Review Article

From the perspective of embryonic tendon development: various cells applied to tendon tissue engineering

Fangjie Qi[1#], Zhantao Deng[1#], Yuanchen Ma[1], Shuai Wang[1], Chang Liu[1], Fengjuan Lyu[1], Tao Wang[1,2], Qiujian Zheng[1,2]

[1]Department of Orthopedics, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, School of Medicine, South China University of Technology, Guangzhou Higher Education Mega Centre, Guangzhou 510006, China; [2]Centre for Orthopaedic Translational Research, School of Biomedical Sciences, University of Western Australia, Nedlands, Western Australia, Australia

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[#]These authors contributed equally to this work.

Correspondence to: Qiujian Zheng or Tao Wang. Guangdong Provincial Hospital, Guangdong Academy of Medical Sciences, School of Medicine, South China University of Technology, 106 Zhongshan 2nd Rd., Yuexiu Qu, Guangzhou 510080, China. Email: zhengqiujian@gdph.org.cn; tao.wang@uwa.edu.au.

Abstract: There is a high risk of injury from damage to the force-bearing tissue of the tendon. Due to its poor self-healing ability, clinical interventions for tendon injuries are limited and yield unsatisfying results. Tissue engineering might supply an alternative to this obstacle. As one of the key elements of tissue engineering, various cell sources have been used for tendon engineering, but there is no consensue concerning a single optimal source. In this review, we summarized the development of tendon tissue from the embryonic stage and categorized the used cell sources in tendon engineering. By comparing various cell sources as the candidates for tendon regeneration, each cell type was found to have its advantages and limitations; therefore, it is difficult to define the best cell source for tendon engineering. The microenvironment cells located is also crucial for cell growth and differentiation; so, the optimal cells are unlikely to be the same for each patient. In the future, the clinical application of tendon engineering might be more precise and customized in contrast to the current use of a standardized/generic one-size-fits-all procedure. The best cell source for tendon engineering will require a case-based assessment.

Keywords: Tendon; tissue engineering; stem cells; cell types

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Introduction

Tendons are unique connective tissues that not only connect the muscles and bones, but they are also important for maintaining posture and locomotion through transmitting muscle-contraction force to the skeleton. The tendon is composed predominantly of tenocytes surrounded by extracellular matrices (ECM) such as collagen I fibers, proteoglycans, and glycoproteins. It forms a solid structure and can support high repetitive mechanical loading (1). However, tendon tissue has poor healing ability and limited regenerative ability; the damage may become irreversible, and the healing process will be difficult, leading to chronic disability. Although the current wide use of topical or systemic anti-inflammatory drugs can reduce the perception of pain, and surgical repair of ruptured tendons through autograft or allograft seems to maintain the physiological function of the tendon (2), the functional, structural, and biochemical properties of the damaged tendon cannot be fully restored to an uninjured status (3). In addition, the

repair process may induce the formation of scar tissue (4), of which the tensile strength is only one-third that of an undamaged tendon, which can be a triggering factor for a large number of cases of secondary damage (5). Furthermore, autograft may cause donor site morbidity, while allograft may elicit an immune rejection (6).

Therefore, tissue engineering has been explored in an attempt to improve tendon healing and eventually reach a complete biological repair. A classic tissue engineering (7) technique is to culture seed cells in an engineered structure that is made of a biodegradable scaffold with the supplementation of growth factors or either mechanical or chemical factors to promote cell proliferation and differentiation *in vitro* before it is transplanted into the damaged site *in vivo*. Subsequently, the scaffold could be substituted by a newly formed organization that can replace damaged tissues and ultimately reconstitute the tissue functions (8). In tendon tissue engineering, cells also play a vital role in producing ECM for the reconstruction of the tendon tissue structure (9). Thus, the source of the seed cells becomes one of the key points in tendon tissue engineering. To find more potential candidates suitable for tendon tissue engineering, we explore the embryological origin of the limb tendons, analyze the developing processes of tendons, and summarize the availability of various types of seed cells using tendon tissue engineering. So, at the beginning of the article, we will reconstruct the development of the tendon from the embryo to maturity and explain the availability of these cells.

Embryological origin and development of tendons

Human embryonic development begins with the cleavage of the fertilized egg. It then divides into many smaller cells leading to the formation of the blastula. Through the cell movements of gastrulation, the embryo is rearranged to form the three main germ layers: the ectoderm, mesoderm, and endoderm. The mesoderm then gives rise to chordamesoderm, paraxial mesoderm, intermediate mesoderm, and lateral plate mesoderm. With the establishment of body axes and formation of the neural tube, limb buds arise from lateral plate mesoderm at the appropriate levels along the ventral domain of the body (10). The early limb bud has two major components: an outer layer of ectodermal epithelial cells, and a core of loose undifferentiated mesenchymal cells derived from the lateral plate mesoderm (11,12). The skeletal elements and connective tissues (including tendon structure) of the limb develop from these mesenchyme cells, but the limb muscles are derived from the somites which stem from the region of paraxial mesoderm and migrate into the limb bud. Therefore, the origin of tendon tissue is the same as that of bones, cartilage, and any other connective tissues, but not muscle. Analysis of the expression of scleraxis (Scx), a tendon specific transcription factor, revealed that the limb tendon progenitors originate from the subectodermal mesenchyme in proximomedial domains of the limb bud (13). Regulated by multiple morphogens and growth factors, three pairs of tendon primordium appear in a proximo-distal sequence in the developing limb (14,15). Proximal and intermediate tendon primordium appears the earliest on the dorsal side around limb junction. Following closely, intermediate tendon primordium appears on the ventral side around intermediate limb junction. The ventral proximal tendon primordium forms after the appearance of ventral intermediate tendon primordium. Subsequently, distal tendon primordium appears at both the dorsal and ventral sides of the distal limb. After the stimulation of growth factors and mechanical stress (16), the three pairs of tendon primordium will then differentiate into adult tendon structure in a proximal-to-distal sequence in the developing limb (*Figure 1*).

Various types of seed cells for tendon tissue engineering

Based on the process of limb tendon development, tenocytes originate from mesenchymal stromal cells (MSCs), which are also progenitor cells of skeletal elements and other connective tissues. Limb bud MSCs are derived from the lateral plate mesoderm of the embryo. These cells at different stages of tendon differentiation are candidate types of seed cells in tendon tissue engineering.

In the process of tendon development, tenocytes are the terminal product and the major component of the tendon's structure. Dermal fibroblasts belong to the class of mesenchymal cells, which are differentiated from MSCs. As dermal fibroblasts are labile cells and have the same precursors as tenocytes, they can be used in tendon repair (17).

Tenocytes are derived from tendon progenitor cells, which are called tendon-derived stem cells (TDSCs) (18). TDSCs are a type of stem cell that possess some characteristics of multipotent stem cells (19). Defined by the specific stem-cell niche, MSCs can be classified into bone marrow-derived mesenchymal stromal cells (BMSCs), adipose-derived stem cells (ADSCs), TDSCs, and other

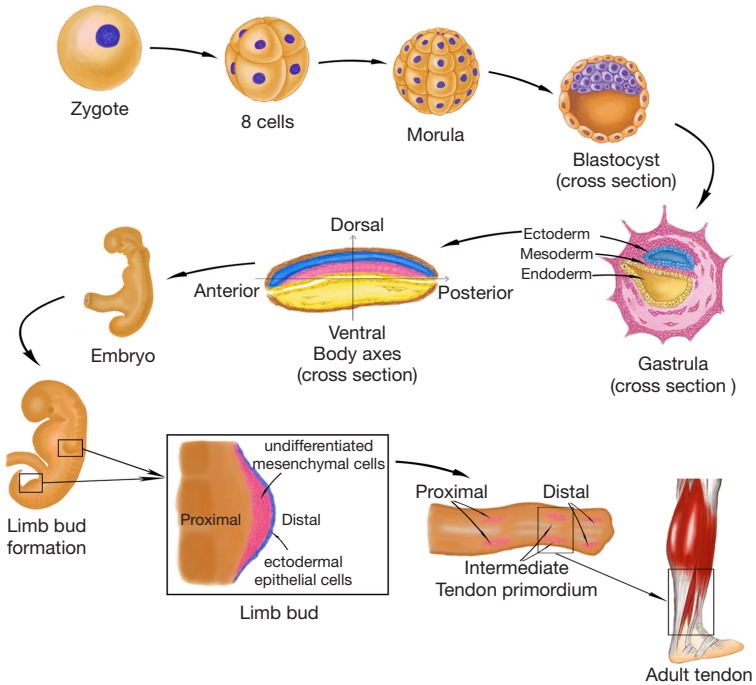

Figure 1 The process of human limb tendon development.

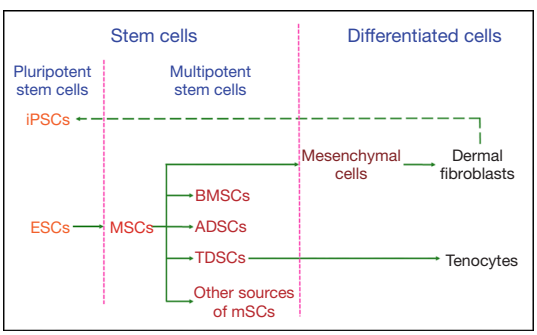

Figure 2 The derivation of tenocytes from ESCs and classification of cell types. Green solid arrows show the direction of differentiation, green dotted arrow shows that iPSCs can be obtained from dermal fibroblasts by dedifferentiation. The deepening of the font color means that the ability of cells to proliferare and differentiate is gradually reduced. ESCs, embryonic stem cells; iPSCs, induced pluripotent stem cells; MSCs, mesenchymal stromal cells; BMSCs, bone marrow-derived mesenchymal stromal cells; ADSCs, adipose-derived stem cells; TDSCs, tendon-derived stem cells.

sources of MSCs (20). These MSC-derived stem cells can be differentiated into tenocytes under appropriate stimulation *in vitro*.

Another available cell type is pluripotent stem cells, which can differentiate into all types of cells constituting the human body. These include embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs), which can be derived from differentiated human dermal fibroblasts (21).

In summary, the available seed cells for tendon tissue engineering include ESCs, iPSCs, MSCs (included BMSCs, ADSCs, and TDSCs), dermal fibroblasts, and tenocytes, as summarized in *Figure 2*. Next, we will discuss the respective advantages and disadvantages of these different cell types.

Comparison between different cell types

The cells in the human body can be divided into two categories based on their differentiation status (*Table 1*). One is differentiated cells, such as tenocytes and dermal fibroblasts, which lack self-renewal capability *in vivo*. Differentiated tenocytes and dermal fibroblasts can be expanded *in vitro* in the presence of serum but have a limited expansion capacity. Culturing *in vitro* with the supplementation of growth factors may activate their ability of proliferation, but these cells still lack the capacity of differentiating into other cell types. Besides, their phenotype may change, which will cause a deficiency in their functions with increasing passaging (18). The

Table 1 Relative comparison between two human cell types using tissue engineerin

Cell types	Category	Advantage	Disadvantage
Differentiated cells	Tenocytes, dermal fibroblasts	Low risk of teratoma and ectopic tissue formation	Terminal differentiated cells Limited proliferation rate Phenotype change and functional loss during expansion *in vitro*
Stem cells	ESCs, MSCs	Proliferative capacity Multidirectional differentiation potential	Teratoma and ectopic tissue formation

ESCs, embryonic stem cells; MSCs, mesenchymal stromal cells.

other is stem cells, which can replicate themselves as well as differentiate into specialized cells under appropriate conditions (22). At the same time, their ability to proliferate and differentiate is difficult to control *in vivo*, which makes them susceptible to forming of tumor and undesired tissue cells during differentiation.

Differentiated cells

Tenocytes

Tenocytes are highly specialized mesenchyme-derived cells with important roles in synthesizing ECM and maintaining tendon structures *in vivo* (23). Cao *et al.* constructed tissue-engineered artificial tendons for the first time (24), but they also indicated that tenocytes are relatively difficult to grow and expand *in vitro*. Furthermore, some researchers indicated that with increased passaging, the gene expression of tendon-associated proteins such as collagen type I (col I), collagen type III (col III), tenascin, and tenomodulin (TNMD) exhibited a trend of decrease (25). In addition, there is also a change in the tenocyte cell phenotype, represented by more rounded cell morphologies instead of longer and thicker configurations (18). Thus, many researchers have explored the strategies to promote proliferation and at the same time, support a stable phenotype of tenocytes. At present, it has been reported that thyroid hormone T3, transforming growth factor (TGF)-b1, glycine, platelet-rich plasma, and insulin-like growth factor 1 could enhance the proliferation and differentiation capacity of tenocytes, as well as stimulate the secretion of ECM (23,26-29). Mechanical force can also regulate tenocyte differentiation (30).

Dermal fibroblasts

Dermal fibroblasts are terminally differentiated cells that originate from mesoderm. *In vitro*, dermal fibroblasts exhibit similar cell morphology as tenocytes and mainly produce col I and col III. Compared with tenocytes, the harvest of dermal fibroblasts is less defective as only an easily accessible, small piece of skin is needed. Also, the cell expansion is less likely during *in vitro* culture (31). It has been revealed that there is no difference in their gross view between neo-tendon tissues engineered by human dermal fibroblast or tenocytes. There was also no difference found in the histologic structure, collagen superstructure, or mechanical property under the static strain *in vitro* (32-34). Therefore, researchers have used dermal fibroblast-engineered tendon to repair animal tendon defect, and the results are satisfactory in that the tensile stiffness and maximum load are expressly higher than those of non-dermal fibroblast scaffolds (35-38).

When dermal fibroblasts and tenocytes are compared, both originate from mesoderm and have similar morphologies (36), and it was determined that dermal fibroblasts were more advantageous compared to tenocytes. First, dermal fibroblasts have good proliferative capacity and self-renewal potential (39). Second, dermal fibroblasts have been shown to be easy to harvest with no major tissue defects at the donor site since the skin can regenerate in a short time (40). In contrast, tenocytes are more difficult to collect because the density of tenocytes in a tendon is low, and there is an issue of donor site morbidity (41). However, dermal fibroblasts have a disadvantage in that they may produce fibrotic ECM which is involved in scar formation (42) (*Table 2*).

Stem cells

According to the differentiation potential, stem cells can be divided into distinct kinds of cell types. Pluripotent stem cells can differentiate into all cell types of all organs,

Table 2 Comparison between two differentiated cells types

Cell types	Advantage	Disadvantage
Tenocytes	Major cell type in the tendon Produce ECM for tendon function maintenance	Low cell number in the tendon Donor site morbidity
Dermal fibroblasts	Easy to harvest from skin punch biopsy Production similar to the tenocyte	Not tenocyte Unstabled phenotype Scar formation

ECM, extracellular matrix.

Table 3 Comparison between stem cells

Cell types	Category	Advantages	Disadvantages
ESCs	–	Unlimited proliferative ability Pluripotent	Risk of teratoma formation (Ethical issue with the use of embryos for cell isolation The challenge to acquire patients' own ESCs
iPSCs	–	Unlimited proliferative ability Pluripotent No ethical concern for tissue source	Risk of teratoma formation Genotype change in the transfection process Low efficiency of the transfection process Less reported in tendon regeneration
MSCs	BMSCs ADSCs TDSCs	Low cancerization rate Easily available tissue source for cell isolation No ethical concern for tissue source	Senescence and loss of stem cell characteristics as the number of passages increase *in vitro*

ESCs, embryonic stem cells; iPSCs, induced pluripotent stem cells; MSCs, mesenchymal stromal cells; BMSCs, bone marrow-derived mesenchymal stromal cells; ADSCs, adipose-derived stem cells; TDSCs, tendon-derived stem cells.

like ESCs and iPSCs (43). Multipotent stem cells can develop into many cell types within a particular lineage. For instance, the MSCs can give rise to bone cells, cartilage cells, adipose cells, and tendon cells. As ESCs have unlimited self-renewal potential and can differentiate into cells of all three embryonic germ layers (44), the risk of developing teratoma is expected to increase (45).

Meanwhile, considering that ESCs originate from the blastocyst, the harvest of human ESCs requires the destruction of the embryos, which may give rise to ethical concerns (46). iPSCs derived from differentiated cells may obviate these ethical issues. But, as they are pluripotent stem cells, the problem of forming teratoma during proliferation and differentiation remains unsolved. Furthermore, there are serious problems in the process of inducing iPSC formation (47).

By contrast, MSCs are more safe due to their limited proliferation capacity and the restricted multilineage differentiation potential of cells of the mesodermal lineage (48,49). The use of MSCs also bypasses certain ethical obstacles as they are adult stem cells that can be harvested from non-embryonic sources (50). However, it has been accepted that MSC expansion in culture results in their accelerated aging, which will cause the deficiency of proliferation and multilineage differentiation potential (51,52) (*Table 3*).

ESCs

ESCs can give rise to all tissues derived from the three germ layers (53). Because of this, ESCs hold great promise as seed cells for tendon tissue engineering (54). Thus, how to differentiate them into the tendon lineage has become a key point. Some researchers have investigated a stepwise differentiation approach by first inducing human ESCs to differentiate into MSCs, and subsequently allowing the MSCs to form tendon-like tissues. The results *in vivo* and *in vitro* showed that human ESC-derived MSCs exhibited tenocyte-like morphology and positively expressed tendon-related gene markers such as Scx, col I and col III, as well as other mechano-sensory structures and molecules (55,56). Moreover, the formation of teratomas could be avoided if ESCs are induced into MSCs before the transplantation (55).

In addition, they demonstrated that the use of dynamic mechanical stress (1 HZ, 10% for 2 h/day) and bone morphogenetic protein (BMP)12 and BMP13 could promote differentiation of human ESCs into tenocytes (57-60).

iPSCs

The use of ESCs may be limited due to the need to sacrifice an embryo, which has aroused some ethical controversy. The discovery of iPSCs resolves the ethical problem of using ESCs, and recently, researchers were able to generate iPSCs from terminally differentiated cells (21,61). However, as their iPSCs were generated using retroviruses or lentiviruses (62), it might cause mutagenesis that would pose a risk for adverse effects in therapy (63). The efficiency of the transfection process also remains low. Thus, for the purpose of the safety of cell transplantation therapy, mRNA-delivered transcription factors have been applied to generate integration-free iPSCs (64,65). While these studies address some of the issues raised by the use of iPSCs in regenerative medicine, it has not been reported in tendon tissue engineering. For now, iPSCs are being used as a potential seed cell source for tendon regeneration research.

MSCs

MSCs are non-hematopoietic adult stem cells derived from the mesoderm germinal layer that can differentiate into mesenchymal-derived cell types and have the ability to self-renew (66). The membrane surface of MSCs expresses several antibodies, such as stromal cell antigen-1, CD271, stage-specific embryonic antigen-4, CD146, and so on, which can be considered as specific markers of MSCs (67,68). MSCs were initially isolated from bone marrow as precursors of stromal elements (69). From recent research, it is now clear that MSCs can be isolated from a wide range of adult and perinatal mesenchymal tissues, including those of bone, synovial membranes, periosteum, adipose tissue, tendons, skeletal muscles, and others (70). The use of MSCs for tendon repair has been extensively explored and may promote tendon regeneration.

BMSCs

The BMSCs have active self-proliferative and multi-differentiate capacity. The use of autologous BMSCs in the animal model could induce matrix production and organization of injured tendon as well as restore histological structure and function (71). Because of the easy isolation from bone marrow and the enrichment of colony-forming units, BMSCs have become an attractive cell source for tissue engineering approaches. However, BMSCs may differentiate into osteoblasts instead of the expected tenocyte lineage when transplanted into the injured tendon, and form ectopic bone *in vivo* (72,73). To overcome such issue, a number of approaches are presently being developed to navigate the tenogenic differentiation of BMSCs (74). They have shown that cyclical uniaxial stretching and BMP14, TGF-β, connective tissue growth factor (CTGF), vascular endothelial growth factor (VEGF), and myostatin can initiate and maintain highly efficient growth and differentiation of BMSCs towards tenocytes *in vitro* (75-80). Furthermore, Zhang *et al.* (78) and Xie *et al.* (81) used a 3D culture environment combined with BMSCs sheets that have therapeutic effects on improving the healing quality of the tendon *in vivo*.

ADSCs

ADSCs are advantageous in tissue engineering due to their multipotency, high proliferation, easily isolated amounts of cells from the subcutaneous tissue, and low donor site morbidity (82,83). ADSCs have been regarded as one type of seed cell for tendon tissue engineering that can differentiate into tenocytes *in vivo* and increase the tensile strength of the repaired tendon (84,85). However, their innate tendency towards adipogenesis may hinder the application of ADSCs in tendon regeneration (1,86). For this purpose, intense research was conducted to overcome this obstacle. Yu *et al.* confirmed that hypoxia or activating the expression of hypoxia-inducible factor-1 could improve the tenogenesis of ADSCs (87). Additionally, several studies have indicated that the supplementation of growth factors could improve cell proliferation of ADSCs and promote tendon repair efficiency (88-90). Tendon ECM components (91) and TNMD (92) enhance the proliferation and tenogenesis of ADSCs. Physical stimulation such as uniaxial tensile cyclic loading (2% strain and 0.1 Hz frequency) (93) and extracorporeal shock waves in tenogenic medium (94) can also boost the differentiation of human ADSCs toward tendon-like cells.

TDSCs

TDSCs isolated from human tendons have general stem cell characteristics such as clonogenicity, multipotency, and self-renewal capacity (95,96). TDSCs can spontaneously

Table 4 Comparison between MSCs

Cell types	Advantage	Disadvantage
BMSCs	Extensive research history A large number of research results are available for reference	Ectopic bone formation *in vivo* Small quantity of viable cell yield *in vitro* Harvested by an invasive method with many complications on donor site
ADSCs	High cell yield and excellent expansion ability Harvest through liposuction aspirates with less trauma and at lower risk	Ectopic adipose formation
TDSCs	Lineage superiority Express higher tendon-related gene markers and differentiation factors	Donor site morbidity Less practical research data
Other sources of MSCs	New source	Lack of research data

BMSCs, bone marrow-derived mesenchymal stromal cells; ADSCs, adipose-derived stem cells; TDSCs, tendon derived stem cells.

regenerate tendon-like tissue structures *in vivo* and avoid differentiating into other kinds of cell lines. Extensive progress and deep insights have emerged in the study of these cells for tendon tissue engineering and regeneration (19). ECM (97), biglycan (98), hepatocyte growth factor (99), and mechanical stimulation (100) that can promote TDSCs proliferation and tenogenic differentiation *in vitro* have been verified in research. CTGF and ascorbic acid can enhance the survival time, proliferation, and migration abilities of TDSCs *in vivo* (101). Recently, Zhang *et al.* demonstrated that genetic alterations of TDSCs following culture expansion could be prevented by pretreating TDSCs with histone deacetylase inhibitor, to retain their ability to accelerate tendon repair *in vivo* (102). Furthermore, Yin *et al.* identify a subpopulation of nestin+ TDSCs which exhibited a superior tenogenic capacity compared with nestin- counterparts (103). This study not only redefines the subpopulation of tendon stem cells but also provides new insights into a novel cell line for tendon tissue engineering.

Other sources of MSCs

Moshaverinia *et al.* tested the capacity of encapsulated dental MSCs to differentiate into tendon tissue *in vitro* and *in vivo*. Their findings indicate that periodontal ligament and gingival tissue-derived MSCs can be considered as suitable stem cell sources for tendon engineering (104). Chen *et al.* explored dental pulp stem cells (DPSCs) for potential application in tendon tissue engineering and found that mature tendon-like tissue was formed after transplantation of DPSCs in a special fiber scaffold constructs under mechanical loading in a mouse model (105).

Comparison of the potential of various types of MSCs for tendon tissue engineering

MSCs can be harvested from various sources, such as bone marrow, adipose fat, and tendon tissue. They have paracrine effects, including immunomodulation, promoting angiogenesis, or suppressing inflammation and immune cell functions through secretory factors (106). BMSCs were the first discovered MSCs and the most widely used seed cells in tissue engineering. They are easy to harvest through bone marrow aspiration, but their limitations include relatively small quantities of viable cell yield through an invasive method, which cause many complications on the donor site and ectopic ossification after transplantation *in vivo* (107,108). ADSCs can be obtained from liposuction aspirates, which is less invasive and involves lower risk. With the relatively large storage of adipose tissue *in vivo*, a mass of ADSCs can be isolated and expanded *in vitro* (109,110). However, the main disadvantage of ADSCs is their tendency to undergo adipogenesis *in vivo* (111). TDSCs express higher tendon-related markers and differentiation factors than BMSCs and ADSCs (112,113), but the main drawback of TDSCs is that their isolation will lead to the injury of the donor site (114). Overall, there is not enough data from practical research on TDSCs to make firm or extensive conclusions (*Table 4*).

Conclusions

Tendons are an important component in the musculoskeletal system. Due to the limited regenerative ability of tendons, the healing process after an injury is slow, and the functions of the tendon are likely to be compromised. This results in

a serious decline in the quality of life of patients. Cell-based tendon tissue engineering is a promising research area that aims to deliver adequate, regeneration-competent cells to the injured tendon and ultimately promote the restoration of its functions (20). This review provides an overview of tendon tissues from an embryonic stage and discusses the relative merits of each of the candidates that could be used as cell sources for tendon regeneration. Depending on the characteristics of each cell type, the researchers tested the most appropriate mechanical stimulation conditions and selected the different biological factors for improving the healing quality of the damaged tendon and reducing the adverse reactions during use (*Table 5*). Some major findings are described below: Mechanical stimulation will enhance the tenocyte differentiation in different cell types. Growth factors can promote cell proliferation in differentiated cells. However, in stem cells, growth factors not only enhance tenogenic differentiation but also increase the rate of cell growth. Furthermore, cell ECM also can accelerate cell proliferation and the tenogenesis of MSCs. Therefore, the results of these studies may provide new concepts or methods in clinical treatment to improve the level of tendon repair in patients. Doctors can select different cells to treat tendon disease by measuring a patient's expression level of growth factors, tendon transcription factors, the expression of collagen and cytoskeletal proteins in the extracellular matrix, and the microenvironment of the tendon. Clinical treatment of tendon injury can also provide an appropriate cell plan by avoiding the drawbacks of these seed cells. Massive ectopic ossification and fatty vesicles forming in the tendinopathy indicate that BMSCs and ADSCs are not the best choices in the treatment of tendinopathy (115). In addition, scar formation and disorganization of fibers at tendon damage or stump are factors to be considered when selecting candidate cells.

Since there is such a large variety of individual complexity for each of the patients undergoing clinical treatment, it is difficult to define optimal cell sources in tendon engineering. There are various types of tendon damage, including tendon rupture, tear, degeneration, tendinopathy, etc., which might change the cellular status at the damage site (116), and eventually affect the treatment outcomes. Furthermore, stem cell quality varies widely for different individuals. Therefore, there is no best cell source for tendon engineering in general. The determination of the most suitable cell source should be based on a comprehensive assessment of each patient. In the future, clinical treatment of tendon injury by tissue engineering

Table 5 Stimulation methods of different cell types for promoting tenogenesis and tendon healing

Cell types	Stimulation methods	Conditions	Results	Author	Year
Tenocytes	Mechanical stimulation	1 Hz rate and 8% strain for 2 h/day	Enhances tenocyte differentiation	Wu YF	2017
	Biological factor	TGF- β1	Improves tenocyte differentiation and ECM	Theiss F	2015
		Ascorbic acid + thyroid hormone T3	Promotes tenocyte proliferation	di Giacomo V	2017
		Glycine	Enhances the production of ECM	Vieira CP	2018
		Platelet-rich plasma	Enhances tenocyte proliferation	Alzyoud JAM	2019
		IGF-1	Improves tenocyte proliferation	Disser NP	2019
Dermal fibroblasts	Con-culture with scaffolds	Nanofiber scaffold	Promotes tenogenesis *in vitro* and enhances tendon regeneration *in vivo*	Wang W	2016
		Aligned polycaprolactone/silk fibroin nanofiber scaffold	Repairs the gap defects of Achilles tendons *in vivo* and effectively restores the function and structure of tendons	Chen CH	2017
		Hierarchical electrospun tendon-ligament bioinspired scaffold	Increases maximum load of tissue-engineered tendon	Sensini A	2019
	Static mechanical strain	Moved 2 mm to the right side weekly in order to maintain the traction force	Enhances tendon formation using HDFs *in vitro*	Nakanishi Y	2019

Table 5 (*Continued*)

Table 5 (*Continued*)

Cell types	Stimulation methods	Conditions	Results	Author	Year
ESCs	Dynamic mechanical stress	1 HZ, 10% for 2 h/day	Induces tendon differentiation	Chen X	2012
	Biological factor	BMP12/13, ascorbic acid	Induces tendon differentiation	Dale TP	2018
iPSCs	–	–	–	–	–
BMSCs	Cyclical uniaxial stretch	1 Hz rate and 8% strain	Promotes the tenogenesis of BMSCs and protein and gene expression	Nam HY	2019
	Biological factor	CTGF + TGF-β1	Promotes tenogenesis of BMSCs	Yin Z	2016
		VEGF + BMP12/14	Enhances the BMSC tenogenic differentiation	Bottagisio M	2017
		Myostatin	Increases BMSC's growth and tenogenesis of BMSCs	Le W and Yao J	2017
		BMP14	Induces the tenogenic differentiation of BMSCs	Wang D	2018
ADSCs	Physical stimulation	Uniaxial tensile cyclic loading (2% strain and 0.1 Hz frequency)	Induces tenogenic differentiation of ADSCs	Subramanian G	2017
		Extracorporeal shock waves	Improves differentiation of ADSCs toward tenoblast-like cells	Rinella L	2018
	Biological factor	Hypoxia-inducible factor-1	Improves the tenogenesis of ADSCs	Yu Y	2016
		Basic fibroblast growth factor + IGF-1 + PDGF-BB	Improve cellular proliferation of ASCs	Farnebo S	2017
		CTGF	Promotes early flexor tendon healing *in vivo*	Shen H	2018
		PDGF-BB	Promotes the proliferation of ADSCs *in vitro* and upregulated the expression of tendon-related genes	Chen QJ	2018
		Tendon ECM components	Enhances the proliferation and tenogenesis of ADSCs	Yang G	2017
		TNMD	Induces tenogenic lineage differentiation of ADSCs	Goncalves AI	2018
TDSCs	Mechanical stimulation	6% strain, 0.25 Hz, 8 h, followed by 16 h rest	Enhances tenogenic-specific differentiation	Wang T	2018
	Biological factor	Fibroblasts ECM	Promotes proliferation and tenogenesis of ADSCs	Jiang D	2014
		Biglycan	Promotes tenogenic differentiation	Zhang YJ	2019
		Hepatocyte growth factor	Promotes TDSCs proliferation and Migration and inhibits osteogenic differentiation	Han P	2019
		CTGF + ascorbic acid	Inhibits osteogenic differentiation	Lui PP	2016
		Histone deacetylase inhibitor	Promotes proliferation and upregulates the expression of tendon-related genes	Zhang C	2018

ESCs, embryonic stem cells; iPSCs, induced pluripotent stem cells; MSCs, mesenchymal stromal cells; BMSCs, bone marrow-derived mesenchymal stromal cells; ADSCs, adipose-derived stem cells; TDSCs, tendon-derived stem cells; BMP, bone morphogenetic protein; TGF, transforming growth factor; CTGF, connective tissue growth factor; VEGF, vascular endothelial growth factor; BMP, bone morphogenetic protein; IGF, insulin-like growth factor; PDGF-BB, platelet-derived growth factor-BB; ECM, extracellular matrix.

should be customized designed on a case-by-case basis to achieve the best clinical outcomes.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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