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What is This?

Radial Glia: Progenitor, Pathway, and Partner

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.

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, multi-faceted 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
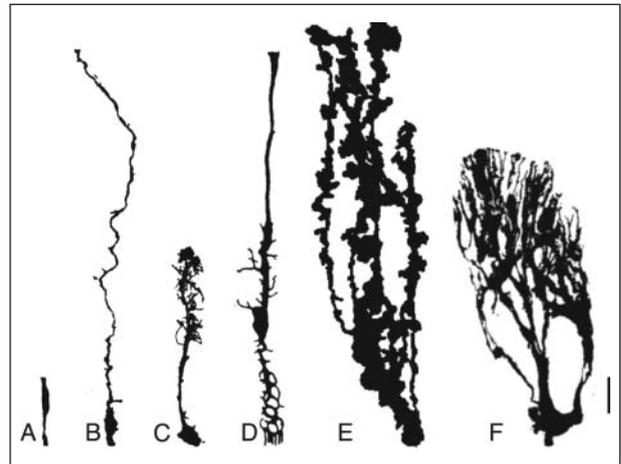
Figure 1. Diversity of radial glial cell types. (*A*) Neuroepithelial stem cell. (*B*) Ventricular radial glia (RG) cell from E20 rat neocortex (adapted from Weissman and others 2004). (*C*) Ventricular RG cell from Xenopus tadpole optic tectum (adapted from Tremblay and others 2009). (*D*) Müller glia 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 simultenously 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,
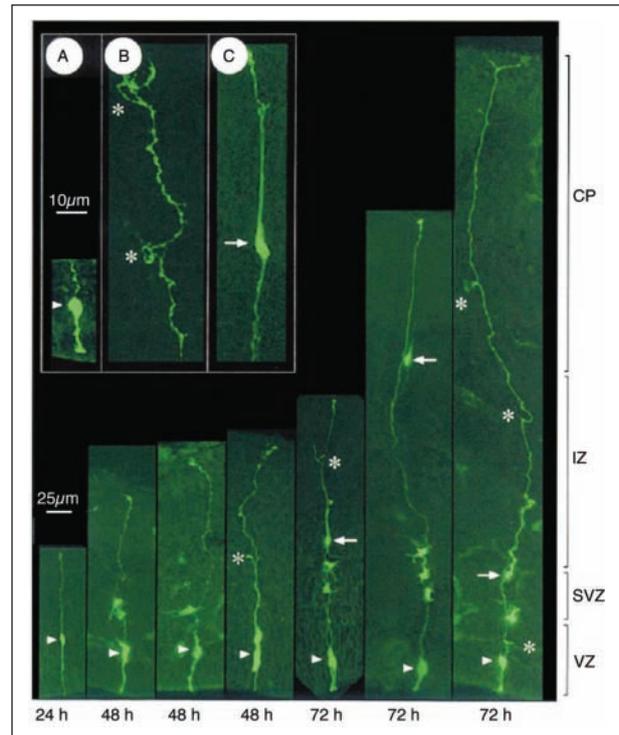
Figure 2. Radial glia as a neural progenitor. Radial clonal units 24 to 72 hours after green fluorescent protein (GFP)–expressing retrovirus infection. (*A*) Typical radial glia cell body. (*B*) Radial glia contacting blood vessels (*asterisks*). (*C*) Presumptive migrating neuron (*arrow*) on a related 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).

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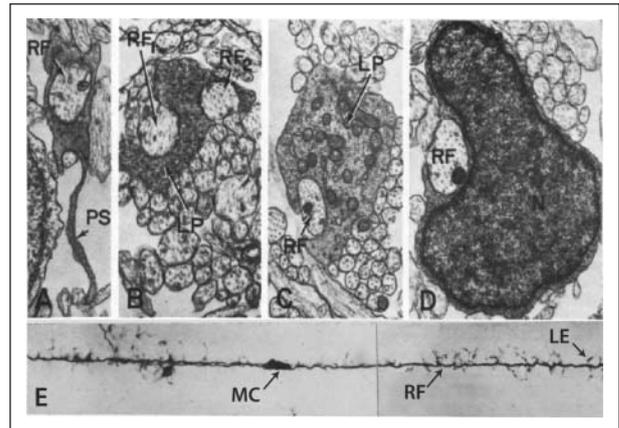
Figure 3. Radial glia as a migrational pathway for neurons. (*A–D*) Cross-section examples of neurons migrating on radial fibers in the E80 *Macacus rhesus* neocortex. (*E*) Side-view example of a radial fiber with a migrating neuron in E97 *M. rhesus* telencephalon. RF = radial fiber; LP = leading process;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

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).

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
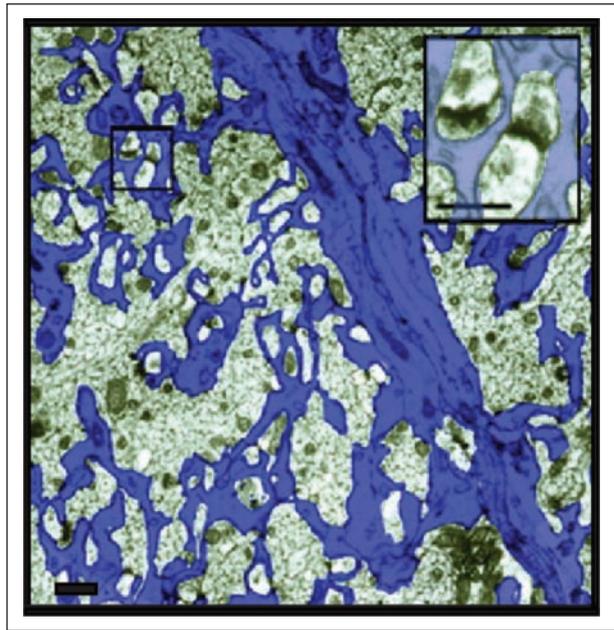

Figure 4. Radial glia interacts with synapses. Electron micrograph of Bergmann glia ensheathment of synaptic spines in the molecular layer of the adult rat cerebellar cortex. Bergmann glia processes are false-colored blue. Scale bar = 1 µm and 0.5 µm in the inset. Adapted from Iino and others (2001).

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
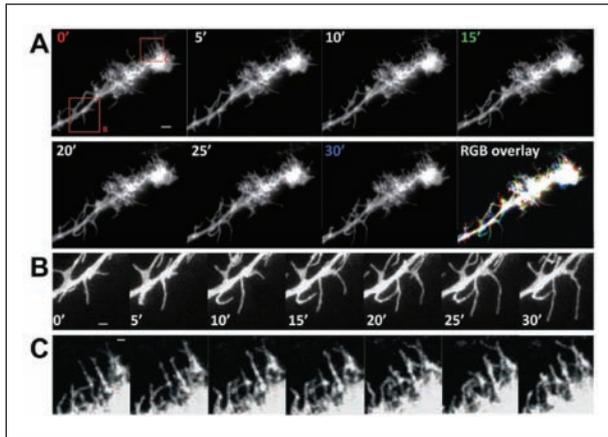
Figure 5. Radial glia processes are highly dynamic. Radial glia in intact stage 48 *Xenopus laevis* tadpole tectum, expressing farnesylated enhanced green fluorescent protein (EGFP). Images are taken after every 5 minutes for 30 minutes. RGB overlay represents overlay of red (0′), green (15′), and blue (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).
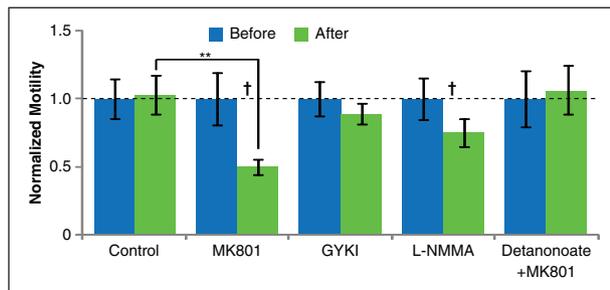
Figure 6. Radial glia structural remodeling is regulated by neuronal N-methyl-D-aspartate receptor (NMDAR) activation and nitric oxide (NO) signaling. Relative motility of stage 48 *Xenopus laevis* tectal radial glia before and after treatment with various pharmacological agents. MK801 = noncompetitive 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
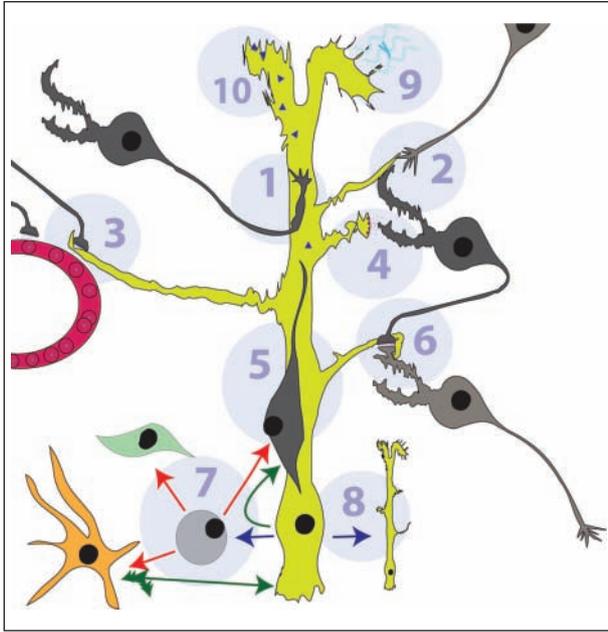
Figure 7. Radial glial (RG) activities. Schematized summarized overview of the reported properties of the different RG subtypes. 1 = RG guide the path finding of axons (vRG, BG). 2 = RG direct dendritic growth and mediate synapse formation (BG, sRG). 3 = RG regulate hormone release into the blood (T). 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.

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