STEM CELLS

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Stepwise Differentiation of Human Embryonic Stem Cells Promotes Tendon Regeneration by Secreting Fetal Tendon Matrix and Differentiation Factors

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Introduction

Ligaments and tendons (T/L) are frequently damaged during sports and other rigorous activities. It is well known that T/L do not heal by a regenerative process; instead, their healing occurs via the formation of a fibrotic scar and causes significant dysfunction and disability. Clearly, better alternative methods need to be developed.

Human embryonic stem cells (hESCs) are ideal seed cells for tissue regeneration, but no research has yet been reported concerning their potential for tendon regeneration. This study investigated the strategy and efficacy of using hESCs for tendon regeneration as well as the mechanism involved.

Materials and methods

Isolation and characterization of MSC derived from ESC

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Construct of hESC-MSC-engineered tendon *in vitro* under static mechanical stress

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In vivo remodeling of *in vitro* engineered tendons

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Rat tendon repair model

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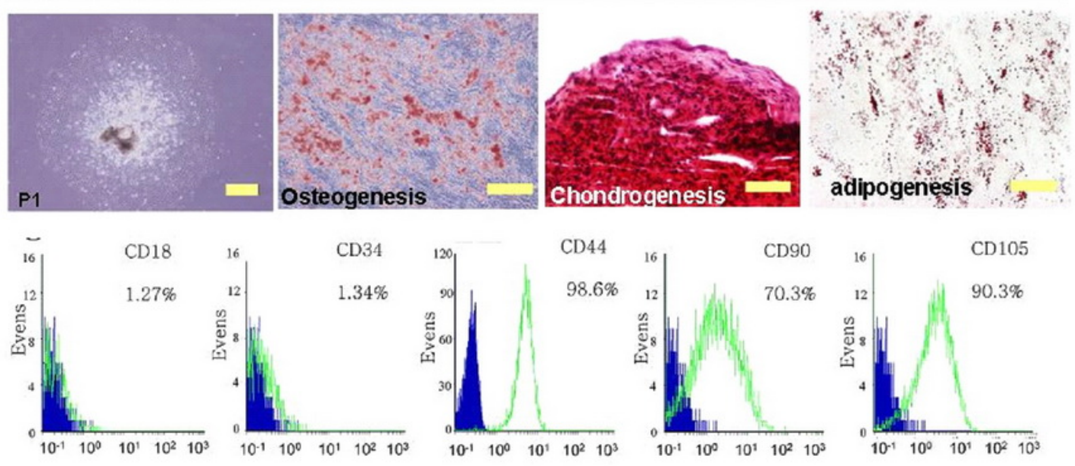
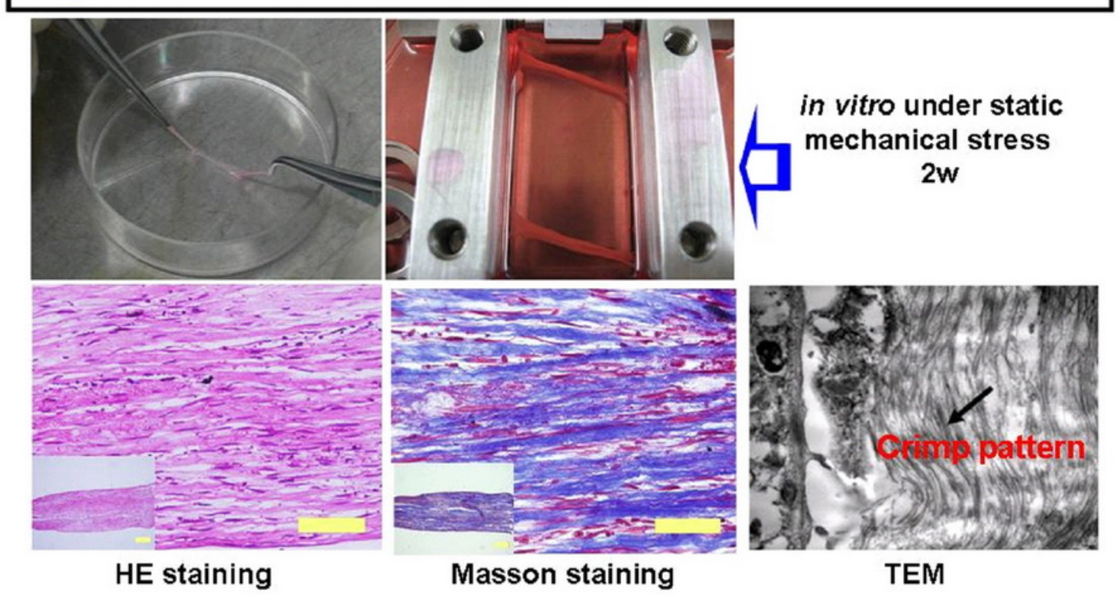
In situ molecular imaging
Histological examination and Masson trichrome staining
RT-PCR
Mechanical testing
Determination of the collagen content of repaired tendons
Transmission electron microscopy (TEM)

Results

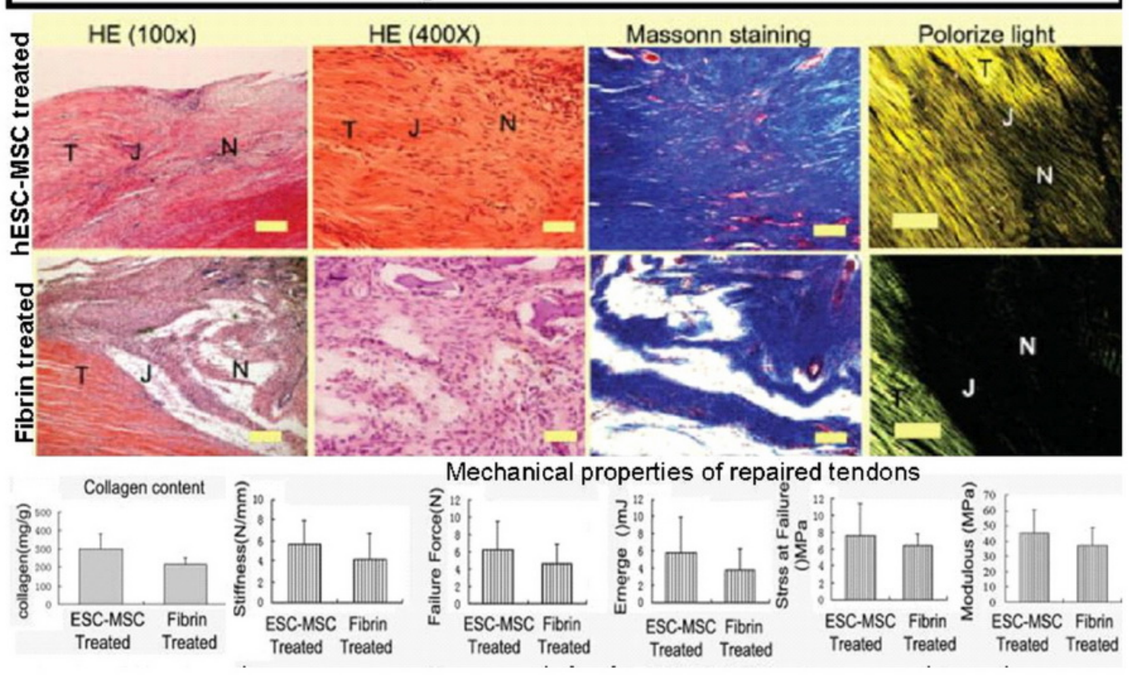
Stage I. Isolation and characterization of MSC derived from ESC)

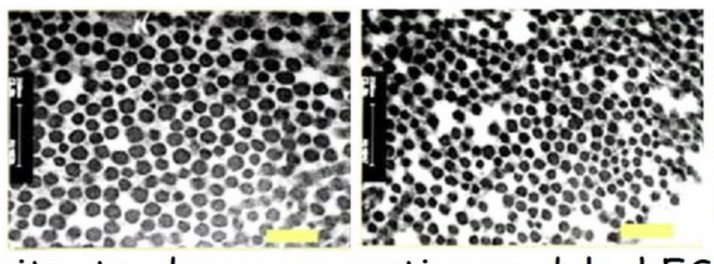


Stage II. hESC-MSC formed tendon-like tissues *in vitro* with mechanical stress



Stage III. Tendon regeneration in a partial-defect model in the patellar tendon of a rat at 4 weeks

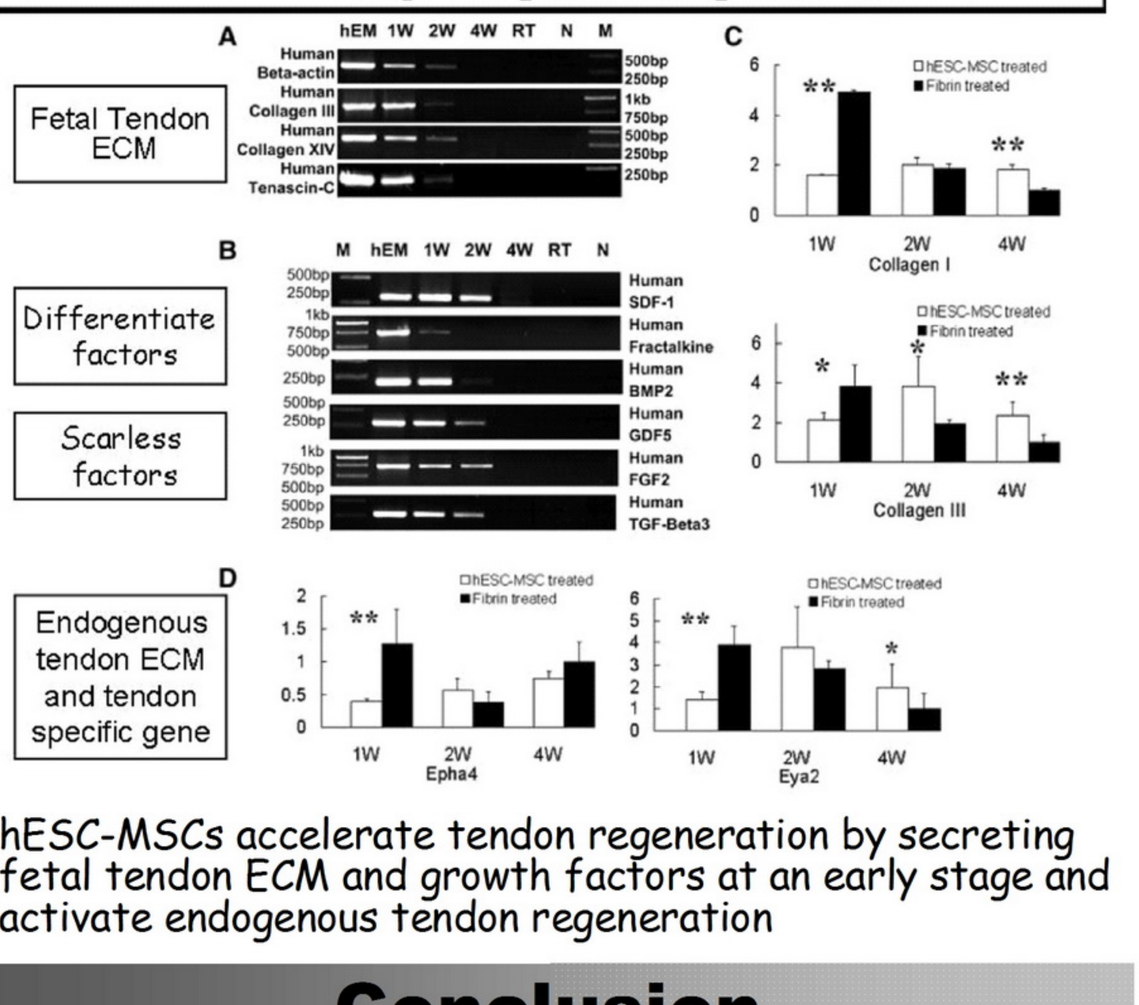




Ultrastructure and histogram of collagen fiber diameters of hESC-MSC-treated (right) are larger than fibrin-treated (left) tendons.

In in situ tendon regeneration models, hESC-MSCs improved tendon regeneration both structurally and functionally.

Stage V. To investigate the roles of hESC–MSCs in improving tendon regeneration



hESC-MSCs accelerate tendon regeneration by secreting fetal tendon ECM and growth factors at an early stage and activate endogenous tendon regeneration

Conclusion

The present study demonstrated that hESCs improve tendon regeneration after stepwise differentiation from hESCs to tenocytes through a MSC transmission stage. Our results suggest that the progenitor cells derived from hESCs promote tendon regeneration by both acting as seed cells and as paracrine biological factors to initiate tendon regeneration. It is highly likely that the novel platform with hESC-derived MSCs has implications for the development of new therapeutic applications for tendon repair.

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