Science Education Collection

An Introduction to Organogenesis

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Abstract

Organogenesis is the process by which organs arise from one of three germ layers during the later stages of embryonic development. Researchers studying organogenesis want to better understand the genetic programs, cell-cell interactions, and mechanical forces involved in this process. Ultimately, scientists hope to use this knowledge to create therapies and artificial organs that will help treat human diseases.

This video offers a comprehensive overview of organogenesis, starting with historical highlights describing the breakthrough studies done in the 1800\'s, all the way to the first human surgery using tissue-engineered organs performed in 2008. Next, key questions asked by developmental biologists are introduced, followed by a discussion of how tissue transplantations, imaging, and in vitro culture techniques can be used to answer these queries. Finally, we describe how these methods are currently being employed in developmental biology laboratories.

Transcript

Scientists in the field of organogenesis investigate the development of organs with highly specialized forms and functions.

Organs arise relatively late during development, after the embryonic cells have arranged themselves into three discrete cell layers known as the germ layers. By considering how organs are formed, researchers can better understand how individual organs function, and create therapies that will correct human disease related to organ failure.

This video presents a brief history of organogenesis research, introduces key questions asked by embryologists who study organ formation, describes some tools available to answer those questions, and finally discusses current experiments being conducted in the field.

Let's start by reviewing some landmark studies in the history of organogenesis research.

In the 1820s, Karl von Baer and Christian Heinrich Pander described the germ layer theory of development. Based on the chick model, von Baer and Pander proposed that all vertebrate embryos are composed of three distinct primary cell layers, which together give rise to all adult organs. The endoderm gives rise to deep tissues such as the lining of the intestine and respiratory tract, the mesoderm forms middle tissues including muscle and blood, and the ectoderm generates more superficial tissues like skin and nerves.

Sixty years later in 1885, Wilhelm His published the first atlas of human embryos reconstructed from microscopic sections. This collection provided one of the first detailed descriptions of organogenesis, and hypothesized about how various groups of cells arrange themselves to form organs such as the heart, eyes, and brain.

In 1924, embryologists Hans Spemann and Hilde Mangold took a more experimental approach to studying organogenesis: they performed tissue transplantations in amphibians to study a region of the developing embryo now known as the Spemann organizer. Transplanting the organizer from one embryo to another induced the formation of secondary neural tissues. This change in developmental patterning due to cellular interactions became known as "induction," and is a critical first step in the formation of many organs.

In the decades following this major discovery, advances in microscopy and molecular biology meant that embryos could now be studied at the cellular and molecular levels. In the 1940s, Salome Gluecksohn-Waelsch used the mouse as a model to understand that specific genes could regulate organ development. She showed that mice with mutations in the T-locus gene lacked important structures in the developing nervous system, like the notochord.

This work paved the way for W. T. Green to investigate the generation of tissues *in vitro* during the 1970s by implanting healthy cartilage cells cultured in the laboratory into nude mice. Although unsuccessful, in 1981 Green's findings helped researchers, such as Ioannis Yannas and Eugene Bell, introduce tissue grown *in vitro* back into living animals. This technique led to a major breakthrough in 2008, when Paolo Macchiarini carried out the first tissue-engineered whole-organ transplant by replacing a patient's left bronchus with tissue that was grown in a laboratory.

Now that we have reviewed some historical highlights, let's examine a few fundamental questions facing the field of organogenesis today.

We'll begin with perhaps the broadest question asked by embryologists: how do groups of cells transform into highly structured organs? For answers, researchers often focus on defined morphological events, like the branching of simple tubes into complex tubular networks. The mechanisms controlling these processes in one tissue may be similar to those used in other tissues with analogous structures, which gives researchers clues about how to design their experiments.

Embryologists are also interested in how specific genes direct organogenesis. Some focus on individual genes and how their products function to control the size and shape of cells, as well as how cells generate and respond to signals in order to form a functioning organ.

Others investigate the mechanisms that determine when and where genes are expressed. Transcription factors, for example, are proteins that attach to specific DNA sequences to control the expression of nearby genes. By simultaneously regulating whole sets of genes that define each particular cell identity, a relatively small number of transcription factors can direct the formation of entire organs.

Since cells are also sensitive to mechanical cues, many scientists explore how physical forces guide organogenesis. Some look at how the force generated by fluids flowing over cell surfaces, known as shear stress, influences cell differentiation. Others consider how tissue tension promotes connections between cells, which are important for the integrity of tissues like muscles and bones.

Finally, because there are not enough healthy human organs available to meet the need for transplants, scientists are devising new ways to engineer organs in the laboratory. Their primary goals include creating scaffolds, or artificial structures capable of supporting three-dimensional tissues, and optimizing conditions for organ growth. Cells used to construct an organ, for example, must be able to expand their population quickly while remaining genetically stable. When cells are successfully assembled into tissues, ensuring that the organ develops a functional blood supply is an added challenge.

Now that you have a feel for some key questions raised by embryologists, let's look at a few research tools they use to find answers.

Various imaging techniques are used to look at cells assembling into more complex organs. Fate mapping is one approach that relies heavily on imaging, since it involves tracking single cells and their progeny throughout development. To create fate maps, scientists can monitor cells of interest by labeling them with fluorescent peptides.

Imaging is also necessary in cell grafting and transplantation experiments. Here, cells are transplanted between two organisms, a donor and a host, and organism-specific markers are then used to determine how the identity and placement of the transplanted cells determines their contribution to developing organs.

To examine the genetic control of organ development, scientists have a number of strategies to manipulate gene expression in developing tissues. Using transgenic technology, for example, animal genomes can be modified to increase or decrease expression of specific genes in either the whole animal or in select tissues. For a simpler approach to genetic manipulation, techniques like viral transduction are frequently used to rapidly deliver gene expression or silencing constructs into smaller populations of cells.

To study the role of mechanical forces during development, scientists often turn to *in vitro* culture systems that imitate *in vivo* physiology. For example, cells grown on flexible substrates can be stretched as they grow. Cells are also frequently grown in specialized microfluidic chambers to mimic shear stress. Immunofluorescence and other microscopy methods are then used to look at how tissue development and cellular contacts are affected.

Tissue engineering is a technique focused on translating knowledge of organ formation into clinical therapies, and involves culturing healthy cells on biological scaffolds. Scaffolds can be constructed by removing cellular materials from tissues using detergents, salts, and enzymes, and then repopulating the tissue of interest with stem cells. Alternatively, scaffolds can be created from biodegradable polymers using electrical charge. Regardless of how they are made, scaffolds are seeded with cells and cultured under controlled conditions in specialized setups known as bioreactors.

Now that you're familiar with some common approaches to studying organogenesis, let's look at how these methods are being applied.

Organisms that contain cells from more than one genome, known as embryonic chimeras, are useful tools to track cell movements. In this experiment, zebrafish chimeras were made by transplanting fluorescently labeled donor cells to unlabeled host embryos. These transplants were used to study the role of migration and cell fate determination in the development of embryonic structures like the muscle and brain.

To understand the roles specific genes play in organ development, scientists alter gene expression. In this experiment, gene-specific antisense oligonucleotides, known as morpholinos, were first injected into fertilized zebrafish eggs. Next, developing hearts were analyzed using a fluorescent marker selectively expressed in heart muscle. Here, the combined knockdown of two genes completely blocked heart development.

Tissue engineering allows scientists to investigate interactions between different cell types, and bridge the gap between *in vitro* and *in vivo* studies. In this experiment, reconstructions of human skin were generated in the laboratory. To look at skin development, as well as cancer progression, skin stem cell migration was tracked using fluorescently tagged proteins. Skin reconstructions were then grafted onto mice in order to study skin cell fate and physiology in a living system.

You've just watched JoVE's introduction to organogenesis. In this video, we have reviewed the history of organogenesis research and introduced key questions asked by embryologists. We also explored prominent research strategies in the field, and discussed some of their current applications. Thanks for watching!