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The past, present and future in scaffold-based tendon treatments ☆

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ABSTRACT

Tendon injuries represent a significant clinical burden on healthcare systems worldwide. As the human population ages and the life expectancy increases, tendon injuries will become more prevalent, especially among young individuals with long life ahead of them. Advancements in engineering, chemistry and biology have made available an array of three-dimensional scaffold-based intervention strategies, natural or synthetic in origin. Further, functionalisation strategies, based on biophysical, biochemical and biological cues, offer control over cellular functions; localisation and sustained release of therapeutics/biologics; and the ability to positively interact with the host to promote repair and regeneration. Herein, we critically discuss current therapies and emerging technologies that aim to transform tendon treatments in the years to come.

Contents

Abbreviations: ACL, anterior cruciate ligament; ADSC, adipose derived stem cell; bFGF, basic fibroblast growth factor; BMSC, bone marrow stem cell; BMP, bone morphogenic protein; DNA, deoxyribonucleic acid; ECM, extracellular matrix; EGR, early growth response protein; GAG, glycosaminoglycan; GDF, growth differentiation factor; HA, hyaluronic acid; IGF, insulin-like growth factor; MMP, matrix metalloproteinase; MRI, magnetic resonance imaging; MSC, mesenchymal stem cell; NSAIDs, non-steroidal anti-inflammatory drugs; NO, nitric oxide; Oct 4, octamer-binding transcription factor 4; PDGF, platelet-derived growth factor; PCL, poly-ε-caprolactone; PLGA, poly(lactic-co-glycolic acid); PRP, platelet rich plasma; PG, proteoglycan; SSARD, slow acting anti-rheumatic drugs; SSEA-4, stage-specific embryonic antigen-4; TGF-β, transforming growth factor-β; TC, tenocyte; TSC, tendon stem cells; VEGF, vascular endothelial growth factor.

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1. Introduction

Tendon injuries constitute an unmet clinical need for both human and equine patients. Over 30 million human tendon-related procedures take place annually worldwide with an estimated healthcare expenditure in excess of €140 billion per year [1]. As the human population ages and life expectancy increases, it is estimated that 25% of all adults will suffer a tendon related condition that will put a further physical and financial strain on healthcare systems [2,3]. Proportional is the situation with equine patients: 46% of the racehorses will suffer a tendon-related injury that will negatively impact the industry, which is valued at €400 billion worldwide [4,5].

Subject to the severity of the injury, from a small sprain to a complete rupture, numerous therapeutic strategies of variable efficacy are currently available (Table 1). Unfortunately, preclinical and clinical data to-date indicate, regardless of injury severity, no current therapies have achieved complete pre-injury state recovery [6]. Further, severe injuries are often associated with compromised function, joint instability and long-term pain and disabilities, due to the inherent poor regeneration capacity of tendon [7].

These findings impose the need for the development of functional therapies for injured tendon tissues. However, for successful tissue engineered therapies, it is important to understand epidemiological data of the different injuries, the function of cellular and extracellular components in tendon physiology and healing, and pioneered technologies that have become available in recent years. Upon this knowledge, it is likely to revolutionise functional tendon treatments in the years to come.

2. Epidemiology and clinical description of human tendon injuries

The most frequently injured tendons are the shoulder rotator cuff, the forearm extensor, the hand flexor, the Achilles, the tibialis posterior and the patellar [8,9], whilst the anterior cruciate ligament (ACL) is one of the most painful and debilitating of knee injuries [8,9]. Previously, the tendon research community recognised inflammation as the underlying cause of tendon injury, however, with advancements in imaging technologies and understanding of histopathology, it is widely accepted that tendon injuries are more degenerative in nature [10–14]. These degenerative conditions, referred to as tendinopathies, comprise of typical pathological changes, including islands of high cellularity and initial tissue disorganisation in mild degeneration, whilst in severe degeneration is accompanied by chondrocyte appearance [15]. Macroscopically, degenerative tissue appears to be yellow/brown due to mucoid degeneration and the loss of the highly organised appearance of collagen fibre bundles [14,16]. Further, microscopic changes occur within the collagen structure itself and fibrosis and neovascularisation are evident [17–19]. In addition, current data suggest that the formation of additional blood vessels is responsible for the pain prevalent in tendinopathies [20,21], and not inflammatory infiltration, as previously suspected [22,23].

Table 1
Common injuries presented in human and equine subjects, provided along with current treatment strategies and respective limitations.

Species	Tendon injury	Treatment	Limitation	Ref
Human	Hand extensor/flexor tendon	Immobilisation (splint)	Scar tissue leads to loss/reduction of motion. Joint stiffness is often experienced.	[28,450,451]
		Steroid injection	Serious doubts over effectiveness.	
		Open surgery: Kessler stitch	Re-rupture rate following surgery is as high as 4 to 18% worldwide.	
	Achilles tendon (rupture)	Cast immobilisation	Susceptible to re-rupture at a rate of about 11%.	[23,452,453]
		Functional cast	Low re-rupture rate of 1–2%, but high complication rate of 12.5%.	
		Open Surgery: Kessler stitch	High re-rupture rate of 8% and nerve injury of 13%.	
		Tissue grafts	Failures seen at tissue intersect points.	
		Biomaterial repair	Inadequate mechanical strength and foreign body response.	
	Rotator cuff (tear)	Steroid injection	Up to 40% failure rates have been reported.	[2,454–458]
		Open surgery: Decompression and debridement	Often associated with deltoid dysfunction and postoperative pain.	
		Biomaterial repair	Inadequate mechanical strength and foreign body response.	
	Patellar tendon (tear)	End-to-end suture	10 out of the 13 repairs are effective.	[459]
		Tissue grafts	Limited availability, pain at donor site.	
	ACL (rupture)	Tissue grafts	Up to 13% re-rupture rate.	[460]
Equine	Superficial digital flexor tendon injury	Cold therapy & compression bandaging	23 to 67% will re-injure their tendons within 2 years of the original injury.	[43,46]
		Immobilisation (splint)	Associated with stiffness and fibrosis.	
		Autologous cell therapy	Questionable cell survival/localisation.	[44,461,462]
	Deep digital flexor tendon injury	Conservative treatment (rest and reduced activity)	Return to exercise is not recommended.	[51,52]
	Digital extensor tendon laceration	Three-loop pulley tenorrhaphy technique	Adhesions and septic tenosynovitis are common complications.	[54]
	Suspensory ligament	Conservative treatment (rest and reduced activity)	Return to exercise is not recommended for several months.	[463,464]
		Shock wave therapy	Evidence of disorganised tissue. Not suitable in severe cases.	[465,466]
		PRP treatment	No standardised treatment protocol.	[467–469]

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