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Biomaterials for Tendon/Ligament and Skin Regeneration

Xingguo Cheng

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Abstract

Tendon/ligament injury or skin injuries due to diseases, trauma, and surgery are common. Timely functional repair and tissue regeneration is a key to improve the quality of life of the patient while reducing health care cost. Tendon/ligament/skin is also enriched in a common extracellular matrix (ECM), collagen I, III, and elastin. Tissue engineering and regenerative medicine, the combination of (stem) cells, growth factors, and biomaterial scaffolds, is an emergent field, which has attracted substantial attention over the years. Biomaterials are considered the foundation of regenerative medicine. A key to find a new solution to tendon/ligament/skin healing is to synthesize new functional biomaterials, which have better biomechanical properties, biodegradability, and cell supporting properties. This chapter will review existing FDA-approved biomaterial-based therapy, as well as those in development.

Keywords: biomaterials, tendon, skin, regeneration

1. Introduction

From material science point of view, tendon/ligament and skin tissue are similar in that they are mainly composed of collagen and elastin. Up to 80% of the dry weight is collagen type I. However, their micro and hierarchical structures and functions are very different from each other. Tendon/ligament is composed of densely packed, aligned collagen fiber bundles, whereas skin is composed of a layered structure of collagen random nanofibril network. **Table 1** summarizes the key properties of tendon/ligament and skin tissue in human.

The regeneration of a large size, lost tendon/ligament, and skin tissue normally involves a type of stem cells/progenitor cells of endogenous origin or exogenous origin combined with a

	Tendon/ligament	Skin
Main composition	>80% Collagen, ~5% elastin	>80% Collagen, ~5% elastin
Minor composition	Fibronectin, proteoglycan	Fibronectin, proteoglycan
Main cells	Fibroblast	Fibroblast and keratinocytes
Vasculature	Few	Abundant
Structure	1D Aligned fiber bundles (nano-macro)	2D random nanofibrils (weave basket pattern)
Mechanical properties	Strong and elastic	Weak and elastic

Table 1. A general comparison of two different connective tissues: tendon/ligament and skin.

biomaterial. Stem cells can be derived from tendon/ligament or skin, or from embryo, placenta, adipose tissue, bone marrow, umbilical cord, etc. This review focuses only on regeneration using exogenous stem cells coupled with a biomaterial matrix/carrier implanted to the wound site. Biomaterial can play a key role in protection of the cells from dehydration while it serves as a temporary substrate for stem cells to proliferate, or differentiate, and synthesize tissue-specific matrix. The morphology, topography, composition, stiffness of biomaterials may play a key role in controlling the differentiation of stem cells, in addition to biochemical factors, mechanical cues, or genetic/cellular cues. This chapter focuses on biomaterial explored for tendon/ligament/skin tissue regeneration applications.

1.1. Research methods

We performed a comprehensive search of PubMed using keywords “tendon,” “ligament,” “skin,” “regeneration,” “scaffold”, over the years 1970–2016. All articles relevant to the subject were retrieved, and their bibliographies hand searched for further references in the context to biomaterials for tendon/ligament/skin regeneration

2. Results

2.1. Biomaterial directly derived from patients

2.1.1. PRP

Platelet-rich plasma (PRP) is derived from blood and PRP gel is widely used for tendon/ligament repair. Recently, PRP was combined with adipose-derived stem cells (ADSCs) and it was found that PRP combined with stem cells resulted in improved mechanical strength in a rabbit tendon model compared to PRP gel alone [1]. Similar results were also observed using PRP with tendon-derived stem cells (TDSCs) [2]. However, in a sheep model, no differences were observed between the PRP group and PRP-stem cell group [3]. This approach is highly translational, since both autologous stem cells and PRP can be obtained from the same patients. The concern may be the leucocytes-containing PRP (L-PRP) that have a catabolic

effect, whereas pure PRP (P-PRP) without leucocytes have anabolic effects and results in over-proliferation and scar tissue formation. The complex interaction between PRP and stem cells may explain the different preclinical outcome and warrant a large random clinical trial.

2.1.2. Fibrin

Fibrin can be derived from human plasma. After addition of thrombin, it will form a gel, a process used for blood clotting. Stem cells can be added together with fibrin and thrombin and sprayed onto the wound for the promotion of wound closure and healing. The fibrin combined with bone marrow stem cells spray was successfully tested to prevent ulceration and accelerate wound closure in mice [4]. A small human clinical trial showed this approach accelerates wound closure and resurfacing without adverse effects [5]. Poly(ethylene glycol) PEG-modified fibrin combined with adipose-derived stem cells (ADSCs) also showed promising results in a pig burn model [6].

2.1.3. Amniotic membrane

Human placenta-derived biomaterial is unique in that it has immune privilege while it contains multiple growth factors. Human ADSCs (hADSCs) seeded onto radiosterilized human amnion are viable and can proliferate. These cells are able to migrate over these scaffolds as demonstrated by using time-lapse microscopy. In addition, the scaffolds induce hADSCs to secrete interleukin-10, an important negative regulator of inflammation [7]. This suggests that placenta-derived biomaterial may be a good substrate for stem cells and used for skin/tendon applications.

3D micronized (300–600 μm) amniotic membrane (mAM) was made by means of repeated freeze-thawing cycles to deplete cell components and homogenized with a macrohomogenizer in liquid nitrogen. These mAM loaded with epidermal stem cells (ESCs) (ESC-mAM) was further transplanted to full-thickness skin defects in nude mice. ESCs survived well and formed a new epidermis. Four weeks after transplantation, papilla-like structures were observed, and collagen fibers were well and regularly arranged in the newly formed dermal layer. In conclusion, the mAM as a novel natural microcarrier possesses an intact basement membrane structure and bioactivities [8].

2.2. FDA-approved ECM grafts for tendon augmentation and skin regeneration

A recent study showed that decellularized matrix from different tissues (tendon, bone, and skin) affect the differentiation of stem cell in a different way. Decellularized bone matrix may induce the undesirable osteogenic differentiation of stem cells, while tendon or skin matrix does not have such an effect [9]. The ECM components provide a niche for proper differentiation of stem cells. For example, ECM without biglycan (Bgn) and fibromodulin (Fmod) will affect the differentiation of tendon stem cells by modulating bone morphogenetic protein signaling and impairs tendon formation *in vivo* [10]. Autologous origin, but decellularized dermal matrix using trypsin and Trion X-100, after combined with ADSCs, was found to enhance wound healing in a murine model of a full-thickness skin defect [11].

Many FDA-approved human or animal decellularized tissue matrixes have been approved for direct tendon/ligament/skin repair without any (stem) cells (**Table 2**). The key advantages of decellularized tissue grafts are that they largely maintain the main architecture, composition, and mechanical properties of native tissues. These allografts/xenografts are processed to remove immunogenic cells, DNAs, and certain immunogenic molecules. Typical problems are that these grafts are slower to repair the tissue and some fail to restore the proper functions (e.g., scarring). For tissue regeneration using these ECM biological grafts, stem cells may need to be reseeded onto the grafts for recellularization. For a dense tendon allograft, direct cell seeding may be difficult. The recellularization onto the surface may be achieved using a cell-loaded gel coating [12]. However, it is highly desirable to get cells inside the grafts as well. Thus, ECM grafts may be processed to have a much higher porosity than the original tissue. Proration/incision into the ECM grafts may help the penetration of cells and nutrients. Instead of being coated with cell-laden gel, an interesting approach is to use a stem cell-sheet to wrap around a frozen tendon graft for implantation [13]. Interesting, a case report showed that a dermal allograft combined with PRP and autologous mesenchymal stem cells (MSCs) derived from peripheral blood (PB-MSCs) resulted in enhanced healing of human rotator cuff [14].

Some of the FDA-approved ECM biomatrices were combined with stem cells, and investigated for tendon/ligament/skin regeneration applications. Human acellular allograft (Alloderm) was investigated for direct cell seeding using ADSCs. It was concluded that human ADSCs can attach to Alloderm with the dermis side up in a petri dish [15]. ADSC seeded onto Alloderm was also implanted *in vivo* for skin regenerations with promising results [16]. Strattice was evaluated for seeding with rat MSCs [17]. Thus, the stem cell-seeded biologic graft can be used as a tendon wrap or a skin regeneration material. A study was performed to compare the survival and proliferation of stem cells via bioluminescent imaging. The use of biologic graft

Alloderm	Human skin (decellularized)
GraftJacket	Human skin
Restore	10-layered porcine small intestine submucosa (SIS) treated with peracetic acid/ethanol (90% collagen, 5–10% lipids)
TissueMend	Noncrosslinked fetal bovine dermal matrix [19]
BioBlanket	Crosslinked porous bovine dermis
Permacol or Zimmer collagen repair patch	Porcine acellular dermis treated with trypsin, solvent, and crosslinked with hexamethylene diisocyanate (HMDI)
Strattice	Porcine acellular dermal matrix
Cuffpatch	EDC-crosslinked matrix from eight layers of treated SIS (97% collagen, 2% elastin)
OrthoADAPT	Crosslinked equine pericardium (90% collagen I, 10% collagen II)

Table 2. An example list of biologic ECM grafts with potential for tendon/skin regeneration.

patch (SIS) as carrier of ADSCs significantly increases the survival of stem cells as compared to direct injection of ADSCs into the skin wounds [18]. There may be a synergistic angiogenesis promoting effects of biologic graft with stem cells, which may be important for tendon/skin wound healing [19].

Another interesting approach is to use ECM directly secreted by the cells as a carrier for stem cells. For example, stem cells can be incubated at 37°C in a temperature-responsive flask (e.g., upcell™, Cellseed, Japan) and they will product ECM after addition of ascorbic acid. The cell sheets can be lifted at room temperature since the Poly-n-isopropylacrylamide (Poly-NIPAM)-based substrate will become soluble at lower temperature. The cell-ECM sheet has been explored for promotion of tendon/ligament healing [20] as well as diabetic skin wound healing [21].

2.3. FDA-approved biomaterial

2.3.1. Collagen sponge scaffold

(5 mm × 2 mm) collagen sponge scaffolds (Zimmer Dental) were used for the culture of (BM) MSCs. Cell-seeded scaffolds were placed in culture dishes and incubated for 2 hours in a minimum volume of growth medium, after which more medium was applied to submerge the scaffolds. After an additional 24-hour culture, cells seeded in scaffolds were treated with 10 ng/mL of recombinant (BMP) 12 for 12 hours. The medium was then replaced with fresh growth medium and scaffolds were either cultured for an additional 7 days or immediately implanted into partial calcaneal tendon defects in rats. It was shown that after 21 days, the BMP12-treated, collagen-cell scaffold results in robust formation of tendon-like tissue [22]. Similarly, a collagen carrier combined with ASDCs showed they did not improve the biomechanical properties of the tendon-to-bone healing. However, the ADSCs group showed less inflammation, which may lead to a more elastic repair and less scarred healing in a rat model.

2.3.2. Integra bilayer

Integra® bilayer wound Matrix (LifeSciences Corp., Plainsboro, New Jersey) is a dermal acellular analog composed of bovine collagen type I crosslinked with glycosaminoglycans. Importantly, inclusion of WJ-MS-C into Integra induced significant up-regulation of prototypical angiogenic and healing factors, stimulating pleiotropic aspects of neovascularization in experimental settings of angiogenesis, without altering the inflammatory response in the animals, thus demonstrating their potential benefit in therapeutic care of wounds and skin grafts [23]. Recently, Integra dermal matrix scaffold engineered with adult mesenchymal stem cells and platelet-rich plasma was investigated *in vitro* and demonstrated promising preliminary results [24].

2.4. Synthetic biopolymer matrix

Biopolymer matrix such as collagen, gelatin, hyaluronic acid, chitosan, silk, cellulose are the essential ECM components of human, animal, or plant cells. They have showed great promise for attachment, proliferation, and differentiation of stem cells and have been explored for tendon and skin regeneration.

2.4.1. Collagen

Collagen monomer solution can be extracted from skin of fetal bovine calf in close herd. Collagen-based biomaterial has been widely used for tendon/skin regeneration. For tendon application, it is highly desirable to prepare aligned collagen fiber scaffolds. Anisotropic collagen biomaterial can be prepared by directional freeze drying [25], electrospinning, or a novel process called electrochemical process. Electrochemically aligned collagen fiber and skin substrate have been coupled with stem cells for both tendon [26] and skin regeneration [27], respectively. Collagen carrier/gel [28] or collagen combined with stem cell accelerated the wound healing in healing-impaired db/db mice [29].

2.4.2. Pullulan-collagen hydrogel

A biomimetic pullulan-collagen hydrogel was used to create a functional biomaterial-based stem cell niche for the delivery of MSCs into wounds. Murine bone marrow-derived MSCs were seeded into hydrogels and compared to MSCs grown in standard culture conditions. Hydrogels induced MSC secretion of angiogenic cytokines and expression of transcription factors associated with maintenance of pluripotency and self-renewal. MSC-seeded hydrogels showed significantly accelerated healing and a return of skin appendages [30].

2.4.3. Gelatin

Gelatin is denatured collagen. Human ADSCs laden gelatin microcryogels (GMs) were evaluated *in vitro* as a stem cell carrier. The cell phenotype markers, stemness genes, differentiation, secretion of growth factors, cell apoptosis, and cell memory were compared against cells without a carrier. The priming effects of GMs on upregulation of stemness genes and improved secretion of growth factors of hASCs were demonstrated.

2.4.4. Hyaluronic acid (HA)

Hyaluronic acid (HA) is a nonsulfated, linear polysaccharide with the repeating disaccharide, β -1,4-D-glucuronic acid - β -1,3-N-acetyl-D-glucosamine (Mw: 100–8000 KDa). It is an ECM component. ADSCs combined with hyaluronic acid (ADSC-HA) dermal filler were implanted in rats and compared with HA alone. It was demonstrated that ADSC-HA has better filling effects than HA alone. A total of 70% of stem cells remain in the injection site after 3 months. These suggested stem cells have the potential to improve the esthetic effects and longevity of dermal fillers [31].

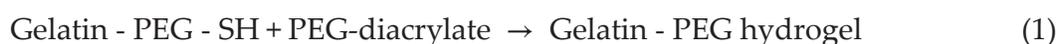
2.4.5. Chitin/Chitosan

Chitosan-hyaluron membrane: Hsu et al. investigated adult ADSCs spheroids combined with a chitosan-hyaluron membrane and showed biomaterial combined with stem cells promoted wound healing in a rat skin repair model [32]. Dense and porous chitosan-xanthan membranes seeded with multipotent mesenchymal stromal cells were evaluated for the treatment of skin wounds. The membranes showed to be nonmutagenic and allowed efficient adhesion

and proliferation of the mesenchymal stromal cells *in vitro*. *In vivo* assays performed with mesenchymal stromal cells grown on the surface of the dense membranes showed acceleration of wound healing in Wistar rats [33].

2.4.6. Gelatin/PEG

A thiol-ene Michael-type addition was utilized for rapid encapsulation of MSCs within a gelatin/PEG biomatrix according to Eq. (1). The MSCs/gelatin/PEG biomatrix was applied as a provisional dressing to full-thickness wounds in Sprague-Dawley rats. Biomatrix resulted in attenuated immune cell infiltration, lack of foreign giant cell (FBGC) formation, accelerated wound closure and re-epithelialization, as well as enhanced neovascularization and granulation tissue formation by 7 days [34].



2.4.7. Silk

Electrospun nanofibrous scaffolds prepared from silk fibroin protein were seeded with bone marrow-derived mesenchymal stem cells (MSCs) and epidermal stem cells (ESCs). The constructs were evaluated for wound re-epithelization, collagen synthesis, as well as the skin appendages regeneration. It was shown that both the transplantation of MSCs and ESCs could significantly accelerate the skin re-epithelization, stimulate the collagen synthesis. Furthermore, the regenerative features of MSCs and ESCs in activating the blood vessels and hair follicles formation, respectively, were suggested [35]. Combination of silk with collagen or poly(lactic-co-glycolic acid) (PLGA) [18] and stem cells were evaluated in a rabbit tendon defect model [36].

2.4.8. Fibrin-agarose

A stroma skin substitute was first generated by using a mixture of human fibrin obtained from frozen human plasma and 0.1% agarose. An average of 250,000 cultured skin fibroblasts were added to 5 mL of the mixture immediately before inducing the polymerization of the artificial stroma on Transwell (Corning Enterprises, Corning, NY, <http://www.corning.com>) porous inserts. Once the stromas jellified, human umbilical cord Wharton's jelly stem cells (HWJSCs) were seeded on top of the skin artificial stromas and cultured. It was demonstrated that this 3D bioactive scaffold can stratify and form epithelial cell-like layers and well-formed cell-cell junctions [37]. The authors also demonstrated similar strategy can be used for regeneration of oral mucosa using human Wharton's jelly stem cells (HWJSCs)-seeded fibrin-agarose-mucosal fibroblasts.

2.4.9. Sodium carboxymethylcellulose (CMC)

Sodium CMC was evaluated as a substrate for ADSCs and implanted in adult male Wistar rats. CMC at 10 mg/mL associated with ADSCs increased the rate of cell proliferation of the granulation tissue and epithelium thickness when compared to untreated lesions (Sham).

CMC is capable to allow the growth of ADSCs and is safe for this biological application up to the concentration of 20 mg/mL. These findings suggest that CMC is a promising biomaterial to be used in cell therapy [38].

2.5. Synthetic nondegradable polymer-based biomaterial

Table 3 summarizes common nondegradable polymer used as a biomaterial or as a modifier of ECM-based biopolymer for skin and tendon tissue engineering applications. The incorporation of such polymer allows biopolymer (collagen, gelatin, HA) to be able to gelled at physiological condition (e.g., under UV/blue light, ambient temperature, or room temperature aqueous free radical initiator). Stem cells can be directly encapsulated inside the substrate during gel formation.

2.5.1. Poly(NIPAM)-based

A biodegradable, multifunctional crosslinker and an n-isopropylacrylamide (NIPAM)-based, thermosensitive hydrogel was synthesized to carry BMSCs to treat diabetic skin ulcers. The crosslinker contains an arginyglycylaspartic acid (GRD)-like motif that promotes cell attachment and differentiation of BMSCs. After hydrogel association with BMSCs treated the diabetic skin wound in mice, significantly greater wound contraction was observed in the hydrogel + BMSCs group. Histology and immunohistochemistry results confirmed that this treatment contributed to the rapid healing of diabetic skin wounds by promoting granulation tissue formation, angiogenesis, extracellular matrix (ECM) secretion, wound contraction, and re-epithelialization. These results show that a hydrogel laden with BMSCs may be a promising therapeutic strategy for the management of diabetic ulcers [39].

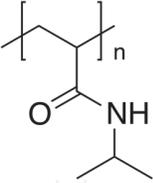
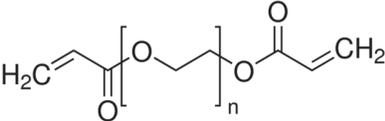
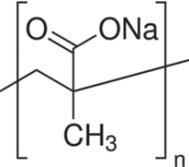
Poly(NIPAM)	PEGDA	Poly(methyl acrylate) (PMA)
		

Table 3. Common synthetic, nondegradable polymer used as hydrogel or gel components.

2.6. Polyester-based degradable polymer biomaterial

The structure of common polyester is shown in **Table 4**. Stem cell-coated polyester suture was evaluated for tendon applications in a rat model [40]. Electrospun PLGA fiber may be more suitable for tendon regeneration than film [41]. (PGA/PLA) fiber combined with ADSCs improve tendon in a rabbit tendon model [42]. Open cell PLGA seeded with stem cells produced more collagen type I [43]. Knitted PLGA encapsulated with stem cell/alginate gel [44]. PGA sheet with MSCs were able to regenerate tendon-bone insertions and the tendon in rabbit [45]. Electrospun polycaprolactone/gelatin (PCL/GT) membrane and human urine-derived stem cells (USCs) were evaluated for skin wound healing in a rabbit model [46]. USCs-PCL/GT-treated wounds closed much faster, with increased re-epithelialization, collagen formation, and

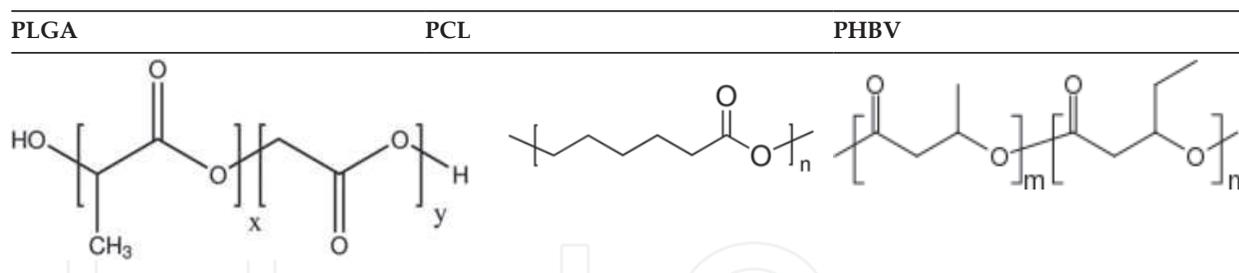


Table 4. Common synthetic, degradable polymer used for tendon/skin regeneration applications.

angiogenesis. Moreover, USC_s could secrete vascular endothelial growth factor (VEGF) and transforming growth factor (TGF)- β 1, and USC-conditioned medium enhanced the migration, proliferation, and tube formation of endothelial cells. This data suggested that USC_s in combination with PCL/GT significantly prompted the healing of full-thickness skin wounds in rabbits. Similarly, electrospun poly (L-lactide-co- ϵ -caprolactone)/poloxamer (PLCL/P123) scaffolds combined with ADSC_s enhanced skin wound healing in a rat model [47]. Chitosan-crosslinked poly (3-hydroxybutyrate-co-3-hydroxyvalerate) (PHBV) was used to load unrestricted somatic stem cells. The cell-laden scaffold showed better results during the healing process of skin defects in rat models [48, 49].

3. Conclusion

Biomaterials play an important role for attachment, survival, and function of stem cells. Many biomaterials are either used alone or as one component of the product for the regeneration of tendon/ligament/skin. Despite abundance of biomaterial developed, the optimal biomaterials that meet the structural, mechanical, functional requirement of tendon/ligament tissues to be regenerated remain a challenge. Novel biomaterial fabrication process, biomaterial design, and biomaterial synthesis toward tendon/ligament and skin regeneration are urgently needed.

Author details

Xingguo Cheng

Address all correspondence to: xcheng@swri.org

Southwest Research Institute, San Antonio, TX, USA

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