REGENERATIVE MEDICINE

Growing mouse kidneys in rats

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Kidney transplantation is considered as the most effective treatment for patients with end-stage renal disease; however, the number of donated kidneys is limited, and many patients have to wait years to receive a transplant. Several approaches to solve organ shortage are being investigated, including the generation of transplantable human kidneys from pluripotent stem cells (PSCs). In a new study, a Masumi Hirabayashi and colleagues report for the first time the generation of mouse PSCs-derived kidneys in anephric rats; these findings could inform future stem cell-based strategies to produce human organs in animals.

The investigators used a method called blastocyst complementation: PSCs are injected into a blastocyst-stage embryo genetically modified to prevent the formation of a specific organ; PSCs integrate into the growing embryo and the targeted organ develops exclusively from the injected PSCs. The team had successfully used this approach to grow functional pancreas in interspecies rodent models. "As the next step, we decided to investigate whether the method could be used to generate functional kidneys, which would have greater application in regenerative medicine owing to the high demand for donor kidneys," says Hirabayashi.

"We did not know whether species direction change between host blastocysts and PSCs (mouse-to-rat versus rat-to-mouse) would become the key of the success," he adds. *Sall1* is a gene essential for kidney development and *Sall1*-mutant homozygous mice (*Sall1*$^{mut/mut}$) die soon after birth because of kidney agenesis or severe dysgenesis. Initial attempts to grow rat kidneys in *Sall1*$^{mut/mut}$ mice by blastocyst complementation were unsuccessful because rat PSCs failed to differentiate into basic kidney structures. The reverse scenario was therefore attempted and mouse PSCs were injected into rat blastocysts. This approach worked: two thirds of neonatal *Sall1*$^{mut/mut}$ rats grew mouse kidneys. "Our findings confirm that interspecific blastocyst complementation is a viable method for kidney generation," says Hirabayashi.

Next, the investigators plan to establish an anephric rat model that lacks multiple genes essential for kidney generation, including genes regulating blood vessel formation in the kidney, for complete replacement of the kidney by PSCs-derived cells. Co-author Tomoyuki Yamaguchi will also attempt a blastocyst complementation approach for kidney generation in large animal models. "Pig is considered as the best host animal species for human organ regeneration but we do not know whether differences in the gestation periods will allow human kidney regeneration in chimeric pigs," explains Hirabayashi. "I can expect this strategy to work; however, I cannot imagine when the practical application comes true," he concludes.

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