Institute of DNA Medicine
Project Laboratory for Kidney Regeneration

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General Summary

Kidney regeneration is gaining considerable attention as the ultimate treatment strategy for renal failure, thus replacing kidney dialysis. However, the kidney is believed to be the most difficult organ to regenerate because it is anatomically complicated and because each cell in the kidney must be precisely placed to achieve renal function. Therefore, it is difficult to imagine such a complicated organ being created from pluripotent stem cells through genetic or chemical manipulation. However, in every individual this sophisticated structure is present at birth in the proper position due to perfect programming of the developmental kidney during embryogenesis. Therefore, if we can unravel this entire process and follow it, kidneys could be regenerated even after birth. We are investigating the potential for reconstructing an organized and functional kidney structure, using the developing xeno-embryo as an organ factory.

Research Activities

A thermoreversible polymer mediates controlled release of glial-cell—derived neurotrophic factor to enhance kidney regeneration

We have previously reported that human mesenchymal stem cells (hMSCs) cultivated in growing embryos differentiated in an appropriate developmental milieu, thereby facilitating the development of a functional renal unit. However, this approach required transfection with an adenovirus that expressed glial-cell—derived neurotrophic factor (GDNF) to enhance the development of hMSC-derived renal tissue, and safety issues restrict the clinical use of such viral vectors. To circumvent this problem, we tested an artificial polymer as a means to diffuse GDNF. This GDNF polymer, which exists in liquid form at 4°C but becomes a hydrogel upon heating to 37°C, was used as a thermoreversible switch, allowing the injection of hMSCs at low viscosity using a mouth pipette, with subsequent slow diffusion of GDNF as it solidified. The polymer, which was dissolved in a solution of GDNF at 4°C and then maintained at 37°C, acted as a diffuser of GDNF for more than 48 hours. *LacZ*-transfected hMSCs and the GDNF polymer (at 4°C) were placed in nephrogenic sites of growing rat embryos maintained at 37°C. Forty-eight hours later, the resultant kidney anlagen were dissected out and allowed to continue developing for 6 days *in vitro*. Whole-organ X-Gal staining and fluorescence-activated cell sorter analysis showed that the number of hMSC-derived cells was significantly greater in developed anlagen that have been generated from hMSCs plus GDNF polymer than in anlagen generated from hMSCs plus GDNF-containing medium and was comparable to those from adenovirus-transfected hMSCs. These findings suggest that the GDNF polymer can be used as a diffuser of GDNF for kidney organogenesis.

Publications

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Reviews

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