Neurogenesis in Stroke

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Harmonic mechanisms orchestrate neurogenesis in the healthy brain within specific neurogenic niches, which generate neurons from neural stem cells as a homeostatic mechanism. These newly generated neurons integrate into existing neuronal circuits to participate in different brain tasks. Despite the mechanisms that protect the mammalian brain, this organ is susceptible to many different types of damage that result in the loss of neuronal tissue and therefore in alterations in the functionality of the affected regions. Nevertheless, the mammalian brain has developed mechanisms to respond to these injuries, potentiating its capacity to generate new neurons from neural stem cells and altering the homeostatic processes that occur in neurogenic niches. These alterations may lead to the generation of new neurons within the damaged brain regions. Notwithstanding, the activation of these repair mechanisms, regeneration of neuronal tissue within brain injuries does not naturally occur.

neurogenesis neuroblast migration epilepsy

1. Introduction

Pathologies that affect the central nervous system (CNS) and that involve neuronal death are the origin of important and burdensome neurological symptoms [1]. The search for the genetic, molecular, and environmental initiating factors that trigger neuronal death in not only neurodegenerative diseases [2][3][4][5] but also stroke and trauma [6][7] has received a great deal of attention within the last two decades with the goal of finding and designing new therapies. However, despite the efforts, no novel disease-modifying therapies have been proven significant at providing an effective benefit for patients with these devastating disorders. In this scenario, the discovery of new neurons being generated daily from neural stem cells (NSCs) within the adult mammalian brain has brought optimism for the treatment of these pathologies, and the search for therapeutic strategies based on stimulating neurogenesis in the adult brain has gained prominence over the past 10 years. Neurogenesis is the process by which new neurons are generated from neural stem cells (NSCs). NSCs are characterized by their capacity to divide both symmetrically—giving rise to other NSCs—and asymmetrically, producing new cells with a higher degree of differentiation but with the ability to generate a new progeny of neural cells [8][9]. This process has been extensively studied in the adult rodent brain, and it has been observed in the brains of other mammalian species. One of the pioneering studies in the field was the work of Gould et al. in 1999, in which the existence of newly generated cells with neuronal characteristics was described in the prefrontal, temporal, and parietal cortices of monkeys [10][11].

In order for neurogenesis to take place, the environment in which NSCs are located, known as the neurogenic niche, is almost as important as their own existence since the inflammatory molecules, growth factors, and matrix-bound signaling molecules condition NSCs fate towards mature functional neurons [12][13]. The neurogenic niche is a microenvironment characterized by a complex structure containing NSCs anchored to the basement membrane, soluble factors, extracellular matrix-bound molecules, and a high rate of vascularization [14][15]. Most of these soluble factors are produced locally and play a key role in the neurogenic process by favoring, among other roles, the constant production of new neurons [16]. In the adult brain, there are basically two neurogenic regions, which contain remnant populations of NSCs, that continue to produce neurons throughout life. These regions are the subventricular zone (SVZ), adjacent to the ependyma in the lateral walls of the lateral ventricles (LV), and the dentate gyrus (DG) of the hippocampus [15]. In the case of rodents SVZ, it has been well described that neuroblasts have the ability to migrate from the SVZ to the olfactory bulb (OB) through the rostral migratory stream (RMS) [17]. The microenvironment generated within the RMS allows neuroblasts to migrate tangentially from the SVZ to the OB. Once in the OB, neuroblasts change their migration pattern from tangential to radial and finally finish their differentiation process, becoming interneurons that integrate in the OB [18][19]. A recent in vivo study [20] demonstrates the existence of active NSCs within the OB core, meaning that the OB is another niche capable of generating neurons that then integrate into the preexisting circuits. New cells originating in the different niches participate in injury repair [21]. The DG of the hippocampus is another neurogenic niche, and it is involved in tasks such as memory and learning [22]. In the DG, neurogenic and proliferative activity is maintained in the adult mammalian brain, even in old individuals. Specifically, the sub granular zone (SGZ) contains astrocytes with radial glia characteristics, which can divide and form neural precursors or neuroblasts. These have the ability to proliferate and mature, giving rise to granular neurons that will settle in the granular layer [23], contributing to memory and learning processes [24]. The migration route in the SGZ is much shorter than in the SVZ, where neuroblasts need to cover a long distance after reaching the OB [25]. Other niches were described and are being studied, as in the case of the striatum, the neocortex or the hypothalamus [26][27][28][29].

As mentioned before, neurogenesis has been extensively studied in mammals, especially rodents, but also in humans. However, it has been described as having several differences between species. For example, striatal neurogenesis is only present in humans [30], while OB neurogenesis is present in other mammals but not in humans [31]. In this regard, adult human hippocampal neurogenesis (AHN) is now in the spotlight because of the high level of controversy surrounding the aging process. In nonhuman primates and mice, it was reported a clear decline of AHN neurogenesis [32][33] through aging. However, Boldrini et al. used healthy human autopsy samples of the hippocampus and observed a similar number of intermediate neural progenitors and immature neurons in the DG of individuals at different stages of life (from 14 to 79 years old) [34]. Simultaneously, Sorrells et al. described a sharp decline in the production of new neurons in the human DG during the first year of life, becoming nearly nonexistent after the first year [35]. These apparently contradictory results aroused great controversy, and authors including Flor-García et al. identified the problem in how the human post-mortem samples were handled and provided an alternative and promising protocol to better control immunohistochemistry [36].

An association of alterations in neurogenesis in both niches with cognitive impairment has been described in mouse models of metabolic alterations [37][38][39], cerebrovascular damage [40], aging [41], and neurological

disorders [42][43] and in general, increased organized, non-aberrant neurogenesis leads to improved cognitive performance. In addition to the generation of neuroblasts and their maturation, post-neurogenic migration is another mechanism that undergoes significant changes during different disease processes. However, more extensive studies are required to properly understand the migration mechanisms and their role in different neurological disorders. Neurodegenerative diseases such as Parkinson's disease (PD), Alzheimer's disease (AD), or Huntington's disease (HD) have a deep impact on brain configuration, even modifying the anatomical structure and its associated physiological conditions. These structural modifications could be observed also in stroke and trauma. The neuronal loss generates distinctive consequences, including decreased cognitive function, impaired attention, and even personality alterations [16][44]. In order to find strategies to compensate this neuronal loss, researchers worldwide have contributed to the understanding of the neurogenic processes, including migration, as well as the intrinsic characteristics of the neurogenic niches, which play a key role in neurogenesis as they harbor the NSCs from which new neurons derive.

2. Neurogenesis in Stroke

A stroke is a serious medical emergency that occurs when blood flow to the brain is interrupted. This can be due to a vessel blockage (ischemic stroke, which occurs in over 80% of cases) or a hemorrhage (hemorrhagic stroke). The lack of oxygen and glucose caused by the loss of blood flow leads to the death of neurons and results in an acute loss of function in the area of the brain supplied by the affected vessel. The initial cell death is followed by a longer structural and functional reorganization period. Stroke can cause symptoms such as weakness, difficulty speaking, sensory deficits, and difficulty walking [45][46]. Stroke represents the second leading cause of death and the third leading cause of disability globally [47].

The CNS has a limited capacity for repair, as demonstrated by previous research [48]. However, it has been observed that a certain degree of spontaneous recovery from brain ischemia can occur [49]. Several mechanisms, such as neurogenesis, angiogenesis, axonal sprouting, and synaptogenesis, mediate this recovery process [50][51]. Experimental evidence suggests that functional improvement following stroke may be mediated by the replacement of lost neurons by activating endogenous NSCs [52]. The proliferation of NSCs and their progeny in the adult brain following stroke has been demonstrated in both human and animal models [53]. In animal models, stroke has been found to stimulate the proliferation of NSCs in the SVZ and the SGZ of the DG. These progenitor cells can potentially migrate to the affected area and differentiate into neurons, contributing to improved functional outcomes post-stroke [54][55][56]. This migration begins 3–4 days after stroke and is able to continue for at least 4 months, where reactive astrocytes, activated microglia/macrophages, blood vessels, and migratory scaffolds formed by astrocytic processes are essential for the movement of neuroblasts toward the injured site. In fact, after a stroke, there is an increase in the density of blood vessels, which increases blood supply to the injured brain regions. Endothelial cells secrete growth factors such as BDNF and angiopoietin that promote neuroblast recruitment within the lesion area, promoting proliferation and migration from the SVZ. The molecular and migratory capacities of SVZ neuroblasts are altered in stroke; genes such as Hif-1α or Notch4 are upregulated, and molecules such as MMPs are overexpressed in SVZ neuroblasts in response to stroke in order to facilitate emigration [57].

The timeline of the neurogenic process after stroke varies depending on the location and severity of the stroke, as well as the species studied. In general, studies have found that neurogenesis begins within a few days after the stroke and can continue for several weeks [52]. The in vivo studies performed by Zhang et al. have shown that following a stroke, there is a significant increase in the proportion of dividing cells within the SVZ. This increase starts at 2 days post-stroke (24%), peaks at 7 days post-stroke (31%), and at 14 days post-stroke, the proportion of dividing cells returns to the baseline level observed at 2 days post-stroke. Additionally, the cell cycle length of SVZ cells undergoes dynamic changes over a period of 2–14 days following a stroke. The shortest cell cycle length observed was 11 h at 2 days post-stroke, which is significantly shorter than the cell cycle length of 19 h in non-stroke SVZ cells. There is a gradual increase in the cell cycle length by 4 days post-stroke, and by 14 days post-stroke, it reaches the length of non-ischemic progenitor cells [58][59][60]. Studies in human subjects have demonstrated that the extent of neurogenesis following a stroke is less extensive than in animal models. Jin et al. found an increase in the number of new neurons in the hippocampus during the initial week post-stroke; however, this number returned to pre-stroke levels within 2–3 months [61]. It is important to note that while neurogenesis has been observed in certain brain regions following a stroke, the extent and duration of this process are still an active area of research. Stroke triggers neurogenesis in the DG [62], but the newly generated neurons produced post-stroke show an aberrant morphology [63][64]. The authors refer to this abnormal neurogenesis as responsible for the cognitive impairment found in mice after stroke and propose abolishing abnormal neurogenesis as a mechanism to improve cognitive performance post-stroke [40].

In this scenario, the activation of astrocytes in the SVZ and hippocampus after stroke results in the secretion of growth factors that promote the proliferation and differentiation of neural stem cells into new neurons. Faiz et al. have shown that SVZ-derived NSCs give rise to reactive astrocytes at the stroke site and can be converted to neurons in vivo following overexpression of Ascl1 [65]. This process is thought to be critical for the repair and recovery of the brain after a stroke. Reactive astrocytes also play an important role in forming new blood vessels after stroke, which is essential for the survival and integration of new neurons in the brain [66][67]. Several signaling pathways have been proposed to play roles in the adult neurogenic response to ischemia-induced stroke. The Notch signaling pathway regulates cell proliferation and differentiation during development and in adult tissue repair. In cooperation with ciliary neurotrophic factor (CNTF), Notch signals guide neural stem cells to generate astrocytes. Notch-CBF1 knockdown results in the conversion of neural stem cells to intermediate progenitor cells, which then generate neurons [68]. Studies have found that after a stroke, the Notch pathway assists the proliferation and differentiation of NSCs in the SVZ and hippocampus, leading to the formation of new neurons [69][70][71][72]. The sonic hedgehog (Shh) signaling pathway also plays a crucial role in early CNS development, influencing oligodendrocyte development [73]. After a cerebral ischemic stroke, Shh signaling improves the recovery of neurological function by increasing angiogenesis, neurogenesis, and oligodendrogenesis and reducing astrogliosis [74]. The upregulation of Shh expression and its transcription factor Gli1 in NPCs improved motor function in stroke mice, indicating its protective role in stroke [75][76].

Stroke-induced neurogenesis has been found to occur in humans, although the process is more limited compared to animal studies. Jin et al. found an increase in the number of new neurons in the hippocampus during the initial week post-stroke; however, this number returned to pre-stroke levels within 2–3 months [61]. An examination of

brain tissue from advanced-age humans who have experienced ischemic stroke reveals an increase in the proliferation of SVZ cells and neuroblasts [77]. It is noteworthy that the mechanisms and extent of neurogenesis in stroke patients are not yet fully comprehended, and ongoing studies continue to investigate this process in humans.

References

1. Wingo, T.S.; Liu, Y.; Gerasimov, E.S.; Vattathil, S.M.; Wynne, M.E.; Liu, J.; Lori, A.; Faundez, V.; Bennett, D.A.; Seyfried, N.T.; et al. Shared mechanisms across the major psychiatric and neurodegenerative diseases. Nat. Commun. 2022, 13, 4314.
2. Wang, H.; Yang, F.; Zhang, S.; Xin, R.; Sun, Y. Genetic and environmental factors in Alzheimer's and Parkinson's diseases and promising therapeutic intervention via fecal microbiota transplantation. NPJ Park. Dis. 2021, 7, 70.
3. Golde, T.E. The therapeutic importance of understanding mechanisms of neuronal cell death in neurodegenerative disease. Mol. Neurodegener. 2009, 4, 8.
4. Pardillo-Díaz, R.; Carrascal, L.; Ayala, A.; Nunez-Abades, P. Oxidative stress induced by cumene hydroperoxide evokes changes in neuronal excitability of rat motor cortex neurons. Neuroscience 2015, 289, 85–98.
5. Pardillo-Díaz, R.; Pérez-García, P.; Castro, C.; Nunez-Abades, P.; Carrascal, L. Oxidative Stress as a Potential Mechanism Underlying Membrane Hyperexcitability in Neurodegenerative Diseases. Antioxidants 2022, 11, 1511.
6. Qin, C.; Yang, S.; Chu, Y.-H.; Zhang, H.; Pang, X.-W.; Chen, L.; Zhou, L.-Q.; Chen, M.; Tian, D.-S.; Wang, W. Signaling pathways involved in ischemic stroke: Molecular mechanisms and therapeutic interventions. Signal. Transduct. Target. Ther. 2022, 7, 215.
7. Tuo, Q.-Z.; Zhang, S.-T.; Lei, P. Mechanisms of neuronal cell death in ischemic stroke and their therapeutic implications. Med. Res. Rev. 2022, 42, 259–305.
8. Morrison, S.J.; Kimble, J. Asymmetric and symmetric stem-cell divisions in development and cancer. Nature 2006, 441, 1068–1074.
9. Obernier, K.; Alvarez-Buylla, A. Neural stem cells: Origin, heterogeneity and regulation in the adult mammalian brain. Development 2019, 146, dev156059.
10. Gould, E.; Reeves, A.J.; Graziano, M.S.; Gross, C.G. Neurogenesis in the neocortex of adult primates. Science 1999, 286, 548–552.
11. Gould, E.; Vail, N.; Wagers, M.; Gross, C.G. Adult-generated hippocampal and neocortical neurons in macaques have a transient existence. Proc. Natl. Acad. Sci. USA 2001, 98, 10910–

10917.

12. Doetsch, F.; Garcia-Verdugo, J.M.; Alvarez-Buylla, A. Cellular composition and three-dimensional organization of the subventricular germinal zone in the adult mammalian brain. J. Neurosci. 1997, 17, 5046–5061.
13. Suh, H.; Consiglio, A.; Ray, J.; Sawai, T.; D'Amour, K.A.; Gage, F.H. In vivo fate analysis reveals the multipotent and self-renewal capacities of Sox2+ neural stem cells in the adult hippocampus. Cell Stem Cell 2007, 1, 515–528.
14. Alvarez-Buylla, A.; Lim, D.A. For the long run: Maintaining germinal niches in the adult brain. Neuron 2004, 41, 683–686.
15. Bond, A.M.; Ming, G.L.; Song, H. Adult Mammalian Neural Stem Cells and Neurogenesis: Five Decades Later. Cell Stem Cell 2015, 17, 385–395.
16. Abrous, D.N.; Koehl, M.; Le Moal, M. Adult neurogenesis: From precursors to network and physiology. Physiol. Rev. 2005, 85, 523–569.
17. Alvarez-Buylla, A.; Garcia-Verdugo, J.M. Neurogenesis in adult subventricular zone. J. Neurosci. 2002, 22, 629–634.
18. Lim, D.A.; Alvarez-Buylla, A. The Adult Ventricular-Subventricular Zone (V-SVZ) and Olfactory Bulb (OB) Neurogenesis. Cold Spring Harb. Perspect. Biol. 2016, 8, a018820.
19. Lledo, P.M.; Saghatelyan, A. Integrating new neurons into the adult olfactory bulb: Joining the network, life-death decisions, and the effects of sensory experience. Trends Neurosci. 2005, 28, 248–254.
20. Defterali, C.; Moreno-Estelles, M.; Crespo, C.; Diaz-Guerra, E.; Diaz-Moreno, M.; Vergano-Vera, E.; Nieto-Estevez, V.; Hurtado-Chong, A.; Consiglio, A.; Mira, H.; et al. Neural stem cells in the adult olfactory bulb core generate mature neurons in vivo. Stem Cells 2021, 39, 1253–1269.
21. Menn, B.; Garcia-Verdugo, J.M.; Yaschine, C.; Gonzalez-Perez, O.; Rowitch, D.; Alvarez-Buylla, A. Origin of oligodendrocytes in the subventricular zone of the adult brain. J. Neurosci. 2006, 26, 7907–7918.
22. van Praag, H.; Schinder, A.F.; Christie, B.R.; Toni, N.; Palmer, T.D.; Gage, F.H. Functional neurogenesis in the adult hippocampus. Nature 2002, 415, 1030–1034.
23. Seri, B.; Garcia-Verdugo, J.M.; McEwen, B.S.; Alvarez-Buylla, A. Astrocytes give rise to new neurons in the adult mammalian hippocampus. J. Neurosci. 2001, 21, 7153–7160.
24. Butti, E.; Cusimano, M.; Bacigaluppi, M.; Martino, G. Neurogenic and non-neurogenic functions of endogenous neural stem cells. Front. Neurosci. 2014, 8, 92.

25. Sun, G.J.; Zhou, Y.; Stadel, R.P.; Moss, J.; Yong, J.H.; Ito, S.; Kawasaki, N.K.; Phan, A.T.; Oh, J.H.; Modak, N.; et al. Tangential migration of neuronal precursors of glutamatergic neurons in the adult mammalian brain. Proc. Natl. Acad. Sci. USA 2015, 112, 9484–9489.

26. Dayer, A.G.; Cleaver, K.M.; Abouantoun, T.; Cameron, H.A. New GABAergic interneurons in the adult neocortex and striatum are generated from different precursors. J. Cell. Biol. 2005, 168, 415–427.

27. Luzzati, F.; Nato, G.; Oboti, L.; Vigna, E.; Rolando, C.; Armentano, M.; Bonfanti, L.; Fasolo, A.; Peretto, P. Quiescent neuronal progenitors are activated in the juvenile guinea pig lateral striatum and give rise to transient neurons. Development 2014, 141, 4065–4075.

28. Ernst, A.; Alkass, K.; Bernard, S.; Salehpour, M.; Perl, S.; Tisdale, J.; Possnert, G.; Druid, H.; Frisen, J. Neurogenesis in the striatum of the adult human brain. Cell 2014, 156, 1072–1083.

29. Recabal, A.; Caprile, T.; Garcia-Robles, M.L.A. Hypothalamic Neurogenesis as an Adaptive Metabolic Mechanism. Front. Neurosci. 2017, 11, 190.

30. Bergmann, O.; Spalding, K.L.; Frisen, J. Adult Neurogenesis in Humans. Cold Spring Harb. Perspect. Biol. 2015, 7, a018994.

31. Bergmann, O.; Liebl, J.; Bernard, S.; Alkass, K.; Yeung, M.S.; Steier, P.; Kutschera, W.; Johnson, L.; Landen, M.; Druid, H.; et al. The age of olfactory bulb neurons in humans. Neuron 2012, 74, 634–639.

32. Leuner, B.; Kozorovitskiy, Y.; Gross, C.G.; Gould, E. Diminished adult neurogenesis in the marmoset brain precedes old age. Proc. Natl. Acad. Sci. USA 2007, 104, 17169–17173.

33. Ben Abdallah, N.M.; Slomianka, L.; Lipp, H.P. Reversible effect of X-irradiation on proliferation, neurogenesis, and cell death in the dentate gyrus of adult mice. Hippocampus 2007, 17, 1230–1240.

34. Boldrini, M.; Fulmore, C.A.; Tartt, A.N.; Simeon, L.R.; Pavlova, I.; Poposka, V.; Rosoklija, G.B.; Stankov, A.; Arango, V.; Dwork, A.J.; et al. Human Hippocampal Neurogenesis Persists throughout Aging. Cell Stem Cell 2018, 22, 589–599 e585.

35. Sorrells, S.F.; Paredes, M.F.; Cebrian-Silla, A.; Sandoval, K.; Qi, D.; Kelley, K.W.; James, D.; Mayer, S.; Chang, J.; Auguste, K.I.; et al. Human hippocampal neurogenesis drops sharply in children to undetectable levels in adults. Nature 2018, 555, 377–381.

36. Flor-Garcia, M.; Terreros-Roncal, J.; Moreno-Jimenez, E.P.; Avila, J.; Rabano, A.; Llorens-Martin, M. Unraveling human adult hippocampal neurogenesis. Nat. Protoc. 2020, 15, 668–693.

37. Carrasco, M.; Rabaneda, L.G.; Murillo-Carretero, M.; Ortega-Martinez, S.; Martinez-Chantar, M.L.; Woodhoo, A.; Luka, Z.; Wagner, C.; Lu, S.C.; Mato, J.M.; et al. Glycine N-methyltransferase

expression in the hippocampus and its role in neurogenesis and cognitive performance. Hippocampus 2014, 24, 840–852.

38. Rabaneda, L.G.; Geribaldi-Doldan, N.; Murillo-Carretero, M.; Carrasco, M.; Martinez-Salas, J.M.; Verastegui, C.; Castro, C. Altered regulation of the Spry2/Dyrk1A/PP2A triad by homocysteine impairs neural progenitor cell proliferation. Biochim. Biophys. Acta 2016, 1863, 3015–3026.
39. Gomez-Oliva, R.; Geribaldi-Doldan, N.; Dominguez-Garcia, S.; Carrascal, L.; Verastegui, C.; Nunez-Abades, P.; Castro, C. Vitamin D deficiency as a potential risk factor for accelerated aging, impaired hippocampal neurogenesis and cognitive decline: A role for Wnt/beta-catenin signaling. Aging (Albany N. Y.) 2020, 12, 13824–13844.
40. Cuartero, M.I.; de la Parra, J.; Pérez-Ruiz, A.; Bravo-Ferrer, I.; Durán-Laforet, V.; García-Culebras, A.; García-Segura, J.M.; Dhaliwal, J.; Frankland, P.W.; Lizasoain, I.; et al. Abolition of aberrant neurogenesis ameliorates cognitive impairment after stroke in mice. J. Clin. Investig. 2019, 129, 1536–1550.
41. Berdugo-Vega, G.; Arias-Gil, G.; López-Fernández, A.; Artegiani, B.; Wasielewska, J.M.; Lee, C.C.; Lippert, M.T.; Kempermann, G.; Takagaki, K.; Calegari, F. Increasing neurogenesis refines hippocampal activity rejuvenating navigational learning strategies and contextual memory throughout life. Nat. Commun. 2020, 11, 135.
42. Terreros-Roncal, J.; Moreno-Jimenez, E.P.; Flor-Garcia, M.; Rodriguez-Moreno, C.B.; Trinchero, M.F.; Cafini, F.; Rabano, A.; Llorens-Martin, M. Impact of neurodegenerative diseases on human adult hippocampal neurogenesis. Science 2021, 374, 1106–1113.
43. Moreno-Jiménez, E.P.; Flor-García, M.; Terreros-Roncal, J.; Rábano, A.; Cafini, F.; Pallas-Bazarra, N.; Ávila, J.; Llorens-Martín, M. Adult hippocampal neurogenesis is abundant in neurologically healthy subjects and drops sharply in patients with Alzheimer’s disease. Nat. Med. 2019, 25, 554–560.
44. Blennow, K.; Hardy, J.; Zetterberg, H. The neuropathology and neurobiology of traumatic brain injury. Neuron 2012, 76, 886–899.
45. Dirnagl, U.; Iadecola, C.; Moskowitz, M.A. Pathobiology of ischaemic stroke: An integrated view. Trends Neurosci. 1999, 22, 391–397.
46. Murphy, T.H.; Corbett, D. Plasticity during stroke recovery: From synapse to behaviour. Nat. Rev. Neurosci. 2009, 10, 861–872.
47. Johnson, W.; Onuma, O.; Owolabi, M.; Sachdev, S. Stroke: A global response is needed. Bull. World Health Organ. 2016, 94, 634A.
48. Nakagomi, T.; Molnar, Z.; Nakano-Doi, A.; Taguchi, A.; Saino, O.; Kubo, S.; Clausen, M.; Yoshikawa, H.; Nakagomi, N.; Matsuyama, T. Ischemia-induced neural stem/progenitor cells in the pia mater following cortical infarction. Stem Cells Dev. 2011, 20, 2037–2051.

49. Yu, T.S.; Washington, P.M.; Kernie, S.G. Injury-Induced Neurogenesis: Mechanisms and Relevance. Neuroscientist 2016, 22, 61–71.
50. Rahman, A.A.; Amruta, N.; Pinteaux, E.; Bix, G.J. Neurogenesis After Stroke: A Therapeutic Perspective. Transl. Stroke Res. 2021, 12, 1–14.
51. Jones, T.A.; Adkins, D.L. Motor System Reorganization After Stroke: Stimulating and Training Toward Perfection. Physiology 2015, 30, 358–370.
52. Arvidsson, A.; Collin, T.; Kirik, D.; Kokaia, Z.; Lindvall, O. Neuronal replacement from endogenous precursors in the adult brain after stroke. Nat. Med. 2002, 8, 963–970.
53. Kojima, T.; Hirota, Y.; Ema, M.; Takahashi, S.; Miyoshi, I.; Okano, H.; Sawamoto, K. Subventricular zone-derived neural progenitor cells migrate along a blood vessel scaffold toward the post-stroke striatum. Stem Cells 2010, 28, 545–554.
54. Nakatomi, H.; Kuriu, T.; Okabe, S.; Yamamoto, S.; Hatano, O.; Kawahara, N.; Tamura, A.; Kirino, T.; Nakafuku, M. Regeneration of hippocampal pyramidal neurons after ischemic brain injury by recruitment of endogenous neural progenitors. Cell 2002, 110, 429–441.
55. Komitova, M.; Mattsson, B.; Johansson, B.B.; Eriksson, P.S. Enriched environment increases neural stem/progenitor cell proliferation and neurogenesis in the subventricular zone of stroke-lesioned adult rats. Stroke 2005, 36, 1278–1282.
56. Marlier, Q.; Verteneuil, S.; Vandenbosch, R.; Malgrange, B. Mechanisms and Functional Significance of Stroke-Induced Neurogenesis. Front. Neurosci. 2015, 9, 458.
57. Young, C.C.; Brooks, K.J.; Buchan, A.M.; Szele, F.G. Cellular and molecular determinants of stroke-induced changes in subventricular zone cell migration. Antioxid. Redox Signal. 2011, 14, 1877–1888.
58. Zhang, R.L.; Zhang, Z.G.; Lu, M.; Wang, Y.; Yang, J.J.; Chopp, M. Reduction of the cell cycle length by decreasing G1 phase and cell cycle reentry expand neuronal progenitor cells in the subventricular zone of adult rat after stroke. J. Cereb. Blood Flow. Metab. 2006, 26, 857–863.
59. Zhang, R.L.; Zhang, Z.G.; Roberts, C.; LeTourneau, Y.; Lu, M.; Zhang, L.; Wang, Y.; Chopp, M. Lengthening the G(1) phase of neural progenitor cells is concurrent with an increase of symmetric neuron generating division after stroke. J. Cereb. Blood Flow. Metab. 2008, 28, 602–611.
60. Zhang, R.L.; Zhang, Z.G.; Chopp, M. Ischemic stroke and neurogenesis in the subventricular zone. Neuropharmacology 2008, 55, 345–352.
61. Jin, K.; Peel, A.L.; Mao, X.O.; Xie, L.; Cottrell, B.A.; Henshall, D.C.; Greenberg, D.A. Increased hippocampal neurogenesis in Alzheimer’s disease. Proc. Natl. Acad. Sci. USA 2004, 101, 343–347.

62. Lichtenwalner, R.J.; Parent, J.M. Adult neurogenesis and the ischemic forebrain. J. Cereb. Blood Flow. Metab. 2006, 26, 1–20.
63. Woitke, F.; Ceanga, M.; Rudolph, M.; Niv, F.; Witte, O.W.; Redecker, C.; Kunze, A.; Keiner, S. Adult hippocampal neurogenesis poststroke: More new granule cells but aberrant morphology and impaired spatial memory. PLoS ONE 2017, 12, e0183463.
64. Niv, F.; Keiner, S.; Krishna; Witte, O.W.; Lie, D.C.; Redecker, C. Aberrant neurogenesis after stroke: A retroviral cell labeling study. Stroke 2012, 43, 2468–2475.
65. Faiz, M.; Sachewsky, N.; Gascon, S.; Bang, K.W.; Morshead, C.M.; Nagy, A. Adult Neural Stem Cells from the Subventricular Zone Give Rise to Reactive Astrocytes in the Cortex after Stroke. Cell Stem Cell 2015, 17, 624–634.
66. He, T.; Yang, G.Y.; Zhang, Z. Crosstalk of Astrocytes and Other Cells during Ischemic Stroke. Life 2022, 12, 910.
67. Patabendige, A.; Singh, A.; Jenkins, S.; Sen, J.; Chen, R. Astrocyte Activation in Neurovascular Damage and Repair Following Ischaemic Stroke. Int. J. Mol. Sci. 2021, 22, 4280.
68. Wang, L.; Chopp, M.; Zhang, R.L.; Zhang, L.; Letourneau, Y.; Feng, Y.F.; Jiang, A.; Morris, D.C.; Zhang, Z.G. The Notch pathway mediates expansion of a progenitor pool and neuronal differentiation in adult neural progenitor cells after stroke. Neuroscience 2009, 158, 1356–1363.
69. Carlen, M.; Meletis, K.; Goritz, C.; Darsalia, V.; Evergren, E.; Tanigaki, K.; Amendola, M.; Barnabe-Heider, F.; Yeung, M.S.; Naldini, L.; et al. Forebrain ependymal cells are Notch-dependent and generate neuroblasts and astrocytes after stroke. Nat. Neurosci. 2009, 12, 259–267.
70. Xiao, M.J.; Han, Z.; Shao, B.; Jin, K. Notch signaling and neurogenesis in normal and stroke brain. Int. J. Physiol. Pathophysiol. Pharm. 2009, 1, 192–202.
71. Li, Z.; Wang, J.; Zhao, C.; Ren, K.; Xia, Z.; Yu, H.; Jiang, K. Acute Blockage of Notch Signaling by DAPT Induces Neuroprotection and Neurogenesis in the Neonatal Rat Brain After Stroke. Transl. Stroke Res. 2016, 7, 132–140.
72. Santopolo, G.; Magnusson, J.P.; Lindvall, O.; Kokaia, Z.; Frisen, J. Blocking Notch-Signaling Increases Neurogenesis in the Striatum after Stroke. Cells 2020, 9, 1732.
73. Falcon-Urrutia, P.; Carrasco, C.M.; Lois, P.; Palma, V.; Roth, A.D. Shh Signaling through the Primary Cilium Modulates Rat Oligodendrocyte Differentiation. PLoS ONE 2015, 10, e0133567.
74. Liu, L.; Zhao, B.; Xiong, X.; Xia, Z. The Neuroprotective Roles of Sonic Hedgehog Signaling Pathway in Ischemic Stroke. Neurochem. Res. 2018, 43, 2199–2211.
75. Dai, R.L.; Zhu, S.Y.; Xia, Y.P.; Mao, L.; Mei, Y.W.; Yao, Y.F.; Xue, Y.M.; Hu, B. Sonic hedgehog protects cortical neurons against oxidative stress. Neurochem. Res. 2011, 36, 67–75.

76. Jin, Y.; Raviv, N.; Barnett, A.; Bambakidis, N.C.; Filichia, E.; Luo, Y. The shh signaling pathway is upregulated in multiple cell types in cortical ischemia and influences the outcome of stroke in an animal model. PLoS ONE 2015, 10, e0124657.

77. Macas, J.; Nern, C.; Plate, K.H.; Momma, S. Increased generation of neuronal progenitors after ischemic injury in the aged adult human forebrain. J. Neurosci. 2006, 26, 13114–13119.