Neural stem and progenitor cells in cortical development

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Abstract. Recent work has begun to identify neural stem and progenitor cells in the embryonic and adult brain, and is unravelling the mechanisms whereby new nerve cells are created and delivered to their correct locations. Radial glial (RG) cells, which are present in the developing mammalian brain, have been proposed to be neural stem cells because they produce multiple cell types. Furthermore, time-lapse imaging demonstrates that RG cells undergo asymmetric self-renewing divisions to produce immature neurons that migrate along their parent radial fibre to reach the developing cerebral cortex. RG cells also produce intermediate progenitor (IP) cells that undergo symmetric division in the subventricular zone of the embryonic cortex to produce pairs of neurons. The symmetric IP divisions increase cell number within the same cortical layer. This two-step process of neurogenesis suggests new mechanisms for the generation of cell diversity and cell number in the developing cortex and supports a model similar to that proposed for the development of the fruit fly CNS. In this model, a temporal sequence of gene expression changes in asymmetrically dividing self-renewed RG cells could lead to the differential inheritance of cell identity genes in cortical cells generated at different cell cycles.

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The mature human cerebral cortex comprises approximately 20 billion neurons (Pakkenberg & Gundersen 1997), and 40 billion glial cells (Pakkenberg et al 2003). Most cortical neurons are generated before birth, while glial cell production extends into the postnatal period (Bhardwaj et al 2006). The proliferative cells that produce cortical neurons and glial cells are located in two zones that surround the ventricular lumen during development: the ventricular zone (VZ), which is adjacent to the ventricle, and the subventricular zone (SVZ), which is superficial to the VZ (Boulder Committee 1970). Radial glial (RG) cell bodies are located in the embryonic VZ, and intermediate progenitor (IP) cells reside in the embryonic SVZ. Recent work has demonstrated that both of these embryonic cell types generate neurons during cortical development. However, RG and IP cells exhibit important

differences in mitotic behaviour and morphology. RG cells are bipolar neuroepithelial cells that have a long thin pial-contacting process, undergo interkinetic nuclear migration during the cell cycle, and divide at the margin of the lateral ventricle. IP cells lack the pial process, do not undergo interkinetic nuclear migration, and most divide away from the margin of the ventricle in the SVZ (reviewed in Noctor et al 2007). In addition to the aforementioned differences, RG and IP cells appear to adopt distinct modes of division (Haubensak et al 2004, Noctor et al 2004).

Neural stem cells have been isolated *in vitro* from several regions of the embryonic and adult CNS, including the embryonic neocortex. Neural stem cells isolated from the embryonic neocortex have the capacity to undergo self-renewing divisions and to generate multiple cell types (Davis & Temple 1994). Recent work has shown that embryonic neural stem cells share properties with RG cells (Conti et al 2005), suggesting that RG cells may be a form of neural stem cell in the embryonic neocortex. Here we review evidence supporting the hypothesis that RG cells are a neural stem cell type, and that IP cells are committed progenitor cells with restricted potential. We consider the features that RG and IP cells *in situ* share with neural stem cells that have been isolated from embryonic and adult brain, and whether unique features that identify RG and IP cells serve as useful indicators of neural stem, or neural progenitor cell status in the developing cerebral cortex. For the purposes of this discussion we define stem cells as proliferative cells that undergo self-renewing divisions and produce multiple daughter cell types, and progenitor cells as proliferative cells that have limited potential for self-renewal and that are dedicated to the production of single cell types.

Radial glial cells as neural stem cells

Recent research has conclusively demonstrated that RG cells generate cortical neurons during embryonic development. This has been shown in dissociated cell cultures (Malatesta et al 2000), through time-lapse imaging of fluorescently labelled precursor cells in organotypic slice cultures (Miyata et al 2001, Noctor et al 2001, 2004, Tamamaki et al 2001), and through the expression of fluorescent reporter genes in mutant mice lines (Anthony et al 2004, Haubensak et al 2004). The neuronal identity of RG daughter cells has been verified through immunolabelling with neuronal specific markers, and also through electrophysiological recordings obtained from RG daughter cells and progeny (Noctor et al 2001, 2004). The evidence that RG cells function as neural stem cells, rather than restricted potential neural progenitor cells, rests on two properties: the production of multiple cell types, and self-renewal of the RG cells.

Generation of multiple cell types

RG cells in the dorsal telencephalon are generally thought to produce only excitatory glutamatergic neurons, while progenitor cells in the ventral telencephalon produce inhibitory GABAergic neurons (Parnavelas 2000). Nonetheless, RG cells produce cortical neurons that are destined to populate each of the cortical layers. It is not yet known if there are multiple subtypes of RG cells that are committed to the production of specific cortical neuron subtypes, whether cortical neuron subtype is determined by environmental factors after birth, or whether cell fate is specified earlier during the cell cycle as reported for laminar fate specification (McConnell & Kaznowski 1991). However, it remains possible that individual RG cells generate multiple subtypes of excitatory cortical neurons. RG cells also generate several additional cell types during cortical development: IP cells (Noctor et al 2004), astroglial cells (Schmechel & Rakic 1979, Voigt 1989, Noctor et al 2004), additional RG cells (Noctor et al 2004), and at later stages of development, ependymal cells (Spassky et al 2005), and neurogenic astrocytes that reside in the adult SVZ (Merkle et al 2004). RG cells in the developing spinal cord can produce both neurons and oligodendrocytes (Fogarty et al 2005), but it has yet to be determined if neocortical RG cells can also produce oligodendrocytes. Thus RG cells have been shown to produce at least five distinct cell types, and may generate additional cell types. The potential of RG cells *in vivo* matches that described for neural stem cells that have been isolated from the embryonic cerebral cortex; lineage studies performed *in vivo* and *in vitro* have described clones that consist of the same multiple cell types (e.g. Noctor et al 2004, Shen et al 2006). These data strengthen the argument that RG cells function as neural stem cells, but we cannot rule out the possibility that subsets of RG cells are dedicated to the production of specific lineages.

Self-renewal of radial glial cells

A requisite for claiming stem cell identity is the demonstration that a particular cell type undergoes self-renewing divisions: candidate stem cells must produce daughter cells that are identical to, or share key characteristics with, their parental cell in order to be classified as a stem cell. Following this line of reasoning, RG cells must produce daughter cells that are identical or very similar to the mother cell to be classified as a type of neural stem cell. RG cells can be identified based on several criteria such as morphology, marker expression, mitotic behaviour, and function. These identifying characteristics can therefore be used to determine whether mother and daughter cells are each radial glial cells.

RG cells have several unique morphological characteristics, but the pial fibre is a classical feature that has identified these cells in the developing CNS for more

than 100 years (Ramón y Cajal 1995). This long, thin process ascends from the cell body in the VZ through overlying structures to terminate in the pial basement membrane (reviewed in Bentivoglio & Mazzarello 1999). The pial fibre is relatively short during early stages of development when the neocortex consists of a single neuroepithelial layer, but grows progressively longer throughout development and spans distances that are greater than 5 mm in primates (Rakic 1972). RG cells can also be identified by the expression of markers such as vimentin (Dahl et al 1981), nestin (Hockfield & McKay 1985), RC2 (Misson et al 1988b), BLBP (Feng et al 1994), Pax6 (Gotz et al 1998), and GLAST (Malatesta et al 2000). The combination of morphological and marker expression criteria provide a useful standard for RG cell classification, but additional unique characteristics can be used to identify RG cells. For example, RG cell bodies undergo a to-and-fro movement during the cell cycle that is termed interkinetic nuclear migration (Misson et al 1988a, Noctor et al 2001, 2004). These nuclear movements are correlated with the cell cycle such that during S-phase RG cell bodies are situated away from the ventricle in the superficial portion of the VZ. During G2-phase the RG cells move toward the ventricle and during M-phase RG cells undergo division at the margin of the ventricle. Interkinetic nuclear migration distinguishes RG cells from other mitotic cells in the developing neocortex that do not display this behaviour, such as the IP cells (Takahashi et al 1995). Finally, RG cells guide the migration of newborn neurons and thus RG cell processes can be identified by their association with migrating neurons (Rakic 1972).

Identifying individual RG cells can be difficult because VZ cells are tightly packed in the embryonic cortex. In addition, other cell types, such as tangentially migrating interneurons, are found in the VZ (Nadarajah et al 2002), and other mitotic cell types may also be present in the VZ. Pioneers of CNS research in the 19th century, such as Wilhelm His, believed that the VZ included two cell classes, 'spongioblasts' (today known as radial glial cells), and non-process bearing 'germinal cells' that divided at the ventricular margin (see Ramón y Cajal 1995). Later work determined that spongioblasts and germinal cells were actually the same cell type at different stages of interkinetic nuclear migration (Sauer 1935). Nonetheless, the idea that the ventricular zone contains two distinct populations of progenitor cells, one dedicated to the production of neurons, and a second dedicated to the production of glial cells remained widely accepted, and was bolstered by the report that GFAP positive and negative cells coexist in the primate VZ (Levitt et al 1983). Studies of the developing neocortex that utilized scanning electron microscopy (EM) of transverse sections, or reconstruction of ultra-thin material concluded that all ventricular cells undergoing division at the ventricle, whether neuronal or glial in nature, lacked identifiable processes (e.g. Hinds & Ruffett 1971). Subsequent work showed that RG cells are mitotic and divide at the ventricular margin (Misson et al 1988a), where mitotic 'non-process bearing' cells were identified in

EM studies. This led to two assumptions: (1) that VZ cells are a mixed population of neuronal and glial precursor cells, and (2) since EM work did not detect pial fibres it was assumed that RG cells must lose or retract the pial process during division, and then presumably extend a new process to the pial surface at the start of the next cell cycle. The loss and re-growth of a pial fibre would be a formidable task given the energy expense and time that would be required to repeat this process at each successive cell cycle, especially in large cortices where pial fibres span long distances. In addition, the loss of the pial fibre during mitosis would raise important questions concerning migratory guidance. If young cortical neurons were repeatedly deprived of pial fibre guidance during the M-phase of each cell cycle, would they temporarily lose their 'sense' of direction and halt migration, or re-associate with the pial fibre of a neighbouring RG cell that was not dividing? These problems were potentially resolved by more recent studies that utilized fluorescent dyes or fluorescent reporter genes to label mitotic cells in the developing neocortex. Fluorescent markers produce an extremely bright signal that reveals fine cellular processes in great detail (Chamberlin et al 1998), making it possible to study the morphology, physiology, marker expression and behaviour of labelled cells. Contrary to the earlier morphological findings, fluorescent marker studies demonstrated that RG cells retain the entire pial process throughout division (Miyata et al 2001, Noctor et al 2001, 2002 2004, Tamamaki et al 2001, Gotz et al 2002, Weissman et al 2003; Figs 1 and 5). This finding demonstrates that retention of the pial or radial process is a common feature in cortical structures: both Bergmann glia in the postnatal cerebellum (Basco et al 1977, Noctor et al 2002), and radial astrocytes in the subgranular zone of the adult dentate gyrus (Seri et al 2004), retain radial processes during division. But, even if one assumed that dividing non-process bearing cells exist side by side with RG cells in the VZ, the demonstration that RG cells are numerous and retain a pial fibre during division raises the following question: why have EM studies failed to detect the pial process of dividing VZ cells? Several features of RG pial fibres may provide the explanation. Pial processes ascend from the VZ along a radial trajectory that is largely perpendicular with respect to the ventricular surface. The ventricular and pial contact points of RG cells appear to remain fixed during neurogenesis (Noctor et al 2004), but the pial fibre does not course along a direct path to the pia and often follows a curving course that changes across time (Fig. 2). Furthermore, the trajectory followed by pial fibres is related to the location of the RG cell along the medial–lateral and the anterior–posterior axes (Fig. 3). Thus, the orientation of a section of tissue along the medio–lateral and/or antero–posterior axis can influence whether the trajectory of a single pial fibre is contained within a single section of tissue, and pial fibres might therefore appear to be truncated, short or missing entirely. In addition, cell cycle specific changes in the pial fibre morphology may also make it difficult to trace the fibre in M-phase cells, as described below.

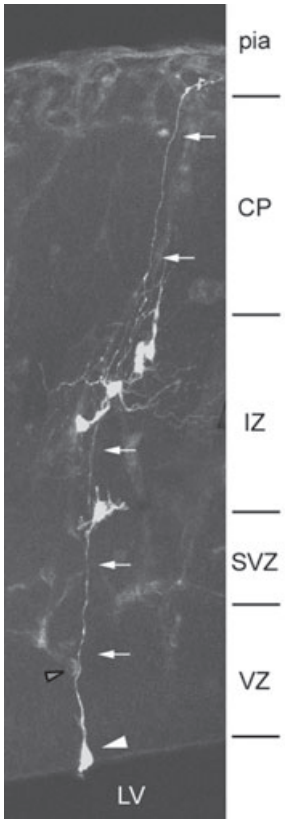

FIG. 1. Radial glial cells (white arrowhead) undergo division at the edge of the lateral ventricle and retain their pial fiber. During M-phase the cell body rounds at the margin of the ventricle, and the pial fibre (small arrows) remains intact. Several daughter cells that were produced during previous divisions are located along the pial fibre in the subventricular zone (SVZ) and intermediate zone (IZ). Blood vessels are slightly autofluorescent and can be appreciated in outline in the embryonic brain. Pial fibres contact and course adjacent to blood vessels (grey arrowhead, black outline). LV, lateral ventricle; VZ, ventricular zone; CP, cortical plate.

We further examined the RG pial fibres with an eye towards identifying features that may correlate with neural stem cell properties. We labelled mitotic RG cells with *in utero* injections of a retrovirus that carries the eGFP reporter gene (for detailed methods see Noctor et al 2004), and prepared coronal sections of fixed tissue one to three days after retroviral injections. We imaged pial fibres in time-lapse movies and confirmed that pial fibres do not retract during M-phase as previously reported (see above). In addition, we found that the diameter of the pial fibre

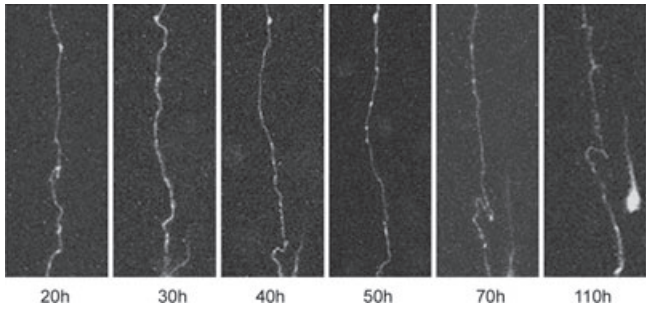

FIG. 2. The pial fibre is a dynamic structure. A RG cell was labelled with eGFP and time-lapse imaged on a laser scanning confocal microscope. The series of images show that the pial fibre course changes regularly. In the right hand panel a daughter neuron generated by the same RG cell enters the field of view as it migrates toward the cortical plate. Time elapsed is shown below each panel. From Noctor et al (2004).

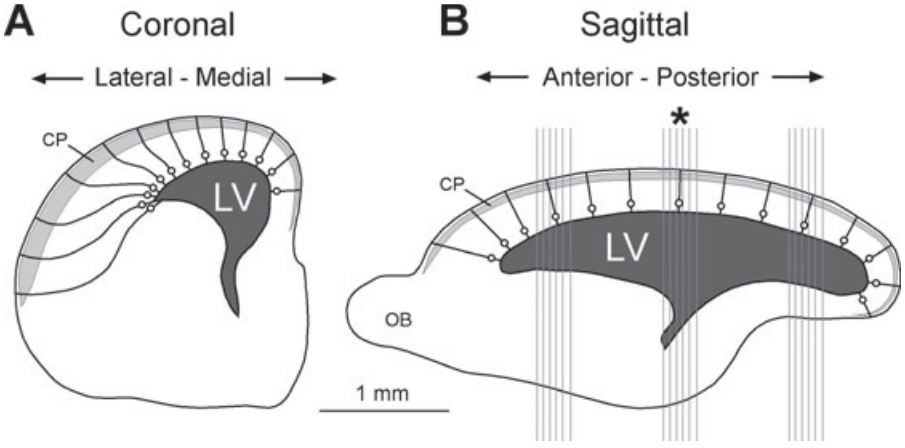

FIG. 3. Schematic drawings of cut sections prepared from the embryonic day (E)18 rat brain in the coronal plane (A), and sagittal plane (B), indicating the trajectory of RG cells (black). (A) Representation of a coronal section at the level of the anterior commissure. RG cells radiate from the surface of the lateral ventricle (dark grey) through the cortical plate (light grey) to the pia. In the dorsal neocortex pial fibres course along a trajectory that is largely perpendicular to the ventricular surface. In lateral regions the pial fibres course along a curving 'S'-shaped trajectory to the pia. (B) The trajectory of RG cells also varies along the anterior–posterior axis as shown in this sagittal section drawn to scale from an E18 rat brain. A sampling of 50 m thick sections (grey lines drawn to scale) shows that only a subset of sections in the dorsal telencephalon (asterisk) will contain the entire trajectory of the RG pial fiber. Sections obtained <500 m more anterior or posterior will contain RG cell bodies in which the pial fibre appears truncated, short or entirely missing. The same principle holds true for cortical tissue cut in any plane: i.e. only a subset of sections will contain RG cells with the entire pial fiber. Analysis in thicker sections (i.e. >200 m) yields a greater proportion of RG cells with long pial fibres. LV, lateral ventricle; CP, cortical plate; OB, olfactory bulb.

undergoes regular changes that are correlated with the RG cell cycle. The pial process is approximately 1 m in diameter during interphase, but becomes extremely thin during M phase (Figs 4 and 5). We also noted the consistent appearance of varicosities along the length of the thin pial fiber during M-phase (Fig. 4), and found that many of the varicosities stream toward the RG soma prior to the initiation of cytokinesis (Fig. 5). Upon completion of cytokinesis the pial fibre rapidly become thicker and most varicosities are no longer present or visible. The extremely thin diameter, curving trajectory, and diaphanous bridging between the fibre and the cell body during division (see Fig. 4 in Weissman et al 2003), may have further contributed to the difficulty of process identification and thus led to the conclusion that mitotic cells at the ventricular margin lack processes. The inability of previous EM based studies to find any process bearing cells in the VZ suggests that this approach is not best suited for all aspects of morphological determination in the developing neocortex.

Determining whether RG cell divisions are self-renewing is dependent on the reliable identification of both RG daughter cells. Time-lapse imaging studies have shown that only one daughter cell inherits the pial process after RG divisions (Miyata et al 2001, Noctor et al 2001, 2004, Tamamaki et al 2001), and that from

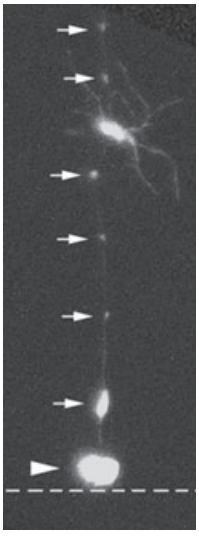

FIG. 4. M-phase radial glial cells (arrowhead) divide at the surface of the lateral ventricle (dashed line). The pial fibre becomes very thin during division but can be identified by conspicuous varicosities (arrows) along the length of the pial fibre. Shown is a radial glial cell in anaphase. A daughter cell generated at the previous cell cycle is positioned on the parental pial fibre in the SVZ. Some pial fibre varicosities are large and measure up to 3 m in diameter.

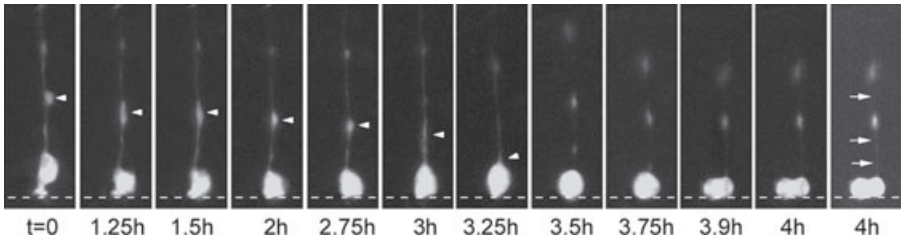

FIG. 5. Pial fibre varicosities stream toward the radial glial cell body prior to cytokinesis. A radial glial cell at the G2/M phase transition is shown in the left panel at (t = 0). The dotted white line represents the ventricular surface, and time elapsed is shown below each panel. As the radial glial cell enters M phase the soma rounds up at the surface of the ventricle, the fibre becomes thinner, and varicosities (arrow) become apparent. The varicosities stream toward the cell body prior to cytokinesis. At 4 h the cell body is in telophase, and the thin pial fibre is difficult to detect. However, increased laser power or post-hoc image contrast demonstrate that the pial fibre (white arrowheads) is still present.

mid-stages of neurogenesis until the completion of cortical neurogenesis, some RG divisions produce daughter cells that inherit the pial process, detach from the ventricle, and translocate toward the cortical plate (Miyata et al 2001, Tamamaki et al 2001, Noctor et al 2004). Miyata et al (2001) reported that daughter neurons inherit the pial process from their parent RG cell. This interpretation might indicate that RG cells do not undergo self-renewing divisions, since mother and daughter cells do not share a ventricular contacting process. However, the translocating cells described in these studies match previous descriptions of RG cells that transform into GFAP expressing astrocytes at the end of cortical neurogenesis (Schmechel & Rakic 1979, Voigt 1989). In addition, electrophysiological recordings obtained from translocating daughter cells demonstrate that they lack the inward voltage gated currents that are expressed by immature neurons (Noctor et al 2004). Furthermore, studies in the developing human neocortex have reported that translocating cells do not express neuronal specific markers (deAzevedo et al 2003). The conclusion that neurons inherit the pial process in rodents may have been flawed since it relied on the Hu antibody to identify neurons (Miyata et al 2001). This antibody is restricted to neuronal lineages, but it labels both progenitor cells and immature neurons (Miyata et al 2004). Thus, translocating cells identified as neurons on the basis of Hu immunoreactivity in previous publications (Miyata et al 2001), may have been mitotically active translocating astrocytes that are known to be present at the end of cortical neurogenesis, and that may retain the potential to produce neurons (Merkle et al 2004). GFAP positive astrocytes produce neurons in the postnatal SVZ (Doetsch et al 1999), and therefore this interpretation could link the later stages of embryonic neurogenesis with postnatal neurogenesis in the cortical SVZ. Furthermore, this interpretation suggests that

translocating cells are produced at the end of the RG lifespan, and does not rule out the hypothesis that RG cells undergo self-renewing divisions during cortical neurogenesis. In fact, live imaging studies have reported that mitotic RG cells produce daughter cells that retain the long pial process after division, resume interkinetic nuclear migration and divide at the ventricular surface, produce daughter cells with neuronal membrane properties and also support neuronal migration (Noctor et al 2004). Thus, these experiments demonstrate examples where both parent and daughter cells are RG cells based on at least three identifying criteria. These data indicate that RG cells undergo self-renewing divisions *in situ*, but do not rule out the possibility that the mother and daughter RG cells may differ in the expression of transcription factors or other genes.

The finding that embryonic neural stem cells exhibit characteristics that are similar to those described for RG cells further strengthens the claim that RG cells are neural stem cells. For example, during embryonic stem cell derivation of mouse and human neurons, the neurogenic cells appear to pass through an obligatory RG-like phase that is characterized by the formation of epithelial rosettes, the development of tight junctions, the expression of a variety of markers that are expressed by RG cells *in vivo*, and movements that resemble interkinetic nuclear migration (Perrier et al 2004, Conti et al 2005, Glaser & Brustle 2005). RG cells share additional characteristics with neural stem cells identified in other regions. For example, the RG pial fibre not only supports neuronal migration, but also makes frequent contact with blood vessels in the developing cortex (Misson et al 1988b, Noctor et al 2001; see Fig. 1, grey arrowhead). Recent work has demonstrated that neural stem cells in other regions of the brain share this feature. For example, stem cells in the adult dentate gyrus are located in clusters that are adjacent to blood vessels (Palmer et al 2000, Seri et al 2004), leading to the suggestion that endothelial cells or circulating factors influence neurogenesis in neural structures such as the embryonic neocortex (Shen et al 2004).

Temporal changes in gene expression increase cellular diversity

Neurogenesis in *Drosophila* involves the sequential expression of different genes during production of distinct neuroblasts (Brody & Odenwald 2005). Previous work in the developing neocortex has provided evidence to support this molecular model in the developing cerebral cortex. For example, the transcription factor Otx1 is expressed in the VZ only during the generation of deep layer cortical neurons (Frantz et al 1994). Additional genes and transcription factors such as M-fng (Ishii et al 2000), Svet1 (Tarabykin 2001), Cux1 and 2 (Nieto et al 2004), and Er81 (Yoneshima et al 2006), have been identified that are expressed first by proliferating cells in the VZ or SVZ, and later by cortical neurons in specific layers

of the cortex. Temporal changes in gene expression by RG and IP cells during development may reflect changes in the cell generation potential. Thus, RG cells may progress along a maturational pathway of changing molecular expression patterns that might correlate with the known RG transitional cell forms: neuroepithelial cell → neurogenic RG cell → IP-genic RG cell → translocating astroglial cell → neurogenic astrocyte (see Alvarez-Buylla et al 2001). The progressive increase in GFAP expression by VZ cells that has been reported in the developing primate neocortex (Schmechel & Rakic 1979, Levitt et al 1983), may thus reflect the transition of some RG cells from the neurogenic phase to the translocating astroglial phase that is common at the end of cortical neurogenesis.

IP cells as restricted neural progenitors

At the onset of cortical neurogenesis RG cells begin producing IP cells (Haubensak et al 2004). The first generated IP cells reside within the VZ, but at later stages IP cells migrate away from the ventricle and form the SVZ (Noctor et al 2007). At this point both RG and IP cells produce cortical neurons (Haubensak et al 2004, Noctor et al 2004). However, unlike RG cells that largely divide asymmetrically during cortical neurogenesis, most embryonic IP cells primarily undergo symmetrical terminal divisions to produce paired daughter neurons (Haubensak et al 2004, Noctor et al 2004). It has not been determined whether IP cells undergo asymmetric self-renewing divisions during embryonic development, but a minority have been shown to undergo symmetrically self-renewing divisions based on the proliferative characteristics of both daughter cells (Noctor et al 2004). Embryonic IP cells are thus analogous in function to transit amplifying 'C' cells that have been identified in the postnatal and adult SVZ, since both cell types can rapidly amplify the number of specific neuronal cell types in developing and adult cortical structures (Doetsch et al 1997, Alvarez-Buylla et al 2001). In addition to neurogenic IP cells, additional distinct subsets of progenitor cells likely reside in the embryonic SVZ. For example, Olig2-expressing oligodendrocyte precursor cells are generated in the ventral forebrain, and migrate tangentially into the overlying dorsal cortex, taking a position in several structures including the embryonic SVZ (Takebayashi et al 2000). These Olig2 cells may represent the precursor cells that generate oligodendrocytes in the postnatal SVZ (Levison & Goldman 1993). Nonetheless, the relationship between IP cells and oligodendrocyte precursor cells in the SVZ remains to be determined.

Summary

RG cells undergo self-renewing divisions and generate multiple cell types including neurons, which supports the idea that RG cells are a form of neural stem cell in

the developing cortex. Embryonic IP cells, on the other hand, are more restricted in their potential and appear to be dedicated to the production of cortical neurons. Pluripotency is often used to define stem cells, but another requisite for stem cell classification is self-renewal. Neural stem cells derived from various CNS structures have the potential to self-renew indefinitely under controlled conditions (Weiss et al 1996). Neural stem cells in the adult SVZ or dentate gyrus have limited potential to generate diverse cell types *in situ*, but retain the capacity to undergo self-renewing divisions throughout adulthood. In contrast, embryonic RG cells have a greater potential to generate diverse cell types, but are only present in the neocortex during development. However, many RG cells transform into astroglial cells (Schmechel & Rakic 1979, Voigt 1989, Noctor et al 2004) after neurogenesis, and some of these transitional cell forms retain the capacity for self-renewing divisions and appear to seed the neurogenic niche in the postnatal SVZ (Merkle et al 2004). Additional transformed RG cells may persist in other regions of the cortex and reveal their neurogenic potential only under special conditions (Magavi et al 2000). Thus, RG cells may represent the embryonic form of a self-renewing lineage of cortical neural stem cells that persist in the neocortex from early development through adulthood, while embryonic IP cells and adult C cells in the SVZ may represent the unipotent progeny of the RG lineage that amplify cell numbers, but have a limited potential for self-renewal.

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