CellPress

Adult neurogenesis: bridging the gap between mice and humans

Sebastian Jessberger[1] and Fred H. Gage[2]

[1] Laboratory of Neural Plasticity, Brain Research Institute, University of Zurich, Winterthurerstrasse 190, 8057 Zurich, Switzerland
[2] Laboratory of Genetics, Salk Institute for Biological Studies, 10010 N. Torrey Pines Road, La Jolla, CA 92037, USA

Neural stem/progenitor cells (NSPCs) generate new neurons in the mammalian brain throughout life. Over the past two decades, substantial progress has been made in deciphering the cellular and molecular mechanisms underlying adult neurogenesis and in understanding the role played by new neurons in brain function in animal models of health and disease. By contrast, knowledge regarding the extent and relevance of neurogenesis in the adult human brain remains scant. Here we review new concepts about how new neurons shape adult brain circuits, discuss fundamental, unanswered questions about stem cell-associated neural plasticity, and illustrate how the gap between the animal-based basic research and current efforts to analyze life-long neuronal development of the human brain may be overcome by using novel experimental strategies.

From thymidine analogs to nuclear bomb testing: discovery of adult neurogenesis in humans

After the days of the pioneering neuroscience research of Ramon y Cajal, scientists assumed that the birth of neurons in the mammalian brain was restricted to embryonic and early postnatal development. Given the complexity of neural networks, it was assumed to be impossible for any newborn cells to integrate into the adult brain in a meaningful way; if they were to do so, they would destabilize existing information and acquired skills by disrupting preexisting circuits. Given this prevalent thinking, the publication in the mid-1960s of the first data suggesting that the postnatal mammalian brain continued to harbor sites of active neurogenesis was met with skepticism and largely rejected by the neuroscience community [1]. However, in the 30 years thereafter, several key findings – such as the discovery that songbirds remodel substantial parts of their vocal center every year through newborn neurons, and the isolation and cell-culture propagation of cells with stem cell properties (i.e., self-renewal and multipotency) from the adult mammalian brain – softened this resistance [2–4]. The breakthrough for the field came with the use of thymidine analogs such as bromodeoxyuridine (BrdU) to label dividing cells and their progeny, allowing the combined use of antibodies detecting BrdU-labeled nuclei with neuronal markers such as NeuN (Fox3) to unambiguously identify adult-born cells within the neuronal lineage [5]. Thus, it was not until the late 1990s that adult neurogenesis was broadly accepted as an integral part of adult brain plasticity, first in rodents and then in nonhuman primates; finally, the existence of human brain neural stem/progenitor cells (NSPCs) that retain the capacity to generate new neurons was discovered [6,7]. However, neurogenesis in the adult mammalian brain is not widespread; rather, it is restricted to distinct areas, with the main sites of postnatal neurogenesis in rodents being the hippocampal dentate gyrus (DG) and the subventricular zone (SVZ) lining the lateral ventricles, with newborn cells migrating toward the olfactory bulb (OB) where they differentiate into olfactory neurons [8,9]. There is now clear evidence that new neurons in rodents are of pivotal importance for several behavioral tasks that depend on the DG and OB [9–11]. Furthermore, failing or altered neurogenesis has been characterized in numerous rodent models of neuropsychiatric disease, such as major depression and epilepsy [9]. However, recent data revealed significant differences between the brains of laboratory rodents and humans with regard to the extent and magnitude of neurogenesis: whereas neurogenesis is substantial in the human DG, it may be absent in the human SVZ/OB [12,13]. However, the human brain also appears to retain its neurogenic potential outside the hippocampal formation, because new striatal interneurons that become depleted in disease states, such as Huntington's disease (HD), are generated throughout life, most likely by local astrocytic cells [14,15]. Nevertheless, there is a gap between current knowledge regarding the regulation, function, and molecular mechanisms that govern the neurogenic process in the rodent brain and the human brain. Here we discuss current key questions and illustrate novel approaches striving to extend the field's focus on laboratory rodents to more clinically relevant studies by characterizing the role of adult neurogenesis in human health and disease.

Analyzing neurogenesis in rodents and humans

Measuring the extent of neurogenesis in rodents is largely based on histological techniques using thymidine analogs, transgenic marker expression in NSPCs and immature neurons, transgenesis-based lineage tracing, and retroviral vectors that selectively label dividing cells and their progeny [16]. Using these approaches, the developmental

Corresponding authors: Jessberger, S. (jessberger@hifo.uzh.ch); Gage, F.H. (gage@salk.edu).
Keywords: neurogenesis; neural stem cell; hippocampus; cognition; iPSC; hESC; disease modeling.

0962-8924/
© 2014 Elsevier Ltd. All rights reserved. http://dx.doi.org/10.1016/j.tcb.2014.07.003

CrossMark

steps that take the dividing NSPC toward the integrating neuron were extensively characterized, showing that in the DG glutamatergic granule cells are generated whereas in the SVZ a set of heterogeneous NSPCs generates diverse subtypes of olfactory neuron that integrate into the OB after migration through the rostral migrator stream (RMS) [17–19]. In addition, numerous studies revealed that neurogenesis is a highly dynamic process, influenced by positive and negative regulators such as physical exercise and environmental enrichment but also stress and age [9,20,21]. The first evidence that neurogenesis occurs within the human hippocampus was based on analyses of tissue obtained from deceased cancer patients that had received BrdU injections before tumor-removing surgery and using markers such as doublecortin that are transiently expressed in immature neurons [6,22]. However, similar studies conducted in the SVZ/OB led to controversial conclusions, with some groups reporting neurogenesis whereas others found no evidence for sustained neurogenesis in the human OB [23,24].

A novel approach was developed by the Frisen group, who introduced the use of carbon dating (based on elevated ^{14}C levels following terrestrial nuclear bomb testing) to birth date neurons and glial cells in human tissue samples [25]. Strikingly, this innovative strategy confirmed the existence of substantial amounts of neurogenesis in the human DG whereas no evidence of ongoing neurogenesis was detected in the human OB [12,13]. However, it appears that NSPCs in the human SVZ retain their neurogenic potential by generating a subset of striatal interneurons, a neurogenic route that is absent in the rodent brain [15]. The use of carbon dating to birth date neural cells marks a major advance for the field and is expected to substantially increase our knowledge regarding the turnover of neurons (and glial cells) in the human brain (Figure 1). However, this technique has its limitations, given the highly specialized and expensive infrastructure required to perform this type of birth-dating analysis (e.g., accelerators) and the fact that ^{14}C levels in the atmosphere and biomass have declined substantially over past decades, resulting in a natural date of expiration for this technique [25]. An alternative approach to measure levels of neurogenesis in humans may be the use of noninvasive imaging strategies based on magnetic resonance imaging (MRI) and positron emission tomography (PET). Several studies have described associations between MRI-measured hippocampal blood volume and specific lipid peaks, as measured by magnetic resonance spectroscopy, with levels of neurogenesis [26–28]. However, the specificity and sensitivity of these approaches remain controversial. Nonetheless, noninvasive imaging strategies raise the possibility of performing longitudinal studies of individuals (for example, before and after manipulations that may affect levels of neurogenesis such as physical activity) and of testing the effects of potential proneurogenic treatments in the context of neuropsychiatric disease. Undoubtedly, the ^{14}C-based data confirming the relevance of neurogenesis in the human brain will spur additional efforts to validate existing imaging approaches and to develop novel tools required to measure levels of neurogenesis noninvasively in the human brain.

Mechanisms regulating NSPC activity, neuronal differentiation, and integration

Besides confirming the existence of neurogenesis in the adult mammalian brain, substantial progress has been made in elucidating the mechanisms regulating NSPC activity and subsequent neuronal differentiation and integration (Box 1). Key mechanisms include transcriptional programs mediated through, for example, SOX2, NeuroD1, PAX6, GSX2, and Prox1, as well as epigenetic mechanisms acting through, for example, histone modifications (e.g., MeCp2 and MDB1), in addition to noncoding RNAs (e.g., miR-124) [29–31]. Furthermore, niche-derived morphogens, neurotransmitters, growth factors, and cytokines are important in controlling NSPC activity and neuronal differentiation [examples include gamma aminobutyric acid (GABA), glutamate, brain-derived neurotrophic factor (BDNF), epidermal growth factor (EGF), fibroblast growth factor (FGF)-2, Wnt ligands, Shh, bone morphogenetic protein (BMP), interleukin (IL)-6, and tumor necrosis factor alpha (TNFα)] [9]. Furthermore, there is now compelling evidence showing how network activity directly affects the neurogenic process in the DG and SVZ [32–35]; however, these findings are exclusively based on rodent data. How can this knowledge be transferred or tested for its relevance to human neural development and how can we study the mechanisms of neurogenesis using human tissue?

The use of human pluripotent embryonic stem cells (hESCs) has revolutionized our understanding of the molecular mechanisms underlying fate-choice decisions and the differentiation of human neural cells (Figure 1). It is now possible to study in the culture dish which genes/pathways are involved in the developmental steps from multipotent NSPCs toward region-specific neuronal differentiation [36]. Moreover, the use of patient-derived induced pluripotent stem cells (iPSCs) allows the study of mechanisms of stem cell activity and neuronal differentiation within defined patient populations, thus allowing testing of the relationships between clinical, genetic, and molecular regulators directly within human tissue [37]. Currently, substantial efforts are underway to develop techniques and culturing methods that yield neuronal subtypes generated in the adult brain and approaches that will allow us to study complex structures such as the whole hippocampal circuitry in the dish [36,38]. One spectacular example of how we may study human development is the recent finding of how to generate cerebral organoids derived from human cells [39]. Once we are able to reconstruct whole circuitries such as the hippocampus (or parts of it) with human-derived cells in the dish, we will be able to study how NSPC-derived human cells may integrate into these preexisting circuitries. However, developing true models that resemble the structural organization of human neurogenic regions will remain a major challenge in the near future [40]. Complementing these cell culture-based strategies will be the approach to transplant human-derived cells (genome-edited ESC derived or iPSC derived) into the developing or adult rodent brain. This will allow the study of the behavior and functionality of human cells (healthy and diseased) within neurogenic niches. These experiments will need close ethical monitoring and may be technically challenging; however, this approach holds

Download English Version:

https://daneshyari.com/en/article/2204406

Download Persian Version:

https://daneshyari.com/article/2204406

Daneshyari.com