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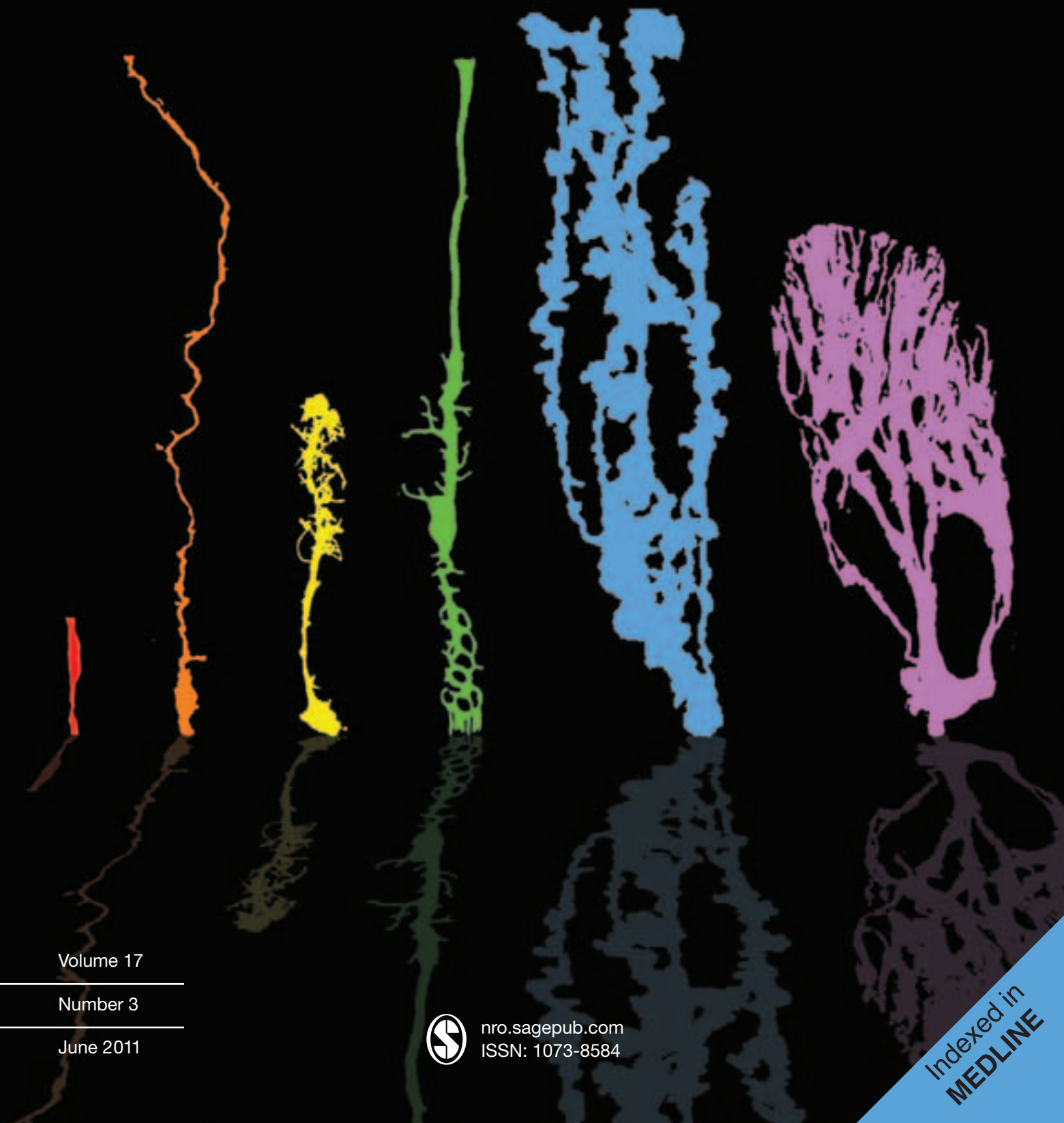

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Review

Radial Glia: Progenitor, Pathway, and Partner

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Mari Sild[1] and Edward S. Ruthazer[1]

Abstract

Radial glia (RG) are a glial cell type that can be found from the earliest stages of CNS development. They are clearly identifiable by their unique morphology, having a periventricular cell soma and a long process extending all the way to the opposite pial surface. Due to this striking morphology, RG have long been thought of as a transient substrate for neuron migration in the developing brain. In fact, RG cells, far from exclusively serving as a passive scaffold for cell migration, have a remarkably diverse range of critical functions in CNS development and function. These include serving as progenitors of neurons and glia both during development as well as in response to injury, helping to direct axonal and dendritic process outgrowth, and regulating synaptic development and function. RG also engage in extensive bidirectional signaling both with neurons and one another. This review describes the diversity of RG cell types in the CNS and discusses their many important activities.

Keywords

migration, progenitor, stem cell, synapse, central nervous system, radial glia

A Brief History of a Long Cell

Cells with long radial morphology had already been identified in the pioneering human tissue histology work of Kölliker and His (Kölliker 1879, 1882, 1896; His 1904), but it was Golgi who, by means of the silver impregnation stain, first comprehensively described radially aligned cells of apparent glial lineage, distinct from epithelial cells, in the embryonic chick spinal cord (Golgi 1885). Further investigations by Magini focused on varicosities observed on the radial glia (RG) of the developing cerebral cortices of several mammals, which Magini hypothesized to be nerve cell precursors (Magini 1888a). Magini performed double staining of cerebral wall sections using the Golgi method and hematoxylin and could identify nuclei in the varicose structures, which led him to propose that RG could function as a migrational substrate for neurons (Magini 1888b; Bentivoglio and Mazzarello 1999; Garcia-Marin and others 2007). Magini's contemporaries, Ramon y Cajal and von Lenhossék, wondering whether these elongated cells were not neuroblasts, noticed transitional states that suggested that the RG differentiate into astrocyte-like structures, thus adding support for the idea that these cells had a glial nature (von Lenhossék 1895; Ramon y Cajal 1909).

With the advent of electron microscopy came further support for the idea of RG as a scaffold for neuronal migration from the ventricular zone to cortical layers in midgestational human and monkey. The majority of young neurons were observed to be in close contact with RG fibers, having attained different distances on their journey from the ventricular zone to the upper cortical layers (Rakic 1972; Sidman and Rakic 1973). The apparent postnatal disappearance of the RG in mammals coincided with the appearance of astrocytes, which was attributed to RG differentiation into astrocytes (Schmechel and Rakic 1973, 1979). Later investigations of midgestational rat embryos using confocal time-lapse imaging, electrophysiological input resistance measurement, and immunostaining corroborated the migration of neurons along RG fibers and additionally revealed that RG are actually precursors for a diverse cell population, consisting of both neurons and glia (Noctor and others 2001). Serendipitously, adult rodent brain was discovered to actually contain populations of RG-like cells in the ventral lateral ventricle (Sundholm-Peters and others 2004), which may persist throughout adulthood (Gubert and others 2009), probably acting as

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late-stage progenitors for neurons, oligodendrocytes, ependymal cells, and astrocytes (Merkle and others 2004). In addition, RG appear to have the capacity to reemerge by dedifferentiation of mature astrocytes to support subsequent neuronal migration even in the adult brain (Leavitt and others 1999; Gubert and others 2009). To perform those different functions in a spatially and temporally correct manner, RG or astrocytes must be in constant reciprocal communication with the surrounding neuroblasts, neurons, and other elements of the environment (Ebens and others 1993; Feng and others 1994; Klaes and others 1994; Feng and Heintz 1995).

These findings, which constitute just a fraction of our increasing appreciation of the complexity of RG, illustrate that RG are not merely a passive and transient substrate for cell migration but rather a dynamic, multifaceted cell type that persists and changes its roles in response to signals from its surroundings throughout an organism's lifetime.

Radial Cells in the CNS: Radial Glia or Not?

Cells with an elongated "bottle brush" shape, extending from the ventricular zone to the pial surface of the brain and spinal cord, are not only found during embryonic neurogenesis and migration (Fig. 1). Similar morphological forms can be seen at different times in development, albeit at different locations in different vertebrate species. Fish and frogs retain a large, easily visualizable population of RG at the ventricular zone their entire lifetimes, whereas in mature mammals, the ventricular RG population is greatly reduced (Sundholm-Peters and others 2004). However, all vertebrates retain specialized RG populations in the cerebellum, retina, and spinal cord throughout life. These spatially and temporally distinct patterns have caused some confusion about the identity of the RG and resulted in usage of mixed terms in the literature. In this review, we use RG as a general term to indicate vimentin-positive glia with radial morphology, including cells with branched radial morphologies like Bergmann glia in the cerebellum.

Neuroepithelial Cells Give Rise to Ventricular Radial Glia

The neuroepithelial cells that constitute the neural plate are the first progenitors committed to a neuronal-glial fate. They give rise to RG and share a number of morphological features with the RG. Both are similarly positioned with their endfeet in the ventricular zone and their basal pole contacting the basal lamina at the pial surface (Levitt and Rakic 1980). Both neuroepithelial cells and RG exhibit interkinetic nuclear migration, where the nucleus migrates

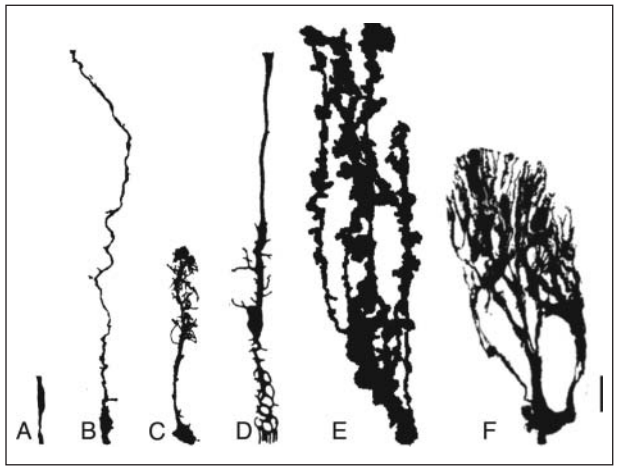

Figure 1. Diversity of radial glial cell types. (*A*) Neuroepithelial stem cell. (*B*) Ventricular radial glia (RG) cell from E20 rat neocortex (adapted from Weissman and others 2004). (*C*) Ventricular RG cell from Xenopus tadpole optic tectum (adapted from Tremblay and others 2009). (*D*) Müller glia from central retina in rabbit (Reichenbach and others 1992). (*E*) Bergmann glia from rat cerebellum (Siegel and others 1991). (*F*) Infundibular tanycyte (adapted from Fleischhauer 1972). Scale bar = 15 μm.

within the cytoplasm of the elongated cells in phase with the cell cycle (Sauer and Walker 1959; Misson and others 1988b), but unlike neuroepithelial cells, the RG nucleus does not migrate along the entire length of the cytoplasm but stays in the ventricular zone (Gotz and Huttner 2005). Both cell types express the RC1 (Edwards and others 1990) and RC2 antigens (Misson and others 1988a). The RC2 antigen has been identified as posttranslationally modified intermediate filament nestin (Park and others 2009), which is also expressed by reactive astrocytes (Clarke and others 1994).

However, neuroepithelial and RG cells are generally considered to be distinct cell types, which can be distinguished based on the expression by RG of certain astroglial markers—for example, vimentin (Schnitzer and others 1981; Perez-Alvarez and others 2008), the glial glutamate/aspartate transporter GLAST (Shibata and others 1997), tenascin C (Ferhat and others 1996), glutamine synthetase (GS), and the brain lipid binding protein (BLBP; Feng and others 1994), which are lacking in the neuroepithelial cells. Later in development (around E17 in rat), RG exchange vimentin expression for another intermediate filament marker, glial fibrillary acidic protein (GFAP), or, in some cases, coexpress vimentin and GFAP, consistent with RG having astrocyte-like properties (Dahl and others 1981; Rickmann and others 1987). Another important indication that these constitute distinct cell populations is the fact they exhibit differential regulation of a number of transcription factors. For example, neurogenic RG in the dorsal

telencephalon express the transcription factor Pax6 (Heins and others 2002), whereas neuroepithelial cells express transcription factors Sox1-3 (Bylund and others 2003). Sox1 is important for maintenance of the neuroepithelial progenitor stage, and expression of Pax6 triggers neuroepithelial cells to differentiate into RG and neurons (Suter and others 2009). RG, unlike neuroepithelial cells, have an electron-lucent cytoplasm, contact blood vessels, and contain glycogen granules, which are also characteristic features of astrocytes (Choi 1981).

The developmental transition from self-renewing, symmetrically dividing neuroepithelial cells into neurogenic RG constitutes a critical event in regulating the balance between brain growth and differentiation. During the formation of the neural tube from E8 to E9 in the mouse embryos, neuroepithelial expression of the transmembrane tight junction proteins occludin and E-cadherin, which may facilitate symmetric division, is down-regulated (Redies 1995; Aaku-Saraste and others 1996). On the other hand, RG cells become coupled by gap junctions that mediate intercellular communication, much like in astrocytes, and use connexin hemichannels for neuronal guidance purposes (Decker and Friend 1974; Nadarajah and others 2003; Elias and others 2007).

Müller Glia

Müller glia are retinal RG cells that persist in the adult retina where they constitute a major retinal cell type. Their processes traverse all the cellular and plexiform layers of the retina, forming microvilli on the apical surface, whereas their cell bodies lie in the inner nuclear layer (Dowling 1987). In the course of the development of the retina from the optic vesicle (a part of the neural tube), six major types of neurons and a single type of glial cell, the Müller glia, are formed. An important feature that distinguishes Müller glia from the neurogenic RG in other brain areas is that Müller glia appear in the retina only after the first types of neurons have already been born (Sidman 1961; Ellerbroek and others 2003). However, following injury, Müller glia have been reported to dedifferentiate into proliferating, neuronal progenitor cells (Fischer and Reh 2003; Bernardos and others 2007). Under normal conditions, Müller glia express vimentin and GS (Hojo and others 2000) but become GFAP immunopositive in response to injury (Dyer and Cepko 2000; Fischer and Reh 2003). Trace GS staining can already be detected in Müller glia progenitors and is apparent by P5 in rats (Riepe and Norenberg 1978).

Interestingly, the optical properties and radial organization of Müller glia permit them to serve as optic fibers in the retina, transferring light from the vitreous to the photoreceptors at the back of the retina. Müller glia cytoplasm contains few mitochondria, helping to reduce light scattering, and is enriched with long thin filaments that create a dielectric anisotropy. The properties of the Müller glia contrast with the rest of the retina, which is surprisingly light scattering (Franze and others 2007). Müller glia metabolize glucose and provide photoreceptor cells with lactate, α-ketoglutarate, and alanine (Poitry-Yamate and others 1995). The rate of glycolysis by these glia is regulated by the amount of ammonium and glutamate released by the photoreceptors (Tsacopoulos and others 1997a, 1997b). Müller glia, being the only macroglia in the retina, appear to be involved in a wide range of functions that elsewhere could possibly be distributed between several types of macroglia—for example, potassium homeostasis, scavenging of free radicals, release of gliotransmitters, and neurotransmitter uptake and recycling (Bringmann and others 2006). Müller glia processes seem to be adapted to the structure of the surrounding retinal layers, reaching out processes in the plexiform layers but maintaining an unbranched, smooth structure in the central retina. In addition, the Müller cell body shape is adapted to the thickness of the retina, varying from a short corpulent shape in the periphery to a thin elongated strcture in the central retina (Reichenbach and others 1989).

Bergmann Glia

Bergmann glia are a cerebellar cell type that, despite having a radial bottle brush–like morphology characteristic of RG cells, is often referred to as a "specialized astrocyte." Unlike the columnar morphology of ventricular RG, mature Bergmann glia cell somata, residing in the Purkinje cell layer, extend multiple branched processes that reach out into the molecular layer to terminate with endfeet at the pial surface or on blood vessels (Hanke and Reichenbach 1987). Bergmann glia are among the earliest cells to develop in the cerebellum and assist in the migration of Purkinje and granule cells through the molecular layer (Del Cerro and Swarz 1976; Hatten and Heintz 1995; Yuasa and others 1996). Mature Bergmann glia cell processes ensheath Purkinje neuron somata, dentrites, and both excitatory and inhibitory synapses, clearing GABA and glutamate from the synapses via transporters. A single Bergmann glia cell probably contacts several Purkinje cells, and the glial sheaths on Purkinje cell dentritic segments can be formed by processes of multiple Bergmann glia (Chaudhry and others 1995; Conti and others 1999; Ango and others 2008). Adult Bergmann glia express GS as well as intermediate filament proteins GFAP and vimentin (Schnitzer and others 1981; Bovolenta and others 1984). Vimentin-positive radial cells have been noticed in the cerebellum as early as E15 in mouse (Bovolenta and others 1984), but these fibers probably still represent progenitor ventricular

RG, which after relocation of their somata within the first postnatal days in rodents divide their process into several branches and transform into Bergmann glia (Hanke and Reichenbach 1987; Yuasa 1996; Yamada and Watanabe 2002). Bergmann glia appear to persist in the cerebellum, at least of rodents, for a lifetime, elongating their processes in concert with the thickening of the cerebellar molecular layer (Hanke and Reichenbach 1987).

Radial Glia in the Spinal Cord

At E13 in rat embryonic development, cells with radial morphology first appear among the pseudostratified layer of nestin immunopositive neuroepithelium in the nascent spinal cord. A large number of nestin- and vimentin-expressing radial cells are already visible in the spinal cord by E14, and GLAST and BLBP immunoreactivity is found in both halves of the cord by E16. GFAP expression in rat spinal cord starts at around E18 (Barry and McDermott 2005). As in the brain, neurogenic RG demonstrate regional patterns of expression of transcription factors, leading to generation of distinct neuronal progeny. In the spinal cord as early as E12.5, dorsoventral regulation of the transcription factors Pax3, Pax7, Pax6, and Nkx2.2 appears to predict the diversity and locations of progenitors (Ogawa and others 2005).

The specific roles of spinal cord RG seem to vary from organism to organism. Based on the distribution of GFAP expression, spinal cord RG in amphibians appear to have distinct functions in white and gray matter, possibly replacing the functions of both protoplasmic and fibrous astrocytes (Miller and Liuzzi 1986). Compared to amphibians, rodent spinal RG have a shorter reach and more homogeneous GFAP staining (Liuzzi and Miller 1987), probably due to relinquishing some of their functions to astrocytes. Amphibian RG surrounding the spinal cord, as observed in axolotl, target their processes to the nodes of Ranvier of the spinal white matter, which is reminiscent of perinodal astrocyte behavior in mammals. The axonal cytoplasm adjacent to the glial processes appears to be more enriched with vesicles and endoplasmatic reticulum, suggesting intercellular interaction (Sims and others 1991).

Embryonic RG-Like Cells in Adults

It is not clear whether and to what extent the adult RG-like cells in the subventricular area and dentate gyrus differ from the ventricular RG cells seen during embryonic development. RG-like cells found to reside in the subventricular zone and dentate gyrus of adult rodents share the expression of the embryonic RG marker vimentin but simulatenously express GFAP (Cameron and others 1993; Sundholm-Peters and others 2004). BLBP and GLAST have been reported to disappear from the processes of later stage subventricular RG-like cells but are still maintained in the somata (Sundholm-Peters and others 2004); according to other sources, GLAST is expressed by a small fraction of vimentin-positive cells throughout their entire structures (Gubert and others 2009). Adult RG in the dentate gyrus divide slowly but steadily and likely support the migration of newly born neurons from the hilus to the granule cell layer (Cameron and others 1993; Gould and others 1997). Indeed, the main region of neurogenesis in the adult hippocampus coincides with the localization of RG between the hilus and the granule cell layer, and the proliferating progenitors have been reported to be GFAP immunopositive (Kuhn and others 1996; Seri and others 2001; Steiner and others 2004), suggestive of RG. Mature astrocytes that express several markers in common with RG have the capability to switch on nestin expression in response to brain injury, resulting in even more overlapping marker expression with RG and possibly differing from them almost exclusively by their stellate shape (Duggal and others 1997).

Outer Ventricular Zone RG-Like Cells

The most intriguing RG-like cells are the newly discovered outer ventricular zone RG-like cells (oRG). A hallmark of the brains of primates is an expanded cerebral cortex, with three more cortical layers than reptiles and birds, which most likely accounts for their exceptional cognitive functionality (Abdel-Mannan and others 2008). The corticogenesis of primates is different as well, including appearance of a special area during midgestation known as the outer subventricular zone. This event is concurrent with the main wave of neurogenesis and proliferation that has been detected in the outer subventricular zone at that time (Rakic 1974; Lukaszewicz and others 2005). Morphological characterization of these cells revealed that they resemble RG but lack apical processes. The oRG make contact with the pial surface by means of their processes but do not contact the ventricular surface. Unlike ventricular RG and neuroepithelial cells in which the nucleus migrates along the cytoplasm without changing overall cell morphology, the nucleus of an oRG cell migrates together with the whole soma toward the pial surface before cell division, leaving no process behind. Following cell division, the daughter cell then produces its own process. oRG daughter cells appear to be progenitors for both excitatory and inhibitory neurons. Interestingly, unlike ventricular RG, which have only passive membrane properties upon depolarization, oRG cells exhibit brief inward tetrodoxin-sensitive currents, evidence that they express voltage-gated sodium channels, a property more

characteristic of excitable neurons in the central nervous system (Hansen and others 2010).

Tanycytes

Tanycytes are elongated RG-derived ependymal cells located on the floor and walls of the third ventricle that establish connections with hypothalamic neurons and with blood vessels. Tanycytes constitute a link between CSF, neurons, and blood circulation and are suggested to participate in bidirectional transportation (Brightman and Reese 1969; Wittkowski 1998; Peruzzo and others 2004). Tanycytes are morphologically similar to the ventricular RG but only appear in the ventricle around the end of embryonic development. Tanycyte populations are thought to appear as a result of the differentiation of a ventricular RG subpopulation (Rodriguez and others 2005). Tanycytes share the expression of the intermediate filament proteins GFAP and vimentin with astrocytes and RG (Redecker 1989). They also possess gap junctions (Nakai and others 1980). There are four tanycyte subclasses with different anatomical positioning, unique protein expression profiles, and distinct responses to hormones (Akmayev and others 1973; Peruzzo and others 2004). In the median eminence, tanycytes take over the maintenance of the blood-brain barrier from the endothelial cells by forming an impermeable tight junction continuum. In the arcuate nucleus, however, the tanycyte layer is permeable (Mullier and others 2010). Tanycytes are associated with neuroendocrine events—for example, regulation of the transport of gonadotrophin-releasing hormone and luteinizing hormone–releasing hormone from their source neurons to the portal blood. Tanycyte tips form a dynamic barrier between nerve endings and capillaries, which is removed in response to hormonal signals (Hokfelt 1973; King and Letourneau 1994). Although not formally considered to be an RG cell, tanycytes and RG do express some common intermediate filaments and appear to participate in similar functions such as axon guidance and synaptic plasticity regulation.

Active Participation of Radial Glia in CNS Development and Function

Radial Glia as Stem Cells

One of the most important functions of RG cells is their role as multipotent progenitors that ultimately give rise to additional progenitors, astrocytes, and neurons that will exit the proliferative zone and migrate along the processes of the radial glia that spawned them (Noctor and others 2001; Noctor and others 2008; Fig. 2). During development,

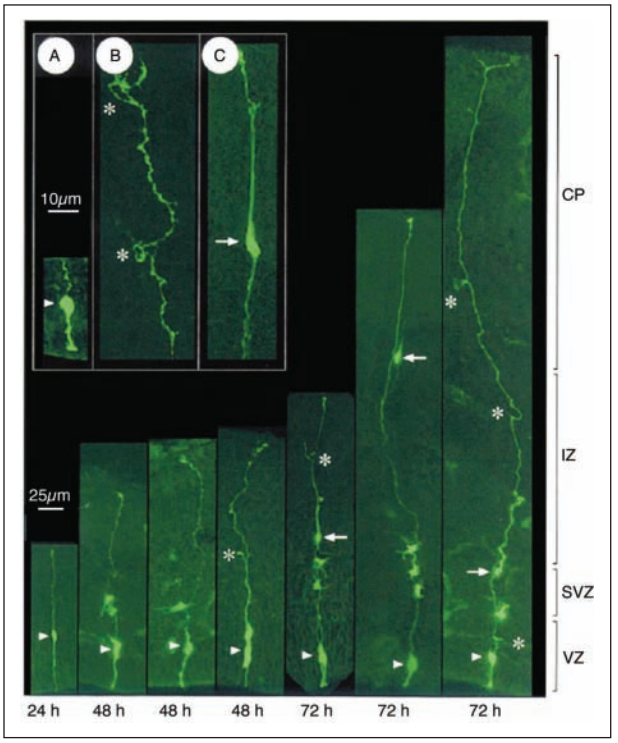

Figure 2. Radial glia as a neural progenitor. Radial clonal units 24 to 72 hours after green fluorescent protein (GFP)–expressing retrovirus infection. (*A*) Typical radial glia cell body. (*B*) Radial glia contacting blood vessels (*asterisks*). (*C*) Presumptive migrating neuron (*arrow*) on a related radial fiber. Boundaries: VZ = ventricular zone; SVZ = subventricular zone; IZ = intermediate zone; CP = cortical plate. Obtained from Noctor and others (2001).

neuroepithelial cells first differentiate into RG cells, which undergo increasingly asymmetric divisions during the period of neurogenesis. In this process, RG typically give rise to other RG cells and either a neuron or an intermediate progenitor cell (Noctor and others 2004; Gotz and Huttner 2005). The nature of RG and RG-derived progenitors depends on the local environment (Chambers and others 2001; Malatesta and others 2003), time of the development (Anthony and others 2004), exposure to signals such as Notch and Fibroblast Growth Factor 2 (Del Bene and others 2008; Shimizu and others 2008), and intrinsic signaling responsiveness (Mizutani and others 2007). Recent work in Xenopus tadpoles has revealed that sensory experience can also regulate RG proliferation (Sharma and Cline 2010).

Although it was once held that adult neurogenesis in mammals was extremely limited, newer evidence suggests that mammals are in fact not so different from other vertebrates in which extensive adult neurogenesis has long been accepted. Among the cells derived from RG is a population of GFAP-positive astrocytes called intermediate

progenitor cells that reside in the subventricular zone in adult animals and serve as neuronal precursors throughout adulthood (Doetsch and others 1999; Merkle and others 2004). Adult RG cell types such as Müller glia and adult rat spinal cord radial glia have also been demonstrated to be capable of sustained production of many differentiated cell types in the adult, mainly in response to injury. Interestingly, the prevalent cell types produced differ between spinal cord and retina, with RG in the spinal cord giving rise predominantly to oligodendrocytes and Müller glia producing neuronal cell types (Fischer and Reh 2001, 2003; Kulbatski and others 2007; Bernardos and others 2007). Bergmann glia are also a candidate adult stem cell based on their transcription factor expression profiles (Sottile and others 2006).

Several excellent reviews have recently covered the multipotent progenitor nature of RG in detail, and thus this topic will not be discussed further here (Doetsch 2003; Gotz and Huttner 2005; Pinto and Gotz 2007; Howard and others 2008; Kriegstein and Alvarez-Buylla 2009).

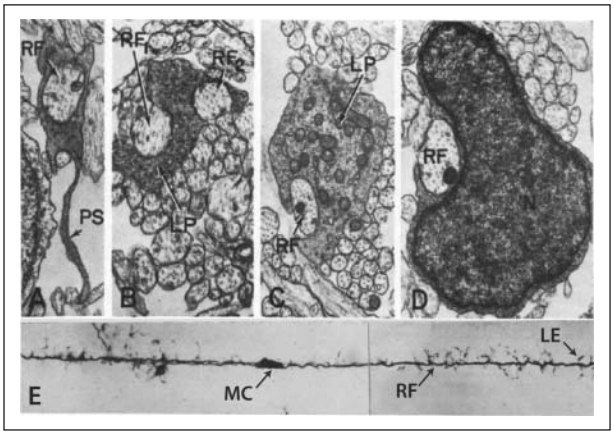

Figure 3. Radial glia as a migrational pathway for neurons. (*A–D*) Cross-section examples of neurons migrating on radial fibers in the E80 *Macacus rhesus* neocortex. (*E*) Side-view example of a radial fiber with a migrating neuron in E97 *M. rhesus* telencephalon. RF = radial fiber; LP = leading process; PS = pseudopodia; MC = migrating cell; LE = lamellate expansion; N = nucleus of migrating cell. Adapted from Rakic (1972).

Adult Generation of Radial Glia

RG can be also formed in the adult organism. It has been reported that epidermal growth factor signaling induces adult forebrain neural stem cells and ependymal cells to differentiate into functional RG in vitro and in vivo (Gregg and Weiss 2003). Mature astrocytes share several markers with RG but normally not stemness markers such as Nestin. It appears that certain cells may have the capability of shuttling between characteristics of RG and astrocytes in the mature organism, blurring the border between the natures of these two cell types. Following an ischemic insult in the brain, reactive astrocytes surrounding the ischemic site start expressing Nestin (Duggal and others 1997). In an experiment where embryonic neuroblasts were transplanted into the brains of adult mice undergoing targeted pyramidal cell apoptosis, astrocytes adjacent to the transplantation site developed a RG-like morphology and even served as migrational scaffolds for the transplanted neuroblasts (Leavitt and others 1999).

Organizing Neuronal Migration

The classic role of RG as a supportive scaffold for neuronal migration to the correct layers during early development in the neocortex and cerebellum is well accepted (Rakic, Rakic 1972; Edmondson and Hatten 1987; Noctor and others 2001). In electron microscopic images, neurons that appear to be migrating toward the cortical plate can be seen in close apposition with one or more RG, spiraling their cell body and immature processes around the radial fibers (Rakic 1971; Fig. 3). In the adult rat brain, a number of vimentin-positive RG-like cells have been found to persist and even appear to participate in neuronal migration—a small number of neurons expressing Doublecortin, a marker of migrating neurons, have been observed in close apposition with radial processes in the adult cortex (Gubert and others 2009).

It may be possible for a neuron to complete its migration to the cortical plate along a single radial fiber, but neurons have been observed with morphologies indicative of switching to adjacent radial fibers along the journey (Edmondson and Hatten 1987; O'Rourke and others 1992; O'Rourke and others 1995). In some cases, migrating cells have been observed to rapidly spring up to the pial surface upon detaching from the radial process (Morest 1970; Brittis and others 1995; Miyata and Ogawa 2007). In addition, around 30% of migrating neurons in the developing cerebral cortex slices have been inferred to travel tangentially to the glial fibers (O'Rourke and others 1992; O'Rourke and others 1995), a notion that is supported for GABAergic neurons by in vivo observations and time-lapse imaging in explants (Wichterle and others 2001; Tanaka and others 2003). Excitingly, RG have also been implicated in nonradial migration. Tangentially moving neurons in the developing ferret cortex have been shown to form several contact points between their leading process and RG cells, which implicates a mechanism of cell travel from one glial guidepost to another (O'Rourke and others 1995). Connexin 43–mediated gap junctional connections between migrating neurons and radial glia are required for normal tangential migration of excitatory neurons. Interestingly, for inhibitory neurons, knockdown of Connexin 43 does not impair tangential migration but rather impedes the switch from tangential to radial migration, necessary for interneurons to reenter the cortex after lateral migration

within the marginal zone (Elias and others 2010). These observations demonstrate that RG are not simply passive tracks for cell migration but rather actively engage in neuron-glia signaling that guides neuronal behavior.

In addition to guiding neuronal cell migration, RG also appear to interact with growth cones to help direct growing axons (Vanselow and others 1989; Norris and Kalil 1991). Callosal afferent growth cones in the P3 hamster cortex closely follow RG on their way to upper cortical layers, without being disturbed by migrating neurons on the same fibers (Norris and Kalil 1991). Cerebellar stellate cell axons proceed toward Purkinje cell dendrites by aligning to the Bergmann glial fibers (Ango and others 2008). Even the immature Purkinje cell dendrites themselves seem to extend along Bergmann glia fibers (Lordkipanidze and Dunaevsky 2005). In addition to bringing together stellate axons and Purkinje cell dendrites in the cerebellum, the adhesion molecule CHL1, expressed on Bergmann glia, appears to play a role in the formation of stellate-Purkinje synapses (Ango and others 2008). Similarly, motor neuron dendrites in the embryonic mouse spinal cord align with RG fibers that possibly mediate their encounters with axons (Henrikson and Vaughn 1974).

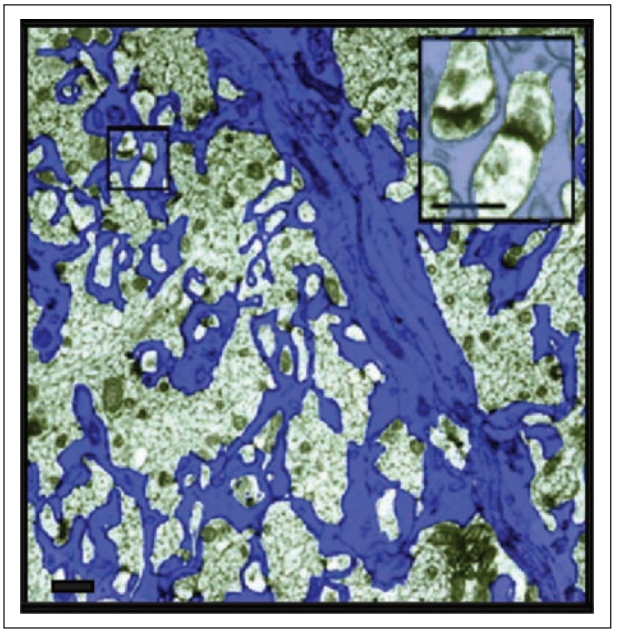

Figure 4. Radial glia interacts with synapses. Electron micrograph of Bergmann glia ensheathment of synaptic spines in the molecular layer of the adult rat cerebellar cortex. Bergmann glia processes are false-colored blue. Scale bar = 1 μm and 0.5 μm in the inset. Adapted from Iino and others (2001).

Forming, Maintaining, and Changing Synapses

Several lines of evidence implicate RG cells in various stages in the process of synaptogenesis, including by serving as a direct substrate for transient synapse formation. In the E11-14 mouse spinal cord, RG form various *puncta adherentia* contacts with axons and dendrites. Some of these contacts appear to be axoglial synapses, complete with accumulations of clear presynaptic vesicles. This phenomenon has been proposed to be a kind of mistargeted synapse. However, these axoglial synapses could conceivably have an as yet undetermined role in normal development, as the synapses onto RG disappear entirely by E15 in concert with the formation of classic axodendritic synapses in the mouse spinal cord (Henrikson and Vaughn 1974; Wolff and others 1979). Axo–radial glial contacts also have been noticed in the developing chick spinal cord, but only before E10 (Oppenheim and others 1978). There are additional descriptions of axoglial synapse-like structures in the developing rat pyramidal tract formed by glial cells that, in electron micrographs, bear a resemblance to radial glia (Gorgels 1991). Although direct experimental proof is still lacking, embryonic glia have also been speculated to support the establishment of the postsynaptic terminals through their release of GABA (Wolff and others 1979).

RG have also been shown to regulate developmental plasticity of some synapses. For example, the highly motile processes of immature Bergmann glia gradually reduce their motility over time as they form contacts that ensheath Purkinje cell synapses by late synaptogenesis (Lippman and others 2008; Fig. 4) to form microdomains within which local calcium signaling is spatially restricted to areas less than 100 μm^2 (Grosche and others 1999). In this system, reduction of glial ensheathment by experimentally reducing Bergmann glial process motility has been shown to enhance synapse formation, implying that ensheathment stabilizes certain synapses while allowing the pruning of others (Lippman and others 2008). Ventricular RG in developing optic tectum in amphibians have also been observed to extend fine processes that contact retinotectal synapses and are highly motile (Tremblay and others 2009; Fig. 5). Interestingly, the rate of their motility appears to be regulated by neural activity and sensory input through a neuronal nitric oxide–dependent signaling pathway (Fig. 6). This behavior suggests the possibility of RG participation in activity-dependent synapse remodeling in sensory system development.

In addition to a role in early synaptogenesis, persistent RG populations can also interact with synapse to maintain and modulate mature synaptic connectivity. The optic tectal radial glia persist into adulthood in fish and amphibia and presumably continue to subserve an astrocyte-like function. Tanycytes in the median eminence, for example, retain a high amount of plasticity throughout an animal's lifetime, periodically enwrapping or exposing the gonadotropin-releasing hormone and luteinizing

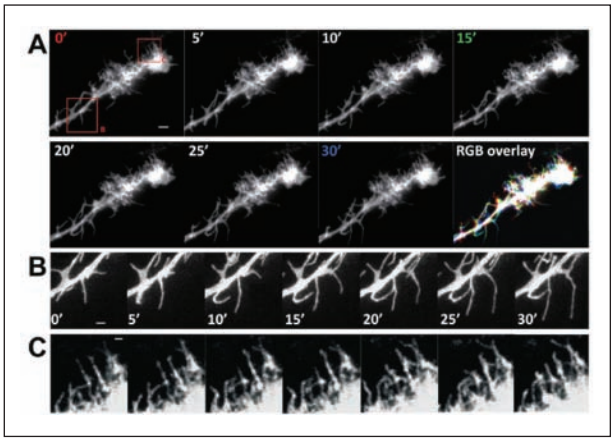

Figure 5. Radial glia processes are highly dynamic. Radial glia in intact stage 48 *Xenopus laevis* tadpole tectum, expressing farnesylated enhanced green fluorescent protein (EGFP). Images are taken after every 5 minutes for 30 minutes. RGB overlay represents overlay of red (0'), green (15'), and blue (30') images. Insets (B) and (C) are magnified in panels (*B*) and (*C*). Scale bar = 10 μm in (*A*) and 2 μm in (*B, C*). Adapted from Tremblay and others (2009).

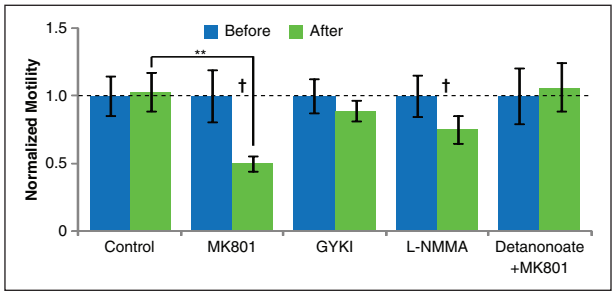

Figure 6. Radial glia structural remodeling is regulated by neuronal N-methyl-D-aspartate receptor (NMDAR) activation and nitric oxide (NO) signaling. Relative motility of stage 48 *Xenopus laevis* tectal radial glia before and after treatment with various pharmacological agents. MK801 = noncompetitive NMDAR antagonist; GYKI = GYKI-54266– noncompetitive AMPAR antagonist; L-NMMA = nitric oxide synthase inhibitor; detanonoate = NO donor molecule. Adapted from Tremblay and others (2009).

hormone axon terminals. This motility regulates hormone release to the vasculature (Hokfelt 1973; Flament-Durand and Brion 1985; King and Letourneau 1994).

The signaling pathways influencing contact-mediated synaptogenesis by RG are not clear but based on information about other types of glia they might include netrin-DCC (Colon-Ramos and others 2007), protocadherins (Garrett and Weiner 2009), ephrin-A3/EphA4 (Murai and others 2003), or thrombospondin/α2δ receptor interactions (Christopherson and others 2005; Eroglu and others 2009). Astrocyte and oligodendrocyte conditioned media are known to be synaptogenic even in glia-free cell cultures (Pfrieger and Barres 1997; Mauch and others 2001), presumably due to their content of secreted thrombospondin (Christopherson and others 2005), cholesterol (Mauch and others 2001), and D-serine, which in addition to astrocytes has been reported to be produced by Müller glia (Stevens and others 2003). Given the similarities between RG and astrocytes (Barry and McDermott 2005), the RG could well produce and release some or all of these synaptogenic agents.

A Sensitive Partner

RG are able to respond to the diverse signals from the extracellular environment that determine whether they will divide vertically or horizontally, proliferate, differentiate into glial or neuronal subtypes, act as migrational support, or change the plastic state of a synapse. One such example is the regulation of expression of the RG-specific protein BLBP, which is an important factor for maintenance of the RG phenotype (Feng and others 1994; Feng and Heintz 1995). In vitro BLBP expression by RG requires coculture with differentiating neurons, which regulates BLBP transcription via activation of multiple regulatory sequences, including the RG-specific element (RGE). One candidate for this signaling from neurons to RG is reelin, a neuronally secreted molecule, levels of which have been demonstrated to correlate with BLBP expression in vivo and in vitro and to promote RG process formation in cell culture (Hartfuss and others 2003).

From the other side, signals derived from RG also influence their neighboring neurons. Experiments in which RG signaling is perturbed lead to a failure to form proper neuronal progenitors and to regulate neuronal guidance. For example, selective loss of tuberous sclerosis complex Tsc2 and activation of the mTORC1 pathway in GFAP-positive RG in mice result in the appearance of abnormally large cells in the brain and an imbalance in the glia/neuron ratio, together with lamination and myelination defects (Way and others 2009). Deletion of the GFAP promoter-regulated ubiquitin ligase Huwe1 in the cerebellum distorts and misaligns Bergmann glia, impairs BLBP expression in the Bergmann fibers, prevents granule cell differentiation, and disrupts cerebellar lamination. Furthermore, even the Purkinje neurons in which protein expression is not manipulated appear abnormal, demonstrating the necessity of the RG-neuron interactions (D'Arca and others 2010).

Similarly to astrocytes, RG can exhibit fast changes in their intracellular Ca concentration, both spontaneously and in response to external stimuli. Müller RG in the retina respond instantly to mechanical stretch by increasing intracellular calcium concentration, subsequently followed by mitogen-activated protein kinase (MAPK) pathway,

c-fos, and basic fibroblast growth factor (bFGF) induction (Lindqvist and others 2010). Imaging experiments in awake, behaving mice, either voluntarily moving or at rest, revealed three different patterns of Ca transients in Bergmann glia, depending on the physical activity state of the mouse. The most pronounced Ca response occurred at the onset of locomotion when intracellular Ca elevation was observed to spread over hundreds of Bergmann glia cells (Nimmerjahn and others 2009). RG in the *Xenopus* optic tectum appeared to respond to visual stimulation with a significant increase in the frequency of somatic Ca transients, together with a corresponding increase in process motility (Tremblay and others 2009). Studies of RG in the rodent cortical ventricular zone have pinpointed ATP as a signaling molecule being released from the initiator RG cell to induce propagation of a Ca wave through the surrounding RG cells. ATP is thought to be released from the connexin hemichannels and acts on the purinergic P2Y1 receptors followed by activation of the phospholipase C pathway, IP3 production, and release of Ca from IP3-sensitive intracellular stores. Furthermore, disruption of RG Ca waves reduces rates of cell proliferation in the developing cortex (Weissman and others 2004). Another study demonstrated that gap junction proteins Cx43 and Cx30 are also necessary for RG proliferation and granule neuron production in adult mice (Kunze and others 2009). Even though Ca concentration was not investigated in this study, it points to gap junctions as likely bridges for the spread of Ca waves and triggering of subsequent effects. This is similar to what has been reported in astrocytes in which gap junctions are also involved in astrocyte calcium wave propagation (Venance and others 1997) and even the propagation of waves between astrocytes and neurons in culture (Nedergaard 1994). Given that RG give rise to many different progeny (Pinto and Gotz 2007), it would be of great value to understand how Ca fluctuations might translate into distinct outcomes (Yokota and Anton 2004). It is not currently known whether Ca waves in RG influence the identities of their progeny.

The existence of Ca transients in RG raises the question of whether fluctuations in intracellular Ca might participate in synaptic regulation. For astrocytes, the role of Ca transients is still contentious. It has been demonstrated in hippocampal slices that clamping astrocytic Ca levels can interfere with synaptic plasticity, apparently by preventing release of the gliotransmitter D-serine (Henneberger and others 2010). On the other hand, genetic manipulations that selectively alter astrocytic G-protein-coupled receptor Ca signaling fail to interfere with plasticity (Agulhon and others 2010). One possible explanation for this discrepancy is that local, rather than somatic, Ca signaling is critical. If this turns out to be the case, the localized Ca signaling domains that have been observed in some RG cells may contribute significantly to synaptic modulation (Grosche and others 1999). Modulation of synaptic function could also be indirectly mediated by glial functions such as neurotransmitter uptake. For example, Iino and coworkers virally overexpressed GluR2 subunits of glutamate receptors in Bergmann glial cells, resulting in decreased Ca permeability (Iino and others 2001). In response, glial processes were withdrawn from Purkinje cell spines, resulting in a decrease in glutamate clearance from synapses by glia.

Regardless of the specific contributions of Ca transients, astrocytes can participate in synaptic transmission in many ways. One of the best studied examples of glial modulation of neuronal responses is in osmoregulation in the magnocellular secretory cells in the supraoptic nucleus of the hypothalamus. Under hyperosmotic conditions and during lactation in rats, the astrocytic processes that are normally richly ramified among the somata and dendrites of the magnocellular secretory neurons withdraw, resulting in elevated ambient glutamate levels and increased activation of presynaptic metabotropic receptors (Oliet and others 2001). Furthermore, astrocytes in the supraoptic nucleus actively release the amino acid taurine under hypo-osmotic conditions to activate glycine receptors on the magnocellular secretory cells, thereby directly influencing osmoregulation (Hussy and others 1997). In brain regions where RG persevere throughout life, as well as in species such as fish and frogs where RG constitute a major CNS glial population throughout life, it is likely that Ca signaling in RG may subserve many astrocytic functions, including regulation of the extracellular milieu and gliotransmitter release.

Conclusions

The distinctive morphology and developmental profile of RG cells has long identified them as a scaffold for neuronal migration and a potential neuronal and glial progenitor. More recent work taking advantage of time-lapse imaging and functional analysis has revealed that far from simply serving a passive or predetermined role in this process, RG constitute a dynamic population of cells that changes its behavior in response to diverse cues from the environment, including neuronal activity, and even participates in the normal function of certain mature brain circuits (Fig. 7). The small cache of persistent RG cells in the mammalian CNS appears to play an important role in adult neurogenesis, especially in response to injury. In the cerebellum, the Bergmann glia may also participate more directly in synaptic function and maintenance, roles normally reserved for astroglia in other brain areas. On the other hand, in the vast majority of vertebrate species, RG are far more prevalent in the adult brain where astrocyte-like functions may be a fundamental part of their basic activity. As our ability to treat neurological disorders and injuries

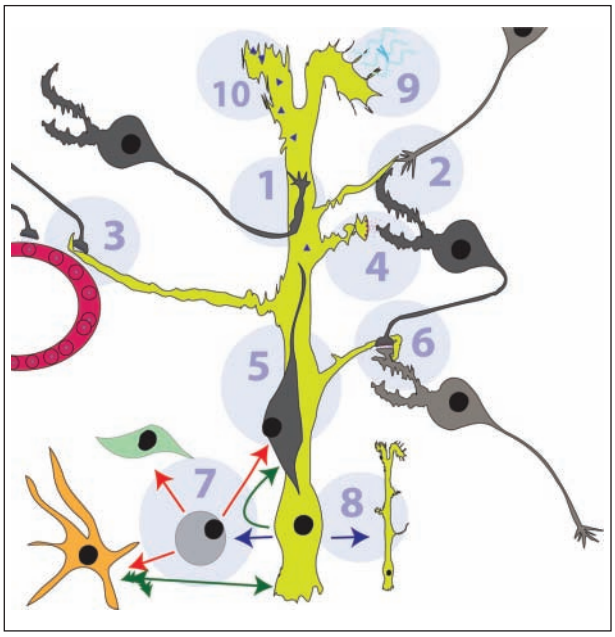

Figure 7. Radial glial (RG) activities. Schematized summarized overview of the reported properties of the different RG subtypes. 1 = RG guide the path finding of axons (vRG, BG). 2 = RG direct dendritic growth and mediate synapse formation (BG, sRG). 3 = RG regulate hormone release into the blood (T). 4 = RG initiate synaptic structures by forming transient neuroglial synapses (vRG, sRG). 5 = RG serve as migrational scaffolds for neurons (vRG, BG). 6 = RG regulate plasticity at synapses (BG, vRG, T). 7 = RG are precursors for neurons (gray), oligodendrocytes precursors (green), and astrocytes (orange) and can reemerge (e.g., following injury) by dedifferentiation of astrocytes (vRG, MG). 8 = New RG are created by symmetric division. 9 = RG act as optical fibers (MG). 10 = RG transport substances (e.g., peptides) between cerebrospinal fluid and brain compartments (T). vRG = ventricular radial glia; BG = Bergmann glia; sRG = spinal cord radial glia; MG = Müller glia; T = tanycytes.

by manipulating stem cells in the adult brain inevitably improves, these multifaceted functions of RG cells will become increasingly relevant and important to understand.

Declaration of Conflicting Interests

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References

Aaku-Saraste E, Hellwig A, Huttner WB. 1996. Loss of occludin and functional tight junctions, but not ZO-1, during neural tube closure—remodeling of the neuroepithelium prior to neurogenesis. Dev Biol 180(2):664–79.

Abdel-Mannan O, Cheung AF, Molnar Z. 2008. Evolution of cortical neurogenesis. Brain Res Bull 75(2–4):398–404.

Agulhon C, Fiacco TA, McCarthy KD. 2010. Hippocampal short- and long-term plasticity are not modulated by astrocyte Ca2+ signaling. Science 327(5970):1250–4.

Akmayev IG, Fidelina OV, Kabolova ZA, Popov AP, Schitkova TA. 1973. Morphological aspects of the hypothalamic-hypophyseal system: IV. Medial basal hypothalamus. An experimental morphological study. Z Zellforsch Mikrosk Anat 137(4):493–512.

Ango F, Wu C, Van der Want JJ, Wu P, Schachner M, Huang ZJ. 2008. Bergmann glia and the recognition molecule CHL1 organize GABAergic axons and direct innervation of Purkinje cell dendrites. PLoS Biol 6(4):e103.

Anthony TE, Klein C, Fishell G, Heintz N. 2004. Radial glia serve as neuronal progenitors in all regions of the central nervous system. Neuron 41(6):881–90.

Barry D, McDermott K. 2005. Differentiation of radial glia from radial precursor cells and transformation into astrocytes in the developing rat spinal cord. Glia 50(3):187–97.

Bentivoglio M, Mazzarello P. 1999. The history of radial glia. Brain Res Bull 49(5):305–15.

Bernardos RL, Barthel LK, Meyers JR, Raymond PA. 2007. Late-stage neuronal progenitors in the retina are radial Muller glia that function as retinal stem cells. J Neurosci 27(26): 7028–40.

Bovolenta P, Liem RK, Mason CA. 1984. Development of cerebellar astroglia: transitions in form and cytoskeletal content. Dev Biol 102(1):248–59.

Brightman MW, Reese TS. 1969. Junctions between intimately apposed cell membranes in the vertebrate brain. J Cell Biol 40(3):648–77.

Bringmann A, Pannicke T, Grosche J, Francke M, Wiedemann P, Skatchkov SN, and others. 2006. Muller cells in the healthy and diseased retina. Prog Retin Eye Res 25(4):397–424.

Brittis PA, Meiri K, Dent E, Silver J. 1995. The earliest patterns of neuronal differentiation and migration in the mammalian central nervous system. Exp Neurol 134(1):1–12.

Bylund M, Andersson E, Novitch BG, Muhr J. 2003. Vertebrate neurogenesis is counteracted by Sox1-3 activity. Nat Neurosci 6(11):1162–8.

Cameron HA, Woolley CS, McEwen BS, Gould E. 1993. Differentiation of newly born neurons and glia in the dentate gyrus of the adult rat. Neuroscience 56(2):337–44.

Chambers CB, Peng Y, Nguyen H, Gaiano N, Fishell G, Nye JS. 2001. Spatiotemporal selectivity of response to Notch1 signals in mammalian forebrain precursors. Development 128(5): 689–702.

Chaudhry FA, Lehre KP, van Lookeren Campagne M, Ottersen OP, Danbolt NC, Storm-Mathisen J. 1995. Glutamate transporters in glial plasma membranes: highly differentiated localizations revealed by quantitative ultrastructural immunocytochemistry. Neuron 15(3):711–20.

Choi BH. 1981. Radial glia of developing human fetal spinal cord: Golgi, immunohistochemical and electron microscopic study. Brain Res 227(2):249–67.

Christopherson KS, Ullian EM, Stokes CC, Mullowney CE, Hell JW, Agah A, and others. 2005. Thrombospondins are astrocyte-secreted proteins that promote CNS synaptogenesis. Cell 120(3):421–33.

Clarke SR, Shetty AK, Bradley JL, Turner DA. 1994. Reactive astrocytes express the embryonic intermediate neurofilament nestin. Neuroreport 5(15):1885–8.

Colon-Ramos DA, Margeta MA, Shen K. 2007. Glia promote local synaptogenesis through UNC-6 (netrin) signaling in C. elegans. Science 318(5847):103–6.

Conti F, Zuccarello LV, Barbaresi P, Minelli A, Brecha NC, Melone M. 1999. Neuronal, glial, and epithelial localization of gamma-aminobutyric acid transporter 2, a high-affinity gamma-aminobutyric acid plasma membrane transporter, in the cerebral cortex and neighboring structures. J Comp Neurol 409(3):482–94.

Dahl D, Rueger DC, Bignami A, Weber K, Osborn M. 1981. Vimentin, the 57 000 molecular weight protein of fibroblast filaments, is the major cytoskeletal component in immature glia. Eur J Cell Biol 24(2):191–6.

D'Arca D, Zhao X, Xu W, Ramirez-Martinez NC, Iavarone A, Lasorella A. 2010. Huwe1 ubiquitin ligase is essential to synchronize neuronal and glial differentiation in the developing cerebellum. Proc Natl Acad Sci U S A 107(13):5875–80.

Decker RS, Friend DS. 1974. Assembly of gap junctions during amphibian neurulation. J Cell Biol 62(1):32–47.

Del Bene F, Wehman AM, Link BA, Baier H. 2008. Regulation of neurogenesis by interkinetic nuclear migration through an apical-basal notch gradient. Cell 134(6):1055–65.

Del Cerro M, Swarz JR. 1976. Prenatal development of Bergmann glial fibres in rodent cerebellum. J Neurocytol 5(6): 669–76.

Doetsch F. 2003. The glial identity of neural stem cells. Nat Neurosci 6(11):1127–34.

Doetsch F, Caille I, Lim DA, Garcia-Verdugo JM, Alvarez-Buylla A. 1999. Subventricular zone astrocytes are neural stem cells in the adult mammalian brain. Cell 97(6):703–16.

Dowling JE. 1987. The retina—an approachable part of the brain. Cambridge, MA: Harvard University Press.

Duggal N, Schmidt-Kastner R, Hakim AM. 1997. Nestin expression in reactive astrocytes following focal cerebral ischemia in rats. Brain Res 768(1–2):1–9.

Dyer MA, Cepko CL. 2000. Control of Muller glial cell proliferation and activation following retinal injury. Nat Neurosci 3(9):873–80.

Ebens AJ, Garren H, Cheyette BN, Zipursky SL. 1993. The Drosophila anachronism locus: a glycoprotein secreted by glia inhibits neuroblast proliferation. Cell 74(1):15–27.

Edmondson JC, Hatten ME. 1987. Glial-guided granule neuron migration in vitro: a high-resolution time-lapse video microscopic study. J Neurosci 7(6):1928–34.

Edwards MA, Yamamoto M, Caviness VS Jr. 1990. Organization of radial glia and related cells in the developing murine CNS: an analysis based upon a new monoclonal antibody marker. Neuroscience 36(1):121–44.

Elias LA, Turmaine M, Parnavelas JG, Kriegstein AR. 2010. Connexin 43 mediates the tangential to radial migratory switch in ventrally derived cortical interneurons. J Neurosci 30(20):7072–7.

Elias LA, Wang DD, Kriegstein AR. 2007. Gap junction adhesion is necessary for radial migration in the neocortex. Nature 448(7156):901–7.

Ellerbroek SM, Wennerberg K, Burridge K. 2003. Serine phosphorylation negatively regulates RhoA in vivo. J Biol Chem 278(21):19023–31.

Eroglu C, Allen NJ, Susman MW, O'Rourke NA, Park CY, Ozkan E, and others. 2009. Gabapentin receptor alpha2delta-1 is a neuronal thrombospondin receptor responsible for excitatory CNS synaptogenesis. Cell 139(2):380–92.

Feng L, Hatten ME, Heintz N. 1994. Brain lipid-binding protein (BLBP): a novel signaling system in the developing mammalian CNS. Neuron 12(4):895–908.

Feng L, Heintz N. 1995. Differentiating neurons activate transcription of the brain lipid-binding protein gene in radial glia through a novel regulatory element. Development 121(6): 1719–30.

Ferhat L, Chevassus au Louis N, Jorquera I, Niquet J, Khrestchatisky M, Ben-Ari Y, and others. 1996. Transient increase of tenascin-C in immature hippocampus: astroglial and neuronal expression. J Neurocytol 25(1):53–66.

Fischer AJ, Reh TA. 2001. Muller glia are a potential source of neural regeneration in the postnatal chicken retina. Nat Neurosci 4(3):247–52.

Fischer AJ, Reh TA. 2003. Potential of Muller glia to become neurogenic retinal progenitor cells. Glia 43(1):70–6.

Flament-Durand J, Brion JP. 1985. Tanycytes: morphology and functions: a review. Int Rev Cytol 96:121–55.

Fleischhauer K. 1972. Ependyma and subependymal layer. In: Bourne GH, editor. The structure and function of nervous tissue. New York: Academic Press. p 1–46.

Franze K, Grosche J, Skatchkov SN, Schinkinger S, Foja C, Schild D, and others. 2007. Muller cells are living optical fibers in the vertebrate retina. Proc Natl Acad Sci U S A 104(20): 8287–92.

Garcia-Marin V, Garcia-Lopez P, Freire M. 2007. Cajal's contributions to glia research. Trends Neurosci 30(9):479–87.

Garrett AM, Weiner JA. 2009. Control of CNS synapse development by {gamma}-protocadherin-mediated astrocyte-neuron contact. J Neurosci 29(38):11723–31.

Golgi C. 1885. Sulla fina anatomia degli organi centrali del sistema nervoso. Reggio Emilia: Tipografia di Stefano Calderini e Figlio.

Gorgels TG. 1991. Junctional specializations between growth cones and glia in the developing rat pyramidal tract: synapse-like contacts and invaginations. J Comp Neurol 306(1):117–28.

Gotz M, Huttner WB. 2005. The cell biology of neurogenesis. Nat Rev Mol Cell Biol 6(10):777–88.

Gould E, McEwen BS, Tanapat P, Galea LA, Fuchs E. 1997. Neurogenesis in the dentate gyrus of the adult tree shrew is regulated by psychosocial stress and NMDA receptor activation. J Neurosci 17(7):2492–8.

Gregg C, Weiss S. 2003. Generation of functional radial glial cells by embryonic and adult forebrain neural stem cells. J Neurosci 23(37):11587–601.

Grosche J, Matyash V, Moller T, Verkhratsky A, Reichenbach A, Kettenmann H. 1999. Microdomains for neuron-glia interaction: parallel fiber signaling to Bergmann glial cells. Nat Neurosci 2(2):139–43.

Gubert F, Zaverucha-do-Valle C, Pimentel-Coelho PM, Mendez-Otero R, Santiago MF. 2009. Radial glia-like cells persist in the adult rat brain. Brain Res 1258:43–52.

Hanke S, Reichenbach A. 1987. Quantitative-morphometric aspects of Bergmann glial (Golgi epithelial) cell development in rats: a Golgi study. Anat Embryol (Berl) 177(2):183–8.

Hansen DV, Lui JH, Parker PR, Kriegstein AR. 2010. Neurogenic radial glia in the outer subventricular zone of human neocortex. Nature 464(7288):554–561.

Hartfuss E, Forster E, Bock HH, Hack MA, Leprince P, Luque JM, and others. 2003. Reelin signaling directly affects radial glia morphology and biochemical maturation. Development 130(19):4597–609.

Hatten ME, Heintz N. 1995. Mechanisms of neural patterning and specification in the developing cerebellum. Annu Rev Neurosci 18:385–408.

Heins N, Malatesta P, Cecconi F, Nakafuku M, Tucker KL, Hack MA, and others. 2002. Glial cells generate neurons: the role of the transcription factor Pax6. Nat Neurosci 5(4): 308–15.

Henneberger C, Papouin T, Oliet SH, Rusakov DA. 2010. Long-term potentiation depends on release of D-serine from astrocytes. Nature 463(7278):232–6.

Henrikson CK, Vaughn JE. 1974. Fine structural relationships between neurites and radial glial processes in developing mouse spinal cord. J Neurocytol 3(6):659–75.

His W. 1904. Die Entwickelung des menschlichen Gehirns wahrend der esten Monte. Leipzig: Hirzel.

Hojo M, Ohtsuka T, Hashimoto N, Gradwohl G, Guillemot F, Kageyama R. 2000. Glial cell fate specification modulated by the bHLH gene Hes5 in mouse retina. Development 127(12): 2515–22.

Hokfelt T. 1973. Possible site of action of dopamine in the hypothalamic pituitary control. Acta Physiol Scand 89(4):606–8.

Howard BM, Zhicheng M, Filipovic R, Moore AR, Antic SD, Zecevic N. 2008. Radial glia cells in the developing human brain. Neuroscientist 14(5):459–73.

Hussy N, Deleuze C, Pantaloni A, Desarmenien MG, Moos F. 1997. Agonist action of taurine on glycine receptors in rat supraoptic magnocellular neurones: possible role in osmoregulation. J Physiol 502(pt 3):609–21.

Iino M, Goto K, Kakegawa W, Okado H, Sudo M, Ishiuchi S, and others. 2001. Glia-synapse interaction through Ca2+-permeable AMPA receptors in Bergmann glia. Science 292(5518): 926–9.

King JC, Letourneau RJ. 1994. Luteinizing hormone-releasing hormone terminals in the median eminence of rats undergo dramatic changes after gonadectomy, as revealed by electron microscopic image analysis. Endocrinology 134(3): 1340–51.

Klaes A, Menne T, Stollewerk A, Scholz H, Klambt C. 1994. The Ets transcription factors encoded by the Drosophila gene pointed direct glial cell differentiation in the embryonic CNS. Cell 78(1):149–60.

Kölliker RAv. 1879. Entwicklungsgeschichte des Menschen und der höheren Thiere. Leipzig: Engelmann, W.

Kölliker RAv. 1882. Embryologie ou traité complet du développement de l'homme et des animaux superieurs. Schenider A, translator. Paris: Reinwald.

Kölliker RAv. 1896. Handbuch der Gewebelehre des Menschen. Leipzig: Engelmann, W.

Kriegstein A, Alvarez-Buylla A. 2009. The glial nature of embryonic and adult neural stem cells. Annu Rev Neurosci 32:149–84.

Kuhn HG, Dickinson-Anson H, Gage FH. 1996. Neurogenesis in the dentate gyrus of the adult rat: age-related decrease of neuronal progenitor proliferation. J Neurosci 16(6):2027–33.

Kulbatski I, Mothe AJ, Keating A, Hakamata Y, Kobayashi E, Tator CH. 2007. Oligodendrocytes and radial glia derived from adult rat spinal cord progenitors: morphological and immunocytochemical characterization. J Histochem Cytochem 55(3):209–22.

Kunze A, Congreso MR, Hartmann C, Wallraff-Beck A, Huttmann K, Bedner P, and others. 2009. Connexin expression by radial glia-like cells is required for neurogenesis in the adult dentate gyrus. Proc Natl Acad Sci U S A 106(27):11336–41.

Leavitt BR, Hernit-Grant CS, Macklis JD. 1999. Mature astrocytes transform into transitional radial glia within adult mouse neocortex that supports directed migration of transplanted immature neurons. Exp Neurol 157(1):43–57.

Levitt P, Rakic P. 1980. Immunoperoxidase localization of glial fibrillary acidic protein in radial glial cells and astrocytes of the developing rhesus monkey brain. J Comp Neurol 193(3):815–40.

Lindqvist N, Liu Q, Zajadacz J, Franze K, Reichenbach A. 2010. Retinal glial (Muller) cells: sensing and responding to tissue stretch. Invest Ophthalmol Vis Sci 51(3): 1683–90.

Lippman JJ, Lordkipanidze T, Buell ME, Yoon SO, Dunaevsky A. 2008. Morphogenesis and regulation of Bergmann glial processes during Purkinje cell dendritic spine ensheathment and synaptogenesis. Glia 56(13):1463–77.

Liuzzi FJ, Miller RH. 1987. Radially oriented astrocytes in the normal adult rat spinal cord. Brain Res 403(2):385–8.

Lordkipanidze T, Dunaevsky A. 2005. Purkinje cell dendrites grow in alignment with Bergmann glia. Glia 51(3):229–34.

Lukaszewicz A, Savatier P, Cortay V, Giroud P, Huissoud C, Berland M, and others. 2005. G1 phase regulation, area-specific cell cycle control, and cytoarchitectonics in the primate cortex. Neuron 47(3):353–64.

Magini G. 1888a. Nervoglia e cellule nervose cerebrali nei feti; Pavia. Tipografia Fratelli Fusi. p 281–91.

Magini G. 1888b. Ulteriori ricerche istologiche sur cervello fetale. Rendiconti della R. Accademia dei Lincei 4:760–3.

Malatesta P, Hack MA, Hartfuss E, Kettenmann H, Klinkert W, Kirchhoff F, and others. 2003. Neuronal or glial progeny: regional differences in radial glia fate. Neuron 37(5):751–64.

Mauch DH, Nagler K, Schumacher S, Goritz C, Muller EC, Otto A, and others. 2001. CNS synaptogenesis promoted by glia-derived cholesterol. Science 294(5545):1354–7.

Merkle FT, Tramontin AD, Garcia-Verdugo JM, Alvarez-Buylla A. 2004. Radial glia give rise to adult neural stem cells in the subventricular zone. Proc Natl Acad Sci U S A 101(50):17528–32.

Miller RH, Liuzzi FJ. 1986. Regional specialization of the radial glial cells of the adult frog spinal cord. J Neurocytol 15(2):187–96.

Misson JP, Edwards MA, Yamamoto M, Caviness VS Jr. 1988a. Identification of radial glial cells within the developing murine central nervous system: studies based upon a new immunohistochemical marker. Brain Res Dev Brain Res 44(1):95–108.

Misson JP, Edwards MA, Yamamoto M, Caviness VS Jr. 1988b. Mitotic cycling of radial glial cells of the fetal murine cerebral wall: a combined autoradiographic and immunohistochemical study. Brain Res 466(2):183–90.

Miyata T, Ogawa M. 2007. Twisting of neocortical progenitor cells underlies a spring-like mechanism for daughter-cell migration. Curr Biol 17(2):146–51.

Mizutani K, Yoon K, Dang L, Tokunaga A, Gaiano N. 2007. Differential Notch signalling distinguishes neural stem cells from intermediate progenitors. Nature 449(7160):351–5.

Morest DK. 1970. A study of neurogenesis in the forebrain of opossum pouch young. Z Anat Entwicklungsgesch 130(4): 265–305.

Mullier A, Bouret SG, Prevot V, Dehouck B. 2010. Differential distribution of tight junction proteins suggests a role for tanycytes in blood-hypothalamus barrier regulation in the adult mouse brain. J Comp Neurol 518(7):943–62.

Murai KK, Nguyen LN, Irie F, Yamaguchi Y, Pasquale EB. 2003. Control of hippocampal dendritic spine morphology through ephrin-A3/EphA4 signaling. Nat Neurosci 6(2):153–60.

Nadarajah B, Alifragis P, Wong RO, Parnavelas JG. 2003. Neuronal migration in the developing cerebral cortex: observations based on real-time imaging. Cereb Cortex 13(6):607–11.

Nakai Y, Kudo J, Hashimoto A. 1980. Specific cell membrane differentiation in the tanycytes and glial cells of the organum vasculosum of the lamina terminalis in dog. J Electron Microsc (Tokyo) 29(2):144–50.

Nedergaard M. 1994. Direct signaling from astrocytes to neurons in cultures of mammalian brain cells. Science 263(5154): 1768–71.

Nimmerjahn A, Mukamel EA, Schnitzer MJ. 2009. Motor behavior activates Bergmann glial networks. Neuron 62(3):400–12.

Noctor SC, Flint AC, Weissman TA, Dammerman RS, Kriegstein AR. 2001. Neurons derived from radial glial cells establish radial units in neocortex. Nature 409(6821):714–20.

Noctor SC, Martinez-Cerdeno V, Ivic L, Kriegstein AR. 2004. Cortical neurons arise in symmetric and asymmetric division zones and migrate through specific phases. Nat Neurosci 7(2):136–44.

Noctor SC, Martinez-Cerdeno V, Kriegstein AR. 2008. Distinct behaviors of neural stem and progenitor cells underlie cortical neurogenesis. J Comp Neurol 508(1):28–44.

Norris CR, Kalil K. 1991. Guidance of callosal axons by radial glia in the developing cerebral cortex. J Neurosci 11(11): 3481–92.

Ogawa Y, Takebayashi H, Takahashi M, Osumi N, Iwasaki Y, Ikenaka K. 2005. Gliogenic radial glial cells show heterogeneity in the developing mouse spinal cord. Dev Neurosci 27(6):364–77.

Oliet SH, Piet R, Poulain DA. 2001. Control of glutamate clearance and synaptic efficacy by glial coverage of neurons. Science 292(5518):923–6.

Oppenheim RW, Chu-Wang IW, Maderdrut JL. 1978. Cell death of motoneurons in the chick embryo spinal cord: III. The differentiation of motoneurons prior to their induced degeneration following limb-bud removal. J Comp Neurol 177(1):87–111.

O'Rourke NA, Dailey ME, Smith SJ, McConnell SK. 1992. Diverse migratory pathways in the developing cerebral cortex. Science 258(5080):299–302.

O'Rourke NA, Sullivan DP, Kaznowski CE, Jacobs AA, McConnell SK. 1995. Tangential migration of neurons in the developing cerebral cortex. Development 121(7):2165–76.

Park D, Xiang AP, Zhang L, Mao FF, Walton NM, Choi SS, and others. 2009. The radial glia antibody RC2 recognizes a protein encoded by Nestin. Biochem Biophys Res Commun 382(3):588–92.

Perez-Alvarez MJ, Isiegas C, Santano C, Salazar JJ, Ramirez AI, Trivino A, and others. 2008. Vimentin isoform expression in the human retina characterized with the monoclonal antibody 3CB2. J Neurosci Res 86(8):1871–83.

Peruzzo B, Pastor FE, Blazquez JL, Amat P, Rodriguez EM. 2004. Polarized endocytosis and transcytosis in the hypothalamic tanycytes of the rat. Cell Tissue Res 317(2):147–64.

Pfrieger FW, Barres BA. 1997. Synaptic efficacy enhanced by glial cells in vitro. Science 277(5332):1684–7.

Pinto L, Gotz M. 2007. Radial glial cell heterogeneity—the source of diverse progeny in the CNS. Prog Neurobiol 83(1):2–23.

Poitry-Yamate CL, Poitry S, Tsacopoulos M. 1995. Lactate released by Muller glial cells is metabolized by photoreceptors from mammalian retina. J Neurosci 15(7, pt 2):5179–91.

Rakic P. 1971. Guidance of neurons migrating to the fetal monkey neocortex. Brain Res 33(2):471–6.

Rakic P. 1972. Mode of cell migration to the superficial layers of fetal monkey neocortex. J Comp Neurol 145(1):61–83.

Rakic P. 1974. Neurons in rhesus monkey visual cortex: systematic relation between time of origin and eventual disposition. Science 183(123):425–7.

Ramon y Cajal S. 1909. Histologie du système nerveux de l'homme et des vertébrés. Paris: Maloine.

Redecker P. 1989. Immunogold electron microscopic localization of glial fibrillary acidic protein (GFAP) in neurohypophyseal pituicytes and tanycytes of the Mongolian gerbil (Meriones unguiculatus). Histochemistry 91(4):333–7.

Redies C. 1995. Cadherin expression in the developing vertebrate CNS: from neuromeres to brain nuclei and neural circuits. Exp Cell Res 220(2):243–56.

Reichenbach A, Schneider H, Leibnitz L, Reichelt W, Schaaf P, Schumann R. 1989. The structure of rabbit retinal Muller (glial) cells is adapted to the surrounding retinal layers. Anat Embryol (Berl) 180(1):71–9.

Reichenbach A, Siegel A, Senitz D, Smith TG Jr. 1992. A comparative fractal analysis of various mammalian astroglial cell types. Neuroimage 1(1):69–77.

Rickmann M, Amaral DG, Cowan WM. 1987. Organization of radial glial cells during the development of the rat dentate gyrus. J Comp Neurol 264(4):449–79.

Riepe RE, Norenberg MD. 1978. Glutamine synthetase in the developing rat retina: an immunohistochemical study. Exp Eye Res 27(4):435–44.

Rodriguez EM, Blazquez JL, Pastor FE, Pelaez B, Pena P, Peruzzo B, and others. 2005. Hypothalamic tanycytes: a key component of brain-endocrine interaction. Int Rev Cytol 247:89–164.

Sauer ME, Walker BE. 1959. Radioautographic study of interkinetic nuclear migration in the neural tube. Proc Soc Exp Biol Med 101(3):557–60.

Schmechel DE, Rakic P. 1973. Evolution of fetal radial glial cells in rhesus monkey telencephalon: a Golgi study. Anat Res 175:436.

Schmechel DE, Rakic P. 1979. A Golgi study of radial glial cells in developing monkey telencephalon: morphogenesis and transformation into astrocytes. Anat Embryol (Berl) 156(2): 115–52.

Schnitzer J, Franke WW, Schachner M. 1981. Immunocytochemical demonstration of vimentin in astrocytes and ependymal cells of developing and adult mouse nervous system. J Cell Biol 90(2):435–47.

Seri B, Garcia-Verdugo JM, McEwen BS, Alvarez-Buylla A. 2001. Astrocytes give rise to new neurons in the adult mammalian hippocampus. J Neurosci 21(18):7153–60.

Sharma P, Cline HT. 2010. Visual activity regulates neural progenitor cells in developing xenopus CNS through musashi1. Neuron 68(3):442-55.

Shibata T, Yamada K, Watanabe M, Ikenaka K, Wada K, Tanaka K, and others. 1997. Glutamate transporter GLAST is expressed in the radial glia-astrocyte lineage of developing mouse spinal cord. J Neurosci 17(23):9212–9.

Shimizu T, Kagawa T, Inoue T, Nonaka A, Takada S, Aburatani H, and others. 2008. Stabilized beta-catenin functions through TCF/LEF proteins and the Notch/RBP-Jkappa complex to promote proliferation and suppress differentiation of neural precursor cells. Mol Cell Biol 28(24): 7427–41.

Sidman RL. 1961. Histogenesis of the mouse retina studied with [3H] thymidine. In: Smelser G, editor. The structure of the eye. San Diego: Academic Press. p 487–506.

Sidman RL, Rakic P. 1973. Neuronal migration, with special reference to developing human brain: a review. Brain Res 62(1):1–35.

Siegel A, Reichenbach A, Hanke S, Senitz D, Brauer K, Smith TG Jr. 1991. Comparative morphometry of Bergmann glial (Golgi epithelial) cells: a Golgi study. Anat Embryol (Berl) 183(6):605–12.

Sims TJ, Gilmore SA, Waxman SG. 1991. Radial glia give rise to perinodal processes. Brain Res 549(1):25–35.

Sottile V, Li M, Scotting PJ. 2006. Stem cell marker expression in the Bergmann glia population of the adult mouse brain. Brain Res 1099(1):8–17.

Steiner B, Kronenberg G, Jessberger S, Brandt MD, Reuter K, Kempermann G. 2004. Differential regulation of gliogenesis in the context of adult hippocampal neurogenesis in mice. Glia 46(1):41–52.

Stevens ER, Esguerra M, Kim PM, Newman EA, Snyder SH, Zahs KR, and others. 2003. D-serine and serine racemase are present in the vertebrate retina and contribute to the physiological activation of NMDA receptors. Proc Natl Acad Sci U S A 100(11):6789–94.

Sundholm-Peters NL, Yang HK, Goings GE, Walker AS, Szele FG. 2004. Radial glia-like cells at the base of the lateral ventricles in adult mice. J Neurocytol 33(1):153–64.

Suter DM, Tirefort D, Julien S, Krause KH. 2009. A Sox1 to Pax6 switch drives neuroectoderm to radial glia progression during differentiation of mouse embryonic stem cells. Stem Cells 27(1):49–58.

Tanaka D, Nakaya Y, Yanagawa Y, Obata K, Murakami F. 2003. Multimodal tangential migration of neocortical GABAergic neurons independent of GPI-anchored proteins. Development 130(23):5803–13.

Tremblay M, Fugere V, Tsui J, Schohl A, Tavakoli A, Travencolo BA, and others. 2009. Regulation of radial glial motility by visual experience. J Neurosci 29(45):14066–76.

Tsacopoulos M, Poitry-Yamate CL, Poitry S. 1997a. Ammonium and glutamate released by neurons are signals regulating the nutritive function of a glial cell. J Neurosci 17(7):2383–90.

Tsacopoulos M, Poitry-Yamate CL, Poitry S, Perrottet P, Veuthey AL. 1997b. The nutritive function of glia is regulated by signals released by neurons. Glia 21(1):84–91.

Vanselow J, Thanos S, Godement P, Henke-Fahle S, Bonhoeffer F. 1989. Spatial arrangement of radial glia and ingrowing retinal axons in the chick optic tectum during development. Brain Res Dev Brain Res 45(1):15–27.

Venance L, Stella N, Glowinski J, Giaume C. 1997. Mechanism involved in initiation and propagation of receptor-induced intercellular calcium signaling in cultured rat astrocytes. J Neurosci 17(6):1981–92.

von Lenhossék M. 1895. Centrosom and Sphäre in den Spinalganglienzellen des Frosches. Arch mirk Anat 46:345–69.

Way SW, McKenna J III, Mietzsch U, Reith RM, Wu HC, Gambello MJ. 2009. Loss of Tsc2 in radial glia models the brain pathology of tuberous sclerosis complex in the mouse. Hum Mol Genet 18(7):1252–65.

Weissman TA, Riquelme PA, Ivic L, Flint AC, Kriegstein AR. 2004. Calcium waves propagate through radial glial cells and modulate proliferation in the developing neocortex. Neuron 43(5):647–61.

Wichterle H, Turnbull DH, Nery S, Fishell G, Alvarez-Buylla A. 2001. In utero fate mapping reveals distinct migratory pathways and fates of neurons born in the mammalian basal forebrain. Development 128(19):3759–71.

Wittkowski W. 1998. Tanycytes and pituicytes: morphological and functional aspects of neuroglial interaction. Microsc Res Tech 41(1):29–42.

Wolff JR, Rickmann M, Chronwall BM. 1979. Axo-glial synapses and GABA-accumulating glial cells in the embryonic neocortex of the rat. Cell Tissue Res 201(2):239–48.

Yamada K, Watanabe M. 2002. Cytodifferentiation of Bergmann glia and its relationship with Purkinje cells. Anat Sci Int 77(2):94–108.

Yokota Y, Anton ES. 2004. Calcium waves rule and divide radial glia. Neuron 43(5):599–601.

Yuasa S. 1996. Bergmann glial development in the mouse cerebellum as revealed by tenascin expression. Anat Embryol (Berl) 194(3):223–34.

Yuasa S, Kawamura K, Kuwano R, Ono K. 1996. Neuron-glia interrelations during migration of Purkinje cells in the mouse embryonic cerebellum. Int J Dev Neurosci 14(4): 429–38.