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POTENTIAL THERAPEUTIC APPLICATIONS OF NOVEL BIOENGINEERED TISSUES AND ORGANS USING METHODS OF DECELLULARIZATION AND RECELLULARIZATION

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin vid Göteborgs Universitet kommer att offentligen försvaras i hörsal Åke Goransson, Medicinaregatan 11, tisdag den 25 september 2018, kl. 13.00

av

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Avhandlingen baseras på följande delarbeten

I. Kuna, VK, Xu B and Sumitran-Holgersson S. Decellularization and recellularization methodology for Human Saphenous Veins. Journal of Visualized Experiments. 2018; 137, e57803.

II. Kuna VK, Padma AM, Håkansson J, Nygren J, Sjöback R, Petronis S and Sumitran-Holgersson S. Significantly accelerated wound healing of full-thickness skin using a novel composite gel of porcine acellular dermal matrix and human peripheral blood cells. Cell Transplantation. 2017; 26(2): 293-307.

III. Elebring E, Kuna VK, Kvarnström N and Sumitran-Holgersson S. Cold-perfusion decellularization of whole-organ porcine pancreas supports human fetal pancreatic cell attachment and expression of endocrine and exocrine markers. Journal of Tissue Engineering. 2017; 8: 2041731417738145.

IV. Kuna VK, Paul S, Xu B, Sjöback R and Sumitran-Holgersson S. Human fetal kidney precursor cells regenerate acellular porcine kidneys via upregulation of key transcription factors involved in kidney development. *Manuscript.*

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POTENTIAL THERAPEUTIC APPLICATIONS OF NOVEL BIOENGINEERED TISSUES AND ORGANS USING METHODS OF DECELLULARIZATION AND RECELLULARIZATION

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ABSTRACT

The transplantation of personalized organs or tissues will benefit patients with various diseases and disorders. Decellularization is a method to generate an acellular, non-immunogenic natural scaffold. The personalized tissue can be generated after recellularization with recipient stem cells and it can be transplanted to recipient without the need for immune suppression. The current thesis focuses on developing decellularization and recellularization strategies for simple tissue (human saphenous veins), complex tissue (porcine skin) and organs (porcine pancreas and kidneys). In Paper I, decellularization of human saphenous veins is demonstrated followed by recellularization with peripheral blood and endothelial media perfusion in a bioreactor to show cell attachment at the lumen of the vein. In Paper II, the application of acellular porcine skin as a gel mixed with peripheral blood mononuclear cells (PBMC) in mice with skin wounds revealed a faster healing rate, complete wound closure, increased collagen deposition and improved angiogenesis. Papers III and IV demonstrate that porcine pancreas and kidneys decellularized in 4°C and room temperatures respectively resulted in loss of nuclei and the preservation of extracellular matrix proteins. The recellularization of pieces of acellular pancreas and kidney with human fetal pancreatic or kidney progenitor cells showed the attachment, infiltration and proliferation of human cells. The recellularized pancreas pieces expressed the characteristic exocrine (α-amylase) and endocrine (c-peptide, glucagon) markers. The recellularized kidney pieces also showed cell growth over the acellular matrix and the increased expression of important transcription factors involved in kidney development. Taken together, protocols for the decellularization of saphenous veins, skin, pancreas and kidneys were established. The recellularization of veins with peripheral blood and the application of porcine skin gel with PBMC may benefit patients with vascular diseases and burns respectively. The recellularization of the acellular pancreas and kidney with human fetal stem cells demonstrates the potential of fetal cells in further functional studies and may be in whole-organ recellularization experiments. The technique of decellularization and recellularization to bioengineer tissues and organs may thus have important implications in the field of regenerative medicine and ultimately organ transplantation.

Keywords: Tissue engineering, Decellularization, Recellularization, Saphenous vein, Bioreactor, Wound healing, Skin gel, Pancreas, Kidneys, Ephrins and Human fetal stem cells

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