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DEVELOPMENT AT A GLANCE

Adult neurogenesis: mechanisms and functional significance

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ABSTRACT

New neurons are generated throughout life in distinct regions of the mammalian brain. This process, called adult neurogenesis, has been implicated in physiological brain function, and failing or altered neurogenesis has been associated with a number of neuropsychiatric diseases. Here, we provide an overview of the mechanisms governing the neurogenic process in the adult brain and describe how new neurons may contribute to brain function in health and disease.

KEY WORDS: Neural stem cell, Neurogenesis, Neurons, Neuropsychiatric disease

Introduction

Contrary to the long-held belief that neurogenesis tapers off with the end of early postnatal development, the mammalian brain retains the capacity to generate new neurons throughout life. Adult neural

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stem/progenitor cells (NSPCs) are responsible for the generation of new neurons and reside in two main locations in the adult brain: the subventricular zone (SVZ) lining the lateral ventricles, and the hippocampal dentate gyrus (DG) (reviewed by Gage, 2000).

Adult neurogenesis is emerging as an important player in brain homeostasis and disease. Perturbations in normal neurogenesis have been associated with a number of diseases, such as major depression and epilepsy (reviewed by Zhao et al., 2008). In the rodent brain, thousands of new neurons are generated every day, with newborn cells contributing to tissue homeostasis and brain functions that underlie certain forms of learning and memory (Deng et al., 2010).

The finding that neurogenesis persists throughout adulthood has initiated tremendous efforts to (1) characterize how new neurons differentiate and integrate into adult neural circuitries, (2) understand the implications of failing neurogenesis in neuropsychiatric disease processes, and (3) analyze whether endogenous NSPCs may be harnessed for brain repair. However, we are only just beginning to understand the cellular and molecular mechanisms that regulate the neurogenic process in the adult brain, and how this may contribute to neurological disease. Here, we provide a brief overview of the mechanisms of adult neurogenesis associated with health and disease
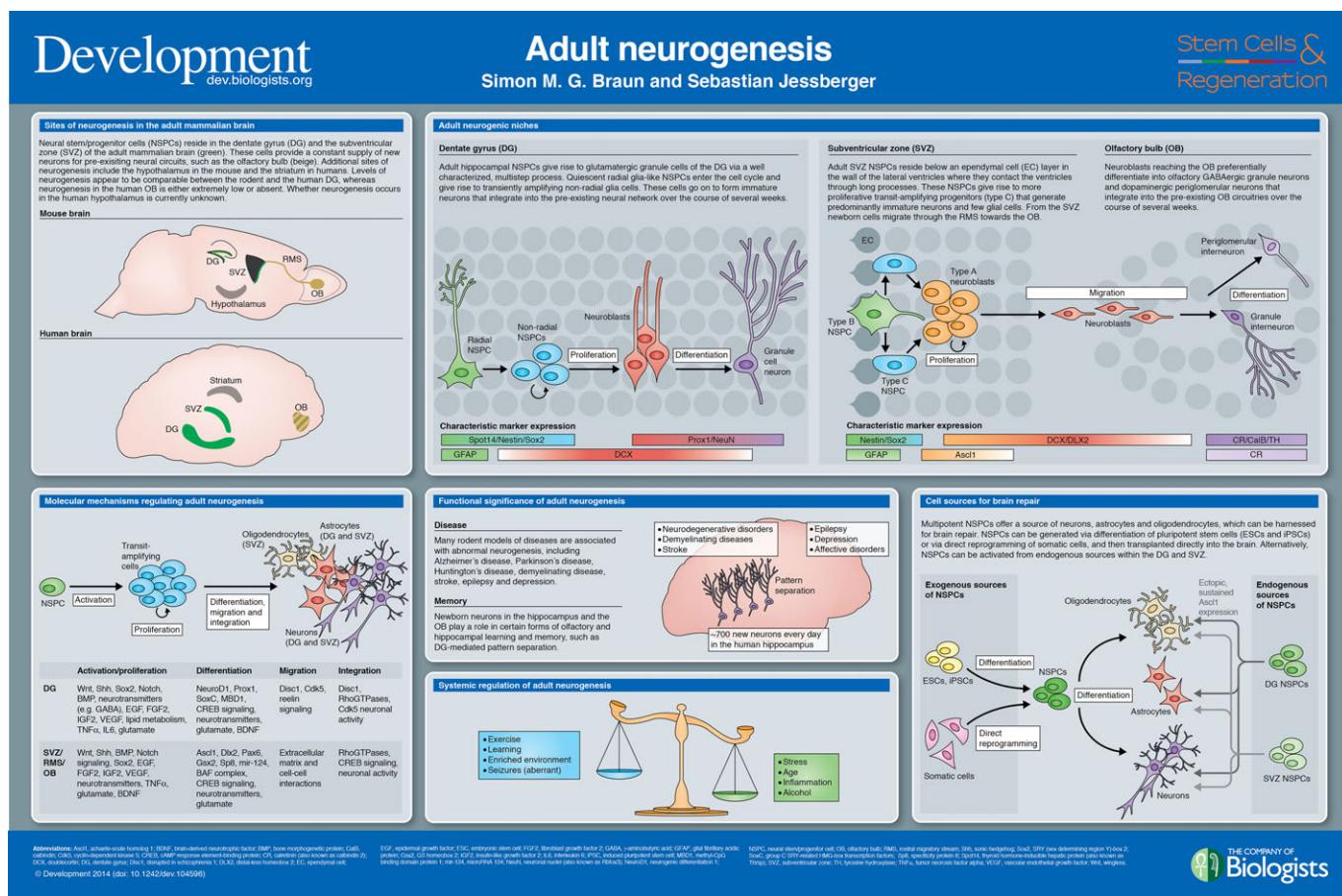
and discuss perspectives for future research and possible therapeutic applications.

NSPC niches in the adult mammalian brain

Even though neurogenic cells in the adult mammalian brain are commonly referred to as neural stem cells or NSPCs, this nomenclature asks for two cardinal features to be fulfilled: (1) self-renewal and (2) multipotency. It has been difficult to prove these properties on a single cell level *in vivo* owing to the lack of longitudinal studies observing the behavior of individual cells within their endogenous niche. However, recent evidence from Bonaguidi and colleagues (Bonaguidi et al., 2011) strongly supports the existence of stem cell properties of individual cells within the adult neurogenic niches, although the longevity of such stem cells remains controversial (Encinas et al., 2011). Therefore, throughout this manuscript we use the term NSPCs to describe neurogenic cells in the adult mammalian brain.

NSPCs reside primarily in the DG and the SVZ, where they are maintained in a largely quiescent state (Doetsch et al., 1999; Bonaguidi et al., 2011). Upon activation by niche-derived and/or intrinsic signals, they undergo proliferation, which leads to the birth of new neurons. Newborn cells then undergo differentiation predominantly into neuronal cells before they mature and integrate over the course of several weeks into the pre-existing circuitries (Zhao et al., 2008). In the DG, newborn cells differentiate into excitatory granule cells, the principal neurons of the DG. NSPCs in the SVZ generate restricted neural progenitor cells that migrate through a glial cell scaffold via the rostral migratory stream (RMS) towards the olfactory bulb (OB) (Lepousez et al., 2013). Here, neurogenesis continues as the cells differentiate into distinct types of olfactory neurons. Thus, although NSPCs mainly reside in two locations (the SVZ and the DG), the neurogenic process continues in the OB where newborn olfactory neurons mature and functionally integrate. In addition to these main sites of neurogenesis, the generation of new neurons has also been observed in the hypothalamus (Kokoeva et al., 2005; Lee et al., 2012). Whether neurogenesis occurs in neocortical areas remains controversial (Gould et al., 1999b; Bhardwaj et al., 2006; Zhao et al., 2008).

NSPCs in the SVZ and DG share certain characteristics on the cellular and molecular levels (Bracko et al., 2012). NSPCs in both areas express a set of proteins including the intermediate filament nestin and the Sry2-related transcription factor Sox2. Together with other cellular features, such as vascular endfeet, the expression profiles of largely quiescent adult NSPCs suggest that they display certain astrocytic features (Doetsch et al., 1999; Seri et al., 2001; Bracko et al., 2012). Interestingly, the niche in the SVZ appears to contain heterogeneous populations of NSPCs, most prominently at the dorsoventral axis, that display differentiation bias, i.e. preferentially generating one type of olfactory neuron over another (Merkle et al., 2007; Ihrie et al., 2011).

Adult neurogenesis: of mice and men

Our knowledge regarding neurogenesis in the adult human brain lags dramatically behind the numerous studies that characterized the neurogenic process in rodents and non-human primates. However, there is now solid evidence that new neurons are generated in the human brain in numbers comparable to those observed in rodents, at least in the hippocampal DG (Eriksson et al., 1998; Knoth et al., 2010; Spalding et al., 2013). In the human SVZ, the situation remains somewhat controversial, but current evidence suggests that neurogenesis in the SVZ/OB ceases during the early postnatal period, even though quiescent NSPCs may persist in the SVZ (Sanai et al., 2004, 2011; Curtis et al., 2007). In support of this, it has recently been found that striatal interneurons are generated throughout life in

the human striatum and that turnover of this neuronal subtype is affected in Huntington's disease (Ernst et al., 2014).

Despite these seminal data showing that neurogenesis clearly persists in distinct areas of the adult human brain, one must keep in mind that the mechanisms of neurogenesis and disease associations described herein are largely and sometimes exclusively based on animal research. To overcome this apparent gap between animal and human studies, a number of groups currently aim to develop novel methods to measure levels of neurogenesis in the human brain, for example by using non-invasive magnetic resonance imaging (Ho et al., 2013).

Lineage progression and molecular regulation of adult neurogenesis

From the largely quiescent NSPCs, also called type-1 cells (DG), B-cells (SVZ) or radial glia-like cells (DG and SVZ), to a fully integrated and functional neuron, NSPCs and their newborn progeny must pass through several developmental steps (reviewed by Kempermann et al., 2004; Merkle and Alvarez-Buylla, 2006). First, the quiescent population of NSPCs is activated to generate proliferating, non-radial transit-amplifying cells (TAPs) that enlarge the pool of neurogenic cells that are called type-2 cells (DG) and C-cells (SVZ). These cells give rise to immature neurons (named A-cells in the SVZ), which progress through neuronal differentiation and begin to branch out processes (Carleton et al., 2003; Kempermann et al., 2004). Within the DG, immature neurons migrate up into the granule cell layer and over a period of three weeks mature into newborn granule cell neurons, projecting out a large dendritic arbor into the adjacent molecular layer and axons that innervate target cells in the hilus and area 3 of the *cornu Ammonis* (Zhao et al., 2006; Toni et al., 2008). A similar maturational speed has been observed for the growth and integration of newborn olfactory neurons (Carleton et al., 2003).

Each step during this lineage progression is tightly controlled by niche-derived as well as intrinsic mechanisms, which together ensure the appropriate levels of proliferation of NSPCs, as well as the correct differentiation, migration and integration of newborn cells. Important transcriptional regulators of neurogenesis in the DG and/or SVZ include Sox2, NeuroD1, Pax6, Gsx2, Sp8, Prox1, Ascl1, TLX (also known as NR2E1; nuclear receptor subfamily 2, group E, member 1) (Zhao et al., 2008). Furthermore, epigenetic mechanisms are important to control levels of neurogenesis, for example through histone modifications recognised by MBD1, or via small non-coding RNAs such as mir-124 (Zhao et al., 2008). In addition to these intrinsic regulators, a number of niche-derived morphogens, neurotransmitters, growth factors and cytokines have been implicated in controlling NSPC activity and neuronal differentiation. These include γ-aminobutyric acid (GABA), glutamate, brain-derived neurotrophic factor (BDNF), epidermal growth factor (EGF), fibroblast growth factor 2 (FGF2), Wingless (Wnt) ligands, sonic hedgehog (Shh), bone morphogenic protein (BMP), interleukin 6 (IL6) and tumor necrosis factor alpha (TNFα), among others (Zhao et al., 2008).

In contrast to embryonic development, in which NSPC proliferation, neuronal differentiation and migration occur in sequential temporal waves, the different steps of adult neurogenesis occur in parallel with each other within the adult neurogenic niches. This is especially true of the DG, where quiescent NSPCs, committed progenitors, and immature neurons can exist as immediate neighbors, indicating a mode of neuronal differentiation and integration that must be controlled on a single-cell level. Similar to embryonic development, a surplus of neurons is generated in the adult brain and neuronal survival is subsequently regulated via selection processes that require synaptic activation of newborn cells (Tashiro et al., 2006).

Systemic regulation of adult neurogenesis

The number of neurons born in the adult brain is not static but instead is dynamically regulated by a number of extrinsic environmental cues. The most highly studied positive regulators include physical activity, environmental enrichment, and olfactory or hippocampus-dependent learning, which enhance NSPC proliferation and/or the survival of new neurons (Kempermann et al., 1997; Gould et al., 1999a; Van Praag et al., 1999a, b; Alonso et al., 2006). Reduced numbers of newborn neurons occurs with stress, certain forms of inflammation, alcohol abuse and age, among other factors (Herrera et al., 2003; Zhao et al., 2008). Different regulators can affect distinct aspects of neurogenesis, ranging from the dividing NSPCs to the integrating neuron (Lugert et al., 2010; Dranovsky et al., 2011). Additional regulators of neurogenesis in the SVZ/OB include olfactory enrichment and/or deprivation (Lepousez et al., 2013). Importantly, the regulation of neurogenesis is region specific, meaning that the same environmental factor may affect neurogenesis in one region but not another (Zhao et al., 2008).

Functional significance of adult neurogenesis

Newborn neurons contribute to olfactory- and hippocampus-dependent learning and memory (Deng et al., 2010). Increased levels of neurogenesis correlate with improved performance in hippocampus-dependent learning and memory tasks, such as the Morris water maze (Kempermann et al., 1997; van Praag et al., 1999a). More direct experimental evidence comes from studies that use transgenesis- and virus-based strategies to deplete or selectively enhance neurogenesis in the adult brain. Together these studies have identified a role for hippocampal neurogenesis in spatial and object recognition memory (Jessberger et al., 2009), fear conditioning and synaptic plasticity (Saxe et al., 2006) and pattern separation (Clelland et al., 2009; Sahay et al., 2011a; Nakashiba et al., 2012; reviewed by Sahay et al., 2011b). Pattern separation is the process of transforming similar representations or experiences into distinct and non-overlapping neural representations, and is an important function of the hippocampal DG for certain forms of learning and memory (Leutgeb et al., 2007). Currently, it is believed that a crucial period of heightened plasticity, which occurs between 3 and 6 weeks after cells are born, is essential for the contribution of new neurons to adult brain behavior (Marin-Burgin et al., 2012).

Experiments aimed at understanding the role of neurogenesis in disease processes have focused more on hippocampal neurogenesis, partially owing to the low numbers of neurons born in the human OB under physiological conditions (Kempermann, 2013). Failing or altered neurogenesis has been associated with a number of neuropsychiatric diseases, including major depression and epilepsy (Sahay and Hen, 2007; Parent and Murphy, 2008). A reduction in the number of neurons generated as well as reduced ectopic integration may contribute to hippocampus-dependent behavioral deficits, both in experimental models as well as in patients suffering from these diseases. In the context of epilepsy, seizure-induced neurons frequently migrate ectopically and show aberrant synaptic integration. Thus, aberrant neurogenesis may contribute to epileptogenic disease and may also be involved in the cognitive decline frequently observed with chronic epilepsy (Scharfman and Hen, 2007). Notably, hippocampal neurogenesis has been also linked to emotional control (Snyder et al., 2011). Thus, targeting neurogenesis for therapeutic interventions in brain diseases may not only be beneficial for cognition but may also have positive effects on stress response in patients suffering from major affective disorders (Spalding et al., 2013).

Contribution of NSPCs for brain repair

The persistence of neurogenesis throughout life may allow endogenous NSPCs to be harnessed for brain repair (reviewed by Lindvall and Kokaia, 2006). Here, the idea is to boost NSPC proliferation and/or newborn cell migration towards lesioned tissue either following acute injury, such as stroke, or during chronic neurodegeneration, for example Parkinson's disease. This may be achieved through chemokine-directed migration towards lesions, although routes of delivery and proper neuronal differentiation within lesions remain complex issues to be solved (Li et al., 2012).

Alternative sources of NSPCs include cells generated *in vivo* by directed differentiation of NSPCs into glial cells (Jessberger et al., 2008), or by reprogramming of cells, for example glial cells, into neuronal cells (Niu et al., 2013). Furthermore, the transplantation of cells with NSPC properties derived from various cellular sources, such as pluripotent cells into the lesioned brain, may hold therapeutic potential for the treatment of diseases of the central nervous system (Yang and Wernig, 2013). In addition, NSPCs may be useful to repair not only neuronal cell loss but also glial dysfunction, for example in the case of the chronic demyelinating disease multiple sclerosis (Franklin and Ffrench-Constant, 2008).

Perspectives

The finding that new neurons are generated throughout life has challenged previously held concepts of adult brain plasticity and opened novel avenues to understand and therapeutically target neuropsychiatric diseases. However, the cellular and molecular mechanisms that guide the progression from a dividing NSPC to a functional neuron need to be understood in more detail and numerous key questions remain. For example, how is NSPC activity controlled and what is the role of the niche in regulating this? What are the mechanisms that govern meaningful neuronal migration, integration and function and how can we harness these to guide newborn cells towards lesioned brain regions? In order to understand how new neurons contribute to hippocampus- and OB-dependent learning and memory, novel experimental strategies are required that allow for high spatial and temporal control over newborn cells. Such control will allow the specific, targeted manipulation of discrete variables, such as the number of neurons produced or their migration and differentiation into existing circuits. Furthermore, there is a clear need for the development of novel methods to measure neurogenic processes in the adult human brain, and to characterize the relevance and therapeutic potential of adult NSPCs for human physiology and disease.

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