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CORR Insights

CORR Insights®: Combined Administration of ASCs and BMP-12 Promotes an M2 Macrophage Phenotype and Enhances Tendon Healing

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Where Are We Now?

Achieving rapid (less than 6 weeks), near-normal tensile strength with minimal or no adhesions is considered the "holy grail" of tendon healing among hand surgeons. Why? With conventional repair techniques, the tendon generally needs at least 6 weeks to heal and regain its tensile properties for unrestricted activity, and this process is always accompanied by the formation of adhesions between the tendon and the surrounding structures (particularly within the flexor sheaths). Because of this, managing injured flexor tendons remains an unsolved challenge. In the current study, Gelberman and colleagues attempt to accelerate tendon healing by avoiding the inflammatory process and its byproducts, namely adhesions.

Generally, hand surgeons attempt to prevent adhesions through early mobilization. But we must also recognize that inflammation is the essential trigger and coordinator to the entire healing process, and macrophages play a key role in initiating this process [2]. Although modulation of inflammation is an attractive prospect, it may create a ripple effect later in the healing process, resulting in poor tensile strength in the repaired tendon.

New approaches have emerged [4, 5, 7], which can be divided into three broad categories: (1) Mechanical strategies, (2) biological manipulation of adhesions, and (3) tissue engineering.

Mechanical Strategies

The mechanical approach involves achieving strong repairs that can withstand early or immediate mobilization. Recently, we have seen an evolution in repairing tendons with an increased number of core sutures (six strand repairs) [7], and the development of strong suture materials with high tensile strength. Although such materials themselves may withstand high degrees of longitudinal forces (that is, less breakage), such materials may cut through the tendon substance, with similar or higher likelihood of pull-out, resulting in failure [4].

Biological Manipulations

The goal of the biological approach is to prevent adhesions without adversely

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affecting healing or the ultimate strength. Topical 5-fluorouracil can reduce adhesions and improve functional outcomes live-animal models [5, 6]. We have seen immediate improvement in gliding properties of repaired tendons in cadaveric or ex-vivo models with various tribologic (lubricating) agents such as hyaluronic acid. These observations may not translate into similar benefits in vivo, as they do not take into account agent dispersal from the site and the ongoing process of adhesion formation [1, 9].

Tissue Engineering

The third approach, tissue engineering, involves the use scaffolds that support cellular colonization, in combination with growth factors and pluripotent stem cells that hasten the process of healing [10, 12]. Although most of these approaches are in experimental stages, tissue engineering may provide an alternate route to achieving functional healing while bypassing the inflammatory process.

The study by Gelberman and colleagues principally employed the tissue engineering approach.

Where Do We Need To Go?

A number of studies involving biomolecule delivery have shown improved cellularity or fibroblastic proliferation with βFGF, VEGF, PDGF, TGFβ, and stem cells in early phases of healing [3]. However, to my knowledge, none have demonstrated early attainment of tensile strength.

In order to restore structural continuity and tensile strength of the tendon, and ultimately return to function, hand surgeons should move away from using sutures to hold the tissue together until the body fills the gap with scars (tendon healing), and instead move towards in-vivo tendon engineering, where the use of biomaterials and cellular elements provide the opportunity to rapidly "construct" new tendon tissue at the site of injury without going through the entire process of scar formation.

Current research in tissue engineering is focused on building scaffolds, such as electrospun polylactic acid and polyglycolic acid. Researchers are attempting to create highly-aligned surfaces that can receive stem-cells or tenocytes so as to create a living bridge while bypassing the normal healing process and the time required for fibroblastic proliferation and migration [8, 11, 12].

However, the function of the tendon relies on the strength of this bridge, and not its cellular characteristics. Can the scaffold withstand the functional demands generated during active motion and grip? The scaffold itself may have high tensile strength, but its anchorage to the tendon again relies on conventional sutures. Future experimental studies should simultaneously address the issues of tensile-strength of the scaffolds and the reliability of the tendon-scaffold interfaces these would, provide the necessary conditions for achieving immediate motion.

How Do We Get There?

In order to gain immediate return to activity after a tendon injury, researchers investigating tissue engineering must first consider examining strong biomaterials that have the characteristics to receive cellular elements while inducing minimal inflammatory response. Additionally, research in this area should consider the tendon-scaffold interface, focusing on the development of surface features such as nano-anchors, which provide a high degree of anchorage at the fibril level, as opposed to sutures, whose strength relies entirely on the tendon substance itself.

Research on manipulation of the biological process of healing, like the current study, is key to the ultimate goal of rapid tendon healing. The research in this area should be aimed towards detailed and precise mapping of quantitative and temporal fluctuation of the numerous biomolecular

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agents that lead to the highly-regulated inflammatory, proliferative, and remodeling phases of tendon healing. Based on this understanding, advanced in-vivo delivery systems should be designed to deliver biomolecules or cells in a phasic manner, with the aim to either hasten or leapfrog one or more steps in the complex healing process.

Beyond tissue engineering, gene-delivery and controlled regeneration of adult tissue are the next frontier in improving the healing of injured flexor tendons.

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