Advancing tendon-to-bone enthesis repair

1 VALORIZATION

Tendons and tendon-to-bone entheses play a fundamental role in the movement of the joints upon muscle contraction. Thus, injuries at the tendon or the entheses can significantly impair movement, locomotion, and the quality of life of the injured patient. This can represent a significant societal and economic burden.

Tendinopathies and enthesopathies refer to different pathological conditions that affect the normal physiological function of the tissue. They can result from inflammation and/or chronic degeneration of the tissues and are usually associated with pain and reduced range of motion of the affected joint. Nevertheless, tendon and enthesis injuries can also occur due to a spontaneous rupture of the tendon or the tendon-to-bone attachment at the enthesis (e.g., total or partial tendon/enthesis tear). Although these ruptures can take place without previous symptoms, they are usually attributed to mechanical weakness of the tendon or the enthesis due to pathological changes in the tissues [1]. Such changes can be due to mechanical overuse, vascularisation, or aging. However, tendon rupture can occur in perfectly healthy tendons and entheses when the tissue is subjected to tensile loads exceeding their capacity. This is more likely to happen during the practice of sports. Hence, the majority of tendon and/or enthesis injuries are related to the practice of sports and high-impact physical activities, accounting for 50% of all sports-related injuries [2].

High-contact sports like basketball, football, or hockey are particularly prone to such injuries. Additionally, repetitive movements and strains in sports like tennis and water sports can lead to injuries such as rotator cuff injuries, tennis elbow, and joint dislocation. In the United States alone, more than 3.5 million sports injuries occur annually, with sprains and strains being the most common. Moreover, the incidence of tendon/enthesis ruptures in Europe has been estimated to be about 80 in 100,000, while in the United States the incidence tends to be higher, about 95 in 100,000 [3]. Furthermore, the prevalence of tendon and enthesis injuries is rapidly growing due to, among other reasons, the increase in the practice of sports by the elderly population (> 60 years old) [4].

Interestingly, the incidence of tendon and enthesis injuries has also seen an increase among the less active members of the population where a sedentary lifestyle and rising rates of obesity, diabetes, and the abuse of mutagens like alcohol and tobacco smoke have been correlated with the increase in tendon and enthesis injuries. In total, tendon and enthesis injuries account for about 30% of all musculoskeletal consultations [5,6].

As it has been extensively discussed in this thesis, the mechanisms of healing of injured tendons and enthesis often fail to regenerate the native morphology and mechanical properties of the uninjured tissue. Moreover, patients suffering from tendon and enthesis injury undergo a long and often painful path to recovery [7].

Tendon injuries are currently treated by conservative therapies or surgery with very limited success. Approximately three out of ten patients suffering from tendon or enthesis injuries undergo surgery after failure of conservative therapies. Moreover, some reports indicate that only about 60 % of all restored tendons are functional [7]. All in all, the currently available treatments for tendon and enthesis injuries suffer from significant limitations, ranging from suboptimal healing to the risk of re-injury, and post-operative complications [2,8,9].

The advances in the development and application of tissue engineering strategies aimed to aid the healing of difficult-to-treat tissues hold significant promise for tendon and enthesis healing. In Chapters 2 and 4 of this thesis, we discussed the use of silk as biomaterial to treat tendon and enthesis defects. Silk-based biomaterials, such as silk fibroin, offer remarkable properties that make them ideal for tendon and enthesis healing. Using silk fibroin, it is possible to mimic the extracellular matrix of tendons and tendon-to-bone attachments, while promoting cell adhesion, proliferation, and tissue growth. Moreover, effective tendon healing involves reducing the formation of scar tissue, as excessive scarring can impair tendon function. Silk-based biomaterials, with their ability to guide tissue growth, may help minimize scar formation. This was demonstrated in Chapter 4, where the use of an enthesis-mimetic silk-fibroin scaffold yielded the best healing of an injured patellar enthesis in our rodent model. Furthermore, the use of silk as biomaterial enhances the mechanical properties of the healing tissue, making it more resilient and less prone to re-injury. This could be especially relevant when treating athletes and other patients with high demands on their tendons.

Additionally, in Chapters 5 and 6 we investigated the potential of microRNAs (miRNAs) for tissue engineering applications. miRNA-based therapies allow for the precise regulation of gene and protein expression, which can be crucial in the modulation of the healing response of an injured tissue. In the same way, they can be used to restore lost function or treat diseases. Such potential has encouraged a multitude of miRNA-based therapies targeting a wide range of diseases, some of which have reached clinical trials with promising results, which demonstrates the translational potential of these therapies to the clinic. The LNA-based antagomir Cobomarsen (MRG-106) that targets miR-155, is currently in phase II trials for the treatment of cutaneous T-cell lymphoma and leukaemia [10]. MRG-107, another inhibitor of the miR-155 has alleviated symptoms and extended the survival in preclinical trials of patients suffering from amyotrophic

lateral sclerosis [10]. Moreover, the liposomal formulation of miR-34a known as MRX34 is currently in phase I clinical trial exploring the tumor-suppressing effect of this miRNA for the treatment of a wide range of cancers, including ovarian cancer, colon cancer, cervical cancer, and others [11].

We explored the synergistic effect of a tendon mimetic microenvironment and the modulation of an antifibrotic miRNA to enhance the tenogenic commitment of mesenchymal stem cells with promising results. Thus, giving the first steps towards novel tissue engineering strategies were the combinations of suitable biomaterials with optimized biomimetic morphology and the regulation of gene expression via the modulation of naturally occurring miRNAs brings us closer to the effective healing of tendon-to-bone attachments.

The work summarized in this thesis offers valuable insights into potentially efficient tissue-engineering approaches to aid the healing of the tendon-to-bone enthesis. As the knowledge about the underlying mechanisms of enthesis and tendon healing growths, our understanding of the potential of morphological and molecular cues to aid the process of regeneration increases, opening more opportunities for innovation and the optimization of treatment strategies. Ultimately, offering faster and more effective recovery, minimizing scar tissue formation, and reducing the risk of re-injury of patients suffering from tendon and enthesis injuries.

2 REFERENCES

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