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DOI

[10.4103/1673-5374.244775](https://doi.org/10.4103/1673-5374.244775)

Publication date

2019

Document Version

Final published version

Published in

Neural Regeneration Research

License

CC BY-NC-SA

[Link to publication](#)

Citation for published version (APA):

Colangelo, A. M., Cirillo, G., Alberghina, L., Papa, M., & Westerhoff, H. V. (2019). Neural plasticity and adult neurogenesis: the deep biology perspective. *Neural Regeneration Research*, 14(2), 201-205. <https://doi.org/10.4103/1673-5374.244775>

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● REVIEW

Neural plasticity and adult neurogenesis: the deep biology perspective

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Funding: This work was supported by grants from the Italian Ministry of University and Research (MIUR) (SYSBIONET-Italian ROADMAP ESFRI Infrastructures to LA, AMC and MP; IVASCOMAR-National Cluster to AMC); Netherlands Organization for Scientific Research (NWO) in the integrated program of WOTRO [W01.65.324.00/project 4] Science for Global Development; Synpol: EU-FP7 [KBBE.2012.3.4-02 #311815]; Corbel: EU-H2020 [NFRADDEV-4-2014-2015#654248]; EpiPredict: EU-H2020 MSCA-ITN-2014-ETN: Marie Skłodowska-Curie Innovative Training Networks (ITN-ETN) [#642691], and BBSRC China [BB/J020060/1] to HVW. Corbel: EU-H2020 [PID 2354] to HVW and AMC.

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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doi: 10.4103/1673-5374.244775

Received: May 18, 2018

Accepted: July 10, 2018

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-myc) 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 environment, 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 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 ambral (Activating Molecule in Beclin1-regulated Autophagy) causes neural tube defects (Yazdankhah et al. 2014), further linking mechanisms of NGF differentiation with Ambral-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,

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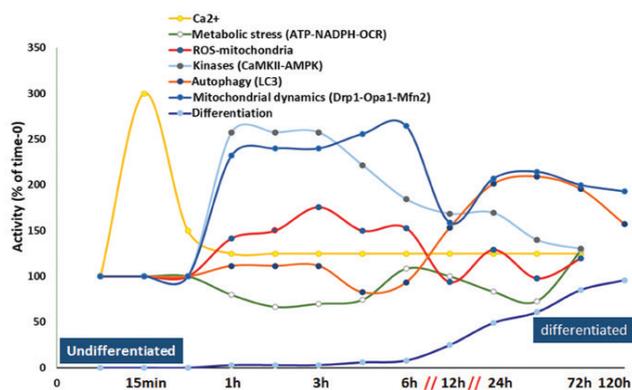


Figure 1 Concept Map of NGF-induced differentiation.

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: Minutes; 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.

Author contributions: Manuscript concept: AMC and HVW; literature search and initial manuscript preparation: GC and MP; manuscript writing: AMC and HVW; critical revision and final approval of the manuscript: AMC, LA, MP and HVW.

Conflicts of interest: The authors declare that there are no competing financial interests in relation to the work described.

Financial support: This work was supported by grants from the Italian Ministry of University and Research (MIUR) (SYSBIONET-Italian ROADMAP ESFR Infrastructures to LA, AMC and MP; IVASCOMAR-National Cluster to AMC); Netherlands Organization for Scientific Research (NWO) in the integrated program of WOTRO [W01.65.324.00/project 4] Science for Global Development; Synpol: EU-FP7 [KBBE.2012.3.4-02 #311815], Corbel: EU-H2020 [NFRADDEV-4-2014-2015#654248], Corbel: EU-H2020 [PID 2354], EpiPredict: EU-H2020 MSCA-ITN-2014-ETN: Marie Skłodowska-Curie Innovative Training Networks (ITN-ETN) [#642691], and BBSRC China [BB/J020060/1].

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Open peer reviewers: Ye Zhou, University of Florida, USA; Isabel Liste, Instituto de Salud Carlos III, Spain.

Additional file: Open peer review reports 1 and 2.

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