Institute of DNA Medicine
Project Laboratory for Kidney Regeneration

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General Summary

Recently, much attention has been focused on the use of embryonic organs as a source for xenotransplantation. This strategy involves transplantation of the embryonic organ before vascularization, with the subsequent development of a mature organ in the recipient. Because the vasculature of the transplant is of host origin and the embryonic organ per se is less immunogenic, intense immunomodulation should not be required. One study has found that a pig metanephros was able to grow and differentiate into mature renal tissue in the rat omentum; the transplanted tissue produced urine and, after intact ureteroureterostomy, anephric rats started to void and showed prolonged lifespans. Previously, we successfully rebuilt metanephroi from human mesenchymal stem cells (hMSCs) using a program of nephrogenesis in a growing xenoembryo. Combining this success with the concept of embryonic organ transplantation should result in the regeneration of an autologous self-kidney. To this end, we transplanted metanephroi derived from hMSCs into rat omentum and were able to establish mature xenokidneys. We demonstrated that the vasculature of the transplant is of host origin and is capable of producing urine by filtration of the host's blood. Furthermore, the transplant expresses xenoerythropoietin, the production of which is regulated by the degree of anemia in the host. Our ultimate goal is to establish an entire functional kidney in patients with end-stage renal disease; however, because the kidney has various other functions in addition to urine production, we believe that each function should be reestablished using separate systems that may be subsequently unified. In previous studies, we transplanted tissue to the omentum; this site is used mainly because it is not confined by a tight capsule and is easily accessed with endoscopy. However, the optimal site for transplantation of each of the renal functions should be determined separately on the basis of anatomical and physiological considerations.
Therefore, this year, we investigated the effect of the transplantation site on the production of renin and erythropoietin as indicators of renal function.

Research Activities

A xenotransplanted metanephros may undergo complete nephrogenesis in the host animal, forming a functional kidney. This suggests that, in the future, xenometanephroi could become an unlimited source of material for renal transplantation. Although the omentum is the primary site for transplantation, we speculate that the growth of the transplant could differ depending on the site of transplantation. Thus, we determined the optimal transplantation site for the metanephros to retain its ability to produce renin and erythropoietin. Rat metanephroi were transplanted into the omentum, the paraaortic

area, or both the omentum and the paraaortic area of unilaterally nephrectomized host rats. After 2 to 3 weeks, blood was rapidly withdrawn to induce production of renin and erythropoietin in the transplants. Histological analysis indicated that transplants in both the paraaortic area and the omentum were well differentiated, demonstrating polarity of the medulla through to the cortex. Plasma renin activity increased in response to the induction procedure, but transplants in the paraaortic area expressed plasma renin activity more effectively than did those in the omentum. Real-time polymerase chain reaction revealed higher levels of renin messenger RNA expression in transplants in the paraaortic area than in transplants in the omentum. Although erythropoietin production increased 24 hours after the induction procedure, the levels did not differ significantly between transplantation to the omentum and transplantation to the paraaortic area. Compared with transplantation to the omentum, transplantation to the paraaortic area results in better renin production, whereas the transplantation site does not affect erythropoietin production.

Publications

Gheisari Y, Yokoo T, Matsumoto K, Fukui A, Sugimoto N, Ohashi T, Kawamura T, Hosoya T, Kobayashi E. A thermoreversible polymer mediates controlled release of glial cell line-derived neurotrophic factor to enhance kidney regeneration. *Artif Organs* 2010; **34:** 642–7.

Reviews and Books

Yokoo T, Yanagita M. Stem cell therapy against oxidative stress and hypoxia. In: Miyata T, Eckardt KU, Nangaku M, editors. Studies in renal disorders. New York: Springer; 2011. p. 673–88.