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Graft immaturity and safety concerns in transplanted human kidney organoids

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Objectives: For chronic kidney disease, regeneration of lost nephrons with human kidney organoids derived from induced pluripotent stem (iPS) cells is proposed to be an attractive potential therapeutic option. It remains unclear, however, whether organoids transplanted into kidneys in vivo would be safe or functional. Here, we transplanted kidney organoids beneath the kidney capsules of immunodeficient mice to test their safety and maturity.

Methods: Kidney organoid were differentiated from the human iPSC cell line by the established protocol invented by Benjamin Freedman. Adherent kidney organoids were microdissected and transplanted under the kidney capsule of NOD-SCID mouse. Mice were sacrificed at 7 days, 10 days, 14 days, 28 days, and 42 days after transplantation (n=3 per each group).

Results: Kidney organoid grafts survived for months after transplantation and became vascularized from host mouse endothelial cells. Nephron-like structures in grafts appeared more mature than kidney organoids in vitro, but remained immature compared to the neighboring mouse kidney tissue. Ultrastructural analysis revealed filtration barrier-like structures, capillary lumens, and tubules with brush border in the transplanted kidney organoids, which were more mature than those of the kidney organoids in vitro but not organized as adult mammalian kidneys. Stroma of transplanted kidney organoid grafts were filled with vimentin-positive mesenchymal cells, and chondrogenesis, cystogenesis, and stromal expansion were observed in the long term. The transcription profiles examination showed that long-term maintenance after kidney organoids transplantation induced transcriptomic reprogramming with prominent suppression of cell-cycle-related genes and upregulation of extracellular matrix organization.

Conclusions: Our data suggest that kidney organoids derived from iPS cells may be transplantable but strategies to improve nephron differentiation and purity are required before they can be applied in humans as a therapeutic option.