should be how to promote its regeneration and maintain its original function. The punch model, which produces stable and highly reproducible injuries, serves as an excellent model for studying meniscal defect regeneration and is particularly suitable for tissue-engineered meniscus research. However, this model significantly deviates from clinical scenarios. To address this, some researchers have created vertical longitudinal tears to mimic common clinical meniscal tears, making this model more clinically relevant compared to the punch model. Despite this, the longitudinal tear model is not closely aligned with current meniscal injury treatments. Given that meniscectomy is the predominant surgical method for meniscal injuries, we have turned our attention to the meniscectomy model. Although meniscectomy can temporarily alleviate pain, it increases the incidence of OA. Therefore, the meniscectomy model is essential for studying how to promote regeneration and repair following meniscectomy. Up to now, all three models involve surgically induced meniscal injuries, which do not align with the mechanisms of meniscal injury. Consequently, researchers have developed the closed TFJ impact model, which effectively simulates the mechanisms of meniscal injury in clinical settings.

The study of meniscus repair based on animal models of meniscus injury is a research topic of great interest. However, there are many challenges to be addressed before applying the results from animal models to clinical practice. First, the meniscus repair capacity changes with age, which may introduce additional variability in the assessment of tissue pathology [168]. If the animal models used in the study are relatively juvenile, it is possible that the reversal of cartilage degeneration after meniscus injury is caused by development rather than intervention, so animal models of corresponding age stages should be selected for different developmental stages of research for preclinical studies [6]. The main purpose of meniscus injury models is to study the factors that promote meniscus injury repair, and prevent joint cartilage from developing KOA after long-term degenerative changes. Therefore, the research results obtained from larger and skeletally mature animals are more clinically relevant [13]. For example, cynomolgus macaques reach sexual maturity at 3–4 years of age and have a lifespan of about 15 years, and it means that 12–13 years old cynomolgus macaques are older macaques, which can be used to establish meniscus injury models that are close to clinical situations [107,169]. Second, most studies evaluated meniscal repair by gross and histological observations of the meniscus, but sometimes these observations alone could not accurately determine whether the meniscus could achieve the corresponding function after intervention. Moreover, it was possible that although the meniscus was judged to be immature histologically, the articular cartilage and subchondral bone were already significantly protected. The researchers speculated that the immature meniscus also had some function, because MRI analysis showed that the T2 value of the meniscus was close to normal [21,98,107,170]. Hence, histological observation alone is insufficient to fully evaluate the functional recovery of the meniscus, and biomechanical analysis is also needed [101,166]. Considering that the meniscal tissue may not be able to undergo mechanical testing after histological observation, the meniscus can be tested in parts after being removed from the animal model, with one part for histological observation and another part for mechanical analysis [101,166]. One important point that is likely to be overlooked is the inflammatory response induced by the model establishment and the postoperative infection [171]. Although the minimally invasive technique using arthroscopy was mentioned to reduce the risk of infection, septic arthritis may still occur in the experimental setting, which may accelerate the progression of cartilage damage [45]. Therefore, it is possible to collect synovial fluid and serum regularly to analyze the inflammatory cytokines, and even perform tissue culture experiments to exclude infection in future studies [172,173].

Collectively, a variety of animal models of meniscal injury, as well as animals that can be used for research, have been established. To choose the optimal animal model, researchers need to take into account various factors. Meanwhile, animal models of meniscal injury have great potential in exploring the role of meniscal repair in reversing cartilage degeneration, but the clinical translation remains challenging. Thus, more extensive research on animal models is needed in the above and other aspects, with the aim of constructing more clinically relevant animal models and evaluation systems.

CRediT authorship contribution statement

Xiaoyao Peng: Conceptualization, Methodology, Writing – original draft, Visualization. **Fashuai Wu:** Conceptualization, Writing – original draft. **Yuxiang Hu:** Writing – original draft, Visualization. **Yangyang Chen:** Conceptualization, Writing – original draft. **Yulong Wei:** Conceptualization, Writing – review & editing. **Weihua Xu:** Supervision, Writing – review & editing.

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Declaration of competing interest

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