Transplantation of autologous endothelial cells and endothelial progenitor cells for angiogenesis

The feasibility of using autologous cells as gene therapy vectors.

Smita DuttaRoy

The PhD dissertation was accepted by the Faculty of Health Sciences of the University of Aarhus, and defended on October 4, 20005.

Official opponents: Claus Andersen, Jens Kastrup, and Lise Wogensen Bach.

Tutors: Thomas Ledet, Daniel Steinbrüchel, Duncan Stewart, and Ren-Ke Li.

Correspondence: Smita DuttaRoy, Medicinkliniken SU/Ö, 416 85 Göteborg, Sweden. E-mail: smita.dutta-roy@vgregion.se

Dan Med Bull 2005;52:259

ABSTRACT

This PhD dissertation is based on studies performed at the Terrence Donnelly Heart Centre, St. Michael's Hospital, Toronto, Department of Cardiovascular Research, Toronto General Hospital, Department of Biochemical Pathology, Aarhus University Hospital, Nørrebrogade, Department of Cardiothoracic and Vascular Surgery and Institute of Clinical Medicine, Skejby Sygehus, Aarhus University Hospital.

There are different mechanisms of blood vessel formation. During angiogenesis blood vessels are formed from preformed vessels, vasculogenesis is the process where completely new blood vessels are formed. In the adult, vasculogenesis occurs through recruitment of endothelial progenitor cells (EPC) from the bone marrow. Several growth factors, such as Angiopoietin-1 (Ang-1) are involved in blood vessel formation.

The aim of the studies was to investigate the persistence of transplanted endothelial and smooth muscle cells (EC and SMC) and to investigate the feasibility of using endothelial cells as gene therapy vectors. Furthermore to investigate whether autologous endothelial progenitor cells (EPC) can be transplanted to enhance myocardial perfusion and cardiac function in chronic ischemia.

EC, SMC and EC transfected with Ang-1 and labelled with a fluorescent marker were transplanted to rat hearts and cell persistence was investigated using fluorescence microscopy of heart sections at different time points. Gene expression was determined using RT-PCR.

Autologous EPC were transplanted to ischemic porcine hearts immediately after placement of an ameroid constrictor around the proximal left circumflex artery. The myocardial blood flow and electrical activity was assessed after four weeks using microsphere counts and NOGA-mapping.

Transplanted cells survived up to 12 weeks post injection in the rat heart. Ang-1 signal could be detected up to 6 weeks after transplantation. The transplanted EC arranged themselves into vessel-like formations, while the SMC arranged into more sheath-like structures. The EC survival did not seem to increase with the Ang-1 transfection.

At four weeks, higher resting blood flow was found in the circumflex area in the transplanted pigs compared to controls, however no difference in stress blood flow could be seen. There was no significant difference in size of infarcted area and mechanical abnormality between the two groups.

The results of the study suggest that EC can be used as gene therapy vectors with a lasting gene expression. EPC can increase myocardial perfusion in the ischemic heart. This can present new therapeutic options for the group of patients with ischemic heart disease that cannot be revascularized with catheter-based intervention or surgery. However, the transplantation and transfection conditions need to be further optimized.