the progression of renal dysfunction even after adjusting for other clinical risk factors, including hypertension, urinary protein excretion of more than 1.0 g/day, and no administration of renin angiotensin system inhibitors. This study supports the role of MUC20 in regulating the Met signaling cascade, which is implicated not only in renal development and maintenance of kidney functions but also in tubular repair and regeneration under pathological conditions in human glomerulonephritis. The tandem repeat polymorphism in MUC20, which may directly affect its oligomerization and binding to Met, is associated with the renal prognosis of IgAN. Factors that regulate the function of MUC20 may be useful therapeutic agents for progression of renal injury.

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Life-supporting pig-to-baboon renal transplantation using GalT knockout donors: Benefit of cotransplanting a vascularized donor thymic graft

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The use of animal organs for human transplantation could potentially alleviate the worldwide critical shortage of donor organs, and thus has stimulated investigation of novel strategies directed at making xenotransplantation applicable to the clinic. The latter will likely require overcoming barriers of rejection through strategies utilizing either immune suppression or tolerance induction, or a combination of the two. We have previously reported that vascularized donor thymic tissue grafts, transplanted either as composite thymokidneys or vascularized thymic lobe grafts, induced tolerance across fully allogeneic barriers in miniature swine. Recently, we have applied the strategy of vascularized thymic lobe transplantation in a model of hDAF pig-to-baboon xenotransplantation and demonstrated that these grafts induced donor-specific unresponsiveness for up to 2 to 3 months following transplantation, at which time the grafts were lost from apparent humoral rejection. We have now extended these studies using cloned α-1,3-galactosyltransferase (GalT) knockout pigs as donors. We report here our initial experience in a preclinical model of pig-to-baboon xenotransplantation. This abstract presents clinical data on recipients of GalT knockout kidneys, especially focusing on four long-term recipients of GalT knockout kidney plus thymus transplantation in detail. Briefly, these four baboons receiving either xeno-thymokidneys or vascularized thymic lobe plus kidney maintained longer than 2 months. Three of four long-term survivors maintained normal plasma creatinine levels for 56, 68, and 83 days, respectively, before expiring from unexpected causes (anesthetic complication during surgery to replace an infected intravenous catheter (day 68), and myocardial infarction, possibly drug-induced on days 56 and an arterial catheter trouble on day 83. Cytotoxic T-lymphocyte assays on day 78 in one long-term acceptor showed that the baboon maintained anti-allo cytotoxic T-lymphocyte responses but lost antipig cyctotoxic T-lymphocyte responses, indicating donor-specific unresponsiveness. The fourth baboon experienced an apparent rejection crisis between days 53 and 65, which reversed with anti-T-cell rejection therapy; subsequently the animal expired on day 81 from pneumonia. Neither hyperacute nor accelerated acute rejection was observed in any animal. Use of GalT knockout donors markedly extends the survival of vascularized thymus plus renal xenografts in baboons. Although the induction regimen still needs to be modified to reduce complications, these initial results are encouraging with regard to the potential of cotransplanting vascularized thymic tissue with organ xenografts as a means of achieving long-term tolerance across pig-to-primate barriers.

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HGF gene transfer increases kidney graft survival

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The introduction of cyclosporine (CsA) into clinical practice has resulted in marked improvement in the short-term outcome of organ transplantation, and 1-year survival of renal allografts has improved significantly. However, the annual rate of kidney graft loss caused by chronic allograft nephropathy (CAN) has remained stable over last decade. CAN may result from perioperative ischemia at the time of transplantation. Furthermore, chronic CsA nephrotoxicity may progress to an irreversible renal lesion characterized by tubular atrophy, striped interstitial fibrosis, hyalinosis of the afferent arteriole, and progressive renal impairment. Recent report demonstrated the therapeutic effects of hepatocyte growth factor (HGF) in preventing CAN using a well-established rat CAN model. They showed that HGF treatment during the initial 4 weeks after engraftment

prevented onset of CAN and associated death and provided longlasting benefit in terms of graft survival. Exogenous HGF is very unstable in the blood circulation due to the rapid clearance by the liver. To circumvent this problem, we developed a new gene transfer system by electroporation in vivo. Therefore, this gene transfer approach represents a useful technique to investigate the therapeutic potential of HGF gene transfer for long-term survival of kidney allograft. The goal of the present study was to assess the renoprotective potential and safety of HGF gene transfer using a porcine kidney transplant warm ischemia injury model or CsA nephrotoxicity model. In the first set of experiments, following left porcine kidney removal, 10 minutes of warm ischemic injury was intentionally induced. Next, the HGF expression vector or vehicle was infused into the renal artery with the renal vein clamped ex vivo, and electric pulses were discharged using bathtub-type electrodes. Kidney grafts were then transplanted after removing the right kidney. Histopathologic examination of vehicle-transfected kidney transplant revealed initial tubular injury followed by tubulointerstitial fibrosis. In contrast, HGF-transfected kidneys showed no initial tubular damage and no interstitial fibrosis at 6 months posttransplant. In the next set of experiments, CsA was subcutaneously administered daily under low sodium diet, and HGF gene was transferred into skeletal muscle by electroporation on days 7 and 14. We also examined the antiapoptotic mechanism of HGF using human proximal tubular epithelial cells. HGF gene transfer rescued CsA-induced initial tubular injury, and suppressed interstitial infiltration of endothelium-1 (ED-1)–positive macrophages in CsA nephrotoxicity. In addition, HGF significantly inhibited tubular cell apoptosis, and increased the number of proliferating tubular epithelial cells. In vitro studies suggest that HGF executes the antiapoptotic function by enhancing the phosphorylation of Akt and Bcl-2. Northern blot analysis demonstrated that HGF gene transfer suppressed cortical mRNA levels of transforming growth factor-β (TGF-β). Consequently, HGF gene transfer significantly reduced a striped interstitial phenotypic alteration and fibrosis. We conclude that electroporation-mediated HGF gene transfection protects the kidney against graft injury.

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The future of renal replacement: Needs and applications

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For those with uremia, renal function is presently replaced by dialysis or allotransplantation. Neither approach is ideal physiologically and allotransplantation suffers from limited availability of donors. In the future, the need to replace or amplify renal function may increase dramatically as molecular diagnosis identifies those at risk for cancer and renal failure, and as small impairments of renal function are found to increase cardiovascular risk. The heightened demand for renal replacement may be met by the development or advancement of technologies, including stem cells, cloning, organogenesis, and xenotransplantation. The ideal replacement of renal function, however, may not be achieved by any one of the technologies, but rather by a combination. Cloning, stem cells, organogenesis and xenotransplantation can potentially be combined for replacement of renal function. New technologies or combinations of technologies for replacement or regeneration of renal function share certain challenges. One challenge is the need to generate organs or organ-like structures that exhibit adequate function. Another challenge is that the achieving of adequate size engenders some risk of tumor formation. Still another challenge stems from the controversy regarding the capacity of stem cells to differentiate or transdifferentiate and the possibility that fusion of stem cells or their progeny with differentiated cells may contribute to regeneration and histogenesis. The implications of cell fusion in such systems were discussed.

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