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Review

A developmental perspective on adult hippocampal neurogenesis

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ABSTRACT

The generation of new neurons from neural stem cells (NSCs) throughout adult life in the mammalian brain is a biological process that fascinates scientists for its uniqueness and restorative potential. In the dentate gyrus (DG) of the hippocampus NSCs are able to self-renew and generate new granule cells and astrocytes through a complex and plastic mechanism that can be regulated by endogenous and exogenous cues at different levels. Unexpected recent findings suggest that the population of NSCs is heterogeneous in morphology and behavior. We herein explore the hypothesis that NSC heterogeneity and the neurogenic potential of the DG depends on their developmental origin. We provide an up-to-date picture of the process of neurogenesis in the adult hippocampus with an especial focus on NSCs and outline key unsolved aspects. Further, we discuss the origin of NSCs in the adult DG from a developmental perspective and explore the possibility of NSC heterogeneity being determined from early postnatal periods and being responsible for the neurogenic output of the DG in the long term.

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1. Neural stem cells and adult neurogenesis in the rodent hippocampus

In adult mice, the neurogenic capacity of the hippocampus is maintained due to the existence of a population of radial glia-like cells that act as neural stem cells (rNSCs) giving rise to new neurons (Seri et al., 2001) that integrate functionally into the granule cell layer (GCL) (van Praag et al., 2002). Because they represent the first step in the neurogenic cascade, they are also referred to as type-1 cells (Kronenberg et al., 2003). The soma of these cells dwells in the subgranular zone (SGZ), a loose and narrow strip of tissue located between the GCL and the hilus. rNSCs extend a single apical process that crosses the GCL tightly contacting the granule cell neurons, and then arborizes profusely in the molecular layer (Filippov et al., 2003; Mignone et al., 2004). In addition, a subpopulation of neural stem or progenitor cells with horizontal morphology that would

Abbreviations: ANP, amplifying neural progenitors; BLBP, brain lipid-binding protein; BMPs, bone morphogenetic proteins; BMPR-1A, BMP-receptor 1A; BrdU, 5-bromo-2′-deoxyuridine; DCX, doublecortin; DG, dentate gyrus; ECS, electroconvulsive shock; GCL, granule cell layer; GFAP, glial fibrillary acidic protein; GFP, green fluorescent protein; GLAST, astrocyte-specific glutamate transporter; KA, kainic acid; NB, neuroblasts; nr/hNSC, non radial/horizontal NSCs; NSCs, neural stem cells; PSA-NCAM, polysialic acid neural cell adhesion molecule; QNP, quiescent neural progenitors; RGCs, radial glia cells; rNSCs, radial glia-like cells NSCs.

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respond differently than their radial counterparts to stimuli and aging has been proposed to exist (Lugert et al., 2010). rNSCs express markers of immature astrocytes and radial glia such as glial acidic fibrillary protein (GFAP), vimentin and brain lipid-binding protein (BLBP) but lack expression of mature astrocytes such as S100β. They also express markers of neuroepithelial stem cells such as nestin, Gli-1, and Sox2 (Ferri et al., 2004; Kempermann et al., 2004; Ahn and Joyner, 2005; Encinas and Enikolopov, 2008). These markers however are not specific to rNSCs in the DG and extreme precaution must be taken when using them to claim that a particular cell belongs to the rNSC population. For instance, Sox2 is also present in astrocytes and intermediate neural precursors in the DG and nestin is expressed by perivascular glial cells and reactive astrocytes.

In a young adult brain, the DG contains dozens of thousands of rNSCs (Encinas et al., 2011a) but in a given time-point only a small proportion (1–2%) of them are undergoing cell division as measured by incorporation of the thymidine analog 5-bromo-2′-deoxyuridine (BrdU), which occurs during the S-phase of the cell cycle (Seri et al., 2001; Kronenberg et al., 2003; Encinas et al., 2006). A major mechanism governing the equilibrium between quiescence and the entrance in cell cycle are bone morphogenetic proteins (BMPs). The rNSCs in the DG express BMP-receptor 1A (BMPR-1A) which binds BMP-2 and BMP-4 and keeps rNSCs in a quiescent state (Mira et al., 2010). When noggin is present it binds to the BMPs preventing their union to BMPR-1A and causing rNSCs to activate and enter cell cycle. In addition, Hedgehog and canonical Notch signaling also contribute to the control of the quiescence/activation balance of the rNSCs of the DG (Ahn and Joyner, 2005; Lugert et al., 2010). The transcription factor Sox1 has been also postulated to play a role in NSC activation, as it marks rNSCs in the DG that are able to produce neuron-generating precursors and generate astrocytes as shown by lineage tracing (Venere et al., 2012). Although the intracellular molecular pathways that intervene in the activation of rNSCs are starting to be unveiled, the mechanism acting as a link between the level of neuronal activity and the recruitment and activation of hippocampal rNSCs is still poorly understood. However, the use of transgenic, constitutive and inducible, reporter mice in combination with optogenetically control of GABA release by interneurons in the DG has allowed to show that the nestin-expressing radial astrocytes that act as stem cells respond tonically to the level of this neurotransmitter (Song et al., 2012) switching from a quiescent state to an activated one.

Once activated, the rNSCs divide several times asymmetrically in a consecutive manner (three times as population average) and then, in a similar fashion to what has been proposed to occur in the developing DG (Brunne et al., 2010), slowly differentiate into astrocytes that migrate into the hilus and the molecular layer, losing their stem cell capabilities and causing a continuous depletion of the NSC population (Encinas et al., 2011a). Moreover the proportion of active, dividing NSCs remains constant over time, thus implying that the number of activated rNSCs depends on the size of the total population (Encinas et al., 2011a). These properties of the rNSCs would explain the noticeable decrease of hippocampal neurogenesis associated with aging (Encinas and Sierra, 2012) as well as the origin of the new astrocytes that result generated in the adult DG in parallel to neurogenesis (Steiner et al., 2004). Importantly their capability to generate astrocytes through direct transformation (Bonaguidi et al., 2011; Encinas et al., 2011a) together with their functioning as source of new neurons argue in favor of they being true stem cells. However the results by Enikolopov and colleagues (Encinas et al., 2011a) imply that their mitotic potential is very limited, being actually reduced to a population average of three cell divisions before differentiating into astrocytes. This restriction argues against their definition as NSCs and made the authors actually refer to these cells as quiescent neural progenitors (QNPs) rather than considering them pure NSCs. It has been recently proposed that rNSCs are able of self-renew through symmetric division; this capability seems to be quantitatively very low in normal conditions (Suh et al., 2007; Bonaguidi et al., 2011), and it remains unclear whether it exerts and impact on the dynamics of the total NCS population. Nevertheless, the current consensus is that adult hippocampus NSC population comprises several sub-populations with different properties (Lugert et al., 2010; Bonaguidi et al., 2012) and should be studied accordingly.

Typically, when hippocampal rNSCs enter cell cycle they divide asymmetrically, meaning that the fate of the mother cell is different from the fate of the daughter cell. The rNSC divides in a horizontal plane that is parallel to the SGZ and generates a daughter cell that only bears short and thin processes and lacks GFAP or vimentin expression while maintaining that of BLBP and nestin (Kempermann et al., 2004; Encinas et al., 2006). The rNSC remains morphologically unchanged and ready for further division as explained above. The daughter cells or type-2 cells (Filippov et al., 2003) are amplifying neural progenitors (ANPs) which divide actively: in a given time-point around 60% of them are in cell cycle as measured by incorporation of the thymidine. ANPs undergo of 2.5 divisions (as population average) (Encinas et al., 2011a), before exiting cell cycle and entering differentiation into neuroblasts (NBs). NBs or type-3 cells are neuronal committed precursors that express markers of immature migrating neurons such as doublecortin (DCX) and polysialic acid neural cell adhesion molecule (PSA-NCAM), as well as neuronal markers which will remain being expressed in the mature neurons, such as Prox1 and NeuN (Filippov et al., 2003; Kempermann et al., 2004; Seri et al., 2004; Encinas et al., 2006). During the transition from type-2 cell to NB around two thirds of the newborn cells die by apoptosis and are efficiently phagocytosed by microglia (Sierra et al., 2010). This transitional step marks also the appearance of excitatory GABAergic tonic input which promotes commitment to neuronal fate and differentiation into neuroblasts (Tozuka et al., 2005). NBs maturate over a period of several weeks: They undergo defined morphological changes evolving from a round cell with short processes to a multipolar cell with several neurites and finally to an oval cell with a well-defined apical dendrite which branches into the molecular layer of the DG (Seri et al., 2004; Encinas et al., 2006). The extension of their axon starts when the cells are approximately one week old (Stanfield and Trice, 1988; Zhao et al., 2006). At this time point NBs commence to receive synaptic GABAergic input (Overstreet Wadiche et al., 2005; Wang et al., 2005) and one week later the spinal dendrites appear (Zhao et al., 2006), together with the onset of the glutamatergic synaptic input which marks their integration into the hippocampal circuitry (van Praag et al., 2002). During these later steps of maturation and synaptic integration another critical period for survival takes place. Although quantitatively much smaller (Sierra et al., 2010) it represents the final selection process for the newly generated neurons and is based on NMDA receptor activation (Ge et al., 2007) (Fig. 1).

2. Non-radial neural stem/progenitor cells

The existence of a subpopulation of non radial/horizontal NSCs (nr/hNSCs) in the DG, has been suggested recently. According to Suh and colleagues a non-radial, Sox2-expressing progenitor would dwell in the SGZ and be able to generate neurons, astrocytes and radial astrocytes (Suh et al., 2007). However, as Sox-2 is expressed in both radial NSCs and ANPs/type-2a cells, as well as in astrocytes, and the fact that they only found one single case of apparent generation of a radial astrocyte from one of this non-radial, Sox-2 putative progenitors, call for further investigation of this possibility. Nonetheless, two other reports also

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