CELL BIOLOGY

Reproducibly generating organ buds *in vitro*

Coculture of three cell types on hydrogel with the appropriate stiffness enables the generation of functional organ buds.

For patients with end-stage organ failure, a transplant is the only treatment option and is often delayed owing to a shortage of donors. The *in vitro* culture of patient-specific organs has long been seen as a solution, as technically challenging as it is desirable. Takanori Takebe of Yokohama City University and Hiroshi Yoshikawa of Saitama University, both in Japan, wanted to take *in vitro* organ bud culture beyond proof of principle and show that it is a robust method.

Takebe and colleagues had demonstrated a few years ago that cocultured induced pluripotent stem cell-derived hepatic endoderm cells, mesenchymal stem cells (MSCs) and endothelial progenitor cells will self-assemble to form liver organ buds that grow into a vascularized, functional liver after transplantation into a mouse. The researchers used Matrigel, a mix of extracellular matrix proteins secreted by mouse sarcoma cells, as the substrate that triggered self-organization, but "little is known about its critical components," says Takebe. "I noticed that some environmental factors affect liver bud self-organization. I wanted to precisely define the physical mechanisms for multicellular assembly as well as their cellular or molecular mechanisms," he says.

In their new work, the researchers studied the crucial components of the culture system by labeling the three cell types with different fluorescent markers and tracking their self-assembly into organ buds with time-lapse imaging. They saw that MSCs contributed the contraction force that drives self-organization and that substrate stiffness influenced condensation.

"Fine-tuned cell-substrate mechanical interaction is one of the keys to generate organ buds," says Yoshikawa. For him, this work calls into question what he refers to as the classical paradigm—that cell aggregates form if the strength of cell-cell adhesion exceeds that of cell-substrate adhesion. The researchers saw good cell-aggregate formation if they cultured the cells on hydrogels with moderate stiffness. Yoshikawa concludes that "the regulation of cell-substrate interaction using gels can potentially become a basic strategy to generate functional organ buds." The researchers generated vascularized organ buds for multiple organs.

How long before this culture system yields human organs? Takebe says it is possible but challenging. "We need a more comprehensive understanding of natural human organogenesis to move forward," he says.

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RESEARCH PAPERS

Takebe, T. *et al*. Vascularized and complex organ buds from diverse tissues via mesenchymal cell–driven condensation. *Cell Stem Cell* **16**, 556–565 (2015).