EPC capturing technology for improving patency of small-diameter (2mm ID) and long (30 cm length) acellular blood vessels

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Statement of Purpose: Small-caliber vascular grafts smaller than 4 mm are unavailable clinically because of the thrombogenic formation and rapid occlusion. To overcome the present situation, we have been studying various antithrombogenic biomaterial surfaces. Very recently, we have achieved excellent patency of small-caliber vascular grafts. Rat abdominal arteries and ostrich carotid arteries (2mm ID and 30cm length) were decellularized with our acellular technology, ultrahigh-hydrostatic pressure treatment (UHP), and their luminal surfaces were modified with a novel peptides which specifically induces the very rapid reendothelialization. Their patency and reendothelialization were studied in rat abdominal and miniature pig femoral-femoral (F-F) bypass models.

Methods: Surrounding tissue of the arteries was removed, and the trimmed arteries were washed, packed in a small plastic bag in saline, and set to the cold isostatic pressurization machine. The pressure was increased at the rate of 65.3MPa/min, kept at 980 MPa for 10min, and return to the atmospheric pressure at a same rate. The treated arteries were washed with saline containing 40U/ml of DNase I, 20mM of $MgCl_2$, and antibiotics for 3days. The artery luminal surface was modified with EPC specific peptide by exposing to 10μM of the peptide solution and being incubated at 60°C for one hour.

Decellulalized rat descending aorta were transplanted into SD-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 (Figure 1) and laser Doppler for one month. The graft was histologically stained to evaluate the reendothelialization. The long-bypass grafts made of ostrich carotid artery were transplanted in miniature pig F-F bypass surgery in which the left femoral artery was bypassed to right femoral artery. The patency and reendothelialization were evaluated up to 1 month.

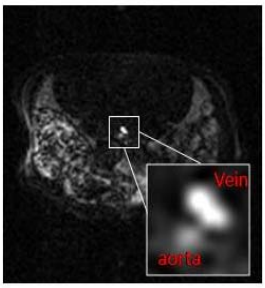

Figure 1 Sagittal images on MIR of transplanted rat around the graft modified with POG7G3REDV peptide.

Results: More than 80 % of seeded HUVEC cells were adhered on the peptide-modified decellularized tissue and spread out, while cells scarcely adhered onto the control surface, indicating that the designed peptide is very useful to improve the cell specific adhesion of the acellular tissue. The rat-rat orthotopic implantation, the graft patency was greatly improved by the peptide-modification. The patency of the peptide modified and unmodified arteries were 0 and 80%, respectively.

The peptide was very effective even in the decellularized ostrich carotid artery system transplanted into porcine F-F bypass system (Figure 2). Surprisingly, the long bypass (2mm ID, 30cm length) were completely patent and the luminal surface was reendothelialized within 3 days even for the central part of the grafts. Since the endothelial cell migration from the both ends toward the center (15 cm distance) seems to be too fast, we are now trying to prove the EPC capturing by the peptide modification.

Conclusions: We succeeded to design excellent surface modifier that impart rapid reendothelialization property to the acellular tissue in addition to the shielding of the exposed collagen at the luminal surface. The good patency of the grafts with 2mm id and 30cm length is meaningful resuls because this size range is useful even in the clinical situation such as distal bypass.

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