Magnetically Assisted Tissue Engineering Technologies for Tendon Regeneration

Reporting

Project Information

MagTendon

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Periodic Reporting for period 4 - MagTendon (Magnetically Assisted Tissue Engineering Technologies for Tendon Regeneration)

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Summary of the context and overall objectives of the project

Musculoskeletal diseases are one of the leading causes of disability worldwide, affecting 1 in 2 adults, which correspond to twice the rate of chronic heart and lung conditions. Tendon injuries account for a considerable share of musculoskeletal pathologies. Their load-bearing and load-transfer functions

predisposes tendons to injuries that can dramatically affect patient's quality of life, being estimated that over 30 million human tendon-related procedures are taking place annually worldwide. Most often, tendon injuries are managed with conservative approaches and/or surgical interventions, using autografts or allografts. Tendon healing process is a complex cascade of biological events that are not yet fully understood, orchestrated by numerous cytokines and initiated by an inflammatory step. This process is never fully accomplished, which explains the fact that tendon never regains its initial biomechanical functionality.
The poor healing ability of tendons as well as the limitations of currently used therapies have motivated tissue engineering (TE) strategies to develop living tendon substitutes. MagTendon aims at exploring conventional and innovative tools such as multimaterial 3 dimensional (3D) bioprinting to design magnetic responsive systems mimicking specific aspects of tendon tissue architecture, composition and biomechanical properties, which, combined with adequate stem cells, will render appropriate behavioural instructions to stimulate the regeneration of tendon tissue. MagTendon proposes expanding the boundaries of research in this field, fulfilling the currently unmet requirements for tendon TE by proposing disruptive technological concepts for achieving novel therapies that more closely recapitulate tendon morphogenesis will be obtained, with the ultimate goal of achieving regeneration over simple repair of tendon tissue, but that can be extended to approaches targeting other tissues and organs of the human body.

Work performed from the beginning of the project to the end of the period covered by the report and main results achieved so far

1) Superparamagnetic nanoparticles (SPMNs) have been synthetized by different methods and are functionalized for target application and uses. For example, SPMNs were conjugated with anti-stage specific early antigen-4 (SSEA-4) or anti-tenomodulin (TNMD) antibodies for sorting of human adipose stem cells (hASCs) subpopulations more prone to tenogenic differentiatio. SPMNs were also functionalized with IL-4 for binding to IL-4 receptor in macrophages and stimulate a more favorable healing response (subtask 1.3)

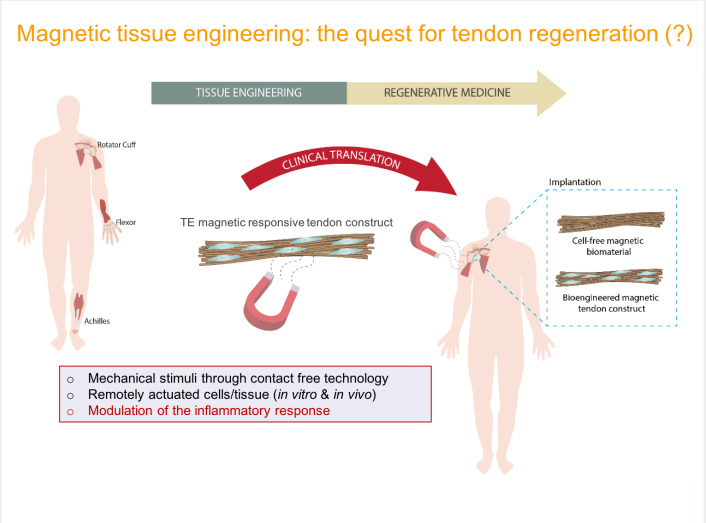
2)3D hierarchical fibrous scaffolds have been developed and the incorporation of SPMNs conferred magnetic responsivess to the scaffolds and enabled their remote actuation by external magnetic fields, which boost the tenogenic commitment of stem cells. This biotextile concept has been further explored to fabricate 3D scaffolds encompassing the topographical mineral gradients requited to engineer constructs for the tendon-to-bone interface. Furthermore, we have developed novel nanocomposite biphasic hydrogels mimicking the tendon and bone using magnetic alignment of anisotropic nanoparticles within an injectable gelatin hydrogel. In addition, SPMNPs have been combined with anisotropic nano- and microparticles that could be aligned within hydrogels recreating the anisotropic architecture of tendon tissues. Moreover, we have demonstrated that besides controlling the biophysical cues, nanoparticles surface chemistry can also be exploited to modulate biomolecule sequestration and presentation to control the behavior of stem cell. Supramolecular hydrogels based on dopamine functionalization of natural polymers and hydrogels with reversible covalent crosslinking (hydrazone reaction) were explored to produce magnetic nanoinks, while platelet lysates (PL) and tendon decellularized matrix have been used to produce intrinsically

bioactive bioinks. When combined with support matrix assisted 3D bioprinting concepts, these bioink hydrogels show superior biological performance without compromising the biofabrication freedom and therefore, were further combined with magnetic nano- and microparticles for the magnetic assisted bioprinting of tendon mimetic constructs. The biological performance and functionality of 3D magnetic hierarchical scaffolds have been assessed by culturing hASCs under the influence or absence of magnetic stimuli. We have demonstrated the activation of cell mechanotranduction processes through the magnetic actuation of magnetic scaffolds, and its benefits on boosting the hASCs tenogenic commitment and positive immunomodulatory potential.
3) The proposed tendon and tendon-to-bone on-a-chip platforms were developed exploring two different fabrication strategies. The fibrous scaffolds developed under subtask 2.1 were first combined with the concept of composite living fibers and used as repressive miniaturized units of tendon tissue. Coupling these units with 3D printed supports, miniaturized models of heathy and tendinophatic (fibrotic phenotype) tissues have been bioengineered using tendon derived cells. On a different concept, a new biofabrication system enabling the direct 3D bioprinting of embedded living constructs within a self-assembled fibrillar support and allowing to use the nanocomposite hydrogels produced under task 2.2.1 as bioink material has been developed. T Finally, magnetic cell sheets have also been developed purposing augmentation strategies and/or uses as 3D models of tendinopathies. Under task 3, in order to study pathological niches, IL-1β treated human tendon derived cells (hTDCs) were exposed to pulsed electromagnetic fields (PEMF). PEMF could reduce the pro-inflammatory effects of IL-1β, on both hTDCs alone or its co-cultures with macrophages, and favored pro-regenerative immune responses. The impact of PEMF in cell-cell and cell-ECM interactions was also investigated in IL-1B-conditioned magnetic cell sheets We also explored the synergistic effect of PEMF and magnetic membranes (magSPCL). The results confirmed that PEMF decreased the MMPs expression in hTDCs, and that NFkB was counteracted by magSPCL exposed to PEMF.
4) widening the therapeutical window of the developed TE approaches by remote activation of the implanted magnetic systems using external magnetic devices: First studies were performed concerning implantation of magnetic constructs in a rat patellar tendon defect model. Other studies are planned using a large animal model (sheep model).

Progress beyond the state of the art and expected potential impact (including the socio-economic impact and the wider societal implications of the project so far)

The MagTendon project developed cutting-edge magnetic actuation systems and technologies to enhance tendon tissue regeneration. These innovations include designing new biomaterials with anisotropic structures, promoting tenogenic differentiation of stem cells, and modulating inflammatory cues. The development of magnetically assisted 3D bioprinting technologies based on embedded extrusion has provided a powerful platform for creating highly functional tissue substitutes and advanced 3D tissue models that closely mimic living tissue interfaces. Building on this work, under the ERC PoC Grant BioChips, the team pioneered a novel bottom-up technology for directly writing 3D microphysiological systems within bioinspired fibrillar supports. This approach offers significant

advantages for in vitro modeling, with cancer modeling as the primary biotechnological application challenge, demonstrating the commercial potential of these innovative systems.



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