Tendon-like Electrospun PLGA Scaffolds with Optimized Physical Cues Induced Tenogenic Differentiation and Boosted Immunomodulatory Properties on Amniotic Epithelial Stem Cells.

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Introduction: The advanced strategies in the field of Tissue Engineering might render possible overcoming the unsatisfactory results of conventional treatments to deal with tendinopathies. In this context, the design of tendon biomimetic electrospun scaffolds engineered with Amniotic Epithelial Stem Cells (AECs), which have shown a high teno-regenerative and immunomodulatory potential in tendon-defect models, can represent a promising solution for tendon regeneration.

Methods: Poly(lactide-co-glycolic) acid (PLGA) scaffolds were fabricated using the electrospinning technique to mimic the native tendon biomechanics and extracellular matrix by optimizing: fiber alignment and diameter size (1.27 and 2.5 μm), and surface chemistry using the Cold Atmospheric Plasma (CAP) Technique. Moreover, the teno-inductive and immunomodulatory effects of these parameters on AECs have been also assessed.

Results: The fabricated PLGA scaffolds with highly aligned fibers and small diameter size (1.27 μm) induced a stepwise tenogenic differentiation on AECs with an early epithelial-mesenchymal transition (EMT), followed by their tenogenic differentiation. Indeed, SCX, an early tendon marker, was significantly more efficiently translated into the downstream effector TNMD, a mature tendon marker. Moreover, 1.27 μm fiber diameter induced on AECs a higher expression of anti-inflammatory interleukin mRNAs (*IL-4* and *IL-10*). The CAP treated PLGA scaffolds showed an improved cell adhesion and infiltration without altering their topological structure and teno-inductive properties. In fact, AECs engineered with CAP treated fibers, expressed in their cytoplasm TNMD. Moreover, CAP treatment did not alter the mechanical properties of PLGA scaffolds.

Conclusions: The developed electrospun PLGA scaffolds with the optimized features represent an ideal tendon-like construct that could be applied in in-vivo models to evaluate their biosafety and teno-regenerative potential.