Module:
Biological Foundations of Mental Health

Week 2
Building blocks of the brain

Topic 2
From embryonic NPCs to AHN – part 3 of 4

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Lecture transcript

Slide 2

So, we have learned about the niche. We have learned that astrocytes are important. But what are the actual molecular controller responsible for adult neurogenesis?

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So this is another view of what we knew about the molecular control of adult neurogenesis ten years ago. This figure is quite sparse. At the time, we understood very well how adult neural stem cells proliferate - with, for example, epidermal and fibroblast growth factors, EGF and FGF2, which are the primary mitogens used to propagate neural stem cells *in vitro* and are believed to be very important for the control of in vivo proliferation of neural stem cells or progenitor cells.

Next, the molecular mechanism underlying fate specification of adult neural stem cells over a decision to actually become neuron at this time had just began to be revealed. So we knew, back in 2004, that adult neural stem cells express member of the bone morphogenic protein, BMP, family that instruct them to adopt a glial cell fate. However, in the neurogenics niche, the BMP inhibitor Noggin is secreted by the ependymal cells and presumably serves to block the gliogenic effect of BMPs, so driving the fate of the neural stem cells towards a neuronal fate in the niche.

When we think about factor control in later step, in neurogenesis, such as functional maturation, synapse formation and integration into the neuronal circuit and the survival, were then, at the time, unknown.

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We now know a lot more on the molecular mechanism controlling all the steps of adult neurogenesis. And I invite you to have a look at this updated review and find your favourite molecule involved in proliferation, differentiation, migration, all the way down to integration.

And for this lecture, I want to give the example of Wnt signalling as one of the key molecular regulator of adult neurogenesis. I chose Wnt, as it is actually secreted by astrocytes, one of our niche key player.

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So in this 2005 Nature article, the author showed for the first time that Wnt signalling regulates adult hippocampal neurogenesis.

The first clue they got was via in situ hybridisation, identifying cells expressing Wnt in the subgranular zone, where neural stem cells reside within the hippocampal niche. They then extracted adult hippocampal stem cells and cultured them *in vitro*, with or without Wnt factors. They show here that Wnt-3 pushed them towards a neuronal fate, as indicated by the increased number of neuroblasts, or young neuron, labelled here with doublecortin, or DCX, in red. It is nicely quantified on the graph, with a fourfold increase of neurons produced when neural stem cells are cultured in the presence of Wnt.

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For their next experiment, they moved *in vivo* and injected the hippocampus with a controlled antivirus only expressing a green fluorescent marker, or they injected the hippocampus with a dominant negative Wnt antivirus blocking Wnt signalling. They show here that the number of newborn neurons has decreased of eightfold when Wnt signalling was blocked, their data demonstrating that Wnt signalling was an important regulator of adult hippocampal neurogenesis.

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So we have gone through the importance of the niche. We have looked at some of the molecular control. So now, what is the functionality of adult neurogenesis? What are these newborn neurons for?

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So we know that adult hippocampal neurogenesis is important for learning and memory. The level of neurogenesis in the dentate gyrus is positively correlated with hippocampal-dependent learning tasks. And there is plenty of paper out there showing that type of evidence.

And in many of the studies, if we actually block neurogenesis, then we block hippocampal-dependent learning abilities. And the dotted line I placed there is to illustrate that actually hippocampal-dependent learning can also modulate neurogenesis - so, showing a bi-directional link between learning and neurogenesis.

So multiple mechanisms for the relationship between increased neurogenesis and improved cognition have been suggested, including computational theories to demonstrate that new neurons increase memory capacity, reducing difference between memories - what we call 'pattern separation' - or add information about time to memories. Of these, post-natal new hippocampal neurons could be also involved in forgetting during infancy.

So this is a new field, and we are still trying to understand the implications of this new neuron in memory formation. So research is still ongoing, to explore their exact role.

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Adult hippocampal neurogenesis is also implicated in mood regulation and depression. So, adult hippocampal neurogenesis is reduced in many animal models of depression, and many treatments for depression actually promote adult hippocampal neurogenesis.

So, although more evidence suggests that neurogenesis alone cannot mediate the effect of anti-depressant, it is a key player. Such as, if you give anti-depressant to an animal model of depression, you will alleviate the symptom of depression. But if you block neurogenesis in the same animal model of depression, then you will prevent the efficacy of the anti-depressant - so, showing

a link between neurogenesis and depressive behaviour. And research is still ongoing to understand more precisely the role of this new neuron in mood and depression.