Module:
Biological Foundations of Mental Health

Week 2
Building blocks of the brain

Topic 2
From embryonic NPCs to AHN – part 1 of 4

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Lecture transcript

Slide 2

In this short section, entitled From Embryonic Neural Progenitor Cells To Adult Hippocampal Neurogenesis, I want to link what you heard from Professor Sarah Guthrie about the generation of neurons, or neurogenesis, during development, to what you will hear from Dr. Sandrine Thuret about the generation of new neurons in the adult brain.

As you will remember from Sarah's lecture, during development neurons are generated by radial glial cells. Here we can see a picture of radial glial cells in the developing mouse cortex. In this picture, these cells appear green because they have been labelled with a green fluorescent protein so that they can be observed under a fluorescence microscope.

These cells get their name because of their radial morphology. Their processes span the entire thickness of the developing cortex, from the ventricle, labelled "V", at the bottom of the picture to the peel surface, labelled "P", at the top of the picture. And also because they share certain characteristics with a particular type of glial cell in the brain called an astrocyte.

During development, these radial glial cells are generated from new epithelial cells. These cells are the cells that form the neural tube and are the characteristics of embryonic neural stem cells, as I will explain shortly.

The picture shows a section through a neural tube with the new epithelial cells stained using an antibody that recognises a protein called SOCS-2. This protein is expressed by new epithelial cells.

These cells appear pink in colour because the antibody has been tagged with a fluorescent probe so that these cells can be observed under a microscope. Later in development, these radial glial cells go on to generate adult neural stem cells as required to generate specific types of neurons in the adult brain.

The stem cells reside in two specific locations in the adult brain, the subventricular zones of the lateral ventricles and the subgranular zone of the dentate gyrus, which is part of the hippocampal formation. You will shortly hear more about adult hippocampal neurogenesis from Dr Sandrine Thuret, but what I want to do now is to give you an overview of how we get from the new epithelial cells of the neural tube to the adult neural stem cells via radial glial cells.

Before going any further, I would like to remind you that further information on any of the concepts that I cover here can be found in the references provided to you for this sub-topic.

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As I mentioned earlier, the new epithelial cells that form the neural tube are the founder cells of the central nervous system, and as such, can be thought of as embryonic neural stem cells. This means that they have the capability to generate all the different cell types in the developing central nervous system.

That is, they have the ability to generate all the different types of neurons, and also, two types of glial cells, astrocytes and oligodendrocytes.

All the pictures on this slide show you what these different cell types look like when isolated and grown in the laboratory. Again, they appear coloured because they are labelled with specific markers that have been tagged with a fluorescent probe, allowing these cells to be observed under a microscope.

Slide 4

Like all other stem cells, embryonic neural stem cells are non-specialised cells that have two specific characteristics. They can self-renew and differentiate. They differentiate into appropriate specialised cell types, which for neural stem cells are neurons, astrocytes, and oligodendrocytes. Let's look at each of these characteristics in a little more detail.

Self-renewal is the ability of a cell to divide and generate two cells that are identical to the parent cell. Self-renewal is needed to make sure the cells don't run out. In other words, that sufficient numbers of embryonic stem cells are present to enable the generation of all the different brain cells that we need.

Differentiation is the ability to divide and generate more specialised cell types. This process is important for making all the different kinds of cells that are required to generate a proper functioning brain.

Differentiation can occur in a number of ways. To explain this, I will consider the different ways that neurons may be generated.

An embryonic neural stem cell may divide and generate another embryonic neural stem cell and a neuron. Or an embryonic neural stem cell may divide, generating a progenitor cell, like a radial glial cell, and a neuron. This radial glial cell also has ability to self-renew, but it does this mainly by dividing to generate one cell that is like itself and a neuron, but the radial glial cell might also divide to generate a dedicated progenitor cell.

That is, a progenitor cell that has the ability to only generate a single cell type. For instance, a neuron. And while doing this, it also generates a neuron.

This process of differentiation, where a parent cell makes two different progeny, is called asymmetric differentiation.

However, radial glial cells cannot make embryonic neural stem cells, and dedicated progenitor cells cannot make radial glial cells or embryonic neural stem cells. And as I'm sure you know, neurons are terminally differentiated, so do not divide at all.

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So if we think about specialisation, the embryonic neural stem cell is the least specialised cell. Then we have the radial glial cell, then the dedicated progenitor cell, and then the neuron.

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Let me now put these ideas together and link these to the generation of adult neural stem cells. Initially during development, embryonic neural stem cells self-renew to expand the progenitor pool. They will then begin to generate neurons, because during development, neurons are generated before glial cells.

As well as generate neurons, embryonic neural stem cells will also generate radial glial cells. These cells, as I told you, also have the ability to self-renew and generate neurons either directly or via a dedicated progenitor cell. That is, a cell that will only generate neurons in this case.

Just to complicate matters further, embryonic stem cells can also generate neurons via dedicated progenitor cells, too. Why are there so many different ways to generate neurons? Well, we consider that this is because there are many different types of neurons that need to be made over a very specific time period during development, and this is especially true when we consider the complexity of the human brain.

Later in development, radial glial cells begin to generate oligodendrocytes and astrocytes, again via dedicated progenitor cells.

Radial glial cells also generate another type of cell, the adult neural stem cell. As their name implies, these cells retain the capacity to generate new neurons throughout our lifetime.

You will now explore the characteristics and function of adult neural stem cells with Dr Sandrine Thuret.