

Advanced glycation end productions and tendon stem/progenitor cells in pathogenesis of diabetic tendinopathy

Liu Shi, Pan-Pan Lu, Guang-Chun Dai, Ying-Juan Li, Yun-Feng Rui

ORCID number: Liu Shi [0000-0002-8990-4019](https://orcid.org/0000-0002-8990-4019); Pan-Pan Lu [0000-0002-9751-2947](https://orcid.org/0000-0002-9751-2947); Guang-Chun Dai [0000-0003-1440-4850](https://orcid.org/0000-0003-1440-4850); Ying-Juan Li [0000-0002-5580-1003](https://orcid.org/0000-0002-5580-1003); Yun-Feng Rui [0000-0001-9019-5531](https://orcid.org/0000-0001-9019-5531).

Author contributions: Shi L wrote the paper; Lu PP provided assistance with the figure preparation; Dai GC assisted in performing the search and collection of the relevant publications; Li YJ provided input during the drafting of the paper; Rui YF revised and proofread the paper.

Supported by National Natural Science Foundation of China, No. 81572187 and No. 81871812; Jiangsu Provincial Medical Talent, The Project of Invigorating Health Care through Science, Technology and Education, No. ZDRCA2016083; Natural Science Foundation of Jiangsu Province for Young Scholars, China, No. BK20200398; Entrepreneurship and Innovation Program of Jiangsu Province, China, No. 1190000054; and The Six Projects Sponsoring Talent Summits of Jiangsu Province, China, No. LGY2017099.

Conflict-of-interest statement: The authors have no conflict of interest for this manuscript.

Open-Access: This article is an

Liu Shi, Pan-Pan Lu, Guang-Chun Dai, Yun-Feng Rui, Department of Orthopaedics, Zhongda Hospital, School of Medicine, Southeast University, Nanjing 210009, Jiangsu Province, China

Ying-Juan Li, Department of Geriatrics, Zhongda Hospital, School of Medicine, Southeast University, Nanjing 210009, Jiangsu Province, China

Corresponding author: Yun-Feng Rui, MD, PhD, Deputy Director, Professor, Department of Orthopaedics, Zhongda Hospital, School of Medicine, Southeast University, No. 87 Ding Jia Qiao, Nanjing 210009, Jiangsu Province, China. ruiyunfeng@126.com

Abstract

Tendinopathy is a challenging complication observed in patients with diabetes mellitus. Tendinopathy usually leads to chronic pain, limited joint motion, and even ruptured tendons. Imaging and histological analyses have revealed pathological changes in various tendons of patients with diabetes, including disorganized arrangement of collagen fibers, microtears, calcium nodules, and advanced glycation end product (AGE) deposition. Tendon-derived stem/progenitor cells (TSPCs) were found to maintain hemostasis and to participate in the reversal of tendinopathy. We also discovered the aberrant osteochondrogenesis of TSPCs *in vitro*. However, the relationship between AGEs and TSPCs in diabetic tendinopathy and the underlying mechanism remain unclear. In this review, we summarize the current findings in this field and hypothesize that AGEs could alter the properties of tendons in patients with diabetes by regulating the proliferation and differentiation of TSPCs *in vivo*.

Key Words: Tendinopathy; Diabetes mellitus; Tendon stem/progenitor cells; Advanced glycation end products

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Core Tip: Patients with diabetic tendinopathy usually suffer from chronic pain, restricted joint motion, calcium deposition, and even tendon rupture. Advanced glycation end products (AGEs) have been shown to affect tendon biology and biomechanical properties. In addition, tendon-derived stem/progenitor cells (TSPCs) play an important role in tendon hemostasis, regeneration, and repair. However, the

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Manuscript source: Invited manuscript

Specialty type: Cell and tissue engineering

Country/Territory of origin: China

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B, B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

Received: April 6, 2021

Peer-review started: April 6, 2021

First decision: May 12, 2021

Revised: May 26, 2021

Accepted: August 17, 2021

Article in press: August 17, 2021

Published online: September 26, 2021

P-Reviewer: Cigrovski Berkovic M, Saengboonmee C

S-Editor: Gao CC

L-Editor: Wang TQ

P-Editor: Xing YX



relationships between diabetic tendinopathy, AGEs, and TSPCs remain unclear. Thus, in this review, we summarize the current findings and discuss the possible relationships between AGEs and TSPCs. This might provide new guidance for the development of effective treatments for diabetic tendinopathy.

Citation: Shi L, Lu PP, Dai GC, Li YJ, Rui YF. Advanced glycation end productions and tendon stem/progenitor cells in pathogenesis of diabetic tendinopathy. *World J Stem Cells* 2021; 13(9): 1338-1348

URL: <https://www.wjgnet.com/1948-0210/full/v13/i9/1338.htm>

DOI: <https://dx.doi.org/10.4252/wjsc.v13.i9.1338>

INTRODUCTION

Tendinopathy is a common musculoskeletal complication of diabetes mellitus (DM)[1, 2]. Patients with DM have a higher incidence of tendinopathy than healthy patients of the same age[3]. The Achilles tendon, patellar tendon, and rotator cuffs are the most frequently affected[4]. The classic symptoms of diabetic tendinopathy usually manifest as chronic pain, limited range of joint motion (ROM), and tendon rupture[2,4,5]. With the progression of diabetic tendinopathy, increased stiffness and thickness and decreased biomechanical properties of Achilles tendons have been reported, and these symptoms usually result in an altered gait and accelerated plantar ulcer formation in DM patients with poor glucose control[2]. Disordered arrangements of excessive collagen fibers and even calcified sites were observed by ultrasound at the entheses of the Achilles tendons[6]. In their electron microscopy study, Grant *et al*[7] also reported that the collagen fibers of the Achilles tendon presented in twisted, curved, and overlapping arrangements in DM patients.

Histological analysis has revealed prominent fibrochondral metaplasia and granulation tissue hyperplasia in DM patients with stenosing flexor tenosynovitis[8]. We also observed microtears in disorganized collagen fibers, blood vessels, and rounded changing cells in the patellar tendons of rats with experimental DM[9]. Moreover, as the characteristic products of DM, advanced glycation end products (AGEs) were discovered in DM tendons[10,11]. Once irreversible AGEs accumulate, they can modify proteins and ultimately damage tendon tissues. Among the various types of cells in tendon tissue, tendon-derived stem/progenitor cells (TSPCs) show multidifferentiation potential and exhibit the ability to maintain hemostasis and reverse tendinopathy[12-16]. Our previous study reported that the impaired functions of diabetic tendon-derived TSPCs showed abnormal osteochondrogenic differentiation *in vitro*, which might also account for the dysfunctions of DM tendons[9]. The histopathological alterations in the tendons of diabetic subjects could partially explain the weakened tension, decreased biomechanical properties, limited ROM, and even the ease of rupture in DM patients. However, the underlying pathological mechanism of diabetic tendinopathy remains unclear. In this review, we summarize the current findings in the fields of diabetic tendinopathy, AGEs, and TSPCs and hypothesize that AGEs could alter the fates of TSPCs to exacerbate tendinopathy in DM patients.

HISTOPATHOLOGICAL FEATURES OF DIABETIC TENDINOPATHY

Many efforts have been made to investigate the histopathological changes associated with diabetic tendinopathy. Ji *et al*[17] observed blood vessel hyperplasia and excessive collagen fibers in leptin-deficient mice. In some subjects, microtears were found to have red blood cell (RBC) deposition and chondrocyte-like cells surrounding the sites of the microtears[17]. In streptozotocin (STZ)-induced DM rats, we also found characteristic histopathological features in DM tendons, such as RBC deposition and microtears, by hematoxylin and eosin staining[9]. By immunohistochemical staining, the expression of vascular endothelial growth factor was found to be significantly increased in the experimental tendons of patients with diabetes, which may contribute to vascularization changes[18]. As characteristic products of DM, AGEs have been reported to be deposited in various organs and tissues[19,20]. In tendons of patients with diabetes, AGEs accumulate in the extracellular matrix (ECM) of tendon cells.

During the early stage of STZ-induced type I DM, we also found the deposition of AGEs in the ECM of rat patellar tendons. Moreover, we discovered decreased expression levels of type I collagen (Col I), tenomodulin (TNMD), and decorin (DCN) in tendons of patients with diabetes. Nevertheless, these tendon cells express higher levels of osteochondrogenesis-associated proteins [osteopontin (OPN), osteocalcin (OCN), SOX9, and collagen type II (Col II)] in the ECM[9]. These results suggested that the pathologic manifestations of chondrification and ossification observed in tendons of patients with diabetes might be ascribed to the aberrant differentiation of these autologous TSPCs in tendon tissue into chondrocytes and osteocytes. However, current studies cannot fully explain the alterations, especially heterotopic calcification and chondrogenesis, in tendons of patients with diabetes at the cellular and histological levels[1,9].

FORMATION AND ACCUMULATION OF AGES IN TENDONS OF PATIENTS WITH DIABETES

The niche of TSPCs in tendon tissue is complicated. Numerous studies have demonstrated the importance of niches in mediating the proliferation and differentiation of stem cells[21-23]. Many factors, such as ECM, biomechanical stimulation, biologically active factors, and pH, could affect the functions of TSPCs *in vivo*[21].

As a distinctive product of DM, AGEs can excessively deposit in connective tissues [10,24-27]. AGEs are derived from nonenzymatic products of the interactions of long-lived proteins with glucose[19,28]. The formation of AGEs is quite slow and spontaneous in healthy subjects[29]. In low metabolic tissues, such as tendons and ligaments, AGEs can accumulate with aging. In addition to aging, the base level of glucose can also affect the formation and accumulation of AGEs *in vivo*[11]. The main component of tendon ECM is collagen type I (Col I), whose half-life ranges from 1 to 2 years; due to this longevity, it is sensitive to the glycoxidation process, which in turn highlights the accumulation of AGEs in tendons of patients with diabetes, which further alters the qualities of tendon ECM[11,26,30,31]. AGEs are mainly deposited in the outer layer or the most distal and proximal regions of the tendons instead of in the core regions in aged tendon samples[32]. However, to date, no studies have focused on region-specific histological analysis of AGE deposition in tendons of patients with diabetes.

Among the subtypes of AGEs, AGE-2 (glyceraldehyde-derived AGEs) and AGE-3 (glycolaldehyde-derived AGEs) are the main subtypes that can be detected in the sera of diabetic patients and they exhibit toxic bioactivities in various cells[33]. In osteoarthritis patients with DM, AGE deposition could lead to increased skeletal fragility and a higher fracture risk in aged people[34,35]. The main reason for this might be the cross-links formed by AGEs between the collagen strands[36]. The formation of these cross-links could result in increased stiffness and decreased biomechanical properties of diabetic cartilage and tendons.

In addition to the cross-links among the collagen fibers in DM tendons, the expression of the receptor for AGEs (RAGE) was also evaluated. Activation of AGE-RAGE could mediate many downstream signaling pathways in many kinds of cells and lead to many functional responses[37,38]. For instance, it induces cell death[39], regulates the expression of the inflammatory response[39], and degrades the ECM[40]. The study by Yokosuka *et al*[27] demonstrated the accumulation of AGEs in the ossified spinal ligament and suggested that the interaction of AGEs with RAGE is an important factor for the progression of spinal ligament ossification. In osteoblast-like cells, AGEs can regulate the differentiation stages *via* specific receptors[41]. Moreover, the latest research revealed that AGEs inhibited the osteogenic differentiation of mouse adipose-derived stem cells (ASCs) *in vitro*[42]. These studies demonstrated that the chronic accumulation of AGEs has negative impacts on these tissues and organs. Therefore, more attention has been given to determining the influences or underlying mechanisms of AGEs on musculoskeletal systems.

AGES ALTER THE BIOMECHANICAL PROPERTIES OF TENDONS

It has been documented that tendon tissue exhibits an inherent triple helix structure [43]. Accumulated AGEs could cross-link neighboring collagen molecules within the tendons[20]. The intermolecular cross-links between neighboring collagen molecules

may connect lysine to arginine residues or lysine to lysine[44]. In DM patients, the arrangement of collagen fibers in the Achilles tendon exhibited a highly disorganized structure under electron microscopy, and these structural abnormalities might be ascribed to the deposition of AGEs[7].

Various studies have demonstrated that cross-links between collagen fibers could affect the biomechanical properties of the musculoskeletal system. Currently, few studies have investigated the biomechanical effects of AGEs on human tendon tissues. In osteoarthritis, cross-links caused by AGEs increased the stiffness of the collagen network in human articular cartilage[36].

However, the conclusions about the effects of AGEs on tendon mechanics are contradictory. Sell and Monnier[45] reported that the cross-links formed by AGEs could increase the C57BL/6 mouse tendon strain. In isolated rabbit Achilles tendons, after glycation *in vitro*, the maximum load, stress, strain, and Young's modulus of elasticity were increased compared with those of the nonglycated tendons[46]. Biochemical analysis revealed significantly increased expression of pentosidine, which is recognized as a marker of AGEs, in glycated rabbit Achilles tendons. The cross-links formed by AGEs between collagens increased the stiffness of the matrix[47]. Thus, the authors concluded that cross-links could directly affect the matrix stiffness and stimulate the biomechanical properties of tendons. In addition, AGEs have been reported to damage the biomechanical properties of tendon collagen in various species by diminishing tendon fiber sliding[11,48,49]. In rat tail tendons, Fessel *et al*[48] discovered that lateral molecular interconnectivity by AGEs could reduce the side-by-side sliding of collagen fibers, thus leading to increased collagen fiber failure resistance *in vivo*. An *in vitro* study also revealed dramatically decreased tendon fiber sliding and viscoelastic behavior by tissue glycation[11]. In bovine tail tendons, Lee and Veres[20] found that the cross-links formed by AGEs could significantly inhibit biomechanical plasticity *in vitro*. Some other researchers considered that the cross-links could affect the biomechanical properties by taking up space in the ECM[50]. In both aged tendons and glycated tendons *in vitro*, the molecular spacing was linearly increased[11], which might be ascribed to the formation of cross-links by AGEs between collagen fibers. Another argument was that AGEs primarily affect the mechanical properties at the failure regions of tendons of patients with diabetes[51,52].

RELATIONSHIPS BETWEEN AGES AND THE ECM OF TENDONS OF PATIENTS WITH DIABETES

In addition to the cross-links formed between collagen fibers, the deposited AGEs in the ECM could also interact with various kinds of cytokines and proteins, cause biological effects, and subsequently impair their material properties[44,45,48]. It has been reported that Fe²⁺ in tendons of patients with diabetes could promote the accumulation of AGEs in collagens, which in turn stimulated the glycosylation of Col I and other matrix proteins *in vivo*[53]. Once deposited in the ECM, these AGEs could suppress the function of the mitochondria of Achilles tendon-derived fibroblasts and impair their proliferation, further leading to reduced remodeling of the ECM[54]. In porcine patellar tendons, the proteoglycan level was decreased after sustained hyperglycemia caused the production of AGEs *in vitro*[55]. Nevertheless, only a few studies have focused on the interactions of AGEs and factors in the ECM of tendon cells, especially TSPCs. In other tissues or cell types, such as ligaments and fibroblasts, AGEs have been demonstrated to affect the expression levels of matrix metalloproteinases (MMPs), bone morphogenetic proteins (BMPs), and other factors. Accumulated AGEs in the ossified spinal ligament could elevate the expression levels of BMP-7, BMP-2, alkaline phosphatase (ALP), and OCN, an osteoblast-specific transcription factor 1[27]. In human fibroblasts, AGEs could decrease Col I and increase MMP-1 levels *in vitro*[56]. In osteoblast-like cells, AGEs could promote the degradation of Col I by stimulating the secretion of MMP-2 and MMP-9 *in vitro*[57] and stimulate the mRNA expression and serum levels of fibroblast growth factor 23 in chronic disease[58]. The expression of MMP-1 in human gingival fibroblasts was also significantly increased at both the mRNA and protein levels *in vitro* after treatment with AGEs[59].

AGEs INDUCE CELLULAR EVENTS IN TENDON CELLS AND THE UNDERLYING MECHANISM

AGEs induce cellular effects on various kinds of cells mainly by activating the RAGE *in vivo*. Many studies have reported that the AGE-mediated events of various kinds of cells are activated through the interactions of AGE-RAGE[60,61]. RAGE is a receptor that can activate many kinds of ligands and it exists in normal tendon tissues. It is expressed at low levels under normal blood glucose levels, and its expression could be increased while AGEs accumulate under sustained hyperglycemia[21,62]. In addition to RAGE, many other molecules have been shown to act as receptors of AGEs, such as scavenger receptor class AI/AII[63], scavenger receptor class B type I[64], and CD36 [65]. In our unpublished research, we also observed the expression levels of AGEs and RAGE in the ECM of diabetic tendon cells *in vivo* and in isolated TSPCs *in vitro*. After the receptors for AGEs are activated, a variety of downstream cellular signaling pathways can be excited and they subsequently alter cell functions, such as proliferation, migration, apoptosis, and differentiation.

Proliferation

Generally, AGEs have been demonstrated to attenuate the proliferation abilities of various kinds of cells, such as bone mesenchymal stem cells (MSCs) and retinal pericytes[29,66]. In human MSCs, Kume *et al*[29] found that higher concentrations of AGE-2 and AGE-3 (1-100 µg/mL) could inhibit their proliferation ability and stimulate apoptosis *in vitro*, probably by upregulating intracellular reactive oxygen species (ROS). The generation of ROS has been reported to regulate these AGE-RAGE-induced cellular events[61,67]. Yang *et al*[68] reported that AGEs inhibited bone MSC proliferation and migration by inducing chemokine/cytokine secretion *via* the p38 pathway *in vitro*. Moreover, AGE-2 could suppress the proliferation of cultured bovine retinal pericytes through downregulation of the expression ratio of BCL-2/BAX[66]. In addition, AGEs could stimulate the proliferation abilities of several other kinds of cells. In osteoblastic cell lines, the effects of AGEs on cell proliferation were reported to depend on their stage of differentiation[69]. Low concentrations of AGEs could stimulate mesangial cell proliferation[70]. AGEs enhance vascularization in diabetic retinopathy by interacting with RAGE and promoting vascular endothelial cell proliferation[71]. However, few studies have investigated the impacts of AGEs on TSPCs, and further research is required.

Apoptosis

In addition to their influence on proliferation, AGEs also induce the apoptosis of many kinds of cells, including TSPCs, retinal pericytes, myoblastic cell lines, mononuclear cells, and endothelial progenitor cells[67,72-75]. Xu *et al*[72] reported that AGEs could induce TSPC apoptosis, and pioglitazone showed the ability to rescue AGE-induced apoptosis and other abnormal alterations both *in vitro* and *in vivo*. In bovine retinal pericytes, AGE-initiated apoptosis was reported to be ascribed to the activation of the caspase-10 pathway[67]. AGEs could induce the apoptosis of mouse myoblastic C2C12 cells and inhibit myogenic differentiation, while insulin-like growth factor-I exhibited therapeutic potential to attenuate the detrimental effects of AGEs on C2C12 cells[73]. In human mononuclear cells isolated from the peripheral blood of patients with type II DM, increased cellular apoptosis and decreased osteoblastic differentiation ability were highly correlated with RAGE expression[74]. The activation of ROS, Akt/eNOS, MAP kinases, and the FOXO1 transcription factor have all been reported to participate in AGE-induced apoptosis progression[54,75].

Differentiation

Several studies have illustrated that accumulated AGEs could affect the differentiation properties of stem cells in the musculoskeletal system. In TSPCs, AGEs have been reported to exacerbate osteogenic differentiation potential *in vitro*[72]. For other kinds of cells, AGEs could inhibit the osteogenic differentiation potential of mouse ASCs by suppressing the expression of OPN and runt-related transcription factor 2 (Runx2) through activating the Wnt/ β -catenin signaling pathway[42]. In human periodontal ligament stem cells, AGEs attenuate osteogenesis *in vitro*, and the canonical Wnt/ β -catenin and JNK signaling pathways might be involved[76-78]. RAGE in MSCs could be activated by AGE-2 and AGE-3; thus, the AGE-RAGE interaction was found to participate in the osteogenic and chondrogenic differentiation processes of MSCs[29]. AGE-3 was reported to inhibit the osteogenic differentiation and bone nodule formation of MSCs by activating RAGE and upregulating the expression of TGF- β *in*

vitro[29,79]. The expression levels of ALP and intracellular calcium in MSCs were upregulated by AGEs, while mineralization and bone nodule formation were both decreased *in vitro*. The chondrogenic and adipogenic differentiation potentials of the MSCs were also attenuated by AGEs *in vitro*[29].

AGEs and TSPCs

To date, only a few studies have focused on the influence of AGEs on TSPCs. Xu *et al* [72] reported that AGEs could reduce cell viability and increase apoptosis and autophagy of TSPCs *in vitro*. In that study, they found that AGEs induced senescence and enhanced the ossification of TSPCs *in vitro*. However, the researchers did not further investigate the underlying mechanisms of AGE-induced ossification of TSPCs. In MSCs, AGE-2 and AGE-3 showed the ability to enhance ALP activity and intracellular calcium content by activating RAGE *in vitro*[29]. Therefore, we speculate that the activation of RAGE in TSPCs could also lead to apoptosis, senescence, and aberrant differentiation by activating several signaling pathways, such as the Wnt/ β -catenin, P38/MAPK, Notch, ROS, and Akt/eNOS pathways.

TSPCs IN DIABETIC TENDINOPATHY

The progression of diabetic tendinopathy is complicated and involves various kinds of factors and types of cells. Previously, we have summarized the current findings of diabetic tendinopathy, especially the cellular and underlying mechanisms[80]. In addition to tenocytes, there are many other types of cells inside the tendons. Bi *et al*[12] and Rui *et al*[13] proved the existence of stem/progenitor cells in the tendons of mice and rats. TSPCs exhibit self-colony ability and multidifferentiation properties *in vitro* [14-16]. In the patellar tendon of a collagenase-induced rat tendinopathy model, TSPCs presented lower proliferation capacity and higher osteogenic and chondrogenic differentiation potentials[16]. In an injury-induced rat tendinopathy model, TSPCs showed increased proliferation ability and higher type III collagen (Col III) and α -SMA expression than in collagenase-induced rats[15]. These findings indicate the involvement of TSPCs in maintaining tendon tissue homeostasis and mediating the pathological process of chronic tendinopathy[81]. During the development of diabetic tendinopathy, as tissue-specific cells are contained in tendon tissue, TSPCs are the most likely cells to participate in the early response. TSPCs are thought to differentiate into tenocytes and play key roles in maintaining, regenerating, and replacing differentiated tenocytes in tendon tissues. In rats with experimental DM, we found that the fate of TSPCs isolated from patellar tendons was altered, and these cells exhibited decreased proliferation properties and enhanced osteochondrogenic potential[9]. High glucose (11.1 mmol/L) could stimulate an inflammatory response of TSPCs in the human patellar tendon *in vitro*[82]. Our previous study found that high glucose (15 mmol/L and 25 mmol/L) could inhibit rat TSPC proliferation and induce apoptosis *in vitro*[83]. Moreover, insulin has been reported to increase ALP activity and the expression levels of osteogenesis-associated markers in TSPCs isolated from horse superficial digital flexor tendons[84]. Taken together, these studies indicate that the aberrant proliferation and differentiation of TSPCs are possible underlying mechanisms of diabetic tendinopathy. AGEs have been shown to induce apoptosis and to exacerbate the osteogenic differentiation potential of TSPCs *in vitro*[72]. However, the mediating mechanisms of AGEs on diabetic TSPC multidifferentiation potential are still unclear, and future studies are required to investigate the underlying processes.

CONCLUSION

In summary, we have described the enhanced osteochondrogenic differentiation ability of TSPCs from experimental diabetic rats cultured in induction medium[9]. Additionally, the outstanding expression of osteochondrogenic-associated markers and AGE accumulation were also noted. *In vitro* studies revealed that AGEs could affect the proliferative capacity, apoptosis, and multidifferentiation potential of TSPCs and other kinds of stem cells under certain pathological conditions. Taken together, we hypothesize that the accumulated AGEs in the ECM of diabetic TSPCs lead to aberrant differentiation fates and futures, contributing to the development of chronic tendinopathy in DM subjects (Figure 1). Understanding the relationships among

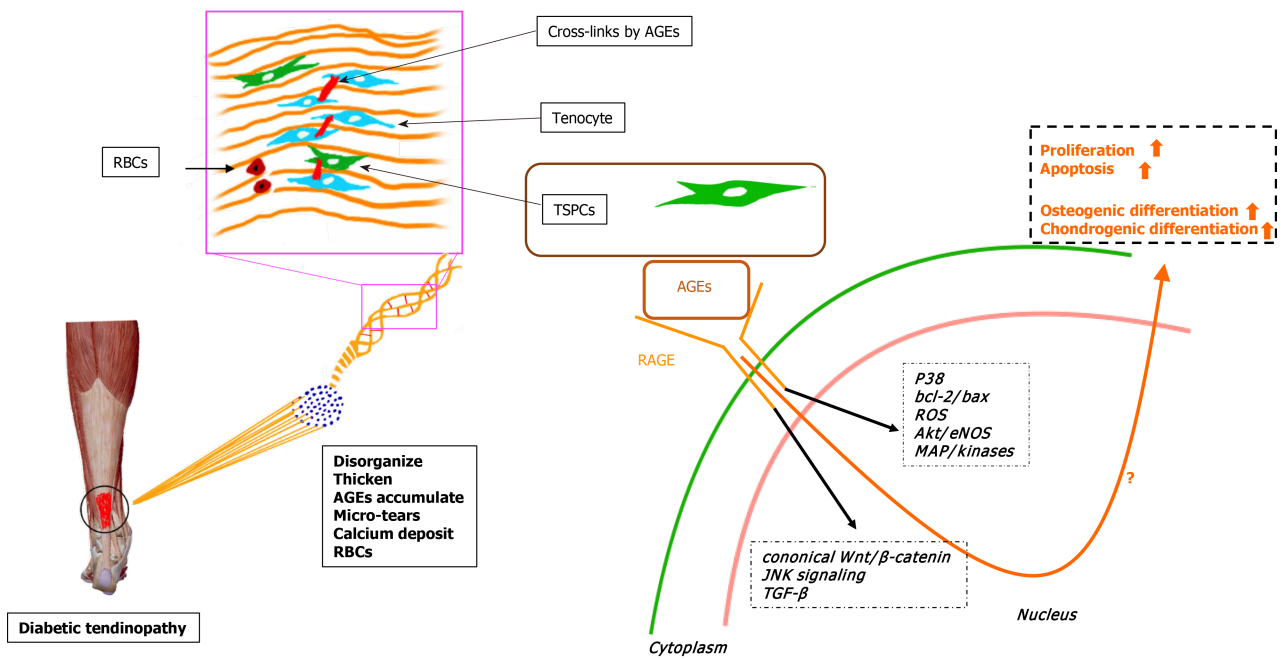


Figure 1 Hypothesis of the molecular mechanism by which advanced glycation end products regulate the fate of tendon-derived stem/progenitor cells in diabetic tendinopathy. RBCs: Red blood cells; AGEs: Advanced glycation end products; TSPCs: Tendon-derived stem/progenitor cells; RAGE: Receptor for advanced glycation end product; ROS: Reactive oxygen species; TGF- β : Transforming growth factor β .

diabetic tendinopathy, TSPCs, and AGEs will be crucial for developing new treatments for diabetic tendinopathy therapy.

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