Neuroscience and Biobehavioral Reviews xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

Review

New neurons for injured brains? The emergence of new genetic model organisms to study brain regeneration

Q1 Ismael Fernandez-Hernandez [1], Christa Rhiner*

Institute of Cell Biology, IZB, Baltzerstrasse 4, 3012 Bern, Switzerland

ARTICLE INFO

Article history:
Received 9 March 2015
Received in revised form 22 June 2015
Accepted 23 June 2015
Available online xxx

Keywords:
Adult neurogenesis
Adult neural stem cells
Regenerative neurogenesis
Activation of quiescent stem cells
Traumatic brain injury models

ABSTRACT

Neuronal circuits in the adult brain have long been viewed as static and stable. However, research in the past 20 years has shown that specialized regions of the adult brain, which harbor adult neural stem cells, continue to produce new neurons in a wide range of species. Brain plasticity is also observed after injury. Depending on the extent and permissive environment of neurogenic regions, different organisms show great variability in their capacity to replace lost neurons by endogenous neurogenesis. In Zebrafish and *Drosophila*, the formation of new neurons from progenitor cells in the adult brain was only discovered recently. Here, we compare properties of adult neural stem cells, their niches and regenerative responses from mammals to flies. Current models of brain injury have revealed that specific injury-induced genetic programs and comparison of neuronal fitness are implicated in brain repair. We highlight the potential of these recently implemented models of brain regeneration to identify novel regulators of stem cell activation and regenerative neurogenesis.

Contents

Q2 * Corresponding author. Tel.: +41 788123056.
E-mail address: christa.rhiner@izb.unibe.ch (C. Rhiner).
[1] Present address: Institute for Research in Biomedicine, IRB, Baldiri Reixac 10, 08028 Barcelona, Spain.

http://dx.doi.org/10.1016/j.neubiorev.2015.06.021
0149-7634/

1. Introduction

For a long time, it was assumed that little or no neurogenesis occurred in the adult vertebrate brain. Nowadays, it is well recognized that adult neural stem cells (NSCs) exist in the mature brain of all mammalian organisms (Gould, 2007; Grandel and Brand, 2013; Kempermann, 2012) including humans (Eriksson et al., 1998; Kukekov et al., 1999; Spalding et al., 2013). Such adult NSCs self-renew and continuously give rise to new neurons throughout adulthood. Moreover, adult neurogenesis is not restricted to mammals, but equally occurs in other species such as birds (Goldman and Nottebohm, 1983), lizards (Garcia-Verdugo et al., 1989), fish (Easter and Hitchcock, 2000; Zupanc et al., 2005) and, as discovered only recently, in fruit flies (Fernandez-Hernandez et al., 2013).

Adult neurogenesis is a complex process, which involves genesis, migration, differentiation, selection and maintenance of new neurons in the adult brain. In mammals, NSCs self-renew and can differentiate both into neural or glial lineages (Gage, 2000). A subset of newly generated neurons will incorporate into preexisting neuronal circuits, thereby contributing to structural and functional plasticity of the adult brain.

The significance and functional implications of adult neurogenesis in mammals is still a matter of ongoing debate and research. Newborn neurons have been proposed to play a role in learning, pattern separation (reviewed in Deng et al., 2010; Ming and Song, 2011), the formation of new memories (Aimone et al., 2011; Clelland et al., 2009; Zhang et al., 2008) and the regulation of anxiety behavior (Saxe et al., 2006; Snyder et al., 2011). However, these suggested functions are still controversial.

New genetic techniques have been introduced, which allow more specific and inducible inhibition of adult neurogenesis compared to earlier methods using irradiation or anti-mitotic drugs, but conflicting results persist. For example, neurogenesis has been found to be important for spatial navigation in the water maze, a hippocampus-dependent task, by some studies (e.g. Zhang et al., 2008), but not others (Groves et al., 2013; Saxe et al., 2006). Possible reasons for the inconsistent results are heterogeneities in behavioral protocols, age of experimental animals, distinct genetic backgrounds or treatments, which can influence behavior on its own (Lazic et al., 2014), apart from changing rates of neurogenesis.

Therefore, the function of adult neurogenesis in mammals still remains unsettled. Current efforts in the field to standardize procedures, employ computational models and refine the tools to specifically and locally interfere with neurogenesis seem to be the key to understand the role of new neurons in the mammalian hippocampus.

The extent of adult neurogenesis has also been studied in relation to brain pathology. Adult-born neurons have been shown to benefit the remission of effects in the major psychiatric disorders of depression, schizophrenia and drug addiction (Jun et al., 2012). Seizures enhance the proliferation in neurogenic regions and cause migration defects of newly generated neurons (Jessberger and Parent, 2007).

Moreover, altered neurogenesis in the adult hippocampus can represent an early event in the course of Alzheimer's disease (reviewed in Mu and Gage, 2011; Lazarov and Marr, 2010) or in the appearance of intellectual disability disorders (Pons-Espinal et al., 2013).

Because adult neurogenesis is conserved in the animal kingdom, it has also been addressed from an evolutionary perspective (Kempermann, 2012; Tanaka and Ferretti, 2009). Nevertheless, in this review we will focus mainly on studies performed in rodents, Zebrafish, and *Drosophila*, where research is facilitated by an extensive genetic toolbox. We compare relevant features such as the location and types of adult neural progenitors and – if known – the regulatory mechanisms. Finally, we comment on the regenerative potential of these different systems and strategies to identify new factors involved in physiologic and damage-induced neurogenesis. Adult neurogenesis has been extensively studied in rats and mice. In Zebrafish and *Drosophila*, the knowledge is still limited and started to emerge only recently, since research initially concentrated on regulation of neurogenesis during development.

Because fish and flies show robust neurogenesis upon injury, current efforts are directed to understand neurogenesis in the context of brain regeneration. However, both systems are likely to contribute to our understanding of normal adult neurogenesis in the future, especially if tools become available to specifically target the adult neural stem cell pool.

2. Adult neurogenesis in mammals

Adult neurogenesis is a conserved trait in the animal kingdom and occurs in all mammalian species studied so far (Kempermann, 2012).

In mammals, adult neurogenesis is restricted mainly to two neurogenic regions: the subgranular zone (SGZ) of the dentate gyrus in the hippocampus, and the subventricular zone (SVZ) lining the lateral ventricles (Fig. 1A and B) (reviewed in Zhao et al., 2008).

The SGZ resides between the granule cell layer and the hilus of the hippocampal dentate gyrus (Fig. 1A and B). In the adult human brain, it represents the most relevant neurogenic zone (Spalding et al., 2013) (Fig. 1A). However, our knowledge about the SGZ mainly derives from studies with rats and mice (Fig. 1B). There, radial glia-like stem cells (type I cells) proliferate to yield intermediate progenitor cells (also named transient amplifying cells), which migrate towards the granule cell layer (reviewed in Zhao et al., 2008). Here, they undergo several rounds of division and differentiation to produce a population of post-mitotic immature granule cells that differentiate into one neuronal subtype, the excitatory glutamatergic granule neurons and establish nascent network connections.

However, only a small fraction of newly generated neurons in the SGZ survives and finally integrates into hippocampal circuits; the bulk of them die by apoptosis (Biebl et al., 2000). The percentage of surviving neurons, but also their connectivity can be increased by experience such as spatial learning or exposure to an "enriched environment" (Bergami et al., 2015; Kee et al., 2007; Ramirez-Amaya et al., 2006). It has been shown that newborn neurons (4–6 weeks old) in the mouse hippocampus do preferentially respond to activity-dependent stimulation (Tashiro et al., 2006) during learning because they display hyperexcitability and enhanced synaptic plasticity compared to mature dentate granule cells (Ge et al., 2007; Schmidt-Hieber et al., 2004). The selective activation and recruitment of newborn neurons in the course of learning tasks (Dupret et al., 2007) indicates that they may play a role for hippocampus-directed storage of new information in the brain.

In the other major neurogenic zone, the rodent subventircular zone (SVZ) (Fig. 1B), astrocyte-like cells with stem cell characteristics divide asymmetrically to produce transient amplifying cells, which in turn form neuroblasts (reviewed in Zhao et al., 2008). Chains of neuroblasts migrate then to the olfactory bulb through a tube formed by astrocytes in the so-called rostral migratory stream (RMS) (Doetsch and Alvarez-Buylla, 1996; Lois et al., 1996) (Fig. 1B). Once in the olfactory bulb, neuroblasts spread out in a radial fashion and differentiate into several types of interneurons, integrating with the granule cells and periglomerular layers. This process of neurogenesis in the olfactory bulb of mice is very robust and persists throughout life. In contrast, the SVZ of primates becomes

Please cite this article in press as: Fernandez-Hernandez, I., Rhiner, C., New neurons for injured brains? The emergence of new genetic model organisms to study brain regeneration. Neurosci. Biobehav. Rev. (2015), http://dx.doi.org/10.1016/j.neubiorev.2015.06.021