Small diameter acellular vascular grafts with integrin α4β1 positive cell-caputuring surface

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Introduction: Cardiovascular diseases, especially arteriosclerotic vascular diseases in the coronary artery, are the leading cause of death in Japan and in the world. Although autologous vessels are the standard for their treatments, many patients do not have available vessels. Therefore, small diameter vascular grafts are in large demand not only for the coronary artery bypass but also for distal bypass in peripheral arterial disease (PAD). Non-degradable synthetic materials such as ePTFE is widely used clinically as large- or middle-diameter blood vessels but cannot be used as the small-diameter ones. The ePTFE blood vessels with the inner diameter of 3-6mm can be used for BT shunt, but their length was 2-3 cm and they were used only for a couple of years with anticoagulant drugs. Therefore, tissue engineered blood vessels have emerged as a promising solution. We have been studying acellular porcine aorta and heart valves prepared by the chemical-free high-hydrostatic pressure (HHP) technology[1]. Excellent patency,neointima formation, and reduced calcification were achieved in up to one year in porcine-porcine transplantation models. However, the patency of the small diameter blood vessels was not satisfactory if anticoagulant or antiplatelet drugs were not used. It may be due to the rapid coagulation on the luminal surface of acellular tissues because the main component is collagen, a strong coagulant. To achieve higher patency of small-diameter acellular vascular grafts, we have developed novel surface modification of the acellular tissues with a bioactive peptide (REDV) that is recognized by integrin α4β1 and improves re-endothelialization and subsequent neointima formation. Cytospecific adhesion of HUVECs on the REDV-modified acellular tissues were evaluated in vitro. REDV-modified acellular small-diameter vascular grafts with the internal diameter of 1-2 mm were transplanted and the patency was monitored by the non-invasive manner.

Methods: REDV sequence-containing peptides were synthesized by the conventional F-moc solid carrier method and thoroughly purified. The peptide immobilization onto the luminal surface was carried out by the strand invasion procedure based on the high affinity of the vessel wall collagen and the synthetic peptides. As a control sequence, RDEV sequence-containing peptides were also prepared and compared.

In vitro cell affinity experiment was done using porcine descending aorta. The wall tissue was cut into 8×8 mm pieces, decellularized by HHP treatment, and modified. A given number of HUVECs and NIH/ 3T3 cells were seeded and cell behavior was observed. The modified blood vessels were transplanted to rat abdominal aorta (N=5) in end-to-end fashion with 8-0 proline under anesthetized condition. The patency of the graft was evaluated by MRI images and laser Doppler measurements. After the transplantation, graft was histologically stained to evaluate the regeneration of intimal tissue.

Results: REDV-modified acellular tissues showed excellent HUVEC specificity with low 3T3 or platelet adhesion. MRI image revealed that the patency of the rat abdominal aorta replacement after 1 month was increased from 20 % to 80% even when no anticoagulant or antiplatelet drugs was used. Moreover, histological staining indicated that the in vivo endothelialzation was enhanced only in the case of REDV-immobilized small vascular blood vessels when evaluated by vonWillebrand factor immunostaining.

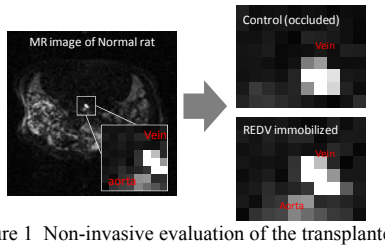

Figure 1 Non-invasive evaluation of the transplanted acelllar small-diameter vascular grafts under MRI. Tr=30 msec.

Conclusions: The results presented here demonstrated very large efficacy of the REDV modification on patency may be due to the improved haemocompatibility and specifically accelerated intimal formation. We are now challenging to much longer bypasses in large animal models.

Reference:

1. Fujisato T.et al., In: Cardiovascular regeneration therapies using tissue engineering approaches (Mori H and Matsuda H eds.; Springer, 983 (2005)

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