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BRAIN RESEARCH REVIEWS

Review

What determines neurogenic competence in glia?

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ABSTRACT

One of the most intriguing discoveries during the last decade of developmental neurobiology is the fact that both in the developing and adult nervous system neural stem cells often turn out to have a glial identity: Radial glia generates neurons in the developing telencephalon of fish, birds and mammals and astro/radial glial stem cells in specialized neurogenic zones give rise to new neurons throughout life. What are the extrinsic signals acting on and the intrinsic signals acting within these glial populations endowing these with a neurogenic potential, whilst most other glia seemingly lack it? Studies on postnatal astroglia shed interesting light on this question as they are the intermediate between neurogenic radial glia and mature parenchymal astrocytes. At least in vitro their decision to acquire a glial fate is not yet irrevocable as forced expression of a single neurogenic transcription factor enables them to transgress their lineage and to give rise to fully functional neurons acquiring specific subtype characteristics. But even bona fide non-neurogenic glia in the adult nervous system can regain some of their radial glial heritage following injury as exemplified by reactive astroglia in the cerebral cortex and Müller glia in the retina. In this review first we will follow the direction of the physiological times' arrow, along which radial glia become transformed on one side into mature astrocytes gradually losing their neurogenic potential, while some of them seem to escape this dire destiny to settle in the few neurogenic oases of the adult brain where they generate neurons and glia throughout life. But we will also see how pathophysiological conditions partially can reverse the arrow of time reactivating the parenchymal astroglia to re-acquire some of the hallmarks of neural stem cells or progenitors. We will close this review with some thoughts on the surprising compatibility of the co-existence of a neural stem cell and glial identity within the very same cell from the perspective of the concept of transcriptional core networks.

Contents

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1. Introduction

The last ten years have seen the rise of specialized glial cells to the rank of neuronal precursors both in the developing and adult nervous system. In the developing telencephalon neuroepithelial cells differentiate into radial glia which in turn generate either directly or indirectly via intermediate progenitors most forebrain neurons (Anthony et al., 2004; Kriegstein and Alvarez-Buylla, 2009; Malatesta et al., 2003; Malatesta et al., 2000; Pinto and Gotz, 2007). While most of the radial glia (RG) eventually transform into parenchymal astrocytes at the end of neurogenesis (Alves et al., 2002; Voigt, 1989), some of them give rise to astroglial stem cells in the adult subependymal zone (SEZ) or ependymal cells (Merkle et al., 2007; Spassky et al., 2005). Both, radial glia and astroglial stem cells display hallmark features of classical astrocytes [for a detailed review on the glial nature of radial glia see (Pinto and Gotz, 2007)]. Thus the question arises as to what endows these glial cells with a neurogenic competence so noticeably lacking in astroglia in most other regions of the brain, such as e.g. the cerebral cortex. What signals are required for the neurogenic endowment of glia and what processes take place in radial glia while they transform into non-neurogenic astrocytes? Does the loss of neurogenic potential occur abruptly or gradually? Is it in fact irreversible? Our studies during the last few years have led to the recognition that astroglial cells at an early stage of postnatal development are not irrevocably fixed in their lineage, but forced expression of single neurogenic transcription factors can render these cells capable of transgressing their own lineage and generating diverse types of neurons, at least in vitro (Berninger et al., 2007a; Heins et al., 2002). However, similar processes might be evoked in the early postnatal brain by damage such as caused by hypoxia (Fagel et al., 2009; Fagel et al., 2006). Finally, partial neurogenic competence can be regained by glial cells in the adult nervous system following injury as they de-differentiate and resume proliferation, as shown in the retina and the cerebral cortex (Buffo et al., 2008; Fischer and Reh, 2001; Karl et al., 2008). Thus it appears that not all the radial glial heritage is spent during early life, but some of it is latently preserved stimulating the hope that it might be possible to unearth this potential for the development of novel strategies for brain repair.

2. Radial glia: the founding fathers of the telencephalon and the adult neurogenic zones

Radial glial cells (RGCs) comprise a specialized cellular population in most regions of the vertebrate brain during restricted developmental periods, the functions of which have been highly disputed since their first description at late 19th century [reviewed in (Rakic, 2003)]. Nowadays, there is a general consensus that RGCs differentiate from neuroepithelial cells acquiring typical astroglial features, as for instance the presence of glycogen storage granules and the expression of astroglial markers, such as e.g. the astrocyte-specific glutamate and aspartate transporter (GLAST), brain lipid-binding protein (BLBP) and tenascin-C [for review see (Pinto and Gotz, 2007)]. In addition, it is now well established that RGCs function both as neuronal and glial progenitors at least in the developing telencephalon (Anthony and Heintz, 2008; Anthony et al., 2004; Malatesta et al., 2003; Malatesta et al., 2000; Miyata et al., 2001; Noctor et al., 2001; Tamamaki et al., 2001). Finally, with completion of most neuro- and gliogenesis they sign responsible for generating ependymal cells as well as particular astro/radial glial cells that function as neural stem cells (NSCs) in the adult brain (Chojnacki et al., 2009; Kriegstein and Alvarez-Buylla, 2009; Merkle et al., 2004). The fact that at least some RGCs are multipotent, i.e. can generate both neuronal and glial progeny, and are capable of self-renewing cell divisions generating either two new RGCs (symmetric division) or one RGC and a fate-restricted progenitor (asymmetric division) (Miyata et al., 2001; Noctor et al., 2004) indicate that RGCs exhibit defining stem cell hallmarks and are thus often considered as embryonic NSCs (Kriegstein and Alvarez-Buylla, 2009). The generation of adult NSC from RGCs may be considered as a particular case of RGC self-renewal raising interesting points about the precise lineage relationships between RGCs and adult NSCs. For example, given the evidence that there are virtually no quiescent RGCs during embryonic development (Hartfuss et al., 2001), consequently all adult NSCs must be derived from RGCs that have been previously contributing to neuro- or gliogenesis. Moreover, given the notion that NSCs in the adult SEZ are quite heterogeneous with respect to the distinct progenies they give rise to (Brill et al., 2009; Brill et al., 2008; Hack et al., 2005;