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REVIEW ARTICLE

Advances of stem cell based-therapeutic approaches for tendon repair

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Summary Tendon injuries are significant clinical problems. Current treatments often result in incomplete repair or healing, which may be lead to reduced function and rupture. Stem cell-based therapy is a promising intervention for tendon repair. In this review, we provide an overview on the recent progress in the field, current understanding of the underlying mechanisms of the approach, and the potential of stem cell approaches beyond cell implantation. We conclude the review by sharing our viewpoints on the challenges, opportunities, and future directions of this approach.

The translational potential of this article: This review overviews recent progress on stem cell-based therapies for tendon repair, which highlights the potential and challenges of bench to clinical translation.

Introduction

Tendon injuries represent a common clinical problem that affects 30 million people annually [1]. They can occur as a result of trauma, overuse, and aging, and are typically characterised by pain, inflammation, and dysfunction [2–5]. Tendon injuries are currently managed by conservative treatment and surgical intervention [6]. Conservative treatments include injection corticosteroids, over-the-counter nonsteroidal anti-inflammatory drugs, physical therapy, and extracorporeal shock wave therapy [7]. However, tendons tend to heal slowly and may fail to regain their full function with only conservative treatment [8]. Surgical options are frequently considered for severe acute tendon injuries, such as rupture [9]. Surgical repair with grafts is the current standard to treat tendon ruptures, but significant limitations with this approach include continued

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pain and risk of re-rupture [10], formation of scar tissue, ectopic bone formation, and adhesions or the lack of regeneration of fibrocartilage at the tendon-to-bone junction [8]. Furthermore, these conservative and surgical treatment approaches have not been able to completely restore tendon to their native composition, structure, and mechanical properties. Therefore, there is a critical need for more effective treatments.

The tendon, as an anatomical structure, generally functions as connective tissue between muscle and bone [11]. It is a complex structure that is relatively acellular and avascular consisting of a hierarchical arrangement of collagen fibre bundles [12,13]. Tenocytes are the primary cell type within tendon, and they are responsible for the overall maintenance of tendon [11,14]. Tendon-resident stem cells, termed tendon-derived stem progenitor cells, (TSPCs), were identified by Bi et al. [15]. TSPCs are found in parallel collagen fibrils surrounded by the extracellular matrix, and have a specific niche, which includes extracellular matrix proteins biglycan and fibromodulin, that allows for tenocyte differentiation [15]. However, the function and fate of TSPCs may decline with age [16,17], in tendinopathy [18], or as a result of injury [19].

Advances in stem cell-based therapies have shown great potential for tissue repair and regeneration and may be a promising new intervention for tendon repair and regeneration. In this paper, we will primarily review the recent progress on stem cell implantation-based therapy, their therapeutic potential and underlying mechanisms. We will also discuss the potential of stem cell-based approaches beyond cell implantation, such as using stem cell-derived exosomes and enhancing endogenous stem homing. Finally, we will conclude the review by sharing our perspectives on the challenges, opportunities, and future directions for stem cell-based approaches for tendon repair and regeneration.

Stem cell-based approaches for tendon repair: an overview

Stem cells for tendon repair

Stem cells can be classified based on their lineage differential potential. Pluripotent stem cells such as embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs), can differentiate into any cell in the body. Multipotent stem cells, such as mesenchymal stem cells (MSCs), can develop into more than one cell type, but their differentiation potential is more limited compared to pluripotent cells.

ESCs represent a single source of cells that could be used to replace any other cell type in the body lost to damage or disease, and therefore have a significantly broad potential in regenerative medicine, including the repair and regeneration of tendon [20]. Chen et al. demonstrated that human ESCs (hESCs) differentiated into MSCs (hESC-MSCs) incorporated into a fibrin gel [21] or onto a knitted silk-collagen sponge scaffold [22], and implanted into a tendon defect in rats, resulted in improved tendon structural and mechanical properties. Despite these promising results, whether this therapeutic strategy also benefits patients with chronic tendon injuries such as tendinopathy requires further investigation [23].

Induced pluripotent stem cells (iPSCs) are pluripotent stem cells that can be generated directly from adult cells by introducing four specific genes encoding transcription factors which convert adult somatic cells into pluripotent stem cells [23,24]. The implantation of cells differentiated from iPSCs have negligible immunogenicity [25], which is one reason why they have become attractive cell sources for tissue repair. Xu et al. [26] first reported iPSC-derived neural crest stem cells (NCSCs) suspended within a fibrin gel and implanted into a rat patellar tendon window defect significantly enhanced tendon healing, compared to non-iPSC-NCSC-treated tendons. Interestingly, the implantation of the multipotent NCSCs are, led to healed wound tissue that exhibited no ectopic bone or cartilage formation from the use of iPSC-NCSCs during the experimental study for 4 weeks [26]. iPSCs might be a potential source for stem cell-based therapy for tendon repair, but long-term outcome evaluation is critically required. Furthermore, a recent study indicated that although equine iPSCs expressed tendon-associated genes and proteins in two-dimensional differentiation assays, in contrast to equine embryonic stem cells, equine iPSCs failed to generate artificial tendons when cultured in three-dimensional collagen gels [27]. Therefore, a thorough investigation of the regulatory mechanism that is critical for iPSCs to obtain the reparative capacity for tendon repair is required.

MSCs can differentiate into a variety of connective tissue cell types including tenocytes. MSCs can be derived from various tissue sources, such as bone marrow [(BM): BM-derived stem cells, (BMSCs)], tendon (TSPCs), and adipose tissue [adipose-derived stem cells, (ADSCs)]. Numerous animal studies have demonstrated that MSCs have the ability to improve tendon repair (reviewed in [28,29]). Q3

Emerging cell sources for tendon regeneration include peripheral blood MSC, umbilical cord blood-mesenchymal stem cells (UCB-MSCs), and periodontal ligament cells. For example, injection of peripheral blood MSCs improved histologic features of a diseased tendon, in a collagenase-induced tendinopathy model in sheep [30]. Allogeneic UCB-MSCs injected into naturally occurring tendinitis of the superficial digital flexor tendon led to higher performance and strength, as well as improved healing as assessed by ultrasound imaging [31]. Efficacy of UCB-MSCs in improving tendon-bone healing following anterior cruciate ligament reconstruction has also been demonstrated in a rabbit model [32]. Injection of UCB-MSCs into the interface between the bone tunnel and tendon graft improved the histologic appearance in the bone-tendon interface [32]. Furthermore, periodontal ligament-derived stem/progenitor cells, obtained from patients undergoing orthodontic treatment, improved healing of a full-size Achilles tendon defect, compared to an untreated defect, and resulted in similar efficacy compared to Achilles tendon-derived cells [33]. While many stem cell types have shown efficacy in animal models, a standard treatment protocol may be required to evaluate and identify the most promising stem cell option for a specific type of tendon repair.

Many studies only use one type of stem cell. Interestingly, combining multiple stem cells in one treatment led to an enhanced therapeutic effect. Coculture of BM-MSCs and