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EDITORIAL

Neural stem cells: developmental mechanisms and disease modeling

Xinyu Zhao[1,2] · Darcie L. Moore[1]

Summary

The astonishing progress in the field of stem cell biology during the past 40 years has transformed both science and medicine. Neural stem cells (NSCs) are the stem cells of the nervous system. During development they give rise to the entire nervous system. In adults, a small number of NSCs remain and are mostly quiescent; however, ample evidence supports their important roles in plasticity, aging, disease and regeneration of the nervous system. Because NSCs are regulated by both intrinsic genetic and epigenetic programs and extrinsic stimuli transduced through the stem cell niche, dysregulation of NSCs due to either genetic causes or environmental impacts may lead to disease. Therefore, extensive investigations in the past decades have been devoted to understanding how NSCs are regulated. On the other hand, ever since their discovery, NSCs have been a focal point for cell-based therapeutic strategies in the brain and spinal cord. The limited number of NSCs residing in the tissue has been a limiting factor for their clinical applications. Although recent advancements in embryonic and induced pluripotent stem cells have provided novel sources for NSCs, several challenges remain. In this special issue, leaders and experts in NSCs summarize our current understanding of NSC molecular regulation and the importance of NSCs for disease modeling and translational applications.

Stem cells

The term "stem cells" first appeared in the scientific literature in 1868 by the German biologist Ernst Haeckel (Haeckel 1868). In his writings (Haeckel 1868), "stem cells" had two distinct meanings: one is the unicellular evolutionary origin of all multicellular organisms and the other is the fertilized egg giving rise to all other cell types of the body. The latter definition has evolved into the modern definition of stem cells—cells that can divide to self-renew and to differentiate into other cell types in tissues and organs (Li and Zhao 2008; Ramalho-Santos and Willenbring 2007).

The behavior and fate of stem cells are strongly influenced by their specific anatomical locations and surrounding cell types, called "the stem cell niche." The niche provides physical support to host or anchor stem cells and supplies factors to maintain and regulate them (Li and Zhao 2008). Stem cells are also regulated by intrinsic signaling cascades and transcriptional mechanisms, some of which are common among all stem cells and others that are unique to specific types. Some of the best known regulators include TGF-β, BMP, Smad, Wnt, Notch and EGF fibroblast growth factors (Jobe et al. 2012; Li and Zhao 2008). Therefore, stem cells are regulated by complex mechanisms in both temporal- and context-specific manners to maintain their unique characteristics. Understanding stem cell regulation gives us the opportunity to explore mechanisms of development, as well as disorders resulting from their dysfunction.

NSCs in development

During development, the central nervous system (CNS) is generated from a small number of neural stem cells (NSCs) lining the neural tube (Kriegstein and Alvarez-Buylla 2009). A great deal of experimental evidence has demonstrated that radial glia, the NSCs during mammalian CNS development, undergo both symmetric divisions to expand the NSC pool and asymmetric divisions to give rise to intermediate

✉ Xinyu Zhao
xinyu.zhao@wisc.edu

Darcie L. Moore
darcie.moore@wisc.edu

[1] Department of Neuroscience, Waisman Center and University of Wisconsin-Madison, Madison, WI 53705, USA

[2] Waisman Center and University of Wisconsin-Madison, Madison, WI 53705, USA

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progenitors (IPCs) and the differentiated cell types. The three major cell types in the CNS arise from NSCs in a temporally defined sequence, with neurons appearing first, followed by astrocytes and then oligodendrocytes (Okano and Temple 2009). The technical advancement of live imaging and genomic tools have allowed for the identification of human-specific NSC populations (e.g., outer radial glia, or oRG) located at the outer subventricular zone (SVZ) (Gertz et al. 2014). These oRG are essential for cortical expansion to achieve the large size of the human cortex. Single-cell genomic technologies have identified specific oRG markers that might be used for further characterization of these cells (Liu et al. 2016, Pollen et al. 2014). Investigating the regulatory mechanisms governing the self-renewal and fate specification of NSCs, especially human-specific developmental features, has significantly contributed to our understanding of human brain development and developmental diseases. In addition, this knowledge has also helped scientists refine protocols for pluripotent stem cell differentiation into specific nervous system cell types for both therapeutic goals and disease modeling.

NSCs in the adult brain

In adult brains, NSCs are reduced and become restricted to specific brain regions. In rodents, both NSCs and ongoing neurogenesis have been widely documented in the SVZ of the lateral ventricles and the subgranular zone (SGZ) of the dentate gyrus (DG) of the hippocampus (Kempermann et al. 2015). In humans, experimental evidence has supported ongoing neurogenesis in the hippocampus (Eriksson et al. 1998; Spalding et al. 2013). The confirmation of mammalian adult neurogenesis in the 1990s was one of the most exciting moments in science in the 21st century. Not only did it overthrow the prevailing dogma suggesting no neurons were made in the adult brain but it also hinted that these adult NSCs could be utilized for neural repair in disease and following injury. Forty years later, we have learned a lot about NSCs. In the adult rodent SVZ, neurogenesis has been shown to be important for olfactory function and olfactory learning (Alonso et al. 2006). During development, a subset of slowly-dividing NSCs are set aside to be the NSCs of the SVZ in the postnatal and adult brain (Fuentealba et al. 2015; Furutachi et al. 2015). The majority of neurogenic radial glia, however, become astrocytes and ependymal cells at the end of embryonic neurogenesis (Noctor et al. 2004). A subset of these astrocytes persist as NSCs in specialized niches in the adult brain and continuously generate neurons that functionally integrate into restricted brain regions (Doetsch 2003). In the hippocampus, radial glia-like stem cells of the SGZ make newborn neurons throughout life (Goritz and Frisen 2012). These newborn neurons integrate into the circuity of the DG, contributing to behaviors such as pattern separation (Aimone et al. 2011) and spatial learning (Dupret et al. 2008), as well as hippocampus-associated learning, memory and executive functions (Kempermann et al. 2015).

Significant effort has been devoted into understanding the regulation of adult neurogenesis. As a result, we now know that many extrinsic stimuli and intrinsic mechanisms can affect this process. Mouse genetic studies have clearly demonstrated the important role of transcriptional regulation of NSCs through intrinsic genetic mechanisms (Hsieh and Zhao 2016). Some examples include SOXC family proteins (Kavyanifar et al. 2018, in this issue), Bmi-1 (Molofsky et al. 2003), Sox2 (Ferri et al. 2004; Graham et al. 1999), PTEN (Bonaguidi et al. 2011) and Notch (Zhang et al. 2018, in this issue). In addition, epigenetic regulation by DNA methylation pathways (e.g., Mbd1, Mecp2, Dnmt, Tet) (Noguchi et al. 2015; Smrt et al. 2007; Tsujimura et al. 2009; Zhang et al. 2013; Zhao et al. 2003), chromatin remodeling (e.g., BAF, BRG1) (Ninkovic et al. 2013; Petrik et al. 2015; Tuoc et al. 2017) and noncoding RNAs (Liu et al. 2010; Anderson and Lim 2018, in this issue) play important roles. Many growth factors, signaling molecules and neurotransmitters have been shown to regulate neurogenesis (Kempermann et al. 2015). Catavero et al. (2018, in this issue) review the role of GABA circuits, signaling and receptors in regulating development of adult-born cells, as well as the molecular players that modulate GABA signaling. Because progenitors with multipotent differentiation potentials have been found in brain regions without active neurogenesis (Palmer et al. 1997), it is hypothesized that these progenitors might be manipulated to become neuron-competent in vivo so that they can contribute to brain generation (Wang and Zhang 2018, in this issue).

A great amount of literature has documented how physiological activities and an enriched environment influence adult neurogenesis (Kempermann et al. 2015). However, as summarized by Eisinger and Zhao (2018, in this issue), the genes and gene network involved in these changes within NSCs have not been systematically analyzed at genome wide levels. Adult neurogenesis is also influenced by diseases including epilepsy (Parent and Lowenstein 1997), stroke (Zhang and Chopp 2016), depression (Dranovsky and Hen 2006; Kempermann et al. 2003) and injury (Morshead and Ruddy 2018, in this issue). Thodeson et al. (2018, in this issue) further summarize the contribution and dysregulation of adult neurogenesis in epilepsy and discuss how we can translate these findings to human therapeutics by using patient-derived neurons to study monogenic epilepsy-in-a-dish.

Aging affects every individual and is a major risk factor for many diseases. One of the strongest negative regulators of adult neurogenesis is aging. Both intrinsic and extrinsic components regulate the limitations of NSC proliferation and function (Moore and Jessberger 2017; Seib and Martin-Villalba 2015). In this issue, Mosher and Schaffer (2018)

and Morshead and Ruddy (2018) examine factors such as secreted signals, cell contact-dependent signals and extracellular matrix cues that control neurogenesis in an age-dependent manner and define these signals by the extrinsic mechanism through which they are presented to the NSCs. Smith et al. (2018, in this issue) discuss how age-related changes in the blood, such as blood-borne factors and peripheral immune cells, contribute to the age-related decline in adult neurogenesis in the mammalian brain.

Despite the extensive knowledge we have gained regarding adult neurogenesis, critical questions remain. For example, the control of the functional integration of new neurons remains a mystery. It has been shown that adult NSC-differentiated newborn neurons exhibit a critical period for sensitivity to external stimuli (Bergami et al. 2015) and a heightened sensitivity to seizures (Kron et al. 2010). It remains unclear how new neurons choose their connections. Jahn and Bergami (2018, in this issue) further discuss the critical period and its regulators during adult-newborn neuron development.

Understanding the extrinsic and intrinsic regulation of adult NSCs and their newborn progeny and their response to both positive and negative stimuli will further illuminate their role in disease, injury, stress and brain function.

Pluripotent stem cell-derived NSCs

Human pluripotent stem cells (PSCs), including human embryonic stem cells (ESCs) and induced PSCs (iPSCs), offer a model system to reveal cellular and molecular events underlying normal and abnormal neural development in humans. ESCs are pluripotent cells derived from the inner cell mass of blastocyst stage preimplantation embryos, which were first isolated in 1981 from mouse by Evans and Kaufman (1981) and later, in 1998, from humans by Thomson et al. (1998). Human ESCs are invaluable in the study of early embryonic development, allowing us to identify critical regulators of cell commitment, differentiation and adult cell reprogramming (Dvash et al. 2006; Ren et al. 2009). iPSCs are reprogrammed from somatic cells by forced expression of stem cell genes and have the characteristics of ESCs (Okita et al. 2007; Yu et al. 2007). The development of iPSC technology has allowed us access to cells of the human nervous system through reprogramming of patient-derived cells, revolutionizing our ability to study human development and diseases.

To generate neural cells from either ESCs or iPSCs, the first step is neural induction. Through actions of a number of activators and inhibitors of cell signaling pathways, this process yields neural epithelial cell-like NSCs and then intermediate neural progenitors, resembling embryonic development. Despite many advances, a major hurdle of neural differentiation is lineage control. Using a "standard" dorsal forebrain neural differentiation protocol, most neural progenitors obtained are forebrain excitatory progenitors that produce mostly forebrain glutamatergic excitatory neurons. However, the purity and layer-specific composition of these progenitors, as well as neurons, vary significantly from experiment to experiment, cell line to cell line and lab to lab. In addition, differentiation into specific types of neurons with high purity has always been a challenging goal. Much effort has been devoted into improving the efficiency of dopaminergic neuron and GABAergic neuron differentiation with great success (Hu et al. 2010). However, the brain has many other types of neurons. Vadodaria et al. (2018, in this issue) discuss how to generate serotonergic neurons, a type of neuron highly relevant to psychiatric disorders. To better understand the molecular control of human PSC and NSC differentiation, where protocols result in a large amount of cellular heterogeneity in identity and response, analysis must be done at the level of single cells. Harbom et al. (2018, in this issue) summarize how new state-of-the-art single-cell analysis methods may help to define differentiation from pluripotent cells.

The advancement in iPSC and gene editing technology has transformed the field of human disease modeling. As in many human disorders, especially neuropsychiatric disorders, mouse models have been useful. Yet there are several critical reasons why it is necessary to use human cells to define the underlying mechanisms that lead to human patient characteristics, particularly those affecting the nervous system. For example, in fragile X syndrome (FXS), the epigenetic silencing of the Fragile X Mental Retardation Gene 1 (*FMR1*) gene that causes FXS occurs only in humans. Mice engineered to mimic the human mutation in the *FMR1* gene do not show the same methylation and silencing characteristics of the gene as in humans (Brouwer et al. 2007). These results indicate that some epigenetic mechanisms in human and mice are different and preclude the ability to study epigenetic mechanisms of *FMR1* silencing in mouse models of FXS (Bhattacharyya and Zhao 2016). In this issue, Li and Shi discuss disease modeling using human PSC-differentiated neural progenitors (Li et al. 2018), and Brito et al. specifically focus on modeling autism spectrum disorder (Brito et al. 2018).

Use of NSCs as therapy

The use of NSCs as a treatment strategy in CNS disease and injury has been tested for decades. Parkinsons' disease specifically has gained the most momentum for potential therapeutic benefits (Studer 2017); however, similar work has been performed in Huntington's disease, stroke and following spinal cord injury (for a review on this topic, see Vishwakarma et al. 2014). In some of these paradigms, NSCs are expected to differentiate into a specific cell type in the local CNS environment; in other cases, they are in a supportive role. In this issue,

Kameda et al. explore progress in using NSCs as a therapy following spinal cord injury (Kameda et al. 2018).

Bypassing NSCs?

While the development of PSC technologies has been a scientific breakthrough for future studies, there are limitations and risks that may be associated with their use. ESCs, iPSCs and their differentiated NSCs are dividing cells. Either transplantation of NSCs or in vivo reprogramming of endogenous cells into NSCs could lead to tumorigenesis. In addition, reprogramming somatic cells into iPSCs results in a loss of some epigenetic signatures of disease and aging, which are critical for disease modeling (Mertens et al. 2015; Miller et al. 2013; Ocampo et al. 2016). In recent years, direct reprogramming of fibroblasts or other cell types into induced neurons (iN) has been developed (for review, see Mertens et al. 2016). Remarkably, a growing number of studies have demonstrated that such direct reprogramming also can be effective in vivo. Wang and Zhang (2018, in this issue) summarize recent progress of in vivo reprogramming into new neurons and present how this method can be used for spinal cord injury.

In cellular reprogramming, the cells targeted and the genetic factors used vary; however, the biggest difference is that some protocols push cells through a NSC stage, whereas others skip these stages (Gascon et al. 2017; Guo et al. 2014; Wang et al. 2016). Bypassing this developmental stage has both pros and cons and may lead to a completely novel path towards lineage commitment (discussed by Falk and Karow 2018 in this issue).

Perspective

NSCs are fascinating and promising cells because of their capability, flexibility and multiplicity. Understanding how NSCs function provides important knowledge in the development, adaptation, disease, regeneration and rehabilitation of the nervous system. The studies of cortical development and adult neurogenesis using rodent models have contributed significantly to our knowledge about NSCs and will continually yield important new information, taking advantage of novel genetic and imaging technologies. However, using human NSCs provides us with a window to investigate human-specific aspects of development and disease mechanisms, which is potentiated by the fast advancement of stem cell and gene editing technologies. Challenges still remain regarding cell lineage control, in vivo NSC behavior, three-dimensional cellular interactions and preservation of epigenetic and aging marks.

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