Engineering a tendon extracellular matrix-functionalized elastomer scaffold for effective repair of large-to-massive tendon defects

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INTRODUCTION: A significant clinical challenge in large rotator cuff tendon injuries is the need to sustain high mechanical demands in spite of limited tissue regeneration, which often leads to high retear rates and long-term functional deficiencies [1]. Hence, the goal of our study is to design and fabricate a bioactive, mechanically competent hybrid scaffold that is specially intended for repair of large-to-massive tendon defect.

METHODS: We have developed tendon extracellular matrix (tECM)-hybrid scaffold, called Teno-HyS, a unique hybrid core-shell biomaterial that: (i) uses the ECM's rich biocomplexity for tissue-specific regeneration via bioactive, urea-extracted tECM and (ii) mimics the physical attributes of native tendon to sustain long-term physiological loading via a mechanically robust, slow degradation polyurethane elastomer (Fig. 1A). A comprehensive assessment approach was applied, including: (i) *ex vivo* characterization of hybrid construct bonding integrity and mechanical property; (ii) *in vitro* cytocompatibility, proliferation, and tenogenic differentiation of human adipose-derived stem cells (hASCs) encapsulated in Teno-HyS; (iii) *in vivo* evaluation of the Teno-HyS biocompatibility in mice; (iv) and tendon healing efficacy of Teno-HyS on large-to-massive rotator cuff tendon defects in both rats and rabbits.

RESULTS: Comprehensive assessments revealed outstanding performance of Teno-HyS, characterized by robust core-shell interfacial bonding (Fig. 1B-C), outstanding suture retention (Fig. 1D), human rotator cuff tendon-like mechanical properties (Fig. 1E), cytocompatibility (Fig. 1F, G), promoting tendon differentiation of human adipose-derived stem cells (Fig. H, I). Importantly, *in vivo* study demonstrated that Teno-HyS is biocompatible (Fig. 1J). When being applied in large-to-massive tendon defect models, Teno-HyS did not show any breakage or ruptures during entire tendon healing process and induced noteworthy tendon healing, including accelerated recovery of rat gait performance, and > 1 cm rabbit tendon regeneration with wavy, aligned collagen matrix and tendon-like biomechanical features (Fig. 1K).

DISCUSSION: Our Teno-HyS scaffold demonstrates high potential for efficient repair of large-to-massive tendon defects. Future study will focus on identification of the underlying mechanism and further validation of the Teno-HyS scaffold in larger, more clinically relevant animal models.

SIGNIFICANCE/CLINICAL RELEVANCE: Our findings offer a synergistic strategy to overcome the limitations of spontaneous regeneration and meet the stringent mechanical requirements, particularly in the treatment of large-to-massive tendon defects. Our synergistic strategy may change the clinical notion that certain large-to-massive rotator cuff tears are irreparable, and the technical advances reported here can be broadly applied towards regenerating difficult-to-heal, load-bearing musculoskeletal and non-musculoskeletal tissues.

REFERENCES: [1] Shearn J T et al. JMNI, 11 (2), 163, 73, 2011; [2] Ker D F et al. Adv, Funct, Mater, 28, 1707107, 2018.

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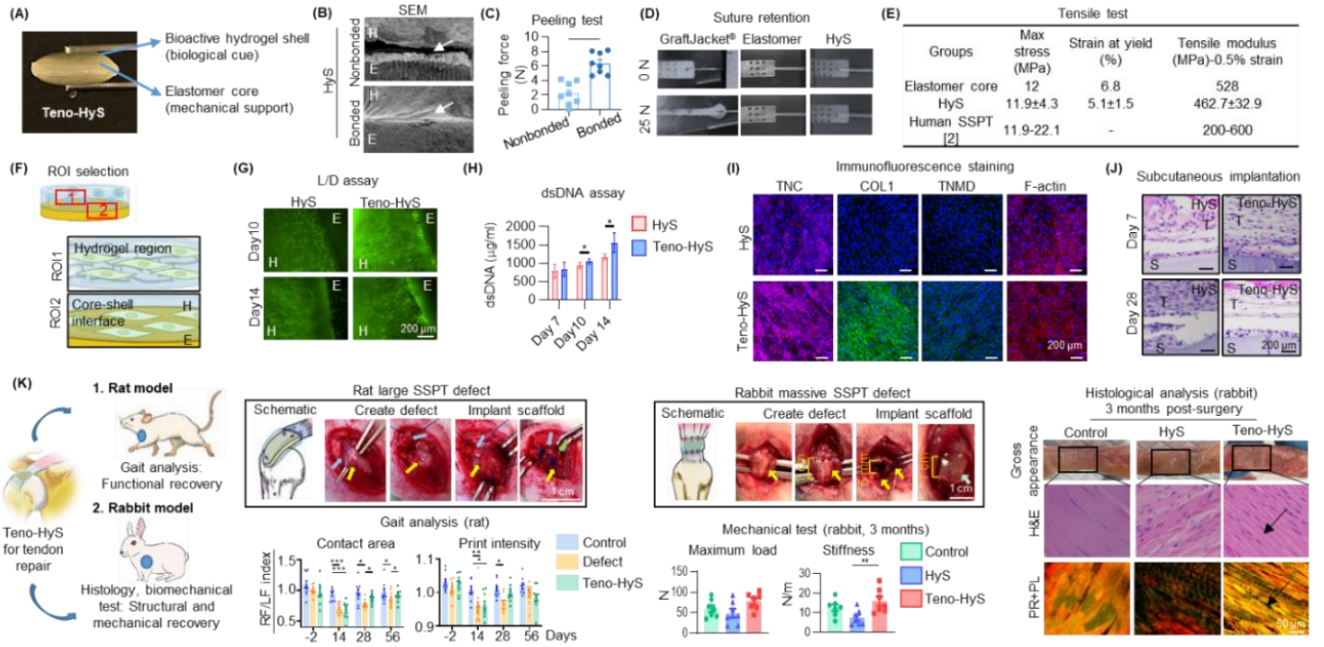

Fig. 1. Characterization for Teno-HyS tendon healing efficacy. (A) Schematic diagram. **(B-C)** SEM (n=3; E: elastomer core, H: hydrogel) and 90°-peeling test. **(D-E)** Suture retention test (n=7) and mechanical test (n=7). **(F-I)** hASCs in Teno-HyS exhibited high viability as well as enhanced proliferation and tenogenic differentiation (n=3). **(J)** HyS and Teno-HyS demonstrated biocompatibility in mice (n=3; T: tissue, S: scaffold). **(K)** Teno-HyS induced comparable gait performance with the intact control groups in a rat large SSPT defect model (n=10), and over 1 cm tendon-like tissue regeneration with robust biomechanical strength in a rabbit massive rotator cuff tendon defect model (PR: picrosirius red; PL: polarized light). mean ± SEM; * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.