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Endogenous neurogenic cell response in the mature mammalian brain following traumatic injury

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ABSTRACT

In the mature mammalian brain, new neurons are generated throughout life in the neurogenic regions of the subventricular zone (SVZ) and the dentate gyrus (DG) of the hippocampus. Over the past two decades, extensive studies have examined the extent of adult neurogenesis in the SVZ and DG, the role of the adult generated new neurons in normal brain function and the underlying mechanisms regulating the process of adult neurogenesis. The extent and the function of adult neurogenesis under neuropathological conditions have also been explored in varying types of disease models in animals. Increasing evidence has indicated that these endogenous neural stem/progenitor cells may play regenerative and reparative roles in response to CNS injuries or diseases. This review will discuss the potential functions of adult neurogenesis in the injured brain and will describe the recent development of strategies aimed at harnessing this neurogenic capacity in order to repopulate and repair the injured brain following trauma.

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Introduction

Traumatic brain injury (TBI) is the leading cause of death and disability worldwide, with no cure available for the enduring deficits induced by TBI. It has long been thought that the mature brain cannot be repaired following injury. Recent findings have revealed that multipotent neural stem/progenitor cells (NS/NPCs) persist in selected regions of the brain throughout the lifespan of an animal, rendering the mature brain capable of generating new neurons and glia (Lois and Alvarez-Buylla, 1993; Gage et al., 1998). Over the past 25 years, extensive studies have demonstrated that the adult generated neurons in the dentate gyrus (DG) of the hippocampus in the mature brain play important roles in hippocampal dependent learning and memory functions (Deng et al., 2009; Clelland et al., 2009; Aimone et al., 2014), whereas the subventricular zone (SVZ) derived new olfactory interneurons are required for the normal functioning of the olfactory bulb network and some selected olfactory behaviors (Moreno et al., 2009; Breton-Provencher et al., 2009; Sakamoto et al., 2014b). Following TBI, increasing evidence has suggested that these endogenous NS/NPCs may play regenerative and reparative roles in response to CNS injury as an enhanced neurogenic response has been identified in varying types of brain injury models in varying types of brain injuries in animal studies and also in human studies. Furthermore, TBI-induced hippocampal neurogenesis has been linked to the innate cognitive functional recovery following TBI. These studies indicate that the mature brain has

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the inherent potential to restore populations of damaged or destroyed neurons. This raises the possibility of developing therapeutic strategies aimed at harnessing this endogenous neurogenic capacity in order to regenerate and repair the injured brain.

Adult neurogenesis in the normal mammalian brain

In the mature mammalian brain, the endogenous neurogenic regions are primarily confined to the SVZ surrounding the lateral ventricle and the DG of the hippocampus (Altman and Das, 1965; Lois and Alvarez-Buylla, 1993). Neural stem/progenitor cells (NS/NPCs) reside in the SVZ give rise to neuronal and oligodendroglial progenies (Ortega et al., 2013). The majority of new neurons derived from the SVZ migrate along the rostral migratory stream and are destined to the olfactory bulb becoming olfactory interneurons (Gritti et al., 2002). A small number of SVZ-derived new neurons migrate into cortical regions for reasons yet to be identified, but probably related to repair or cell renewal mechanisms (Parent et al., 2002). Likewise, the newly generated cells of the DG migrate laterally into the dentate granule cell layer and exhibit properties of fully integrated mature dentate granule neurons (Kempermann and Gage, 2000; van Praag et al., 2002). Most importantly, the newly generated DG granule neurons form synapses and extend axons into their correct target area, the CA3 region (Hastings and Gould, 1999).

Thus far, multiple studies have quantified the degree of cytogenesis occurring in these regions and have clearly shown that large numbers of new cells are constantly produced (Lois and Alvarez-Buylla, 1993; Cameron and McKay, 2001). Specifically, the rat dentate gyrus produces ~9000 new cells per day which equates to ~270,000 cells per month (Cameron and McKay, 2001). Considering that the total granule cell population in the rat is 1–2 million cells, this degree of new cell addition is certainly large enough to affect network function. A more recent study found that in the olfactory bulb almost the entire granule cell population in the deep layer and half of the super layer were replaced by newly adult generated neurons over a 12-month period (Imayoshi et al., 2008). The same study also reported that in the hippocampus, the adult generated neurons comprised about 10% of the total number of dentate granule cells and they were equally present along the anterior–posterior axis of the DG (Imayoshi et al., 2008). However, studies have also found that in normal adult rodent brains under normal housing condition, approximately half of the newly generated neurons in the DG and olfactory bound SVZ cells have a transient existence of two weeks or less (Gould et al., 2001; Mouret et al., 2008; Sultan et al., 2011b; Dayer et al., 2003). While this interval is long enough for supportive glial roles; neuron formation and integration into an existing network takes approximately 10–14 days (Alvarez-Buylla and Nottebohm, 1988; Kirn et al., 1999). It must be noted, however, that most of the surviving neurons become mature neurons and are sustained for months to years (Gould et al., 2001; Dayer et al., 2003; Sultan et al., 2011a), strongly supporting the theory of network integration. Furthermore, this dramatic loss of newly generated cells might be a recapitulation of network pruning seen in early mammalian development. Whether the limited life-span represents network pruning or merely distinct cell specific roles is yet to be understood.

Following the discovery of persistent adult neurogenesis throughout life in the mature mammalian brain, the physiological roles and the importance of this adult neurogenesis particularly hippocampal neurogenesis in relationship with learning and memory functions has been extensively studied. Studies have shown that conditions which enhance hippocampal neurogenesis such as exposure to enriched environments, physical exercise, or growth factor treatment, can improve cognitive abilities (van et al., 1999; Kempermann et al., 1997; Brown et al., 2003; Sun et al., 2009). Additionally, studies that aim to inhibit adult neurogenesis using varying types of approaches have further confirmed the causal relationship between neurogenesis and hippocampal function. For example, in studies that use either brain irradiation, systemic or focal administration of anti-mitotic agents, or genetic ablation of dividing progenitor cells to eliminate adult neurogenesis, it has been shown that adult-generated dentate granule neurons have important roles on many types of hippocampal-dependent learning and memory tasks in rodents. These include trace eyeblink and fear conditioning (Shors et al., 2001; Shors et al., 2002), formation of contextual fear memory (Saxe et al., 2006; Imayoshi et al., 2008; Hernandez-Rabaza et al., 2009), long-term retention of spatial memory in the water maze task (Snyder et al., 2005; Jessberger et al., 2009), object recognition task (Jessberger et al., 2009; Suarez-Pereira et al., 2015) and active place avoidance task (Burghardt et al., 2012). Moreover, targeted deletion of adult generated dentate granule neurons at the maturation stage induced retrograde memory deficits in contextual fear, water maze and visual discrimination memories (Arruda-Carvalho et al., 2011). Although some variable and partially contradictory results have been reported from these studies due to the methods used to knockdown neurogenesis or the nature of behavioral tasks, this growing body of data provides compelling evidence that adult hippocampal neurogenesis is directly involved in many aspects of hippocampal-dependent learning and memory functions.

Compared to hippocampal neurogenesis, the role of SVZ neurogenesis in normal brain is less defined. The majority of newly generated neurons derived from the SVZ reaches the olfactory bulb and differentiates into granule cells; approximately 5% become periglomerular cells in the olfactory bulb (Moreno et al., 2009; Lemasson et al., 2005). The newly generated olfactory inhibitory interneurons integrate into the olfactory circuity and are involved in some, but not all, olfactory functions. Studies that inhibit olfactory neurogenesis using similar approaches as hippocampal neurogenesis inhibition have found that adult generated neurons in the olfactory bulb are involved in olfactory discrimination (Gheusi et al., 2000; Moreno et al., 2009; Kageyama et al., 2012), olfactory perceptual learning functions and the acquisition of new odor-related behaviors (Moreno et al., 2009; Moreno et al., 2012), innate olfactory responses (Sakamoto et al., 2011), short-term olfactory memory function (Breton-Provencher et al., 2009), flexible olfactory associative learning and memory function (Sakamoto et al., 2014a).

The proliferation and maturational fate of cells within the SVZ and DG is modulated by a number of physical and chemical cues. For example, biochemical factors such as serotonin, glucocorticoids, ovarian steroids, and growth factors tightly regulate the proliferative response, suggesting that cell proliferation within these regions have a physiologic importance (Banasr et al., 2001; Tanapat et al., 1999; Cameron and Gould, 1994; Kuhn et al., 1997). In addition, physical stimuli such as exercise, enriched environment, or stress produce alterations in cell production suggesting a role in network adaptation (Gould et al., 1997; Kempermann et al., 1997; van et al., 1999; Kempermann et al., 2000). For example, physical exercise or environments that are cognitively and physically enriched increase cell proliferation and neurogenesis in both the SVZ and DG, while stress reduces this type of cellular response (Kempermann et al., 1997; Gould et al., 1999; Gould and Tanapat, 1999; Kempermann et al., 1998). Nevertheless, a functional role for these new cells is dependent upon a significant number of cells being generated, their survival, differentiation and integration into existing neuronal circuitry.

TBI-induced neurogenesis in experimental studies in TBI animal models

Studies from our lab and others have shown that TBI significantly increases cell proliferation in both the SVZ and DG in adult mice and rats in varying TBI models including fluid percussive injury (FPI) (Chirumamilla et al., 2002; Rice et al., 2003), controlled cortical impact injury (CCI) (Dash et al., 2001; Gao et al., 2009), closed head weight drop injury (Villasana et al., 2014) and acceleration-impact injury (Bye et al., 2011). Common to all reported TBI models, the most prominent endogenous cell response in both the DG and SVZ following TBI is an increase in cell proliferation. This injury-enhanced cell proliferation

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