

Science Education Collection

An Introduction to Developmental Neurobiology

URL: <https://www.jove.com/science-education/5207>

Abstract

Developmental neuroscience is a field that explores how the nervous system is formed, from early embryonic stages through adulthood. Although it is known that neural progenitor cells follow predictable stages of proliferation, differentiation, migration, and maturation, the mechanisms controlling the progression through each stage are incompletely understood. Studying development is not only important for understanding how complex structures are assembled, but also for characterizing and treating developmental disorders. Since injury repair processes are similar to those that occur in development, this field is also a promising source of insight into when and how nervous system tissues regenerate.

This video provides a brief overview of the field of developmental neuroscience, including some key experiments that have advanced our understanding of the mechanisms controlling the formation of early neural tissue and the further specialization of those cells into discrete subsets of neurons. The discussion focuses on prominent questions that developmental biologists are asking and then demonstrates some of the methods that they use to investigate these questions. Finally, applications of the techniques are presented to provide insight into what it means to be a developmental neuroscientist today. The range of experiments demonstrated includes genetic manipulation of intact embryonic brains, targeted differentiation of stem cells into nervous system cells, and staining techniques that allow for the quantification of specific developmental events, like the formation of new connections between neurons.

Transcript

Developmental neurobiology explores how a few early embryonic cells can transform into an intricately organized nervous system that controls an entire organism.

Scientists in this field are interested in how cells take on specific identities, migrate to defined regions, and connect to form a functional system. These processes are important for understanding how the nervous system functions as well as the diagnosis and treatment of a broad range of neurological diseases rooted in abnormal development.

This video will take you on a brief tour of the history of developmental neurobiology, outline key questions in the field, and explore prominent methods used to answer those questions. Finally, we'll have a look at some practical applications of neurodevelopmental research.

Let's begin with some landmark studies from the history of developmental neurobiology.

Early neurodevelopmental research dates back to the 19th century. In the 1880s, Wilhelm His established the study of histogenesis, or the embryonic origins of tissue. He was one of the first people to watch developing neurons extend processes like axons and dendrites.

In 1924, embryologists Hans Spemann and Hilde Mangold studied the function of a cluster of cells known as the Spemann organizer. They found that the transplantation of the organizer to another embryo induced the formation of secondary neural tissue.

Then in the 1950's, Rita Levi-Montalcini and Stanley Cohen observed that transplanting pieces of tumors onto developing chicken embryos led to rapid neuron growth. They speculated that the tumor secreted a substance that caused this growth, and soon identified that protein as nerve growth factor, or NGF, which is essential to neuron survival.

In another transplant study, Nicole Le Douarin replaced parts of chick embryos with those from quails. By tracking the quail cells through development, she showed that a highly migratory group of cells, known as the neural crest, gives rise to mature peripheral nerves.

A few years later, Pasko Rakic studied how cells of the central nervous system arrange themselves into highly ordered structures during development. Rakic labeled dividing cells in developing fetuses with radioactive nucleotides, allowing him to determine when brain cells were born and where their final destination was in the mature brain.

During the last decades of the 20th century, a new era of research emerged that focused on the cell and molecular signals guiding nervous system development.

For example, in the mid '90s, Tom Jessell showed that certain transcription factors, or proteins that help control gene expression, influenced the development of unique subtypes of neurons in the developing mouse spinal cord. Following on this work, today's researchers are still identifying new genes that control neural development.

Now that you've seen a few historical highlights, let's go over some key questions in modern developmental neurobiology.

Many researchers study patterning and fate specification of nervous system cells. For example, they are interested in the genetic programming that guides early stem cells to differentiate into either neurons or glia, which are the support cells of the nervous system. They may also investigate secreted signals that influence more specialized identities within a class of cells or in specific locations.

Another major focus is how developing neurons and glia are able to organize themselves and assemble into the mature nervous system. Some researchers study cytoskeletal dynamics of cells migrating from their origin to the site at which they function. Others are interested in how signals from the extracellular environment influence migratory behavior.

Developmental neuroscientists also evaluate how connections between cells are formed and refined over the course of development. Some studies focus on the function of axon guidance receptors, which are cell surface proteins that detect external cues and guide developing axons, or neurites, to their target cells. Another focus is the study of the physical and chemical connections involved in synaptogenesis, which is the formation of new signaling connections, or synapses, between cells.

Now, let's look at a few prominent methods used to answer some of these neurodevelopmental questions.

To study the genetic control of cell identity and nervous system patterning, it is helpful to manipulate the expression of specific genes in developing embryos. One popular method is *in utero* electroporation, in which exogenous DNA is delivered into the brain of developing rodents. By exposing the uterus of an anesthetized, pregnant mouse DNA can be injected into the embryonic brains and current applied to force the DNA into surrounding cells. Depending on the experiment, electroporated material can be used to either promote gene expression or prevent it, allowing researchers to examine the impact of individual proteins on brain development.

Explanted central nervous system tissue is commonly used to study cell migration during development. This technique involves dissecting small pieces of brain or spinal cord and culturing them *in vitro*. A major advantage to this approach is that the tissue is highly accessible for capturing cell movements via time-lapse imaging. Additionally, the effects of specific molecules on migration can easily be studied in explants through application of growth factors or pharmacological inhibitors to the culture media.

To study the molecules that are essential to the formation of neuronal networks, immunohistochemistry can be used. This technique takes advantage of the specificity of antibodies to mark the location of specific proteins in cells and tissues. Visualization of protein localization using fluorescent microscopy can help researchers make hypotheses regarding how these molecules influence the formation and function of structures like the synapse.

Now that you're familiar with some approaches to studying developmental neuroscience let's look at applications of this research in labs today.

A major goal of the study of neurodevelopment is to figure out how cell identity and morphology are determined. To study the genetic control of neuron development, these researchers delivered gene knockdown constructs into the developing chick nervous system via electroporation. Electroporated neurons within the neural tube were also labeled by dye injection, so that axon morphology could be compared between control and genetically altered cells.

To study how neurons establish connections, these researchers cultured neurons extracted from young rat pups. After several days in culture, cells were fixed and stained with antibodies specific to synaptic proteins, allowing for quantification of synapse formation under multiple experimental conditions, such as gene overexpression, or culture in modified growth medium.

Using their knowledge of the program driving neural development, today's researchers can now force early embryonic cells, like stem cells, down specific differentiation pathways *in vitro*. These researchers treated human stem cells with the vitamin A derivative, retinoic acid, which resulted in reduced expression of transcription factors that maintain stem cell identity and enhanced expression of neuronal markers. This technique provides researchers with a valuable source of human neurons for investigating the mechanisms behind neurological disease.

You've just watched JoVE's introduction to developmental neuroscience. This video reviewed historical highlights, key questions asked by developmental neuroscientists and some of the techniques they use.

Thanks for watching!