REVIEW

# Neural plasticity and adult neurogenesis: the deep biology perspective

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## Abstract

The recognition that neurogenesis does not stop with adolescence has spun off research towards the reduction of brain disorders by enhancing brain regeneration. Adult neurogenesis is one of the tougher problems of developmental biology as it requires the generation of complex intracellular and pericellular anatomies, amidst the danger of neuroinflammation. We here review how a multitude of regulatory pathways optimized for early neurogenesis has to be revamped into a new choreography of time dependencies. Distinct pathways need to be regulated, ranging from neural growth factor induced differentiation to mitochondrial bioenergetics, reactive oxygen metabolism, and apoptosis. Requiring much Gibbs energy consumption, brain depends on aerobic energy metabolism, hence on mitochondrial activity. Mitochondrial fission and fusion, movement and perhaps even mitoptosis, thereby come into play. All these network processes are interlinked and involve a plethora of molecules. We recommend a deep thinking approach to adult neurobiology.

***Key Words:*** *neurogenesis; adult brain; neuroregeneration; neuron; differentiation; nerve growth factor; energy homeostasis; mitochondria; deep biology; systems biology*

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## Introduction

Brain regeneration has become a big issue in regenerative medicine, due to the increased incidence of brain disorders linked to the increased life expectancy. Multiple pharmacological and genetic approaches attempt to both elucidate mechanisms of neurodegeneration and define new targets for potential therapeutic molecules. More recently, much effort has been devoted to understand the mechanism of endogenous neurogenesis as a potential target for brain repair and regeneration in several pathological conditions. We here review current knowledge of brain neurogenesis and neuronal differentiation, and propose the concept of deep biology as an effective approach to unravel key processes of neural regeneration.

## Functional Adult Neurogenesis and Neural Plasticity

After the central nervous system had been branded "perennial" tissue, the subsequent discoveries of neurogenesis and differentiation in the adult central nervous system re-opened gateways. The adult central nervous system contains neural precursor stem cells (NPSCs) that can generate neurons, astrocytes, and/or oligodendrocytes (Gage, 2000; Zhao et al., 2008), thus bringing the complexity of neural plasticity and regeneration to a new age. Changes in neuronal phenotypes and connectivity may be associated with neurogenesis and new neurons may be functionally integrated into pre-existing networks (van Praag et al., 2002). NPSCs reside in at least three main areas of the brain, the subventricular zone, the subgranular zone of the dentate gyrus of the hippocampus, and the periventricular area of the spinal cord (Gage, 2000; Taupin and Gage, 2002). NPSCs proliferate and differentiate into neuroblasts: in the subventricular zone, they migrate through the rostral migratory stream to the olfactory bulb to become interneurons; in the subgranular zone, they mature into granule neurons of the granule cell layer, suggesting a central role in memory processes (Zhao et al., 2008; Ming and Song, 2011).

It is now well established that adult neurogenesis occurs throughout life in all mammalian species, including non-human primates (Kuhn et al. 1996; Kempermann et al., 1997; Kornack and Rakic, 1999, 2001). It is remarkable that functional neurogenesis is modulated by experience and enriched environments (Kempermann et al., 1997), as well as by pathological conditions. A decreased, or altered, neurogenesis has been found in aged rodents and in animal models of Alzheimer's disease (Faure et al., 2011; Wirths, 2017) and Parkinson's disease (Zhao et al., 2003; Höglinger et al., 2004; Yoshimi et al., 2005; Shan et al., 2006), as well as in other neuropathological conditions, including traumatic brain injury, ischemia, and mood disorders (Shruster et al., 2012; Spaccapelo et al., 2013; Lindvall

and Kokaia, 2015; Dokter and von Bohlen und Halbach, 2012; Mahar et al., 2014).

The evidence of neurogenesis has been also found in the adult human brain (Eriksson et al., 1998; Höglinger et al., 2004; Knoth et al., 2010; Ihunwo et al., 2016), although it is still controversial (Sorrells et al., 2018). Therefore, a decline in neurogenesis may underlie cognitive impairment associated with aging and brain disorders, and may be the target for disease modifying therapeutic strategies.

## Multifarious Regulation of Adult Neurogenesis in Response to Morphogens and Brain Damage

Several signaling cascades regulate neurogenesis, balancing the maintenance of a NPSCs pool with the differentiation and maturation of new neurons (Ming and Song, 2011). In addition to transcription factors (such as Sox2, FoxOs and c-myb) regulating cell cycle and proliferation and thereby the maintenance of neurogenic niches, a number of transcription factors (such as Prox1, Pax6, Dlx-2, NeuroD) regulate both the cell fate of neural precursors and adult neurogenesis in neurogenic and non-neurogenic areas (Doetsch et al., 2002; Suh et al., 2007; Gao et al., 2009; Paik et al., 2009; Lavado et al., 2010). They are differentially activated through complex intracellular signaling pathways triggered by growth factors, neurotrophins, cytokines and hormones under physiological conditions and in response to experience and enriched enviroment, as well as following brain damage, neuroinflammation and loss of synaptic homeostasis. Among the signal transduction vehicles, the Wnt/β-catenin pathway, which is known to regulate proliferation and differentiation of NPSCs in the adult brain, is involved in the increased neurogenesis following ischemia or traumatic brain injury (Shruster et al., 2012; Spaccapelo et al., 2013; Lindvall and Kokaia, 2015). On the other hand, neurotrophins are generally recognized as pivotal molecules in brain development and function. They are known to regulate neuronal fate and differentiation, and may a hold therapeutic potential in brain regeneration (Chao 2003; Alberghina and Colangelo, 2006).

Neuronal differentiation further requires extensive remodeling of cellular structures, including cytoskeleton and organelles (Gallo, 2011). Cytoskeletal rearrangement requires reorganization of filamentous proteins (actin, intermediate filaments, and microtubules) and is essential for cell morphology remodeling, growth cone motility, axonal growth, neurite branching and synapse formation in response to a complex cross-talk between intracellular and extracellular environment. The latter includes neurotrophins and the extracellular matrix. In the extracellular matrix of the central nervous system, matrix metalloproteinases, which participate in many neurogenesis-associated processes, regulate the levels of neurotrophins, such as nerve growth factor (NGF) and brain-derived neurotrophic factor and are regulated by NGF (Cirillo et al. 2016; De Luca et al., 2016). NGF regulates various stages of neuronal precursor maturation in the subventricular zone. Its neutralization in AD11 anti-NGF transgenic mice causes a significant reduction in NPSCs (Scardigli et al., 2014). It is remarkable that the decrease of neurogenesis in the aging brain correlates with the age-dependent decrease of NGF and other growth and hormonal factors (Colangelo et al., 1998).

## Multiple Molecular Events in NGF-Induced Neuronal Differentiation

NGF activates the tyrosine kinase TrkA and p75 receptors. In addition to the canonical NGF-TrkA-PI3K-Akt signaling axis, essential for axonal growth and neuronal survival (Chao 2003; Alberghina and Colangelo, 2006), NGF induces cell differentiation through: i) G protein induced microtubule rearrangement, ii) release of cyclic adenosine monophosphate (AMP), and iii) expression of shootin-1, a potential mediator of axon formation and neuron polarization (Ng et al., 2009; Sierra-Fonseca et al., 2014; Ergin et al., 2015). Moreover, neurite outgrowth requires trafficking and accumulation of mitochondria at the growth cones of axonal branches (Spillane et al. 2013) and an increased mitochondrial membrane potential (Bianco et al., 2011; Martorana et al., 2018). NGF-induced differentiation downstream of TrkA activation is a Gibbs energy-consuming process, modulating cross-talk between signaling pathways that regulate autophagy and mitochondrial bioenergetics (Martorana et al., 2018).

Genetic reprogramming during neuronal differentiation must also meet the higher Gibbs energy demand. This is accomplished by increasing oxidative phosphorylation (Zheng et al., 2016) through an increased NADH/FADH supply to the respiratory chain, perhaps triggered by $Ca^{2+}$-mediated activation of mitochondrial dehydrogenases (De Bernardi et al., 1996; Griffiths and Rutter, 2009;. Martorana et al., 2018).

This intense redox-push energetics produces reactive oxygen species (ROS) and correlates with an increased activity of NADPH oxidase 1 (NOX1) and NOX2 activity *via* the TrkA-Rac1 pathway, which is essential for axonal growth (Suzukawa et al., 2000; Vieira et al., 2011; Olguín-Albuerne and Morán, 2015). Enhanced NOX-derived ROS at the level of growth cones regulates F-actin organization and filopodial dynamics during neurite outgrowth of Aplysia neurons and cerebellar granule neurons (Munnamalai et al., 2014). ROS increases immediately before filopodia formation, peaks during differentiation and drops to the basal value at the end of the process. ROS depletion by N-acetylcysteine, as well as genetic or pharmacological inhibition of NOX, produces shorter neurites [Munnamalai et al., 2014; and references in Martorana et al. (2018)].

Increased Gibbs energy consumption is also evident after NGF supply to PC12 cells, a cell line commonly used to study NGF signaling because of its embryonic origin from the neural crest. NGF-induced differentiation results in altered ATP and NADPH contents, higher respiration, increased glucose metabolism, higher glucose transport rates, higher activities of hexokinase and of the pentose phosphate pathway, which is involved in the production of fatty acids and neurotransmitters required for the growth of neurites (Waki et al., et al., 2001; Martorana et al., 2018 and references therein). In our model of NGF-induced differentiation, the required energy balance is achieved by an early induction of AMP-activated protein kinase (AMPK), as well as by autophagy processes. Increased phosphorylation of both AMPK (P-AMPK) and $Ca^{2+}$/calmodulin-dependent protein kinase (P-CaMK) during NGF differentiation acts as early sensors of metabolic stress in response to $Ca^{2+}$ signaling and a higher AMP:ATP ratio in a ROS-dependent manner (Martorana et al., 2018). Energy and

protein turnover during the differentiation process are related to the recycling of cytosolic components by autophagy, including mitophagy, in response to the cellular redox status (Martorana et al., 2018).

Brain has one of the highest specific demands of Gibbs energy per unit mass of the human body and thereto relies on oxidative phosphorylation for ADP rephosphorylation. Mitochondria are crucial also for Gibbs energy supply at the growth cones and synaptic terminals. This in itself comes with a problem of spatial reorganization. Newly synthesized mitochondria, which also depend on the nuclear genome in their genesis, need to reach the active growing regions of the neuron that can be very far away from the cell body. They do this by moving through the developing neurons and by turning into smaller mitochondria in a fission-fusion cycle that is under the control of the Drp-1 protein. Mitochondrial fusion, regulated by multiple factors among which Mitofusin 2 (Mfn2), contributes to the maintenance of the mitochondrial network. When damaged or flawed, mitochondria are fragmented and eliminated by a mitophagy process (Westermann, 2010; Ashrafi and Schwarz, 2013; Martorana et al., 2018).

Much damage comes with the essential role that mitochondria play, *i.e.*, the fast re-phosphorylation of ADP that is generated by neurons as they maintain the electric potential across their plasma membrane or as they restore it after lateral neural transmission or synaptic excitation. ATP hydrolysis is also required for the regeneration of neurotransmitters and this all competes with the ATP required for cell growth and differentiation. That role requires molecules of highly negative redox potential in and around Complexes I and II of the mitochondrial electron transfer chain to be in the vicinity of the molecular oxygen that is required by complex IV. When the network is well tuned, NADH provision, oxygen consumption and oxygen diffusion balance such that complex I is not too reduced and oxygen tensions are low. The challenges met by the redifferentiating neuron would include sudden transient damage to the plasma membrane with consequent depolarization and requirement of ATP resynthesis. Precisely, the transient nature of this would cause phases of coexistence of highly reduced Complex I and high oxygen tensions, which would then lead to increased generation of ROS. This ROS is removed by glutathione dependent metabolism, but before then it may cause a mitochondrial permeability transition and release of cytochrome c. In the one but worst case this would lead to apoptosis of the entire differentiating neuron with consequent risk of local inflammation. In a better case, the affected mitochondria would commit suicide through what has been named 'mitoptosis' so as to refer to its cell-protective action (Brady et al., 2006). This mitoptosis may also serve differentiation or regeneration. It may select for the better individuals in the mitochondrial population at moments when the mitochondrial network has dissolved into a population of isolated mitochondria; indeed such dissolution of the network appears to be associated with cell stress. Our working hypothesis is that moderate mitoptosis inclusive of mitochondrial turnover is required for neurons to remain healthy, as well as for brain development and neurogenesis. In this sense the term "autophagy" may not be appropriate: in neurogenesis, some of it is regeneration and increase of best mitochondrial function rather than the eating away of cell function. Indeed, and otherwise paradoxically, interference with the autophagic machinery involving Atg-related proteins, prevents brain development and NGF-mediated differentiation (Martorana et al., 2018, and references therein). Deficiency of ambra1 (Activating Molecule in Beclin1-regulated Autophagy) causes neural tube defects (Yazdankhah et al. 2014), further linking mechanisms of NGF differentiation with Ambra1-mediated mitoptosis during neurogenesis.

In conclusion, NGF-dependent differentiation involves a plethora of biochemical modifications that affect energy transduction and promote mitochondrial function and remodeling, with the mediation of a number of processes that relate to both mitochondrial and cellular death, *i.e.*, mitoptosis and apoptosis.

## Where is the Rub?

This mini-review is meant as a game changer for research in neuroregeneration, but why does this game need changing? At present the game is that the research field detects ever more key factors involved in ever more facets of neurobiology. To deal with this, we attempt to identify the key factor for each process. What the 'keyness' is, is ill defined however.

**Figure 1** sketches the biochemical and molecular processes occurring during NGF-induced differentiation. It is meant to reflect the consensus of the field and is thereby at the same time paradoxical: rather than displaying "the" single gene that at any one point fully determines neuroregeneration, it entertains entire subnetworks as determinants. Their amplitude and perhaps importance varies with time. Therefore, for those searching for the key gene, the scheme has a disenchanting message: there is none.

It has been a while since the Ansatz of Kacser and Burns (1973), and Heinrich and Rapoport (1974), that important processes in Biology are controlled by multiple factors at the same time, was validated for mitochondrial oxidative phosphorylation (Groen et al., 1982), parasite (Bakker et al., 1999) and host metabolism (Haanstra et al., 2017), gene expression (Snoep et al., 2002) and signal transduction (Hornberg et al., 2006). In addition, various aspects of signal transduction, such as the onset, amplitude, decay time and area under the curve of phosphorylation of ERK, tend to be controlled by different factors at different times (Hornberg et al., 2005). Apparently, "keyness" does exist but it is subtle in the extensive networks of biology: it depends on time, a function aspect, and is shared between a number of molecules at the same time. Indeed, this may be the rub also here: Neurobiology is inherently multifactorial too and we have to find a way to deal with this and the many simultaneous 'key factors', *i.e.*, with their networks (Kolodkin et al., 2012).

## Our Perspective: Deep Biology

Human ratio is not fit for dealing with multiple nonlinearly interwoven processes. Should we therefore give up? How could we understand thousands of mechanisms revolving at the same time? How could we achieve such 'deep biology'? The perspective we here offer is that we can now move into deep biology by getting a little help from four friends, *i.e.*, (i) from algorithms that specify the relevant properties of each molecule, as well as the connections between them in mechanistic network models,

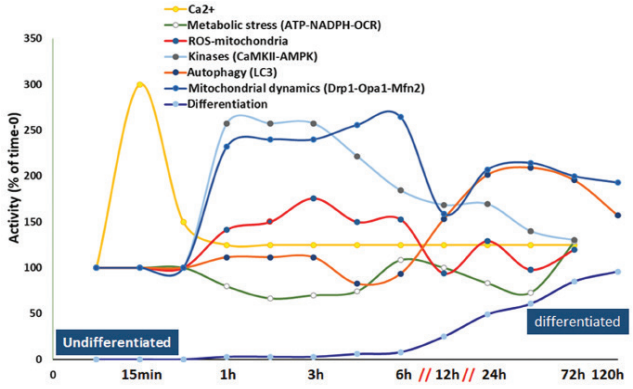


**Figure 1 Concept Map of NGF-induced differentiation.**
Schematic representation of multiple biochemical and molecular processes occurring during the first three days of NGF differentiation. The *Y* axis reports the % activity relative to the activity at time zero. The map is based on experimental data from Martorana et al. (2018). Min: Minures; h: hour(s); ROS: reactive oxygen species; OCR: oxygen consumption rate; LC3: microtubule-associated protein 1 light chain 3 (MAP1LC3).

(ii) from computers integrating this information, (iii) from improved, systems-biology informed quantitative experimentation that informs the models and removes much of the apparent irreproducibility of cell biology (Wright Muelas et al., 2018), and (iv) from equally 'deep (functional) genomics' such as deep sequencing. We can then ask the mechanistic models to what extent neuroregeneration depends on each of the subnetworks of the living cell (and organism), how one may intervene so as to improve neuroregeneration, and how such interference may be tuned to and optimized for human individuals.

Such deep biology will also enable us to deal with the data deluge deriving from the new technologies, such as single-cell RNA sequencing and proteomics: such data deluges are mind-boggling, but not computer-boggling. In the era of omics (genome, proteome, metabolome, interactome, connectome, *etc*.) mathematical modeling enables integration of the huge amounts of data into comprehensive mechanistic models of pathways and networks. Our perspective is that if there is a way ever to understand the complexity of neuroregeneration, then this deep biology should be that way. We note that the 'Deep Biology' we here propose would profit from the recent statistical approaches that identify multiple factors simultaneously from multiple genomic data sets (Pirhaji et al., 2016).

## Conclusions

Neurobiology has entered a second exciting era: as a resultant from an ongoing balance between neurogenesis and neurodegeneration, the state of the adult brain depends on a plethora of factors that are dynamic rather than static. Rather than merely retarding a slow degeneration process, we now have the prospect of intervening with a multitude of both generation and degeneration processes, in order to optimize how their balance shifts with age. Deep biology, or deeply thinking about neurobiology, as made possible by systems biology, offers a perspective that stimulates thinking in more than one way.

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## References

Alberghina L, Colangelo AM (2006) The modular systems biology approach to investigate the control of apoptosis in Alzheimer's disease neurodegeneration. BMC Neurosci 7 Suppl 1:S2.
Ashrafi G, Schwarz TL (2013) The pathways of mitophagy for quality control and clearance of mitochondria. Cell Death Differ 20:31-42.
Bakker BM, Michels PA, Opperdoes FR, Westerhoff HV (1999) What controls glycolysis in bloodstream form Trypanosoma brucei? J Biol Chem 274:14551-14559.
Bianco MR, Berbenni M, Amara F, Viggiani S, Fragni M, Galimberti V, Colombo D, Cirillo G, Papa M, Alberghina L, Colangelo AM (2011) Cross-talk between cell cycle induction and mitochondrial dysfunction during oxidative stress and nerve growth factor withdrawal in differentiated PC12 cells. J Neurosci Res 89:1302-1315.
Brady NR, Hamacher-Brady A, Westerhoff HV, Gottlieb RA (2006) A wave of reactive oxygen species (ROS)-induced ROS release in a sea of excitable mitochondria. Antioxid Redox Signal 8:1651-1665.
Chao MV (2003) Neurotrophins and their receptors: a convergence point for many signalling pathways. Nature Rev Neurosci 4:299-309.
Cirillo G, Colangelo AM, De Luca C, Savarese L, Barillari MR, Alberghina L, Papa M (2016) Modulation of matrix metalloproteinases activity in the ventral horn of the spinal cord restores neuroglial synaptic homeostasis and neurotrophic support following peripheral nerve injury. PLoS One 11:e0152750.
Colangelo AM, Follesa P, Mocchetti I (1998) Differential induction of nerve growth factor and basic fibroblast growth factor mRNA in neonatal and aged rat brain. Brain Res Mol Brain Res 53:218-225.
De Bernardi MA, Rabins SJ, Colangelo AM, Brooker G, Mocchetti I (1996) TrkA mediates the nerve growth factor-induced intracellular calcium accumulation. J Biol Chem 271:6092-6098.
De Luca C, Savarese L, Colangelo AM, Bianco MR, Cirillo G, Alberghina L, Papa M (2016) Astrocytes and microglia-mediated immune response in maladaptive plasticity is differently modulated by NGF in the ventral horn of the spinal cord following peripheral nerve injury. Cell Mol Neurobiol 36:37-46.
Doetsch F, Petreanu L, Caille I, Garcia-Verdugo JM, Alvarez-Buylla A (2002) EGF converts transit-amplifying neurogenic precursors in the adult brain into multipotent stem cells. Neuron 36:1021-1034.
Dokter M, von Bohlen und Halbach O (2012) Neurogenesis within the adult hippocampus under physiological conditions and in depression. Neural Regen Res 7:552-559.
Ergin V, Erdogan M, Menevse A (2015) Regulation of Shootin1 gene expression involves NGF-induced alternative splicing during neuronal differentiation of PC12 cells. Sci Rep 5:17931.
Eriksson PS, Perfilieva E, Björk-Eriksson T, Alborn AM, Nordborg C, Peterson DA, Gage FH (1998) Neurogenesis in the adult human hippocampus. Nat Med 4:1313-1317.
Faure A, Verret L, Bozon B, El Tannir El Tayara N, Ly M, Kober F, Dhenain M, Rampon C, Delatour B (2011) Impaired neurogenesis, neuronal loss, and brain functional deficits in the APPxPS1-Ki mouse model of Alzheimer's disease. Neurobiol Aging 32:407-418.

Gage FH (2000) Mammalian neural stem cells. Science 287:1433-1438.
Gallo G (2011) The cytoskeletal and signaling mechanisms of axon collateral branching. Dev Neurobiol 71:201-220.
Gao Z, Ure K, Ables JL, Lagace DC, Nave KA, Goebbels S, Eisch AJ, Hsieh J (2009) Neurod1 is essential for the survival and maturation of adult-born neurons. Nat Neurosci 12:1090-1092.
Griffiths EJ, Rutter GA (2009) Mitochondrial calcium as a key regulator of mitochondrial ATP production in mammalian cells. Biochim Biophys Acta 1787:1324-1333.
Groen AK, Wanders RJ, Westerhoff HV, Van der Meer R, Tager JM (1982) Quantification of the contribution of various steps to the control of mitochondrial respiration. J Biol Chem 257:2754 - 2757.
Haanstra JR, Gerding A, Dolga AM, Sorgdrager FJH, Buist-Homan M, du Toit F, Faber KN, Holzhütter HG, Szöör B, Matthews KR, Snoep JL, Westerhoff HV, Bakker BM (2017) Targeting pathogen metabolism without collateral damage to the host. Sci Rep 7:40406.
Heinrich R, Rapoport TA (1974) A linear steady-state treatment of enzymatic chains. General properties, control and effector strength. Eur J Biochem 42:89-95.
Höglinger GU, Rizk P, Muriel MP, Duyckaerts C, Oertel WH, Caille I, Hirsch EC (2004) Dopamine depletion impairs precursor cell proliferation in Parkinson disease. Nat Neurosci 7:726-735.
Hornberg JJ, Bruggeman FJ, Binder B, Geest CR, de Vaate AJ, Lankelma J, Heinrich R, Westerhoff HV (2005) Principles behind the multifarious control of signal transduction. ERK phosphorylation and kinase/phosphatase control. FEBS J 272:244-58.
Hornberg JJ, Bruggeman FJ, Westerhoff HV, Lankelma J (2006) Cancer: a systems biology disease. Biosystems 83:81-90.
Ihunwo AO, Tembo LH, Dzamalala C (2016) The dynamics of adult neurogenesis in human hippocampus. Neural Regen Res 11:1869-1883.
Kacser H, Burns JA (1973) The control of flux. Symp Soc Exp Biol 27:65-104.
Kempermann G, Kuhn HG, Gage FH (1997) More hippocampal neurons in adult mice living in an enriched environment. Nature 386:493-495.
Knoth R, Singec I, Ditter M, Pantazis G, Capetian P, Meyer RP, Horvat V, Volk B, Kempermann G (2010) Murine features of neurogenesis in the human hippocampus across the lifespan from 0 to 100 years. PLoS One 5:e8809.
Kolodkin A, Simeonidis E, Balling R, Westerhoff HV (2012) Understanding complexity in neurodegenerative diseases: in silico reconstruction of emergence. Front Physiol 3:291.
Kornack DR, Rakic P (1999) Continuation of neurogenesis in the hippocampus of the adult macaque monkey. Proc Natl Acad Sci U S A 96:5768-5773.
Kornack DR, Rakic P (2001) The generation, migration, and differentiation of olfactory neurons in the adult primate brain. Proc Natl Acad Sci U S A 98:4752-4757.
Kuhn HG, Dickinson-Anson H, Gage FH (1996) Neurogenesis in the dentate gyrus of the adult rat: age-related decrease of neuronal progenitor proliferation. J Neurosci 16:2027-2033.
Lavado A, Lagutin OV, Chow LM, Baker SJ, Oliver G (2010) Prox1 is required for granule cell maturation and intermediate progenitor maintenance during brain neurogenesis. PLoS Biol 8:e1000460.
Lindvall O, Kokaia Z (2015) Neurogenesis following stroke affecting the adult brain. Cold Spring Harb Perspect Biol 7:a019034.
Mahar I, Bambico FR, Mechawar N, Nobrega JN (2014) Stress, serotonin, and hippocampal neurogenesis in relation to depression and antidepressant effects. Neurosci Biobehav Rev 38:173-192.
Martorana F, Gaglio D, Bianco MR, Aprea F, Virtuoso A, Bonanomi M, Alberghina L, Papa M, Colangelo AM (2018) Differentiation by nerve growth factor (NGF) Involves mechanisms of crosstalk between energy homeostasis and mitochondrial remodeling. Cell Death Dis 9:391.
Ming GL, Song H (2011) Adult neurogenesis in the mammalian brain: significant answers and significant questions. Neuron 70:687-702.
Munnamalai V, Weaver CJ, Weisheit CE, Venkatraman P, Agim ZS, Quinn MT, Suter DM (2014) Bidirectional interactions between NOX2-type NADPH oxidase and the F-actin cytoskeleton in neuronal growth cones. J Neurochem 130:526-540.
Ng YP, Wu Z, Wise H, Tsim KW, Wong YH, Ip NY (2009) Differential and synergistic effect of nerve growth factor and cAMP on the regulation of early response genes during neuronal differentiation. Neurosignals 17:111-120.
Olguín-Albuerne M, Morán J (2015) ROS produced by NOX2 control in vitro development of cerebellar granule neurons development. ASN Neuro 7:1759091415578712.
Paik JH, Ding Z, Narurkar R, Ramkissoon S, Muller F, Kamoun WS, Chae SS, Zheng H, Ying H, Mahoney J, Hiller D, Jiang S, Protopopov A, Wong WH, Chin L, Ligon KL, DePinho RA (2009) FoxOs cooperatively regulate diverse pathways governing neural stem cell homeostasis. Cell Stem Cell 5:540-553.
Pirhaji L, Milani P, Leidl M, Curran T, Avila-Pacheco J, Clish CB, White FM, Saghatelian A, Fraenkel E (2016) Revealing disease-associated pathways by network integration of untargeted metabolomics. Nat Methods 13:770-776.
Scardigli R, Capelli P, Vignone D, Brandi R, Ceci M, La Regina F, Piras E, Cintoli S, Berardi N, Capsoni S, Cattaneo A (2014) Neutralization of nerve growth factor impairs proliferation and differentiation of adult neural progenitors in the subventricular zone. Stem Cells 32:2516-2528.
Shan X, Chi L, Bishop M, Luo C, Lien L, Zhang Z, Liu R (2006) Enhanced de novo neurogenesis and dopaminergic neurogenesis in the substantia nigra of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced Parkinson's disease-like mice. Stem Cells 24:1280-1287.
Shruster A, Ben-Zur T, Melamed E, Offen D (2012) Wnt signaling enhances neurogenesis and improves neurological function after focal ischemic injury. PLoS One 7:e40843.
Sierra-Fonseca JA, Najera O, Martinez-Jurado J, Walker EM, Varela-Ramirez A, Khan AM, Miranda M, Lamango NS, Roychowdhury S (2014) Nerve growth factor induces neurite outgrowth of PC12 cells by promoting Gβγ-microtubule interaction. BMC Neurosci 15:132.
Snoep JL, van der Weijden CC, Andersen HW, Westerhoff HV, Jensen PR (2002) DNA supercoiling in Escherichia coli in under tight and subtle homeostatic control, involving gene-expression and metabolic regulation of both toposiomerase 1 and DNA gyrase. Eur J Biochem 269:1662-1669.
Sorrells SF, Paredes MF, Cebrian-Silla A, Sandoval K, Qi D, Kelley KW, James D, Mayer S, Chang J, Auguste KI, Chang EF, Gutierrez AJ, Kriegstein AR, Mathern GW, Oldham MC, Huang EJ, Garcia-Verdugo JM, Yang Z, Alvarez-Buylla A (2018) Human hippocampal neurogenesis drops sharply in children to undetectable levels in adults. Nature 555:377-381.
Spaccapelo L, Galantucci M, Neri L, Contri M, Pizzala R, D'Amico R, Ottani A, Sandrini M, Zaffe D, Giuliani D, Guarini S (2013) Up-regulation of the canonical Wnt-3A and Sonic hedgehog signaling underlies melanocortin-induced neurogenesis after cerebral ischemia. Eur J Pharmacol 707:78-86.
Spillane M, Ketschek A, Merianda TT, Twiss JL, Gallo G (2013) Mitochondria Coordinate Sites of Axon Branching through Localized Intra-Axonal Protein Synthesis. Cell Rep 5:1564-1575.
Suh H, Consiglio A, Ray J, Sawai T, D'Amour KA and Gage FH (2007) In vivo fate analysis reveals the multipotent and self-renewal capacities of Sox2+ neural stem cells in the adult hippocampus. Cell Stem Cell 1: 515-528.
Suzukawa K, Miura K, Mitsushita J, Resau J, Hirose K, Crystal R, Kamata T (2000) Nerve growth factor-induced neuronal differentiation requires generation of Rac1-regulated reactive oxygen species. J Biol Chem 275:13175-13178.
Taupin P, Gage FH (2002) Adult neurogenesis and neural stem cells of the central nervous system in mammals. J Neurosci Res 69:745-749.
van Praag H, Schinder AF, Christie BR, Toni N, Palmer TD, Gage FH (2002) Functional neurogenesis in the adult hippocampus. Nature 415:1030-1034.
Vieira HL, Alves PM, Vercelli A (2011) Modulation of neuronal stem cell differentiation by hypoxia and reactive oxygen species. Prog Neurobiol 93:444-455.
Waki A, Yano R, Yoshimoto M, Sadato N, Yonekura Y, Fujibayashi Y (2001) Dynamic changes in glucose metabolism accompanying the expression of the neural phenotype after differentiation in PC12 cells. Brain Res 894:88-94.
Westermann B (2010) Mitochondrial Fusion and Fission in Cell Life and Death. Nat Rev Mol Cell Biol 11:872-884.
Wirths O (2017) Altered neurogenesis in mouse models of Alzheimer disease. Neurogenesis 4:e1327002.
Wright Muelas M, Ortega F, Breitling R, Bendtsen C, Westerhoff HV (2018) Rational cell culture optimization enhances experimental reproducibility in cancer cells. Sci Rep 8:3029.
Yazdankhah M, Farioli-Vecchioli S, Tonchev AB, Stoykova A, Cecconi F (2014) The autophagy regulators Ambra1 and Beclin 1 are required for adult neurogenesis in the brain subventricular zone. Cell Death Dis 5:e1403.
Yoshimi K, Ren YR, Seki T, Yamada M, Ooizumi H, Onodera M, Saito Y, Murayama S, Okano H, Mizuno Y, Mochizuki H (2005) Possibility for neurogenesis in substantia nigra of parkinsonian brain. Ann Neurol 58:31-40.
Zhao M, Momma S, Delfani K, Carlen M, Cassidy RM, Johansson CB, Brismar H, Shupliakov O, Frisen J, Janson AM (2003) Evidence for neurogenesis in the adult mammalian substantia nigra. Proc Natl Acad Sci U S A 100:7925-7930.
Zhao C, Deng W, Gage FH (2008) Mechanisms and functional implications of adult neurogenesis. Cell 132:645-660.
Zheng X, Boyer L, Jin M, Mertens J, Kim Y, Ma L, Ma L, Hamm M, Gage FH, Hunter T (2016) Metabolic reprogramming during neuronal differentiation from aerobic glycolysis to neuronal oxidative phosphorylation. eLife 5:e13374.

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