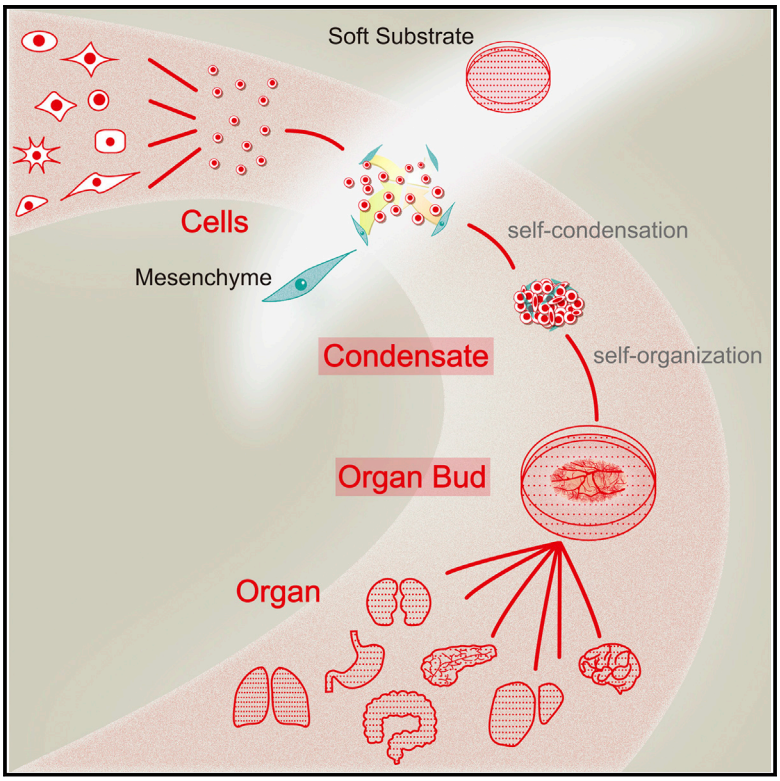
Short Article

Cell Stem Cell

Vascularized and Complex Organ Buds from Diverse Tissues via Mesenchymal Cell-Driven Condensation

Graphical Abstract



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In Brief

Takebe et al. report a generalized method for organ bud formation from diverse tissues, including kidney, pancreas, intestine, heart, lung, and brain, using heterotypic cell mixtures including mesenchymal stem cells to guide cell condensation. After transplantation, renal and pancreatic buds are readily vascularized and exhibit tissue-specific organization and function.

Highlights

- Transplantable organ buds self-assemble from diverse and heterotypic cells
- Mesenchyme-driven condensation on soft matrix is crucial for organ bud generation
- Transplanted diverse organ buds quickly become vascularized in vivo
- Vascularized organ buds generate functional tissues via in vivo self-organization

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Vascularized and Complex Organ Buds from Diverse Tissues via Mesenchymal Cell-Driven Condensation

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SUMMARY

Transplantation of in-vitro-generated organ buds is a promising approach toward regenerating functional and vascularized organs. Though it has been recently shown in the context of liver models, demonstrating the applicability of this approach to other systems by delineating the molecular mechanisms guiding organ bud formation is critical. Here, we demonstrate a generalized method for organ bud formation from diverse tissues by combining pluripotent stem cell-derived tissue-specific progenitors or relevant tissue samples with endothelial cells and mesenchymal stem cells (MSCs). The MSCs initiated condensation within these heterotypic cell mixtures, which was dependent upon substrate matrix stiffness. Defining optimal mechanical properties promoted formation of 3D, transplantable organ buds from tissues including kidney, pancreas, intestine, heart, lung, and brain. Transplanted pancreatic and renal buds were rapidly vascularized and self-organized into functional, tissue-specific structures. These findings provide a general platform for harnessing mechanical properties to generate vascularized, complex organ buds with broad applications for regenerative medicine.

INTRODUCTION

Current stem cell therapies primarily target diseases that are treatable by cell transplantation, which is accomplished via cell-type specification of stem cells and reprogramming factors (Sasai, 2013b). However, these prevailing transplantation approaches produce limited clinical therapeutic outcomes as well as potential side effects compared with organ-based therapy (also termed organ transplantation). Given the limitations of cell-based approaches, the development of innovative technologies that enable the reconstitution of 3D organs from stem cells is urgently required to potentially address the severe donor organ shortage and to lower the high medical costs incurred by the increasing numbers of waiting patients.

Despite the recent remarkable progress in "organoid technology," including the generation of the optic cup (Eiraku et al., 2011), the pituitary epithelium (Suga et al., 2011), the intestine (Sato and Clevers, 2013), and the cerebrum (Lancaster and Knoblich, 2014), the reported examples are composed entirely of epithelial structures and generally lack complex structures such as blood vessels. These characteristics limit their application, especially in the context of clinical transplantation. Specifically, much of the reported examples have relied on tissues with a high level of intrinsic self-organizing capacity from unilineage progenitor aggregates such as pluripotent stem cells; however, the likelihood of growing a complex and well-vascularized organ in dishes has seemed much less plausible (Ding and Cowan, 2013).

In general, the organ develops from a condensed tissue mass prior to blood perfusion, termed the "organ bud," emerging at early stages of organogenesis through the process of cell condensation. For instance, the multicellular orchestration that occurs between mesenchymal cells, undifferentiated vascular endothelial cells, and endoderm cells is required for the initiation of 3D liver bud condensation, which is characterized by a drastic delamination from an endodermal sheet-like tissue (Matsumoto et al., 2001). By mimicking this early organogenetic event, we have recently developed a groundbreaking culture method for deriving a 3D and transplantable organ bud in a dish from human induced pluripotent stem cells (iPSCs) cocultured with mesenchymal and endothelial progenitors. This system enables multiple progenitors to interact in a 4D (spatiotemporal) manner in vitro and in vivo, demonstrating the growth of a vascularized and functional organ via a human iPSC-derived organ bud transplant (Takebe et al., 2012, 2013, 2014b). The most notable aspect of our previous findings is the extremely large-scale morphogenetic changes that occurred even in 2D culture, in which transplantable tissues can be grown on a millimeter or even a centimeter scale from multiple heterotypic cell collectives.

The next critical steps would be to gain insight regarding the mechanisms underlying this dynamic process in culture and to