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**REVIEW**

- 565** Effects of environmental stressors on stem cells
Worley JR, Parker GC
- 578** Suitability and limitations of mesenchymal stem cells to elucidate human bone illness
Mitxitorena I, Infante A, Gener B, Rodríguez CI
- 594** Breast cancer stem cells: The role of sex steroid receptors
Giovannelli P, Di Donato M, Galasso G, Di Zazzo E, Medici N, Bilancio A, Migliaccio A, Castoria G
- 604** Immunomodulatory properties of dental tissue-derived mesenchymal stem cells: Implication in disease and tissue regeneration
Andrukhov O, Behm C, Blufstein A, Rausch-Fan X
- 618** Cell membrane and bioactive factors derived from mesenchymal stromal cells: Cell-free based therapy for inflammatory bowel diseases
da Costa Gonçalves F, Paz AH
- 634** Using induced pluripotent stem cells for modeling Parkinson's disease
Ke M, Chong CM, Su H
- 650** Impelling force and current challenges by chemicals in somatic cell reprogramming and expansion beyond hepatocytes
Ge JY, Zheng YW, Liu LP, Isoda H, Oda T
- 666** Induction of differentiation of human stem cells *ex vivo*: Toward large-scale platelet production
Lei XH, Yang YQ, Ma CY, Duan EK
- 677** Tendon stem/progenitor cell ageing: Modulation and rejuvenation
Dai GC, Li YJ, Chen MH, Lu PP, Rui YF
- 693** Bioactive lipids in cancer stem cells
Begicevic RR, Arfuso F, Falasca M

ORIGINAL ARTICLE**Basic Study**

- 705** Enhanced hepatic differentiation in the subpopulation of human amniotic stem cells under 3D multicellular microenvironment
Furuya K, Zheng YW, Sako D, Iwasaki K, Zheng DX, Ge JY, Liu LP, Furuta T, Akimoto K, Yagi H, Hamada H, Isoda H, Oda T, Ohkohchi N

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Tendon stem/progenitor cell ageing: Modulation and rejuvenation

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Abstract

Tendon ageing is a complicated process caused by multifaceted pathways and ageing plays a critical role in the occurrence and severity of tendon injury. The role of tendon stem/progenitor cells (TSPCs) in tendon maintenance and regeneration has received increasing attention in recent years. The decreased capacity of TSPCs in seniors contributes to impaired tendon functions and raises questions as to what extent these cells either affect, or cause ageing, and whether these age-related cellular alterations are caused by intrinsic factors or the cellular environment. In this review, recent discoveries concerning the biological characteristics of TSPCs and age-related changes in TSPCs, including the effects of cellular epigenetic alterations and the mechanisms involved in the ageing process, are analyzed. During the ageing process, TSPCs ageing might occur as a natural part of the tendon ageing, but could also result from decreased levels of growth factor, hormone deficits and changes in other related factors. Here, we discuss methods that might induce the rejuvenation of TSPC functions that are impaired during ageing, including moderate exercise, cell extracellular matrix condition, growth factors and hormones; these methods aim to rejuvenate the features of youthfulness with the ultimate goal of improving human health

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during ageing.

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Core tip: Tendon stem/progenitor cells (TSPCs) play an essential role in tendon maintenance, regeneration and repair. Recent studies indicate that an association between the decreased capacities of aged TSPCs and the impaired tendon functions observed with increasing age. In this review, we briefly discuss novel updates in research investigating TSPCs characteristics. Then, we summarize the epigenetic variations in TSPCs that occur with ageing and provide a detailed description of the pathways that play essential roles in the cellular ageing process. Finally, we propose potential methods to rejuvenate ageing TSPCs and provide additional therapeutic targets for the treatment of age-related tendon diseases.

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INTRODUCTION

Ageing is an intricate physiological progress caused by multiple factors that result in variations in the structure and composition of cells, organs and tissues and a decrease in the capacity and activity of mammals. The global population over the age of 60 years is growing rapidly^[1] and the occurrence of tendon-related injuries increases upon ageing^[2]. Moreover, the consequences of tendon damage in elderly patients are more severe^[3], and older populations also experience a higher occurrence of sport-related tendon injuries and more difficulties in healing process^[4], which places a heavy burden on the health systems of individual countries^[5]. Epidemiological studies have highlighted the importance of obtaining an in-depth understanding of the pathogenesis of aged-related tendon diseases, with the aim of developing appropriate therapeutic approaches.

Recently, studies focused on stem cells have become emerging areas in regenerative and biomedical medicine because these cells have been confirmed to be remarkably important for tissue maintenance, repair and remodeling; and they have also been used to cure various diseases with satisfactory outcomes^[6-9]. Pluripotent stem cells can differentiate into various tissue types under different conditions and serve as an internal repair system, which is also restricted to the embryonic layer of origin^[10]. In adults, tendon stem/progenitor cells (TSPCs), as a type of mesenchymal stem cell (MSC), were first confirmed to be present in tendon tissues by Bi *et al*^[11] in 2007, and they have been found to possess self-renewal ability, clonogenicity and multidifferentiation potential. Compared with bone marrow stromal cells, TSPCs show express higher level of Oct4, which is known to positively modulate mesodermal lineage differentiation, and have greater ability of proliferative and clonogenicity. Thus, TSPCs potentially represent an more appropriate cell source for the regeneration of musculoskeletal tissue, particularly tendon tissue, which has limited repair and healing abilities with traditional tenocytes^[12]. Based on these findings, scholars have a strong interest in identifying the potential role of TSPCs in tendon regenerative medicine and the injury healing process; thus, numerous related studies have been published on this topic in recent years.

However, ageing exerts negative effects on TSPCs functions, which could limit the application of TSPCs in tendon injury repair and the choice of cell sources for regenerative medicine. Ageing also affects cell the genetics of cells, through a series of pathways involved in both accelerating and delaying the ageing process. In the MSC ageing process, the P16/RB pathway and P53/P21 pathway have vital roles in modulating the cellular senescence by regulating telomere length and function. In addition to telomeres, DNA damage, mitochondria dysfunction and reactive oxygen species are involved in suppressing the expression of genes that promote the stem cell cycle progression of stem cells and induce the expression of cell cycle inhibitors^[13].

Up-regulation of P53, P16, P14 and P21 genes related to cell cycle arrest and activation of the P53 pathway and P21 pathway have also been observed in aged TSPCs, which are thought to function as accelerators of the cellular ageing process^[14]. What's more, stem cell markers expression declines with age in TSPCs, indicating potential causes of the alterations in cell differentiation ability^[15]. In this regard, a novel hypothetical model of altered TSPCs fates in the ageing process has been formulated based on the observation of ectopic metaplasia and the decline in the tenogenic differentiation capacity of tendon tissue during the ageing process, which ultimately increases the occurrence of age-related tendon diseases^[1]. Recently, the discovery of induced pluripotent stem cells (iPSCs), particularly cells isolated from mature adult, inspired researchers to develop potential therapies to cure clinical diseases and ponder the eternal topic of regaining our youth. Thus, iPSCs provided inspiration to reverse the stem cell fate by modulating the factors that influence cell growth^[16-18].

With limited treatment options for tendon diseases and unsatisfactory healing outcomes, studies aimed to explore the biological link between tendon ageing and TSPCs are very meaningful for the development of age-related diseases treatments. In this review, we initially discuss recent studies addressing the characteristics of TSPCs. Then, we summarize the epigenetic variations in TSPCs that occur with age and provide a detailed description of the pathways that play essential roles in the cellular ageing process. Finally, we propose potential pathways to rejuvenate ageing TSPCs, providing further therapeutic targets for the treatment of age-related tendon diseases.

TENDON STEM/PROGENITOR CELLS

Traditionally, tenocytes were considered the only cell present in tendon tissue and play a critical role in tendons metabolism. This hypothesis did not change until the isolation and identification of TSPCs in many tendon fascicles, including mouse^[11], human^[19], rat^[20], rabbit^[21], turkey^[22], porcine^[23] and fetal bovine tendon fascicles^[24] in recent years. Although TSPCs represent a minor percentage of the tendon cell composition, these cells possess features such as self-renewal, clonogenicity and multidifferentiation and TSPCs are distinguished by the presence of stem cell markers^[21]. Since these discoveries, substantial interest and progress in the study of the roles of this cell type in tendon maintenance, repair, remodeling and tendon tissue engineering have been reported.

Compared with tenocytes, TSPCs express stem cell markers, proliferate faster, exhibit multidifferentiation potential and express tenogenic markers at higher levels^[21,25]. Although Berglund *et al*^[26] proposed a different hypothesis that major histocompatibility complex (MHC) mismatched MSCs were not immune privileged because they induced both cell-mediated and humoral immune responses, the majority of studies consistently shown that MSCs display low immunogenicity and immuno-modulatory properties, which avoid immunological rejection. Thus MSCs are a potential allogeneic cell source for transplantation, and TSPCs, a subtype of MSCs, may possess features similar to MSCs^[27]. According to Lui *et al*^[28], TSPCs expressed lower levels of MHCII, cluster differentiation 86 and cluster differentiation 80 on the cell surface; these proteins are essential for inducing a T-cell response. Additionally, the infiltration of inflammatory cells was not observed in tendon injuries treated with allogeneic TSPCs, revealing the low immunogenicity of TSPCs *in vitro* and *in vivo*^[28,29]. Based on these facts, researchers have confirmed that these active TSPCs are immune-privileged and can be used for allogeneic transplantation. Benefiting from the positive aspects, particularly the multi-differentiation capacities and immune-privilege, TSPCs potentially represent an ideal cell source for musculoskeletal tissue regenerative medicine and therapeutic targets for numerous related diseases. Although important research has shown that TSPCs might reside within the tendon fascicles, others researchers have suggested that the epitenon might be another source of TSPCs^[30]; subsequent studies have confirmed this hypothesis^[30-33]. Although all TSPCs generally exhibit the characteristics of tendon stem cells, they have their own unique features when isolated from different sites in the tendon. These findings reveal the presence of more than one source of distinct TSPCs in tendon tissue, and these populations represent a seed cells source for application in different tendon injuries according to the different cellular characteristics^[30,34-36].

Moreover, numerous studies have confirmed that TSPCs play an essential role in the progression of tendon diseases and/or tendon tissue engineering, and the biological features of TSPCs are altered by many factors, which is why many treatment strategies for tendon-related injuries have primarily focused on TSPCs. For example, platelet-rich plasma augments and accelerates the effects of TSPCs on the healing process^[37], and the mechanistic basis for the treatment of tendon tear is

attributed to increased DNA synthesis, increased cellular migration velocity and the supplements of TSPCs^[38,39]. In several cases, growth and differentiation factor-5 was reported to promote the tenogenic differentiation of TSPCs, and transforming growth factor- β 1 and insulin-like growth factor 1 (IGF-1) promotes TSPC proliferation and phenotype maintenance^[40]. Additionally, the expression of inflammatory cytokines is dramatically upregulated in injured tendons^[41-43], some of which inhibit the proliferation and tenogenic and osteogenic differentiation of TSPCs^[43]. Moreover, TSPCs are essential for tendon healing and the regulation of inflammation, and the production of the pro-inflammatory cytokine Interleukin-6 (IL-6) and anti-inflammatory cytokine Interleukin-10 (IL-10), is significantly up-regulated at the late stage of inflammation in injured tendons^[7,44]. Based on these findings, IL-6 and IL-10 evidently up-regulate cell proliferation, and IL-10 significantly enhances cell migration. However, both IL-6 and IL-10 inhibit the production of gene and protein functioning as tenocytes markers, including scleraxis and tenomodulin, and dramatically activate the JAK/Stat3 signaling pathway, which has a crucial role in modulating inflammation in TSPCs^[45], indicating that IL-6 and IL-10 may exert dual effects on TSPCs *in vitro*^[7,44], and connective tissue growth factor plays a role in anti-inflammatory by regulating the IL-6 and IL-10 expression^[45]. Decreased annexin A1 (an anti-inflammation protein) expression resulted in elevation of inflammation during the mouse tendon injury process; thus, annexin A1 potentially represents a novel curative target in clinical applications^[46]. In addition, many drugs and proteins exert effects on TSPCs that promote tendon healing. Celestrol exerts beneficial effects on human TSPCs stemness and the vital role of HIF1 α -Smad7 signaling in the process is elucidated^[47]. Celecoxib inhibits the tenogenic differentiation of TSPCs but has no effects on cell proliferation^[48], and a high concentration of aspirin induces apoptosis in TSPCs by delaying the activation of Wnt/ β -catenin pathway^[49]. All these factors might affect the quality of tendon healing by targeting TSPCs, regardless of whether the effects are positive or negative. The recent main factors are summarized in Table 1.

In addition, an altered fate of TSPCs was observed in a collagenase-induced tendon injury model of tendinopathy due to the presence of tenocytes lacking the multidifferentiation capacity^[21], consistent with similar results presented in other studies and supporting the hypothesis that TSPCs might play an essential role in the pathogenesis of tendinopathy. A series of recent studies revealed important roles for TSPCs in tendon healing by replacing mature tendon cells that are lost under normal circumstances, which might be the cause of age-related changes in the pathogenesis of tendon disorders^[15,50]. Thus, TSPCs are considered to play a crucial role in maintaining tendon homeostasis by affecting tendon repair and regeneration^[15,20,51,52]. Recently, Li *et al.*^[1] proposed that the altered fate of TSPCs contributes to tendon ageing. Other scholars have also observed alterations in TSPCs features during tendon degeneration and the progression of ageing^[14,15,50,53,54]. Overall, a range of TSPCs functions are altered, and TSPCs might serve as a potential target due to these alterations. Therefore, a relationship between altered TSPCs features and tendon ageing has been hypothesized, highlighting the importance of TSPCs in the treatment of tendon-related diseases.

AGEING AND ALTERATIONS IN EPIGENETIC AND THE UNDERLYING MECHANISMS

Age-related markers in TSPCs

TSPCs undergo a series of significant cellular epigenetic alterations with age, which are viewed as age-related markers in TSPCs for that can be used in future studies, and these results are consistent with similar results obtained from other types of stem cells. The main findings are summarized in Table 2.

Ageing and cell morphology

In vitro aged-TSPCs (A-TSPCs) exhibit cell shape of star-like flattened, while young-TSPCs (Y-TSPCs) exhibit spindle-shaped morphology^[14]. In addition, aged TSPCs are obviously larger in size, have more podia, spread further, and exhibit more robust actin stress fibers and a higher actin content that distorts the balance of the actin cytoskeleton organization^[14,55,56], which has also been confirmed by analyses of microarray data in aged TSPCs^[14]. Additionally, aged TSPCs display a large, flat and heterogeneous morphology, while younger cells exhibit the morphology of uniform elongated^[57]. An increase in the size is often associated with cell senescence^[50,55,56]. In addition, the number of heterogeneous and cobblestone-shaped TSPCs is dramatically down-regulated with ageing, and the oldest TSPCs have only a few percent displaying the cobblestone shape^[15]. Kohler *et al.*^[14] reported an important role for

Table 1 Recent main factors for regulating tendon stem/progenitor cells biological features

Factor	Cell source	Interventional details	Results	Ref.
PRP	SD rats	10% PRP	10% PRP augments and accelerates the effects of TSPCs on the healing process	[37]
BMACs and PRP complex	Human	A T75 flask (450 μ L of BMACs and PRP)	BMAC-PRP enhances the proliferation and migration of TSPCs	[38]
PRP	SD rats	2% PRGF	PRP can activate TSPCs to improve the quality of Achilles tendon rupture healing	[39]
IGF-1, GDF-5 and TGF β 1	Lewis rats	Each growth factor (1, 10, and 100 ng/mL)	GDF-5 promotes TSPCs tenogenic differentiation, and TGF β 1 and IGF-1 increase TSPCs proliferation and are beneficial for phenotype maintenance	[40]
IL-1 β	Dogs	-	The expression of inflammatory cytokines is dramatically up-regulated in injured tendon	[41,42]
IL-1 β	Mouse	IL-1 β (1, 5 or 10 ng/mL)	IL-1 β strongly and irreversibly impairs tenogenic and osteogenic differentiation potentials of TSPCs	[43]
IL-6	SD rats	IL-6 (0, 0.1, 1, 10, and 100 ng/mL)	IL-6 enhances proliferation and inhibits tenogenic differentiation in TSPCs <i>via</i> the JAK/Stat3 pathway	[44]
IL-10	SD rats	IL10 (0, 0.1, 1, 10 or 100 ng/mL)	IL10 enhances cell proliferation and migration, and inhibits tenogenic differentiation in TSPCs	[7]
CTGF	SD rats	CTGF (100 ng/mL)	CTGF plays a role in anti-inflammatory, leading to enhanced tendon healing	[45]
Annexin A1	WT and DF508 mice	-	Decreased annexin A1 expression resulted in elevation of inflammation during the mouse tendon injury process	[46]
Celastrol	Human	celastrol (0, 1, 2, and 4 μ M)	Celastrol exerts beneficial effects on human TSPCs stemness and the vital role of the HIF1 α -Smad7 pathway in the process is elucidated	[47]
Celecoxib	C57 mouse	celecox (0.1, 1, 10 and 100 μ g/mL)	Celecoxib inhibits tenogenic differentiation of TSPCs but has no effects on cell proliferation	[48]
Aspirin	SD rats	Aspirin (1, 2, and 5 mM)	A high concentration of aspirin induces apoptosis in TPSCs by delaying the activation of Wnt/ β -catenin pathway	[49]

PRP: Platelet-rich plasma; SD: Sprague-Dawley; TSPCs: Tendon stem/progenitor cells; BMACs: Bone marrow aspirate concentrates; PRGF: Platelet-rich growth factors; CTGF: Connective tissue growth factor; IL-10: Interleukin-10; IL-1 β : Interleukin1 β ; TGF β 1: Transforming growth factor- β 1; GDF-5: Growth and differentiation factor-5; IGF-1: Insulin-like growth factor1.

increased Rho associated coiled-coil forming protein kinase (ROCK) activity in accelerating the ageing progress of A-TSPC, and A-TSPCs revert to a morphology similar to Y-TSPCs upon treatment with Y-27632, a common ROCK inhibitor. Similar results have also been detected in aged tenocytes as well as in other types of stem cells^[58,59].

Ageing and cell proliferation

Growth rate: A-TSPCs showed a proliferation deficit after 120 d of culture and had an

Table 2 Age-related markers of tendon stem/progenitor cells

Object	Species model	Groups	Tendon type	Main findings	Ref.
Cell morphology	Human	Y-TSPC group: 28 ± 5 yr; A-TSPC group: 63 ± 14 yr	Achilles tendon	A-TSPC exhibit cell shape of star-like flattened, while Y-TSPCs exhibit spindle-shaped	[14]
	Human	Y-TSPC: 28 ± 5 yr and A-TSPC: 63 ± 14 yr	Achilles tendons	Aged TSPCs are obviously larger in size, have more podia, spread further, and exhibit more robust actin stress fibers, and exhibit higher actin content	[55]
	Rat	old rats: 20 mo and young rats: 8 wk	Achilles tendons	Aged TSPCs display a morphologies of large, flat and heterogeneous morphology, while younger cells exhibit the morphology of uniform elongated	[57]
	Mice	young (2.5, and 5 mo) and aging (9 and 24 mo) mice	Patellar tendons	The number of heterogeneous and cobblestone-shaped TSPCs is dramatically down-regulated with ageing, and the oldest TSPCs have only a few percent displaying the cobblestone shape	[15]
Growth rate	Human	Y-TSPC group: 28 ± 5 yr; A-TSPC group: 63 ± 14 yr	Achilles tendon	A-TSPCs showed a proliferation deficit after 120 d of culture and had an early plateau phase, while Y-TSPCs didn't exhibit the plateau	[14]
	Rat	3–4 (young) and 24–26 mo (aged)	Patellar tendons	Proliferation rate is decreased and cell cycle progression is delayed with increasing age	[53]
	Rat	three different post-natal stages: 1 d, 7 d and 56 d	Achilles tendon	TSPCs-7d displayed that a higher proliferation rate than the groups of TSPCs-1d and TSPCs-56d	[61]
	Rat	Early P5, mid P10, and late P20 and P30 passages were used	patellar tendons	TSPCs at late P20 and P30 proliferate more rapidly than those at early P5 and mid P10	[62]
Cell clonogenicity	Human	Y-TSPC group: 28 ± 5 yr; A-TSPC group: 63 ± 14 yr	Achilles tendon	Age-dependent clonogenic deficits in TSPCs are based on a decreased in the colony number and CFU efficiency with ageing	[14]
	Human	Group 1: aged 20 (female) and 22 (male); group 2: aged 28 (female) and 31 (male) and Group 3: aged 49 (male) and 50 (female)	Hamstring tendons	The clonogenic potential is dramatically decreased with age; in addition, the size of the colonies was heterogeneous in patients, as the size of colonies produced by cells from aged patients was obviously larger than the colonies composed of cells from younger patients	[50]

Cell migration	Rat	three different post-natal stages: 1 d, 7 d and 56 d	Achilles tendon	TSPCs-7d have an obviously higher clonogenic ability than TSPCs-1d and TSPCs-56d	[61]
	Rat	early P5, mid P10, and late P20 and P30 passages were used	patellar tendons	The colony numbers of TSPCs increase with passaging,	[62]
	Human	Y-TSPC group: 28 ± 5 yr; A-TSPC group: 63 ± 14 yr	Achilles tendon	The migration of TSPCs exhibits a decreasing trend with advanced age	[14]
Cell differentiation	Rat	three different post-natal stages: 1 d, 7 d and 56 d	Achilles tendon	TSPCs from different time groups displays multidifferentiation capability, while the ability of TSPCs-7d is higher than TSPCs-1d and TPSCc-56d, and a similar trend is observed in the tenogenic differentiation capacity	[61]
	Human	Y-TSPC: 25 ± 8 yr, and A-TSPC: 65 ± 10 yr	Achilles tendon	Tenogenic differentiation capacity of TSPCs significantly decreases with ageing	[54]
	Mice	young (2.5, and 5 mo) and aging (9 and 24 mo) mice	Patellar tendons	Aged TSPCs formed adipocytes more readily than younger cells and expressed higher levels of adipogenic markers	[15]
	Rat	early P5, mid P10, and late P20 and P30 passages were used	patellar tendons	TSPCs tend to differentiate into osteoblasts, while the adipogenic, chondrogenic and tenogenic differentiation capacities in TSPCs decline during in vitro subculture	[62]
	Mice	early P0, and late P5 passages were used	Achilles tendon	The TSPCs experiences a gradual loss of tenogenic differentiation with passaging due to increased expression and activity of Hdac	[65]
	Human	Y-TSPC group: 28 ± 5 yr; A-TSPC group: 63 ± 14 yr	Achilles tendon	A-TSPC have been reported to display an evident self-renewal and clonogenic decrease, multipotency is maintained <i>in vitro</i>	[14]
	Human	Group 1: aged 20 (female) and 22 (male); group 2: aged 28 (female) and 31 (male) and Group 3: aged 49 (male) and 50 (female)	Hamstring tendons	Multi-potency assays were not influenced by advanced ageing, although Y-TSPCs produced higher levels of some osteogenic and adipogenic genes, while chondrogenic genes were expressed at high levels in A-TSPCs	[50]
	Rat	3–4 (young) and 24–26 mo (aged)	Patellar tendons	Aged TSPCs express lower levels of CD90.1 than young cells, but higher levels of CD44	[53]
CD marker	Rat	early P5, mid P10, and late P20 and P30 passages were used	patellar tendons	CD90 and CD73 is down-regulated with increasing numbers of passaging	[62]

Cell stemness marker	Mice	young (2.5, and 5 mo) and aging (9, and 24 mo) mice	Patellar tendons	The expression of the stem cell markers Oct-4, NS, Sca-1 and SSEA-1 in TSPCs decreased in an age-dependent manner	[15]
Cell viscoelasticity	Rat	old rats: 20 mo and young rats: 8 wk	Achilles tendons	An overall increase in G' , G'' and h_{TSPC} with ageing, revealing an important increase in stiffness of aged TSPCs	[57]
Cell senescence markers	human	Y-TSPC: 28 ± 5 yr and A-TSPC: 63 ± 14 yr	Achilles tendons	Cell stiffness and size increase in A-TSPCs	[55]
	human	Y-TSPC group: 28 ± 5 yr A-TSPC group: 63 ± 14 yr	Achilles tendon	A-TSPCs undergo an early appearance of cellular senescence, as determined by quantifying the number of β -gal- positive cells at different time points	[14]
	rat	Early P5, mid P10, and late P20 and P30 passages were used	patellar tendons	The significant up-regulation of β -gal activity in TSPCs with increasing passaging	[62]

Y-TSPC: Young-TSPC; A-TSPC: Aged-TSPCs; TSPCs-7d: TSPCs-7days; P5: Passage 5; CFU: Colony-forming unit; Hdac: Histone deacetylase; CD: Cluster differentiation; NS: Nucleostemin.

early plateau phase, while Y-TSPCs didn't exhibit the plateau^[14]. Zhou *et al*^[53] also observed this decrease in TSPCs proliferation with increasing age, consistent with similar results observed in TSPCs from other aged vertebrate animals^[15,50,56,60]. Additionally, TSPCs-7 day (TSPCs-7d) displayed that a higher proliferation rate than the groups of TSPCs-1 day (TSPCs-1d) and TSPCs-56 day (TSPCs-56d)^[61]. However, Tan *et al*^[62] observed more rapid proliferation of TSPCs at late passage 20 (P20) and P30 than cells at an early P5 and middle P10, revealing a different perspective of the increased proliferation with additional passaging. Moreover, the increased proliferation of aged TSPCs was restored by treatment with ephrin receptor A4-Fc (EphA4-Fc), a moderate treadmill running (MTR) intervention and other factors, revealing that the proliferation rate of TSPCs can be modulated^[15,56,60].

Ageing and cell clonogenicity (colony-forming unit numbers and colony size): Age-dependent clonogenic deficits in TSPCs are based on a decreased in the colony number and colony-forming unit efficiency with ageing^[14,56,63]. Ruzzini *et al*^[50] bserved a dramatic decrease in the clonogenic potential with ageing; in addition, the size of the colonies was heterogeneous in patients, as the size of colonies produced by cells from aged patients was obviously larger than the colonies composed of cells from younger patients. Another study reported an obviously higher clonogenic capacity of TSPCs-7d than TSPCs-1d and TSPCs-56d^[61]. In summary, the mainstream hypothesis is that ageing exerts negative impact on the clonogenicity of TSPCs. However, Tan *et al*^[62] revealed an increase in the numbers of TSPCs colonies with passaging, in contrast to the findings from other studies.

Ageing and cell migration

The migration of TSPCs exhibits a decreasing trend with advanced age in a series of studies^[14,56,60]. Popov *et al*^[56] observed a significant decrease in the migratory of aged TSPC, and EphA4-Fc and ephrin receptor B2-Fc (ephB2-Fc) restore the decreased migration of A-TSPCs by inducing cell motility. Additionally, young hypoxic conditioned culture medium (HCCM) and inhibition of ROCK, a factor related to accelerate ageing, promote the restoration of cell migration^[14,60].

Ageing and cell differentiation

The TSPC pool becomes exhausted considering the size and functional fitness with ageing. However, the maintenance of the multidifferentiation capacities of TSPCs from animals and humans is widely accepted, although a consensus on the direction of alteration has not been reached.

TSPCs from different time groups display multidifferentiation potential, while the ability of TSPCs-7d was greater than TSPCs-1d and TSPCs -56d, and a similar trend was observed in the tenogenic differentiation capacity^[61]. The capacity of TSPCs to differentiate into tenocytes is reduced with ageing^[61], consistent with the observation that the tenogenic differentiation capacity of TSPCs is profoundly diminished during ageing^[54]. Moreover, aged TSPCs are not sensitive to transforming growth factor- β 3, a

sublineage of the TGF- β superfamily that regulates cell growth and differentiation^[64]. However, A-TSPCs transformed into adipocytes more readily than younger cells and produced higher levels of adipogenic markers that further resulted in the appearance of adipose tissue, which is generally related to aged tendons, while they presented no obvious difference in the capacity to transform into osteoblasts or chondrocytes^[15]. Moreover, TSPCs tend to differentiate into osteoblasts as the number of passages *in vitro* increases, while the adipogenic, chondrogenic and tenogenic differentiation capacities in TSPCs decline during *in vitro* subculture^[62]. Furthermore, Can Zhang *et al.*^[65] detected that a gradual loss of the tenogenic differentiation capacity of TSPCs with passaging due to the increased expression and activity of histone deacetylase (Hdac). Additionally, conflicting evidence shows a lack of age-related changes. Although, A-TSPCs have been reported to display an evident decrease in self-renewal and clonogenic capacities, multipotency is maintained *in vitro*^[14]. Another research concluded that the multipotency assays were not influenced by advanced ageing, although Y-TSPCs produced higher levels of some osteogenic and adipogenic genes, while chondrogenic genes were expressed at high levels in A-TSPCs^[50]. Overall, researchers have concluded that the multidifferentiation capacities of TSPCs are maintained during the ageing process without a conclusive determination of the trends in their variations, but most studies conclude that ageing impairs the tenogenic differentiation capacity of TSPCs.

Ageing and cell specific cluster differentiation (CD) markers

Greater than 98% of TSPCs are positive for CD73, CD90, CD105, STRO-1, CD146, Musashi-1 and CD44, but are negative for CD19, CD34, CD45 and HLA-DRA^[14,50]. Compared with young TSPCs, aged cells exhibit lower CD90.1 level, but higher CD44 expression^[53]. CD44 is involved in the healing processes of numerous tissues and its levels are reduced in the process of scar less fetal tendon healing^[66]; moreover, an improvement in mouse patellar tendon healing might attributed to a deficiency in CD44^[67]. Based on these findings, the up-regulation of CD44 in A-TSPCs might result in a decrease in the self-repair ability of TSPC with ageing. Additionally, the production of CD90 and CD73 decreases with increasing numbers of passage *in vitro*^[62].

Ageing and cell stemness markers

Approximately all TSPCs are positive for stem cell markers, including nucleostemin, Oct-4, and SSEA-4 in different age groups, revealing that the cells still maintained stemness features with age^[53]. However, the levels of stem cell markers are dramatically decreased with ageing. Additionally, moderate mechanical stretching (4%) dramatically upregulated the stem marker NS expression of A-TSPCs *in vitro*, but 8% stretching reduced its production; similarly, 4% stretching also upregulated the production of another stem cell marker, Nanog^[13].

Ageing and cell viscoelasticity

One study revealed an overall increase in G' , G'' and H_{TSPC} with ageing, which are valuable indicators of the cellular viscoelasticity that correspond to the storage modulus (G'), loss modulus (G'') and average thickness (H_{TSPC}), respectively. A dense cytoskeletal organization might result in a larger cell size and anomalous cell shape and is the cause of the increase in stiffness and viscosity^[57]. Other authors had also detected an increase in the cell stiffness and size of A-TSPCs, as well as a denser and well-structured actin cytoskeleton. Moreover, treatment with a ROCK inhibitor rejuvenated these age-related variations in morphology and stiffness^[55]. As it is known, ECM is another critical factor for the viscoelasticity of TSPCs and intervened in the receptor-substrate ligand interactions of cell adhesion^[57]. Although, Kostrominova *et al.*^[68] showed alterations of ECM protein expression in rat tendons with ageing, while composition of ECM related to the cell adhesion was not analyzed. Related experiments can be carried out because ECM proteins and cell niche are likely to highly influence both TSPCs maintenance and turnover in the future.

Ageing and cell senescence markers

A-TSPCs undergo cellular senescence at an early stage, as determined by quantifying the number of β -gal-positive cells at different time points, and at P4, more A-TSPCs displayed positive staining. In addition, the quantity of β -gal positive A-TSPCs was dramatically increased at later passages. Moreover, the P16 protein was already detected in the P1 A-TSPCs, and its expression was evidently upregulated at P14^[14], accompanied by the evident upregulation of β -gal activity in TSPCs with increasing passaging^[62]. In addition, an up-trend in the levels of senescence-related markers was observed in A-TSPCs in other studies^[53,54,60,63,69,70], and the inhibition of ROCK, up-regulation of Pin1 (peptidyl-prolylcis-trans isomerase NIMA-interacting1) or miRNA

(miR)-135a, down-regulation of P16, or modulation of other molecules involved in the ageing process reversed the senescence of TSPCs and effectively delayed the ageing process^[14,63,69].

Mechanisms involved in the ageing process

Because TSPCs ageing is an intricate process, its progression is also affected by multiple factors, including hormones, cytokines, enzymes, the oxygen content, mechanical force and exercise. Although the occurrence of epigenetic alterations in TSPCs with ageing has been observed, few scholars have focused on the underlying mechanisms partially because of the ambiguous conclusion regarding changes in aged TSPCs. The following section summarizes recent progress in the discovery of molecules and pathways involved in the TSPC ageing process and their various roles in mediating the ageing process, providing future research directions for TSPCs ageing and potential treatment targets for age-related tendon diseases. The mechanisms involved in the TSPC ageing process are listed in Figure 1.

Compared with Y-TSPCs, cAMP-responsive element-binding protein/p300-interacting transactivator with ED-rich tail 2 (CITED2) was dramatically down-regulated in older-TSPCs (O-TSPCs) at both the mRNA and protein levels and O-TSPCs showed reduced proliferation and elevated senescence. Furthermore, upon induction with TGF β -2, the nuclear expression of CITED2 and SP1 was significantly decreased, indicating that TGF β -2 mainly suppresses nuclear expression of CITED2. At the same time, P21 expression was increased, and myelocytomatosis viral oncogene homolog (MYC) was up-regulated following the silencing of CITED2, revealing that the TGF β 2-CITED2-MYC-SP1/P16 pathway mediates TSPC senescence. These findings were further supported by the results of a previous study showing that MYC functions as a transcriptional activator or repressor in regulating cell cycle progression and that the TGF β receptor kinase inhibitor SB525334 modulates the activity of this pathway^[71]. By comparing genome-wide RNA microarray data obtained from human Y-TSPCs and A-TSPCs, an intriguing difference was found: Altered genes were mainly distributed in categories such as cell-cell contact, cell adhesion, motility, migration, cytoskeleton and actin-associated transcripts, which might be the cause of the phenotypic and behavioral variations in A-TSPCs. In addition, the changes in features related to actin in A-TSPCs also significantly disrupted the formation of actin stress fibers and cell-matrix interactions^[14]. Moreover, collagen I expression and the corresponding integrins was decreased^[14], while Rho-associated coiled-coil protein kinase1/2 (ROCK1/2), a downstream molecule that modulates the stabilization of actin filaments by phosphorylating LIMK, was up-regulated in A-TSPCs^[72]. Recently, another study illustrated an apparent increase in cell stiffness in aged TSPCs, which was associated with an increase in the activation of ROCK and a satisfactory rejuvenating effect of ROCK inhibition with Y-27632, because A-TSPCs exhibited similar features to Y-TSPCs after the intervention^[55]. Based on these findings, ROCK activity plays an essential role in TSPC ageing, primarily by regulating actin stress fibers and/or cell stiffness. Chen *et al*^[63] detected an obvious decrease in miR-135a level in A-TSPCs through direct bind to the 3'-untranslated region of ROCK1 compared with Y-TSPCs. Overexpression of miR-135a inhibits cell senescence, increases proliferation, and enhances migration and tenogenic differentiation of Y-TSPCs, while the inhibition of miR-135a produces the opposite results in A-TSPCs. The effects of miR-135a on TSPCs were attributed to its interaction with the ROCK1 mRNA, which was confirmed by a series of functional studies. Overall, miR-135a-ROCK1 plays a crucial role in TSPC senescence. Han *et al*^[54] showed a substantial decrease in the A-TSPC tenogenic differentiation capacity, along with a decrease in the expression of P16 and the senescence-associated β -gal with age. P16 overexpression was responsible for the decrease in the tenogenic differentiation capacity of young TSPCs, and an analysis of the underlying mechanism revealed that this effect was mediated by P16, which enhanced the expression of miR-217 and subsequently inhibited the production of its direct target EGR1. According to these studies, A P16-miR-217-EGR1 pathway modulates TSPC the tenogenic differentiation and senescence of TSPCs. In addition, the EphA4, EphB2 and EphB4 and ephrin ligand B1 (EFNB1) in A-TSPCs is decreased compared with Y-TSPCs, which accelerates the decrease in self-renewal, migration, and actin turnover in A-TSPCs caused by advanced age. Upon stimulation with recombinant EphA4-Fc and EphB2-Fc proteins, significant effects on the key downstream signaling pathways mediated by ephrin-EPN binding were observed, including the activation of the cellular kinases focal adhesion kinase (FAK), extracellular signal-regulated kinase (ERK), Akt, c-Jun N-terminal kinase (JNK), and p38 in A-TSPCs; however, stimulation with EphB4-Fc and EFNB1-Fc did not exert an obvious effect on kinase activity in A-TSPC. Moreover, following stimulation with EphA4-Fc, FAK and JNK activity increased in A-TSPCs and more importantly, ERK phosphorylation was reduced to levels similar to the

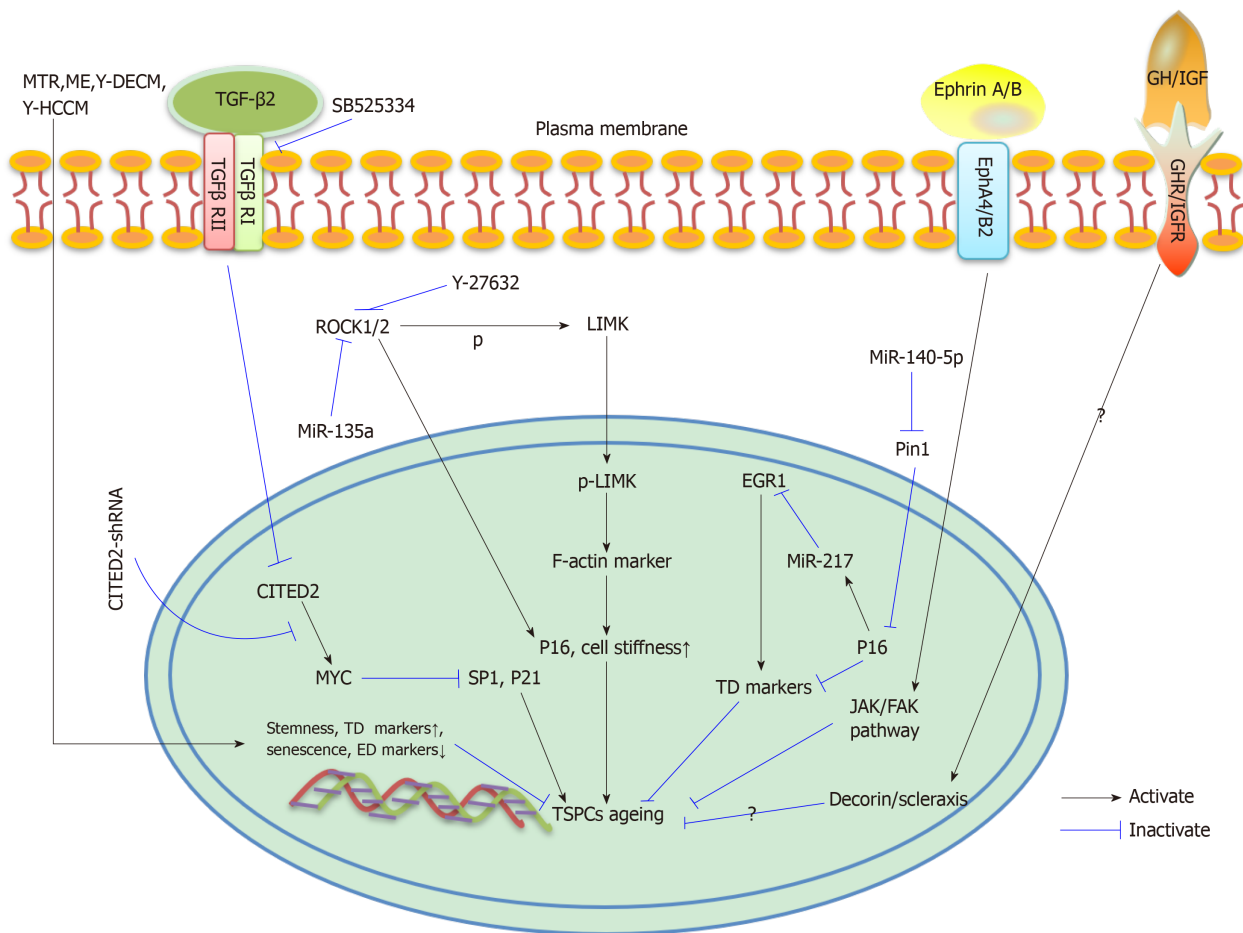


Figure 1 Mechanisms involved in the tendon stem/progenitor cell ageing process and strategies aimed to rejuvenate the impaired features in aged cells. TGFβ2 promotes the expression of CITED2. CITED2 up-regulates the expression of MYC, which inhibits the expression of SP1 and P21, revealing TGFβ2-CITED2-MYC-SP1/P21 pathway mediates cell senescence. And this pathway is delayed with the intervention of SB525334, which targets TGF-β2. Moreover, ROCK1/2 plays an important role in accelerating TSPC senescence and stiffness that can be delayed by the inhibition of Y-27632 on ROCK1/2 and miR-135a on ROCK1. MiR-140-5p reduces the expression of pin1 that downregulates the expression of P16 and ultimately delays TSPCs ageing. P16-miR-217-EGR1 pathway negatively modulates the cell tenogenic differentiation and senescence process. JAK/FAK pathways are involved in the modulation of Ephrin A/B and EphA4 and EphB2 by affecting cell self-renew, migration and actin dynamics. GH/IGF-I pathway may participate in TSPCs ageing process by increasing the expression of decorin and scleraxis, resulting in delaying TSPCs ageing. Additionally, there are many cell external environment conditions, such as moderate treadmill running, moderate exercise, young decellularized extracellular matrix and young hypoxic-conditioned culture medium, can rejuvenate age-related alterations in aged-TSPCs. TD: Tenogenic differentiation; ED: Erroneous differentiation; MYC: Myelocytomatosis viral oncogene homolog; ROCK: Rho associated coiled-coil forming protein kinase; TGF-β2: Transforming growth factor-β2; TSPCs: Tendon stem/progenitor cells; IGF: Insulin-like growth factor; Pin1: Peptidyl-prolylcis-trans isomerase NIMA-interacting 1; miR: miRNA; CITED2: cAMP-responsive element-binding protein/p300-interacting transactivator with ED-rich tail 2; FAK: Focal adhesion kinase; P16/21: Passage 16/21.

levels detected in Y-TSPCs. Additionally, EphB2-Fc dramatically up-regulated the levels of phosphorylated JNK and P38 kinases in A-TSPCs, suggesting that EphA4 and EphB2 signaling overlap mainly in the activation of JNK; however, other ephrins showed evident differences in their abilities to activate ERK, FAK, and P38. EphA4, but not EphB2, restores the self-renewal deficit in A-TSPCs, and both EphA4 and EphB2 positively modulate the deficit in migration and increased actin dynamics. Thus, a decrease in EphA4 and EphB2 production with ageing contributes to the limited cell-cell interactions and decreased cell proliferation, motility and actin turnover that play essential roles in the human TSPC ageing process, changes that are potentially mediated by the abovementioned pathways^[56]. Other studies revealed a correlation between ageing and a decrease in both plasma growth hormone (GH) and IGF-I levels^[73], and the reduced activity of the GH/IGF-I axis in elderly might result in a lower collagen content^[74]. Moreover, according to Holladay *et al.*^[40], IGF-1 affects TSPC proliferation and the maintenance of cellular phenotypes by increasing the levels of decorin and scleraxis; thus, other signaling pathways modulated by the GH/IGF-I pathway might participate in the TSPC ageing process^[74].

REJUVENATION OF AGED TENDON STEM/PROGENITOR

CELLS

As a result of in-depth explorations of age-related changes in TSPCs during the cellular ageing process, scholars are now more likely to develop methods to reverse the deficits in TSPC function that result from advanced age. Numerous factors, including macroscopic factors associated with an the uncomfortable exercise intensity and microscopic factors associated with an impaired estrogen balance, deteriorated ECM conditions and inappropriate drug use, alter the features of TSPCs, particularly during ageing, and these alterations are mainly deleterious to TSPC function and the maintenance of tendon homeostasis. Furthermore, repair might be achieved by adjusting these factors, which have potential roles in the rejuvenation of aged TSPCs and are listed in [Figure 1](#).

MTR has also been studied to determine the effects of motion on wound healing in aged tendons^[75], resulting in faster healing and a better healing quality through the restoration of the TSPC pool, which is beneficial for delaying TSPC senescence, enhancing the production of collagen fibers and reversing the erroneous differentiation of TSPCs. This approach eventually reverses the histopathological alterations that observed in subjects with age-related tendon diseases^[76-78]. Furthermore, the role of moderate exercise in the effects of ageing on TSPCs has been investigated. Moderate exercise ameliorates the depletion of the TSPC pool by up-regulating the expression of cell proliferation and stem cell markers coupled with decreased lipid deposition, proteoglycan accumulation and calcification formation, and it is beneficial for delaying the undesirable effects of age^[15]. The impaired capacities of aged TSPCs were rejuvenated in a recent study by culturing cells with young decellularized extracellular matrix (DECM) because the young DECM increased the proliferation and tenogenic differentiation of aged TSPCs. Moreover, the expression of senescence-related marker in aged TSPCs was decreased and that of stem cell markers was increased after culture with young DECM, suggesting that the ECM is an important factor contributing to TSPCs ageing and the modulation of the ECM might be a promising anti-ageing approach^[79]. Similar results were also obtained from young TSPCs cultured with HCCM, which restored the impaired function of aged TSPCs^[60]. Pin 1 plays an important role in delaying the TSPC senescence process, which was confirmed by the decreased production of senescence markers and P16 and increased telomerase activity coupled with the opposite results following transfection with the Pin1-siRNA. Overexpression of Pin1 also effectively deferred late-stage TSPC senescence progression, but had no evident effect on the progression of early-stage cellular senescence, and miR-140-5p was involved in regulating of Pin1 production, leading to a substantial decrease in Pin1 expression. Thus, Pin1 might be an anti-senescence target in TSPCs, together with miR-140-5p^[69]. Numerous studies have reported an important role for ROCK activity in the TSPCs ageing process, and after inhibition of ROCK, A-TSPCs re-established a phenotype and cell stiffness similar to Y-TSPCs^[14,55]. Notably, miR-135a also has a crucial role in modulating TSPCs senescence by facilitating the proliferation, migration and tenogenic differentiation of these cells and decreasing the expression of senescence markers inhibiting target downstream molecules of ROCK1 activity^[63], revealing that the blockade of ROCK activity is another promising strategy for combating TSPC ageing. A similar process is modulated by CITED2, providing an additional novel direction for fighting TSPC ageing^[71]. Culture-expanded TSPCs (an *in vitro* ageing process) tend to exhibit a loss of phenotype, resulting in impaired function of TSPC, and Zhang *et al*^[65] found that altered gene expression was related to the increased activity and expression of Hdac subtypes with passaging. Overall, these molecules and their functional states represent potential therapeutic targets for reversing age-related pathological changes in TSPCs.

As shown in the study by Popov *et al*^[56], the ephrin receptors EphA4, EphB2 and EphB4 and ligand EFNB1 is decreased in A-TSPCs, and the down-regulation of EphA4 and EphB2 plays crucial roles in the age-associated reductions of the self-renewal, migration, and actin turnover in human TSPCs. Moreover, the activation of EphA4 or EphB2-dependent pathways reverses these harmful consequences, further revealing essential roles in preventing TSPC ageing. According to another study, ageing induces a progressive loss of activity of the GH/IGF-I axis, and the level of IGF-I decreases with age^[73,80,81]. At the same time, IGF-1 promotes the proliferation and maintenance of TSPC phenotypes by increasing the expression of decorin and scleraxis^[40], indicating that the altered fate of TSPCs is able to be reversed by modulating the relative expression levels of hormones. In addition, rapamycin slows ageing in mice^[82,83], and metformin, pentosidine and multiflorum increase the lifespans of animals and humans^[84-86]. However, the relationships between these drugs and the mechanisms underlying the increase in lifespans are unknown due to the limited and insufficient number of studies conducted in this area^[84-86]. Additionally,

based on most recent development in regenerative medicine, Dale *et al*^[87] induced human embryonic stem cells to differentiate into tendon-like cells in the presence of exogenous bone morphogenetic protein (BMP) 12 and BMP 13 and directed parthenogenetic stem cells to differentiate into tenocytes. Moreover, mechanical stretching improved the tenogenic differentiation of pMSCs^[88]. Similar results were also obtained using iPSCs^[89,90]. Thus, these cells may represent an exogenous supplementation to TSPCs or tenocytes, which is also an ideal way to method for rejuvenating ageing of tendons and provides alternative healing strategies for reversing tendon ageing in the future.

CONCLUSION

As a result of advanced studies on tendons and the ageing of TSPCs, tendon ageing can be considered to be partially due to the aging of TSPC. TSPCs sustain regeneration at the site of tendon injury, and the loss of their function with advanced age causes aged-related tendon diseases. Although limited studies have been performed and the conclusions regarding the altered differentiation capacities and mechanisms involved are controversial, particularly regarding the erroneous differentiation, researchers generally agree that the cell number and tenogenic differentiation decrease with ageing, providing future directions for studies of TSPCs ageing. In particular, alterations in the ECM environment have been shown to re-establish the regenerative capacity of aged TSPCs, indicating that alterations in stem cell activity may be tractable for intervention, a hypothesis that is supported by the effects of alterations in cell-intrinsic pathways involved in TSPC ageing. Because humans are living longer, improvements in our understanding of the mechanistic networks underlying the age-associated in TSPCs and the tendon repair ability are critical for combating age-related tendon diseases.

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