Göteborg, 2024

Uterine Tissue Engineering

Translational approaches using animal models

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i sal 2119 Hus 2, Hälsovetarbacken, Arvid Wallgrens backe 5, fredagen den 19 januari 2024, kl. 13:00

av **Edina Sehic**

Fakultetsopponent:

Prof. Claus Yding Andersen

Institute of Clinical Medicine, Faculty of Health and Medical Science, University of Copenhagen, Copenhagen, Denmark

Avhandlingen baseras på följande delarbeten

I. **Sehic E,** Thorén E, Gudmundsdottir I, Oltean M, Brännström M, Hellström M. **Mesenchymal stem cells establish a pro-regenerative immune milieu after decellularized rat uterus tissue transplantation**. *Journal of Tissue Engineering*. 2022;13. doi:10.1177/20417314221118858

II. **Sehic E**, Miguel-Gómez L, Rabe H, Thorén E, Gudmundsdottir I ,Oltean M, Brännström M, Hellström M. **Transplantation of a bioengineered tissue patch promotes uterine repair in the sheep**. *Submitted to Acta Biomaterialia*

III. **Sehic E**, Miguel-Gómez L, Thorén E, Sameus J, Bäckdahl H, Oltean M, Brännström M, Hellström M. **Decellularization and enzymatic preconditioning of bovine uterus for improved recellularization**. *Submitted to Translational Medicine Communications*

IV. Miguel-Gómez L, **Sehic E**, Rabe H, Thorén E, Ahlström J, Oltean M, Brännström M, Hellström M. **Towards uterus tissue engineering: a standardized cross-species decellularization protocol exemplified with the baboon uterus**. *In manuscript*

SAHLGRENSKA AKADEMIN
INSTITUTIONEN FÖR KLINISKA VETENSKAPER

GÖTEBORGS UNIVERSITET

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Uterine Tissue Engineering

Translational approaches using animal models

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Abstract

Recent advancements, such as uterus transplantation (UTx), have led to groundbreaking solutions for complete uterine dysfunction. Yet, there are inherent risks and limitations, including challenges of sourcing compatible donor organs and potential post-transplantation complications. These limitations underscore the need for innovative approaches that can improve infertility treatments while mitigating these risks.

This thesis describes the development of bioengineering techniques for patient-specific uterine tissue segments with regenerative potential. Our approach was centered on utilizing modified uterine tissue as a scaffold to facilitate the reconstruction of defective uterine tissue. While these techniques are still experimental and require optimization and safety evaluation, our work concentrated on translating well-established scaffold production protocols from small to large animal models, including the rat, sheep, cow, and the clinically relevant non-human primate (baboon). Results showed that our established sheep decellularization protocol was feasible in the larger cow and baboon tissue, with effective removal of cellular content without excessive damage to the extracellular matrix (ECM). Furthermore, we conducted *in vivo* experiments in both the rat and the sheep model to evaluate the feasibility of our biomaterial together with mesenchymal stem cells (MSCs). It is crucial to understand the regenerative processes after transplantation, particularly the involvement of the immune response, which plays a pivotal role in the success or failure of biomaterial integration. Results from the in vivo studies highlight the pro-regenerative effect of MSCs when combined with our biomaterial in the rat model. In addition, the same effect from MSCs was not observed in the sheep model, but instead, T-cell subpopulations seemed to play an important role in the transplantation outcomes.

In conclusion, this thesis demonstrates that our scaffold generation protocols are translational and applicable with minor adjustments to different large animal models, which facilitates clinical translations and scientific conclusions. Moreover, we evaluated the feasibility of transplanting larger grafts into both a small and large animal model, where we also gained essential and novel insights into the immune response following transplantation of tissue-engineered uterine grafts. The collective knowledge gained through these efforts not only contributes to the growing field of regenerative medicine but also to the development of clinically applicable products to treat uterus-related infertility.

Keywords: tissue engineering, female infertility, translational models, rat, sheep, cow, baboon, uterus

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