Available online at www.sciencedirect.com

ScienceDirect

www.elsevier.com/locate/brainres

Brain Research

Research Report

# Coupling of neurogenesis and angiogenesis after ischemic stroke

Linhui Ruan[a,1], Brian Wang[b,c,1], Qichuan ZhuGe[a], Kunlin Jin[a,b,c,*]

[a]Zhejiang Provincial Key Laboratory of Aging and Neurological Disorder Research, First Affiliated Hospital, Wenzhou Medical University, Wenzhou, China

[b]Department of Pharmacology and Neuroscience, University of North Texas Health Science Center, 3500 Camp Bowie Boulevard, Fort Worth, TX 76107, USA

[c]Institute of Aging and Alzheimer's Disease Research, University of North Texas Health Science Center at Fort Worth, TX 76107, USA

ARTICLE INFO

*Article history:*
Accepted 20 February 2015
Available online 28 February 2015

*Keywords:*
Stroke
Neurogenesis
Angiogenesis
Ischemia
Cell interaction

ABSTRACT

Stroke is a leading cause of mortality and severe long-term disability worldwide. Development of effective treatment or new therapeutic strategies for ischemic stroke patients is therefore crucial. Ischemic stroke promotes neurogenesis by several growth factors including FGF-2, IGF-1, BDNF, VEGF and chemokines including SDF-1, MCP-1. Stroke-induced angiogenesis is similarly regulated by many factors most notably, eNOS and CSE, VEGF/VEGFR2, and Ang-1/Tie2. Important findings in the last decade have revealed that neurogenesis is not the stand-alone consideration in the fight for full functional recovery from stroke. Angiogenesis has been also shown to be critical in improving post-stroke neurological functional recovery. More than that, recent evidence has shown a highly possible interplay or dependence between stroke-induced neurogenesis and angiogenesis. Moving forward, elucidating the underlying mechanisms of this coupling between stroke-induced neurogenesis and angiogenesis will be of great importance, which will provide the basis for neurorestorative therapy.

*This article is part of a Special Issue entitled SI: Cell Interactions In Stroke.*



## 1. Introduction

Stroke is a leading cause of mortality and severe disability worldwide. Currently, the number of patients suffering from stroke is steadily increasing. The only proven therapy for acute ischemic stroke approved by the FDA is systemic thrombolysis with recombinant tissue plasminogen activator (rtPA). However, it must be administered within 4.5 h after the onset of stroke for rtPA to be effective. As a result, the short therapeutic time window and the potential complication from intracranial hemorrhage benefit only a minority of stroke patients (Zhang and Chopp, 2009). Even with successful rtPA thrombolysis, most stroke survivors still suffer from permanent neurological functional deficits. Therefore, extending the therapeutic time

*Corresponding author at: Department of Pharmacology and Neuroscience, University of North Texas Health Science Center, 3500 Camp Bowie Boulevard, Fort Worth, TX 76107, USA. fax: +1 817 735 0480.
E-mail address: kunlin.jin@unthsc.edu (K. Jin).
[1]These authors contributed equally to this work.

http://dx.doi.org/10.1016/j.brainres.2015.02.042
0006-8993/

window of rtPA or uncovering new therapeutic strategies for the treatment of ischemic stroke is highly sought after.

In the past decade, several independent research groups have reported that neurogenesis continues into adulthood (Wang and Jin, 2014). Neurogenesis is the process of producing new functional neurons from neural stem/progenitor cells (NSCs), including proliferation of endogenous NSCs, migration, and differentiation into mature functional neurons. It is well accepted now that neurogenesis occurs at two distinct regions in the intact brain throughout life: the subventricular zone (SVZ) of the lateral ventricles and subgranular zone (SGZ) in the dentate gyrus of the hippocampus (Wang and Jin, 2014). In pathological conditions such as ischemic stroke, enhanced neurogenesis has been reported in animal models of stroke and even in stroke patients (Jin et al., 2001; Jin et al., 2006; Thored et al., 2006), suggesting a potential avenue for the treatment of ischemic stroke. However, it is now apparent that neurogenesis is not the stand-alone consideration in the fight for full functional recovery from stroke. One should now also factor in the role of angiogenesis as it has been shown to be critical in improving post-stroke neurological functional recovery.

Angiogenesis, defined as new microvessel formation via branching off from pre-existing vessels (Carmeliet and Jain, 2011), is a multi-step biological process, including proliferation and sprouting of endothelial cells, formation of tube-like vascular structures, branching and anastomosis (Risau, 1997). Angiogenesis is found in the penumbra of the brain infarct region in animal models of stroke and even in the brains of stroke patients (Hayashi et al., 2003; Krupinski et al., 1994; Zhang et al., 2002). It has been reported that neurogenesis and angiogenesis occur in the brains of stroke patients and a positive correlation was seen between patient survival and density of microvessels (Krupinski et al., 1994). Several findings in addition to this prove that neurogenesis and angiogenesis are coupled processes after an insult such as ischemic stroke, and should be acknowledged and pursued as concurrent and non-mutually exclusive events to further develop neurorestorative therapy.

This mini-review aims to establish the underlying mechanisms of how ischemic stroke induces endogenous neurogenesis and angiogenesis, and then address the interplay between neurogenesis and angiogenesis after ischemic stroke.

## 2. Mechanisms underlying stroke-induced neurogenesis

In the following sections, we review cellular and molecular mechanisms underlying stroke-induced neurogenesis and how factors released by endothelial cells may participate in the process.

### 2.1. *Proliferation*

Endogenous NSC proliferation is the first step in stroke-induced neurogenesis. It was demonstrated that ischemic stroke is sufficient to increase the endogenous NSC proliferation to result in the expansion of the NSC pool (Tang et al., 2009). Ischemic stroke injury promotes the proliferation of NSCs and expands the NSC pool by regulating NSC cytokinetics such as shortening the length of the cell cycle to increase the percentage of proliferating cells (Zhang et al., 2006). As reported by Zhang et al., the proportion of actively dividing SVZ NSCs is about 15–21% in the adult rat brain. Stroke increases the proportion of proliferating SVZ cells to 24% just two days after stroke, and this proportion reaches a maximum level of 31% 7 days after stroke (Zhang et al., 2006). The length of the SVZ NSC cell cycle is 18–21 h in the normal rat brain throughout its lifetime. However, stroke reduces the length of the cell cycle to 11 h at 2 days after stroke onset.

Switching from asymmetric to symmetric NSC division may be another underlying mechanism, which contributes to the expansion of the NSC pool. Symmetric divisions generate two identical daughter cells that go into maintaining the NSC pool while asymmetric or self-renewing divisions generate one daughter cell and a differentiated cell such as a neuron or non-stem-cell progenitor (Chenn and McConnell, 1995; Gotz and Huttner, 2005; Smart, 1973). It was shown that in the adult rat, stroke briefly increases the number of dividing SVZ NSCs with vertical cleavage orientation, and decreases the number of SVZ NSCs with horizontal cleavage orientation (Zhang et al., 2004). This suggests that the NSCs switch from asymmetric to symmetric division to expand the NSC pool, whose numbers were shown to be significantly increased after stroke. Interestingly, 4 days after stroke, the frequency of neuronal phenotype in symmetrically divided cells increased to 47% from 33% in asymmetrically divided cells. Thus, it is possible to conclude that stroke increases the neuronal phenotype though no evidence was shown to what degree this phenotype is preferred *versus* other glial cell fates.

Several extracellular signals such as growth factors that regulate stroke-induced proliferation of NSCs have been identified and extensively examined (Fig. 1).

#### 2.1.1. *FGF-2*

The mRNA expression of fibroblast growth factor-2 (FGF-2) is upregulated significantly after ischemic stroke injury in the adult rat brain (Naylor et al., 2005) as well as in patients who died from acute ischemic stroke (Navaratna et al., 2009). It was also shown

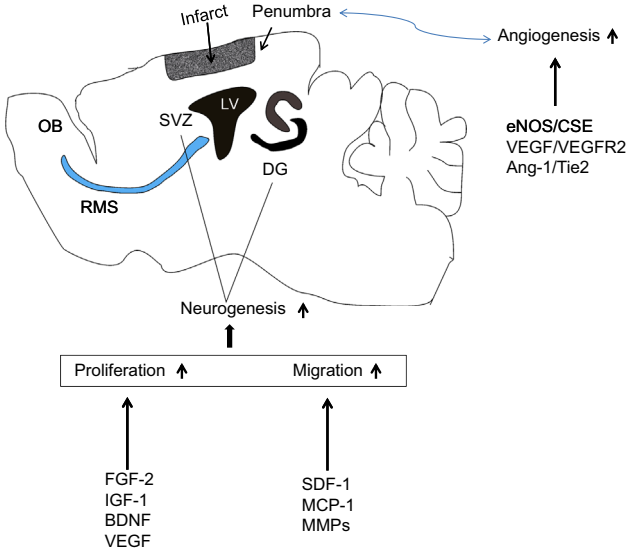


**Fig. 1 – Key pathways potentially involved in the coupling of neurogenesis and angiogenesis after ischemic stroke.**