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Biomaterials based strategies for rotator cuff repair

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Highlights

- The rotator cuff is a highly complex tissue, chemically and mechanically.
- Rotator cuff tear can be repaired using various biomaterials.
- Biomaterials mimicking structure of natural rotator cuff are desirable.

Abstract

Tearing of the rotator cuff commonly occurs as among one of the most frequently experienced tendon disorders. While treatment typically involves surgical repair, failure rates to achieve or sustain healing range from 20 to 90%. The insufficient capacity to recover damaged tendon to heal to the bone, especially at the enthesis, is primarily responsible for the failure rates reported. Various types of biomaterials with special structures have been developed to improve tendon-bone healing and tendon regeneration, and have received considerable attention for replacement, reconstruction, or reinforcement of tendon defects. In this review, we first give a brief introduction of the anatomy of the rotator cuff and then discuss various design strategies to augment rotator cuff repair. Furthermore, we highlight current biomaterials used for repair and their clinical applications as well as the limitations in the literature. We conclude this article with challenges and future directions in designing more advanced biomaterials for augmentation of rotator cuff repair.

Keywords

Rotator cuff regeneration Biomaterials Mechanical properties Biocompatibility Degradation

1. Introduction

Between 30% and 50% of patients over 50 years of age experience rotator cuff tears (RCTs) that frequently result in reduced strength of the shoulder and function-limiting pain [1], [2]. Surgery is becoming increasingly common as a large number of patients have intensifying or disabling symptoms, and accordingly, a 500% inflation in the rate of repair has been observed since 2001 [3]. As the population ages with more significant demands for functionality, the number of rotator cuff surgeries carried out in the United States is expected to increase from the current figure of approximately 75,000 [4].

One challenge in the healing of a torn rotator cuff is the failure of tendon-bone fixation, which occurs in up to 26% in small (<1 cm) to medium (1–3 cm) tears and in up to 94% of large (3–5 cm) and massive (>5 cm) tears [5], [6], [7], [8], [9], [10], [11]. Numerous factors including old age, tissue quality, bone mineral density, muscle atrophy, fatty infiltration, tear size,

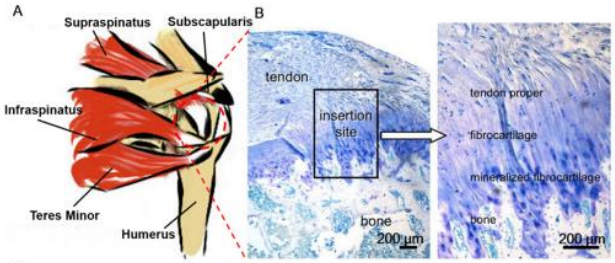
chronicity and repair mechanisms contribute to the retear rate in patients [12], [13], [14].

Advances in understanding the pathoanatomy of RCTs have urged the evolution of treatment strategies over the past decades. Major biomaterial-based clinical options available for the surgical treatment of RCTs include: transplantation of autografts or allografts and utilization of natural or synthetic substitutes composed of polymers and/or osteoconductive inorganic materials. Autografts have limitations including shortage of the graft material itself, loss of function at the donor sites, formation of scar tissues and structural differences between the donor and recipient grafts. Similarly, allo-transplantations suffer from significant drawbacks including immune rejection and the potential transmission of infectious diseases from the host. To overcome the limitations associated with these approaches, a variety of natural and synthetic biomaterials have been fabricated as fillers or patches to repair, regenerate and restore damaged tendon-to-bone tissues [15]. Biomaterials that mimic natural extracellular matrices (ECM) are regarded as having a perfect chemical and structural environment for tissue integration. Unlike natural tissues, the main advantage of synthetic scaffolds is that they can be manipulated and their properties such as mechanical stability can be readily tuned [2]. The ideal material capable of meeting the physiological demands required for regeneration of native tendons into a fully functional rotator cuff, however, has not yet been developed [16], [17], [18], [19].

The aim of this article is, therefore, to provide a review of recently developed biomaterials that are used for the augmentation of rotator cuff repair surgeries. We will begin by briefly introducing the anatomy of the rotator cuff before discussing various biomaterials and their characteristics which may be appropriate for the use as rotator cuff repair scaffolds. These biomaterials will be discussed in the context of their clinical applicability as well as their limitations. Finally, we will conclude this article with the challenges and future directions in designing more advanced biomaterials for the augmentation of rotator cuff repairs.

2. Anatomy of the rotator cuff

To help understand the ideal properties of the biomaterials for rotator cuff regeneration, we first briefly introduce the anatomy of the rotator cuff. The rotator cuff acts to stabilize the shoulder joint and consists of the following four muscles: supraspinatus, infraspinatus, subscapularis, and teres minor (Fig. 1A). These muscles originate from the scapula and their tendons converge into a continuous sheet which forms the rotator cuff before inserting into the greater and lesser humeral tubercles. As a group, this set of muscles acts to internally rotate (subscapularis), externally rotate (infraspinatus, teres minor), and abduct (supraspinatus) the humeral head. The cuff muscles provide the humerus with rotating capabilities to maintain its position with respect to the humeral head against the glenoid cavity. Since the insertions are close to the axis of motion, this area is often subject to wide angular changes resulting in cumulative damage leading to RCTs [20], [21].



C

Tissue	Cell type	Major matrix component
Tendon	Fibroblasts	Collagen types I, III
Non-mineralized fibrocartilage	Fibrochondrocytes	Collagen types I, II, III
Mineralized fibrocartilage	Hypertrophic fibrochondrocytes	Collagen types I, II, X
Bone	Osteoblasts, osteocytes, osteoclasts	Collagen types I

Fig. 1. The anatomy of rotator cuff (A), the histologic characteristics (B) and composition (C) of the tendon-to-bone insertion site where tendon attaches to bone across a transition site (rat supraspinatus tendon-to-bone insertion stained with toluidine blue is shown). (For color images of this figure, the reader is referred to the web version of this article.)
Image modified with permission from [25,26].

The rotator cuff often ruptures at its enthesis, which is a connective tissue between the tendon and the bone [1]. An enthesis is a highly complex and heterogeneous area at which soft tissue is anchored to bone. Four unique transition zones constitute the area: tendon, fibrocartilage, mineralized fibrocartilage, and bone (Fig. 1B) [22]. From tendon to bone, the enthesis consists of a gradually increasing mineral content along with a decrease in the collagen fiber organization, resulting in a unique transitional zone characterized by tapered mechanical properties [23]. Such graduated mechanical properties help in minimizing stress forces propagated from soft tissues (tendon) to hard tissues (bone). Additionally, the presence of a transitional zone supports the heterotypic cellular interactions necessary for maintaining homeostasis and function [24]. It is important to note that the collagen content of these transition zones differs based on the tissue type. The tendinous, fibrocartilaginous, and mineralized fibrocartilage zones are composed of different types of collagen as summarized in Fig. 1C [25], [26]. These differences are the basis for the varying elastic moduli of these zones which adds to the complexity as well as difficulty in recreating such structures. Due to the individual varying properties within the structure of tissues and the complexity of the structure of the native tendon-to-bone interface, it is challenging to develop biomaterials that reflect the property of the native tissues or the complex tendon-to-bone insertion site.

3. Procedure of repair of RCTs

Strategies for the reconstruction of RCTs range from pharmacological treatments to exercise based on surgical therapies. The choice of treatment largely depends on the size of the defect and the duration of the symptoms. Small tears (<1 cm) of a relatively short duration (<1 year) can initially be managed with physiotherapy and adequate pain management. However, once conservative treatments fail to relieve symptoms, surgery can be considered [20]. Despite the presence of controversies regarding the optimal surgical technique (single-row, double-row, transosseous sutures, or transosseous-equivalent techniques) to repair small to large RCTs, the ultimate goal is to reattach the torn tendons to the humeral tuberosity. The procedure of RCT repair mainly involves the following fundamental steps: (1) preparation of rotator cuff bony footprint; (2) insertion of suture anchors into the humeral tuberosity or drilling bone tunnels; and (3) passage of the sutures from the anchors or bone tunnels through the torn tendon. More

recently, a change from single-row to double-row and transosseous-equivalent techniques has been observed as it is hoped that maximizing the tendon-bone contact area may accelerate healing. Restoration of larger RCTs frequently employs biomaterials in the form of a film or patch which is inserted between the tendon and bone to serve as an interface to bridge larger gaps and promote faster healing (Fig. 2).

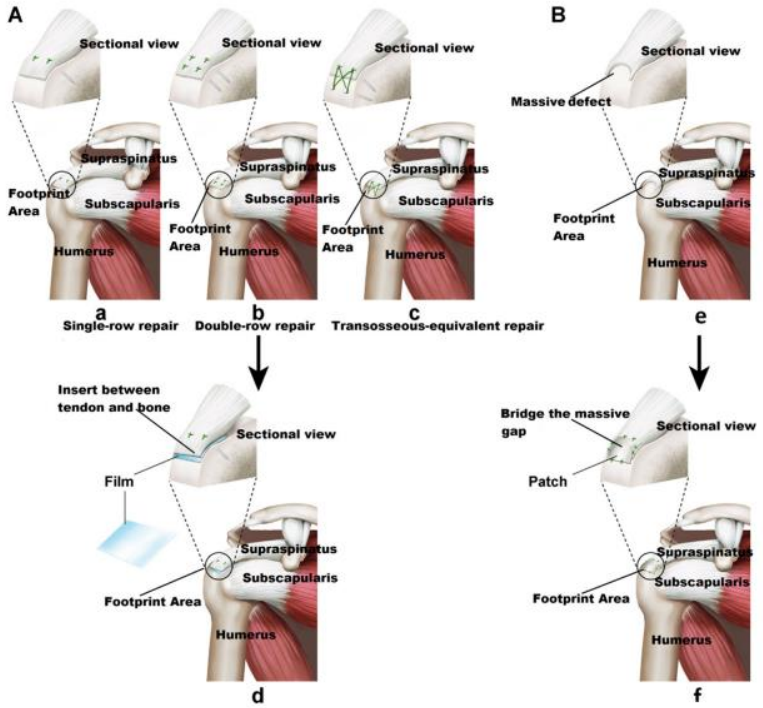


Fig. 2. RCT repair techniques. (A) Repair techniques for small to large RCTs using single-row (a), double-row (b), and transosseous-equivalent (c) sutures as well as biomaterials (d) interposed in the enthesis of the rotator cuff. (B) Repair techniques for massive RCTs (e) using patches (f). RCT repair mainly involves (1) preparation of rotator cuff bony footprint, (2) insertion of suture anchors into humeral tuberosity, and (3) suture passage from anchors through torn tendon. Biomaterial in the form of a film or patch is frequently inserted to bridge between tendon and bone to maximize tendon-bone contact area to accelerate healing.

Despite considerable effort in the development of efficient surgical techniques for RCT repairs, the failure rates remain high, generating a need for alternative strategies that provide effective mechanical reinforcement whilst stimulating and enhancing the patient's intrinsic healing potential [27], [28], [29]. One of the main reasons for RCT repair failure is due to the inability to fully restore the original insertion, or footprint, of the rotator cuff along the tuberosities of the humerus. To determine the best possible repair method for massive RCT, Hinse et al. compared three fixation methods in a cadaveric porcine model. Single-row suture anchor repairs were observed to only restore 67% of the tear, whereas transosseous simple sutures achieved as much as 85% [30]. Whilst this is a definite improvement, any gaps along the points of fixation introduce a potential weak spot for re-tearing, a variety of biomaterials are thus developed to augment rotator cuff regeneration.

4. Biomaterials used for RCT treatment

Due to the inability of a torn tendon to fully heal back to its insertion on the humerus, novel tissue engineering strategies involving natural and synthetic materials supplemented with chemical signaling factors as well as stem cells have been proposed to enhance rotator cuff healing. Currently available biomaterials used in the surgical reinforcement of RCTs are mainly derived from mammalian ECM. GraftJacket® Regenerative Tissue Matrix (Wright Medical

Technology, USA) is a human dermal collagen template which has previously demonstrated good clinical outcomes for treatment of rotator cuff injury [31], [32], [33], [34]. In addition, an rhBMP-2-coated acellular dermal patch, isolated from a human cadaveric donor, has been developed and sutured in a rabbit chronic rotator cuff injury model for in vivo study [35]. ECM from the dermal tissue of the patch has allowed for augmented biomechanical properties through cytokines inducing cell chemotaxis, matrix synthesis in addition to cell proliferation and differentiation. Moreover, new bone formation was found to significantly improve at 4 and 8 weeks post-operatively, along with biomechanical properties like ultimate tensile strength at the 8-week mark. Histology examinations showed rich cell penetration of rhBMP-2 at the tendon-bone interface. However, the relatively limited availability of human donor collagen and associated costs limit its clinical applications. Restore® Orthobiologic Soft Tissue Implant (DePuy Orthopaedics, USA), which is derived from porcine small intestinal submucosa (SIS) and mainly consists of collagen, has also been used as a scaffold for RCT reinforcement [8], [36]. However, their success rate was compromised due to the associated inflammatory reactions.

More advanced and suitable biomaterials have therefore been developed for rotator cuff repair. These include natural polymers, synthetic non-degradable and degradable polymers, as well as osteoconductive inorganic biomaterials. Natural polymers can enhance the patient's intrinsic healing potential whereas synthetic polymers can provide effective mechanical reinforcement for rotator cuff repair [12]. As the site of RCT is partially made of bone, osteoconductive inorganic materials are particularly appealing for the regeneration of bony tissues. Details of each type of biomaterial with their respective advantages and disadvantages are discussed in the following paragraphs and summarized in Table 1.

Table 1
Summary of advantages and disadvantages of commonly used biomaterials for rotator cuff repair.

Material	Advantages	Disadvantages	Reference
Natural biomaterials	Biodegradability and biocompatibility	Poor mechanical properties	
Collagen	Biodegradability and biocompatibility	Poor mechanical properties	[37,102,103]
Chitosan	Biodegradability and biocompatibility	Low strength, inconsistent behavior with seeded cells	[38,46,103]
Silk fibroin	Biodegradability and biocompatibility	Poor mechanical properties	[104,105]
Fibrin	Biodegradability and biocompatibility	Poor mechanical properties	[106,107]
ECM	Biodegradability and biocompatibility	Poor mechanical properties	[108–116]
Degradable polymers	Mechanical strength and degradability	Acidic degradation products	
PGA	Mechanical strength and degradability	Acidic degradation products	[59,60]
PLA	Mechanical strength and degradability	Acidic degradation products	[54–58]
PLGA	Mechanical strength and degradability	Acidic degradation products	[2,61–65]
Non-degradable polymers	Strong mechanical property	No bioactivity	
Polycarbonate and polyurethane	Availability and low cost	Poor biocompatibility	[68–70]
PTFE	Variety of processing methodologies	Poor biocompatibility	[71–73]
Polyester	Availability and low cost	Poor biocompatibility	[74–76]
Osteoconductive materials	High similarity to the mineral content of native bone	Brittleness	
HA	Osteoinduction and osteointegration	Slow biodegradation	[88]
β-TCP	Osteoinduction and osteointegration	Brittleness	[85]
CPS	Osteoinduction and osteointegration	Brittleness	[88]

β-TCP = β-tricalcium phosphate.

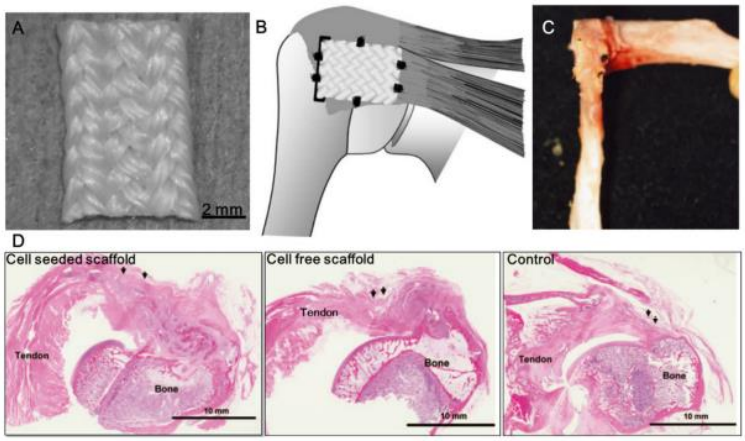


Fig. 3. Regeneration of rotator cuff using chitosan-hyaluronan hybrid scaffolds. (A) Macroscopic image of the braided chitosan-hyaluronan hybrid scaffolds. (B) Surgical procedure showing scaffold insertion by removal of the infraspinatus tendons in rabbits. (C) The appearance of the cell-seeded scaffold 12 weeks after surgery. (D) Micrographs of each group 12 weeks after surgery (hematoxylin and eosin staining) showing the well-aligned collagen fibers (black arrows) in the cell seeded scaffolds; unaligned collagen fibers (black arrows) in the cell free scaffolds and the presence of a thin membranes with many fibroblasts linked the end of the torn cuff and the bone (black arrows) in the control samples with no implants.

4.1. Natural polymers

Natural polymers such as collagen [37] and chitosan [38] are frequently used for tendon regeneration in RCT treatment. They contain specific molecular domains capable of supporting and guiding cells at various stages of tissue development. They thus have the ability to support and enhance the biological interactions between the scaffolds and the host environment [39].

Collagen is the main component of the ECM of connective tissues [40], [41] and has been used extensively for the regeneration of RCTs. Collagen possesses many desirable features such as the ability to promote cell attachment, proliferation and thus tissue regeneration [42]. For example, type I collagen fibrous scaffolds were sutured to the superficial surface of the infraspinatus tendon of adult sheep to determine if collagen scaffolds with high porosity and low tensile modulus (6 MPa) would assist in maturation and alignment of tendon-like tissue [43]. It was found that after 6 weeks of implantation, the scaffolds increased the thickness of the rotator cuff tendon by inducing the formation of a well-integrated and dense, regularly oriented tendon-like tissues. The scaffolds were found to be completely absorbed at 26 weeks leaving only a stable layer of mature tissues over the host tendon. These results have suggested that collagen of low tensile modulus can be used to promote functional alignment of regenerated tendon tissues.

Chitosan is another type of natural polymer used to regenerate RCTs, particularly tendons. As it typically exists as ordered macrofibrils, chitosan is the primary structural component in crab exoskeletons and shrimp shells as well as the cell walls of fungi and yeast [44]. Chitosan is a biodegradable and biocompatible material capable of promoting cellular proliferation and migration. In addition, the mechanical strength of chitosan can be easily controlled by altering the pore size and the thickness of the chitosan-based scaffolds [45]. Nonwoven chitosan fibrous scaffolds have been used to promote rotator cuff regeneration in rabbits [46]. It was found that the grafted infraspinatus tendons showed increased collagen deposition compared to the control group which received no treatment. The chitosan-based fibrous scaffolds were further coated by hyaluronan to increase their mechanical properties and accelerate tendon regeneration (Fig. 3) [38]. The chitosan based hyaluronan fibers were then braided into a strong fabric with tensile strength of up to 72 MPa, which falls within the range of native tendon. The fibers were subsequently seeded with fibroblasts to further facilitate tendon regeneration. It was found that these chitosan-based hyaluronan hybrid scaffolds enhanced production of type I collagen and improved tensile strength and tangent modulus of the regenerated tendons compared to the non-fibroblast seeded counterparts [38].

Natural polymers are an important class of biomaterials in rotator cuff regeneration due to their intrinsic biocompatibility and biodegradability. They are inherently bioactive (consisting of cell-recognition signals for cell-material interactions) which facilitates tissue development [47]. They are known to have low toxicity (the degree to which a substance can harm organisms) and a minor chronic inflammatory response. However, the bioactivity of natural polymers may lead to a strong immunogenic response [48]. In addition, their lack of suitable mechanical properties for mimicking the bony area of the rotator cuff generates a need for scaffolds based on synthetic polymers.

4.2. Synthetic polymers

Synthetic polymers exhibit excellent physical properties and their elastic moduli, tensile strengths and degradation rates can be fine-tuned, making them particularly attractive as tissue engineering scaffolds. As biocompatibility is broadly considered “the ability of a material to perform with an appropriate host response in a specific application,” synthetic biopolymers are regarded as having superb biocompatibility and widely used in tissue engineering applications [49], [50]. This is in part due to the reproducibility of synthetic polymers and that they can be manufactured under controlled conditions to limit material impurities. Such ability to control the purity of synthetic polymers with constituent monomeric units and simple structures, reduces the chance of toxicity, immunogenicity, or the provocation of an immune response, and infection [51]. Synthetic polymers can be categorized into degradable and non-degradable polymers to suit different tissue regeneration purposes.

4.2.1. Degradable polymers

Degradable polymers are mainly used when the body requires a temporary presence of a biomaterial or device [52]. These polymers are considered “degradable” due to the presence of ester-, amide- or anhydride bonds which can be easily hydrolyzed and enzymatically degraded [53]. Some of the commonly used degradable synthetic polymers include saturated poly-α-

hydroxy esters, such as polylactic acid (PLA) [54], [55], [56], [57], [58], polyglycolic acid (PGA) [59], [60], and poly lactic-co-glycolic acid (PLGA) copolymers [2], [61], [62], [63], [64], [65].

The chemistry of PLA involves the processing and polymerization of lactic acid monomer. PLA has stereoisomers, such as poly(L-lactide) (PLLA), poly(D-lactide) (PDLA), and poly(DL-lactide) (PDLLA), each with different properties and applications [66]. X-Repair® (Synthasome, USA) is a mesh fabricated from PLLA, which performed favorably when implanted as a synthetic patch in 18 patients as a reinforcement device along with sutures to repair large to massive RCTs [55]. Another study investigated a novel form of layered PLLA scaffold in a rabbit torn rotator cuff model. The PLLA scaffolds were fabricated by superimposing two fabrics with varying finishes of smooth and pile-finished surfaces. These PLLA scaffolds were transplanted into 28 rabbits after infraspinatus tendon defects were introduced. After 16 weeks of implantation, cell migration into the developed scaffolds and regeneration of new tendon tissues were demonstrated [54].

PGA is composed of glycolic acid, void of any methyl side groups and shows highly crystalline structure in contrast to PLA. This endows PGA with a high rate of absorbability and makes it attractive for rotator cuff regeneration [67]. For example, PGA sheets seeded with mesenchymal stem cells have been used to regenerate fibrocartilaginous tendon-bone insertion sites [59]. The PGA sheets were found to induce regeneration of the fibrocartilage histologically, with enhanced collagen deposition and improved mechanical properties compared to the naked PGA sheet [60]. Unfortunately, the mechanical properties of the regenerated tissues were still inferior to the natural tissues due to the lack of similarity of the developed PGA sheet to the natural tissues.

PLGA is a copolymer of lactic and glycolic acid [65]. By altering the ratio of lactic or glycolic acid, the mechanical properties and degradation rates of PLGA can be controlled [65]. For example, Tayler et al. used poly (85 lactic acid-co-15 glycolic acid) particles in an animal study of RCT and reported a substantial increase in the repair strength at 8 weeks after augmentation with the scaffolds [64]. Upon histological analysis, it was found that the tendon to bone insertion tissues regenerated using the PLGA scaffolds exhibited stronger expression of proteoglycans at the tendon-bone junction after 16 weeks of implantation, indicating improved regeneration potential (Fig. 4) [63]. Alternative strategies for rotator cuff restoration have evolved, for example, by utilizing basic fibroblast growth factor (bFGF) loaded electrospun fibrous PLGA membranes [2]. The bFGF-PLGA membranes showed an increase in the area of glycosaminoglycan production at the tendon-bone interface, improving collagen organization, load-to-failure strength and stiffness compared with the control group with no implantation of PLGA membranes. Furthermore, aligned PLGA nanofibrous scaffolds on which fibroblasts were cultured have been found to result in elongated cell morphology and improved mechanical properties of the regenerated tissues when compared to the unaligned scaffolds [61], [62]. The above results have shown that the alignment of nanofibers can be used to guide the cellular response based on alignment and to facilitate the rotator cuff regeneration. Degradable polymers are especially useful when only a temporary presence of biomaterial is required in the

body, however, in order to satisfy a more ongoing need or where the RCT cannot regenerate, non-degradable biomaterials should be utilized.

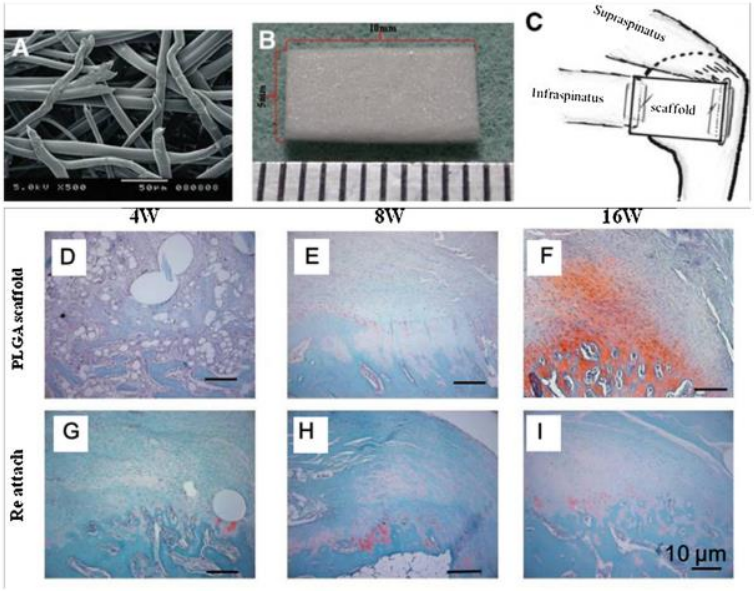


Fig. 4. Rotator cuff regeneration using PLGA scaffolds. (A) Scanning electron microscopic view of PLGA scaffold. (B) Macroscopic view of the scaffold. (C) Schematic diagram depicting the repair of the rotator cuff defect using PLGA scaffold in a rabbit model. PLGA scaffolds were transplanted and fixed to tendon or bone by No. 4-0 nylon sutures. D–I. Safranin O (S-O) staining of tendon-bone interface: scaffold group at (D) 4 weeks, (E) 8 weeks, and (F) 16 weeks and reattachment group at (G) 4 weeks, (H) 8 weeks, and (I) 16 weeks. Note that strong staining with proteoglycan was observed at 16 weeks postoperatively in the tendon-bone insertion site treated using PLGA scaffolds. Image modified from [63] with permission.

With progressively advanced designs and functions, the complexity of the synthetic degradable polymers increases exponentially. The major advantage of this kind of highly tunable polymer is the ability to engineer the degradability to match the RCT regeneration speed. While particular degradation properties may be achieved in degradable synthetic materials from the adjustment of chemical formulations, cell-based degradation or natural deterioration may lead to the release of inflammatory or cytotoxic small molecules [47].

4.2.2. Non-degradable polymers

Non-degradable synthetic polymers such as polycarbonate polyurethane [68], [69], [70], polytetrafluoroethylene (PTFE) [71], [72], [73] and polyester [74], [75], [76] have been used for repairing massive RCTs. Systems that require materials to endure high mechanical loading can benefit from the lasting structural integrity of these materials. These polymers are usually characterized by robustness, mechanical strength and durability and they are less susceptible to enzymatic degradation due to their strong and stable bonds and do not usually produce acidic by-products which may reduce local pH and induce inflammation when being generated in large amounts. However, it may fail to integrate with the native tissue, and thus a fibrotic response can occur and result in implant failure as well as further complication.

Polycarbonate polyurethanes possess appropriate resistance to mechanical loading and demonstrate excellent recovery [77], making it a suitable augmentation device for repairing massive RCTs. For example, polyurethanes have been fabricated as a patch to repair massive RCT with a tissue in-growth of 80% with no inflammatory reaction [70]. Moreover, the tendons repaired using polyurethane scaffolds exhibited increased mechanical property compared to the control group repaired using traditional suture anchor repair techniques [69]. This is because

greater mechanical strength was provided by the polyurethane scaffolds in the critical healing period than experienced with the traditional suture anchor repair. Such patches have also shown significant improvements in function and healing rates in repairing massive RCTs clinically [68].

PTFE is also a stable polymer that is chemically and biologically inert [78]. In a study conducted on canine infraspinatus tendons, the PTFE exhibited excellent mechanical properties and tissue affinity to bone and to tendon [73]. In a case study on human subjects, PTFE patches were found to be able to repair massive RCTs. One year post-operatively, a tight connection between the PTFE patch and the bone of the cuff tissue was observed with no presence of inflammatory cells in the synovium [79]. Moreover, pain relief was achieved when such patches were used to repair massive RCTs clinically [71], [72].

To sum up, synthetic polymers have shown tunable mechanical and degradation properties to regenerate torn rotator cuffs. However, they may have limited capability to regenerate bone in a torn rotator cuff due to the dissimilarity of their chemical components compared to bone. Osteoconductive materials which can facilitate bone generation are therefore developed [80].

4.3. Osteoconductive inorganic materials

Osteoconduction refers to the process of bone growth on the surface commonly observed in the case of bone implants [81]. Osteoconductive inorganic materials are similar to the bone mineral in composition and can enable the migration of osteoprogenitor cells into porous spaces of the implant to assist the formation of a carbonate hydroxyapatite (HA) layer and new bone formation [82]. These materials are characterized by their excellent biocompatibility as well as resistance to corrosion and high compression [83]. Calcium-phosphate (Ca-P) based biomaterials are the main categories of osteoconductive inorganic materials. The osteoconductive nature of Ca-P has been found to inhibit fibrous tissue formation and facilitate bone growth into the interfacial gap at the tendon-bone insertion site, increasing the success rate of treatment of RCTs [84].

Osteoconductive Ca-P matrix injection at the site of a ruptured tendon-bone interface in a rat rotator cuff model has been shown to enhance tendon-to-bone healing [85], [86], [87]. The Ca-P fillers were found to promote new bone formation, increase the area of fibrocartilage, and improve the organization of collagen in the early postoperative period. Moreover, when transforming growth factor-β3 (TGF-β3) was added into the Ca-P matrix, a significant improvement in the strength and a higher collagen type I and III expression ratio at the tendon-bone interface was observed after 4 weeks of repair. Additionally, repair with Ca5(PO4)2SiO4 (CPS) bioceramic interposition was found to have better results compared to the conventionally used HA in the promotion of cell attachment and proliferation as well as new bone formation, possibly due to the increased degradability allowing for better new bone regeneration [88], [89]. Moreover, magnesium-based bone adhesives are also an alternative for rotator cuff repair. It was found that application of a magnesium-based bone adhesives resulted in more cartilage and bone formation and a higher mechanical strength after repair of the RCT compared to the bone adhesives with no magnesium [90]. This has suggested that magnesium-based adhesives could

be a promising alternative for augmenting tendon-to-bone repair. However, the most promising biomechanical results occurred at time zero and negative effects which appeared as an allergic or inflammatory reaction to the foreign material was observed after 21 days. Therefore, further study is necessary to determine the biocompatibility of magnesium-based bone adhesive for further in vivo as well as clinical application of this biomaterial.

Osteoconductive inorganic materials can be used to improve the organization of collagen and promote cell attachment and proliferation and assist in new bone and fibrocartilage formation. However, osteoconductive inorganic materials usually suffer from brittleness, low fracture strength, low mechanical reliability and lack of resilience [91]. In addition, they may increase the risk of hypertrophic bone growth in the greater tuberosity of which might create severe impingent symptoms. To obtain best results and create an optimal system, it is essential to take the advantages of all the above-mentioned materials and create hybrid materials. Hybrid materials will enable one to obtain all of the advantages of individual types of materials while minimizing potential weaknesses. They are considered very attractive options in the regeneration of a torn rotator cuff as they reflect the heterogenous structure of the rotator cuff.

4.4. Hybrid biomaterials

Hybrid biomaterials, mainly co-polymers, polymer–polymer blends or polymer-ceramic composites have also been developed to repair RCTs [92]. This strategy is particularly interesting as it can better mimic the native structure of the rotator cuff and therefore provide superior therapeutic efficacy.

For example, strong and porous silk-collagen sponge scaffolds incorporating growth factors and cells such as tendon stem cells or cytokines have been observed to facilitate rotator cuff tendon regeneration [93], [94]. Also, composite PLLA-type I collagen scaffolds seeded with human tendon fibroblasts were found to promote the expression of type I, type III, type X collagen and decorin compared with the PLLA control group [95]. It was also found that the local application of electrospun gelatin-PLLA fibrous membrane was associated with increased fibrocartilage formation with improved collagen organization after rotator cuff surgery in a chronic RCT model compared to the naked PLLA fibrous scaffolds [96]. Moreover, a biomimetic biphasic scaffold with contiguous non-mineralized and mineralized regions was designed to promote the regeneration of the tendon-bone insertion site [97]. Specifically, the non-mineralized region was composed of PLGA nanofibers and the mineralized region consisted of composite PLGA nanofibers encapsulating HA nanoparticles (PLGA-HA). The results showed that the biphasic scaffolds facilitated the synthesis of collagen-rich (types I and II) matrix. Also, a continuous non-calcified and calcified fibrocartilage interface was observed in vivo using the biphasic scaffold. However, the mechanical performance of the regenerated rotator cuff is less than ideal. This may be because the biphasic scaffolds could not mimic the native enthesis as the calcium content of the scaffolds was not continuous and gradually changing.

To mimic the natural structure of the enthesis of rotator cuff which has a mineral gradient, a four-layered tendon-to-bone construct consisting of a collagen scaffold with varying content of

HA has been developed (Fig. 5) [98]. Mechanical evaluation of the structure produced showed a gradual change in the mechanical properties along the scaffold: from the tendon to the bone layer, there was an increase in Young's modulus. In addition, when human fibroblasts, chondrocytes and osteoblasts were co-cultured on the multi-layered scaffolds, increased proliferation of fibroblasts in the tendon layer, chondroblasts in the fibrocartilage layer, both chondroblasts and osteoblasts in the mineralized fibrocartilage layer, and osteoblasts in the bone layer were observed. These results have demonstrated that the cell proliferation was dependent on the specific matrix composition. Moreover, dense structures and a large amount of secreted and accumulated ECM was found in all the cell seeded scaffolds when compared with the unseeded scaffolds, indicating the potential for regenerating massive RCTs using the multi-layered scaffolds. Similar results were also found in a nonwoven mat of electrospun PCL nanofibers coated with a gradual change of β-tricalcium phosphate (β-TCP) concentration along the scaffolds [99], [100] or a hydrogel scaffold encapsulating Ca-P crystals transformable to HA [101]. Collectively, the above results have demonstrated that hybrid materials are highly recommended for the regeneration of RCTs as they can better reflect the structure and function of the native rotator cuff.

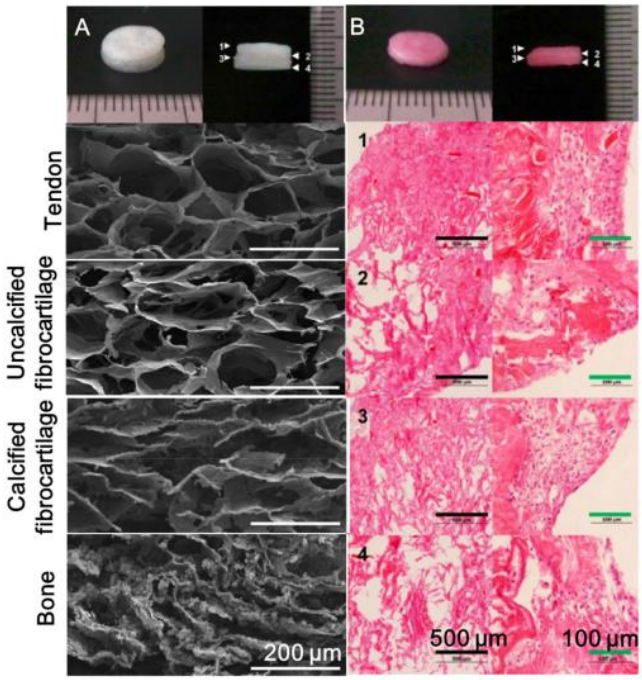


Fig. 5. Collagen-based multi-layered scaffolds for rotator cuff regeneration. The collagen scaffolds consist of four layers including a tendon layer, an uncalcified fibrocartilage layer, a calcified fibrocartilage layer and a bone layer. The SEM images show that the four layers have increased content of hydroxyapatite (HA, see arrows) (A). The tendon layer was seeded with fibroblasts, uncalcified fibrocartilage layer with chondrocytes, calcified fibrocartilage layer with chondrocytes, and bone layer with osteoblasts. Histological analysis show that the cell-seeded scaffolds display dense structures and a large amount of secreted and accumulated extracellular matrix (ECM) (B).
Image modified from [98] with permission.

5. Summary and future perspectives

The ultimate goal for rotator cuff repair and regeneration is to restore the normal enthesis of tendon to bone. Biomaterials for repairing and regenerating rotator cuff tissues should not only be capable of mimicking their key microstructures, compositions and mechanical properties, but also enable the recovery of functional loss. Recent findings have demonstrated that hybrid biomaterials take advantage of different biomaterials' properties as the stratified scaffolds establish a mineral gradient reflecting the native enthesis and meet the requirements of repairing RCTs, providing a more biomimetic cell micro-environment to repair a damaged rotator cuff.

Although advanced scaffolds in the broader categories of natural, synthetic, osteoconductive or hybrid biomaterials have been widely examined for rotator cuff repair and regeneration, most studies are still in their infancy and are limited to in vitro studies. To facilitate the translational research of the newly designed biomimetic scaffolds for repairing orthopedic tissue injuries, more in vivo and clinical studies are needed to comprehensively test their performance. Although there are various preclinical efforts in the field of biomaterial development for rotator cuff regeneration, very few have reached clinical trials.

In the last ten years, operative intervention has become a more popular approach to treat RCTs. Given this trend and an aging population, this type of procedure could become one of the more widely performed soft tissue treatments. Evaluation of new augmentation techniques carried out in long-standing follow-up studies are vital in order to identify the exact effect of the scaffold and its degradation products. Furthermore, animal models can replicate the degree of chronicity that is regularly seen in torn rotator cuffs and these studies contribute to the investigation of the tendon-bone interface to ultimately improve present day results from surgery. At this time, scaffolds with varying compositions have been assessed in the literature; however, none have been reported to restore the mechanical properties of an unharmed graded enthesis. The use for interpositional grafts in the treatment of large and massively retracted RCTs as well as in the repair of substandard degenerative tendons has shown promise although continued work is required prior to the introduction of these scaffolds into routine clinical practice.

Furthermore, it is essential to understand the development of boundaries between various gradients and tissue types in ECM as well as their maintenance in the body since the enthesis of the rotator cuff is transitional in nature. More studies should thus focus on exploring how the graded structures between different types of connective tissues are formed in the body. It is anticipated that the increased understanding of the mechanism of tendon-to-bone healing will guide novel design of biomaterials to facilitate rotator cuff repair. The optimal scaffold design may combine different biomaterials, consisting of ECM-like structure with a gradient in the mineral content and fiber organization with resemblance to the natural rotator cuff.

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