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Neurosurg Clin N Am 18 (2007) 21–30

NEUROSURGERY
CLINICS
OF NORTH AMERICA

Astrocytic Stem Cells in the Adult Brain

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Most contemporary neuroscientists and neurologic surgeons were educated according to the classic view that the central nervous system (CNS) is a peculiarly nonhealing tissue. Severed nerve fibers generally do not regrow to form appropriate synaptic connections, and no new neurons are generated after perinatal development is completed. This view is colorfully encapsulated by the often-cited statement of Santiago Ramon y Cajal [1]:

> Once development was ended, the fonts of growth and regeneration of the axons and dendrites dried up irrevocably. In the adult centers, the nerve paths are something fixed, and immutable: everything may die, nothing may be regenerated. It is for the science of the future to change, if possible, this harsh decree.

Many believe that the science of the future has arrived in the form of the relatively recently discovered indigenous neural stem cells (NSCs) that persist within the brain throughout life. Although there was a small historical body of anticanonical reports hinting at persistent adult neurogenesis, appreciation for the existence of NSCs within the mature brain became widespread only after the publication of innovative methods to culture and expand these cells under highly specialized conditions in the form of clonal neurospheres (Fig. 1). Since then, substantial literature has accumulated demonstrating the presence of multipotent NSCs across virtually all regions of the neuraxis and persistent and functionally relevant neurogenesis within the subependymal zone (SEZ) and the hippocampal dentate gyrus in rodents and primates, including human beings [2]. In particular, the SEZ has been shown to generate mitotic neuronal precursors that undergo long-range migration within the rostral migratory stream (RMS) to the olfactory bulb [3]. Although most die en route to or within the olfactory bulb [4], many survive to differentiate and functionally integrate as granule cell or periglomerular cell interneurons that help to modulate incoming olfactory sensory information from the nasal epithelium. Similarly, the subgranular zone (SGZ) of the dentate gyrus has been shown to contain mitotically active cells that give rise to neuroblasts that migrate out into the granule cell layer before differentiating and sending an axonal projection to the CA3 region [5,6]. Hippocampal neurogenesis is, of course, particularly germane to human neurologic function, because it has been shown to be critically involved in learning and memory. Additionally, hippocampal neurogenesis has proven to be sensitive to a variety of modulating stimuli—positive and negative—that can dramatically influence cognition [7,8], suggesting that it may be possible to augment this system therapeutically to combat the memory decline that accompanies a variety of neurologic diseases and insults.

The connection between NSC activity and higher order brain function exemplified in the hippocampus represents the root of the greatest hope associated with NSCs—their potential use in cell replacement therapies. At some future point,

The investigators on this paper are supported by National Institutes of Health grants NS37556 and HL070143.

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doi:10.1016/j.nec.2006.10.003

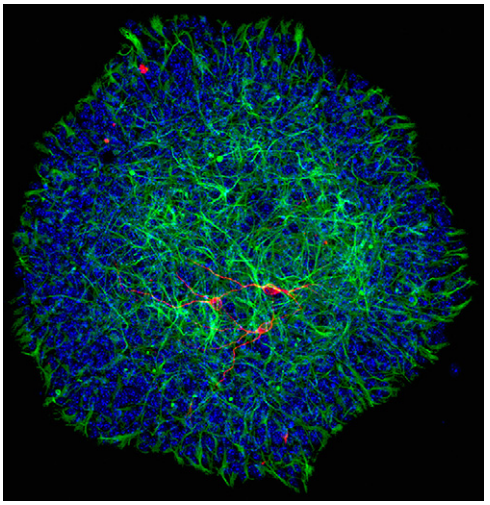

Fig. 1. An astrocytic NSC-derived neurosphere. A fluorescent micrograph of a once free-floating neurosphere in transition to adherent culture conditions demonstrates the multipotential progeny of the sphere-forming NSC. Astrocyte and neuronal progeny are illustrated by glial fibrillary acidic protein (*green*) and β-III tubulin (*red*) immunostaining, respectively. Cellular nuclei are visualized by the Hoechst stain (*blue*).

such replacement may be accomplished by in vitro expansion and transplantation or by directing the migration of indigenous NSC pools toward areas of damage or cell loss. Achieving these future goals requires a deep understanding of the unique biology and activity of these cells, beginning with the most fundamental inquiries into their particular identity.

Investigations into the identity of adult NSCs over the past decade have established with high confidence that a special type of astrocyte is primarily responsible for the persistent neurogenesis seen in vivo in the SEZ and hippocampus and in the formation of multipotent neurosphere clones seen in vitro. Although there is still no foolproof method for prospectively identifying which astrocytes in the CNS have NSC attributes, the identification of the cell type responsible for these phenomena opens the door for detailed study of their intrinsic capacity for self-renewal and differentiation as well as their ultimate suitability for therapeutic transplantation approaches and their potential role in the formation and pathogenesis of neoplasias. In this review, the authors present a historical narrative of some of the early studies that identified the astrocyte as a likely NSC candidate. Next, the authors address the largely semantic issue of whether the astrocytic NSC is a true "astrocyte" or whether a new and distinct designation would be more appropriate. Then, the authors review the defining characteristics of NSCs and compare these properties with those applied to the grandfather of all tissue-specific stem cells, the hematopoietic stem cell (HSC). Finally, the authors conclude with a discussion of the possible role of astrocytic stem cells in the genesis and progression of brain tumors.

Identity of the neural stem cell

An enduring roadblock to the study of NSC biology is the lack of effective prospective markers leading to isolation strategies from whole tissues or cell cultures. The original descriptions of techniques for culturing NSCs relied on a retrospective approach. A population of single cells was obtained from the brain and cultured under optimizing conditions. Eventually, a percentage of these cells formed multipotent clones, proving in hindsight that the starting population harbored NSCs. To prove self-renewal, this process was typically repeated with single-cell dissociates of these multipotent clones, and the formation of secondary multipotent clones was, again, retrospective evidence of the presence of NSCs. Although this approach has been fruitful for localizing, in broad terms, the existence of NSCs, prospective identification is needed if one wishes to understand and, ultimately, control the proliferation and differentiation of NSCs and their progeny. For the sake of comparison, it is instructive to consider the HSC. Once recognized only retrospectively by their ability to reconstitute the bone marrow of myeloablated hosts, living HSCs can now be prospectively identified on the basis of the selective expression of a battery of surface antigens. In fact, this method of prospective isolation now allows for the highly efficient transplantation of single HSCs that are capable of fully reconstituting ablated bone marrow [9].

As was true in the early search for the identity of the HSC, the initial investigations into the identity of the NSC began not by interrogating candidate NSCs with antibodies against surface antigens but by fractionating and testing subpopulations of previously identified cells within the system. Of cells within the mammalian CNS, the ciliated ependymal cell (EC) was perhaps the most "logical" NSC candidate. ECs are immediately subjacent to the neurogenic SEZ, and thus

seem to be appropriately positioned to serve as NSCs. More importantly, perhaps, ECs have a phylogenetic history of functioning as NSCs [10,11]. There is persuasive evidence that adult ECs respond to injury in reptiles and amphibians by dividing to generate replacement neurons throughout the CNS. Moreover, ECs have long been suspected of being responsible for the sporadic reports of adult mammalian neurogenesis after injury [12]. Experimental evidence supporting the NSC role of ECs in mammalian CNS was provided in one of the first functional tests of the NSC attributes of a prospectively identified neural cell type. Johansson and colleagues [13] examined the ability of ECs to form multipotent neurospheres in vitro by prelabeling them by means of diI (1,1′-dioctadecyl-6,6′-di(4-sulfophenyl)-3,3,3′,3′-tetramethylindocarbocyanine) infusion into the lateral ventricle. On dissociation and sorting, they then showed that labeled cells were capable of generating neurospheres with multilineage differentiation potential (ie, neurons, astrocytes, oligodendrocytes). Additionally, in support of their hypothesis that ECs are the in vivo source of NSCs, they showed that ECs ringing the central canal of the spinal cord of adult rats became proliferative and generated astrocytes after spinal cord injury. These were provocative findings, and they caused quite a stir among the nascent NSC biology community. This article was followed in rapid succession by a series of reports that immediately called into question the conclusion that ECs are the NSCs, however. Chiasson and colleagues [14], also in 1999, used mechanical microdissection to isolate the EC layer and showed that although ECs were capable of forming clonal structures, these structures were not true neurospheres because they were invariably unipotent, giving rise only to cells identified as astrocytes on the basis of glial fibrillary acidic protein (GFAP) antigenicity. Almost simultaneously, Doestsch and colleagues [15] repeated the diI labeling protocol used in the Johanssen study [13]. Results from this study indicated that although intraventricular diI does label the EC layer, the dye is apparently transferred to other cells in vivo or in vitro during the neurosphere-culturing step. Additional experiments reported in this same study, using cellular tracers that do not show evidence of intercellular transfer (ie, rhodamine beads, adenovirus), revealed that ECs labeled by means of a contralateral ventricular injection of tracer failed to form neurospheres and, in fact, disappeared from the cultures altogether. Neurospheres were obtained only from periventricular tissue obtained ipsilateral to the injection, and these injections invariably resulted in some labeling of SEZ cells because of leakage of tracer from the needle penetration. Shortly thereafter, we and our colleagues in this laboratory published a study examining the ability of single dissociated ECs, identified visually by their rhythmically beating cilia, to generate neurospheres [16]. Our results were concordant with those described in the study by Chiasson and colleagues [14]; that is, individual ECs formed only unipotent clones of GFAP-positive astrocytic cells. These negative findings, combined with the lack of persuasive confirmatory studies (even to this day) supporting the notion that ECs have NSC attributes, strongly suggest that ECs neither normally divide in vivo nor generate multipotent neurospheres in vitro, and therefore are not likely to represent the NSC. These disparate results are possibly attributable to discrete transfer of diI from ECs to cells of the SEZ before or during the dissociation step of neurosphere culture. It is still not known, however, why Chiasson and colleagues [14] and we were able to show unipotent clone formation by cultured ECs, whereas Doetsch and colleagues [15], using similar culture techniques, were not.

If ECs do not possess NSC attributes, the list of logical candidates can be reduced to the population of cells that inhabit the SEZ—the area of the greatest persistent neurogenesis and the highest density of neurosphere-forming cells [17]. Extensive ultrastructural analysis of the SEZ by investigators in the laboratory of Alvarez-Buylla identified three major constituents of this region [18]. The most abundant SEZ cells are the highly proliferative neuroblasts, called type A cells. Type A cells are the neuronally committed precursors that migrate through the RMS to the olfactory bulb, wherein a fraction of them differentiate into granule or periglomerular interneurons. There is also a second highly proliferative cell with an ambiguous phenotype, called the type C cell, which seems to function as a transit-amplifying intermediary between the NSC and the migrating neuroblasts. Finally, there is a slowly dividing SEZ astrocyte, called the type B cell, that seems to display many characteristics of the NSC. In addition to expressing GFAP, type B cells were shown by ultrastructure to have irregular and invaginated nuclei, and their cytoplasm contained intermediate filaments and dense bodies. Subsequent experiments showed that the highly proliferative SEZ constituents

can be ablated by antimitotic drugs or ionizing radiation but that the normal SEZ anatomy can regenerate after such depletion [15,19]. By careful ultrastructural examination of the SEZ during ablation or regeneration, Doetsch and colleagues [15] of the Alvarez-Buylla group showed that the B-cell astrocyte survives the ablation and divides to generate the type C cell. The type C cell, in turn, divides to generate the rapidly dividing type A cells that migrate to the olfactory bulb. This, then, suggested that a special type of astrocyte residing within the SEZ might be the NSC responsible for persistent neurogenesis in vivo and the generation of multipotent neurospheres in vitro. This same group showed that cells expressing GFAP can give rise to neurons in vivo. Using a transgenic mouse model that allows for the selective retroviral infection of GFAP-expressing cells with a constitutive reporter gene, these investigators showed that labeled astrocytes within the SEZ and SGZ give rise to olfactory bulb interneurons and hippocampal granule neurons, respectively [5,15]. At about the same time, we used the same transgenic system to show that astrocytes cultured from the adult mouse SEZ could form neurospheres capable of glial and neuronal differentiation [16]. We also showed in this study that a subset of GFAP-expressing astrocytic cells obtained from the cerebral cortex, cerebellum, and spinal cord are capable of forming neurospheres but only when obtained from animals younger than approximately postnatal day 12. Because this age corresponds closely to the disappearance of radial glia in most regions of the mouse CNS and because the neurogenic type B-cell astrocyte of Alvarez-Buylla's group maintains some radial glia-like morphologic characteristics, we interpreted this latter result as evidence that radial glia or immature astrocytes are the in vivo representation of the NSC. Since these initial studies, there have been numerous confirmatory studies supporting the astrocytic identity of the NSC, at least in the adult, including the human [20] brain. That is not to say, however, that cells with an astrocyte phenotype are the only cells with apparent attributes of multipotent progenitors. Kondo and Raff [21] published a study showing that cultured oligodendrocyte precursors (OPCs) isolated from the early postnatal rat optic nerve could be induced to generate all three neural lineages by manipulation of the in vitro conditions, including the substrate and the presence of mitogens. These precursors were also able to form sphere-like structures when cultured under conditions of anchorage withdrawal, but the potency of these structures was not reported. One unusual and interesting aspect of this study is that the conversion of OPCs to multipotent progenitors was observed only after the OPCs were induced to differentiate into type 2 astrocytes by culturing in, and then withdrawing, serum, platelet-derived growth factor (PDGF), and bone morphogenetic protein (BMP). Subsequently, another group reported that human white matter contains a glial progenitor cell that can be prospectively enriched on the basis of CNP expression (a protein associated with oligodendroglial progenitor cells) and can be induced to generate neurons and multipotent neurospheres [22]. It may be that with enough experimental manipulation, many different types of cells can be induced to acquire NSC properties. There is evidence that seemingly differentiated neurons can switch their phenotype to acquire astrocyte characteristics, including antigenic profile and membrane physiology [16,23]. The authors have proposed elsewhere that cells exist developmentally along a continuum stretching from noncommitted and multipotent to fully differentiated and functionally mature but that there may be instances in which cell fate may move "backward" along this continuum, especially during early ontogeny [24]. Therefore, it is perhaps not surprising that a variety of cells show NSC attributes in vitro. Nevertheless, a preponderance of the evidence suggests that the cell responsible for normal maintenance of the persistently neurogenic regions of the brain—the NSC—is a cell with apparent astrocytic phenotypy.

Astrocytic family

Astrocytes that display adult NSC characteristics have persuasively been shown to express the astrocytic cytoskeletal protein GFAP [25,26]. These NSCs also lack many of the classically accepted characteristics of astrocytes, however, particularly functional features, such as regulation of extracellular neurotransmitter concentration. Thus, there is a growing chorus of researchers who are uncomfortable with the designation of these cells as astrocytes and agree with the sentiment that "It is far past time to stop calling every neural cell in the brain that is not a neuron, a glial cell" [27]. It is true that allowing diverse and nonoverlapping criteria to define a variety of astrocytic cells is unique for neural lineages. For instance, although there are many different subtypes of neurons, they can all be said to share

the functional property of synaptic transmission. Similarly, a cardinal feature of oligodendrocytes is the production of myelin, and the ensheathment of axons. Thus, has the NSC been inappropriately identified as an astrocyte? Should this classification be reconsidered, perhaps with a view to developing new nomenclature uniquely to describe stem cells in the brain? The authors of the current review think not. Although they agree with Kimelberg [28] that astrocytic identity is sometimes difficult to establish "…because it is unusually multifunctional," they maintain that it is appropriate to expand the functional definition of the astrocyte family to include the subpopulation of cells that possess NSC characteristics for at least three reasons: phylogeny, ontogeny, and convention.

Phylogenetic analysis allows the authors to address the sometimes confusing phenotype of astrocytes by constructing an "astrocytic family" of cells in the mammalian brain that are functionally related to the ependymoglial cell of lower vertebrates (Fig. 2). In lizards and reptiles, the amazingly multifunctional ependymoglial cell is the predominant astrocytic cell type [10,11]. Ependymoglia are radially oriented throughout life and are thought to guide the migration of neuroblasts generated near the periventricular germinal matrix. Additionally, these cells have been shown to divide to generate functional neurons after lesions of the spinal cord [29–33] and cerebral cortex [34–36]. Ependymoglia maintain ciliated connections with the ventricle and are also responsible for phagocytic injury response functions. Thus, it is clear that the functions encapsulated by the ependymoglial cell of lower vertebrates are subserved by an astrocytic family of distinct but related cells in the mammalian brain. Radial glia serve as migration scaffolds for newly generated neurons during early development and have themselves been shown to be neurogenic [37–39]. ECs in the mammalian brain line and project cilia and microvilli into the ventricles [40]. Mature astrocytes can become "reactive" after injury and perform some phagocytic and wound delimiting "scar" functions [41,42]. Finally, as discussed previously, a subpopulation of astrocytic cells within the secondary germinal matrices of the SEZ and hippocampus are persistently neurogenic throughout life.

Ontogenic analysis also reveals the interrelatedness of the major NSC candidates as members of the astrocytic family. Radial glia have long been recognized as antecedents of stellate astrocytes [43,44], and new evidence suggests that ECs also develop from radial glia [40]. Expression of GFAP, at least during certain developmental stages or after injury, is also a feature shared by radial glia, astrocytes, and ECs [45], and there is evidence that mouse ECs of the choroid plexus can differentiate into GFAP-expressing astrocytes after transplantation to the injured spinal cord [46]. Additionally, the authors and others have shown that clones of GFAP-positive cells developed from prospectively identified ECs [14,16].

Finally, convention suggests that adult NSC features be lumped in with the multifunctionality of astrocytes rather than splitting these cells into a separate category. The fact is that, prima facie, adult NSCs in vitro and in vivo simply seem like astrocytes. A picker of nits can and will point out that this or that astrocyte feature that is missing from astrocytic NSCs; however, for years, there has been a large umbrella over the diverse cells that are considered "astrocytes" in the adult brain, and this has seemingly not cast a pall of confusion over the field. Type I and II astrocytes are clearly distinct morphologically and functionally; yet, both are considered to be astrocytes. Likewise, Bergmann glia of the cerebellum and Müller glia of the retina are also commonly subsumed under the astrocyte designation. The authors believe that the overall phenotypic *gestalt* of the adult NSC is that of an astrocyte and that it should be referred to as such for the sake of common understanding.

Neural stem cell characteristics

In comparison to other tissue-specific stem cells, such as the HSC, the defining aspects of NSCs are shrouded in ambiguity. This ambiguity can cause considerable confusion and usually results in NSC biologists talking past researchers from other stem cell fields, who generally have a much more rigorous definition of what constitutes a true stem cell (Box 1).

In the initial glow of excitement over the descriptions of substantial adult neurogenesis and the persistence of neural stem-like cells, the actual fundamental characteristics of NSCs were, for the most part, poorly delineated and varied greatly between laboratories. For instance, within the persistent germinal matrices in vivo—the SEZ and hippocampal dentate gyrus—the most stem cell progeny are neurons. Nevertheless, multilineage differentiation in the form of neurons, astrocytes, and oligodendrocytes is considered an indispensable in vitro characteristic of NSCs.

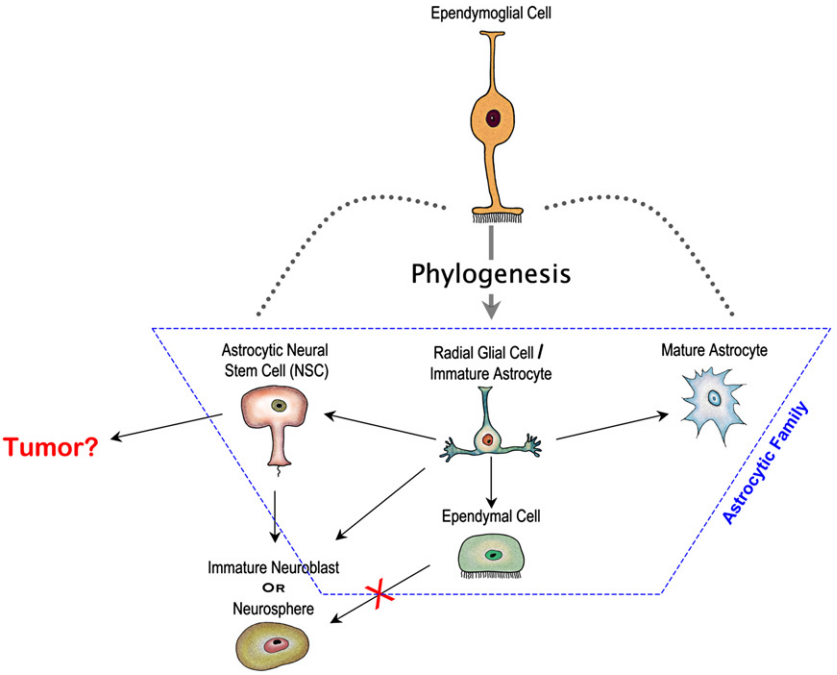

Fig. 2. A synopsis of the research that has led to the current insight into the identity and activity of the astrocytic NSC. When probing for the identity of the NSC, the EC presents a regionally appropriate and phylogenetically "attractive" possibility. Although Johansson and colleagues [13] reported on the stem-like properties of this cell type, scrupulous repetition of their experiments and further examinations have returned conflicting results, thus shedding doubt about the credibility of the ependymal NSC. Therefore, if not the EC, the next logical candidates are the cellular populations of the periventricular SEZ, based on the large proportion of neurosphere-forming cells arising from this highly neurogenic region. By the combination of exhaustive ultrastructural analyses with key ablation and reconstitution studies, persuasive evidence has earmarked an astrocytic cell of the SEZ as the NSC. Therefore, this SEZ-derived astrocyte represents the cell type responsible for multipotent neurosphere generation in vitro and ongoing adult functional neurogenesis in vivo. Phylogenetically, the multiple functions encapsulated by the stem-like ependymoglial cell of cold-blooded vertebrates seem to have been parceled off into individual astrocytic cells, suggesting that the mammalian NSC may also reside within the astrocytic populations of the brain. To complicate matters, although the SEZ is the repository of the greatest neurogenic activity in the adult brain, multipotent stem-like cells have been isolated across essentially all regions of the neuraxis. Evidence suggests that these non-SEZ NSCs represent an additional multipotent astrocyte-like cell, possibly a transitional radial glial cell or immature astrocyte whose astrocytic stem cell qualities are silenced after its eventual transformation into a mature astrocyte. There is a recurring theme within the NSC literature minimizing the similarities and highlighting distinct differences between the astrocytic stem cell of the SEZ and the mature astrocyte population of the adult brain. Consequently, contention mounts over the astrocytic nature of the NSC and the appropriateness of referring to the NSC as an astrocyte. Regardless of whether one refers to the NSC as an astrocyte or more loosely astrocyte-like, however, there is persuasive evidence that the NSC shares many properties of astrocytes; as such, the authors have chosen to consider the NSC as being part of a greater astrocytic family. Seeking the identity of the cell(s) responsible for ongoing neurogenesis in the adult brain has inspired detailed study of the intrinsic capacities of candidate cell types for the cornerstone features of stemness: self-renewal and multipotential differentiation. In addition, these fundamental biologic investigations may translate clinically into the replacement or transplantation approaches wherein these neurogenic cells may be driven to recapitulate neurogenesis in the injured adult brain and make a real impact in the restoration of lost nervous system function. Painted in this glowing light, the promise of the NSC seems without limit. Nevertheless, investigation has highlighted a potential role for these astrocytic stem cells in cancer. Because of their persistent proliferation and resultant risk for genetic mutation, their potential for oncogenic transformation and tumorigenesis must be closely evaluated.

Box 1. Quick reference: comparison of the HSC and the NSC

	HSC	NSC
Multipotential progeny	Yes	Yes
Extensive self-renewal	Yes	Yes
Serial reconstitution of the germinal niche	Yes	No(?)
Consensus surface antigen profile for prospective screening and isolation	Yes	No(?)

Self-renewal is also generally required for NSC designation, although there is considerable confusion regarding how extensive self-renewal should be to distinguish true NSCs from long-term progenitor cells. Most investigators would accept that one round of self-renewal is not enough to determine "stemness," but how many are required? By contrasting with the hematopoietic system, one can see how "loose" is the definition of the functional attributes of NSCs. Although there is some intralaboratory variability in the antigenic profile used to select HSCs from whole blood or bone marrow, there is general agreement that the HSC is defined functionally as an extensively self-renewing cell capable of multilineage differentiation that can fully reconstitute depleted bone marrow in a serial transplantation paradigm. This means that a single HSC transplanted into a myeloablated host must reconstitute all the blood lineages for the duration of that animal's life. Furthermore, it must be possible to again isolate a single HSC from such a recipient and use it to reconstitute the blood lineages of a second myeloablated host for life. Clearly, then, from the perspective of the hematopoietic field, the salient attributes of NSCs may seem relatively inadequate and poorly defined. Nevertheless, although recognizing the need to define the in vitro and in vivo properties that characterize NSCs clearly, the authors believe that each tissue-specific adult stem cell may require its own unique functional definition and that it may be inappropriate to force a simulacrum of the HSC definition onto the NSC. Indeed, to do so is to flirt with unnecessary scrupulosity, given that the CNS is far more static that the hematopoietic system and the constituent cells generally persist throughout life and are not replaced in toto.

Astrocytic stem cells and tumorigenesis

As described previously, there has been significant progress toward identifying the adult NSC, which is a first step in answering Cajal's charge to future science; however, there is also burgeoning evidence implicating the NSC in brain cancer pathogenesis. Because of their persistent proliferation and resultant risk for genetic mutation, the potential of NSCs for oncogenic transformation and tumorigenesis must be respected and evaluated.

Investigators in our laboratory originally showed [47] that human gliomas possess a population of apparently abnormal NSCs that lead to lineage diversity in vitro and potential primary involvement in the same diversity as seen in human cortical gliomas. We found that these cells generated neurons and astrocytes in culture and that cells in these cultures exhibited abnormal *notch-delta* gene expression profiles as well as mutant *p53* expression. Subsequent studies by Hemmati and colleagues [48], Singh and coworkers [49], Galli and colleagues [50], and Phillips and coworkers [51] have supported the cancer stem cell hypothesis in human gliomas, and this field has been nicely summarized in recent review articles on glioma stem cell biology [52,53].

The expression of developmentally regulated extracellular matrix molecules (eg, tenascin glycoprotein) and maintenance of a persistent neurogenic state seem to be hallmarks of astrocytic stem cells during normal development and tumorigenesis. A recent study by Phillips and coworkers [51] using expression profiling of high-grade gliomas to look for genes involved in neurogenesis (proneural genes) as well as angiogenic and mesenchymal signatures has noted strong similarities between gliomagenesis and developmental neurogenesis. This could implicate a neurogenic astrocyte in this abnormal growth process, leading to astrocytoma and glioblastoma. Sanai and colleagues [52] have suggested that a "maturation arrest theory" is feasible in this process, whereby neoplastic transformation of a glial progenitor cell could lead to an astrocytoma and additional mutations and subsequent degeneration of the astrocytoma could lead to rapidly growing glioblastomagenesis with a complete arrest of maturation. Vescovi and colleagues [53] further propose that the different developmental status of cells within neurogenic niches of the adult human brain could contribute to different types of brain tumors after oncogenic transformation. Loss of certain genes,

including $p16_{INK4a}$ and $p19_{ARF}$, enables astrocytic dedifferentiation [54] in response to epidermal growth factor (EGF) receptor activation. These investigators also transduced NSCs and astrocytes with these genes and generated a high-grade glioma phenotype. These genes are normally involved in maintaining astrocytic terminal differentiation; hence, these findings suggest a description of "…NSC and astrocytes as equally permissive compartments for gliomagenesis…" [55]. The concept of dedifferentiation in tumors has received additional support recently from our findings that osteosarcoma has tumor-initiating cells that express the embryonic stem cell genes Oct3/4 and Nanog [56].

A report by Aboody and collaborators [57] showed remarkable tropism of NSCs for intracranial gliomas, and another recent study [58] showed that the "glioma tropic neural stem cells consist of astrocytic precursors" whose homing to tumor cells behavior is mediated by the well-characterized SDF-1/CXCR4 chemokine and its receptor. Just as in normal neuropoiesis and reactive neurogenesis, brain tumorigenesis and stem cell tracking of brain tumors involve the stem cell and morphogenetic molecular interactions mediated by cytokines, growth factors, and the extracellular matrix. Ziu and coworkers [59] have extended these tropism findings by showing that NSC-glioma tropism is mediated by extracellular matrix molecules that may be left as a "trail" by the disseminating invasive metastatic cell, leaving a tumor mass to wreak havoc in distant CNS sites. In this study, tenascin was the "…strongest inducer of a directed human NSC migration (haptotaxis)…," just as the authors find it to be a most prominent matrix molecule component of cultured human glioma stem-like cells [47].

In conclusion, the common theme of normal and abnormal astrocytic stem cells during neuropoiesis and brain tumorigenesis suggests that regardless of nomenclature issues, a cell with astrotypic characteristics seems to be involved in all these tissue-building and remodeling events. Such guilt or glory by association of a cell that not that long ago was viewed as a terminally differentiated macroglial element involved in neuronal caretaking, brain homeostasis, and blood-brain barrier functions suggests there is still a great deal to learn about indigenous CNS stem cell populations. With a goal of cell repopulation after neurologic injury or disease and deterring the hyperplastic growth of potent cells that leads to tumorigenesis within the CNS, elucidating factors that may selectively target the proliferation and differentiation of astrocytic stem cells seems to be worthy for regenerative medicine and restorative neurosurgery.

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