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Radial glial cell: Critical functions and new perspective as a steroid synthetic cell

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ABSTRACT

The radial glial cell (RGC) is a glial cell type in the central nervous system of all vertebrates. Adult teleost fish have abundant RGCs in the brain in contrast to mammals. Adult fish RGCs have many important functions, including forming a structural scaffold to guide neuronal migration and serving as the progenitor cells in the brain to generate neurons. The role of the RGC in adult neurogenesis explains the high regenerative capacity of adult fish brain. There is increasing evidence from several species that some glial cells produce or metabolize steroids. It is now well-known that teleost RGCs express aromatase and produce estrogens from androgen precursors, which may be important for local neuroendocrine functions and regulation of neurogenesis. The question of whether RGCs are capable of *de novo* steroid synthesis from cholesterol remains unanswered. However, the expression of steroidogenic acute regulatory protein, and the key enzyme cytochrome P450 17alpha-hydroxylase in primary cultures of goldfish RGCs indicate the potential to produce 17α-hydroxy-pregnenolone and thus other steroid intermediates. The possibility of synthesizing additional non-estrogenic steroids may indicate new functions for the RGC.

1. Introduction

The radial glial cell is a glial cell type in the central nervous system (CNS) of all vertebrates engaged in many key developmental processes. During CNS development, early progenitors – neuroepithelial cells give rise to RGCs, which represent the major cell type in the neural tube and comprise the neurogenic cell population (Schmechel and Rakic, 1979). At an early stage of development, RGCs predominantly divide to generate more RGCs and expand along the surface area of developing lateral ventricles. With developmental progression, RGCs will generate less daughter RGCs but more intermediate progenitor cells and neurons. At later stages of CNS development, RGCs finally disappear by transforming into neurons and astrocytes (Fig. 1).

After differentiation from neuroepithelial cells, RGCs maintain a very similar morphology as their precursors, with the soma positioned along the ventricle wall and a long radial process extending from its cell body reaching to the basement membrane at the pial surface (Stevenson and Yoon, 1982). This morphological feature enables its major function which is to serve as a guiding scaffold for newborn neurons to migrate to their final destination (Rakic, 1971). In addition to their roles as a structural scaffold to guide neuronal migration, RGCs are also progenitor cells and able to differentiate into neurons (Radakovits et al., 2009). Recently, adult neurogenesis in mammals has attracted great attention after the discovery of neural stem cells and the continuous generation of neurons in the adult CNS. This phenomenon has been found both in mammalian and non-mammalian species. Despite that this idea of adult neurogenesis is well accepted, mammals have very limited capacity for neurogenesis and neuroregeneration. The main reason is that there are only two proliferative and neurogenic regions in the adult mammalian brain. These include the anterior part of the subventricular zone of the lateral ventricle and subgranular zone of the dentate gyrus (Brunne et al., 2010; Ming and Song, 2011). In contrast to mammals, teleost fish exhibit an enormous potential to produce new neurons in the adult CNS and to replace damaged neurons by newly generated ones and neuronal transdifferentiation. Persistent neurogenesis is maintained throughout development and also adulthood, as teleost fish have dozens of proliferative and neurogenic regions that can give rise to new neurons. This extensive neurogenic capacity may be largely due to the abundance of RGCs in the adult teleost brain (Strobl-Mazzulla et al., 2010). Abnormalities in RGC development, functions and differentiation, as well as in cellular interactions between RGCs, and interactions between RGCs and neurons could cause many

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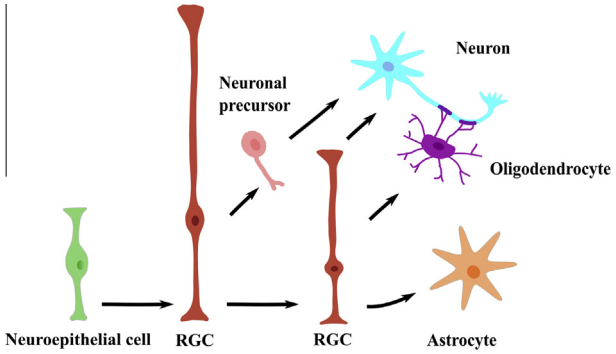

Fig. 1. Differentiation of radial glial cells (RGCs) during CNS development.

developmental brain disorders such as schizophrenia and lissencephaly (Hatten, 2002; Marín and Rubenstein, 2003).

2. Role of RGC in neuronal migration

The expression patterns of RGC marker proteins differ between embryonic and adult mammalian brain. Mammalian RGCs express brain lipid binding protein (BLBP) and glutamate aspartate transporter (GLAST) during development (Anthony et al., 2004). On the other hand, the RGCs along the ventricle in adult mouse brain have little to no GLAST immunoreactivity, yet these RGCs are glial fibrillary acidic protein (GFAP)- and vimentin-positive (Sundholm-Peters et al., 2004). In adult teleost brain, RGCs are GFAP-positive, which is similar to adult mammalian RGCs, but are also BLBP-positive (Takeuchi and Okubo, 2013). These GFAP or BLBP-positive RGCs are involved in neurogenesis and neuronal migration in both intact and injured adult brain and these contributes to the high capacity of neuroregeneration observed in teleost fish (Schmechel and Rakic, 1979; Zupanc and Clint, 2003). The hypothesis that RGCs in the adult brain guide neuronal migration has received strong support from several research groups studying the expression of RGC cell markers. First, the morphology and size of teleost RGCs in adult brain are extremely similar to RGCs in the developing brain, with a long process reaching the basal membrane playing a key structural role during the neuronal migration (Stevenson and Yoon, 1982; Tong et al., 2009; Diotel et al., 2010). Also, RGC fiber distribution and orientation in the adult fish brain matches the migration path of young neurons, indicating that young neurons use the radially-oriented glial fibers as a scaffold to reach their final destination within the cortical plate (Rakic, 1971; Nadarajah, 2003; Zupanc et al., 2012). This strategy appears to be employed when cells migrate over long trajectories. Second, migrating neurons expressing the microtubule-binding protein doublecortin have been observed in a close apposition to radial processes in adult rat brain (Gubert et al., 2009; Radakovits et al., 2009) and this close apposition between young neurons and RGCs can also be seen in electron microscopy images (Rakic, 1971; Brunne et al., 2010). Interestingly, the triple staining result of elongated bromodeoxyuridine (BrdU) and neuronal protein HuC/D labeled new born neurons overlapping with GFAP immunoreactive fibers indicates that neurons are migrating along GFAP-positive RGC fibers (Hatten, 2002; Marín and Rubenstein, 2003; Zupanc and Clint, 2003).

3. Proliferative and neurogenic nature of RGCs

With the onset of neurogenesis, after neuroepithelial cells transform into RGCs, both neuroepithelial cells and RGCs are characterized by apical–basal polarity and nuclear migration (Anthony et al., 2004; Götz and Huttner, 2005). At the end of mammalian CNS development, RGCs withdraw their processes and differentiate into other types of glial cells when neurons reach their final destination in mammals (Fig. 1). It was thought that all RGCs disappear in the late stage of mammalian CNS development and differentiate into astrocytes. However, in the adult mammalian brain, RGCs are still detected in some regions, such as adult olfactory bulbs, telencephalon, subventricular zone and dentate gyrus (Sundholm-Peters et al., 2004; Liu et al., 2006; Brunne et al., 2010; Emsley et al., 2012). Bromodeoxyuridine labeling studies in adult rat brain also reveal strong proliferative sites at the ventricular zone, the region where high numbers of newborn cells and RGCs are located. These BrdU-positive cells also express GFAP, indicating that RGCs at the ventricular surface in the adult brain are proliferative (Pecchi et al., 2007; Takeuchi and Okubo, 2013). Live imaging observations confirmed bipolar RGC division as well as the generation of more than 4–5 daughter RGCs within 40 h (Pilz et al., 2013). Moreover, it has now been established that daughter cells generated by RGCs lead to more RGCs, astrocytes, oligodendrocytes and neurons. For example, neurons in the rodent CNS originate from three classes of neural stem and progenitor cells – neuroepithelial cells, RGCs and intermediate neuronal progenitors. Neurogenic radial glia have also been observed in the outer subventricular zone of human neocortex (Hansen et al., 2010). The neurogenic nature of RGC is supported by the finding that most neurons in the adult mouse brains derive from GLAST-positive RGCs (Anthony and Heintz, 2008). These RGCs also express the transcription factor Pax6, which exists in neuronal RGC during mammalian development (Heins et al., 2002; Gubert et al., 2013). Another study reported the triple staining of LIM homeobox transcription factor 1, alpha (LMX1α), which is expressed by dopamine neuronal progenitors, with condensed chromatin and phosphorylated vimentin, which is the marker of RGCs in M-phase. This result suggests that RGCs are the progenitors of dopamine neurons along the ventricle wall in the human brain (Hebsgaard et al., 2009). Bonilla et al. (2008) also showed that GLAST-positive RGCs in the brain floor plate of mouse can undergo neurogenesis and give rise to dopaminergic neuron progenitors, which then rapidly differentiate into dopaminergic neurons.

In non-mammalian species, RGCs persist throughout an animal's entire life as a neuronal stem cell (Alvarez-Buylla et al., 2002). Indeed, several studies suggest that RGCs in adult fish brain are still in the cell cycle and express markers of a progenitor cell type, such as the intermediate filament nestin (Diotel et al., 2010; Takeuchi and Okubo, 2013). The brains of teleosts keep growing and developing through adulthood, although very little is known about the underlying mechanisms. Several studies have reported the remarkable regeneration capacity of adult fish brain, which relates to the abundance and persistence of RGCs (Strobl-Mazzulla et al., 2010; Kroehne et al., 2011; Diotel et al., 2013; Pellegrini et al., 2007), showed the active proliferation in the adult zebrafish forebrain and reported that newborn cells arising from adult RGCs can differentiate into neurons. However, there is little information about the characterization and function of newborn neurons with the exception of two studies describing newborn tyrosine hydroxylase (TH)-positive neurons in zebrafish telencephalon and newborn serotonin (5-HT) neurons at zebrafish paraventricular organ (Adolf et al., 2006; Pérez et al., 2013). Despite these exciting results from both mammals and teleost fish showing the possibility of RGC transformation into dopaminergic neurons, there is no direct *in vitro* data showing the process of this differentiation. One study showed that the transformation of RGC into astrocytes is bidirectional in the mouse brain, based on the evidence that mature astrocytes can be re-induced to RGCs by epidermal growth factor (EGF) and transforming growth factor α (TGFα) (Ghashghaei et al., 2007). These re-induced mouse RGCs regained the function of guiding neuronal migration. Additionally, with

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