

Universidade Estadual Paulista “Júlio de Mesquita Filho”
Faculdade de Medicina Veterinária e Zootecnia

TENDON DERIVED MAGNETIC HYDROGEL FOR BIOPRINTING

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“Every art and every inquiry, and similarly every action and pursuit, is thought to aim at some good; and for this reason the good has rightly been declared to be that at which all things aim”

Aristotle

RESUMO

ALTHEMAN, V.G. **HIDROGEL MAGNÉTICO DERIVADO DE TENDÃO PARA BIOIMPRESSÃO**. Botucatu – SP. 2026. 61p. Defesa (Doutorado) – Faculdade de Medicina Veterinária e Zootecnia, Campus Botucatu, Universidade Estadual Paulista.

Lesões tendíneas representam uma parcela significativa das afecções musculoesqueléticas, com alta morbidade e limitada capacidade regenerativa. Estratégias de engenharia tecidual têm se mostrado promissoras ao combinar células-tronco, biomateriais e estímulos biofísicos para promover a regeneração funcional do tendão. O presente trabalho teve como objetivo desenvolver um hidrogel magneticamente responsivo derivado da matriz extracelular (MEC) de tendão suíno para uso como biotinta em bioimpressão 3D e avaliar sua biocompatibilidade e potencial de indução da diferenciação tenogênica de células-tronco mesenquimais derivadas de tecido adiposo humano (hASCs). Partiu-se da hipótese de que a funcionalização magnética da MEC permitiria a aplicação de estímulos magnetomecânicos remotos capazes de modular vias de mecanotransdução celular, promovendo alinhamento celular e aumentando a deposição de matriz extracelular tenogênica em comparação a sistemas não magneticamente estimulados. Para isso, tendões suínos foram submetidos a um protocolo otimizado de descélularização, seguido de liofilização e moagem. O pó obtido foi digerido para obtenção do hidrogel. A caracterização reológica confirmou propriedades adequadas à bioimpressão. A incorporação de nanopartículas magnéticas de óxido de ferro dopadas com zinco ($Zn_{0.28}Fe_{2.72}O_4$) conferiu responsividade magnética ao material. Constructos tridimensionais foram bioimpressos com biotintas de MEC descélularizada e hASCs, com ou sem nanopartículas magnéticas, em meio de suporte de cristais de celulose (CNC). Após impressão, os modelos foram cultivados por até 21 dias, com e sem exposição a campos magnéticos externos de baixa intensidade. Os resultados demonstraram alta viabilidade celular e manutenção da atividade metabólica durante todo o período de cultivo, confirmando a biocompatibilidade do hidrogel. A presença das nanopartículas e o estímulo magnético não comprometeram a sobrevivência das células e favoreceram o alinhamento celular, com tendência ao aumento da deposição de colágeno e proteínas não colagênicas nos grupos expostos ao campo magnético. Esses achados sugerem que a estimulação magnetomecânica pode atuar como um modulador de vias de mecanotransdução envolvidas na tenogênese. Conclui-se que o hidrogel derivado da matriz extracelular de tendão suíno apresenta propriedades físico-químicas e biológicas adequadas para aplicação como biotinta em bioimpressão 3D. O hidrogel magnético mostrou-se biologicamente ativo e mecanicamente estimulável, com potencial como modelo funcional para estudo de tenogênese e futuro uso translacional.

Palavras-chave: matriz extracelular, célula-tronco, tenogênese, impressão 3D, biomaterial

ABSTRACT

ALTHEMAN, V.G. **TENDON DERIVED MAGNETIC HYDROGEL FOR BIOPRINTING**. Botucatu – SP. 2026. 61p. Defesa (Doutorado) – Faculdade de Medicina Veterinária e Zootecnia, Campus Botucatu, Universidade Estadual Paulista.

Tendon injuries represent a significant portion of musculoskeletal disorders, with high morbidity and limited regenerative capacity. Tissue engineering strategies have shown promise by combining stem cells, biomaterials, and biophysical stimuli to promote functional tendon regeneration. This study aimed to develop a magnetically responsive hydrogel derived from the extracellular matrix (ECM) of porcine tendon for use as a bioink in 3D bioprinting and to evaluate its biocompatibility and potential for inducing tenogenic differentiation of mesenchymal stem cells derived from human adipose tissue (hASCs). The hypothesis was that the magnetic functionalization of the ECM would allow the application of remote magnetomechanical stimuli capable of modulating cellular mechanotransduction pathways, promoting cell alignment and increasing the deposition of tenogenic extracellular matrix compared to non-magnetically stimulated systems. To this end, pig tendons were subjected to an optimized decellularization protocol, followed by lyophilization and grinding. The resulting powder was digested to obtain the hydrogel. Rheological characterization confirmed properties suitable for bioprinting. The incorporation of zinc-doped iron oxide magnetic nanoparticles ($Zn_{0.28}Fe_{2.72}O_4$) conferred magnetic responsiveness to the material. Three-dimensional constructs were bioprinted with decellularized ECM bioinks and hASCs, with or without magnetic nanoparticles, on a cellulose crystal support medium (CNC). After printing, the models were cultured for up to 21 days, with and without exposure to low-intensity external magnetic fields. The results demonstrated high cell viability and maintenance of metabolic activity throughout the culture period, confirming the biocompatibility of the hydrogel. The presence of nanoparticles and magnetic stimulation did not compromise cell survival and favored cell alignment, with a tendency towards increased deposition of collagen and non-collagenous proteins in the groups exposed to the magnetic field. These findings suggest that magnetomechanical stimulation can act as a modulator of mechanotransduction pathways involved in tenogenesis. It is concluded that the hydrogel derived from porcine tendon extracellular matrix presents physicochemical and biological properties suitable for application as a bioink in 3D bioprinting. The magnetic hydrogel proved to be biologically active and mechanically stimutable, with potential as a functional model for the study of tenogenesis and future translational use.

Keywords: extracellular matrix, stem cell, tenogenesis, 3D printing, biomaterial

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CHAPTER 1

1. INTRODUCTION AND JUSTIFICATION

Tendons are fibrous connective tissues that bind muscles to bones, essential for locomotion, serving as the mechanism for transmitting forces generated by muscles to the skeletal system [1]. They consist predominantly of extracellular matrix (ECM), with collagen being the primary component, accounting for 65-80% of its dry mass. Collagen type I is the most abundant component ($\approx 95\%$), organized in a complex hierarchical structure parallel to the tendon's long axis [2,3].

The collagen fibrils are embedded in a hydrophilic matrix of non-collagenous components including proteoglycans, glycosaminoglycans (GAGs) and non-collagenous glycoproteins, which are essential for fibrillar organization, viscoelasticity, internal lubrication, compression resistance and mechanical adaptation of the tendon [4].

Tendon injuries represent a major proportion of all musculoskeletal injuries globally, affecting both athletic and non-athletic populations with significant morbidity, reaching up to 7 million cases per year [5]. Tendinopathy is a multifaceted pathology characterized by alterations on tendon microstructure, such as fragmented and disorganized collagen fibers, whose healing mechanisms are still not completely understood, with treatments lacking efficacy. [6].

The limited natural healing capacity stems from low cell density and vascularization in tendon tissue, which leads to a failure in recovery of their original mechanical properties, with less elasticity and, consequently, a high re-tear rate [7].

Although conservative therapies and the use of nonsteroidal anti-inflammatory drugs (NSAIDs) can provide temporary relief from pain, they do not restore the tissue homeostasis or structural organization. As a result, many patients experience recurrent injuries and persistent pain, which may ultimately lead to surgical intervention and long rehabilitation periods [8]. The repair tissue typically exhibits reduced elasticity and a less organized collagen structure compared to healthy tendon tissue, further contributing to functional impairment and reduced quality of life [9]. These challenges highlight the need for more effective and biologically restorative treatment approaches capable of promoting true structural and functional regeneration.

Mesenchymal stem cells (MSCs) are increasingly regarded as a therapeutic approach for tendinopathies through their multiple mechanisms of action, including their capacity for multidirectional differentiation, self-renewal, and particularly their immunomodulatory properties that help regulate inflammatory microenvironments [10,11]. They are also emerging as a significant cell source for tendon tissue engineering approaches, due to their ability to differentiate into various mesenchymal cell types, including tenocytes, as well as their high accessibility and ease of isolation [12]. Their differentiation toward tenogenic phenotypes can be directed through multiple strategies, including inductive growth factors, scaffolds, mechanical stimulation, and chemical signals within the stem cell microenvironment [13].

Tissue engineering (TE) has become a promising approach, utilizing combinations of cells, biomaterials, and biochemical factors to regenerate tendon-like tissues with characteristics comparable to native tendons and also to create representative experimental models [7]. Current strategies include stem cell-based therapies that modify the biological environment through regenerative and immunomodulatory factors [14], biomimetic scaffolds that replicate the extracellular matrix microenvironment [15], and advanced mechanical stimulation systems including robotic platforms to better replicate native tissue mechanical environments [16].

One of the available strategies in TE is creating three-dimensional (3D) bioprinted models. These models can better reproduce the native organization and mechanical environment of tendon tissue, enabling the study of neo-tendon formation after acute injury, as well as the dynamic interactions between resident or recruited tendon cells, implanted biomaterials, and other cell populations such as stem cells [17]. Ideally in bioprinting, biocompatible materials should be combined with appropriate cellular sources to produce a bioink that is both printable and capable of promoting cell interactions comparable to those of the native extracellular matrix of the target tissue [18].

Within this context, the use of scaffolds has proven to be a powerful strategy to be associated with MSCs, as their composition and architecture influence cell differentiation and ECM synthesis. Tissue-derived decellularized ECM (dECM) hydrogels are appealing as biomaterials capable of recapitulating the specific biophysical and biochemical complexity of native tissue ECM [19].

ECM plays a key role in supporting resident cell phenotype and tissue homeostasis, as well as in inducing stem-cells fate, as this niche provides not only structural support, but also regulates the biochemical, biomechanical and growth factor signaling mechanisms[20].

However, despite their biological relevance, dECM-based bioinks and bioprinted constructs alone are inherently limited in their ability to reproduce the dynamic mechanical environment required for tendon maturation in vitro. Static culture conditions fail to recapitulate the cyclic tensile forces that are fundamental drivers of tenogenic differentiation, ECM alignment, and functional tissue development. Thus, the absence of controllable and physiologically relevant mechanical stimulation remains a critical bottleneck in current tendon tissue engineering models.

The incorporation of magnetic nanoparticles (MNPs) into dECM hydrogels represents a promising strategy to address this limitation, since it can enhance their functionality as a biomaterial, allowing the fabrication of anisotropic, magneto-responsive scaffolds [21]. When combined with external magnetic fields, MNPs enable the remote, non-invasive application of magneto-mechanical stimuli within 3D constructs, providing spatiotemporal control over mechanical cues without the need for direct physical loading systems [21]. This approach allows the transduction of controlled mechanical forces at the cellular level, promoting cell alignment, cytoskeletal organization, and activation of mechanotransduction pathways relevant to tendon biology. Moreover, magnetically responsive systems offer the possibility of generating anisotropic and dynamically tunable microenvironments that more closely resemble the hierarchical structure and mechanical behavior of native tendon tissue [22].

Therefore, the development of a magnetically responsive, tendon-derived dECM bioink represents a strategic solution to a key unmet challenge in tendon tissue engineering: the integration of biomimetic biochemical composition with controllable, dynamic mechanical stimulation. This work proposes a novel platform that combines tissue-specific ECM cues, 3D bioprinting, and remote magneto-mechanical actuation to advance in vitro models of tenogenesis and support future translational applications in tendon repair.

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