Institute of DNA Medicine
Project Laboratory for Kidney Regeneration

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General Summary

Recent advances in stem cell research have brought the possible use of somatic stem cells for organ regeneration one step closer to realization. Newly developed organs can then be used in clinical organ replacement. However, anatomically complicated organs, such as the kidney, have proven more refractory to stem cell-based regenerative techniques.
The kidney retains the potential to regenerate if the damage is not too severe and if the kidney structure remains intact. However, in cases of irreversible damage to the kidney, as can occur with long-term dialysis, the property of self-renewal is lost. Thus, any application of regenerative medicine in chronic renal disease will require the de novo development of an entire functional kidney.
It was previously believed that bone marrow-derived stem cells could differentiate into renal-resident cells and participate in kidney regeneration after renal ischemia/reperfusion injury; however, recent studies suggest that the number of bone marrow-derived cells that engraft injured tubules and develop into functional renal tissue is extremely small and that, therefore, their overall contribution to renal repair would be minor. For this reason we are attempting to develop entire kidneys using more premature and pluripotent stem cells.
We have used the developmental program of a developing organ by transplanting it into an ectopic site where it continued to develop *in vivo*. This procedure would facilitate the inward migration of autologous stem cells that would then be stimulated by the developmental program of the xeno-organ to mature into tissue-specific cells.

Research Activities

This year, we determined the metabolic function of transplanted metanephroi with particular reference to renin production and effect on blood pressure. Ten-week-old male Wistar rats were divided into 4 groups: a control group (n = 12), a para-aorta-transplanted group (n = 12), an omentum/epididymis-transplanted group (n = 14), and a nontransplanted group (n = 16). Rats in both transplanted groups underwent metanephros transplantation and bilateral nephrectomy. Rats in the other groups underwent bilateral nephrectomy only. Two weeks later, rats in the transplanted and nontransplanted groups underwent residual nephrectomy, and hypotension was induced through intravenous infusion of diltiazem hydrocloride or rapid withdrawal of blood. Mean arterial blood pressure was monitored from the left femoral artery. Plasma renin activity was analyzed at multiple time points. The renin expression of transplanted metanephroi was evaluated with the real-time polymerase chain reaction and immunopathologically when the rats were killed. Metanephros transplantation significantly increased plasma renin activity

and maintained mean arterial pressure compared with those in the nontransplanted group. No significant differences between the para-aorta-translanted, omentum/epididymis-transplanted, and control groups were found with respect to plasma renin activity and mean arterial pressure. The present study has shown that transplantation of metanephroi increases plasma renin activity and contributes to the control of blood pressure variability in hypotensive rats.

Publications

Iwai S*[1]*, Kikuchi T*[1]*, Kasahara N*[1]*, Teratani T*[2]*, Yokoo T, Sakonju I*[1]*, Okano S*[1]*, Kobayashi E*[2] *(*[1]Kitasato Univ,*** [2]***Jichi Med Univ).*** Impact of normothermic preservation with extracellular type solution containing trehalose on rat kidney grafting from a cardiac death donor. *PLoS One.* 2012; **7:** e33157.

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