Decellularized Placental Biomaterials for Management and Protection of Tendon Injuries

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STATEMENT OF PURPOSE:

Tendon injuries present significant clinical challenges, often leading to prolonged rehabilitation and compromised functional outcomes. Despite advancements in surgical techniques and rehabilitation protocols, managing tendon injuries remains a formidable task for clinicians. Current treatment modalities frequently fall short of fully restoring tendon function, underscoring the urgent need for innovative approaches in tendon repair. Decellularized placental biomaterials have emerged as a novel therapeutic option for tissue repair and regeneration, harnessing the regenerative potential of placental tissues while mitigating immunogenicity and promoting tissue integration. The decellularized placental tissue matrix can be derived from the entire placental connective tissue or specific tissues, such as umbilical cord tissue. The resulting matrix can take various formats (e.g., particulate, flowable) for diverse application purposes. The impact of these differences on the interaction between the tissue matrix and cells remains unknown. This work explores the application of various decellularized placental biomaterials, including connective tissue matrix (CTM) and umbilical cord matrix (UCM), in tendon management both in vitro and in vivo. The focus is on assessing their biomechanical properties, immunomodulatory effects, and preclinical outcomes to advance our understanding of their potential in tendon repair. We hypothesize that decellularized placental biomaterials, CTM and UCM, provide a suitable matrix for tendon management and healing.

METHODS:

Three human placental biomaterials were selected for comparison: (1) a minimally manipulated non-viable cellular particulate (MM-CTM); (2) a liquid matrix (L-CTM); and (3) a decellularized flowable CTM (DF-CTM). Outcome variables included tenocyte adhesion, proliferation, migration, phenotype maintenance, and inflammatory response. Adhesion and proliferation were evaluated using cell viability assays and tenocyte migration using a transwell migration assay. Gene expression of tenocyte markers and pro-inflammatory markers were assessed using quantitative polymerase chain reaction. Phenotypic markers included scleraxis (SCX), tenascin-C (TNC), type I collagen (COL1A1), type III collagen (COL3A1), and decorin (DCN). Inflammatory markers included interleukin 8 (CXCL8), tumor necrosis factor α (TNF- α), transforming growth factor beta 1 (TGFβ1) and beta 3 (TGFβ3), and matrix metallopeptidase 1 (MMP1). Additionally, a decellularized, umbilical cord derived matrix (UCM) was evaluated in vitro for tenocyte proliferation and phenotype maintenance. The sheet format of UCM and its barrier properties compared to CTM flowable, made it an ideal choice for testing in vivo. Using a rabbit Achilles partial tenotomy model for tendon healing UCM was compared to a predicate at both 4 and 10 weeks. The UCM was also evaluated in an infraspinatus and patellar stab wound insult model in purpose-bred research beagles 3 months post application.

SUMMARY OF RESULTS:

Although MM-CTM supported significantly more tenocyte adhesion than DF-CTM ($p = 0.004$), tenocyte proliferation was significantly higher on DF-CTM than MM-CTM and L-CTM ($p < 0.001$). Unlike MM-CTM, tenocyte migration was higher for DF-CTM than the control ($p = 0.005$). In tenocytes cultured on DF-CTM, gene expressions (SCX, TNC, COL1A1, and COL3A1) significantly increased over time ($p < 0.001$). Conversely, in tenocytes cultured on MM-CTM, gene expressions remained unchanged (SCX and TNC, $p \geq 0.102$) or significantly decreased over time (COL1A1 and COL3A1, $p \leq 0.018$). DCN expression increased over time for both CTMs ($p < 0.001$). Compared with MM-CTM, DF-CTM diminished the effects of TNF-α, significantly reducing the expression of CXCL8 ($p = 0.024$) and MMP1 ($p < 0.001$). Over time, tenocytes cultured on MM-CTM promoted the expression of CXCL8 and MMP1, while DF-CTM promoted the expression of antifibrotic growth factor TGFβ3. Therefore, of the three forms of CTMs, DF-CTM appeared to best support the functionalities of tenocytes. In the rabbit Achilles model, the findings revealed substantial equivalence between the decellularized UCM and the reference bovine collagen matrix. This was evident in terms of immature and mature tendon fibers at both the 4- and 10-week timepoints, indicating an active and healthy repair process. Furthermore, histological analysis demonstrated substantial equivalence in the extent of tissue attachments between the decellularized UCM and the reference. The observed more advanced degradation and reduced macroscopic tissue attachments in the decellularized UCM treated group suggest a trend towards more advanced healing in animals receiving this treatment. The study in the infraspinatus and patellar stab models showed complete incorporation of the UCM three months post-implantation (Figure 1). Additionally, histological examination showed a mostly absent or mild/moderate inflammatory response (Figure 2), foreign body reaction, and tissue attachment.

During the in vitro evaluation of decellularized placental biomaterials, CTM interacted more favorably with human tenocytes as evidenced by significantly higher tenocyte proliferation, significantly better maintenance of tenocyte phenotype, and a significantly attenuated inflammatory response. Furthermore, in vitro evaluation of UCM showed enhanced tenocyte attachment, growth, and phenotype maintenance. In vivo evaluation in two clinically relevant models demonstrated more advanced healing in the UCM treated group, and complete incorporation of UCM into the tendon, within 3 months post implantation. This data indicates that human placental decellularized biomaterials represent an emerging promising matrix suitable for tendon management and healing.

CONCLUSION:

The favorable interaction observed between cells and decellularized placental tissue matrix (CTM and UCM), both in vitro and in vivo, highlights the promising potential of advanced placental biomaterials in tendon repair. A thorough evaluation of the current state of tendon repair and the drawback of existing methods emphasizes the critical requirement for clinical studies of innovative interventions to enhance clinical outcomes and patient satisfaction.

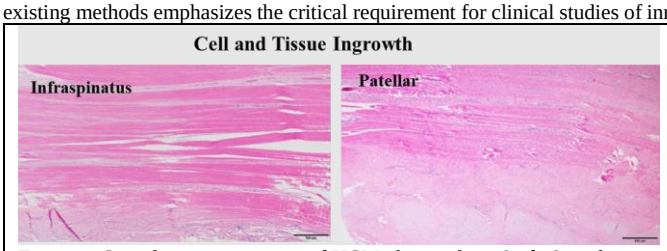

Figure 1. Complete incorporation of UCM observed in 18 of 18 tendon defects in an infraspinatus and patellar stab wound insult model

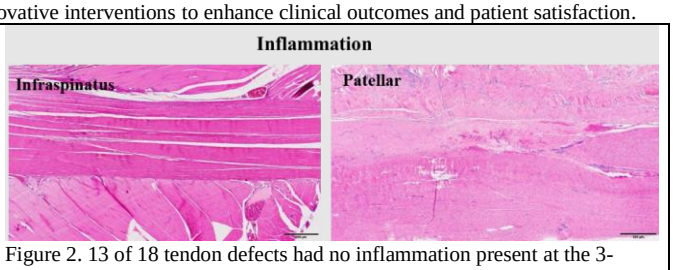

Figure 2. 13 of 18 tendon defects had no inflammation present at the 3-month time point with UCM; 5 of 18 had a mild/moderate inflammation score. Average score: 0.39 (1=Mild inflammation score)

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