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Principles of scaffold generation for bioengineering of the ovary and uterus: A study focusing on decellularisation

AKADEMISK AVHANDLING
Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i 2320 Carl Kylberg, Medicinaregatan 9, fredagen den 2021-06-18, klockan 13:00.

av **Ahmed Baker Alshaikh**

Fakultetsopponent: **Prof. Antonio La Marca, MD., PhD.**, Obstetrics and Gynecology, University of Modena and Reggio Emilia, Modena, Italy

Avhandlingen baseras på följande delarbeten

I. **AB Alshaikh**, AM Padma, M Dehlin, R Akouri, MJ Song, M Brännström, M Hellström. Decellularization of the mouse ovary: comparison of different scaffold generation protocols for future ovarian bioengineering. J. Ovarian Res. 2019; 12:58.

II. **AB Alshaikh**, AM Padma, M Dehlin, R Akouri, MJ Song, M Brännström, M Hellström. Decellularisation and recellularisation of the ovary for bioengineering applications: Studies in the mouse. Reprod Biol Endocrinol. 2020; 18:75.

III. Padma AM, **Alshaikh AB**, Song MJ, Akouri R, Oltean M, Brännström M, Hellström M. Decellularisation protocol-dependent DAMPs in rat uterus scaffolds differentially activate the immune response after transplantation. Tissue Eng Regen Med. *In Press*

IV. Padma AM, **Alshaikh AB**, Song MJ, Akouri R, Akyürek L, Oltean M, Brännström M, Hellström M. Immune response after allogeneic transplantation of decellularized uterine scaffolds in the rat. Biomed Mater. *Under 2nd revision*

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Principles of scaffold generation for bioengineering of the ovary and uterus: A study focusing on decellularisation

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Abstract

Introduction: Cancer therapy often result in fertility problems due to inflicted injury to the reproductive organs. Since most women survive cancer, fertility preservation has become an important consideration during cancer therapy. However, options for young women with blood-related cancers are missing. Papers I-II describe the development and characterization of mouse ovarian scaffolds derived from ovarian extracellular matrix (ECM). Such scaffolds may be used for future ovarian bioengineering applications as a supporting matrix for the expansion of immature follicles isolated from young cancer patients to preserve their fertility. Paper III-IV use the rat model to analyse similar scaffolds for uterus bioengineering applications and evaluate if these scaffolds are immunologically inert after engraftment.

Methods: Three decellularisation protocols based on sodium dodecyl sulfate (SDS) and sodium deoxycholate (SDC) were developed for mouse ovary scaffold production (Paper I). Scaffolds were then characterised using histology and quantitative analysis for ECM components. Recellularisation was tested using mesenchymal stem cells (Paper II). Previously established uterus scaffolds were grafted to syngeneic (Paper III) or allogeneic rats (Paper IV) to investigate if the decellularisation process generated any detrimental damaged associated molecular products (DAMPs; Paper III) and if the allogeneic recipient's immune system remained stable after scaffold engraftment (Paper IV). Immunohistochemistry and gene expression analysis with digital droplet PCR was used quantify infiltrating immune cells and expression of proinflammatory signals.

Results and conclusions: Paper I developed three novel mouse ovarian scaffolds. The SDS and the SDC protocols were found promising, whereas a protocol based on both detergents were found too aggressive on the ECM. Paper III showed that a mild, yet effective decellularisation protocol generated less amounts of DAMPs, and that this scaffold type also remained the most inert to the recipient's immune system in an allogeneic setting (Paper IV).

Keywords: decellularisation, recellularisation, uterus, ovary, infertility, tissue engineering, immune response

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