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EDITORIAL

Tissue engineering: use of scaffolds for ligament and tendon healing and regeneration

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The field of Tissue Engineering has experienced exponential growth since its inception a little more than 20 years ago. In 1987, a small number of bioengineers were invited by the US National Science Foundation (yours truly was fortunate enough to be included) to discuss an emerging concept of combining biology and engineering to appropriately address the structure and function relationship of biological tissues. At that meeting, the term "tissue engineering" was coined by Professor Y. C. Fung of the University of California, San Diego in La Jolla, CA, USA. The first "Tissue Engineering" workshop was then organized and was held in the following year in Lake Tahoe, CA, USA. A number of biologists and bioengineers sat together for 4 days and the discussion centered on vascular endothelial cell technology, skin and connective tissue, implants, musculoskeletal system and orthopaedic surgery, artificial organs, the nervous system, the hematopoietic system, and mathematical modeling [10].

Since then, the field of Tissue Engineering has attracted many players. During the last 3 or 4 years, not a month went by without a major tissue engineering conference around the world. At present, this field has evolved and can be represented by a triad of cells, bioactive molecules (growth factors and cytokines), and scaffolds. The purpose of the latter two is to encourage the cells to proliferate rapidly and to synthesize proteins vigorously. The work on scaffolds, especially bioscaffolds, actually came later, but its importance as a structural support has now been well recognized, and more and more innovations are being made each day.

Thus, reading the manuscript by Iwasa, Engebretsen, Shima and Ochi on "Clinical application of scaffolds for cartilage tissue engineering" and its positive view of scaffolds being as effective as conventional ACI treatment in the current issue of *KSSTA* helps us to realize the potential of these new and exciting approaches, and that is why there are loads of enthusiasm on scaffolds over the last decade. I would like to further encourage the readers to examine a recent review paper on bilayer scaffolds designed for osteochondral tissue engineering [8]. There, the current status of synthetic polymers [such as poly (lactic acid) (PLA) and poly (glycolic acid) (PGA)], and bioceramics [hydroxyl carbonate apatite (HCA)], were beautifully reviewed. In addition, three strategies for osteochondral healing and regeneration were presented, and they are (1) chondrocytes or neo-cartilage tissue (scaffold free) seeded directly onto a bone scaffold base; (2) assembled bilayered scaffolds consisting of distinct cartilage and bone scaffolds joined (or assembled) together either before or during surgical implantations, and (3) integrated bilayered scaffolds of two uniquely different segments amalgamated together via the integration of a mutual material common to both layers.

In the tendon and ligament area, much interest has been given to the use of bioactive molecules including hyaluronic acid (HA), EGF, TGF-beta; and more recently, the ubiquitous platelet rich plasma (PRP) matrices for applications in orthopaedic sports medicine. PRPs have been used to enhance the healing of Achilles tendon tears [9] as well as muscle injuries [2]. The potential of these bioactive molecules has renewed the interest of using them for anterior cruciate ligament (ACL) healing and regeneration. Early works using HA, bFGF, collagen gel with platelet rich plasma (C-PRP) as well as stem cells to heal central ACL

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defects have been reported. All have shown an increased vascularity, increased tissue formation as well as improvements in some of its biomechanical properties. More recently, Murray and co-workers [7] have pioneered the application of C-PRP to aid in the healing of a surgically transected and repaired ACL in a porcine model. These authors found hypertrophic neo-tissue formation as well as increased tensile stiffness and ultimate load following C-PRP treatment. In light of these findings, continued efforts in improving the outcome in the long-term are being made.

However, there is less information available on the positive effects of bioscaffolds on ligament and tendon healing and regeneration. A mesenchymal stem cell (MSC) seeded type I collagen sponge has been used to improve the healing of patellar tendon (PT) injury in a rabbit model [1]. Mechanically stimulating these constructs in bioreactors before implantation was found to further enhance the biomechanical properties of the neo-PT tissues.

In our research center, we have chosen an extracellular matrix bioscaffold, namely, the porcine small intestine submucosa (SIS), to enhance the healing of central third defect of the rabbit PT. We found a 68% increase in neo-PT formation at 12 weeks and a doubling of its stiffness and ultimate load over those untreated [5]. In another study, when one layer of porcine SIS (200-μm thick) was used to treat a 6 mm gap of the medial collateral ligament (MCL), it could limit the hypertrophy of the neo-tissue and improve its tissue quality (the mechanical properties) by the formation of larger collagen fibrils with a concomitant reduction of collagen V/I ratio as well as changes in levels of small leucine rich proteins closer to normal MCL [6].

The success of this approach had prompted us to combine this ECM-bioscaffold with an SIS hydrogel to heal a surgically transected and repaired goat ACL [3]. At 12 weeks, we found a restored ACL with continuous neo-tissue. Its cross-sectional area and shape were similar to those of the sham-operated ACL. Morphologically, its collagen fibers were aligned with spindle shaped fibroblasts. Functionally, the ECM treated ACL could reduce the anterior–posterior knee instability while its in situ forces were similar to the control ACL. Further, its tensile stiffness reached approximately 50% of the normal ACL, which was comparable to the results of ACL reconstruction. The fact that we were using the SIS from genetically modified α gal-deficient pigs is also important; as it would not incite marked immunological reaction in humans thus largely eliminate the immunological issues of porcine SIS in clinical applications. These are indeed exciting results that give us significant confidence on the potential of this approach. As such, additional studies on making even better ECM scaffolds as well as designing new vehicles to control release of growth factors for longer lasting effects for better ACL healing and remodeling are warranted.

On the horizon, there is yet another exciting aspect of scaffolds, namely, biodegradable metallic materials, e.g., porous magnesium or magnesium oxide [4]. The potential advantages of these "smart" scaffolds include their initial stiffness and controllable degradation rate as they are replaced by the tissue. They could also be protein-coated for better tissue integration and control release of growth factors and cytokines to sustain tissue healing as well as to guide tissue regeneration. Clearly, its potential application will include ligament and tendon insertions to bone. Indeed, the complexity of designing and using biomimetic scaffolds will require multidisciplinary efforts and close collaboration of engineers, life scientists, cellular and molecular biologists, morphologists as well as surgeons. Together, we will come up with the right strategies so that they could be appropriately used to restore, regenerate and maintain tissue function.

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