Adeno-associated viral vector 2.9 thymosin β4 application attenuates rejection after heart transplantation: results of a preclinical study in the pig.

Graft survival is the most important factor for morbidity and mortality in cardiac transplantation. Improved immunosuppression significantly reduced early graft rejection. However, acute rejection may predispose to chronic rejection. Targeting both phases of the recipient's immune-reactivity by means of long-acting recombinant adeno-associated viral vectors (AAVs) encoding anti-inflammatory and cardioprotective factors appears to be a promising therapeutic approach. We investigate thymosin β4 (Tβ4) possessing anti-inflammatory and prosurvival abilities, as a means for pretransplant gene therapy. Heterotopic, abdominal transplantation of cardiac allografts into landrace or into Munich mini pigs (n=5 per group) was performed. Transplants were transduced with AAV2.9 before transplantation by means of in situ perfusion of the donor organ. Vascular endothelial growth factor and AAV2.9.Tβ4 or AAV2.9.LacZ were added to the autologous blood used for perfusing the grafts for a period of 45 min. Immunosuppression was applied for 10 days after the operation. Transgene expression, capillary density, graft function, survival, and rejection were assessed. The AAV2.9
transduction induced robust overexpression of the transgene. In addition, Tß4 ameliorated inflammation, necrosis, vascular reaction (acute rejection) and in parallel improved capillary density. In addition, graft survival was significantly prolonged (10±3 days AAV2.9.LacZ vs. 31±4 days AAV2.9.Tß4). In the mini pig model, regional myocardial function of the grafts was improved by Tß4 transduction compared to LacZ (9.1%±0.9% subendocardial segment shortening in AAV2.9.LacZ vs. 15.8%±2.3% in AAV2.9.Tß4). In situ AAV2.9-mediated gene transfer of thymosin ß4 attenuated graft rejection in a heterotopic heart transplantation model. Perioperative cardioprotection by means of gene therapy might improve graft survival in cardiac allotransplantation.