Growing New Organs in Situ

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Allotransplantation of kidneys is an established medical therapy, the application of which is limited by shortage of available organs. The use of animals in lieu of human subjects as donors (xenotransplantation) is a potential solution for the organ shortage. In that humans and pigs are of comparable size, and share a similar renal physiology it has been proposed that pigs represent an ideal animal donor for human kidney replacement. Unfortunately, the transplantation of vascularized organs such as the kidney originating from pigs into the group of primates that includes humans, the great apes and old-world monkeys, is rendered problematic because of the processes of hyperacute and acute vascular rejection that occur across this xenogeneic barrier.

When hyperacute rejection is avoided through the use, for example, of genetically altered kidneys originating from pigs transgenic for the human complement activators, human decay accelerating factor (hDAF) and CD59, vascularized grafts transplanted to susceptible primates become subject to acute vascular rejection and acute rejection. Acute rejection can be circumvented using immunosuppression or co-stimulatory blockade. However, acute vascular rejection represents a major obstacle to the use of porcine organ in human hosts. Several processes implicated as causative of acute vascular rejection reflect a fundamental incompatibility between host proteins/protein systems, and the vascular endothelium of the donor.

Host immune responses directed against endothelial antigens of a transplanted kidney, or mediated by transplant endothelial cells are obviated in proportion to the extent that the organ is nonvascularized. While developed pig kidneys have their own blood vessels, embryonic pig kidneys are initially avascular and can attract a host vasculature from an appropriate bed post-transplantation. For this reason there is an advantage for the use of embryonic pig kidneys (metanephroi) in lieu of developed kidneys for xenotransplantation.

Transplantation of isolated islets of Langerhans to diabetic humans is a proven but still experimental means to treat diabetes mellitus. The shortage of human donors is such that it will not be possible to meet the demand from all the patients with Type 1 diabetes. As for the kidney, limited availability of islets could be overcome through use of tissue derived from pigs since humans are sensitive to porcine insulin. Unfortunately, the limited experience with pig to human islet transplantation suggests that even large quantities of transplanted porcine islets will not translate into insulin sufficiency for human hosts. Problems inherent in the isolation of islets result in diminished viability. Coupled with the limited ability of beta cells within mature islets to replicate, the diminished viability results in a declining pool of functioning engrafted islets over time.

One strategy to overcome the limited potential for growth or division of mature islet cells is to transplant developing fetal or neonatal pancreatic tissues (pancreatic anlagen) that have a greater capacity for beta cell expansion post implantation. The potential for expansion of pancreatic anlagen sufficient to render a diabetic host euglycemic is reflected by the fact that every normal human pancreas originates from a single embryonic precursor
organ.

Following transplantation into animals, metanephroi and pancreatic anlagen undergo differentiation in situ resulting in the growth of new organs. Once differentiated, transplanted metanephroi can extend life in otherwise anephric hosts and transplanted pancreatic primordia can normalize glucose tolerance in diabetic recipients. Xenotransplantation (pig to human) of metanephroi and the developing embryonic pancreas could provide new therapies for end-stage renal disease and type 1 diabetes mellitus.