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Animal Models of Tendinopathy Induced by Chemicals

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Abstract

Tendinopathy is a common disease that a f icts a wide range of people irrespective of age and gender. The underlying pathogenesis is still poorly understood. Since it is impossible to directly conduct experiments on humans, animal models of tendinopathy are essential not only to study its developmental mechanisms, but also to devise new treatment options for tendinopathy. Chemically-induced models are usually low-cost, reproducible, less labor-intensive and easy to perform. Chemicals that are currently being used to produce tendinopathy in animals include collagenase, cytokines, transforming growth factor-β1 (TGF-β1), fuoroquinolone, kartogenin, prostaglandin, statin, carrageenan and elastase. This paper discusses the development and use of animal models induced by chemicals.

Keywords: Tendon; Tendinopathy; Animal model; Chemical-induced; Collagenase

Introduction

Tendinopathy, a disease of the musculoskeletal system which is prevalent in the general population and especially in athletes, is characterized by activity-related chronic pain, focal tendon tenderness, tendon swelling and intratendinous imaging changes. e etiology of the disease is not completely clear. Mechanical overloading of tendons is one of the commonly agreed factors. Other factors including age, gender, body weight, gene polymorphisms, and anatomical and biomechanical variations are thought to be involved in the etiology of tendinopathy [1]. Tendinopathy is becoming one of the most common non-fatal disease of the 21st century, and an important cause of work disability and loss of quality of life [2]. If not adequately treated, tendinopathy may lead to complete tendon rupture, which o en requires surgical repair. Although some progress has been made and various treatments have been applied to treat tendinopathy in recent years, we still know little about the underlying pathogenesis of tendinopathy. One of the principal reasons is the limited availability of specimens. While tissue can be obtained surgically, the tissue obtained from patients undergoing surgical procedures is generally already well developed in terms of histopathology. Additionally it is rarely possible to obtain developing specimens from patients because their condition is usually not su ciently severe to warrant surgical intervention. Hence, a validated animal model is essential to enable in-depth studies on the etiology and pathogenic mechanism of tendinopathy, to nd out how the disease occurs and develops, and to seek new treatment for it.

Currently, there are many ways to establish animal models of tendinopathy, and most of them can be categorized into two groups. One is mechanical overloading which is considered to be the most common extrinsic factor causing tendinopathy [3-5]. e other model group, which relies on intrinsic factors, involves the introduction of chemicals into normal animal tendons [6-8]. is paper discusses the development and use of animal models induced by chemicals, highlights potential outcome measures that may be used in animal tendon research, and reviews current animal models of tendinopathy induced by chemicals.

Materials and Methods

All literatures were retrieved from PubMed database. e keywords “tendinopathy,” “tendinosis” “tendinitis” and “animal model” were used for searching the literature published before September 2020. A er screening the title, abstract and full text of each article, duplicate and irrelevant articles were removed, and 73 articles were nally included in this review. e ow chart of searched results presented in Figure 1.

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in humans to be considered valid. If there are new ndings in human tendinopathy pathology, animal model criteria should be updated accordingly.

Current chemicals to produce animal models of tendinopathy

Collagenase: Among the chemicals to produce animal models of tendinopathy, collagenase is the earliest and most widely used15. It was initially pioneered by Silver et al to study tendinitis by mimicing the intrinsic condition of tendon rupture. Brie y, it was found to induce a reproducible lesion consistent with spontaneous tendon injury which showed tendon degeneration accompanied by a classic in ammatory response which exist about one week [15,16]. Collagenase is currently being used by many research teams to establish tendinopathy models in animals including horse, sheep, rabbit and rat, in various anatomic locations such as the super cial digital exor tendon (SDFT), deep digital exor tendon(DDFT), Achilles tendon, patellar tendon and rotator cu [17-23].

Collagenase is usually applied by intratendinous injection (Table 1). A er injection, the tendon exhibits collagen matrix and ber disorganization, increase in rounded cell density, and s marked increase in vascularity [6,22,24,25]. Altered biomechanical properties including larger cross-sectional area, decreased load to failure, lower sti ness, etc, have all been observed [25-28] (Table 1). ese characteristics are similar to those observed in human samples. And the severity of collagenase induced injury seems to be dose-related [6].

In human, collagen type I is the major collagen type in healthy tendon, but when matrix degeneration resulting from tendinopathy occurs, a decrease in collagen type I and an increase in collagen type III occurs [29,30]. Findings from Liu et al in their collagenase model of rats displayed the same results as previously described [31]. In their research, they also found sustained or increased expression in decorin, biglycan, bromodulin and aggrecan which are consistent with clinical samples [11,32,33] and increased expression in substance P(SP) and calcitonin gene-related peptide(CGRP) which positively correlates with activity-related tendon pain. Dahlgren and colleagues reported type III collagen expression is initially increased in endotenon and subsequently in the parenchyma of healing tendon [34].

Matrix metalloproteinases are thought to participate in the pathogenesis of tendinopathy. MMPs are members of a family of enzymes that can break down proteins such as collagen. It makes tendon more susceptible to microdamage, and further accelerate lesions. Numerous researchers reported a substantial increase in the expression of MMPs (MMP-1,MMP-3,MMP-9,MMP-13), and a decrease in the expression of its counterpart inhibitor, i.e., tissue inhibitor of metalloproteinases (TIMP), in the collagenase model (Table 2). Injury treatments including piperine, low level laser therapy, photobiomodulation therapy, and platelet-rich plasma were performed in these experiments and showed inhibitory e ects on MMPs [19,35-40].

In conclusion, tendinopathy induced by collagenase exhibit many major qualities seen in clinical cases. It can be considered as an e cient and valid model of tendinopathy. However, it should be noted that drawbacks also exist. ere is an acute in ammatory reaction a er injection which is not seen in human. Also, a chronic healing response caused a er collagenase injection is incompatible with clinical cases; for humans, the healing process is usually impaired [16].

Cytokines: Stone and colleagues wished to produce a model that better emulate the reversible lesions that represent the majority of the painful tendons seen in clinical practice. ey injected cytokined the sa

changes in mice which similar to those seen in human tendinopathy. But de ciencies also exist. First, the long-term status of the model is not available because of the short duration of induced changes which only last for 4 weeks. Second, the progression of pathological changes is unstable. For the above reasons, this model may be useful for studies

into the paratenon of the deep digital exor tendon to study the e ect of in ammatory tissue adjacent to tendon. Although the injury was not directly introduced into tendon, remarkable results include presence of MMP-9, degradation of non-collagenous proteins and GAG, cellular in ltrate and less organized collagen bundles were detected in the tendon [67,68]. Experiments conducted by Vieira et al. were nished within 24 hours, which means their ndings were instant consequences of carrageenan. Hypercellularity, ber disorganization, angiogenesis, cell In ltration, nuclear rounding and decreased ultimate failure load were induced in rat tendon by carrageenan injection for weeks [7,69,70] (Table 2). It should be noted that both instant and sustained experiments of carrageenan give clues to mechanism by which inflammatory cells which is usually non-existent in clinical diseased specimens. makes carrageenan-induced tendinopathy less credible. However,

KGN illustrated localized chondrogenesis with neovascularization in rat Achilles tendons. ... also performed in vitro experiments to understand the cellular mechanism of KGN induced ... the formation of cartilage-like tissues in vivo. Results showed that KGN up-regulated the chondrocyte specific genes, e.g. collagen type II and Sox-9 in tendon stem cells(TSCs) treated with KGN in vitro [52] (Table 2). Brie y, certain features of degenerative tendinopathy frequently observed in clinics have been captured by KGN-induced in an animal tendinopathy model. ese ndings suggest KGN has the potential to be a useful model of tendinopathy. Disadvantage is that the implantation procedure is a little more complex than injection and gavage. And further studies should focus on the long-term alterations of KGN model.

Prostaglandin (PG): Prostaglandin has been used to induce tendinopathy, it is based on up-regulated production of prostaglandin-E2 (PGE2) by human tendon broblasts under mechanical stimulation in vitro [53] and increased PGE2 expression exercise in vivo [54]. PGE2 was injected into the rabbit patellar tendon once a week for 4 weeks (Table 1). Following treatment, hypercellularity, abnormal tissue architecture, tendon disorganization and degeneration were evident, coupled with decreased bril diameter (Table 2). Interestingly, despite PGE2 being a known in ammatory mediator, there were no in ammatory cells in the tendon 1 week a s4aer repeated PGE2 injection. is suggests that degeneration may be the principal e ect of PGE2 instead of in ammation [55]. PEG1 Achilles tendon of rats. Acute in ammation was manifested 1 week a s4aer injection, followed by weeks of degeneration characterized by increased vascularity, cellularity and ber disorg term e ects of prostaglandin injections. Evidence in biomechanics and molecular level processes has not been reported.

Statin: Statins are widely prescribed medications used for the treatment of hyperlipidemia. Tendinitis and tendon ruptures have been observed in frequent user of stains. E ected tendons include the distal biceps tendon, the quadriceps tendon, the patellar tendon and the Achilles tendons, the latter of which is the most commonly a ected one [57-60]. Statins, therefore, may be involved in the etiology of tendinopathy and may be used as agents to produce tendinopathy in animals (Table 1). Statins may change the ECM components in the tendon, with increases in GAGs and decrease in collagen I accompanied by active expression of MMPs [61]. e use of atorvastatin and simvastatin in a rat model demonstrated reduced epitenon thickness, ber disorganization, increased amount of ED1+ macrophages and impaired biomechanical strength in the Achilles tendon [62] (Table 2). Other research also reported foci of dystrophic calci cation in Achilles tendon with improved biomechanica properties of the tibias simultaneously [63]. Although statins may induce tendinopathy in human, they are generally not involved in most cases of tendinopathy and neither do they induce tendinopathy in every patient. It may be useful to explore the side-e ect of statins on tendons, but the valid of statin-indued tendinopathy animal model is doubtable.

Carrageenan: Carrageenan is a polysaccharide extracted from the cell wall of Rhodophyta algae. It is widely used to induce in ammation in vivo [64,65]. It has long been debated whether in ammation takes part in the underlying pathogenesis of tendinopathy and carrageenan has been used to study the e ects of in ammation on tendons (Table 1). Tillander et al. revealed that repeated subacromial injection of carrageenan resulted in bursitis featured by degenerative matrix, macrophage in ltration and bone and brocartilaginous metaplasia in the rat supraspinatus tendon [66]. Vieira et al. injected carrageenan

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