Marta Huelin
Ciències Biomèdiques

Neurogenesis after Brain Ischemia

UAB
Universitat Autònoma de Barcelona

Introduction

- There are two neurogenic regions in the normal adult mammalian brain under physiological conditions: the **Subventricular Zone** (SVZ) of the lateral ventricle, and the **Subgranular Zone** (SGZ) of the hippocampus.
- Both regions maintain a population of neural stem cells (NSCs) and neuronal progenitors cells (NPCs).
- **Brain ischemia** alters the normal pattern of adult neurogenesis to stimulate cell proliferation within the SVZ and SGZ as well as migration of newly born, immature neurons to areas of damage.

Objective

- A better **understanding** of **endogenous neurogenesis** in the SVZ and SGZ, both in the intact and injured brain, in order to develop useful therapies for brain repair after ischemic injury or neurodegeneration.

Methodology

- Different sources of information have been used, such as PubMed (papers and reviews), scientific books and lectures offered by experts.
- A final selection of 32 out of 50 papers was done.
- Selection criteria was based on the journal impact, the date of publication and the relation with the main topic of the review.

Neurogenesis in the Subventricular Zone

- In the SVZ there are three main type of cells: type-A (neuroblasts), type-B (astrocytic-like cells) and type-C (transient amplifying cells).

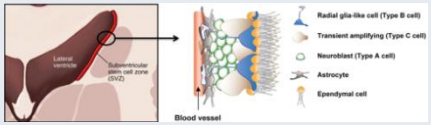
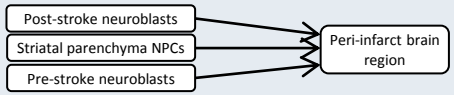


Fig 1. Enlargement of the SVZ shows SVZ cells organized in laminae from superficial to deep. Adapted from Barani IJ et al., 2007 and Inestrosa NC et al., 2013

- Neuroblasts migrate in chain towards the olfactory bulb (OB) enseathed by type-B cells undergoing a tangential migration in the rostral migratory stream (RMS).
- Once in the OB, they mature and differentiate into granule and periglomerular interneurons.
- The RMS pathway is the **single largest area** for **cell proliferation** in the adult human brain discovered to date.

Stroke-induced neurogenesis in the Subventricular Zone

- Stroke increases cell proliferation and reduces migration from the SVZ to the OB. It also redirects some neuroblasts to migrate in chains in close association with astrocytes toward the ischemic area.



- Ischemia promotes a faster division of neuroblasts during migration and induces the newborn neurons to differentiate into the phenotype of the lost neurons.
- The generation of new neurons after stroke is associated with **functional recovery** and offers a long time window for therapeutic manipulations.

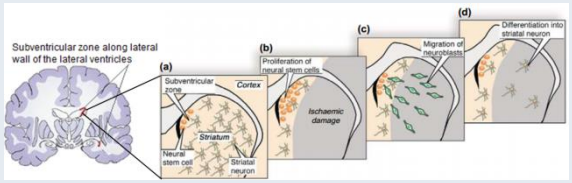


Fig 2. Stroke increases proliferation and migration of NPCs toward the damaged area. Kokaia et al., 2003 and Vescovi AL et al., 2006

Neurogenesis in the Subgranular Zone

- The primary progenitors of the SGZ are radial glia-like cells that give rise to transient-amplifying progenitors.
- The progeny disperse and migrate a short distance into the dentate granule cell (DGC) layer where they mainly differentiate into mature granule neurons. A small number of these cells also differentiate into astrocytes or radial glia-like cells.
- Neurogenesis in this system **remains local** and decreases with age due to a disturbed survival of newborn cells.

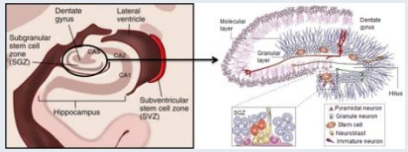


Fig 3. Enlargement of SGZ shows stem cells located between the dentate hilus and the inner margins of the dentate granule cell layer. Adapted from Barani IJ et al., 2007 and Vescovi AL et al., 2006

Stroke-induced neurogenesis in the Subgranular Zone

- Ischemic insult leads to an increased proliferation of stem cells in the SGZ.
- After a stroke, neuroblasts migrate and integrate into the DGC layer following a time course of neuronal maturation similar to that in normal conditions.
- Most hippocampal progenitor cells give rise to DGC neurons, but some subpopulations migrate into the dentate hilus and become astrocytes.

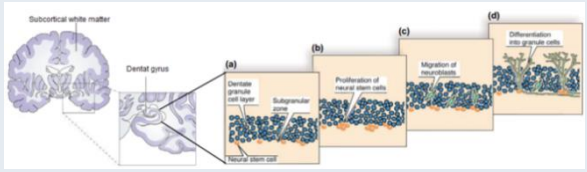


Fig 4. Stroke increases stem cell proliferation, migration and differentiation into the DGC layer. Adapted from Kokaia et al.,2003 and Vescovi AL et al., 2006

- Endogenous progenitors are capable of replacing neurons damaged by ischemia.
- Thus, pharmacological stimulation of SGZ neurogenesis after brain ischemia could promote **neuronal renewal** and functional recovery after stroke.

Conclusions

- Persistence of NSCs in the adult healthy brain raise the possibility of using **endogenous or transplantable NSCs and NPCs** as regenerative therapies to replace neurons lost after ischemic insults.

Cell transplantation	Activation of endogenous NSCs
Requires new technology to differentiate NSCs into mature neurons	Proliferation mechanisms of NSCs are needed to be clarified
Surgical transplantation of mature neurons is needed	Possible drugs' side-effects problems should be resolved
With a cell differentiation technology established, it could be easier to produce the appropriate cells for the damaged areas	Drug preparations could be developed, thus abolishing surgical risks
	Lower risk for tumorigenesis

- Developing methods to expand the endogenous progenitor pool, direct both migration and differentiation of NPCs, as well as promoting survival of the progeny, are research priorities to **develop new therapies** for this worldwide extended condition.

References

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