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Neural Regeneration and Development Theme Issue

REVIEW

Function and Dysfunction of Adult Hippocampal Neurogenesis in Regeneration and Disease

Lei Peng*† and Michael A. Bonaguidi*‡§¶

From the Broad California Institute for Regenerative Medicine (CIRM) Center, the Department of Stem Cell Biology and Regenerative Medicine,† Neuroscience Graduate Program, and the Departments of Stem Cell Biology and Regenerative Medicine,‡ Gerontology,§ and Biomedical Engineering,¶ Zilkha Neurogenetic Institute, University of Southern California Keck School of Medicine, Los Angeles, California*

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Address correspondence to Michael A. Bonaguidi, Ph.D., Broad California Institute for Regenerative Medicine (CIRM) Center and Departments of Stem Cell Biology and Regenerative Medicine, Gerontology, and Biomedical Engineering, Zilkha Neurogenetic Institute, University of Southern California Keck School of Medicine, 1425 San Pablo St, Broad CIRM Center 412, Los Angeles, CA 90033. E-mail: mbonagui@usc.edu.

The hippocampus is the only known brain region where physiological neurogenesis continues into adulthood across mammalian species and in humans. However, disease and injury can change the level of adult hippocampal neurogenesis, which plays an important role in regulating cognitive and emotional abilities. Alterations in hippocampal neurogenesis can mediate treatment of mental illness or affect the brain's capacity for repair and regeneration. In the present review, we evaluate how adult neurogenesis contributes to the repair and regeneration of hippocampal circuitry in the face of diseases and injuries. We also discuss possible future directions for harnessing adult neurogenesis for therapeutic use. *(Am J Pathol 2018, 188: 23–28; https://doi.org/10.1016/j.ajpath.2017.09.004)*

The adult brain has long been considered limited in its regenerative capacity in comparison with other organs or tissues in the body. For most of the 20th century, it was believed that neurogenesis ceased after development. However, in 1962, Altman[1] injected adult rats with radioactive thymidine to label replicating cells and then demonstrated that mitotically active progenitors reside in the adult rat brain and give birth to new neurons. A series of subsequent studies over decades showed that adult neurogenesis exists in nearly all mammals,[2] including humans.[3,4] Under normal conditions, high levels of neurogenesis occur in two adult rodent regions: the subventricular zone of the lateral ventricles and the dentate gyrus of the hippocampus. Of the two regions, the dentate gyrus of the hippocampus is the only region capable of neurogenesis under basal conditions across mammalian species, including humans (Figure 1). This region's residing neural stem cells can generate functional new neurons and glia in response to pathologic and pharmacologic stimuli, maintaining both network plasticity and tissue homeostasis, with possible potential for repair and regeneration on disease and injury.[5,6]

Adult hippocampal neurogenesis has been functionally linked to learning and memory and emotional processing, such as stress and depression.[7–9] New neurons contribute to circuit remodeling in a 3- to 6-week critical period after their birth.[5,6] Enhancing neurogenesis correlates with improved performance on learning and memory tests, such as the Morris and radial-arm mazes,[10,11] and during fear conditioning.[12] On the other hand, ablated neurogenesis affects spatial and object recognition memory, fear conditioning, and pattern separation behaviors.[13,14] In addition, hippocampal neurogenesis is highly regulated by the local and extrinsic environment. Stress suppresses neurogenesis through the corticosteroid and hypothalamic-adrenal axis. In turn, the level of neurogenesis also affects animals' sensitivity to stress.[8,15] Moreover, physiological and pathologic factors (eg, age, exercise, environment, growth factors, hormones, injuries, and diseases) can influence the production and survival of new neurons in the dentate gyrus to alter hippocampal-dependent emotional and

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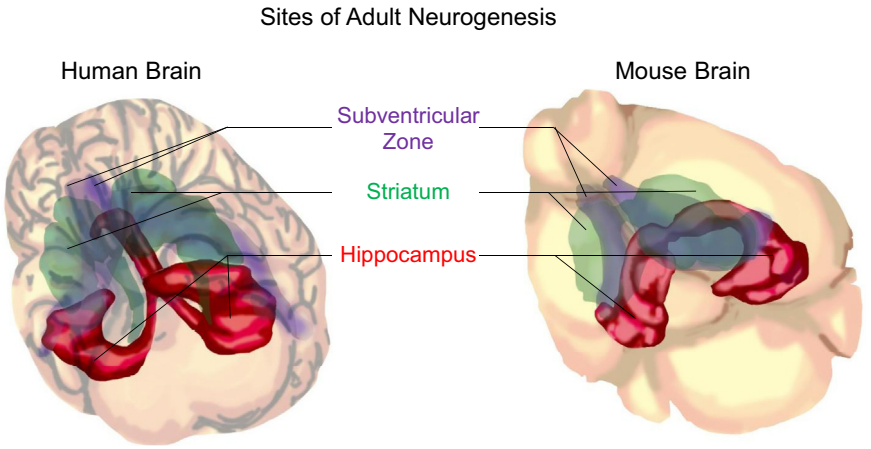

Figure 1 Adult neurogenesis regions. Adult neurogenesis is restricted in specific brain regions in humans and mice. **Left panel:** Human adult neurogenesis occurs under basal conditions in the hippocampus (red) and the striatum (green). **Right panel:** Murine adult neurogenesis occurs in the hippocampus (red) and the subventricular zone (purple). The hippocampus serves as the only brain region where adult neurogenesis is conserved across mammalian species.

cognitive functions.[16–18] We will discuss both the positive and negative relationships among neurogenesis, postinjury repair, and neural disease development.

Neurogenic Capacity Can Be Key for Positive Outcome

The best described role for hippocampal neurogenesis in preventing disease occurs in mental health (Figure 2). The neurogenic hypothesis states that a lack of neurogenesis[8] and synaptogenesis[19] is a cause of depression. This premise is based on several observations: i) decreased hippocampal volume in patients and decreased neurogenesis in animal models of depression can be reversed by selective serotonin reuptake inhibitor antidepressants[20]; ii) depression-associated glucocorticoid elevation appears to inhibit neurogenesis[21]; and iii) selective serotonin reuptake inhibitor antidepressant effects have a delayed onset, consistent with the time frame required for newly generated neurons, despite rapid serotonin-level restoration.[20] Most strikingly, studies ablating neurogenesis have shown selective serotonin reuptake inhibitors then lack an antidepressant effect.[22] Beyond mediating drug efficacy, ventral hippocampal lesions or neurogenic inhibition/depletion can produce animal models of psychiatric diseases, including depression, anxiety, and schizophrenia. Meanwhile, interventions, such as an enriched environment or exercise, can both restore neurogenesis and generate anxiolytic- and antidepressant-like effects.[23] These studies strongly suggest that adult hippocampal neurogenesis serves as a key regulator for disease progression and can be used as a target for therapeutic drugs.

Neurogenesis also has importance for neural repair in the context of stroke. Disruption in the brain's blood supply because of hemorrhage or ischemia deprives glucose and oxygen and leads to an imbalance of prodeath and prosurvival signaling pathways. In the early stages after stroke, injury-induced endothelial or microglial cytokines trigger inflammation, which prolongs ischemic lesions. However, in later stages, the same endothelial and microglial cells produce beneficial factors, such as erythropoietin, to promote tissue repair.[24] Patients experience transiently or permanently impaired facial recognition, calculation, or memory retrieval, and these disabilities are linked to cell death and loss of the ischemic and remote regions.[25] Although early reperfusion is the main therapeutic target, thrombolysis is only suitable for <5% of patients. On the other hand, spontaneous recovery is a common, yet inexplicable, phenomenon. In mice, rats, gerbils, monkeys, and humans with either focal or global ischemia, studies using a thymidine analog have shown hippocampal progenitor proliferation increases 48 hours after injury, peaks at 1 to 2 weeks, and continues until 3 to 4 weeks.[26,27] The resulting newborn cells can migrate to the injury

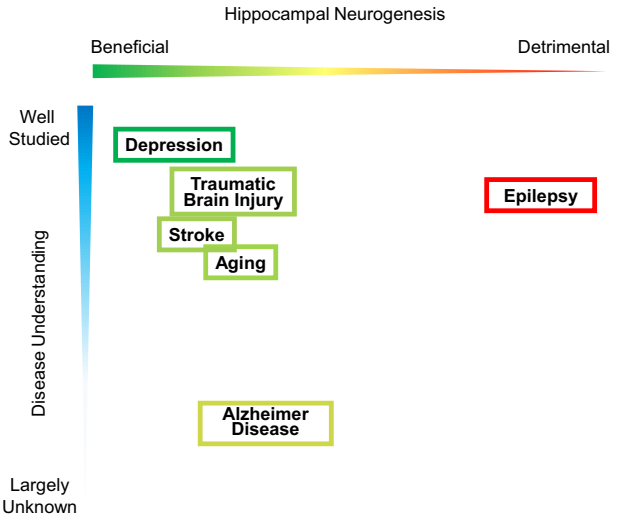

Figure 2 Roles of adult neurogenesis in disease. Hippocampal neurogenesis can be beneficial or detrimental to disease outcome, with varying degrees of data to support these interpretations. Depression is the most well-defined disease where adult neurogenesis acts as a beneficial contributor for treatment and symptom amelioration. Neurogenesis also contributes to more efficient repair and regeneration during stroke and traumatic brain injury. Meanwhile, neurogenesis in epilepsy can be detrimental to disease progression, and aging lowers the ability of neurogenesis to promote hippocampus repair. The conclusive establishment of neurogenesis in either disease progression or regeneration capacity remains largely unknown in Alzheimer disease and other neurodegenerative disorders.