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Institutionen för klinisk vetenskap, intervention och teknik

Enheten för öron-, näs- och halssjukdomar

Restoration of Scarred Vocal Folds with Stem Cell Implantation - Analyses in a Xenograft Model

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ABSTRACT

Background: Tissue defects in the vocal fold (VF) caused by trauma, surgical procedures, post radiotherapy often heal with scar formation. The scar tissue causes stiffness of the lamina propria rendering disturbed viscoelastic properties to the VF. A scarred VF causes severe voice problems. Treatment is difficult and presently there is no treatment that heals VF scars.

Objectives: The aims of this thesis were to evaluate if human stem cell transplantations have the potential to heal scarred VFs, and if transplanted stem cells regenerate lost tissue in scarred VFs.

Study Design: Experimental xenograft model.

Methods: The VFs of New Zealand rabbits were scarred by a 1.5–2 mm resection. Human embryonic (hESCs) or mesenchymal (hMSCs) stem cells were thereafter transplanted into the VFs. Analyses for grade of scaring, lamina propria (Lp) thickness, relative content of collagen type I, elastic and dynamic viscoelasticity (G', η'), fluorescence in situ hybridisation for detection of human cells, Verhoeff staining for detection of elastin, alcian blue staining for detection of hyaluronic acid, RT-PCR species-specific analysis for collagen type I, and for Nanog expression of pluripotency were performed.

Results: Both transplanted hESCs (G')(η') and hMSCs (G') significantly improved the viscoelastic properties of the VFs, analyzed at one month. HMSCs also significantly reduced collagen type I content. At three months hMSC treatment significantly reduced both (G') (η') and showed no significant differences to normal VFs. Also collagen type I content and Lp thickness were significantly reduced and were not significantly higher than in normal VFs. A clinic like setting was studied, where VFs were resected and left to spontaneously heal for 9 weeks. The established scar was thereafter excised, hMSCs transplanted in the wound, and the VFs were analyzed after another ten weeks. The hMSC transplanted VFs showed no significant difference in η', nor in G', nor in Lp-thickness compared to normal VFs, and all three parameters were significantly reduced compared with untreated scarred VFs.

The transplanted hESCs showed after one month, by differentiation, regeneration of epithelium, muscle, cartilage and gland tissue in contact with corresponding rabbit native tissue. HMSCs did not differentiate or regenerate tissue. Pluripotent hESCs were shown to survive one month, and hMSCs survived four but not ten weeks in the rabbit VFs. The transplanted VFs showed no malignancy or teratoma formation.

The immunosuppressant Tacrolimus used to reduce the host versus graft reaction suppressed the anti-scaring effect of the transplanted hMSCs.

Conclusion: Both human embryonic and mesenchymal stem cells have the potential to improve healing and to restore the rheological properties of scarred VFs. Human embryonic stem cells transplanted into scarred rabbit vocal folds differentiate and regenerate human tissue compatible with the surrounding native tissue.

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