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# Injury-Induced DNA Replication and Neural Proliferation in the Adult Mammalian Nervous System

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## 1. Introduction

Neurons located in the mammalian central (CNS) and peripheral (PNS) nervous system are, for the most part, a stable post-proliferative population. Indeed, recent evidence indicates that a vast majority of CNS neurons pushed into the cell cycle will die. Thus, understanding the processes of induced DNA replication, neural proliferation and neurogenesis in adult individuals is a major goal of modern neurobiology. Neurogenesis is a process that produces functional neurons from stem/progenitor cells. It is widespread during development, but in the mature mammalian nervous system, under physiological conditions it occurs only in two discrete regions: the subventricular zone of the lateral ventricle (SVZ) and in the subgranular zone (SGZ) of the dentate gyrus (DG) in the hippocampus (Gage 2002; Kempermann et al. 2004). It is believed that in the adult mammalian CNS, neurogenesis outside of these two regions is extremely limited or non-existent. However, some studies of ganglionic nerve centers located outside the CNS revealed DNA replication leading to neural cell division and differentiation into neurons, presenting the possibility of adult neurogenesis in the PNS (Devor and Govrin-Lippmann 1985; Czaja et al. 2008; Silva et al. 2008; Gallaher et al. 2011). In this chapter we will present background knowledge regarding DNA synthesis leading to production of new neurons in the adult mammalian CNS and PNS.

In the CNS, some external factors, such as brain insults, have been reported to trigger adult neurogenesis in regions otherwise considered to be non-neurogenic (Parent 2003). Several studies support the hypothesis of insult-induced neurogenesis in the CNS and show that during development, damage to the adult nervous system induces factors and mechanisms that control neuronal proliferation, migration, differentiation, and connectivity. However,

an induction of large-scale neurogenesis that results in addition or replacement of a significant number of neurons has not been reported in adult mammalian brain, although it does occur in some non-mammalian vertebrates. The presence of neural stem cells in the brain offers the potential for neuronal replacement and regeneration after injury. The most broadly-studied is ischemia-induced neurogenesis (Parent et al. 2002). However, the outcome of ischemia-induced neurogenesis is not robust and does not produce large numbers of new neurons. Few of the newborn neurons persist for an extended period of time after the insult, and this population is significantly smaller compared with the substantial increase in proliferating and migrating neuroblasts. There is also little evidence to suggest that those newborn neurons that do survive become functional and integrate into the existing circuitry. On the other hand, the response of the CNS after injury is not limited to the production of neurons. Induced stem cells and neural progenitors may also differentiate into astrocytes and oligodendrocytes. Thus, the increase in CNS progenitor cells in response to injury is not limited to neural progenitors, since glial progenitors increase as well. Radial glia cells function as glia progenitors and provide a cellular source for neurogenesis during development but may also act as neuronal progenitors in the adult CNS by dividing and producing astrocytes and neurons. The aim of this chapter also will be to review the current knowledge related to injury-induced neural proliferation in the CNS.

The situation in the PNS may be significantly different than in the CNS. In the PNS, neural crest cells, which drive the development of many different nerve structures, also may play a role in the post-developmental period. This is because some of the migratory elements persist as a peripheral reserve pool of multipotent stem cells that can undergo a late differentiation into mature glia or neurons (Lagares et al. 2007). The recruitment of this reserve pool may be stimulated by various physiological and pathological conditions in which new cells are needed. We will review the current knowledge regarding neural proliferation in the adult PNS and discuss the possibility that adult neurogenesis is not restricted only to very limited regions of CNS. The alternative to late differentiation of multipotent cells may be the process of dedifferentiation in the PNS. This is the process by which differentiated neural cells revert to a pluripotent or multipotent state. The process of induced reprogramming of cell fate, which is the transforming one cell type into another by exogenous factors, might have enormous potential for medical and research advances. However, this potential of cell fate reprogramming has not been well explored. Therefore, in this chapter we will present the body of knowledge suggesting the possible cellular candidates in the PNS for dedifferentiation after injury. The possibility of induced DNA replication, neural proliferation and adult neurogenesis in the PNS is almost completely unexplored territory. Moreover, the few available studies have resulted in contrasting conclusions. However, the PNS has been reported to utilize neural precursors that proliferate *in vitro* and can be induced to differentiate into neurons. The possible existence of *in vivo* damage-induced replacement of neurons destroyed by injury, revealed by several investigators in the CNS, is limited to a few reports in the PNS (Czaja et al. 2008; Gallaher et al. 2011). Therefore, we will review the current literature dealing with DNA synthesis, neural proliferation and neurogenesis in the adult PNS under physiological and pathological conditions, and we will discuss possible mechanisms involved in these phenomena.

The main purpose of this chapter is to highlight the niche for further studies on DNA replication and to direct this powerful and fascinating discipline toward a very exciting but

very challenging nervous system. The extremely high need for studies of DNA replication in neural tissue is reflected by Pub Med searches using two different sets of key words. DNA together with synthesis generated about 70,000 hits, while by adding nervous system to this equation we limited the number to about 400. We believe that the conclusion is obvious.

## **2. Injury to the adult CNS induces neural proliferation: hope for self repair**

Despite the fact that neurogenesis was first described in the adult mammalian brain nearly 100 years ago (Allen 1912), adult neurogenesis has been accepted by the scientific community in the last four decades. One year after Ezra Allen's report of neurogenesis in the adult rat brain in 1912, Santiago Ramón y Cajal, arguably the most recognizable name in neuroscience was quoted as saying, "In the adult centers, the nerve paths are something fixed, ended and immutable. Everything may die, nothing may be regenerated." This claim effectively suppressed further investigations of adult neurogenesis for 50 years; until the use of tritiated thymidine by Joseph Altman in the 1960s (Altman 1962; Altman and Das 1965; Altman and Das 1967). Even then, the prevailing belief in the stability of the adult brain was upheld for roughly 30 years after these initial reports. During that time, more and more sensitive techniques were developed to detect cell division (Nowakowski et al. 1989; Nowakowski and Hayes 2001; Wojtowicz and Kee 2006).

Currently, the idea of adult neurogenesis is widely accepted by the scientific community. However, definitive evidence for generation of new and functional neurons in the adult uninjured mammalian CNS has been restricted to the subventricular zone (SVZ) of the lateral ventricle and to the subgranular zone (SGZ) of the dentate gyrus in the hippocampus (Lee and Son 2009; Ehninger and Kempermann 2008; Taupin 2006; Ming and Song 2005; Kempermann et al. 2004; Alvarez-Buylla and Garcia-Verdugo 2002). The discovery of adult neurogenesis has also uncovered the exciting potential for novel approaches to repair the injured brain and spinal cord. Some animals, such as lizards, can regenerate their injured nervous system. The mammalian CNS does not have this capacity; however, it does appear to have a greater regenerative ability than was previously believed. The traditional idea that lineages for neurons and glia become set aside during development has been challenged, and it is now well accepted that progenitors for each cell lineage persist into adulthood (Gage 2000). Moreover, several studies show that neurogenesis is stimulated in the CNS in response to injury (Emery et al. 2003; Parent et al. 2002; Parent and Lowenstein 2002; Parent 2003; Richardson et al. 2007; Shi et al. 2007). Understanding the developmental process and how injury is recapitulating these developmental stages may provide insights into the regenerative capacity of the adult nervous system and speed up the development of strategies to manipulate this neurogenic potential.

Following brain injury, factors that stimulate proliferation of adult neural stem cells and their respective receptors are upregulated (Bambakidis et al. 2005; Yoshimura et al. 2001). Moreover, several studies have suggested that factors and mechanisms regulating neuronal proliferation, migration, differentiation and connectivity during development are reactivated by injury in the adult nervous system (Zhang et al. 2005; Sun et al. 2007). These factors appear to be sufficient to direct neural precursors to migrate toward a lesion area, differentiate into neurons, mature and establish synaptic contacts (Mori et al. 2005; Fricker-Gates et al. 2002). Transition from stem cells to fully differentiated neurons progresses through defined steps, and different classes of neuronal precursors can be distinguished by their morphology, expressed markers, and mitotic activity (Encinas and Enikolopov 2008).

Moreover, several lines of evidence suggest that glia participate in injury-induced neurogenesis, suggesting that they serve as both stem cells and progenitors from which neuroblasts develop (Englund et al. 2005; Gubert et al. 2008; Alonso et al. 2008; Alvarez-Buylla and Lim 2004; Hevner 2006). During CNS development, both the radial glia and astrocytes were reported to undergo proliferation and differentiation toward both the neurons and glia (Costa et al. 2009). Moreover, behaving as post-mitotic cells under physiological conditions, following injury glia may undergo phenotypic and functional changes and dedifferentiate. It has been previously shown that after injury, quiescent astrocytes reveal features of immature stages or phenotypes of stem cells and proliferate (Buffo et al. 2008). These proliferating astrocytes however, undergo symmetric divisions and remain within their cell lineage *in vivo*, while an altered *in vitro* environment revealed their self-renewal and multipotency.

Based on the current knowledge, the most probable scenario in post-injury brain repair is recruitment of endogenous progenitors to replace lost neurons. Proliferation of neural progenitors in germinal centers can be induced by delivery of trophic factors, such as FGF-2 (Yoshimura et al. 2003; Yoshimura et al. 2001). Recruitment of endogenous progenitors has also been achieved through release of brain-derived neurotrophic factor (BDNF) and induction of neural differentiation (Chmielnicki et al. 2004; Benraiss et al. 2001). The *in vivo* induction of massive proliferation, directed migration, and differentiation of neural cells in the forebrain of the adult rat after lesion of the substantia nigra were observed after infusions of transforming growth factor alpha into the forebrain (Fallon et al. 2000). Studies of injury-induced neurogenesis in CNS generate substantial enthusiasm for the recruitment of endogenous progenitors as the therapeutic strategy for CNS repair. However, the successful development of stem cell recruitment therapy depends on the ability to control proliferation, differentiation, and functional integration of induced pluripotent cells. In order to develop therapies that can recruit endogenous progenitors to repair damaged areas of the adult CNS, it is also important to understand how neural environment changes following injury.

While injury-induced neurogenesis in mammals does not lead to complete recovery, we believe it represents the brain's attempt to repair itself. However, in adulthood, CNS has been associated with a very limited regenerative response to injury, compared to embryonic CNS (Fry and Saunders 2000; Nicholls and Saunders 1996; Fawcett 1992). Therefore, an understanding how to induce and control self repair process in the brain to promote recovery from injury or neurodegenerative diseases would be the main challenge in regenerative medicine of the 21<sup>st</sup> century. Reviewed in subsequent sections of this chapter is recent evidence that after injury, the CNS in adults activates cascades of events and gene expressions that are normally observed during development. We will discuss studies showing that under normal circumstances, damage to the CNS, including stroke and traumatic brain injury (TBI), as well as the experimental use of neurotoxins and other external agents in both the brain and the spinal cord result in an increased cell proliferation and neurogenesis in quiescent regions of the CNS.

## 2.1 Stroke-induced neural proliferation

Stroke, or cerebrovascular accident, results from the middle cerebral artery occlusion (MCAO) leading to brain infarction, is one of the common causes of death and disability in adulthood. However, improvement of brain functions has been reported following stroke,



implying the ability for brain repair (Pascual-Leone et al. 2005). One means by which repair might be achieved is neurogenesis, which occurs in the normal adult brain, and is increased in animal models of brain injury including stroke (Katakowski et al. 2007; Jin et al. 2006; Zhang et al. 2004). Post-stroke neurogenesis is associated with migration of newborn neurons from neurogenic niches to injured regions of the brain (Arvidsson et al. 2002). Neuronal precursors proliferate in the SVZ, and newly formed neurons migrate into the ischemic lesions and differentiate to acquire the phenotype of the neurons which were lost. However, the outcome of ischemia-induced neurogenesis is not robust and does not produce large numbers of new neurons. Few of the newborn neurons survive for an extended period of time after the insult, and this population is significantly smaller when compared to the population of migrating neuroblasts. There is also little evidence to suggest that those newborn neurons that do survive become functional and integrate into the CNS circuitry.

On the other hand, the response of the CNS after injury is not limited to the production of neurons. Induced pluripotent cells may also differentiate into glia. Radial glia function as progenitors and provide a cellular source for neurogenesis during development and may also behave as neural progenitors in the adult CNS by proliferating and generating astrocytes and neurons. Stroke induced by MCAO in adult rodents triggers increased neurogenesis in the SGZ and SVZ (Abrahams et al. 2004; Jin et al. 2006; Katakowski et al. 2007; Liu et al. 2007). The SVZ neuroblasts migrate into the damaged striatal areas and adopt the phenotypes of the projection neurons. Previously published studies show that stroke increases the production of neuroblasts in the SVZ, which express doublecortin and polysialylated neural cell adhesion molecule (Arvidsson et al. 2002; Parent et al. 2002); however, few cells survive to become functional neurons, and this percentage is low compared with the substantial increase in proliferating and migrating neuroblasts (Arvidsson et al. 2002; Parent et al. 2002). It has been also shown that after MCAO, the population of BrdU-positive cells increases in the SVZ, reaching the maximum around a week after ischemia (Arvidsson et al. 2002; Parent et al. 2002). Next, the population of doublecortin-expressing neuroblasts migrates outside the SVZ, as observed during their normal migration along the rostral migratory stream. Stroke-activated neuroblasts may also migrate into the injured striatum (Arvidsson et al. 2002; Parent et al. 2002). These cells become striatal projection neurons and express calbindin, markers of striatal medium spiny neurons (Arvidsson et al. 2002; Parent et al. 2002). Several studies show that cortical lesions produced by MCAO, significantly increase SVZ cell proliferation (Ohab et al. 2006; Gotts and Chesselet 2005). After MCAO cell proliferation also increases in the SGZ, even though this area is not directly affected by the stroke, resulting in the production of new neurons in granular zone of the dentate gyrus (Jin et al. 2001). Together, these studies indicate that mitotically active cells, and not mature cells proliferating in response to injury, comprise the majority of proliferating populations after brain ischemia (Jin et al. 2001).

## 2.2 Traumatic brain injury and neural plasticity

Traumatic brain injury (TBI) is the most common brain injury in humans (Graham et al. 2000). After such injuries, the brain shows a remarkable ability for functional recovery (Nakabayashi et al. 2007). While, mechanisms responsible for this recovery are mostly unknown, the vast majority of neuroscientists hypothesize that synaptic plasticity is responsible for adaptive changes in the CNS following the injury (Zhang et al. 2011; Falo et

al. 2008; Scheff et al. 2005). In the last decades, there has been increasing interest in the ability to provide a continuous renewal of neurons in the adult CNS. This increased interest popularized the alternative mechanism for a recovery following TBI: the injury-induced neurogenesis. In CNS injury in general and TBI in particular, there is little data to suggest how damage to the nervous system may induce the proliferating population to differentiate into functional neurons. The neural environment changes associated with CNS injury are initially related to excitotoxicity associated with glutamate release (Hinzman et al. 2010; Gong et al. 1999; Globus et al. 1995). This is followed by an intense inflammatory response due to activated microglia, macrophages and trophic factors (Khuman et al. 2011; Hellewell et al. 2010). Secondary neuronal damage involves delayed cell death by apoptosis (Kim et al. 2010; Dressler and Vemuganti 2009), and then astrocytes form a scar that acts as a barrier to axonal regrowth.

While processes of synaptic plasticity have been well documented over the last decades, very few experiments have directly addressed the role of newly generated cells in the post-TBI remodeling of the CNS. To test this hypothesis, several groups studied the effects of experimental TBI on hippocampal neurogenesis (Emery et al. 2005; Lu et al. 2011; Kernie and Parent 2010). They detected significant increase in the number of dividing cells in dentate gyrus. Moreover, a significant increase in the number of new cells expressing neuronal markers after appropriate maturation periods has been reported (Sun et al. 2007; Sun et al. 2005). This fact suggests that injury-induced DNA replication and cell proliferation in the adult CNS is primarily neurogenic.

### **2.3 Neural proliferation after spinal cord and brainstem injury**

Spinal cord injury research has greatly expanded in recent years. However, understanding of the mechanisms triggering the functional recovery following the neuronal damage is still incomplete. After spinal cord injury (SCI), tissue damage occurs at the impact site and spreads over time (Tederko et al. 2009). This lesion is accompanied by apoptosis of oligodendrocytes and loss of myelin around surviving axons (Wu and Ren 2009). Axonal demyelination typically peaks during the few days after injury (Wu and Ren 2009; Salehi et al. 2009). Remyelination by oligodendrocytes and Schwann cells usually begins by a few weeks after damage to the spinal cord (Sasaki et al. 2007; Dasari et al. 2007). Several studies, however, suggest that mature oligodendrocytes do not proliferate in response to trauma (Keirstead and Blakemore 1997; Amat et al. 1998; Redwine and Armstrong 1998). However, more recent studies show that neurogenesis can be induced in the spinal cord following specific types of injury. A substantial gliosis was previously reported in the lesion area, which resulted in the formation of a glial scar (Fitch and Silver 2008). However, generation of new and functional neurons was not observed after hemisection or lesion of dorsal column (Vessal et al. 2007; Yang et al. 2006). They revealed significant gliogenesis and reported that new born oligodendrocytes remyelinated host axons in the injury site. Therefore, new born glia may contribute to the neural repair following the damage to the spinal cord.

Studies of neural proliferation in the adult brainstem revealed that production of new neurons occurs in vivo within the dorsal vagal complex (DVC) in adult rats (Bauer et al. 2005). They detected within the DVC newly generated BrdU-positive cells which simultaneously expressed markers of immature and mature neurons (DCX, HuC/D, TUC-4, NeuN). It has been also reported that vagotomy (DVC deafferentation) triggered a large

increase of BrdU incorporation in the ipsilateral DVC, associated with proliferation of microglia and genesis of neurons and astrocytes (Bauer et al. 2005). Injury-induced plasticity, neural proliferation and neuronal replacement were recently revealed after damage to pre-Bötzinger Complex, a cluster of interneurons in the ventrolateral medulla of the brainstem (Neumueller et al. 2011). Neuronal counts and evaluation of neuronal density revealed up to 65% more neurons within the ventral and lateral medulla compared to control animals. Concluding studies dealing with neural proliferation in the brainstem we can hypothesize that injury activates plasticity and reorganization of brainstem circuits, late differentiation and even neurogenesis. However, more rigorous studies are necessary to definitely prove injury-induced neurogenesis in the adult brainstem.

### 3. Neural proliferation in the adult PNS: challenging the dogma

Whereas in the CNS the occurrence of DNA replication and neural proliferation in adult mammals has been broadly accepted from the end of the twentieth century (Johansson et al. 1999), in the PNS it was already documented, or at least hypothesized much earlier. The occurrence of adult neurogenesis in the PNS was suggested by Hatai several decades earlier (Hatai 1902). He reported an increase in sensory neuron counts in DRGs from one-month to five-month-old rats. Later, Miura provided the first evidence of an increase in neuron numbers in the autonomic nervous system, namely in Auerbach's plexus of the rat small intestine (Miura 1913). A confirmation of the possibility that neurogenesis occurs in the autonomic nervous system was later provided by Benninghoff, who showed that partial stenosis of rat small intestine induced, in the upstream intestinal loops, an increase in Auerbach's plexus ganglion neuron numbers (Benninghoff 1951). Moreover, Filogamo and coworkers demonstrated that in the same experimental model, neurogenesis led to a fourfold increase in the number of Auerbach's plexus ganglion neurons of the loops upstream from the intestinal obstruction (Filogamo and Vigliani 1954). Yet, the occurrence of adult neurogenesis was revealed in other sites of the autonomic nervous system including DRGs in the rat (Devor and Govrin-Lippmann 1985; Devor 1991; Popken and Farel 1997). Studies of neural proliferation in the adult PNS were previously reviewed by Geuna (Geuna et al. 2002).

It should be pointed out that the above-mentioned studies, that were based on neuron counts led authors to the conclusion that, since there was no evidence of mitosis by nerve cells detectable by colchicine blocking, the observed increase in neuron number should be attributed to the persistence of poorly differentiated or undifferentiated cells capable of turning into neurons during adulthood and/or under the influence of exceptional stimuli. The introduction of the techniques for investigating DNA replication, especially 3H-thymidine (and afterwards BrdU) administration, cytophotometry/cytofluorimetry and S-phase markers (e.g. PCNA and Ki67), opened new horizons for interpreting the adult neuron addition. In a series of studies, Giacobini-Robecchi and coworkers showed the presence of DNA replication (by autoradiography after 3H-thymidine administration and PCNA immuno-staining) in myenteric neurons from the small intestine loops upstream from a partial stenosis (Corvetti et al. 2001; Poncino et al. 1990; Giacobini Robecchi et al. 1988). However, cytophotometry after Feulgen staining showed that myenteric neuron DNA replication might not be due to a tetraploid DNA content related to cell division, but instead to unscheduled DNA synthesis that leads to a hyper diploid DNA content (Poncino et al. 1990; Giacobini Robecchi et al. 1988). Electrophoretic analysis of total genomic DNA has also



suggested that unscheduled DNA synthesis can be due to DNA amplification (Giacobini Robecchi et al. 1995).

The evidence of DNA replication in the adult sensory ganglia has been also provided in Ciaroni's and Czaja's laboratories (Cecchini et al. 1995; Ciaroni et al. 2000; Czaja et al. 2008; Gallaher et al. 2011; Ryu et al. 2010). However, it should be noted that the occurrence of adult neurogenesis in the PNS has been questioned by several experimental studies that failed to confirm the numerical increase of adult neurons in both the myenteric plexus (Gabella 1984) and DRGs (La Forte et al. 1991; Pover et al. 1994; Bergman and Ulfhake 1998). In this view, cell counting has raised a lively debate over the last years in the neuroscience field, and it appears that in many cases the discrepancy in the results might be due to bias in the counting methods used (Popken and Farel 1997; Geuna 2005). Studies based on unbiased stereological neuronal counts have confirmed again the occurrence of neuron number increases in adult sensory ganglia (Lagares et al. 2007), thus raising a question about the origin of the new neurons. Two possibilities have been tentatively proposed to explain the increase in the number of neurons during adulthood: 1) *de novo* neurogenesis (i.e., based on DNA replication and cell division); 2) neuron addition (i.e., late differentiation of poorly differentiated neuronal precursors without cell division) (Farel 2001; Farel 2002; Geuna et al. 2000). Although the detection of DNA replication (Ciaroni et al. 2000; Farel 2001; Farel 2002; Geuna et al. 2000; Giacobini Robecchi et al. 1988) is considered a predictor of cell division and thus *de novo* neurogenesis, it might also be due to selective amplification of a few DNA sequences (Corvetti et al. 2001; Giacobini Robecchi et al. 1995). On the other hand, the possibility that the neuron number increase is due to the late differentiation of slightly immature neurons is partially ruled out by the difficulty in identifying (even with careful electron microscope investigation) the immature neurons in adult DRGs (Geuna, unpublished). Therefore, a third tentative explanation, which falls between the other two options, is being sought, namely the possibility that a neuronal precursor niche from neural crest origin persists all along adulthood in the PNS (Gallaher et al. 2011; Lagares et al. 2007). Although, sensory ganglia have been reported to contain precursor cells (Arora et al. 2007; Lagares et al. 2007; Li et al. 2007) that can proliferate *in vitro* and can be induced to differentiate into neurons (Liu et al. 2009; Namaka et al. 2001), the possibility of *in vivo* adult neurogenesis in the adult PNS is almost completely unexplored. Moreover, the few published studies have resulted in contradictory conclusions. For example, age-related increases in the number of dorsal root ganglia (DRG) neurons have been reported in rat by two groups (Popken and Farel 1997; Ciaroni et al. 2000), while other investigators have provided data suggesting that adult neurogenesis does not occur in the adult DRG (Pover et al. 1994; Mohammed and Santer 2001). Thus, there is as yet no consensus regarding the neurogenic potential of the adult PNS sensory ganglia.

### 3.1 Injury-induced neurogenesis in sensory ganglia

A strong evidence for the potential of PNS cells to produce new neurons arises from Czaja's laboratory. They have examined the sequels to toxin-induced neuronal destruction. Thus, evidence of neuronal replacement following lesions, which has been reported by several investigators in CNS models, (Hou et al. 2008; Lie et al. 2004; Parent 2003), is limited to our recent reports for the PNS (Czaja et al. 2008; Gallaher et al. 2011). Our key observation is that neuronal losses following capsaicin-induced neuronal destruction are not permanent. In fact, following a precipitous post-capsaicin decline, the numbers of neuronal nuclei in nodose ganglion (NG) from capsaicin-treated rats equaled or exceeded the numbers found

in control rats by 60 days after capsaicin treatment. Furthermore, we observed that restoration of neuronal numbers after capsaicin was accompanied by BrdU incorporation, which ultimately labeled mature neurons (Czaja et al. 2008). Our observation of apparent neuronal number restoration in NG led us to hypothesize that damage to the primary sensory neurons induces proliferation of endogenous progenitors and/or lineage reprogramming and generation of induced multipotent stem cells (iMSCs), which differentiate into new neurons. The satellite cell population housed in DRG or NG may, under adequate conditions, represent a source of multipotent cells for the new neurons (Li et al. 2007; Singh et al. 2009; Gallaher et al. 2011). Moreover, morphological observations have recently provided further support to this hypothesis and revealed that NG cultures from capsaicin-treated rats contained bipolar neurons, normally found only during development (Gallaher et al. 2011). Furthermore, we observed that restoration of neuronal numbers after capsaicin was accompanied by BrdU incorporation that ultimately labeled mature neurons (Czaja et al. 2008; Gallaher et al. 2011). Our observation of apparent restoration of neuronal numbers in NG led us to hypothesize that damage to the primary sensory neurons induces proliferation of endogenous progenitors and/or lineage reprogramming and generation of induced multipotent stem cells (iMSCs) which differentiate into new neurons. The existence of ganglionic MSCs would suggest that PNS could serve as a source of committed autologous cells that are capable of being stimulated to produce neurons *in vivo*, thus avoiding an immune rejection. The discovery of neural progenitors and mechanisms involved in the induced neurogenesis in the adult PNS could enable autologous grafting of new neurons into damaged areas of the CNS to replace neurons lost due to injury or disease.

#### **4. Mechanisms involved in post-injury DNA replication and cell proliferation**

In the brain, new neurons are formed from neural stem cells (NSCs), which are multipotent and self renewing. Neural stem cells can undergo symmetric or non-neurogenic divisions that produce two neuro-epithelial stem cells and cause horizontal expansion of the proliferative population (Gotz and Huttner 2005). Alternatively, they engage in asymmetric divisions that are associated with the generation of neuronal progenitors (Falk et al. 2008). The DNA synthesis and proliferation of NSCs are critical processes which regulate the size and neurogenic potential of the nervous system. Multiple signaling pathways have been implicated in the regulation of neural stem and progenitor-cell proliferation (Riccio 2010; Suh et al. 2009). Signalling pathways controlling NSCs niche and signaling after brain injury, outside NSCs niche share a significant overlap converging on two canonical pathways, mammalian target of rapamycin (mTOR) and mitogen-activated protein kinase (MAPK) (Robel et al. 2011).

One of the key pathways regulating cell proliferation in the nervous system is WNT (wingless-type MMTV integration site family)/  $\beta$ -catenin signaling (Wexler et al. 2009). WNT signaling regulates neural plasticity during development and in the adult nervous system. During development,  $\beta$ -catenin signaling regulates proliferation of neuronal stem cells, leading to the correct number of neurons in the developing embryo. WNT also regulates proliferation and preserves pluripotent and multipotent state of NSC and neural progenitors in the adult brain by keeping them in a dividing stage that prevents differentiation (White et al. 2010). WNT signaling operates through autocrine signaling loop among NSCs. NSCs express WNTs ligands and WNT receptor (Wexler et al. 2009). WNTs are glycoprotein morphogens that interact with G-protein-coupled receptors and initiate

different signaling pathways, including the canonical pathway involving  $\beta$ -catenin. Binding of WNT to the receptor triggers the  $\beta$ -catenin-LEF/TCF signal transduction and activation of a WNT responsive target gene, such as cycline D1, which promotes cellular proliferation. Over-expression of WNTs or persistent activation of the downstream signaling component b-catenin in the CNS promotes cell-cycle progression and negatively regulates cell-cycle exit, resulting in horizontal expansion of precursor populations (Chenn and Walsh 2002).

#### 4.1 Immune system and regulation of neurogenesis

Brain injury induces an excess of factors that modulate plasticity of various cells and induce neurogenic potential within damaged tissue. Several lines of evidence indicate that various components of the immune system may positively regulate neurogenic processes (Yirmiya and Goshen 2011; Ziv and Schwartz 2008). Brain damage activates microglia, which rapidly migrate to the injury site and initiate recruitment and activation of macrophages and lymphocytes. These cells release a number of anti- and pro-inflammatory factors creating a positive feedback loop that results in neural damage and causes both detrimental and positive consequences to neurogenesis. It has been demonstrated that upon severe injuries such as hypoxia or stroke, a portion of microglia proliferate. Furthermore, microglia also reveal in vitro stem cell potential with self-renewal and multipotency (Robel et al. 2011).

Several in vitro and in vivo studies have demonstrated that lymphocytes, specifically T cells may promote neurogenesis. T-cells derived cytokines IL-4 or INF- $\gamma$  activate microglia cells (Ziv and Schwartz 2008). Interestingly, WNT- and  $\beta$ -catenin signal increases in adult proliferating astrocytes and in NG2 glia after traumatic brain injury, suggesting that WNT signaling plays a role in the control of gliogenesis following cortical injury (White et al. 2010). Growth factors including FGF2, EGF and VEGF are released by various cell types after brain injury and activate mTOR or mitogen-activated protein kinase (MAP) pathways. These growth factors also activate ERK and Jun N-terminal kinase (JNK)-dependent MAPK pathways in astrocytes after injury. These signaling pathways act synergistically to phosphorylate the immediate early gene products c-FOS and c-JUN which increase proliferation of astrocytes. Phosphorylation of ERK is specifically detected in reactive astrocytes after injury (Robel et al. 2011).

The activated microglia seemed to exert the neurogenic effect via expression of the anti-inflammatory/neuroprotective cytokine transforming growth factor-beta (TGF- $\beta$ 1), which has a (concentration-dependent) neurogenic effect by acting on the proliferation of neural progenitors (Battista et al. 2006; Ziv and Schwartz 2008). TGF- $\beta$ 1 decreases the expansion of neural stem and precursor cells in a dose-dependent manner (Aigner and Bogdahn 2008). While WNT positively controls expansion of neural stem and progenitor pools, transforming growth factor  $\beta$  (TGF- $\beta$ ) upregulates cell cycle inhibitors and counteracts cell cycle progression. Therefore TGF- $\beta$  signaling controls the size of specific brain areas by antagonizing canonical WNT signaling and negatively regulating self-renewal of neuroepithelial stem cells. TGF- $\beta$  has been associated with neuronal differentiation and survival in CNS under physiological conditions (Falk et al. 2008). Post-injury cell renewal, such as precursor cell proliferation in CNS, is positively regulated by microglia-derived TGF- $\beta$  (Ziv and Schwartz 2008). Three isoforms of TGF- $\beta$  (TGF- $\beta$  1, 2, 3) are expressed in neurons and in glia cells. TGF- $\beta$ 1 isoform is predominantly upregulated and activated after CNS lesions or, in cases of neurodegeneration, TGF- $\beta$  signals through activation of TGF- $\beta$  receptor type I and II (Tgfr1 and Tgfr2) and phosphorylation of the signaling mediators Smad2 and Smad3 (Aigner and Bogdahn 2008). TGF- $\beta$  not only activates the Smad signaling

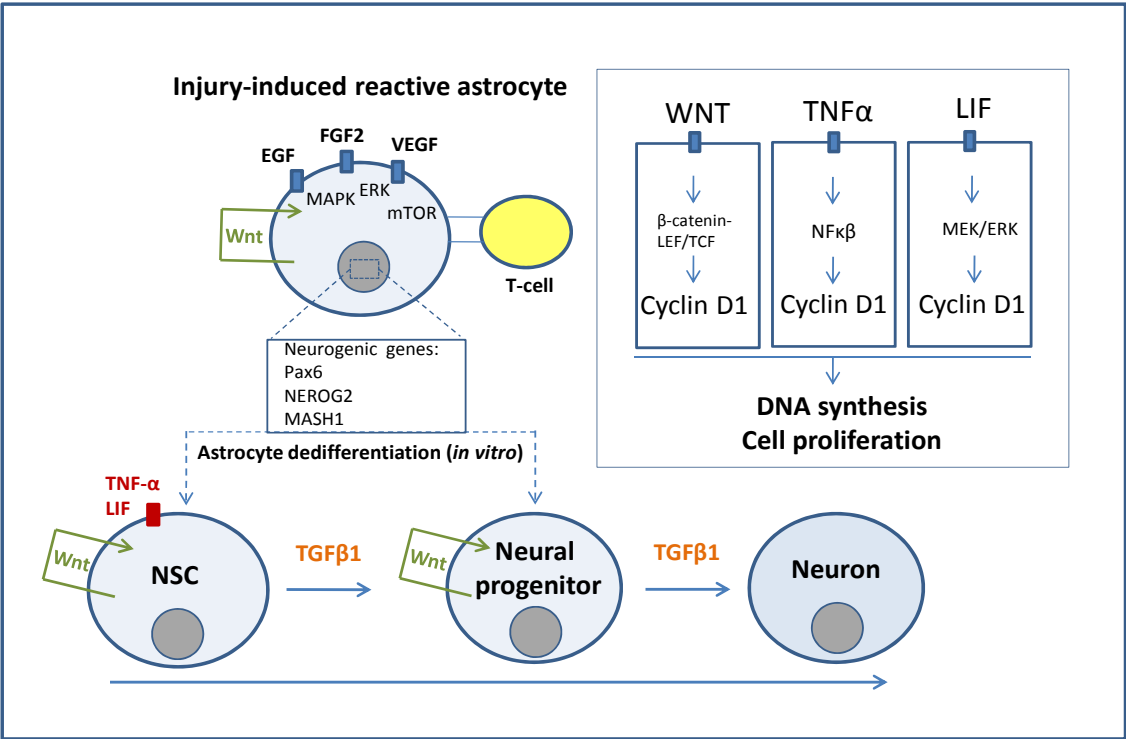


Fig. 1. Mechanism involved in post-injury cell proliferation in CNS

Injury to the brain triggers complex responses between populations of immune cells (yellow circle), microglia, neural stem cells (NSC), neural progenitors and differentiated neurons (all shown as blue circle). The NSC and neural progenitors represent the main precursors of neurons. Two antagonistic signalling pathways WNT and TGF- $\beta$  regulate proliferation and differentiation in adult neurogenesis. While WNT positively control expansion of neural stem and progenitor pools, TGF- $\beta$  counteracts cell cycle progression and is associated with neuronal differentiation and survival in CNS. Injury-activated microglia emerges as a new potential source of NSC and neural progenitors. T-cells may promote neurogenesis by interacting with microglia. T-cells derived cytokines (IL-4 or INF- $\gamma$ ) activate microglia cells. The activated microglia seemed to exert the neurogenic effect via expression of the anti-inflammatory/neuroprotective cytokine TGF- $\beta$ 1. Growth factors including FGF2, EGF and VEGF are released by various cell types after injury, bind to receptors (blue bars) expressed at the surface of activated microglia cells and initiate intracellular signal transduction and activate mTOR, ERK and MAPK pathways in astrocytes. These signalling pathways act synergistically to increase proliferation of astrocytes and they are also involved in up regulation of the neurogenic genes (Pax6, NEROG2, MASH1). WNT- and  $\beta$ -catenin signalling also increases in adult proliferating astrocytes after traumatic brain injury. Glia cells were successfully reprogrammed to NSC or neural progenitors *in vitro* by induced over expression of neurogenic genes. Adult, injury-induced cellular proliferation during neurogenesis is regulated by cytokines (TNF- $\alpha$ , LIF) and morphogens WNTs. Signalling from these molecules has a common target, cycline-D1 which triggers cell cycle entry and DNA synthesis.



pathway, but it may diverge into and modulate other known classical signaling cascades such as RAS/ERK/MAPK. Activation of RAS/ERK/MAPK signaling by TGF- $\beta$  can induce an autocrine amplification loop of TGF- $\beta$ 1 expression. It has been reported that adult rat dorsal root ganglion (DRG) neurons after injury are able to synthesize TGF  $\beta$ -1 isoform, which is able to elicit Schwann cell proliferation and modulates regeneration processes in the PNS (Rogister et al. 1993).

Immune responses modulate the NSCs. Proliferation of NSCs is regulated by cytokines and immuno-modulating polypeptides (Gonzalez-Perez 2010). TNF- $\alpha$  is one of the crucial inflammation mediators. In the CNS, TNF- $\alpha$  binds to TNF receptors expressed by glia cells and neurons. Pro-inflammatory cytokine TNF- $\alpha$  has been associated with the pro-neurogenic role by increasing proliferation of NSCs through activation of NF $\kappa$ B and TGF- $\beta$  activated kinase-1 (TAK-1) signaling cascade. NF $\kappa$ B transcriptionally regulates cyclin-D1 in NSCs (Fig.1). The cyclin-D1/CDK4-complex is necessary for NSC cell cycle progression by promoting passage through G1/S restriction point (Widera et al. 2006). Injury to the peripheral nervous system results in the upregulation of TNF- $\alpha$ . TNF- $\alpha$  is released from neurons, Schwann cells and proliferating satellite cells in DRG. The role of the TNF- $\alpha$  in the injury of peripheral nervous system is not well understood; however it may be an important inducer of the proliferative potential of cells.

Leukemia inhibitory factor (LIF) is another cytokine that displays pro-neurogenic effects in the injured adult brain. LIF has been demonstrated as a key signal for injury-induced neurogenesis in adult mouse olfactory epithelium (Bauer and Patterson 2006). LIF appears to promote NSC self-renewal and expansion. LIF stimulates the initiation of DNA synthesis and cell division through a common signaling mechanism that involves MEK/ERK activation as well as STAT1 cytoplasmic nuclear translocation. LIF acts on NSC and maintains them in a loop of symmetric/self-renewing divisions in vivo (Bauer and Patterson 2006). LIF stimulates DNA synthesis through MEK/ERK; this is a direct mechanistic molecular link between tissue damage inflammation and tissue renewal. The ERK cascade is activated by hormones, cytokines, and growth factors that result in either proliferation or growth arrest, depending on the duration and intensity of the ERK activation. This pathway, consisting of Raf, MEK1/2, and ERK1/2, regulates cell proliferation via its impact on cell cycle control. Activation of this mitogen-activated protein kinase pathway promotes the expression of cyclin-D1. These key events result in the activation of the cyclin-dependent protein kinase CDK4/6, which promote cell cycle entry by phosphorylation of the retinoblastoma tumor suppressor (Rb), leading to the release of the transcription factor E2F. This in turn promotes the transcription of cyclins A and E, resulting in the activation of CDK2. Activated CDK2 phosphorylates Rb at additional sites and, thus, enables DNA synthesis and centrosome duplication via further liberation of E2F. Furthermore, sustained expression of p21cip1 has been shown to be responsible for the ERK-mediated proliferation inhibition (Ussar and Voss 2004).

#### **4.2 Mechanisms involved in the neurogenic potential of glia**

Brain studies provide increasing evidence that adult glia could be a source of new neurons (Robel et al. 2011). Glia in the adult brain may act as neural progenitors and neural stem cells. Following lesion-induced reactivation, astrocytes dedifferentiate to astrocyte-like stem cells. Several studies suggest that the WNT/ $\beta$ -catenin pathway may be involved in the dedifferentiation process following injury. Interestingly, injury-induced WNT/ $\beta$ -catenin



signaling has already been shown to be required for the dedifferentiation of other cells such as epithelial cells to form hair follicles and Mueller glia to form retinal cells (Osakada et al. 2007). Remarkably, WNT signaling has been associated with peripheral nerve injury. Peripheral nerve lesions induce upregulation of the WNT signaling mediator Ryk on DRG neurons, which may potentially indicate a role of WNT in neuroregeneration and/or neurogenesis (Li et al. 2008).

Pax6 neurogenic transcription factor plays a crucial role in neurogenesis, both during development and in adulthood. It is expressed by NSC. Astrocytes forced to express Pax6 acquired neuronal morphology. PAX6 and other neurogenic factors such as NEUROG2, MASH1 signaling can cause a true glia-to-neuron conversion in vitro. NEUROG2 is epigenetically silenced in postnatal astrocytes. Upregulation of neurogenic genes could be induced following injury in proliferating reactive astrocytes, which would acquire potential to dedifferentiate and be reprogrammed to neurons (Robel et al. 2011). Given that the retroviral vectors used in these studies incorporate only in proliferating cells and that neurons are post mitotic, it seems that the origin of these new neurons is the glia whose proliferation is enhanced after injury. Interestingly, some signals promoting astrocytes dedifferentiation may derive from injured astrocytes themselves, as suggested by scratch wound-injured rat spinal cord astrocytes (Robel et al. 2011).

Sox2 is a member of the SRY-related group of transcription factors that plays a significant role during neural cell development. Sox2 maintains the pluripotency and developmental potential of neural stem cells (Li et al. 1998). It has been shown that expression of Sox2 and the transcription factors Oct4, c-Myc and Klf4 is sufficient to reprogram adult fibroblasts to generate pluripotent stem cells (Chang et al. 2010; Park et al. 2008). The constitutive expression of Sox2 has been shown to inhibit neuronal differentiation, while suppression of Sox2 leads to cell cycle exit and neuronal differentiation (Graham et al. 2003). Sox2 expression is also upregulated following injury to the peripheral nerves. It has been shown that Sox2 expression was elevated in glia cells in Krox20 knockout mice (Le et al. 2005). These results indicate that Sox2 is suppressed, either directly or indirectly, by Krox20. Krox20 and Sox2, like Krox20 and c-Jun, inhibit each other. It has been suggested that c-Jun controls Sox2 levels and that some of the inhibitory effects of c-Jun are channeled by Sox2 (Parkinson et al. 2008). Other studies indicate that Sox2 acts downstream of Notch (Woodhoo et al. 2009). Sox2 expression is essential to specify glia cell fate from neural crest cells.

#### **4.3 The molecular events involved in damage-induced DNA replication and cellular proliferation in PNS**

The neurogenic potential of PNS has been recently reported (Gallagher et al. 2011). Formation of new neurons in the adult NG was followed by capsaicin-induced neuronal damage and cell death via apoptosis. Cell proliferation was detected by BrdU incorporation during DNA synthesis, which is a standard marker of dividing cells. The molecular events involved in damage-induced DNA replication and cellular proliferation in PNS are not well understood. However, by analogy to damage-induced neurogenesis in CNS, components of the immune system may play important regulatory roles. This will be under stress and tissue damage condition where components of immune system such as pro-inflammatory cytokines may play a role of molecular triggers affecting cell cycle of differentiated neurons.

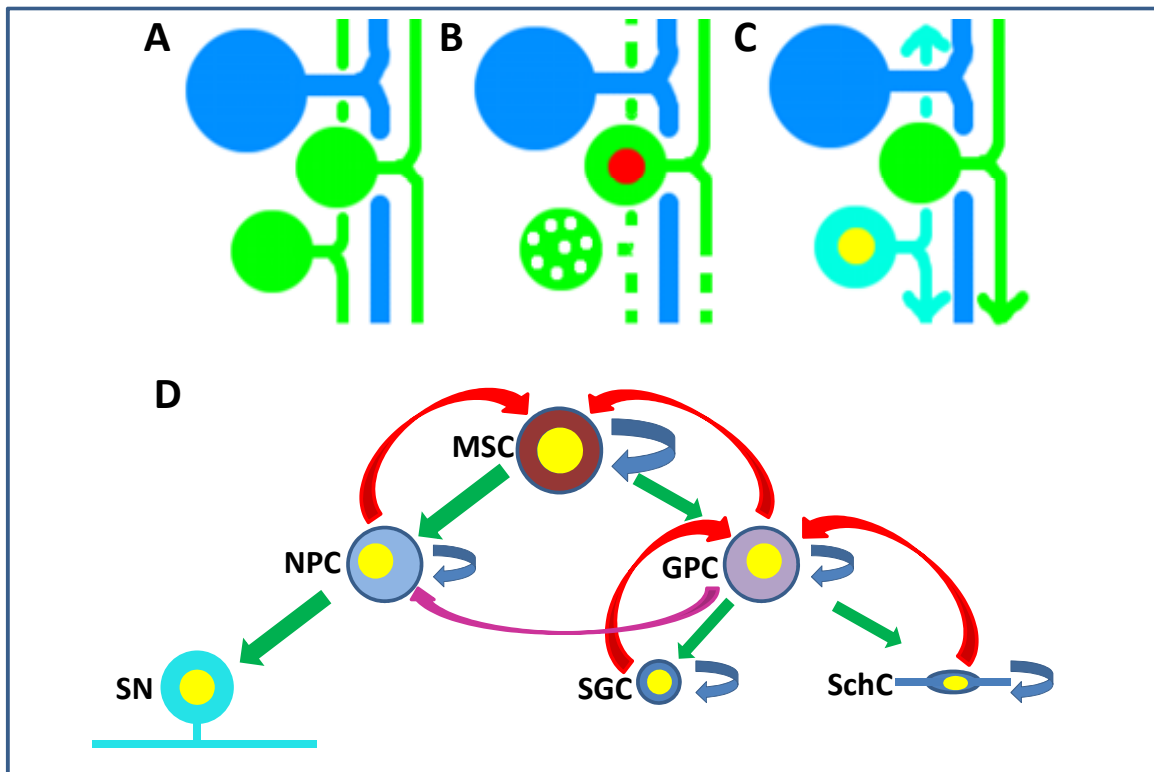


Fig. 2. Post-injury degeneration and regeneration in sensory ganglia

The adult sensory ganglia comprises TRPV-1 expressing (A: green) and non-TRPV-1 expressing neurons (A: blue). Following injury, many neurons will completely degenerate (B: cell body with fragmented nucleus) while others only lose peripheral projections (B: red nucleus). Injury to the NG and loss of neurons will result in the active response from neurons, glia and immune system through upregulation of various cytokines, growth factors and morphogens. These factors may induce DNA synthesis revealed by BrdU incorporation (C, D: yellow) and cell proliferation (D: blue arrows). This cascade of events may change the ganglionic environment and induce dedifferentiation (D: red arrows) of satellite glia cells (SGC), Schwann cells (SchC), glia progenitors (GPC) and neuronal progenitors (NPC) to less-differentiated stage within their own lineage. Dedifferentiated cells may next differentiate (D: green arrows) or transdifferentiate (D: purple arrow) to switch the cell lineage. The mechanisms of differentiation, dedifferentiation and transdifferentiation may be responsible for injury-induced neuronal replacement and generation of sensory neurons (SN) in the ganglia.

It has been well known that adult sensory ganglia are composed of terminally differentiated neurons and glia cells. However, recent studies show that the pool of immature glial precursor cells could be present in the adult sensory ganglia (Gallaher et al. 2011; Lagares et al. 2007). Injury to sensory ganglia triggers an inflammatory response and bursts of pro-inflammatory cytokines, growth factors, and morphogens, which are known to exert their effects through common signaling pathways and modulate neuronal plasticity. Specifically,  $\text{TNF-}\alpha$ ,  $\text{TGF-}\beta$ , and WNT have been activated after a peripheral nerve lesion (Li et al. 2008;

Saade et al. 2002). The MAP Kinases pathway (MAPK/ERK/p38) also has been reported to activate in peripheral nerve injury (Agthong et al. 2006). In the sensory ganglia injury initially damages peripheral axons and depending on the damaging factor, some neurons will die and some will survive and regenerate (Fig. 2A-C). Moreover, the cascade of degenerative events may induce molecular signaling triggering proliferation, differentiation and dedifferentiation of ganglion cells, which provide a source of neural progenitors or induced multipotent cells for new neurons (Fig. 2D).

The identity and function of differentiated, post-mitotic cell is no longer a permanent feature. Studies of the last decade suggest that cell identity is determined by transcriptional and/or epigenetic actions and, more importantly, that it is subject to reprogramming by resetting intrinsic programs (Vogel 2010). The ability of a cell to dedifferentiate to a pluripotent state is critically dependent on the ability of that cell to re-enter cell cycle and replicate its genome. The molecular forces triggering change in cellular identity are not well understood. Injury may trigger programs of regeneration, which may involve changes in cell plasticity and identity. This principle may underline the injury-induced plasticity, lineage reprogramming and neurogenesis in the adult PNS. Therefore, studies of injury-induced neurogenesis in the context of neural plasticity will provide new insights into the complexity of DNA replication and cellular identity at the tissue level.

## 5. Conclusion

The review of the current literature dealing with DNA synthesis, neural proliferation and neurogenesis in the adult nervous system challenges Cajal's dogma that "In the adult centers, the nerve paths are something fixed, ended and immutable. Everything may die, nothing may be regenerated." Moreover, more and more studies show that brain is not the only place in the adult nervous system where new neurons could be generated. The mammalian CNS and PNS appear to have a greater regenerative ability than was previously believed. The factors that regulate proliferation and differentiation in the uninjured adult brain may contribute to increased DNA synthesis and proliferation after injury. In the adult nervous system, development is complete or near complete and new cells are not in high demand. After injury, however, the need and ability for production of new cells in the adult brain radically increases. This demand may recapitulate developmental mechanisms in the injured adult nervous system. Thus, factors that influence NSCs during development may be more likely to contribute to injury-induced neurogenesis than factors regulating NSCs in the uninjured adult brain. Recent advances in regenerative research show that injury may induce cascade of events forcing the pool of endogenous multipotent cells to enter the cell cycle and differentiate toward glia or neurons. What is even more exciting, recent studies strongly support the hypothesis that terminally differentiated cells can be stimulated to go back to less-differentiated stage within their own lineage (dedifferentiation) in response to injury. Dedifferentiation may even go a step further and regress to a point where neural cells may switch lineage (transdifferentiation). However, further studies are necessary to determine the specific intrinsic and micro environmental cues that drive the injured nervous system for adult neurogenesis. Harnessing the mechanisms involved in the induced neurogenesis in the adult nervous system could enable neural replacement therapy as a new approach in the regenerative medicine.

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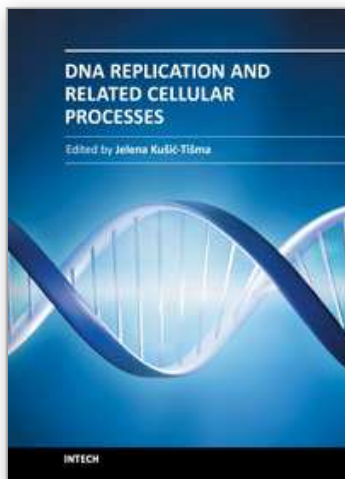
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