Göteborg, 2021

Tissue engineering for novel female infertility treatments: Studies on small and large animal models

AKADEMISK AVHANDLING
Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i sal 2119 på Hälsovetarbacken, Arvid Wallgrens backe 5, fredagen den 2021-03-26, klockan 13:00.

av **Arvind Manikantan Padma**

Fakultetsopponent: **Prof. Pedro M Baptista**, Fundación Instituto de Investigación Sanitaria Aragón, Zaragoza, Spanien

Avhandlingen baseras på följande delarbeten

I. **Padma AM**, Alshaikh AB, Song MJ, Akouri R, Oltean M, Brännström M, Hellström M. Decellularization protocol-dependent DAMPs in rat uterus scaffolds differentially activate the immune response after transplantation. J Tissue Eng Regen Med. *Under revision*.

II. Tiemann TT, **Padma AM**, Sehic E, Backdähl H, Oltean M, Song MJ, Brännström M, Hellström M. Towards uterus tissue engineering: a comparative study of sheep uterus decellularisation. Mol Hum Reprod. 2020;26(3):167-78.

III. **Padma AM**, Carrière L, Krokström-Karlsson F, Sehic E, Bandstein S, Tiemann TT, Olten M, Song MJ, Brännström M, Hellström M. Towards a bioengineered uterus: bioactive sheep uterus scaffolds are effectively recellularized by enzymatic preconditioning. NPJ Regenerative Medicine. *Under revision*.

IV. **Padma AM**, Truong M, Jar-Allah T, Song MJ, Oltean M, Brännström M, Hellström M. The development of an extended normothermic ex vivo reperfusion model of the sheep uterus to evaluate organ quality after cold ischemia in relation to uterus transplantation. Acta Obstet Gynecol Scand. 2019;98(9):1127-38.

SAHLGRENSKA AKADEMIN
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Arvind Manikantan Padma

Avdelningen för obstetrik och gynekologi, Institutionen av kliniska vetenskaper, Sahlgrenska akademin, Göteborgs universitet, Sverige, 2021.

Abstract

Introduction: As with any transplantation (Tx) procedure, uterus Tx is associated with risky donor surgery and adverse side-effects from immunosuppression. With the aim to bypass these risks, this thesis investigated uterus tissue engineering strategies and the potential to develop a patient-specific uterus graft to replace the need for donor surgery and immunosuppression. A translational approach for uterus scaffold production through a process called decellularization (DC) is addressed using the rat and the sheep animal model. The immunological events following engraftment of rat uterus scaffolds was also evaluated. The thesis also assessed cellular reconstruction techniques and perfusion bioreactor protocols that can be useful to recellularize whole sheep uterus scaffolds for future uterus Tx studies.

Methods: The immune response towards three different rat uterus scaffold types were evaluated after transplantation by quantifying infiltrating leucocytes and the expression of pro-inflammatory cytokines. Additionally, three novel whole sheep uterus scaffolds were produced by DC and the scaffold composition, bioactivity, mechanical strength and ability to support seeded stem cells were analyzed. Technique optimization for a perfusion bioreactor was also conducted using normal sheep uterus and a specialized perfusion medium.

Results and conclusions: In *Paper I*, we deciphered DC protocol-dependent differences in the immune response following engraftment. A mild, yet effective DC protocol resulted in an immune-inert scaffold type. In *Paper II-III*, we developed three promising extracellular matrix-derived bioactive sheep uterus scaffolds that after an enzymatic preconditioning were able to support wide-spread cell attachment and migration during recellularization. In *Paper IV*, we were able to maintain normal sheep uterus ex-vivo for 48 hours using a custom made culture medium and a perfusion bioreactor. These parameters should facilitate future whole sheep uterus tissue engineering experiments so that a patient-specific tissue engineered uterus can be made to replace a donor in a uterus Tx setting.

Keywords: rat, sheep, uterus, tissue engineering, decellularization, recellularization

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