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Review Article

Animal model for tendinopathy

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ABSTRACT

Background: Tendinopathy is a common motor system disease that leads to pain and reduced function. Despite its prevalence, our mechanistic understanding is incomplete, leading to limited efficacy of treatment options. Animal models contribute significantly to our understanding of tendinopathy and some therapeutic options. However, the inadequacies of animal models are also evident, largely due to differences in anatomical structure and the complexity of human tendinopathy. Different animal models reproduce different aspects of human tendinopathy and are therefore suitable for different scenarios. This review aims to summarize the existing animal models of tendinopathy and to determine the situations in which each model is appropriate for use, including exploring disease mechanisms and evaluating therapeutic effects.

Methods: We reviewed relevant literature in the PubMed database from January 2000 to December 2022 using the specific terms ((tendinopathy) OR (tendinitis)) AND (model) AND ((mice) OR (rat) OR (rabbit) OR (lapin) OR (dog) OR (canine) OR (sheep) OR (goat) OR (horse) OR (equine) OR (pig) OR (swine) OR (primate)). This review summarized different methods for establishing animal models of tendinopathy and classified them according to the pathogenesis they simulate. We then discussed the advantages and disadvantages of each model, and based on this, identified the situations in which each model was suitable for application.

Results: For studies that aim to study the pathophysiology of tendinopathy, naturally occurring models, treadmill models, subacromial impingement models and metabolic models are ideal. They are closest to the natural process of tendinopathy in humans. For studies that aim to evaluate the efficacy of possible treatments, the selection should be made according to the pathogenesis simulated by the modeling method. Existing tendinopathy models can be classified into six types according to the pathogenesis they simulate: extracellular matrix synthesis-decomposition imbalance, inflammation, oxidative stress, metabolic disorder, traumatism and mechanical load.

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Conclusions: The critical factor affecting the translational value of research results is whether the selected model is matched with the research purpose. There is no single optimal model for inducing tendinopathy, and researchers must select the model that is most appropriate for the study they are conducting.
The translational potential of this article: The critical factor affecting the translational value of research results is whether the animal model used is compatible with the research purpose. This paper provides a rationale and practical guide for the establishment and selection of animal models of tendinopathy, which is helpful to improve the clinical transformation ability of existing models and develop new models.

1. Introduction

Tendinopathy presents as pain and restricted motion. In the upper and lower extremities, tendons with higher mechanical loading, such as the rotator cuff and Achilles tendons, are more prone to tendinopathy [1]. Although the pathological model of tendinopathy has been gradually improved in recent decades, the understanding of the underlying mechanism of its occurrence and development is still limited, which hinders development of tendinopathy treatments.

Animal models are essential in elucidating pathological mechanisms and developing therapeutic approaches. The critical factor affecting the translational ability of animal models is whether the purpose of the research is matched with the model itself. Although multiple tendinopathy models have been reported, we still know very little about the scenarios in which each model is suitable for application, resulting in many models being infrequently applied to pre-clinical studies. One important reason is our lack of understanding of the characteristics of existing models. In addition, we should recognize that the primary purpose of animal models is to provide information, translating basic scientific information into human clinical practice. Therefore, establishing associations between animal models and human tendinopathy are important to enhance the clinical translational value of animal models.

Our aim is to summarize the different animal models used to simulate tendinopathy and to clarify the research purposes appropriate to each animal model, including exploring the pathological mechanisms of the disease and testing the efficacy of therapeutic approaches. We will examine the advantages and disadvantages of each model and classify them according to the human tendinopathy pathogenesis simulated by the modeling method to determine their utility in studying the pathophysiology of tendinopathy and evaluating treatments.

2. Methodological consideration

We reviewed relevant literature in the PubMed database from January 2000 to December 2022 using the specific terms ((tendinopathy) OR (tendinitis)) AND (model) AND ((mice) OR (rat) OR (rabbit) OR (lapin) OR (dog) OR (canine) OR (sheep) OR (goat) OR (horse) OR (equine) OR (pig) OR (swine) OR (primate)). Included studies were animal studies of tendinopathy. There were no restrictions on animal species, modeling methods, intervention methods, and control measures. Reviews, conferences, and letters were excluded. We used predesigned data extraction table to extract required information. The extracted contents included first author, year, animal species, gender, age, initial weight, tendon type, simple size, modeling methods, and follow-up time. Study quality was assessed by a modified 10-point-item checklist, adapted from the Collaborative Approach to Meta-Analysis and Review of Animal Data from Experimental studies [2]. The checklist comprises items of study methodology: randomized allocation to experimental group (1); publication in a peer-reviewed journal with its impact factor (2); blinding of the group allocation during the experiment (3); a statement of sample size calculation (4); a statement of compliance with regulatory requirements (5); a statement on possible conflicts of interest (6); blinded assessment of outcome (7); (semi) quantitative scoring based on HE staining (8); (semi) quantitative scoring based on SO staining (9), and clear data presentation (10). The results of information extraction and quality assessment are presented in Supplemental material 1. Risk of bias was assessed by Systematic Review Centre for Laboratory Animal Experimentation (SYRCLE) [3]. (Supplemental material 2)

3. How to select appropriate tendinopathy models?

3.1. Classification based on human tendinopathy pathogenesis

Extrinsic and intrinsic factors contribute together to the development of tendinopathy. Among them, overload (overuse) is the primary stimulus driving the progression of tendinopathy. Most tendinopathies occur in relation to high-load and/or repetitive activities. Damage-associated molecular patterns (DAMPs) refer to endogenous molecules produced by cell damage or tissue degradation that can activate immune responses, including alarmins, collagen (Col) fragments, nucleic acids and so forth [4]. DAMPs produced by overload may be recognized by Toll-like receptors (TLRs) on tendon cells, vascular endothelial cells, macrophages and mast cells, promoting the production of pro-inflammatory cytokines (e.g., interleukin-1β (IL-1β) and tumor necrosis factor α (TNF-α)), chemokines, lipid mediators and reactive oxygen species (ROS) through myeloid differentiation primary response88 (MyD88) -dependent and MyD88-independent pathway [5,6]. Furthermore, peripheral nerves located in the paratenon and endotenon produce a variety of neurotransmitters in response to tendon damage, such as substance P, glutamine and calcitonin gene-related peptide, which activate mast cells and cause neurogenic inflammation [7]. Mechanosensors, such as integrin, voltage-gated calcium channel and focal adhension kinase, can directly sense mechanical stress [8,9]. In addition, cytoskeletal dynamics are involved in mechanical signal transduction too. Overload can stimulate the shift of tendon cells and macrophages to pro-inflammatory phenotypes [8,10]. Besides, overload also promotes the production of growth factors (e.g., transforming growth factor-β (TGF-β)) and extracellular matrix (ECM) by tendon cells [11]. Inflammatory microenvironment induces angiogenesis and nerve ingrowth. Tendon cells shifted from producing Col 1 to producing Col 3. Furthermore, production of matrix metalloproteinases (MMPs) increased in tendon cells and macrophages. These factors cause the imbalance of ECM synthesis and decomposition. Finally, the inflammatory response becomes chronic and continues to cause tissue damage.

Other common extrinsic factors include acute injury, lack of adequate recovery and use of toxic medications (fluoroquinolones, corticosteroid, and statins). Intrinsic factors include aging and metabolic disorders (diabetes mellitus (DM) and hypercholesterolemia) [12–16]. These factors amplify the effect of overload by regulating the status of tendon cells and immune cells. Animal models should recreate perturbations reflective of the key risk factors for the condition in humans, so we examined the available tendinopathy models according to mechanisms [Fig. 1].

3.2. Establishment of associations between human continuum pathological model and pathological patterns for each animal model

Cook et al. proposed the continuum pathology model in 2008, which has been widely recognized [17,18]. This model suggested that management may be optimized by tailoring interventions to the stage of pathology. They suggested that overload is the core factor driving tendinopathy and divided tendinopathy into three stages: reactive tendinopathy, tendon dysrepair and degenerative tendinopathy. In the reactive

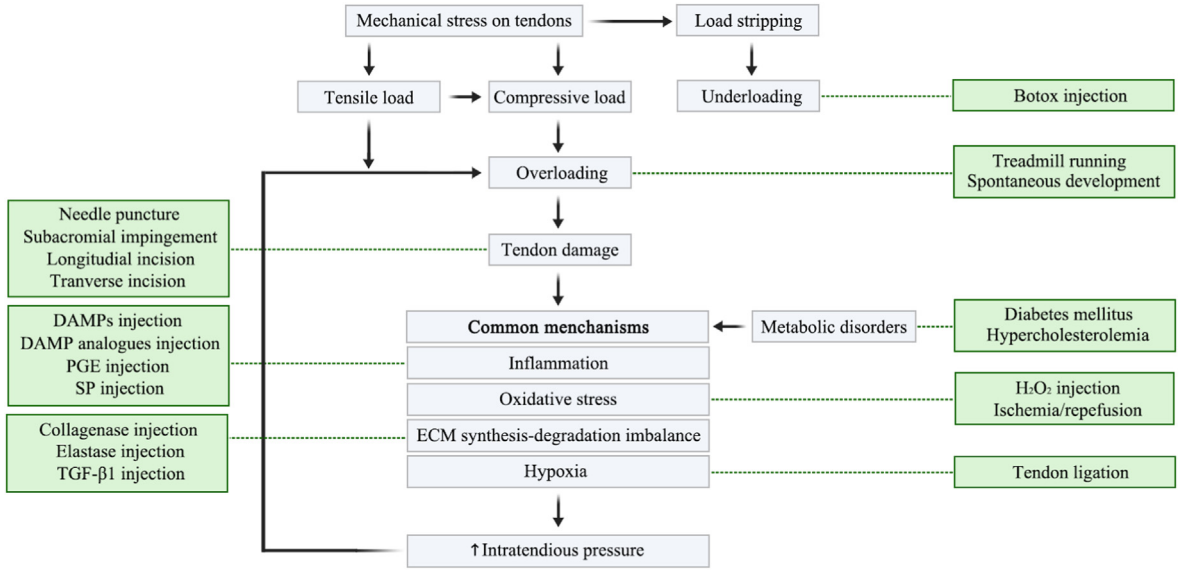

Figure 1. Human tendinopathy mechanisms and corresponding animal models. Grey box: The mechanisms of human tendinopathy. Green box: The methods of establishing tendinopathy models. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

tendinopathy, overload induced non-tendinogenic differentiation and proliferation of tendon cells [19]. The production of large proteoglycans (e.g., aggrecan, versican and hyaluronan), which have a strong ability to bind water, increases. At this stage, Col arrangement and vascularization do not change significantly. Patients may complain of pain and tendon swelling associated with acute overload, which can be completely relieved with adequate rest. The rounded and enlarged tendon cells, increased ECM, and confined space lead to increased intratendinous resting pressure [20]. The accumulation of hydrophilic glycoproteins and proteoglycans reduces matrix permeability, which increases the intratendinous dynamic pressure [21]. Persistent overload leads to further increase of proteoglycan production as well as Col structure destruction and Col arrangement disorder. The inflammatory response caused by overload induces angiogenesis [22]. This stage is called tendon dysrepair. Soreness and stiffness may occur in the morning or after being still for a longer period of time. Imaging may reveal focal structural abnormalities (e.g., thicking) with or without increased vascularization. If the load is optimized, this stage is still considered reversible. If not optimized, overload may impair vascularization and cause hypoxia, which led to leaking vessel and negative feedback increased intratendinous pressure [21]. Finally, the transformation of tendon tissue into scar-like tissue, accompanied by tendon cells exhaustion and significant matrix abnormalities, marks the stage of degenerative tendinopathy. The tendon may have one or more focal nodules, with or without diffuse thickening. If the tendon is under high load or the lesion is extensive enough, it may rupture.

The ultimate goal of animal models is to reproduce the pathological processes of human tendinopathy, so we try to explain the pathological processes of each animal model in the context of human tendinopathy. Histological scores provide a good bridge. Although different studies may have used different histological scoring systems, the major parameters of these scoring systems are the same. We developed a new scoring system based on these major parameters, which allowed us to compare the results of different studies under a uniform standard. The specific parameters included cell morphology, cellularity, vascularization, ground substance and Col arrangement. (score 0–3 for each item) See Supplemental material 3 for details. We included studies that provided scores for parameters or clear representative pictures (Shown in Supplemental marterial 1 with bold). For studies that provided scores for parameters, we calculated the absolute mean difference in the scores, which were the difference between the means in the control and modeling groups, as well as the estimated standard error [23]. For studies that provided clear representative pictures, we scored the parameters according to the new scoring system and calculated the absolute mean difference in scores too. Then, we used the random effects method of meta-analysis to calculate the pooled effect size for the same parameter at the same follow-up time. Finally, the total score of each follow-up time point was calculated. We defined a histopathological score of less than 4 as stage 1, corresponding to reactive tendinopathy; a score of 4–7 as stage 2, corresponding to tendon dysrepair; a score of more than 7 as stage 3, corresponding to degenerative tendinopathy [Fig. 2].

3.3. *Know the characteristics of each animal*

A wide range of species, such as horses, sheep, goats, dogs, rabbits, rats, and mice have been used for establishing tendinopathy model. We should recognize that different species differ in their ability to reproduce characteristics of specific tendon and their surroundings. In addition, large animals have a natural advantage in diagnosing and treating diseases using clinically relevant methodological approaches. Non-human primates, such as the baboon, may be the most desirable specie for tendinopathy research because their anatomical characteristics are most similar to humans, yet they are rarely used due to high cost. The multiple bundle structure of the horses' superficial digital flexor tendon (SDFT) and deep digital flexor tendon (DDFT) are similar to the human Achilles tendon and thus can simulate slip between bundles [24]. In addition, these tendons carry a high load, which means they can spontaneously develop lesions. In sheep and goats, supraspinatus, infraspinatus, Achilles, and DDFTs are the tendons most commonly used to establish tendinopathy model [25,26]. Similar to humans, their infraspinatus tendon is inside the joint and the supraspinatus tendon is outside the joint but on a bursa, thus reproducing an environment containing synovial fluid [27]. The shoulder joint of dogs shows flattened humeral head and the prominent greater tuberosity. Their movement patterns and anatomical characteristics together determine that their supraspinatus tendons bear a high load, and are therefore prone to lesions [28].

As for rabbits, their subscapularis tendon passes under the tuberculum supraglenoidale and coracoid process, similar to the supraspinatus tendon passing under the acromion in humans [29]. Their supraspinatus, subscapularis, patellar, and Achilles tendons are often used to establish tendinopathy model [30,31]. In rodents, supraspinatus, patellar, Achilles, and flexor digitorum longus tendons are most commonly used in

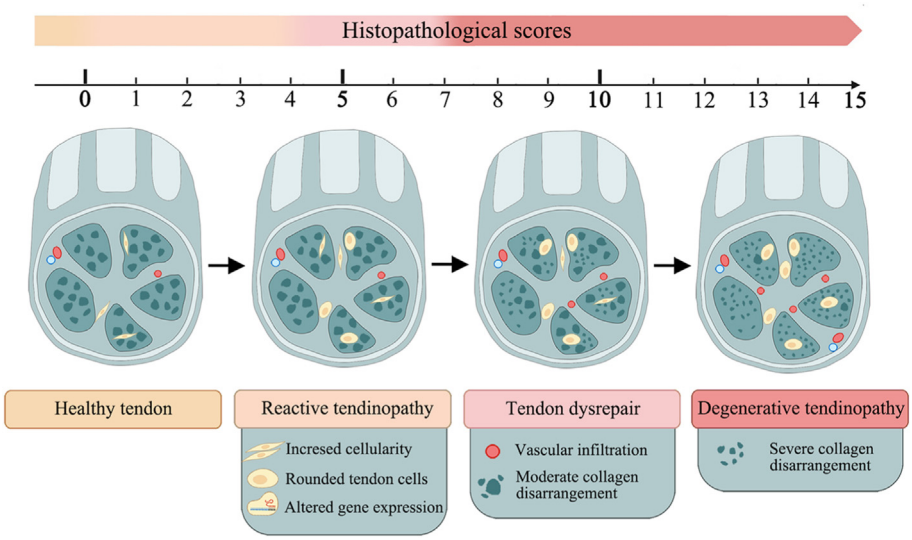

Figure 2. The bridge between human continuum pathological model and pathological patterns for each animal model. Histopathological scores are used to establish associations between human continuum pathological model and pathological processes of each animal model. Histological scores less than 4 are corresponded with reactive tendinopathy, histological scores 4–7 are corresponded with tendon dysrepair, and histological scores greater than 7 corresponded with degenerative tendinopathy.

tendinopathy studies [32–34]. The shoulder anatomy of rats is most similar to that of humans (except primates), with the acromion attached to the clavicle in front of the humerus head, forming a closed arch over the supraspinatus and infraspinatus tendons [35]. Mice shared similar shoulder joint structure.

4. Animal models corresponding to extracellular matrix synthesis - decomposition imbalance

ECM changes throughout different stages of continuum pathological model. Tendon cells play a key role in maintaining the balance between ECM synthesis and decomposition through synthesizing Col, proteoglycans and elastic proteins or producing matrix MMPs and elastases [36]. Immune cells (e.g., neutrophils and macrophages) are also involved in this process by producing degrading enzymes [37]. ECM, in turn, regulates the function of tendon and immune cells. For example, random fiber arrangement is sufficient to drive macrophages to transform to M1 type [38]. Tendinopathy models that disrupt the balance of ECM synthesis and decomposition can be classified into two categories: One that directly degrades ECM and the other indirectly affects the synthesis and decomposition of ECM by regulating cell function. The methods of local injection to induce tendinopathy are shown in Table 1.

4.1. *Extracellular matrix-degrading enzyme injection*

Intratendinous or peritendinous injection of Type 1 collagenase is the most commonly used method. Few studies adopt other enzymes, such as Type 2 collagenase and elastase [59,69].

Tendinopathy models in rats have been extensively studied. Naterstad et al. [70] reported that after injection with 100 μg collagenase in the Achilles tendon, recruitment of neutrophils peaked in the first 24 h and gradually disappeared within 2 weeks. Orfei et al. [71] compared the differences between low (1 mg/ml, 30 μl) and high (3 mg/ml, 30 μl) dose collagenase injections in Achilles tendons. Low doses reached the worst total score at 3 days (9.7 ± 0.4). The presence of a high number of rounded cells was the most distinctive feature in this group. High does reach the maximum score at 15 days (16.5 ± 2.1). Histological analysis showed moderate or more disordered structure and arrangement of Col fibers at 7 and 15 days. The number of vascular cells increased between 3 and 15 days, followed by a decrease from 15 to 45 days. Compared with low doses, fatty deposits are more common in high doses. Besides, Orfei et al. reported up-regulation of chondrogenic genes at 4 weeks. In another study, Chen et al. [42] also found increased expression of osteogenic (osteocalcin, OCN) and chondrogenic (sex determining region Y-box 9, SOX9)-related genes and calcium deposition at 4 weeks. After the injection of collagenase, the tendon tissue rapidly underwent reactive changes, corresponding to reactive tendinopathy. At about 1 week, the pathological changes of the tendon tissue were similar to those of tendon dysrepair [50,72]. The tendinopathy model later entered degenerative tendinopathy, with the most severe pathological changes at 3–4 week [Fig. 3A].

The results from rats can be generalized to other species. Kokubu et al. showed that Bonar scores were 4, 6.67 and 9.5 on 9, 14 and 28 days after local injection of collagenase in mice Achilles tendon [33]. Rabbit tendinopathy models have been widely used in preclinical studies, and most of their study endpoints are set at week 3, 4 and 6 [30,31,53,54]. Netto et al. [55] compared the differences between a single 300 μg injection of collagenase and three 100 μg injections of collagenase (at 14-day

Table 1
The methods of local injection to induce tendinopathy.

Drug	Volume (μl)	Concentration (%)	Does (U/μg)	Animal	Tendon	References
Type 1 collagenase	20–30	1	50–250 U	mouse	Achilles	[33,39–42]
Type 1 collagenase	20–40	0.0015–1	0.3–600 μg	rat	Patellar	[43–46]
Type 1 collagenase	20–100	0.0015–10	0.3–250 μg	rat	Achilles	[33,47–52]
Type 1 collagenase	10–150	1	0.1–1.5 μg	rabbit	Achilles	[30,31,53–55]
Type 1 collagenase	1000	—	400–500 U	sheep	Achilles	[25,26,56–58]
Elastase	20	—	1 U	rat	Achilles	[59]
TGF-β1	6	1.7	0.1 μg	mouse	Achilles	[60–62]
PGE1	500	0.16	0.8 μg	rat	Achilles	[63]
PGE2	—	—	0.05–0.5 μg	rabbit	Achilles	[64,65]
Substance P	50	—	0.67–6.7 μg	rat	Patellar	[66]
Carrageenan	100	2	2 μg	rat	Patellar	[67]
H_2O_2	25	0.0017	0.04 μg	mouse	Achilles	[68]

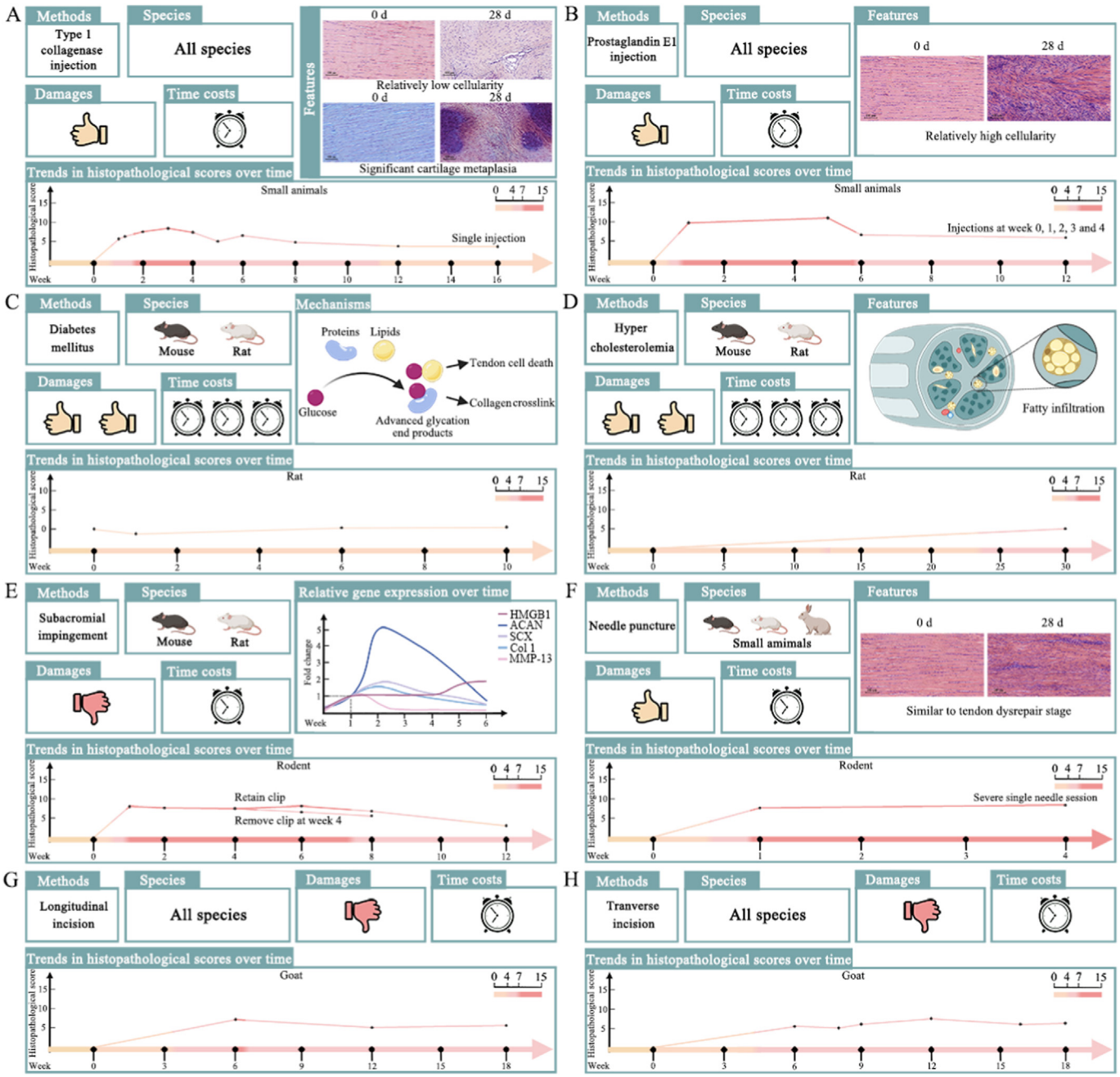

Figure 3. Comparison of different animal models used for tendinopathy research.
Selected characteristics of animal models used for tendinopathy research including applicable species, damages to animals caused by modeling operations, time costs, features (A, B and D), mechanisms (C), changes in gene expression (E), and pathological patterns. Clocks are used to represent time costs, with levels 1, 2 and 3 indicating that the animal model needed less than 4 weeks, less than 8 weeks, and more than 8 weeks to enter stage 2 tendinopathy, respectively. Thumb-up/down is used to represent damages, with levels 1, 2 and 3 indicating non-damage, relatively minor damage, and relatively severe damage, respectively.

intervals). The Bonar scores for the two groups were 12.8, 4.5, 5.6, and 11.6, 8, and 11.8 at 10, 12, and 16 weeks, respectively. This suggested that for studies with long periods, the continuous injection method may be more appropriate. As for large animals, such as sheep, most of their study endpoints were set at weeks 3,4, 6, and 8 [25,26,56–58].

4.2. Cytokines injection

From the standpoint of tissue repair, the three stages of continuum pathological model correspond to proliferation, consolidation and maturation respectively [73]. Myofibroblasts play an important role in the consolidation and maturation stages, participating in the synthesis of Col 3 and the contraction of scar-like tendon tissue [74]. TGF-β is part of a superfamily of related growth factors, which includes three isoforms: TGF-β1, TGF-β2 and TGF-β3. All isomers bind to TGF-β receptor 2 and recruit TGF-β receptor 1 to activate downstream pathways [75]. TGF-β1 promotes the transformation of fibroblasts and macrophages into myofibroblasts through canonical (smad-based) and non-canonical (non-smad-based) signaling pathways [76]. This process may involve activation of HIF-1α signaling pathways and glycolytic reprogramming [61].

The TGF-β1 injection model was established by injecting 100 ng of TGF-β1 into the mice Achilles tendon on days 0 and 2 [60,61]. Rezvani et al. showed that increased cellularity and rounded nucleus on day 6

[60]. Then, cartilage metaplasia and hyaluronan accumulation occurred in the tendon tissue on days 9 and 25. Combining TGF-β1 injection with treadmill has been studied [62,77]. After 24 h of TGF-β1 injection, the mice were forced to uphill (17°) treadmill running at 32 cm/s, 20 min/day, 5 days per week for 2 or 4 weeks.

4.3. Summary

Type 1 collagenase model is the most used tendinopathy model. The advantage of all chemical injection models is that they induce tendinopathy rapidly and with less additional damage. Their disadvantage is that they induce tendinopathy from the intermediate link. The type 1 collagenase model and TGF-β1 model are characterized by low cell density, relatively little vascularization and significant chondrogenesis, similar to the environment in which blood supply is severely disrupted in the late stage of degenerative tendinopathy in humans. In addition, such models may be suitable for the study of calcifying tendinopathy [78].

5. Animal models corresponding to inflammation

Inflammation is an essential process for tissue repair. In the resting state, macrophages and mast cells are the major immune cells in tendon tissue [79]. After activation, they release inflammatory cytokines and chemokines to recruit neutrophils and monocytes [80]. Immune cells release both pro-inflammatory cytokines (i.e., IL-1β, TNF-α, IL-6, etc.) and anti-inflammatory cytokines (i.e., IL-4 and IL-10), pro-inflammatory lipids (i.e., prostaglandin E2) and anti-inflammatory lipids (i.e., lipoxins), matrix degrading enzymes (i.e., MMPs, proteases, tryptases, etc.) and inhibitors of matrix degradation enzymes, thus they regulate the repair process of the tendon [22,81].

5.1. Pro-inflammatory lipid injection

Prostaglandins (PGs) are key lipid mediators in the regulation of inflammatory response. Due to the effect of cyclooxygenases, arachidonic acid is synthesized into PGH2, which is further processed by terminal synthases and generates the major PGs, including prostacyclin, PGE2, PGD2, and PGF2 [82]. PGE2 promotes macrophage production of IL-10 and polarizes into M2 type [83,84]. In stromal cell compartments, PGE2 can inhibit the proliferation of tendon stem cells and promote adipogenic and osteogenic differentiation [83].

Khan et al. [64] compared the effects of local injection with low (50 ng) and high dose (500 ng) PGE2 (days 0, 7, 14, and 21) on the patellar tendon of rabbits. There was no significant difference in Col fiber diameter between the two groups. Fatty infiltration was noted in the highly disorganized region.

Another important lipid mediator is PGE1. This compound is synthesized by cyclooxygenase using dihomo-gamma-linolenic acid as substrate, which had the ability to bind to PGE2 receptors EP2 and EP4 [85]. PGE1 may have potential anti-inflammatory effects, such as the inhibition of macrophage infiltration [86].

Continuous injection of PGE1 is often used to establish tendinopathy models. Sullo et al. [63] showed that after injection of PGE1 (800 ng) in rats Achilles tendon, the pathological scores at weeks 1, 3, and 5 were 8.9, 13.5, and 17.3, respectively. As for rabbits, Gunes et al. [87] reported after injection of PGE1 (1600 ng) for 4 weeks, Movin scores at weeks 4, 6, and 12 were 13.38, 9.83, and 8.59, respectively. These results suggest that about 1 week after PGE1 injection, tendon tissue entered degenerative tendinopathy [Fig. 3B].

5.2. Neurogenic inflammatory mediator injection

Tendon injury promotes the growth of peripheral nerve fibers in the tendon sheath into the tendon parenchyma, which produces neuropeptides (e.g., substance P (SP) and calcitonin gene-related peptide (CGRP)) to regulate the function of immune and stromal cells [88–90]. Mast cells express a variety of neuropeptide receptors, such as neurokinin 1 receptors (bound with SP), calcitonin receptor-like receptors, and glutamate receptors, and upon binding to ligands, inflammatory pathways are activated, causing the release of cytokines (e.g., TNF-α and IL-8) and chemokines [79,91–93]. Mast cell-derived neurotransmitters, such as histamine and dopamine, also in turn act on neurons [94]. SP promotes proliferation of tendon cells and synthesis of Col 3, while negative feedback inhibits infiltration of peripheral nerves [95,96].

Zhou et al. [66] compared differences between low dose (0.5 nmol) and high dose (5 nmol) SP local injections in rat patellar tendons. They found that low and high doses SP significantly enhanced the proliferation ability of tendon stem cells. However, low does induced the expression of tendon related genes and high does induced the expression of non-tendon related genes, especially PPARγ and Col 2. Oh et al. reported the method combining SP injection and treadmill running and set the study endpoint at 2 weeks [97].

5.3. Damage-associated molecular patterns and damage-associated molecular patterns analogue injection

TLRs play an important role in the initiation of inflammatory responses caused by infection and injury. TLR-1/2/4/5/6/11 that localize on cell surfaces recognize lipids, proteins, and lipoproteins, while TLR-3/7/8/9 that localize on endosomes recognize nucleic acids [98]. After binding to DAMPs, the downstream nuclear factor κ-light-chain enhancers of activated B cells (NF-κB) and mitogen-activated protein kinase (MAPK) pathways are activated, causing the release of pro-inflammatory cytokines, such as IL-1β and TNF-α [99]. These receptors have been reported in macrophages, mast cells, dendritic cells, and tendon cells [100,101]. DAMPs and DAMP analogues injection methods have been used to establish tendinopathy model.

Carrageenan is a sulphated linear polysaccharide of D-galactose and 3,6-anhydro-D-galactose derived from red seaweeds, which may activate TLR-4 [102,103]. As early as 2001, Tillander et al. [104] evaluated the effects of carrageenan on rat supraspinatus tendon. They found that injection of 5 μl of carrageenan (3%) per 2 weeks only increased macrophage infiltration without other pathological changes. Double does (10 μl) induced disordered Col fibers and fibrocartilaginous metaplasia at 18 weeks. Berkoff et al. [67] applied the carrageenan model to preclinical studies with weekly injections of 100 μl carrageenan (3%). They set the endpoint at 3 weeks.

5.4. Summary

Inflammation-related models are less commonly used than collagenase models. They are characterized by high cell density and inconspicuous chondrogenesis, similar to the stages of reactive tendinopathy and tendon dysrepair in humans. Different inflammatory mediators simulate tendinopathy dominated by different types of inflammation, which provides the possibility to accurately evaluate the efficacy of drugs.

6. Animal models corresponding to oxidative stress

Oxidative stress refers to the process by which oxidants damage biological macromolecules. In tendinopathy, oxidative stress promote inflammation by oxidize Col protein, membrane lipids and nucleic acids, but the source of the oxidant is unclear [14,105,106]. One possible reason is that the tendon undergoes a transient ischemia during tensile stress, and the production of ROS increases during subsequent reperfusion. Overuse disrupts the balance between ROS production and clearance.

The production of endogenous oxidants begins with the leakage of the electron transport chain. Which leads to the reduction of oxygen molecules (O_2) to superoxide ($O_2^{\bullet-}$) by single electrons. Then, the weak oxidant $O_2^{\bullet-}$ acts as a precursor contributing to the production of hydrogen

peroxide (H_2O_2) and peroxynitrite (ONOO−), and is further transformed into strong oxidants hydroxyl radical (•OH) and nitrogen dioxide ($•NO_2$). Therefore, the rate of H_2O_2 production largely determines whether oxidative stress occurs [107]. Liu et al. induced tendinopathy by injecting hydrogen peroxide into the Achilles tendon for purpose of evaluating the antioxidant effect of drugs [68].

Another approach is to simulate the process of ischemia/reperfusion. Simonin et al. released the suture 2 h after ligating both sides of the Achilles tendon and found that after 3 days the expression of Col 1 and Col 3 decreased and the expression of vascular endothelial growth factor increased in the tendon cells [108].

6.1. Summary

There is still a lot of room for development of oxidative stress-related animal models. Ischemia/reperfusion model induces tendinopathy from the initial link, while H_2O_2 model started from the intermediate link. The pathological changes caused by these modeling methods are similar to the stages of reactive tendinopathy and tendon dysrepair in humans.

7. Animal models corresponding to metabolic disorders

7.1. Diabetes mellitus

Diabetes mellitus (DM) typically triggers hyperglycaemia [109]. Type 1 DM is characterized by insulin deficiency, while type 2 is characterized by insulin resistance. High glucose condition promotes the expression of IL-6, MMP-2, Col 3, and NADPH oxidase (Nox) in tendon cells, while inhibiting the expression of scleraxis (Scx), mohawk (Mkx), and Col 1 [110,111]. In addition, high glucose condition promotes the adipogenic and chondrogenic differentiation of tendon stem cells and increase the expression of myofibroblast marker α-SMA [112–114]. Advanced glycation end products (AGEs) are formed by nonenzymatically glycated and oxidized proteins and lipids after exposure to sugar. In vivo, AGEs can interact with AGE receptors expressed in tendon cells and immune cells to trigger oxidative and inflammatory events via NF-kB signaling [115]. Common modelling strategies include chemical induction (e.g. streptozotocin and alloxan), diet (high fat and high glucose) and genetic modification [116–118].

Studentsova et al. [113] investigated the effects of hyperglycemia on the Achilles tendon in mice with type 2 diabetes induced by a high fat diet. The increase in stiffness occurred firstly at week 24, followed by an increase in gliding resistance and a decrease in metatarsophalangeal flexion angle at week 40 and a reduction in failure load at week 48. The pathological changes of tendon tissue were similar to reactive tendinopathy at week 40, and the diameter of Col fibers was reduced compared to the control group (180.4 nm vs. 200.1 nm).

The Achilles tendon of leptin deficient mice at 12 weeks showed rounded nucleus, variation in cellularity, and the appearance of chondrocyte-like tendon cells [119]. Col fibers showed unequal and irregular crimping, loosening, and increased waviness.

As for rats, intravenous or intraperitoneal injection with streptozotocin (STZ) diluted in 10 mM sodium citrate buffer at pH 4.5 (60–65 mg/kg) to induce type 1 DM is most common methods in preclinical studies of tendinopathy [120,121]. Volper et al. showed that 2 and 10 weeks after STZ intraperitoneal injection, mechanical properties (stiffness, failure load, deformation, stress, strain and Young's modulus) and histopathological results (fiber structure, fiber arrangement and cellularity) in the Achilles tendon were not different across groups [122]. Similar results were reported by Ueda et al., 6 weeks after STZ injection, fiber structure, fiber arrangement, rounding of the nucleus, and regional variations in cellularity were not significantly altered, but the expression of NOX1, MMP-2, TIMP-2 and IL-6 had significantly increased [110]. However, there was also evidence of increased mast cell density and capillary infiltration, mild Col fiber disorder in some areas, and increased nitric oxide production in the Achilles tendon 24 days after STZ injection [123]. [Fig. 3C].

7.2. Hypercholesterolemia

Tendinopathy is closely related to hypercholesterolemia. High serum cholesterol allows the accumulation of low-density lipoproteins (LDL), which are oxidized later in the interstitial compartment by pro-oxidants [124]. Then, oxidized LDL (oxLDL) is engulfed by tissue macrophages and stored as cholesterylester in cytoplasmic-neutral lipid droplets [125]. The balance between cholesterylester storage and the efflux of free cholesterol determines the inflammatory phenotype of macrophages. Cholesterol inhibits the proliferation of tendon cells and promotes apoptosis [16]. In addition, cholesterol promotes ROS generation [16,126]. Common modelling strategies include diet and genetic modification [127,128]. Apolipoprotein E (ApoE) knock-out, which acts as a ligand mediating the uptake of apoB-containing lipoproteins, and low-density lipoprotein receptor (LDLr) knock-out, which acts as a receptor to recognize apoB-containing lipoproteins, are common genetically modified models [129].

Grewal et al. [130] compared the effects of a high-fat diet on tail, patellar, and Achilles tendons in wild-type and ApoE −/− mice. They started the mice on a high-fat diet (21.2% fat) when they reached 7 weeks and sacrificed the mice at 30 weeks. A high-fat diet causes tendons to fail at lower loads, especially in ApoE −/− mice, and increased oxLDL accumulation. The average cross-sectional area of patellar tendons of ApoE −/− mice was larger than that of wild-type mice (0.97 ± 0.03 mm^2 vs. 0.82 ± 0.03 mm^2). Surprisingly, the positivity ratio of oil red O staining was higher in the wild-type mice. Finally, a high fat diet decreased the expression of Col 1, especially in ApoE −/− mice, and increased the expression of MMP-2 [Fig. 3D].

7.3. Summary

The advantage of the metabolic disorder related models are that they reproduce tendinopathy process for specific pathological conditions. Furthermore, they do not produce additional surgical damage. The major limitation of these models is longer modeling time, which may be why they are rarely used in large animals. Combined with other methods, such as treadmill running, it can effectively reduce the time it takes for tendinopathy to develop. Finally, more methods may be needed to evaluate the role of metabolic changes in tendinopathy, such as ligation of both sides of tendon to simulate anoxic conditions.

8. Animal models corresponding to traumatism

The mechanism by which chronic and acute injuries cause tendinopathy involves the production of DAMPs and changes in mechanical loading.

8.1. Microdamage

Due to differences in anatomical structure, only rodents are used as subacromial impingement animal models. A common surgical approach is to make a 5-mm incision above the acromioclavicular joint with blunt dissection of the deltoid and trapezius muscles, exposing the acromion [131,132]. Implants are then placed under the acromion to simulate acromion hyperplasia, leading to supraspinatus and infraspinatus tendon changes. Implants reported include microvascular clip, bone plates, polymer (e.g., polyether-ether-ketone), and allograft Achilles tendon, of which microvascular clip is the most common [133–136]. The expression of alarmins, such as IL-33, HMGB1, and S100A9, was significantly up-regulated by the first week after implantation [137]. Extensive cellular infiltration surrounding the surgical clip can be seen at this stage [138]. After 2 weeks, tendon tissues revealed hazy discoloration. Genes involved in tissue repair (aggrecan and Col 1/3) peak at this stage [134]. Furthermore, the biomechanical properties of tendon tissue are altered,

such as decreased tendon failure load and stiffness [134]. Several studies have reported a decrease in SOD activity at week 4 [139,140]. Between weeks 4 and 12, there was a significant increase in the expression of genes involved in matrix synthesis-degradation, including MMP-3/13/14, SOX9 and TGF-β [138,141]. Fatty infiltration also increased significantly [131]. Eliasberg et al. [141] showed that the failure load (5.20 vs. 1.50 N) and stiffness (4.95 vs. 1.47 N/mm) of the tendon tissue were still lower at week 12 compared with the sham group [Fig. 3E].

The needle puncture model is used mainly in small and medium sizes, such as mice, rats and rabbits. The effect of needle puncture in the tendon was influenced by the number and proportion of Col fibers injured [142]. In humans, needle puncture (acupuncture) promotes the repair of diseased tendons by promoting tendon cell proliferation and local blood circulation [143–146]. Needles of size 18–27 G are used to build the model [147]. The tendon microtear with reference to the rabbit cyclic loading model is approximately 650–1788 tears/mm^2 [148]. In the case of a 23 G needle with a diameter of 641.4 μm, for rats with a fibre diameter of 5–30 μm, a single puncture induces approximately 65–397 tears/mm^2, thus 3–8 times punctures may be necessary [142].

The common modelling strategy is to perform 3 to 9 punctures in the proximal, medial, and distal parts of the patellar or Achilles tendon [142,149]. The expression of COX2 and PGE2 has been shown to increase in the Achilles tendon 30 min after needle puncture [150]. Riggin et al. [151] compared the effects of mild single needling session (3 penetrations using a 27 G 1/2″ needle) and moderate single needling session (6 penetrations using a 27 G 1/2" needle) on the supraspinatus muscle of rats. Moderate group significantly increased cellularity, cell roundness and proteoglycan content at week 1, and returned to normal levels at week 6. While the mild group qualitatively demonstrated increases in these properties as well, there were not statistically significant compared with control group. Furthermore, the production of Col 3, TNF-α and IL-1β significantly increased at week 1 in both groups and recovered to nearly normal levels at week 6. In another study, Diez et al. [152] reported that mild consistent needling session (3 penetrations once per week) only increased the expression of COX2, MMP2, Col 3, and Scx genes at week 4, but did not induce substantial changes including structure and arrangement of Col fibers and inflammatory cell infiltration [151]. Kim et al. [142] showed that severe single needling session (9 penetrations using a 23G needle) induced significant tendon degeneration at week 1 and 4. Bonar scores were 9.0 ± 1.41 and 9.75 ± 1.98, respectively. In addition, needling puncture has also been found to promote tendon mineralization [153]. [Fig. 3F].

8.2. Non-microdamage

Longitudinal and transverse incision methods are used to establish tendinopathy models. One longitudinal incision significantly increased vessel count at weeks 1 (9.8 ± 3.95 vs. 7.19 ± 2.82) and 4 (15.5 ± 4.51 vs. 13.1 ± 4.49) and returned to normal levels at 6 weeks in rabbits' Achilles tendon [154]. No change in the expression of Col 1 and Col 3, Col fiber structure, and arrangement were seen. In another long-term study, one longitudinal incision significantly increased tendon cross-sectional area from day 0 (16 ± 2 mm^2) to day 84 (26 ± 6 mm^2) and peaked at day 21 (36 ± 12 mm^2) [155]. Ultrasonography showed that tendon lesions increased from 21increased form 21 days–84 days and peaked at 42 days. Johnson et al. [156] created 16 longitudinal incisions within the top third of the infraspinatus tendon thickness to replicate tendon tears that induced chronic degeneration in sheep. The tendon cross-sectional area increased at 6 and 12 weeks, and decreased at 18 weeks. Peak stress decreased at 6 and 12 weeks and increased at 18 weeks. This result suggests the formation of scar-like tissue after 12 weeks. Across 6, 12, and 18 week time points, tendon tissue showed decreased fibroblast density, smaller, less frequent blood vessels, and increased Col disorganization with decreased tinctorial intensity. Compared with normal tendon tissue, Bonar scores were increased by 173.7% ($p < 0.001$), 136.8% ($p < 0.001$), and 152.6% ($p < 0.001$) at 6, 12, and 18 weeks, respectively [Fig. 3G].

Depending on the depth of incision and the surgical region, the transverse incision method simulates different types of tendon rupture. Melrose et al. [157] showed that transverse incision in the middle region of sheep infraspinatus tendon induced mild Col fiber disturbance and changed ECM at 4 weeks. In rats, the method of complete transverse incision near the bone insertion point of the Achilles tendon was used in preclinical studies, and histological scores changed by more than 4 points at 8 weeks [158,159]. In sheep, Johnson et al. [160] evaluated the effects of incomplete transverse incision near the bone insertion point of the supraspinatus tendon. The tendon cross-sectional area revealed increases of 60.3%, 62.5%, and 58.8% at 6, 12, and 18 weeks, respectively. Peak stress exhibited decreases of 50.0%, 69.1%, and 45.6%. Bonar scores were 8.67, 8.83, and 9.38, respectively. The amount of organized Col fibers exhibited decreases of 51.0%, 25.7%, and 4.4%. In another study, complete transverse incision of the greater trochanter insertion of the gluteus medius tendon resulted in Movin scores of 14.3 ± 1.6 and 12.9 ± 1.4 at 6 and 16 weeks, respectively [161]. [Fig. 3H].

8.3. Summary

Microdamage tendinopathy models are mainly established in small animals. The subacromial impingement model reproduces the natural course of tendinopathy and is one of the most ideal tendinopathy models. The disadvantage is the relatively large surgical damage. In additioon, the hardness of the implant may affect the rate at which tendinopathy progresses. The needle puncture model is often used for shallower tendons such as the Achilles tendon and the patellar tendon. Puncture times and needle diameter have great influence on the progression of tendinopathy. Mild single needling session may only induce reactive tendinopathy, while severe single needling session may induce tendon dysrepair. Non-microdamage tendinopathy models are mainly established in large animals. The longitudinal incision model simulates the longitudinal tear of the tendon, while the transverse incision model simulates the transverse tear and rupture of the tendon.

9. Animal models corresponding to mechanical load

Moderate mechanical loading is necessary to maintain the normal function of tendon cells. The intratendinous pressure model proposed by Pringels et al. [21] explains the role of overload in terms of cellular response. Excessive mechanical loading promotes the production of Col 2, Col 3, glycosaminoglycans, and proteoglycans by tendon cells, leading to the limitation of tendon internal space and the decrease of tendon permeability [162–164]. Then, the increase of intratendinous pressure impairs vascularization and leads to hypoxia, which in turn accelerates the destruction of ECM. However, mechanical load deprivation also promotes the production of Col 3, MMPs and osteogenic differentiation of tendon cells, leading to the destruction of ECM [165–167].

9.1. Overloading

In rodents, treadmill running methods has been widely used. Common modelling strategies include moderate treadmill running (MTR) and intensive treadmill running (ITR) following a training period of 1–2 weeks. The running frequency is set 5–7 days a week. The specific methods are shown in Supplement 2. We recommend the relatively high intensity MTR methods, such as 15 m/min for 50 min per day or 20 m/min for 30 min per day for mice and 17–19.3 m/min for 60 min for rats [168–174]. (Supplemental marterial 4)

MTR methods did not cause significant fiber structure changes within 8 weeks, but may be accompanied by a slight increase in cellularity and a rounder nucleus [169,175,176]. Some studies showed increased expression of Col 3, MMP-3/13, vascular endothelial growth factor and SOX9, and production of ROS [168,169,177]. At week 12, the expression

of chondrogenic genes (SOX9 and Col 2) and osteogenic genes (bone morphogenetic protein-2) increased significantly [178]. The MTR methods reproduced reactive tendinopathy within 8 weeks [170,171,179]. At this stage, tendon cells may undergo adaptive responses, such as increased production of Col 1 production and expression of tendon related genes (e.g. tenomodulin) [178,180]. ITR methods increased expression of adipogenic, chondrogenic and osteogenic genes and production of PGE2 as early as 4 weeks [169,181].

A special type of over loading model is the spontaneous model, which involves anatomical differences. Horses and dogs can spontaneously develop tendinopathy [182,183].

The distal forelimb of horses consists of the upper and lower carpus, third metacarpals and degenerated second and fourth metacarpals as well as three phalanxes (proximal, middle, and distal). The carpal canal is located on the palmar aspect of the carpus and contains superficial and deep digital flexor tendons (SDFT and DDFT), which end in the middle phalanx and distal phalanx, respectively [184]. The SDFT performs similar functions as the human Achilles tendon, storing and releasing energy by stretching and recoiling, which decreases the energetic cost of locomotion [185]. Thus, approximately 75–95% of tendon injuries occur in the forelimb SDFT [186].

The anatomical structure of the dog's shoulder joint is similar to humans. The most notable differences are elongated humeral head, deep glenoid, and prominent greater tuberosity [187]. The supraspinatus tendons are exposed to high loading due to differences in locomotion patterns and are therefore susceptible to tendinopathy [188–190].

Other methods of overloading model included electrical stimulation of muscle contractions or direct stretching of tendons [148,191–193]. These methods save the time required to induce lesions, but given that human tendinopathy is generally a chronic process, the conclusions drawn from these models are of limited translational value.

9.2. Underloading

Botox intramuscular injection is used to reproduce the conditions of muscle atrophy. Chen et al. [194] showed that 2 weeks after injection with 10 μl botulinum toxin (3 unit/kg) into the vastus lateralis of quadriceps muscles in mice, the volume of the patellar tendon had decreased, and the tenogenic differentiation ability of isolated tendon stem cells had decreased.

9.3. Destabilization loading

Destabilization loading models are established by destroying the surrounding tendons with synergistic or antagonistic functions. Abraham et al. [195] found decreased mechanical strength in rat supraspinatus tendons 4 weeks after infraspinatus tendon transection. In another study, sheep SDFT transection significantly increased expressions of Col 3, versican, biglycan, lumican, and MMP1 in DDFT at 8 weeks [196].

9.4. Summary

In overloading models, treadmill running models and spontaneous models are widely used to study tendinopathy. The advantage of them is roughly reproducing the natural course of tendinopathy. The main reason limiting the use of these models is the high time cost. For treadmill running models, some studies have found that it may be difficult to force animals to exercise at more than a voluntary level, so the final pathological stage may be limited to reactive tendinopathy [197]. For spontaneous models, horses are the most commonly used species. Some studies have suggested that goats may also develop spontaneous tendinopathy, although they are rarely used as spontaneous models [198].

Destabilization loading-related animal models may be able to simulate the failure of adjacent auxiliary fixation structures, while underloading models may be able to simulate muscle atrophy, such as in elderly patients.

10. Future prospects

Animal studies have many advantages in elucidating the pathogenesis of tendinopathy, such as the exploration of mechanisms of early tendinopathy or allowing the assessment of single risk factor. A deep understanding of pathogenesis can help advance the management of tendinopathy. A fundamental deficiency of most tendinopathy models is an attempt to reproduce the chronic process using acute interventions, which increases the difficulty of mapping human tendinopathy pathological models to animal models. In addition, existing studies have shortcomings in the management of postoperative mechanical load, which may amplify variation among individuals.

Recently, Zhang et al. reviewed the application of large animal models in tendinopathy regarding injuries to four tendons: rotator cuff, patellar ligament, Achilles tendon, and flexor tendon [199]. In a systematic review of 409 animal studies on rotator cuff injury, Zhao et al. summarized the research purposes, species, sites of injury and, modeling methods of these studies [200]. However, these studies failed to answer the question of the scenarios in which each model is suitable for application, and how they correspond to pathological models of human tendinopathy. There is no animal model can perfectly reproduce human tendinopathy. As we have done in this review, we should identify the achievable and relevant targets for each of tendinopathy models. Different hypotheses should be tested with different animal models. Furthermore, the establishment of correspondences between the pathological patterns of animal models and the pathological models of human tendinopathy allow us to evaluate the effects of interventions more finely. The filling of these gaps not only enhances the clinical translational ability of the existing models, but also lays a foundation for the development of new ones.

In future studies, we may consider incorporating imaging methods such as magnetic resonance imaging, micro-computed tomography, and ultrasound in tissue evaluation, which can not only provide longitudinal assessment over time but also parallel to what is done in humans, increasing clinical translation abilities. Mice have a variety of transgenic strains that not only allow testing of the role of specific genes in the development of tendinopathy, but also provide lineage tracing capabilities. Non-microdamage models of tendinopathy appear to be rarely established in small animals, possibly due to the complexity of microsurgical techniques. Compared with trying to manipulating genes in large animals, developing microsurgical techniques in small animals may be easier and cheaper.

With the development of technology, more and more methods can be used to analyze the mechanism of disease or evaluate the effect of treatment. Although still immature, tendon organoids allow for the simulation of tendon development and pathology ‘in a dish’. Computer models allow researchers to infinite repeat experiments without concerns related to cost or the ethical considerations. Animal models bear the responsibility for translating the data collected from these models into clinical settings. It is necessary for us to increase the translation value by identifying the scenarios in which each animal model is suitable for application.

11. Concluding remarks

This study examines existing models of tendinopathy with the aim of identifying scenarios in which each model is suitable for application and thereby increasing its translational value. The pathogenesis of human tendinopathy that the modeling method represented, the pathological process that the model presented, and the anatomical characteristics of the species determine the characteristics of the model.

For studies that aim to study the pathophysiology of tendinopathy, naturally occurring models, treadmill models, subacromial impingement models and metabolic models are ideal. They are closest to the natural process of tendinopathy in humans. However, their common disadvantage is time consuming.

For studies that aim to evaluate the efficacy of possible treatments, the selection should be made according to the pathogenesis simulated by the modeling method. Existing tendinopathy models can be classified into six types according to the pathogenesis they simulate: extracellular matrix synthesis-decomposition imbalance, inflammation, oxidative stress, metabolic disorder, traumatism, and mechanical load.

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Declaration of competing interest

A conflict of interest occurs when an individuals objectivity is potentially compromised by a desire for financial gain, prominence, professional advancement or a successful outcome. The Editors of the *Journal of Orthopaedic Translation* strive to ensure that what is published in the Journal is as balanced, objective and evidence-based as possible. Since it can be difficult to distinguish between an actual conflict of interest and a perceived conflict of interest, the Journal requires authors to disclose all and any potential conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jot.2023.06.005.

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