Module:
Biological Foundations of Mental Health

Week 2
Building blocks of the brain

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

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Lecture transcript

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So you have just learned about the concept of neural stem cells and the production of neurons derived from these neural stem cells during development. Now we are going to go through the concept of adult neurogenesis, then explore the location/environment - also called the 'niche' - where adult neurogenesis is occurring. I will also discuss the molecular control of adult hippocampal neurogenesis, the functionality of adult hippocampal neurogenesis, and finally how adult hippocampal neurogenesis can be modulated.

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So the concept of adult neurogenesis, or the birth of a new neuron in the adult brain, is fairly new. And since the early 1900s, it was generally believed that no new neurons can be generated in the adult central nervous system. And, as then stated Cajal, 'Once development has ended... everything may die, nothing may be regenerated'.

Then, 50 years ago, Altman and collaborator suggested, with autoradiographic and histological evidence, that some new neurons were indeed born in the adult hippocampus of rats. But it is not until the early '90s that work started again, with the development of new technology, to definitely prove that neurogenesis was occurring in restricted regions of the adult brain.

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So two adult neurogenic niches have consistently been found in the rodent, during normal physiological conditions - the subventricular zones of the lateral ventricle, where the neural stem cells give rise to newborn neurons that will migrate to the olfactory bulb, and the second niche is the subgranular zone of the dentate gyrus in the hippocampus. Importantly, the generation of new neurons throughout adulthood has not only been demonstrated in the hippocampus of rodents but also in the hippocampus of humans.

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Indeed, elegant work from the group of Jonas Frisen, from the Karolinska Institute, assessed the generation of hippocampal cells in postmortem human brains by measuring the concentration of nuclear-bomb-test-derived C14 in genomic DNA. In this figure, extracted from the original article, we can see C14 concentration in the hippocampal neurogenomic DNA correspond to a time after

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the date of birth of the individual, demonstrating neurogenesis throughout life.

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So when we zoom in to the dentate gyrus of the hippocampus, and then, in the granular cell layer, we have our neural-stem-cell niche, where they will proliferate, differentiate and mature into neurons through the granular cell layer, where they will mature and receive input from the entorhinal cortex and extend projection into the CA3. And it will take up to four to six weeks to go from neural stem cells to mature neurons in rodent, as we see here, on the figure on the right.

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So how relevant is the amount of newborn neuron generating during adulthood? In the adult hippocampus, in human, it is estimated that we produce around 700 new neurons in each hippocampus per day. It does not seem a lot, among the billions of neurons we have in the brain, but by the time we turn 50 we will have replaced the entire granular-cell population we were born with, with adult-born neurons. When investigated adult rodent and a very particular neurogenic niche, it has been found that 70% of the bulbar neurons are replaced then during a six-week period.

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So, now, what makes both two niches so special? Why neural stem cells from only in those privileged areas of the adult brain can generate neurons? What environment makes neurogenesis possible?

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So there has been some classic transplantation studies providing direct evidence for the regulation of fate determination by extrinsic signals that are derived from the neurogenic environment. Such as, if you extract neural stem cells from non-neurogenic regions, like the spinal cord, then grow them in a dish, expand them, then take these cells you have grown in the dish, and then you transplant them back into a non-neurogenic region - so, back into the spinal cord - you still do not get any neurons. However, if you take them, grow them in the dish, and then transplant them in a neurogenic region like the dentate gyrus or the subventricular zone, then these neural stem cells issued from a non-neurogenic region, transplanted in a neurogenic region, give rise to neurons.

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Conversely, if you take neural stem cells from a neurogenic region - let's say, from the dentate gyrus - then transplant them in a non-neurogenic region, like the spinal cord, you do not get neurons. Of course, you transfer them back in a neurogenic region, like the dentate gyrus or the SVZ-- the subventricular zone - then you get a neuron. So, demonstrating direct evidence for the regulation of neuronal fate, determination of stem cells by extrinsic signals that are derived from the neurogenic microenvironment by the niche.

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So, what constitutes a neurogenic niche? We know that endothelial cells and proximity to blood vessels do play a critical role but that also astrocytes within the niche are very important.

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And I would like to highlight here, the first article by Song and collaborator, from the Gage lab, providing evidence that astrocytes are key players in the neurogenic niche, to instruct neural stem cells to adopt a neuronal fate.

So what they did is co-culture experiments. So they extracted neural stem cells from the adult hippocampus - so, here, labelled in green-- and then co-cultured them with astrocytes, either extracted from the adult hippocampus or with astrocytes extracted from a non-neurogenic region, like the spinal cord. So, leaving those neural stem cells to differentiate, together with these astrocytes in cultures, so they did produce more neurons - so, then expressing this neuronal marker mapped to in red - when co-cultured with hippocampal astrocytes.

So it is nicely quantified on the graph, where the neural stem cells produced the most neurons when co-cultured with neonatal hippocampal astrocytes - so, young hippocampal astrocytes. Then the next-best were adult hippocampal astrocytes, and then with spinal-cord-derived astrocytes leading to the lower number of neurons - comparable, actually, to control condition - without any astrocytes.

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