Tubes, Streams, and Arcs How Stem Cells Build the Brain

Rebecca Ihrie

Cell & Developmental Biology and Neurological Surgery rebecca.ihrie@vanderbilt.edu



- Origins of the CNS (with a focus on cortex)
- Differences across species
- Disease states
- What about stem cells in adult brain?

The Brain is Highly Organized (and different across species)











Neurons: information and electrical signal carriers



Santiago Ramon y Cajal, "Estructura de los centros nerviosos de las aves", 1905.

olfactory bulb - Golgi, 1875



Glia - Oligodendrocytes: insulators and dynamic movers



GPR17 regulation of myelination Amyloid plaques in the absence of microglia Nucleus basalis and coding of natural scenes

Glia - Astrocytes: Energy providers and barrier makers



Ramon y Cajal, reprinted in Garcia-Marin et al, Trends Neurosci 2007

In the beginning....

Neurulation: generation and closing of the neural tube



Gilbert, Dev Biol 6th ed., 2000

After neural tube closure, we see ventricular zone progenitors



Copyright © 2002, Elsevier Science (USA). All rights reserved.

Neurons in the cortex have different cell body locations, shapes, and connections









Cajal

Rakic (Science 1988 and others)

How can we *experimentally* show that these cells make the cortex?



Noctor et al Nature 2001



Combinations of labels help us find actively dividing cells and see what they make

Noctor et al Nature 2001

Cortical neurogenesis: early radial glia and inside-out patterning



Kwan et al Development 2012

Relative Sizes and Timing Across Species



mouse: ferret: human

Surface Expansion ~1:100:1000

<u>Neuronogenesis</u> 7:60:120 days

<u>Gestation (d)</u> 19:165:280 Cell Cycle 4X longer

Rakic, 1999

Making a Bigger Brain: More Cells, More Time, and Bigger Cells



Copyright © 2005 Nature Publishing Group Nature Reviews | Molecular Cell Biology

"OSVZ Cells" Outnumber Classic Radial Glia



Hansen et al. Nature 2010

These "Extra" Progenitor Cells Can Divide

oRG cell division highlighting mitotic somal translocation, followed by division of IP daughter



Revising the Model for Which Cells Divide



What happens when it goes wrong?

- Defects in patterning (regions missing)
- Defects in migration (cells in the wrong place)
- Defects in differentiation (small or less "folded" brain)
- Selective loss of progenitors (Zika)

Disrupted migration – smooth or "doubled" cortex

Lissencephaly, Double Cortex







Too few progenitors – a smaller cortex



Baala Nat Neurosci 2007

Cerebral organoids or "mini brains": modeling development in the dish



Lancaster and Knoblich, Nat Protoc 2014

So...what happens after birth??

A Casual Summary of Adult Neural Stem Cell Research Across Species

Does adult neurogenesis exist? No, yes, no, yes, yes, no, yes, yes, yes, YES! Does adult neurogenesis exist in primates? No, no, yes, maybe, yes, yes, YES! Does neurogenesis occur in the neocortex? No friggin way, yes, no way, yes, no way Jose, yes, DEPENDS WHO YOU ASK. Does adult neurogenesis happen in humans? Yes, yes, yes, no, WAIT WTF* DID

YOU SAY NO???

http://snyderlab.com/2018/03/07/wtf-no-neurogenesis-in-humans/

One perspective on the field / its early pioneers: "Rethinking the Brain," New Yorker 2001

Songbird Learning: a Catalyst for the Field





J Neurosci, 1988

Adult Neurogenesis: Two Major Zones





Sanai et al NEJM 2005

Adult Human SVZ is not Highly Proliferative

Although these cells can grow in a dish, it's very rare to detect proliferation in tissue





GFAP, Ki67, DAPI

Proliferation and Immature Cells Disappear Quickly After Birth

1 day

6 months

32 months





vimeintien/tido/ublecort/inD/ADAPI

Sanai et al Nature 2011

Streams and Arcs As Proliferation Declines



Paredes et al, Science 2016

Does increased "complexity" mean less neurogenesis?



Paredes et al, J Comp Neurol 2015

How much neurogenesis happens in adult human brain?



Ernst et al, Cell 2014

How much neurogenesis happens in adult human brain?



Sorrells et al, Nature 2018

National Public Radio, Inc. [US] https://www.npr.org/sections/health-shots/2018/03/07/591305604/sc	Secure https://www.theatlantic.com/science/archive/2018/	/03/do-adult-brains-make-new-neuror	is-a-contentious-	new-study-says-r
C cat station nows arts & life music programs -	AN XXX	1 -197	11/2	The second
\leftarrow \rightarrow C \odot https://www.scientificamerican.com/article/does-the-adult-brain-really-grow-new-neurons/		\$	a. 🖬 📟	V 🛛 🔶 I
SUBSCRIBE	SCIENTIFIC AMERICAN.	English 🗸 Cart 👩 Sign In	Register	
*			SHARE	LATEST

NEUROSCIENCE

Does the Adult Brain Really Grow New Neurons?

A new study stirs up debate over a long-held finding, and could dim hopes for the treatment of neurodegenerative diseases

By Helen Shen on March 7, 2018





Take Home Points

- Patterning and control of cell division and movement over time are essential to building the brain
- The dynamics of division, growth, and persistence of dividing cells vary across species
- "Basic research" can have not-so-basic implications

Thank you for your attention!