Growing new kidneys in situ

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REVIEW ARTICLE

Abstract

One novel solution to the shortage of human organs available for transplantation envisions “growing” new organs in situ via xenotransplantation of developing primordia from animal embryos. Renal primordia (metanephroi) transplanted into animal hosts undergo organogenesis in situ, become vascularized by blood vessels of host origin, and exhibit excretory function. Metanephroi can be stored in vitro prior to transplantation and can be transplanted across both concordant (rat-to-mouse) and highly disparate (pig-to-rodent) xenogeneic barriers. Here we review studies exploring the therapeutic potential for renal organogenesis post-transplantation of kidney primordia.

Key words Embryogenesis · Cell transplantation · Kidney transplantation · Porcine organs · Organogenesis · Renal failure · Xenotransplantation

Introduction

The applicability of kidney allotransplantation to treat endstage renal disease is limited by the number of organs available to transplant. In that humans and pigs are of comparable size, share a similar renal physiology, and because pigs are plentiful and can be bred to be pathogen-free, it has been proposed that pigs represent an ideal substitute donor. Unfortunately, the transplantation of whole 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 humoral rejection (hyperacute and acute vascular rejection). In contrast to xenotransplantation of whole vascularized organs from pig to primates, cell and tissue grafts might be feasible, since they are less susceptible to humoral rejection. Cellular transplants, such as pancreatic islets or neurons from embryonic pigs, can be transplanted into humans without triggering hyperacute or acute vascular rejection.

It has been proposed that metabolic and synthetic liver functions in humans could be augmented by porcine hepatocyte transplantation and that contractile functions of skeletal and cardiac muscle might be enhanced post-integration of transplanted porcine myocytes.

Cellular transplantation has limitations. It is difficult to imagine how the functions of structurally complex organs, such as glomerular filtration and reabsorption in kidneys, can be enhanced or recapitulated by cellular transplants. One potential approach to replacing such functions is through organogenesis, or the growing of whole kidneys in situ post-transplantation of renal primordia.

Renal organogenesis

Metanephroi are the primordia of adult mammalian kidneys. They originate during the fifth week of gestation in humans, during day 12 of embryonic rat development (E12), during day 11 of embryonic mouse development (E11), and during days 21–28 of embryonic pig development (E21–28) when outgrowths of the mesonephric ducts, designated ureteric buds, collect about their distal ends, forming intermediate mesoderm (metanephric blastema). Numerous outgrowths arise from the distal end of the ureteric bud which push radially into the surrounding mass of metanephric blastema. The metanephric blastema differentiates into all tubular structures of the adult nephron, with the exception of the collecting system, which derives from the ureteric bud.

The major vessels supplying the kidney originate from lateral branches of the abdominal aorta that terminates in a plexus of arteries in close proximity to the renal pelvis, the renal artery rete. During its development, the renal anlage...
attracts the major portion of its vasculature, from the developing aorta. In that its blood supply originates from outside the developing organ, the kidney is chimeric. Its ability to attract its own vasculature in situ establishes the potential for a transplanted metanephros to attract a vasculature from a suitable vascular bed.

**Advantages of transplanting metanephros to achieve organogenesis in situ**

The literature provides four reasons why the use of transplantation of metanephros, to achieve organogenesis in situ, might be advantageous relative to the transplantation of developed kidneys. First, if developing metanephros are obtained at a sufficiently early stage, antigen-presenting cells (APCs) that mediate “direct” host recognition of alloantigen or xenoantigen would be expected to be absent from the renal primordia, because they would not have yet developed in the donor and migrated into the metanephros. Second, donor antigens such as MHC class I and II may not be expressed on developing metanephros to the extent they are expressed in adult kidney. Third, the immune response to transplanted fetal tissue differs from that to adult tissue in terms of the elicitation of a T-helper 2-biased response when that target organ is of fetal origin. Fourth, to the extent that the renal vasculature originates from outside the kidney, one would expect a transplanted metanephros to be supplied by blood vessels of host origin.

The first studies to address the question of APC depletion in metanephros were performed by Foglia et al. who transplanted metanephros obtained from outbred Sprague Dawley rat embryos aged embryonic day (E)15–E21 beneath the renal capsule of adult Sprague Dawley hosts. Fetal renal allograft growth and survival was age-dependent, in that the growth and differentiation in situ over a 15–30 day period was best for metanephros obtained from E15 embryos and worsened progressively for renal primordia obtained on E16–E21. The developed E15 metanephros showed maturation of renal elements when examined 10 days post-transplantation, and no sign of rejection, whereas E20 metanephros had a poor renal architecture and a dense lymphocytic infiltrate after a comparable period of time. In contrast to metanephros obtained on E15, liver tissue harvested on E15 and transplanted beneath the renal capsule of hosts underwent little growth and showed prompt rejection.

Velasco and Hegre transplanted metanephros or liver tissue from E15, E17, E18, and E19 Fisher rat embryos (RT1<sup>b</sup>) beneath the renal capsule of MHC (RT1<sup>i</sup>) incompatible Wistar Furth adult rats (RT1<sup>i</sup>). All fetal hepatic grafts were rejected by 10 days post-transplantation. In contrast, the degree of rejection of the metanephros was age-dependent, those from E15 embryos showing minimal or moderate rejection and those from older embryos showing more intense rejection. If liver and metanephros from E15 embryos were co-transplanted at different sites into Wistar Furth rats, metanephros underwent a more severe rejection than if they were implanted without liver.

APCs populate liver well before E15 in rats, but are not present in the circulation until several days later. It was speculated that the absence of APCs in metanephros obtained from E15 embryos, together with their presence in liver tissue obtained concurrently, could explain the differential fate of metanephros transplanted with or without liver. Under the former conditions, but not the latter, direct presentation of donor antigens to host T cells could take place.

Statter et al. transplanted renal tissue originating from E14 to adult C57Bl/6 mice (H-2<sup>b</sup>) beneath the renal capsule of adult congenic B10.A hosts (H-2<sup>a</sup>). Expression of donor and host-specific class I (H2K<sup>a</sup>) and class II (A<sub>H</sub>) transcripts in donor tissue was low at E14 and increased progressively in renal tissue from older mice. After transplantation, surviving kidney grafts showed enhanced expression of class I and class II transcripts. However, neither class I nor class II protein could be detected in transplanted metanephros, in contrast to its presence in transplanted adult renal tissue.

Dekel and co-workers have carried out a series of investigations in which human adult or embryonic kidney tissue is transplanted beneath the kidney capsule of immunodeficient rats (severe combined immunodeficiency [SCID/Lewis and SCID/nude chimeric rats]). Human adult kidney fragments transplanted beneath the renal capsule of such rats survives for as long as 2 months post-transplantation. The overall architecture of the transplanted kidney tissue and the normal structure of individual cells in glomeruli is preserved. The intraperitoneal infusion post-transplantation of allogeneic human peripheral blood mononuclear cells (PBMCs) results in rejection of adult human grafts.

Human fetal kidney fragments transplanted beneath the renal capsule of immunodeficient rats display rapid growth and development. Glomeruli and tubular structures are maintained for as long as 4 months post-transplantation. In contrast to the case for transplanted adult human kidney fragments, the infusion of allogeneic human PBMCs into hosts results in either minimal human T-cell infiltration or in T-cell infiltrates that do not result in rejection, and do not interfere with the continued growth of the human fetal renal tissue. Fetal human grafts have reduced expression of tissue HLA class I and II relative to the adult human grafts, consistent with a reduced effectiveness in inducing an alloantigen-primed T-cell response.

Dekel et al. have shown that transcript levels for interferon gamma and interleukin-2 in grafts of fetal human kidneys grafted under the renal capsule of immunodeficient rats are markedly reduced post-transplantation relative to levels in adult human kidney tissue grafted to the same site. Peak levels of these cytokines appear late after PBMC infusion. Concomitant with these findings, interleukin 4 mRNA is upregulated during the early phase post-PBMC infusion, and interleukin 10 mRNA is expressed throughout the post-PBMC infusion interval. In addition, levels of mRNA coding for the chemokines RANTES and macrophage inflammatory protein (MIP)1 beta, their receptor,