Module:
Biological Foundations of Mental Health

Week 2
Building blocks of the brain

Topic 3
Exploring mental health using stem cells: What are iPSCs? – part 2 of 3

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Lecture transcript

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OK, in the previous session, we learned how Shinya Yamanaka and his colleagues taught us how to make IPS cells, Induced Pluripotent Stem cells, starting really from any tissue sample. And I explained how in our laboratory, we start from hair samples, but you can start from blood, or skin, and probably any tissue-- and how using those, we make these IPS colonies.

From the IPS colonies, we make IPS lines. So in this session, I wanted to explain what you can do with them, particularly what you can do with them if, like me, you're interested in brain development, and you are interested in disorders in brain development.

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We're obviously interested in nerve cells. So the first job for us is to see if we can take these pluripotent cells, which by definition, as you've already heard, can make all the different cell types that make up the body. Can we turn them into neural cells? And, in fact, we can.

So what we're able to do by inducing the cells to adopt a neural fate is get them to make neural progenitor cells. And from neural progenitor cells, to go on and make neurons.

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So let's look at this process in just a little bit more detail. So we start with this IPS cell line. We've made many IPS lines, and many are available now worldwide. And the first job is to induce them to make neuroepithelium, rather than anything else. We've learned to do that by inhibiting what are called the Smad signalling pathways.

And the advantage of that is that we're able to make use of a lot of embryology that we've understood now for really quite a few years. So we know from studies principally of mice, but also of other organisms, precisely what it is at the early stages of normal development that push the pluripotent cells, those inner cell mast cells, to go on and give different tissue types.

And we know that if we inhibit the Smad pathways that are normally driven by a class of morphogens called BMPs, Bone Morphogenic Proteins, then we can induce neuroepithelium. And sure enough, that's what happens. So the first step in our procedure is to add what we call Smad inhibitors to the culture of these induced pluripotent cells.

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And if we culture those cells, we then start to see these neural progenitors. And the first thing to notice about them that makes them really quite distinct from neural stem cells that we've come across in other contexts is that they really can do tissue histogenesis. That's something I'm going to have more to say about in a couple of minutes.

But notice how they make proper polarised neuroepithelium. What these cells are trying to do here is essentially trying to make a neural tube in two dimensions. So this is a two-dimensional culture, so a monolayer culture, if you will. But nonetheless, the cells are rounding up to make these what we call neural rosettes, these sort of flower-shaped structures, where they've got an actual apical centre just as the apical centre is in the neural tube surrounded by the basal processes of these neuroepithelium cells.

So these neural progenitor cells will go on and make neurons. And if you treat them appropriately, you can get them to form post-mitotic neurons. And these post-mitotic neurons will become increasingly mature. And over days and weeks, they will give rise to mature, physiologically-active neurons.

Now, one of the things to point out at this juncture is that this process is really quite slow, which in one sense, is a bit of a nuisance, of course. From an experimental point of view, it takes a long time to start from the immature IPS cells, pluripotent IPS cells, and get all the way out to even halfway mature neurons.

So this is the sort of timing of this progression in days from day one, for example, to day 35 or 50 out here. But of course, that's reassuring, because our human development is slow compared to the kind of experimental animals we're normally used to dealing with such as rodents. So this system really does reproduce the timing and the differentiation processes that seem to underly human neural development.

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And this just gives you an example of what you end up with. So this is a plate of, in this case, cerebral cortical neurons. And it's really remarkable. So there we are. We've got to plate of, I don't know, a billion cortical neurons. Just think how difficult it would be normally to get hold of a plate of a billion human cortical neurons on which you could do experimentation.

But we can get a billion today, and then I can get a billion tomorrow exactly the same. So it really is an enabling technology that finally allows you to look at neural development in a culture dish-- proper human neural development.

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Now, I do want to pick up on this point about histogenesis. So I've pointed out that these cells really do, when they neuralise, take on a neurepithelial structure. And they really do make a proper polarised neuroepithelium. And if you allowed that to develop, the cells really do try and undergo proper histogenesis. So you can see that down here if we look at this lower picture down here.

So here's one of those neural rosettes that I was telling you about a little bit earlier-- these polarised neuroepithelial cells with their apical surface towards the centre and their basal surface towards the outside. And these cells have been making neurons for a couple of days. And the neurons are the cells stained red.

And you can immediately see in this example that the neurons have been generated by the neuroepithelial cells. And just as in vivo, the cells have migrated out to come alive outside the neuroepithelium. And this is an example of a little bit more advanced. And you can see there the

apical surface of the neuroepithelium, here are the neuroepithelial cells.

And out here the neurons starting to form a lamina in what would be the basal surface of the neuroepithelium. And you can let this go further and further, and this is a much more advanced structure. And you can see the collection of neurons out here just as you would normally see them in vivo in a developing cortical plate.

So the cells really have a capacity for histogenesis. That other population of neural stem cells that you might have come across in a different context other such populations simply do not have.

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And you can push this really a long way. So this is a picture taken from this publication of Madeline Lancaster's in 2013. What she's shown is that if you grow the cells appropriately in aggregate cultures, you can actually make them make sort of mini brains-- cerebral organoids, as she calls them.

And you can see that these organoids have got real structure. It's a cortical structure out here developed entirely from these induced pluripotent stem cells growing in a culture dish. So these cells have a capacity for histogenesis that really is remarkable. They really do try and build the nervous system just in a culture.

Now, eventually, this process ceases, and it can only go so far, because obviously, a brain can only get so large before it really does become dependent on a blood supply. And there's no blood supply in these cultures. So there are enormous challenges to carrying this forward infinitely.

Nonetheless, these cells have a capacity for histogenesis we've really never seen before in other neural developing systems in vitro. And the potential use of that for regenerative medicine is one that I'm not going to talk anymore about today, but it's fairly obvious.