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Progress in cell-based therapies for tendon repair ☆

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ABSTRACT

The last decade has seen significant developments in cell therapies, based on permanently differentiated, reprogrammed or engineered stem cells, for tendon injuries and degenerative conditions. In vitro studies assess the influence of biophysical, biochemical and biological signals on tenogenic phenotype maintenance and/or differentiation towards tenogenic lineage. However, the ideal culture environment has yet to be identified due to the lack of standardised experimental setup and readout system. Bone marrow mesenchymal stem cells and tenocytes/dermal fibroblasts appear to be the cell populations of choice for clinical translation in equine and human patients respectively based on circumstantial, rather than on hard evidence. Collaborative, inter- and multi-disciplinary efforts are expected to provide clinically relevant and commercially viable cell-based therapies for tendon repair and regeneration in the years to come.

Contents

Abbreviations: ADSCs, adipose derived stem cells; α-SMA, alpha smooth muscle actin; bFGF, basic fibroblast growth factor; BMSCs, bone marrow stem cells; BMP, bone morphogenic protein; COMP, cartilage oligomeric matrix protein; CD, cluster of differentiation; CTGF, connective tissue growth factor; ESCs, embryonic stem cells; EGF, epidermal growth factor; ECM, extracellular matrix; GAGs, glycosaminoglycans; GDF, growth differentiation factor; HGF, hepatocyte growth factor; iPSCs, induced pluripotent stem cells; IGF, insulin-like growth factor; IL, interleukin; MMP, matrix metalloproteinase; MDSCs, muscle-derived stem cells; Oct-4, octamer-binding transcription factor 4; PDGF, platelet derived growth factor; PRCR, platelet rich clot releasate; PRP, platelet rich plasma; PSCs, perivascular stem cells; PPARγ, peroxisome proliferator-activated receptor γ; PDMS, polydimethylsiloxane; PCL, poly(ε-caprolactone); PLCL, poly(ε-caprolactone-co-lactide); PGA, poly(glycolic acid); PLLA, poly(lactic acid); PLGA, poly(lactic-co-glycolic acid); PGs, proteoglycans; RUNX2, runt-related transcription factor 2; SOX9, sex determining region Y-box 9; SIS, small intestine submucous; SDF1α, stromal cell-derived factor 1α; TSCs, tendon stem cells; TIMP, tissue inhibitor of metalloproteinase; TGF, transforming growth factor; VEGF, vascular endothelial growth factor.

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1. Introduction

Over 30 million musculoskeletal injuries occur annually worldwide and nearly half of them involve tendon and ligament injuries. The US and EU associated expenditure exceeds US $180 billion annually. With the increase in life expectancy, it is predicted that tendon injuries will continue to rise, placing an enormous financial strain on healthcare systems [1]. As tendon healing is slow and leads to fibrotic scarring and adhesions, the natural repair process is not sufficient to functionally repair the injured tissue [2–11]. Current strategies to manage mild tendon injuries resort to conservative treatments (e.g. rest, physiotherapy and pharmacological methods) of questionable efficiency [12–21]. In severe injuries, tissue grafts remain the gold standard in clinical practice. However, autograft-induced site morbidity should be minimal and should result in less disability than the original injury; these prerequisites limit the availability of suitable autologous tissues. Allografts and xenografts, although are more readily available than autografts and have demonstrated proportional clinical outcomes, are associated with a different set of concerns, including inadequate processing that may jeopardise mechanical properties; possibility of disease transmission; and immune mediated rejection [22–29]. These limitations have triggered an intense investigation into biomaterial-based alternatives to tissue grafts. To-date, numerous two- and three-dimensional; nano- to macro-; and bottom-up to top-down fabrication technologies (e.g. self-assembly, electro-spinning, freeze drying, imprinting) and synthetic [e.g. poly(ε-caprolactone), PCL; poly(glycolic acid), PGA; poly(lactic acid), PLLA; poly(lactic-co-glycolic acid), PLGA] or natural (e.g. collagen type I, silk) in origin biomaterials alone or in combination with bioactive/therapeutic molecules (e.g. glycosaminoglycans, GAGs; proteoglycans, PGs; growth factors; genes) have been investigated in vitro and in vivo [30–42]. Despite the very promising preliminary results, so far, these constructs have not completely recapitulated native tendon composition, structure/architecture and mechanical properties. In fact, very frequently, such approaches have been associated with inflammation, hyper-cellularity, calcification, and inadequate mechanical properties and tissue organisation, imposing the need for new functional tendon therapies [43–48].

Cell-mediated tendon engineering therapies are promising alternatives to traditional graft/scaffold treatments, given the low activity/low cell number of tendons. In cell-mediated repair, cell suspensions can be injected at the site of injury or implanted in the form of cell sheets or along with a tissue graft or a scaffolding material to enable homogeneous cell distribution and localisation at the side of injury [1,49–71]. As the interest in cell-based therapies for tendon repair grows, it is becoming apparent that the most important aspect is the choice of cell population. To-date, cell populations that have been assessed for tendon repair are clustered as: permanently differentiated cells (e.g. tenocytes, dermal fibroblasts, muscle cells); undifferentiated/progenitor/stem cell types [e.g. bone marrow stem cells (BMSCs), adipose-derived stem cells (ADSCs), tendon stem cells (TSCs), perivascular stem cells (PSCs), muscle-derived stem cells (MDSCs), and embryonic stem cells (ESCs)]; and reprogrammed/engineered cells [e.g. induced pluripotent stem cells (iPSCs), reprogrammed/engineered/genetically modified cells induced to upregulate the expression/production of a specific molecule]. For all different cell populations, a scientifically sound rationale has been postulated (Table 1). For example, permanently differentiated cells have been studied due to similar marker expression and secretome profile to tenocytes, whilst undifferentiated stem cells have been studied due to their potential to differentiate towards tenogenic lineage and due to the substantial regenerative potential of their secretome in the undifferentiated state that will positively influence the tendon regeneration cascade. However, none of the assessed cell populations is perfect (Table 1). For example, there is limited availability of functional tenocytes; the specificity of dermal fibroblasts and muscle cells is questionable; adult stem cells may induce ectopic bone formation; ESCs are associated with tumour induction; reprogrammed/engineered cells are associated with safety and efficacy concerns, when viral and polymeric vectors are used respectively; and differentiated towards specific lineage cells are associated with developmental stage mismatch. Herein, we critically assessed shortcomings and accomplishments achieved for each cell population in terms of in vitro culture and characterisation, relevant to tendon repair and regeneration. Further, given that previous studies have described in detail the in vivo efficacy of various cells and carriers of thereof in small and large animal models

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