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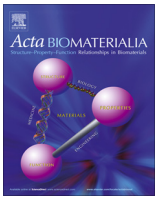

Review article

Cell-material interactions in tendon tissue engineering

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ABSTRACT

The interplay between cells and materials is a fundamental topic in biomaterial-based tissue regeneration. One of the principles for biomaterial development in tendon regeneration is to stimulate tenogenic differentiation of stem cells. To this end, efforts have been made to optimize the physicochemical and bio-mechanical properties of biomaterials for tendon tissue engineering. However, recent progress indicated that innate immune cells, especially macrophages, can also respond to the material cues and undergo phenotypical changes, which will either facilitate or hinder tissue regeneration. This process has been, to some extent, neglected by traditional strategies and may partially explain the unsatisfactory outcomes of previous studies; thus, more researchers have turned their focus on developing and designing immunoregenerative biomaterials to enhance tendon regeneration. In this review, we will first summarize the effects of material cues on tenogenic differentiation and paracrine secretion of stem cells. A brief introduction will also be made on how material cues can be manipulated for the regeneration of tendon-to-bone interface. Then, we will discuss the characteristics and influences of macrophages on the repair process of tendon healing and how they respond to different materials cues. These principles may benefit the development of novel biomaterials provided with combinative bioactive cues to activate tenogenic differentiation of stem cells and pro-resolving macrophage phenotype.

Statement of Significance

The progress achieved with the rapid development of biomaterial-based strategies for tendon regeneration has not yielded broad benefits to clinical patients. In addition to the interplay between stem cells and biomaterials, the innate immune response to biomaterials also plays a determinant role in tissue regeneration. Here, we propose that fine-tuning of stem cell behaviors and alternative activation of macrophages through material cues may lead to effective tendon/ligament regeneration. We first review the characteristics of key material cues that have been manipulated to promote tenogenic differentiation and paracrine secretion of stem cells in tendon regeneration. Then, we discuss the potentiality of corresponding material cues in activating macrophages toward a pro-resolving phenotype to promote tissue repair.

Contents

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1. Introduction

Decades of research on tendon injuries and regeneration have provided substantial understanding of the biological and mechanical functions of these dense connective tissues required to maintain posture and generate motion. Nevertheless, tendon injuries still remain a clinical challenge due to their poor-self healing capacity, with limited cellularity, vascularity, and innervation [1]. Current treatment strategies for tendon defects involving the use of autografts or allografts often fails to restore the functional, structural, and biomechanical characteristics of healthy tendons [2]. Therefore, various biomaterials have been developed and explored as possible alternatives for tendon tissue engineering; Table 1 lists some of the commercially available biomaterials and their clinical applications in tendon repair. However, despite the positive outcomes, both biological and synthetic scaffolds have also been shown to induce undesirable tissue formation and inflammatory response, resulting in fail treatments [2–7].

To ameliorate unfavorable clinical effects associated with current treatment techniques, biomaterials are continuously being developed either alone or in combination with other factors (active groups, soluble mediators, stem cells) [8]. Notably, the application of biomaterials in combination with stem cells is a novel and an extensively explored tissue engineering approach to regenerate injured tissues, providing an opportunity to enhance the repair process with functional cells. However, the fundamental concern in this strategy has been to determine how to effectively and accurately promote the differentiation of stem cells into the desired cell type. Multiple studies reported the ability various stem cells to differentiate into tenocytes [9–12], and that their functions are largely dependent on the extracellular matrix (ECM) cues such as surface chemistry, elasticity, and topography [13–15]. Thus,

Table 1
Clinical studies of commercial scaffolds for tendon injury.

Products	Study type	Tendon	Patients (n)	Failure and complications	Year	Ref
GraftJacket®	Retrospective	Rotator cuff	16	3 patients failed without full incorporation of the graft into the native tissue	2007	[4]
	Retrospective	Rotator cuff	17	3 patients failed with recurrent tears	2007	[3]
	Retrospective	Rotator cuff	16	3 patients failed without full incorporation of the graft into the native tissue	2008	[5]
	Retrospective	Rotator cuff	45	One immunocompromised patient with deep wound infection	2010	[123]
	Retrospective	Achilles	9	No incidence of re-rupture or recurrent pain	2007	[124]
	Retrospective	Achilles	21	3 patients failed tender incision sites, 1 with swelling, 1 with deep vein thrombosis, and another with tendon hypertrophy and pain	2007	[125]
	Retrospective	Achilles	11	No cases of re-rupture or recurrent pain	2008	[126]
	Case report	Achilles	1	NA	2004	[127]
	Case report	Rotator cuff	1	Little to no inflammatory response	2009	[6]
	Case report	Peroneus brevis	2	No incidence of recurrent pain	2011	[128]
	Prospective	Rotator cuff	42	**Scaffold group:** recurrent shoulder bursitis in 1 patient and 3 rotator cuff retears; **Control group:** cellulitis in 2 patients, shoulder bursitis in 1 patient, post-traumatic fibrosis in 1 patient, 9 rotator cuff retears, and 1 biceps tendon rupture.	2012	[129]
Restore™	Retrospective	Rotator cuff	12	1 patient failed with no infections and other complications	2002	[130]
	Retrospective	Rotator cuff	11	10 patients failed with recurrence of large, retracted tears	2004	[131]
	Case report	Rotator cuff	25	4 patients failed with an overt inflammatory reaction	2005	[132]
	Prospective	Rotator cuff	30	11/15 scaffold group and 6/15 control group failed	2006	[133]
	Prospective	Rotator cuff	22	6/10 scaffold and 7/12 control group failed	2007	[134]
Zimmer® (Permacol™)	Retrospective	Rotator cuff	10	No reported adverse effects	2003	[135]
	Prospective	Rotator cuff	10	2 patients failed with graft disruptions	2008	[136]
	Case report	Rotator cuff	4	2 patients failed with reduced range and strength, increased pain; 1 patient failed with pain, catching and weakness; 1 patient failed with inflammation and pain	2007	[137]
Gore-Tex®	Retrospective	Rotator cuff	28	3 patients failed with persisted pain and re-tears	2002	[138]
	Retrospective	Patellar	7	None	2004	[139]
LARS®	Retrospective	Achilles	14	No observed incidence of re-rupture or recurrent pain	2009	[140]
	Case report	Achilles	1	Wound dehiscence	2010	[141]
Ligastic®	Case report	Achilles	1	Failed with immune-response	2010	[7]

NA: Not available.

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