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Review

Classic and novel stem cell niches in brain homeostasis and repair

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ABSTRACT

Neural stem cells (NSCs) critical for the continued production of new neurons and glia are sequestered in distinct areas of the brain called stem cell niches. Until recently, only two forebrain sites, the subventricular zone (SVZ) of the anterolateral ventricle and the subgranular zone (SGZ) of the hippocampus, have been recognized adult stem cell niches (Alvarez-Buylla and Lim, 2004; Doetsch et al., 1999a, 1999b; Doetsch, 2003a, 2003b; Lie et al., 2004; Ming and Song, 2005). Nonetheless, the last decade has been witness to a growing literature suggesting that in fact the adult brain contains stem cell niches along the entire extent of the ventricular system. These niches are capable of widespread neurogenesis and gliogenesis, particularly after injury (Barnabé-Heider et al., 2010; Carlén et al., 2009; Decimo et al., 2012; Lin et al., 2015; Lindvall and Kokaia, 2008; Robins et al., 2013) or other inductive stimuli (Bennett et al., 2009; Cunningham et al., 2012; Decimo et al., 2011; Kokoeva et al., 2007, 2005; Lee et al., 2012a, 2012b; Migaud et al., 2010; Pencea et al., 2001b; Sanin et al., 2013; Suh et al., 2007; Sundholm-Peters et al., 2004; Xu et al., 2005; Zhang et al., 2007). This review focuses on the role of these novel and classic brain niches in maintaining adult neurogenesis and gliogenesis in response to normal physiological and injury-related pathological cues.

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1. Introduction

Stem cells are unique in their remarkable capacity to both self-renew and differentiate into the specialized cells of the body, including the brain (Cheng et al., 2005). In the embryo, multipotent stem cells comprise the neuroepithelial lining of the neural tube. The differentiation of these cells is guided by critical positional cues present at precise times, ultimately resulting in the diverse neuronal and glial phenotypes found in the brain (Temple, 2001). As the nervous system matures, the number of neural stem cells (NSCs) in the CNS rapidly declines. By adulthood, NSCs are found only in discrete regions of the CNS where they reside in "stem cell niches". Until recently, only two brain niches, the subventricular zone (SVZ) of the anterolateral ventricle and the subgranular zone (SGZ) of the hippocampal dentate gyrus, were thought to be capable of generating new neurons throughout adult life (Alvarez-Buylla and Lim, 2004; Doetsch et al., 1999a, 1999b; Doetsch, 2003a, 2003b; Lie et al., 2004; Ming and Song, 2005). However, in the last decade, there has been mounting evidence to show widespread neurogenesis and gliogenesis in the adult brain, particularly after injury (Barnabé-Heider et al., 2010; Carlén et al., 2009; Decimo et al., 2012; Lin et al., 2015; Lindvall and Kokaia, 2008; Robins et al., 2013) or other inductive stimuli (Bennett et al., 2009; Cunningham et al., 2012; Decimo et al., 2011; Kokoeva et al., 2007, 2005; Lee et al., 2012a, 2012b; Migaud et al., 2010; Pencea et al., 2001b; Sanin et al., 2013; Suh et al., 2007; Sundholm-Peters et al., 2004; Xu et al., 2005; Zhang et al., 2007). This review will focus on the role of classic and novel niches in brain homeostasis and in their response to injury.

2. Historical perspective: the classic brain niches of the SVZ and SGZ

For most of the last century, neuroscientists overwhelmingly believed that the adult brain was essentially an inert structure, incapable of the ongoing production of new neurons. This view was supported by the observations of the neuroanatomist, Santiago Ramón y Cajal, who showed that there was little change in the architecture of the brain after birth (Gross, 2008; Ramon y Cajal, 1928). However, in the early 1960s, with technological advances such as autoradiography, it became possible to detect [^{3}H]-thymidine incorporation into newly synthesized DNA, allowing researchers to identify and track dividing cells in the SVZ (Messier et al., 1958) and SGZ (Altman and Das, 1965a, 1965b; Altman, 1963, 1962) in the adult brain. Moreover, in 1965, Altman and Das showed for the first time that labeled cells from the SVZ migrated through the rostral migratory stream (RMS) to the olfactory bulb (OB) where they developed into neurons, providing solid evidence of adult neurogenesis in the adult brain (Altman and Das, 1965a, 1965b). Further supporting this notion, subsequent electron microscopic studies confirmed that [^{3}H]-thymidine-labeled hippocampal and OB cells indeed exhibited the ultrastructural characteristics of newly differentiated neurons (Kaplan and Bell, 1984; Kaplan and Hinds, 1977).

Despite these intriguing early findings, it took another twenty years and the advent of new histological methods for identifying dividing cells and tracking their fate in the brain before there was widespread acceptance of the principle of adult neurogenesis. However, with the discovery by Nottebohm and colleagues of thymidine-labeled neurons which co-labeled with antibodies to the synthetic thymidine analog 5-bromo-3′-deoxyuridine (BrdU) (Gratzner, 1982; Nowakowski et al., 1989) in hippocampal neurons of the adult songbird (Barnea and Nottebohm, 1996, 1994; Burd and Nottebohm, 1985; Goldman and Nottebohm, 1983; Paton and Nottebohm, 1984), the SGZ was finally and firmly established as a site for adult neurogenesis. Similar findings in other species (Cameron et al., 1993; Kempermann et al., 1997; Kuhn et al., 1997, 1996; Seki and Arai, 1995) including primates (Gould et al., 1999a) and humans (Eriksson et al., 1998) lent further credence to this concept. Likewise, by tracking with immunocytochemistry, the phenotypic fate of BrdU-labeled cells in the SVZ, during their migration in the RMS, and at their final destination in the OB, the SVZ was similarly shown to be a second site of neurogenesis in the adult brain (Corotto et al., 1994, 1993; Doetsch et al., 1999a; Lois and Alvarez-Buylla, 1994; Pencea et al., 2001a), including in humans (Curtis et al., 2007).

During this same period, studies in tissue culture played a prominent role in defining and characterizing the cellular and molecular attributes of NSCs from the SGZ and SVZ. In particular, the pioneering work of Reynolds and Weiss and Kilpatrick and Bartlett was pivotal, instituting methods to grow and expand SVZ-derived NSCs as "neurospheres" in the presence of mitogens such as epidermal growth factor. Importantly, these studies established the basic requirements for NSC self-renewal and for their differentiation into neurons and glia (Kilpatrick and Bartlett, 1993; Reynolds and Weiss, 1992). Similarly, protocols were developed to expand and differentiate NSCs from the SGZ of the hippocampus in culture (Gage et al., 1995; Palmer, 1995; Palmer et al., 1997). Together, these in vitro studies provided an important platform for future investigations aimed at probing the developmental potentialities of NSCs and the mechanisms regulating their proliferation and differentiation.

3. NSCs and their niche

As other stem cells of the body, NSCs in the brain were found to reside in specialized structures called niches where cell:cell interactions and local microenvironmental cues were shown to be pivotal in regulating the balance between self-renewal and differentiation. The cellular architecture of the SVZ and SGZ niches and their microenvironment (i.e. growth factors,