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EDITORIAL
Perspectives on adult neurogenesis

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New neurons are generated throughout life. This discovery has challenged firmly held concepts about the structural plasticity and regenerative capacity of the mammalian brain. In this special issue of the EJN, leaders in the field summarize and review recent advances aiming to understand the molecular mechanisms underlying adult neurogenesis and the impact of new neurons on brain function in health and disease. Below we discuss pivotal yet unsolved aspects of adult neurogenesis as well as potential future directions in the field.

Diversity of neural stem cells in the adult brain

New neurons are born throughout life but the generation of substantial amounts of new neurons is restricted, at least under physiological conditions, to two neurogenic regions: the subventricular zone (SVZ) lining the lateral ventricles and the subgranular zone of the dentate gyrus (DG) in the hippocampal formation (Gage, 2000). Although the SVZ and DG both contain neural stem cells (NSCs), the differences between the NSCs of the SVZ and DG remain poorly understood. Clearly, NSCs in the SVZ and DG produce distinct progenies. In the SVZ they give rise to cells that migrate to the olfactory bulb and differentiate into distinct types of olfactory neurons (with the majority being GABAergic or dopaminergic neurons and only a few glutamatergic cells), whereas in the DG, newborn neurons do not migrate long distances and differentiate into one neuronal subtype, excitatory glutamatergic granule neurons (reviewed in this issue by Weinandy *et al.*; Young *et al.*; Nissant & Pallotto; Merz *et al.*). It remains unclear whether this fate divergence is intrinsically predetermined or is due to external cues. Gene expression and protein profiles of NSCs isolated from distinct subregions within the neurogenic areas would indicate how similar NSCs are within (e.g. isolated from dorsal and ventral SVZ) and between neurogenic regions (e.g. comparing SVZ and DG). Such profiles could then be compared with the profiles of their progeny at different maturation stages. However, such an analysis will require reliable markers that are specific for different stages; the absence of such markers continues to represent one of the major limitations in the field of adult neurogenesis (see below). To address the contribution of extrinsic cues towards fate determination, transplantation experiments of NSCs from one region into another, including from non-neurogenic areas such as the spinal cord, were performed. These studies demonstrated that newborn cells adopted the fate of the region they had been grafted in, indicating a major influence of extrinsic cues on fate determination (Suhonen *et al.*, 1996). However, there is also evidence suggesting that the fate of NSC progeny is critically affected by intrinsic cues; NSCs isolated along the dorsoventral axis of the SVZ that can generate a distinct neuronal subtype retain their site-specific behavior even after heterotopic transplantation (Merkle *et al.*, 2007; reviewed in this issue by Weinandy *et al.*). This apparent difference in fate plasticity might have been caused by methodological variations between the studies; NSCs were either quickly retransplanted or cultured for a longer period *in vitro* possibly leading to growth-factor-induced reprogramming of intrinsic programs (Gabay *et al.*, 2003). Furthermore the transplanted NSCs might have already been in an advanced state of determination at the time of initial isolation and therefore simply 'continued' their already defined program. Thus, additional studies are required to analyze the instructive role of the microenvironment and the cell autonomous vs. cell non-autonomous determination of NSCs.

The neural stem cell niche

As outlined above, adult neurogenesis is restricted to the SVZ/olfactory bulb and DG. It is hypothesized that there may be a certain trade-off between structural plasticity and the stability of previously formed connections that may encode experiences and represent the structural correlate of 'memory'. Given the potential compromise between stability and plasticity, life-long neurogenesis may be, at least under normal conditions, unfavorable for all brain regions and therefore not supported (Abraham & Robins, 2005). But what are the mechanisms underlying the permissiveness of SVZ and DG to neurogenesis? Why do these regions have such a different capacity to promote the proliferation of NSCs and integration of newborn neurons compared with other brain regions? Previous data suggested that the 'stem cell niche' is of critical importance. The concept of a specialized stem cell niche has emerged in other fields of stem cell research (e.g. the germ cell niche in *Drosophila* and the niche of the hematopoietic system in bone marrow), where a well-defined population of different cells forms a microenvironment that helps to regulate the quiescence, maintenance and proliferation of stem cells (Morrison & Spradling, 2008). Therefore, it is very likely that specialized niches are also present in the neurogenic areas of the adult brain. In fact, several studies characterized the cellular components of a potential niche in the SVZ, indicating that there are close contacts between NSCs, astroglia, ependymal cells, the vasculature and the cerebrospinal fluid (Doetsch *et al.*, 1997; Palmer *et al.*, 2000; Sawamoto *et al.*, 2006; Mirzadeh *et al.*, 2008). There are also studies addressing the architecture of the niche in the DG showing similar niche components as in the SVZ (Filippov *et al.*, 2003; Seri *et al.*, 2004); however, as the DG does not have direct contact with the ventricle system, the two niches must somehow function differently.

Understanding the cellular and molecular features of the adult NSC niche is complicated by the fact that, in the adult brain, new neurons are born every day throughout life, leading to the situation where many different maturation stages exist in parallel and within close

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proximity to each other. This is in contrast to embryonic development where the generation of new neurons is a coordinated process occurring more or less at the same time (e.g. large waves of neuronal production, followed by neuronal migration and neurite extension). How is this asynchronous process in the adult brain regulated with regard to different microenvironmental cues that are required during different maturation stages? How can a newborn neuron begin neuronal differentiation and find its integration site next to a progenitor cell that needs proliferative stimuli? Are all the necessary stimuli present at the same time and are the cells just selectively sensitive according to their needs or is the apparent uncoordinated maturation more organized than it seems at a first glance (reviewed in this issue by Merz *et al.*; Mongiat & Schinder)? An even bigger challenge than identifying and describing the cells that take part in the niche formation is to understand how the niche might influence NSCs at a molecular level. To what extent is the stem cell program intrinsically regulated and how far is this program influenced or modulated by the niche? To what extent are the NSCs self-sufficient during proliferation and what is the extent of the metabolic support that they get from the niche cells? Again, there are experimental limitations to study these interactions in a clear and controlled way. One of the major problems, not only in the field of adult neurogenesis but in the stem cell field in general, is the limited possibility of studying and culturing stem cells *in vitro*. Although it is possible to expand and differentiate stem cells *in vitro*, once taken out of their *in vivo* environment, they may undergo substantial changes in their potential to self-renew and differentiate (Gabay *et al.*, 2003). Due to these limitations of conventional culturing methods, much effort has been made to improve cell culture systems and to more closely mimic the natural three-dimensional environment, providing the opportunities to control various factors that might be crucial components of the niche (Lutolf *et al.*, 2009). These technical advances may offer novel tools to dissect the complex interplay between single stem cells and their respective niches.

Stem cell quiescence

Whereas newborn neurons and proliferating progenitor cells can be labeled (or visualized) with available techniques (reviewed in this issue by Dhaliwal & Lagace; Couillard-Despres & Aigner), the quiescent stem cell pool is still not unequivocally identified. The lack of reliable markers that are uniquely expressed in 'true' NSCs still represents a problem. In the hematopoietic system, a specific expression pattern of surface markers allows for the identification and isolation of several well-characterized subpopulations of stem/progenitor cells (Schroeder, 2010), whereas the most widely used markers for stem cells in the field of adult neurogenesis, such as Glial fibrillary acidic protein (GFAP) and Sex determining region Y-box 2 (SOX2), are also, at the same time, markers for certain types of astrocytes (Seri *et al.*, 2001; Suh *et al.*, 2007). Other markers, such as Inhibitor of DNA binding proteins (Id) and Hairy and enhancer of split 5 (Hes5) (Nam & Benezra, 2009; Lugert *et al.*, 2010), seem to be dosage dependent and a distinction between high and low expression levels is needed to separate different stem cell pools. It remains uncertain whether this lack of unique markers is biologically significant, meaning that NSCs have certain astrocytic properties and thus share similar markers with other astroglial cells.

The search for a quiescent pool of stem cells in the brain is further hindered by the lack of a specific test to challenge the stem cell features of this population *in vivo*. In the hematopoietic system, a single stem cell, isolated according to its cell surface marker expression, can reconstitute the whole blood system (i.e. erythrocytes, lymphocytes, macrophages and mast cells) after irradiation, a readout that provides proof of the cell's stem cell capacity to self-renew and differentiate into the various lineages (Wilson *et al.*, 2008). Analogous with irradiation, approaches to ablate all proliferating cells in the neurogenic niches with cytostatic drugs, either by systemic administration or direct infusion into the brain, have been taken by several groups (Doetsch *et al.*, 1999; Lugert *et al.*, 2010). Although there seems to be a quiescent pool of NSCs that can at least partially reconstitute the depleted population of proliferating cells, this only tells us something about the capacity of a pool of cells and does not allow for detection at the single cell level. Furthermore, as the ablation of newborn neurons has neither any vital consequences nor easily measurable functional impairment, the degree of reconstitution can so far only be assessed by immunohistological means. Technological advances to ablate a certain pool of cells more selectively, and more sophisticated functional readouts might provide new insights in the future.

Despite the experimental limitations, many studies have addressed the signaling pathways that influence NSCs and keep them in a stem cell state. Several key molecules that regulate neurogenesis during embryonic development, such as Bone morphogenetic protein (BMP) and Notch signaling as well as growth factors such as Fibroblast growth factor (FGF), also play an important role in regulating NSC behavior in the adult brain (Palmer *et al.*, 1995; Colak *et al.*, 2008; Ables *et al.*, 2010; Lugert *et al.*, 2010; Mira *et al.*, 2010). However, the extent to which these pathways act together and integrate into a common endpoint or how redundantly they exert their function remains to be studied.

Neuronal fate determination/specification and maturation

The NSCs in the DG and SVZ generate distinct types of neurons. Despite recent studies identifying several transcription factors required for neuronal differentiation in the DG or SVZ, we are only beginning to understand the transcriptional code governing neuronal fate determination and the subsequent specification into distinct subtypes of neurons (e.g. glutamatergic granule cells in the DG; reviewed in this issue by Weinandy *et al.*). As outlined above, reliable gene and protein expression profiles of NSCs and their progeny at different maturation stages would be very helpful to address at which time-point neuronal fate determination and specification occur. With specific tools such as retroviral vectors or conditional transgenesis-based approaches, the requirement of certain genes and the plasticity of neuronal specification, e.g. the directed differentiation of NSCs into neuronal subtypes, can be tested (Hack *et al.*, 2005). These experiments will be important not only in order to understand the neuronal differentiation of adult-born neurons, but they will also allow us to gain new insights into cell-intrinsic and cell-extrinsic mechanisms that regulate neuronal differentiation and specification in general. The same is true for experiments aiming to understand how newborn neurons identify their targets and how they know where to migrate and extend their processes. The cues that guide neuronal migration and subsequent axonal and dendritic pathfinding are still largely unknown, even though a few genes involved in migration and neurite extension/pathfinding have been identified (Duan *et al.*, 2007; Jessberger *et al.*, 2008), among them cAMP response element-binding (CREB) signaling (reviewed in this issue by Merz *et al.*). In the SVZ, the mode of cell migration has begun to be characterized (Wichterle *et al.*, 1997; Conover *et al.*, 2000; Kaneko *et al.*, 2010) but, within the DG, it remains largely unclear if the processes growing from newborn neurons require a scaffold for neurite growth/pathfinding that is specifically provided by glial cells or pre-existing neurons. Further-

more, many mechanisms that have been identified during embryonic or early postnatal development and that are based on gradients of chemorepellents (e.g. repulsion of granule cell axons by Semaphorins) cannot act in a similar way on adult-born neurons as they still manage to grow processes in an *a–priori* non-permissive environment (Bagri *et al.*, 2003). Thus, the molecular mechanisms underlying neuronal differentiation and maturation still remain largely unclear. Further experiments are required to understand how neuronal lineages are specified and how newborn neurons reach their target areas.

Neuronal integration

Similar to embryonic and early postnatal development, adult-born neurons are generated in excess with only a relatively small fraction of newborn neurons eventually integrating into pre-existing neural networks (reviewed in this issue by Aasebø *et al.*; Toni & Sultan; Young *et al.*; Nissant & Pallotto). New neurons are specifically selected for integration, a process that seems to be activity-dependent (Kempermann *et al.*, 1997; Tashiro *et al.*, 2006). However, we still do not know which types of signals are necessary and sufficient to enhance the survival and integration of new neurons. Do neurons merely require a certain amount of activity for survival or is their survival dependent on input selectivity? Similarly, it remains unclear why new neurons show drastically heightened excitability compared with mature neurons. Is this a functional aspect of neurogenesis or a requirement for integration? Future experiments that selectively manipulate activity in pre-existing neuronal networks or in newborn neurons will be required to better understand the process of neuronal integration, and to address if there is, for example, a competition for synaptic partners between new and old neurons (reviewed in this issue by Toni & Sultan).

Functional significance

There is now quite some evidence, based on correlative studies but also on an increasing number of studies that aimed to selectively deplete neurogenesis in the adult brain, that newborn neurons in the DG and SVZ/olfactory bulb are functionally important for behavior (reviewed in this issue by Aasebø *et al.*; Koehl & Abrous). However, the phenotypes that have been identified are as diverse as the experimental approaches and laboratories involved in these studies (for an overview see Deng *et al.*, 2010). As to date there is no gold standard to test the functional contribution of neurogenesis, we will have to develop more sensitive tests that challenge and require the function of new neurons. In the case of the DG, it seems that pattern separation may be sensitive to the disruption of neurogenesis (Clelland *et al.*, 2009); however, even if there is a test that shows consistent phenotypes, we still have much to learn about how new neurons may be involved. Computational models may prove to be useful tools to uncover mechanisms of how new neurons could contribute to an existing network (reviewed in this issue by Aimone & Gage). Are newborn neurons important when they are immature or at later stages once they share more similar electrophysiological features with mature neurons or are they important at both stages? Do they rather act as local circuit neurons or do they generate functionally important output to area CA3? Even though there are promising data showing that new neurons can generate output onto hilar and CA3 target neurons (reviewed in this issue by Toni & Sultan; Mongiat & Schinder), detailed electrophysiological analyses of outputs generated by newborn neurons will be important for future studies that aim to understand the cellular mechanisms that mediate the function of new neurons in adult brain behavior. As already pointed out above, we will have to develop more precise tools to experimentally manipulate newborn neurons. These tools should also help us to understand the temporal relationship between neuronal birth/integration and functional contribution to behavior.

Disease relevance of adult neurogenesis

The proliferative activity and the number of neurons born and integrated are highly sensitive to environmental stimuli (reviewed in this issue by Kempermann). Further, not only physiological stimuli seem to influence NSCs as adult neurogenesis has also been associated with a number of neuropsychiatric diseases such as major depression, Alzheimer's disease, stroke and epilepsy (reviewed in this issue by Samuels & Hen; Kokaia; Winner *et al.*) as well as neurodevelopmental disorders (reviewed in this issue by Kuhn & Blomgren). However, several key questions remain unclear. Can altered neurogenesis cause disease (e.g. in major depression) and is increasing neurogenesis or restoring it to physiological levels sufficient to alleviate a disease process? To answer these questions, we will need to develop neurogenesis-specific manipulations in animal disease models (e.g. selectively depleting neurogenesis in animal models of temporal lobe epilepsy), followed by multilevel analyses (e.g. morphology, behavior and electrophysiology). Furthermore, we will need new tools to selectively enhance neurogenesis without affecting other aspects of brain plasticity/function, allowing us to determine if neurogenesis is sufficient to affect hippocampus-dependent behavior or mood, for example. Most importantly, we require many more data on neurogenesis in humans (reviewed in this issue by Curtis *et al.*), both under physiological conditions and during disease. Obviously, these analyses are complicated by the fact that labeling NSCs and new neurons cannot be easily performed in humans and that the tools currently available are rather limited. New approaches, such as non-invasive imaging (reviewed in this issue by Couillard-Despres & Aigner), may pave the way for a better understanding of neurogenesis in humans. Even though there is to date no proof for the disease relevance of adult neurogenesis, the finding that NSCs persist in the adult brain and constantly generate new neurons may represent a novel therapeutic target in a number of neuropsychiatric diseases. Furthermore, NSCs may not only be disease-relevant or a therapeutic target in the two neurogenic areas. Under certain disease conditions (such as ischemic stroke), it has been shown that new neurons are generated within normally non-neurogenic areas such as the striatum (Arvidsson *et al.*, 2002; Parent *et al.*, 2002). In addition, initial attempts to induce neuron production in neocortical areas or to reprogram glial cells into neurons have been successful (Magavi *et al.*, 2000; Heinrich *et al.*, 2010). However, to direct and orchestrate the meaningful and functionally correct integration of newborn cells outside the DG and SVZ will remain as a future challenge.

Conclusions

Today there is no doubt that new neurons are generated throughout life, representing a dramatic form of structural plasticity in the adult mammalian brain. Even though many genes and pathways involved in stem cell maintenance/proliferation and neuronal differentiation have been identified over the last 15 years, we are just beginning to understand why neurogenesis is restricted to two neurogenic areas and how and when neuronal fate choices occur. In addition, future studies will need to elucidate how new neurons contribute to adult brain function. We will also need to determine if adult neurogenesis is a disease-relevant feature of adult brain plasticity and if NSCs eventually offer a novel therapeutic approach for various neurodegenerative diseases.

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Abbreviations

DG, dentate gyrus; NSC, neural stem cell; SVZ, subventricular zone.

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