Neurogenesis in Adult Central Nervous System: Death of a Dogma

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Neuroplasticity is a continuous process in reaction to neuronal activity and neuron injury, which involves modulation of structural and functional processes of axons, dendrites, and synapses.
Processes that manifest plasticity

- Synapses (electrical, biochemical, structural)
- Neurite (axon, dendrite)
- Neuron cell bodies
- Transport (anterograde and retrograde)
- Cell interactions (neuron - glia)
- Neural networks
**Structural elements** of plasticity

- **Synaptic**
  - efficacy
  - LTP
  - remodeling
  - genesis
- **Neurite extension**
  - axonal sprouting
  - dendritic remodeling
- **Neurogenesis and recruitment**
Structural elements of plasticity
The Nobel Prize in Physiology
or
Medicine 1906
"in recognition of their work on the structure of the nervous system"

Camillo Golgi
- 1/2 of the prize
- Italy
- Pavia University
- Pavia, Italy
- b. 1843
- d. 1926

Santiago Ramón y Cajal
- 1/2 of the prize
- Spain
- Madrid University
- Madrid, Spain
- b. 1852
- d. 1934

www.nobelprize.org
Ramon y Cajal (1928):

“Once development was ended, the founts of growth and regeneration of the axons and dendrites dried up irrevocably. In the adult centers the nerve paths are something fixed, ended and immutable. Everything must die, nothing may be regenerated. It is for the science of the future to change, if possible, this harsh decree.”
Neural Stem Cells

(Okano H, Keio Med J, 2002)

- Undifferentiated
- Proliferate
- Self-renew
- Generate descendants
- Regenerate tissue?
Neurogenesis

Generation of neurons from stem/progenitor cells
SVZ – Cellular architecture

Migration to Olfactory Bulb

Neural Progenitor Cells in Adult Brain

Dennis A Steindler, David W Pincus
Lancet 2002; 359: 1047–54

Anatomy of Primate Hippocampus

Gyrus dentatus

CA1
CA2
CA3
CA4

Entorhinal cortex
Dentate Gyrus - Neurogenesis

1. Progenitor
2. Immature neuron
3. Mature neuron
Gradual Maturation of New Neurons in DG

Functional Neurogenesis

Levels of Functional Analysis in Adult Neurogenesis

Physiological Conditions Affecting Neurogenesis
(Gyrus dentatus)

• *Increased* proliferation
  ➢ environmental enrichment, learning
  ➢ physical exercise

• *Decreased* proliferation
  ➢ ageing
  ➢ maternal separation
Drugs Affecting Neurogenesis
(Gyrus dentatus)

• *Increased* proliferation
  - antidepressants (TCA & SSRI); ECT
  - haloperidol
  - lithium
  - estrogen, aldosterone
  - inhibitory amino acids (GABA)

• *Decreased* proliferation
  - corticosteroids
  - opiates (morphine)
  - excitatory amino acids (GLU)
Clinical Conditions Affecting Neurogenesis
(Gyrus dentatus)

• *Increased* proliferation
  - ischemia
  - seizures
  - trauma
  - degeneration (dementia)

• *Decreased* proliferation
  - stress (depression)
  - irradiation
  - inflammation (meningitis)
  - chronic alcoholism
Multipotent progenitor

FGF-2, EGF

TGFα, Epo, SCF, HB-EGF

VEGF, Shh, IGF-I, GDNF

Proliferating progenitors

LIF, BMP

IGF-I

BDNF

Astrocyte

Oligodendrocyte

Neuron
Evolution of the view of adult neurogenesis

Vascular Niche for Adult Hippocampal Neurogenesis

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Endothelial Cells Stimulate Self-Renewal and Expand Neurogenesis of Neural Stem Cells

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Natalia Abramova,¹ Peter Vincent,² Kevin Pumiglia,³ Sally Temple¹*

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Neurogenesis
?
Rodent = Monkey
Clinical Applications of Neural Progenitors

- Cerebral ischemic injury
- Neurodegenerative diseases
- Multiple sclerosis
- Brain tumors
- Congenital malformations

* Dennis A Steindler, David W Pincus
  *Lancet* 2002; 359: 1047–54
Sources of Stem Cells for Transplantation

Jakel et al.
Conclusions

• Endogenous progenitor cells reside in adult mammalian brain including that of primates

• Progenitor cells in respond to various environmental stimuli

• Progenitor cells are located in specific cellular niches

• Neurogenesis takes place in an angiogenic environment
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