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Neurogenesis in Adult Hippocampus

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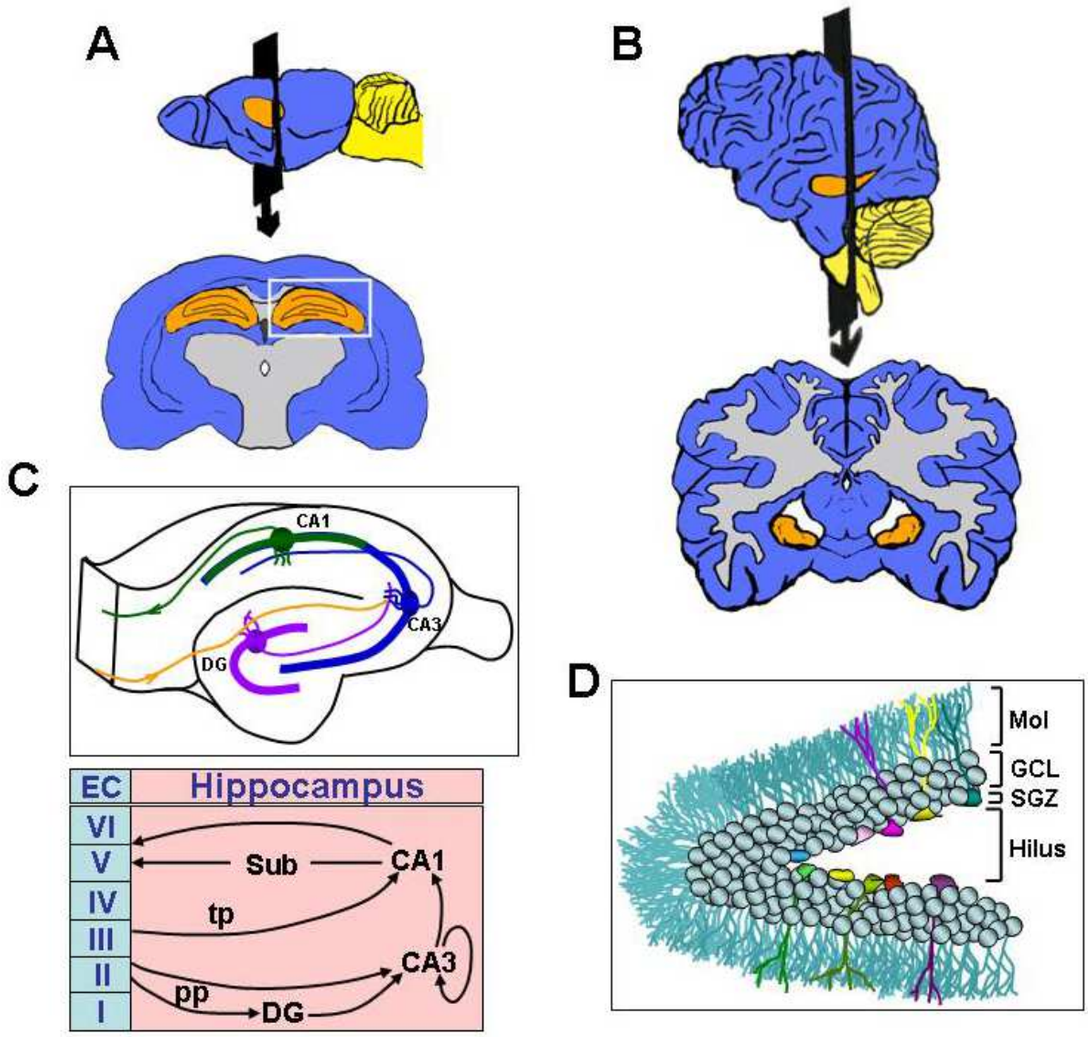
1. Introduction

Hippocampus as a whole has the shape of a curved tube including CA1-CA4 regions with a single layer of densely packed pyramidal neurons which curl into a tight "U" shape. One edge of the "U", field CA4, is embedded into a backward facing strongly flexed V-shaped cortex, the dentate gyrus (DG) which comprises molecular, granular, subgranular cell layers and poly-morph layer called hilus (Figure 1). The ability to learn or form a memory requires a neuron to translate a transient signal into gene expression changes that have a long-lasting effect on synapse activity and connectivity. There are many neural circuits formed by multi-class neurons in hippocampus. One of them is the trisynaptic circuit (Figure 1) that is made up of three major cell groups: granule cells, CA3 pyramidal neurons, and CA1 pyramidal cells. The axons of layer II neurons in the entorhinal cortex (EC) project to the dentate gyrus through the perforant pathway. The dentate gyrus sends projections to the pyramidal cells in CA3 through mossy fibres. CA3 pyramidal neurons relay the information to CA1 pyramidal neurons through Schaffer collaterals. CA1 pyramidal neurons send back projections into deep-layer neurons of the EC. This kind of circuit is involved in long term potentiation (LTP) mediating learning and memory. CA3 also directly receives the projections from EC layer II neurons through the perforant pathway. CA1 receives direct input from EC layer III neurons through the temporoammonic pathway. The dentate granule cells also project to the mossy cells in the hilus and hilar interneurons, which send excitatory and inhibitory projections, respectively, back to the granule cells. The complicated neural circuits in hippocampus form the foundation of hippocampal functions.

The external relation between hippocampus and other brain regions also plays an important role in cognition and attentional behaviors. Hippocampal afferents are from the septal area, the locus coeruleus, and the raphe nuclei via 3 anatomically distinct pathways, cingular bundle (CB), Fimbria Fornix (FiFx) and a ventral pathway whose exact anatomical location is not well defined but is thought to reach the hippocampus after passing in the vicinity of the amygdalar complex (Cassel et al., 1997; Eckenstein et al., 1988; Gage et al., 1994; Hong & Jang, 2010; Saper, 1984). Afferent fibers via the FiFx and CB provide the hippocampus with cholinergic, extrinsic GABAergic, noradrenergic and serotonergic inputs. A very important projection comes from the medial septal area, which sends cholinergic and GABAergic fibers to all parts of the hippocampus. The inputs from the septal area play a key role in controlling the physiological state of the hippocampus: destruction of the septal area abolishes the hippocampal theta rhythm, and severely impairs certain types of memory. Hippocampal efferents carry fibers from hippocampal pyramidal CA2-CA4 cells projecting to the anterior thalamic nucleus,

medial mamillary nucleus, cingular gyrus, and the nucleus basalis of Meynert (Cassel et al., 1997). Cholinergic projections comprise a complex neural network that supports higher brain functions, and the FiFx and CB are the principal cholinergic pathways that communicate between the basal forebrain and hippocampus and cortex.



A) Hippocampus (orange region) sits below the surface of the neocortex in rodent brain. The lower is a coronal section through hippocampus. B) Hippocampus (orange region) in human brain is also located under the surface of the neocortex. The lower is a coronal typical section through hippocampus. C) Basic circuit of the hippocampus. Neurons in EC II project to the DG through the perforant pathway (pp). DG sends projections to pyramidal cells in CA3 through mossy fibres. CA3 also receives the projections from EC II neurons through the perforant pathway. CA3 pyramidal neurons send axons to CA1 pyramidal neurons. CA1 also directly receives input from EC III neurons through the temporoammonic pathway (tp). CA1 pyramidal neurons send back projections into deep layers of EC. D) The details of cell layers in rodent DG indicate the neurogenic cells migrate along SGZ and into GCL, and finally form mature granule cells projecting processes into Mol. Abbreviation: DG, dentate gyrus; EC, entorhinal cortex; GCL, granule cell layer; Mol, molecular layer; SGZ, subgranular zone; Sub, subiculum.

Fig. 1. Location and inner structure of the hippocampus.

2. Distribution and fate of neural progenitor cells in hippocampus

Findings of new neurons in the adult brain challenge the dogma that cells of the central nervous system (CNS) are incapable of regeneration. It is well established that the DG in the hippocampus is one of two adult well-accepted regions with continuous addition of new neurons throughout life (Gage, 2000; Kempermann & Gage, 2000). The adult hippocampal neurogenesis is a complex process that originates from proliferation of neural progenitor cells (NPCs) located in the subgranular zone (SGZ), a germinal layer between the granular layer and hilus. The majorities of NPC progenies are specified to become dentate granule cells (DGCs) and go through the initial differentiation and migrate into the inner granule cell layer within a week of their birth. The adult immature DGCs generated from NPCs in SGZ undergo maturation and make important contributions to learning and memory (Deng et al., 2009).

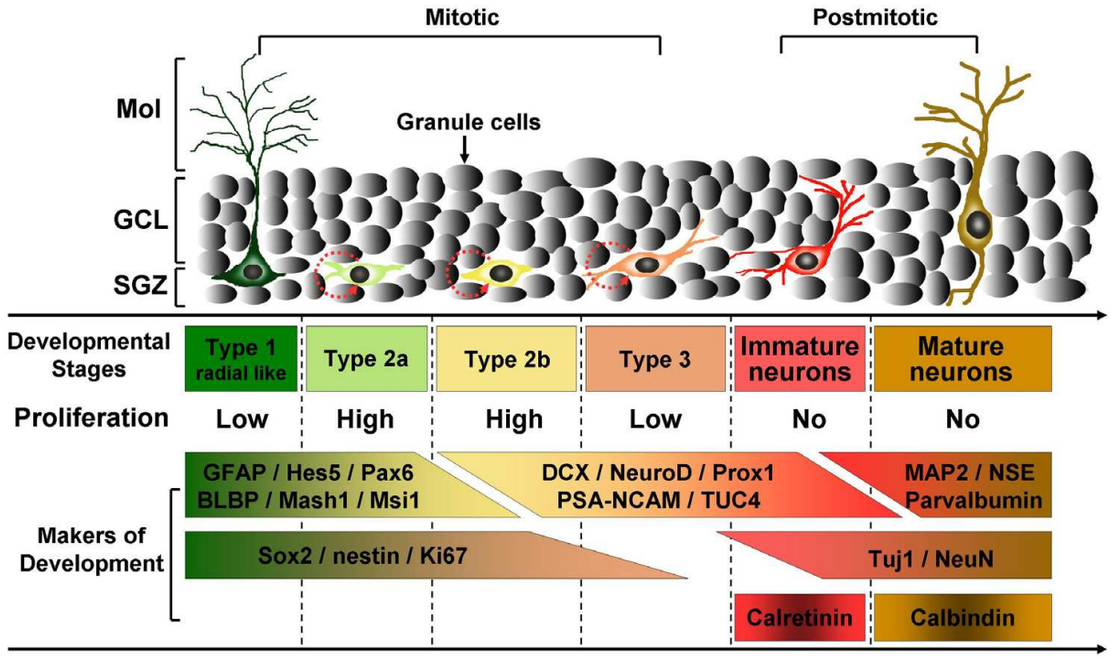
Subventricular zone (SVZ) is another adult region continuously generating new neurons. SVZ NPCs give rise to neuroblasts that migrate in chains to the olfactory bulb through the rostral migratory stream (RMS) where they differentiate into granule and periglomerular neurons (Bovetti et al., 2007; Corotto et al., 1993; Lois & Alvarez-Buylla, 1994; Lois et al., 1996). In the adult DG, new neurons from NPCs are born in the SGZ and migrate a short distance to differentiate into granule cells that project their dendrites into the molecular layer (ML) and axons to the CA3 pyramidal cell layer via the mossy fiber pathway (Markakis & Gage, 1999; Stanfield & Trice, 1988) and establish synaptic connection with local neurons (McDonald & Wojtowicz, 2005).

There are four main cell types in the SVZ: neuroblasts (Type A cells), SVZ astrocytes (Type B cells), immature precursors (Type C cells) and ependymal cells (Doetsch et al., 1997). The neuroblasts (Type A cells) which are from the focal clusters of rapidly dividing precursors (Type C cells) along the SVZ network of chains divide as they migrate as chains through glial tunnels formed by the processes of slowly dividing SVZ astrocytes (Type B cells).

As in the SVZ, there are four types of cells in dentate gyrus: SGZ astrocytes (Type B cells), immature dividing cells (type D cells), granule neurons (type G cells) and endothelial cells. SGZ astrocytes are in close proximity to blood vessels and extend basal processes under the blades of the dentate gyrus and an apical process into the granule cell layer. It is the same as SVZ that SGZ astrocytes are the primary precursors of neurons. The SGZ astrocytes divide to give rise to immature dividing D cells and generate granule neurons. So the type D cells are adjacent to SGZ astrocytes. Neurogenesis in the SGZ occurs in foci formed by these cells suggesting mutual co-regulation between them (Palmer et al., 2000). Endothelial cells are likely an important source of signals for neurogenesis.

Accumulating evidences lead to a detailed classification of the SGZ cells characterized by their properties and specific markers (Figure 2). Adult hippocampal neurons originate from a radial glia-like precursor cell (type-1) which is glial fibrous acid protein (GFAP) positive but negative to S100 beta, doublecortin (DCX) and polysialic acid-neural cell adhesion molecule (PSA-NCAM) in the SGZ of DG through a number of intermediate cell types (type-2, GFAP$^-$, S100$^-$, DCX$^+$, PSA-NCAM$^+$ and type 3 with DCX expression). Type-1 cells correspond to type B cells because they have a proliferative capacity and are marked by GFAP (Seri et al., 2004; Suh et al., 2007; Zhao et al., 2006). Nestin, Sox2, and brain lipid-binding protein (BLBP) are also expressed in type-1 cells suggesting their radial glial features and the expression persists into the type-2 cell stages (Steiner et al., 2006). Although

type 1 cells have a proliferative capacity, their cycles are much slower than the followed type-2 progenitor cells supposed to be the type D cells (Filippov et al., 2003; Fukuda et al., 2003; Kronenberg et al., 2003; Steiner et al., 2004). Type-2 cell stage marks the transition between cells with astrocytic phenotype (type-2a cells, the early stage of type-2 cells) and cells with early features of the neuronal lineage (type-2b cells, the later stage of type-2 cells). A panel of different markers (Sox2, BLBP, DCX, and NeuroD) discriminates between the type 2a and type 2b cells. Type-2a cells feature, to some degree, properties of radial glia-like cells marked with BLBP and Sox2. NeuroD and DCX, the markers of immature neurons, appear in type-2b cells and persist into postmitotic but immature granule cell precursors with transient Calretinin-expression. That is to say, type-2b cells are committed to the neuronal lineage. The type-3 cells are the terminal postmitotic differentiation of granule cells that exits from the cell cycle (Kempermann et al., 2004; Steiner et al., 2006). Finally, these cells mature into granule cell neurons in the DG that express specifically NeuN, calbindin and Prox1 (Figure 2). These newborn granule cells elongate their dendrites and axons integrating into the DG circuitry (Jessberger & Kempermann, 2003; Song et al., 2005; van Praag et al., 2002).



Adult hippocampal neurons originate from type-1 cell with radial glia properties through a number of intermediate type-2 and type 3 cells. Type 2 cells with transit rapid proliferation have two types 2a and 2b. The neuronal determination is at stage type 2b. Type 3 cells gradually exit from the cell cycle and then subsequently form the immature and mature neurons. These newborn granule cells elongate their dendrites and axons integrating into the molecular layer. Cells in different stages of neurogenesis express neural specific markers highlighted in this figure.

Fig. 2. Proposed course of adult hippocampal neurogenesis.

Recent studies in increasing detail showed that a sequence of markers express in the SGZ cells of various stages during the adult hippocampal neurogenesis in mice and rats (Kempermann et al., 2004; Kim et al., 2008; Steiner et al., 2006; Steiner et al., 2008). The stage-

specific expressions of neural markers are summarized in Figure 2. In an addition to the putative markers described above, other genes are expressed in different stages of hippocampal neurogenesis. The neuronal marker Hu appears in the GFAP positive intermediate progenitors committed to the neuronal lineage, while Hu is undetectable in primary progenitors and astrocytes, indicating that Hu is a useful marker for discriminating GFAP+ astrocytes and GFAP+ neural progenitors that generate neurons (Liu et al., 2010). The transcription factor Pax6 is expressed not only in precursor cells during embryonic development of the central nervous system but also in the adult SGZ (Sakurai & Osumi, 2008). It plays an important role in the regulation of cell proliferation and neuronal fate determination (Englund et al., 2005; Gotz et al., 1998; Heins et al., 2002). About half of the Pax6-positive cells in the SGZ display a radial glial phenotype which is marked for GFAP, whereas about 30% of the Pax6-positive cells are immunoreactive to PSA-NCAM or DCX (Maekawa et al., 2005; Nacher et al., 2005). In addition, more than 50% of Pax6-positive cells are immunoreactive to NeuroD (Nacher et al., 2005). Thus, Pax6 may represent a suitable marker for type 1 and type 2a cells. The transcription factor NeuroD is expressed in later stages of neuronal commitment (Lee et al., 1995) and during neurogenesis in the adult DG (Kawai et al., 2004). It is important for the proper development of the DG, the proliferation and postnatal differentiation of neuronal progenitors (Liu et al., 2000; Miyata et al., 1999). Thus it could serve as a specific marker. TUC-4 is not only expressed in postmitotic neurons during brain development as they begin their migration but also re-expressed in adult neurogenesis again. Its expression pattern during neurogenesis resembles that of PSA-NCAM and DCX. Thus, TUC-4 can be used as a marker for different stages of adult neurogenesis in the DG. Calretinin is expressed in specific non-pyramidal γ-aminobutyric acid (GABA)-ergic neurons within the adult hippocampus. At late phases of neurogenesis, new neurons express calretinin and doublecortin or NeuN but do not express GABA (Brandt et al., 2003). At later time-points, the newly generated neurons stop expressing calretinin and start to express calbindin, a marker of mature dentate granule cells (Brandt et al., 2003). So that calretinin expression within the DG is restricted to a short postmitotic time window in which axonal and dendritic target their destination regions (Kempermann et al., 2004; Ming & Song, 2005). FABP7 (BLBP) is expressed in the type 1, 2a, and 2b cells, since FABP7 (BLBP) were found in bromodeoxyuridine (BrdU)-positive newly generated cells whereas Tuj1 or PSA-NCAM positive newborn neurons in the vicinity of the astrocytes express none of the FABPs. (Boneva et al., 2011). Musashi1 (Msi1) is a neural RNA binding protein (Sakakibara et al., 1996) that expressed in early-stage NPCs (Kaneko et al., 2000; Sakakibara et al., 1996). The clarity of the development stage-specific markers is not only helpful for gaining further insights into the genesis of new neurons in the hippocampus, but also might be applicable to the development of strategies for therapeutic interventions.

3. Survival and differentiation of grafted NSCs in hippocampus

In CNS the mature neurons lose the ability to undergo cell division once they fully differentiate. Therefore, cell replacement is recognized as a potential strategy to treat neurodegenerative diseases.

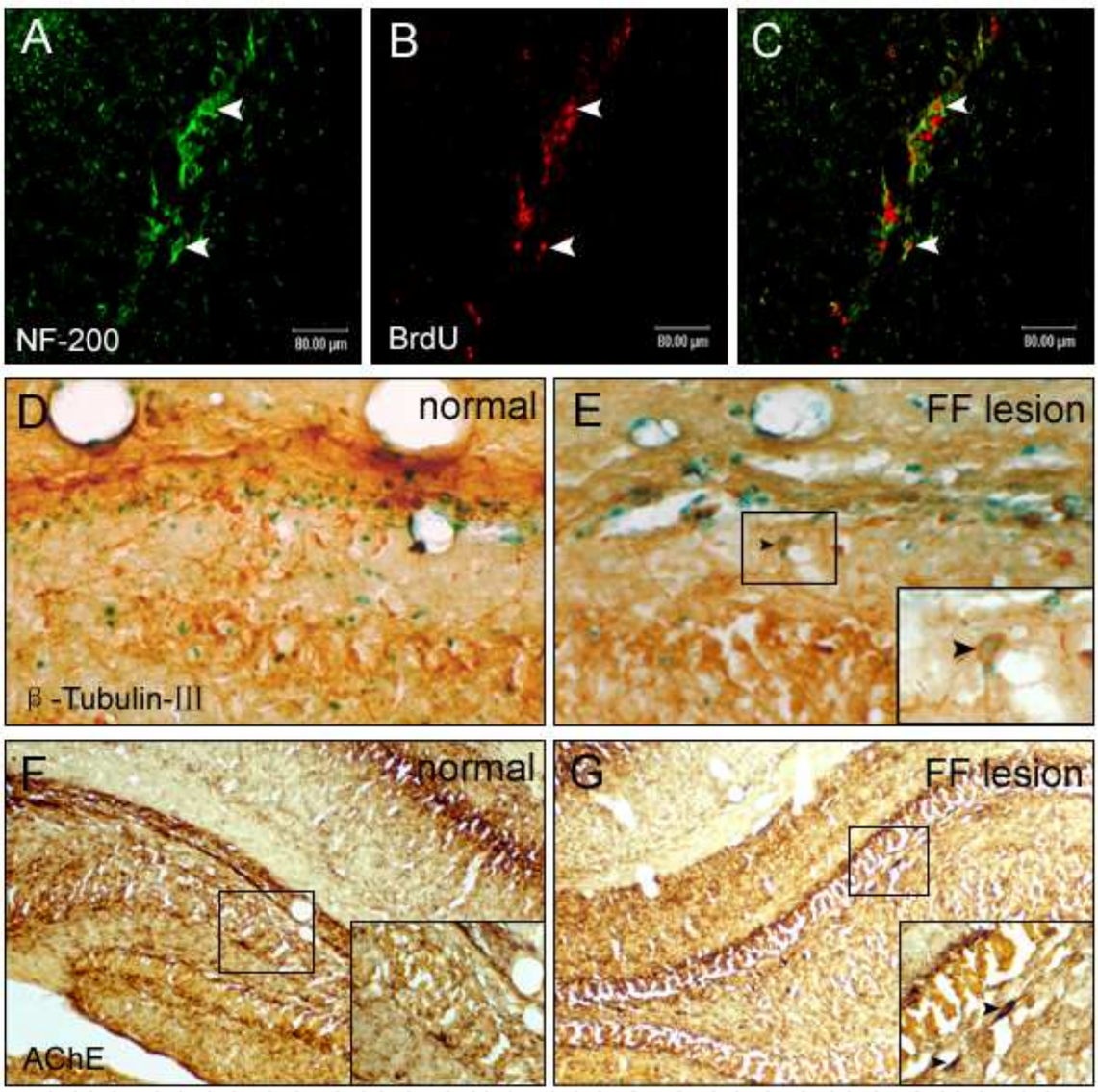
The past studies showed that hippocampus is vulnerable to many pathogenic factors or chemical substances. Since that, the hippocampus is preferred as pathological model to investigate the mechanisms and therapies of nervous disorders, such as ischemia, epilepsy,

aging and excitotoxicity, all of which disturb the physiological balances in the circuits of hippocampus. For example, cholinergic input plays an important role in cognition and attentional behaviors, and cholinergic dysfunction is a prominent feature of dementias including Alzheimer's disease (AD).

Although the pharmacotherapy, such as acetylcholinesterase inhibitors (Gauthier, 2002), secretase inhibitors (Lanz et al., 2003), transition metal chelators (Gnjec et al., 2002) and Aβ immunization (Ferrer et al., 2004; Heppner et al., 2004), has exerted curative effects to some extent on the amelioration of hippocampal neurodegeneration syndromes, but can not completely rescue or replace the dying neurons. Neuro-transplantation has been proposed recent years as a potential treatment for neurodegenerative disorders (Bachoud-Levi et al., 2000; Gaura et al., 2004). Grafts of neural stem/progenitor cells (NSCs/NPCs) present a potential and innovative strategy for the treatment of many disorders of central nervous system, with the possibility of providing a more permanent remedy than present drug treatments.

Cholinergic projections comprise a complex neural network that supports higher brain functions. FiFx and CB are the principal cholinergic pathways that communicate signals between the basal forebrain and hippocampus and cortex. Lesions of the FiFx plus CB lead to substantially reduced cholinergic innervation (Gage et al., 1994) and produce lasting impairments of spatial learning and memory (Liu et al., 2002), all of which are among the earliest events in the pathogenesis of AD (Geula & Mesulam, 1989; Schliebs & Arendt, 2006; Szenborn, 1993). Selective depletion of cholinergic neurons in the basal forebrain elevated APP immunoreactivity in the cerebral cortex and hippocampus, and increased APP levels correlated with decreased cholinergic activity (Leanza, 1998; Lin et al., 1998). The increased expression of APP after cholinergic lesion can potentially lead to increased Aβ production, thereby possibly causing Aβ accumulation and deposition, which is one of the main pathological features.

In our study [(Zhang et al., 2007) and Figure 3] we transplanted SVZ progenitors directly into the denervated and contralateral hippocampi of the AD rat models and determined the effect of different hippocampal environment on the fate of NPCs. The donor neural progenitors in this study were derived from the neonatal SVZ for their features prior to and following transplantation that make them candidates for cell replacement therapy. The grafted cells survived well even through the longest span, 2 months after implantation, and migrate along the subgranular layer after. The same model was treated through neural stem cell transplantation by Xuan and his colleagues (Xuan et al., 2009). The results indicate that the deafferented hippocampus provided proper microenvironment for the survival and neuronal differentiation of neural progenitors and transplanted NSCs can differentiate into cholinergic neurons and enhance the learning and memory abilities. Another kind of AD model produced by injections of amyloid-β peptide (1-40) ($A\beta_{1-40}$) received neural stem cell transplantation into the hippocampus dentate gyrus. The grafted cells can survive, and differentiate with high yield into immunohistochemically mature glial cells and neurons of diverse neurotransmitter-subtypes. More importantly, transplanted cells demonstrate characteristics of proper synapse formation between host and grafted neural cells (Li et al., 2010).



(A–C) Cofocal images of NF-200 positive (green) and BrdU positive (red) neurons in denervated hippocampus at day 30 after transplantation. Arrow showed the neurons double positive to BrdU and NF200. (D and E) β-Tubulin-III (Tuj1, brown) and BrdU (blue) immunohistochemistry on the normal (D) and denervated (E) hippocampus. Arrow showed the β-Tubulin-III and BrdU positive neurons in denervated hippocampus. (F and G) AChE histochemistry on the normal (F) and denervated (G) hippocampus. Arrow showed the AChE positive neurons in denervated hippocampus which may be from differentiation of the grafted cells or endogenous NPCs because there originally are no cholinergic neurons in normal hippocampus.

Fig. 3. Immunodetection to the neuronal differentiation of SVZ NPCs grafted into adult hippocampus.

Prophylactic cranial radiotherapy involves giving radiotherapy to a person's head to prevent or delay the possible spread of cancer cells to the brain, but induces progressive and debilitating declines in cognition that may, in part, be caused by the depletion of the normal neural cells or NSC in hippocampus. Acharya and his colleagues (Acharya et al., 2011) used NSC replacement as a strategy to combat radiation-induced cognitive decline by intrahippocampal transplantation with human neural stem cells (hNSC). Unbiased stereology revealed that 23% and 12% of the engrafted cells survived 1 and 4 months after transplantation, respectively. Engrafted cells migrated extensively, differentiated along glial and neuronal lineages, and expressed the activity-regulated cytoskeleton-associated protein (Arc), suggesting their capability to functionally integrate into the hippocampus. Behaviorally the irradiated animals engrafted with hNSCs showed significantly less decline in cognitive function.

After transplantation if these cells survive the injured and/or degenerative insult(s), they may migrate within damaged areas and promote repair or neuroprotection via cell replacement, integration or neuroprotection. The neuroprotection from grafted NPCs may be the results of in situ release of immunomodulatory molecules (e.g., anti-inflammatory cytokines) and neurotrophic factors [e.g., nerve growth factor (NGF), fibroblast growth factor (FGF)-2, ciliary neurotrophic factor (CNTF) and brain-derived neurotrophic factor (BDNF)] (Martino & Pluchino, 2006; Pluchino et al., 2005). On the other hand, transplanted NPCs may also differentiate into local specific cells to replace the dying cells and integrate within the host neural cells. Thus, we can propose the concept of 'therapeutic plasticity', which can be viewed as the capacity of somatic stem cells to adapt their fate and function(s) to specific environmental needs occurring as a result of different pathological conditions.

It is indicated that NPCs afford a promising strategy for functionally restoring defects induced by hippocampal degenerations or injuries. However, neural transplantation to correct congenital or acquired disorders using multipotent progenitor cells has several major limitations: migration of the transplanted cells is limited; the cells seldom develop into neurons; the limited sources of donor cells and many ethical concerns and political restrictions. Motivating endogenous neural progenitors may be another good strategy for the neurodegenerative disorders.

4. Adult neurogenesis of endogenous NSCs in hippocampus

During the past decade, the progress in the field of stem cells has fueled the hope to cure currently intractable diseases by cell replacement. In regard of ethical concerns and political restrictions that have been raised regarding the use and manipulation of fetal tissue and embryonic stem cells and the limitation of heterogeneous graft, adult endogenous NPCs have been prefered as a cellular source for the treatment of CNS diseases. The use of endogenous sources for cell replacement offer a potential advantage over other cell sources: Immunological reactions are avoided.

After injury or during neurodegenerative processes in restricted brain regions the NPCs frequently reside in niches that regulate their self-renewal, activation and differentiation. Within the niche, both environmental cues and intrinsic genetic programs are two factors required to direct/regulate stem and precursor cell proliferation, differentiation and integration. The adult born functional neurons in the neural networks is believed to

experience sequential steps in a highly regulated fashion: proliferation of the NSC, generation of a rapidly amplifying progenitor cell, differentiation into an immature neuron, migration to the final location, growth of axons and dendrites and formation of synapses with other neurons in the circuits, and ultimately maturation into a fully functional neuron. Although these steps are equivalent to the ones that newborn neurons undergo during development, the fundamental difference between the developmental and adult neurogenesis is that new adult neurons undergo these processes in an already mature environment and integrate into preexisting circuits in adult hippocampal neurogenesis. During this period, the newborn neurons undergo dying, surviving, migrating into the granular layer, sending axons to the CA3 region to form mossy fibers and projecting dendrites to the outer molecular layer (Hastings & Gould, 1999; Kempermann et al., 2003; Markakis & Gage, 1999; Seri et al., 2001; van Praag et al., 2002). Simultaneously, the newly generated neurons receive synaptic inputs from the other region within four to six weeks after birth (van Praag et al., 2002). The complexity and density of their dendritic spines have to continuously grow for several months. Thus, the course of neuronal development for granule neurons born in the adult hippocampus appears much more protracted than those generated during embryonic stages.

The endogenous NPCs in the SVZ and SGZ are the source of adult neurogenesis and remodeling which are implicated in responses to multiple insults including ischemia (Arvidsson et al., 2002; Jin et al., 2001; Miles & Kernie, 2008; Nakatomi et al., 2002), trauma (Johansson et al., 1999; Yoshimura et al., 2001), seizure (Parent et al., 1997; Parent & Murphy, 2008) and neurodegeneration (Fallon et al., 2000; Magavi & Macklis, 2002). Adult neurogenesis in hippocampus can be regulated by numerous factors associated with an animal's behavioural and cognitive states. Indeed, an animal's experiences on cognition and mood, including hippocampus-dependent learning, environmental enrichment, voluntary running and chronic treatment with antidepressants, can affect the rate of neurogenesis. The factors enhancing hippocampal neurogenesis are summarized in the following and Figure 5 which also enumerates the factors decreasing adult hippocampal neurogenesis.

4.1 Enriched environment

Gage and his colleagues have demonstrated that mice placed in an enriched environment where there are more social interactions, inanimate objects for play and a wheel for voluntary exercise have an increased rate of neurogenesis relative to mice that are kept in standard cages (Kempermann et al., 1997). Subsequently, the similar experiments have been repeated and proven by other laboratories (Beauquis et al., 2010; Brown et al., 2003; Ehninger & Kempermann, 2003; Kempermann et al., 2002; Kohl et al., 2002; Llorens-Martin et al., 2010; Olson et al., 2006; Steiner et al., 2008). The dual-birthdating analysis used to study two subpopulations of newborn neurons born at the beginning and end of enrichment suggested that enriched environment induces differential effects on distinct subpopulations of newborn neurons depending on the age of the immature cells and on the duration of the enriched environment itself (Llorens-Martin et al., 2010). This work points to a hypothesis that the effects of physical-cognitive activity on neurogenesis depend on the interaction of two critical parameters: the age/differentiation status of the immature neuron plus the time the individual is under the effects of an enriched environment.

4.2 Exercise

Studies of voluntary exercise demonstrate that running on wheel without other components of enriched environment is sufficient to increase proliferation and recruitment of granule cells into the adult DG (van Praag et al., 1999a; van Praag et al., 1999b). Although the exact mechanism underlying the exercise-induced up-regulation of neurogenesis remains unclear, exercise is reported to increase the expression of certain trophic factors, such as BDNF and FGF-2 (Ding et al., 2011; Gomez-Pinilla et al., 1997; Griffin et al., 2011; Russo-Neustadt et al., 1999), which have also been shown to increase neurogenesis during development or in adult brain (Ding et al., 2011; Zigova et al., 1998).

4.3 Psychotropic drugs

Serotonergic antidepressant drugs have been commonly used to treat mood and anxiety disorders. In experimental animals, chronic antidepressant treatments can facilitate neurogenesis in the DG of the adult hippocampus (Dagyte et al., 2010; Kitamura et al., 2011; Malberg et al., 2000; Nasrallah et al., 2011). The adult hippocampal neurogenesis has been implicated in some of the behavioral effects of antidepressants (Airan et al., 2007; Santarelli et al., 2003; Wang et al., 2008). Two molecular mechanisms are possibly involved in the antidepressant drug-induced hippocampal neurogenesis. One is the increased BDNF in hippocampus. Previous studies have demonstrated that repeated antidepressant administration increases the expression of BDNF in hippocampus (Duman et al., 1997; Duman et al., 2000; Lee & Kim, 2010; Pilar-Cuellar et al., 2011; Reus et al., 2011; Rogoz et al., 2008). In contrast, stress decreases BDNF expression in this brain region (de Lima et al., 2011; Murakami et al., 2005) and causes atrophy of hippocampal neurons and decreased neurogenesis (Gould et al., 1998; Yap et al., 2006). All these results have contributed to a neurotrophic hypothesis of depression and antidepressant action. Antidepressant treatment may block or even reverse these effects of stress via increased expression of BDNF. The other is the Notch1 signaling. New evidences indicated that fluoxetine (antidepressant) administration increased mRNA and protein expression of Notch1 signaling components (including Jag1, NICD, Hes1 and Hes5) and simultaneously up-regulated hippocampal cell proliferation and survival, suggesting that activation of Notch1 signaling might partly contribute to increased neurogenesis in hippocampus (Sui et al., 2009). In addition to promotion of neurogenesis, the psychotropic drugs significantly increased the survival of newborn neurons in dorsal hippocampus by approximately 50% (Su et al., 2009). Results from Kobayashi and his colleagues (Kobayashi et al., 2010) showed that serotonergic antidepressants can reverse the established state of neuronal maturation in the adult hippocampus, termed "dematuration" of mature granule cells, and up-regulate 5-HT4 receptor-mediated signaling which may play a critical role in this distinct action of antidepressants. Such reversal of neuronal maturation could affect proper functioning of the mature hippocampal circuit. Together with these results support the hypothesis that antidepressants exert therapeutic effects on neuropsychiatric disease via not only activating the hippocampal neurogenesis but also reinstating neuronal functions of the matured granular cells.

Evidences have not show the confirmed effects on the repeated antipsychotic drug administration because of the contradictory results that Dawirs et al. work (Dawirs et al., 1998) demonstrated granular cell proliferation by chronic administration of haloperidol while Backhouse et al., (Backhouse et al., 1982) reported a decrease in hippocampal cell

proliferation. Abuse of drugs including opiates and psychostimulants can influence cognition, learning and memory, which is accompanied by decrease of the proliferation of granule cells in adult rat hippocampus (Eisch et al., 2000).

4.4 Ischemia

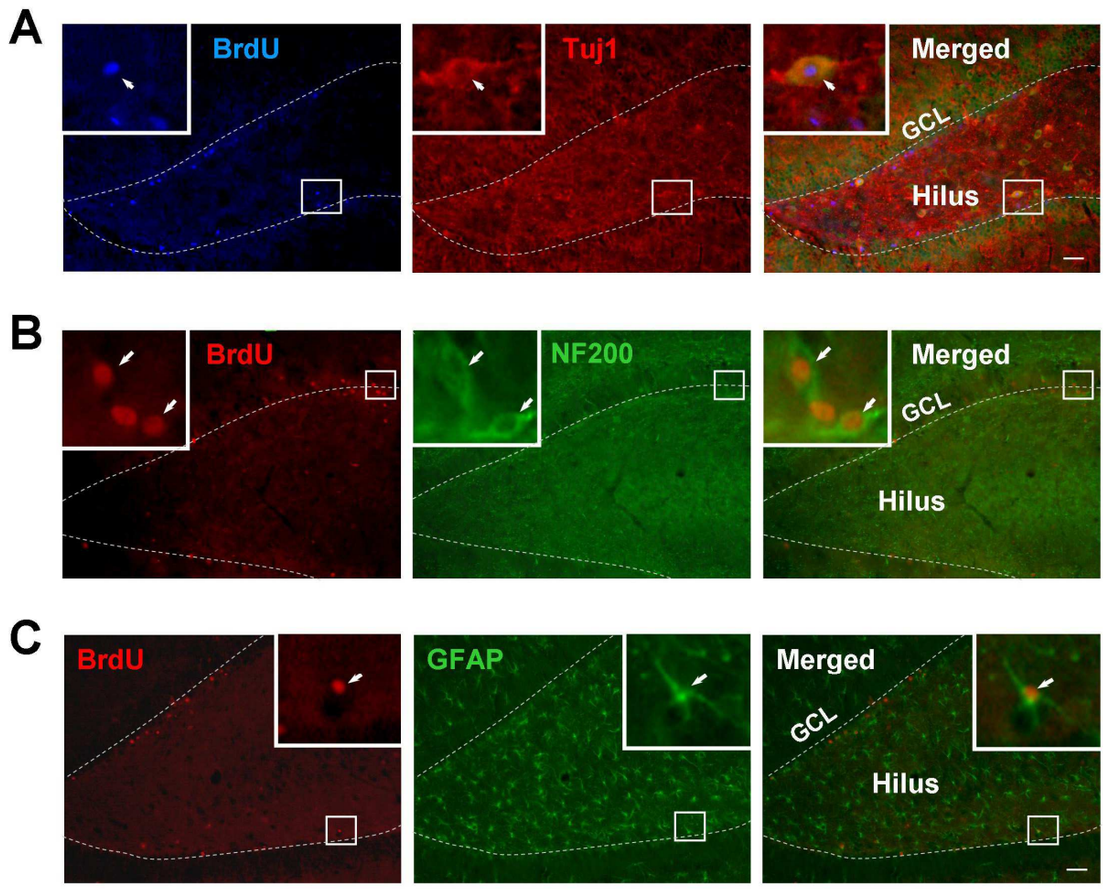
Studies have noted that ischemia also produces enhanced neurogenesis in neuroproliferative regions of the adult rodent brain, including the SVZ of the lateral ventricles and SGZ of DG (Burns et al., 2009; Jin et al., 2001; Parent et al., 2002; Yagita et al., 2001). Proliferation induced by transient focal or global ischemia peaks 7 to 10 days after ischemia and returns to baseline levels within several weeks. Some of the new cells die but others survive to adopt a neuronal fate in the ischemic and uninjured dentate gyrus. Newborn cells labeled EGFP retroviral reporter are found to move from the subgranular proliferative zone to the DGC layer, shift from coexpression of immature to mature neuronal markers, and increase in dendritic length (Tanaka et al, 2004), suggesting that newly generated DGCs in the ischemic brain follow a time course of neuronal maturation. A new report from Liu and his colleagues (Wang et al., 2011) indicated that transient brain ischemia initiates a sustained increase in neurogenesis for at least 6 months and promotes the normal development of the newly generated neurons in the adult DG.

4.5 Traumatic Brain Injury (TBI)

The hippocampus, a region responsible for memory and learning, is particularly vulnerable to brain trauma. Learning and memory deficits are the most enduring and devastating consequences following TBI on hippocampus. A slow but significant improvement in cognitive function after TBI indicates that innate mechanisms for repair exist in the brain (Schmidt et al., 1999). Although the mechanisms underlying this innate recovery remain largely unknown, the findings that NSCs persist in the hippocampal DG throughout life (Gage, 2000; Kempermann & Gage, 2000) and exhibit high activation of proliferation and neurogenesis in response to brain trauma (Chirumamilla et al., 2002; Dash et al., 2001; Urrea et al., 2007; Yu et al., 2008) suggest that neurogenesis may contribute to the cognitive recovery observed following TBI.

In our laboratory transection of FiFx plus CB is deemed as a kind of TBI to produce deafferented hippocampus. The denervated hippocampus provided a proper microenvironment for the survival and neuronal differentiation of exogenous neural progenitors (Zhang et al., 2007). Subsequently, we determined the endogenous NPCs in DG of adult hippocampus after denervation trauma. The results showed that traumatic injury by transecting FiFx and CB which carry cholinergic inputs promoted proliferation of the local NPCs and increased the number of newborn neurons in SGZ of hippocampus (Figure 4). Indicating that the changes in the deafferented hippocampus provided a suitable microenvironment for neurogenesis of endogenous progenitors of adult hippocampus. However, Christiana et al. (Cooper-Kuhn et al., 2004) produced a cholinergic depletion model by infusion of the immunotoxin 192IgG-saporin into lateral ventricle to selectively lesion cholinergic neurons of the cholinergic basal forebrain. Oppositely, their results showed a significant declination of neurogenesis in the granule cell layer of the dentate gyrus and olfactory bulb. Furthermore, immunotoxic lesions led

to increased numbers of apoptotic cells specifically in the SGZ and the periglomerular layer of the olfactory bulb. The model of TBI created by distinct ways may contribute to the conflict results because the immunotoxin might exert negative effects on the neural progenitors and newborn neurons.



A) Immunofluorescence micrographs of anti–BrdU (Blue), β-tubulin III (Tuj1, red) in coronal sections of the hippocampus at day 35 after denervation operation. Arrows show the cells immunoreactive to BrdU and Tuj1. B) Microscope images of sections through deafferented hippocampus stained by BrdU and NF-200 antibodies on day 42 after transection. Arrows show the BrdU and NF-200 double positive neurons. (C) Microscope image of BrdU positive (red) and GFAP positive (green) astrocytes in denervated hippocampus 28 days after transection. Arrow showed the BrdU and GFAP positive astrocytes.

Fig. 4. Endogenous NPCs labeled with BrdU differentiate into neurons and astrocytes in deafferented hippocampus.

4.6 Seizures

Seizures characterize the periodic and unpredictable occurrences of epilepsy. Accumulating evidences indicate that seizures alter not only the amount, but also the pattern of neurogenesis, though the overall effect depends on the type of seizures. Acute seizures abnormally increase the amount of hippocampal neurogenesis and induce aberrant migration of newly born neurons into the dentate hilus and the dentate molecular layer

(Bengzon et al., 1997; Jessberger et al., 2005; Kralic et al., 2005; Parent et al., 1997). Examination of the hippocampus from young temporal lobe epilepsy patients (<4 years of age) suggested increased cell proliferation of neural precursor cells (Blumcke et al., 2001). However, recurrent spontaneous seizures typically observed in chronic temporal lobe epilepsy lead to a radically waned neurogenesis (Hattiangady et al., 2004; Kralic et al., 2005), which, interestingly, coexists with learning and memory impairments and depression. Heinrich et al. (Heinrich et al. 2006) reported a gradual fall in neurogenesis at 1 week and virtual loss of all neurogenesis by 4-6 weeks after the initial seizure episode. However, a modest increase in neurogenesis was observed even at 2 months post status epilepticus in a lithium-pilocarpine model of epilepsy using postnatal day 20 rats (Cha et al., 2004). It emerges that decreased levels of hippocampal neurogenesis in chronic epilepsy depend on the model and the age of the animal at the time of the initial seizure episode.

4.7 Others

Lithium was noticed to have mood stabilizing properties in the late 1800s when doctors were using it to treat gout. Australian psychiatrist John Cade published the first paper on the use of lithium in the treatment of acute mania. Lithium, as a mood stabilizer, is used as an add-on treatment for clinical depression. Recent reports have described that lithium increases cell proliferation and/or promotion of neuronal differentiation of NPCs (Boku et al., 2011; Chen et al., 2000; Fiorentini et al., 2010; Hanson et al., 2011; Kim et al., 2004; Kitamura et al., 2011; Son et al., 2003; Wexler et al., 2008) and blocks the effects of stress on depression-like behaviors through increasing hippocampal neurogenesis in adult rodent models (Silva et al., 2008). Results of these studies suggest that adult hippocampal neurogenesis plays an important role in the therapeutic action of mood stabilizers as well. Inhibition of GSK-3β and subsequent activation of Wnt/β-catenin signalling may underlie lithium-induced hippocampal neurogenesis and therapeutic effect (Boku et al., 2010; Fiorentini et al., 2010; Wexler et al., 2008).

Acupuncture or electroacupuncture, the ancient Chinese treatments through stimulating the acu-points, can ameliorate syndromes of many illnesses pain, metabolic and pathological brain disease, and even mental disorders, such as major depression. Although the mechanisms underlying treatment of acupuncture on these diseases remain unclear till now, neurogenesis must be considered as a potential one of mechanisms in the process of therapy. It has been reported that acupuncture and electroacupuncture in the acu-points ST36 (*Zusanli*) and GV20 (*Baihui*) increase significantly neurogenesis in the normal DG, while electroacupuncture has greater effects on neuroblast plasticity in the DG than acupuncture (Hwang et al., 2010). In addition to normal status, relieves of illnesses were paralleled with the hippocampal neurogenesis in DG. For example, decreased cell proliferation in the DG of dementia model was improved by *Yiqitiaoxue* and *Fubenpeiyuan* acupuncture (Cheng et al., 2008). In addition, electroacupuncture at GV20 and EX17 increased hippocampal progenitor cell proliferation in adult rats exposed to chronic unpredictable stress (Liu et al., 2007). In ischemic models (Kim et al., 2001) and streptozotocin-induced diabetic models (Kim et al., 2002), acupuncture (ST36)-induced alleviation is paralleled with increased cell proliferation in the DG. Acupuncture at *Tanzhong* (CV17), *Zhongwan* (CV12), *Qihai* (CV6), ST36, and *Xuehai* (SP10) improve spatial memory impairment (Yu et al., 2005), maintain

oxidant-antioxidant balance, and regulate cell proliferation in a rodent dementia model (Cheng et al., 2008; Liu et al., 2006).

After comparing the cell proliferation in DG of adult mice fed on hard and soft diet, Yamamoto et al. (Yamamoto et al., 2009) found that sufficient mastication activity enhanced hippocampal neurogenesis since that the total number of BrdU-labeled cells was fewer in the soft-diet group than in the hard-diet group at 3 and 6 months of age.

Additionally, Leuner et al. (Leuner et al., 2010) found that sexual experience that the adult male rats were exposed to a sexually-receptive female increased circulating corticosterone levels and the number of new neurons in the hippocampus and stimulated the growth of dendritic spines and dendritic architecture, suggesting that a rewarding experience actually promotes adult-born neuronal growth.

The persistence of neurogenesis in the adult mammalian forebrain suggests that endogenous precursors provide a potential source of neurons for the replacement of the dying or lost neurons due to brain damage or neurodegeneration. Based on the multiple stimuli inducing hippocampal neurogenesis, strategies that are designed to increase adult hippocampal neurogenesis specifically, by targeting the cell death of adult-born neurons or by other mechanisms, may have therapeutic potential for reversing impairments in pattern separation and DG dysfunction such as those seen during normal ageing.

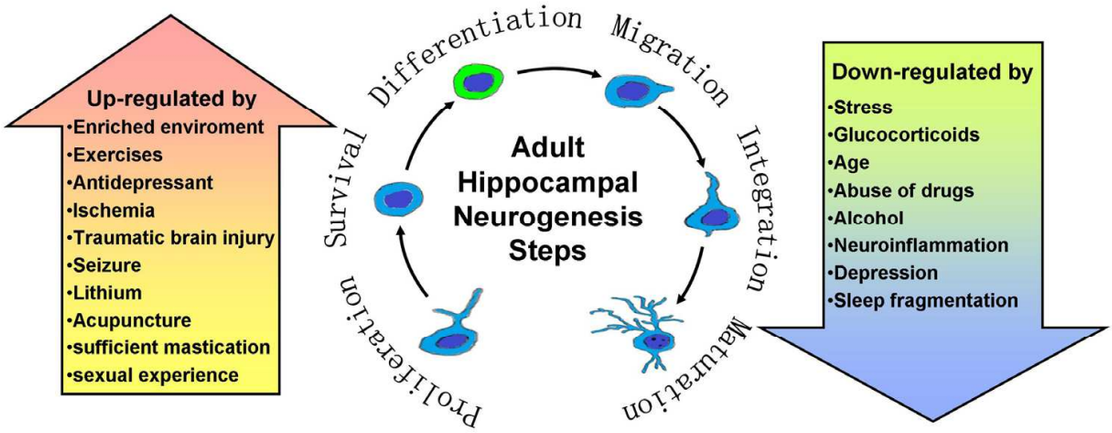


Fig. 5. Adult hippocampal neurogenesis can be up- or down-regulated by various stimuli. This summarizes the sequent steps of adult hippocampal neurogenesis and a variety of stimuli positively or negatively influencing adult hippocampal neurogenesis.

5. Signal pathways involved in hippocampal neurogenesis

Understanding the mechanisms underlying adult neurogenesis and differentiation of NPCs is crucial to delineate the function of NPCs and their progeny and ultimately their therapeutic potential. The initial investigations on environmental niches and intrinsic genetic programs that regulate early and adult neurogenesis have revealed many extrinsic and intrinsic elements playing critical roles in differential phrases of neurogenesis, such as proliferation, migration, differentiation, integration and maturation. The following lists the signal molecules involved in adult hippocampus neurogenesis.

5.1 Wnt (wingless)

Traditionally, Wnt proteins are assumed to act as stem cell growth factors, promoting the maintenance and proliferation of stem cells (Willert et al., 2003) and inducing of neural specification (Muroyama et al., 2002). Interaction of Wnts with their receptors can trigger several signaling pathways, including the β-catenin dependent pathway. Studies of Lie et al. (Lie et al., 2005) show that Wnt signalling components and their receptors were expressed in the adult hippocampal progenitor cells. Overexpression of Wnt3 is sufficient to increase neurogenesis of adult hippocampal progenitors in vitro and in vivo. By contrast, blockade of Wnt signalling reduces neurogenesis of adult hippocampal progenitor cells in vitro and abolishes neurogenesis almost completely in vivo. Evidence also suggests that β-catenin, which is present in neural progenitors and newborn granule neurons, plays an important role in the dendritic development of adult born hippocampal neurons (Gao et al., 2007). These data show that Wnt signalling is a principal regulator of adult hippocampal neurogenesis.

5.2 Notch

Notch (1 – 4 in mammals) signaling pathway is crucial for maintenance of stem cell self renewal, proliferation, and specification of cell fate (Mason et al., 2006). Notch signaling is highly activated in type-B cells of the SVZ of the lateral ventricle and type-1 cells of the SGZ of the DG (Ehm et al., 2010; Imayoshi et al., 2010; Lugert et al., 2010). In postnatal and adult mice, Overexpression of Notch1 in postnatal and adult mice increased hippocampal cell proliferation and maintained GFAP-expressing NSCs, while depletion of Notch signaling led to a decrease in cell proliferation and a shift in the differentiation of newly born cells towards a neuronal lineage suggesting that Notch1 signaling is required to maintain a reservoir of undifferentiated cells and ensure continuity of adult hippocampal neurogenesis (Ables et al., 2010; Breunig et al., 2007). In addition, Notch1 signaling modulates the dendritic morphology of newborn granule cells by increasing dendritic arborization (Breunig et al., 2007). These evidences suggest that Notch1 signaling is involved in the cell proliferation, fate determination, and maturation of adult hippocampal neurogenesis. Pathologically, antidepressant therapy chronic fluoxetine administration increased expression of Notch1 signaling components including Jag1, NICD, Hes1 and Hes5 in the hippocampus, accompanied by cell proliferation and survival (Sui et al., 2009). This indicated that activation of the Notch1 pathway might partly contribute to chronic antidepressant therapy-increased neurogenesis in hippocampus.

5.3 Bone Morphogenetic Protein (BMP)

BMP proteins, the extracellular signaling molecules, regulate cell proliferation and fate commitment throughout development and within the adult SVZ and SGZ neurogenic niches (Bonaguidi et al., 2005; Bonaguidi et al., 2008; Mehler et al., 2000). The cysteine knot proteins noggin, chordin and follistatin regulate BMP actions via competitively binding BMPs in the extracellular space to prevent receptor activation and the downstream signaling activity (Dal-Pra et al., 2006; Ebara & Nakayama, 2002). The inhibition of noggin in vivo by RNA interference decreased hippocampal cell proliferation (Fan et al., 2004). Study of Gobeske et al. indicated that BMP signaling mediates effects of exercise on hippocampal neurogenesis and cognition in mice (Gobeske et al., 2009).

5.4 Sonic hedgehog (Shh)

Shh is reported to be crucial in the expansion and establishment of postnatal hippocampal progenitors (Palma et al., 2005). The Shh receptors patched (Ptc) and smoothened (Smo) are expressed in the dentate gyrus subfield including the neurogenic niche of SGZ and in neural progenitor cells derived from hippocampus (Lai et al., 2003; Traiffort et al., 1998). Recently, it is addressed that Shh signaling regulates adult hippocampal neurogenesis (Han et al., 2008; Lai et al., 2003; Palma et al., 2005). In rats, overexpression of Shh in the DG increased cell proliferation and survival (Lai et al., 2003). On the other hand, inhibition of Shh signaling by injections of inhibitor cyclopamine reduced cell proliferation (Banerjee et al., 2005; Lai et al., 2003). Removal of Shh signaling in these animals resulted in dramatic reduction in number of neural progenitors in both the postnatal SVZ and hippocampus. Consistently, conditional null alleles of hedgehog signaling also resulted in abnormalities in the DG and olfactory bulb (Machold et al., 2003). These studies emphasize the importance of the Shh signaling pathway in adult neurogenesis. Findings from Banerjee et al. (Banerjee et al., 2005) demonstrated that Shh pathway may be involved in electroconvulsive seizure-enhanced adult hippocampal neurogenesis. The primary cilia are important sites of signal transduction which unite the receptors and the signal-transduction components, such as Wnt and Hedgehog (Hh) signaling cascades (Huangfu et al., 2003; Huangfu & Anderson, 2005). It is demonstrated that, in the absence of cilia, there is a dramatic diminution in Shh signaling, decreased early proliferation and a consequent loss of quiescent precursor cell (Breunig et al., 2008).

5.5 PI3K-Akt

PI3K-Akt signalling pathway is the downstream of neurotrophic and growth factor receptors, as well as monoamine receptors (Datta et al., 1999). It is potentially implicated in a number of different functions and especially associated with cell survival by inhibiting the activation of proapoptotic proteins and transcription factors (Aberg et al., 2003). Akt has three different isoforms, Akt1, -2, -3, each encoded by independent genes (Coffer et al., 1998). It was shown that Akt1 and Akt2 knockout mice had lower levels of hippocampal cell proliferation compared to wild type animals (Balu et al., 2008). However, only Akt2KO mice had impairment in the survival of adult born hippocampal progenitors (Balu et al., 2008). Subsequent report also showed the nonredundant roles of Akt in the regulation of hippocampal neurogenesis since that physical exercise activated Akt and three downstream targets, BAD, GSK3b and FOXO1 and inhibition of PI3K-Akt signaling blocks exercise-mediated enhancement of adult neurogenesis and synaptic plasticity in the DG (Bruel-Jungerman et al., 2009).

6. Conclusion

These findings have fuelled the hope of using neurogenesis, exogenous or endogenous, in regenerative medicine for neurological diseases, arguably the most difficult diseases to treat. The proposed regenerative approaches to neurological diseases include (1) cell therapy approaches in which donated cells are delivered by intracerebral injection or infusion through an intravenous or intra-arterial route; (2) stem cell mobilization approaches in which endogenous stem or progenitor cells are activated by cytokines or chemokines; (3) trophic and growth factor support in which the factors, such as BDNF and GDNF, were

delivered through grafted stem cells modulated genetically into the brain to support the injured neurons. These approaches may be used together to maximize therapeutic effects. Although the mechanisms underlying these therapeutic processes are still unclear, the neurogenic cells must survival various complicated and difficult barriers from proliferation to maturation. Understanding the factors in NPC niches and intracellular molecules regulating/directing adult neurogenesis will largely speed the steps to make use of exogenous or endogenous NPCs in treatment of neural disorders. The past evidences indicate that cell therapy to the injured tissue and brain may be contributed by several processes including angiogenesis, neurogenesis and trophic or 'chaperone' support.

7. References

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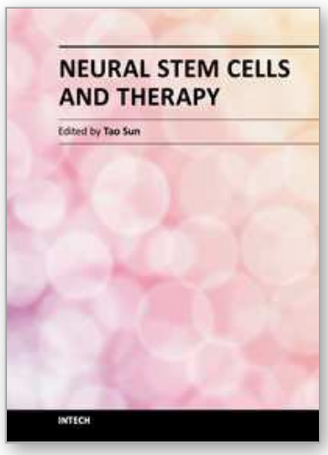

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This book is a collective work of international experts in the neural stem cell field. The book incorporates the characterization of embryonic and adult neural stem cells in both invertebrates and vertebrates. It highlights the history and the most advanced discoveries in neural stem cells, and summarizes the mechanisms of neural stem cell development. In particular, this book provides strategies and discusses the challenges of utilizing neural stem cells for therapy of neurological disorders and brain and spinal cord injuries. It is suitable for general readers, students, doctors and researchers who are interested in understanding the principles of and new discoveries in neural stem cells and therapy.

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