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## Stem Cells, Radial Glial Cells, and a Unified Origin of Brain Tumors

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*AJNR Am J Neuroradiol* 2010, 31 (3) 389-390

doi: <https://doi.org/10.3174/ajnr.A1674>

<http://www.ajnr.org/content/31/3/389>

This information is current as  
of May 10, 2025.

## Stem Cells, Radial Glial Cells, and a Unified Origin of Brain Tumors

It is now clear that what we think of as groups of tumors (eg, astrocytomas, ependymomas, and medulloblastomas), based on their conventional histology, immunohistochemistry, and imaging features, comprise several subtypes of neoplasias that have specific biologic, molecular, and genetic features.<sup>1</sup> Until recently, it was thought that ependymomas originated from neuroepithelial cells, glioblastomas from abnormal astrocytes, and medulloblastomas from primitive cells in the external granular layer, but there is now evidence that all originate from a special type of stem cell called the “radial glial cell” (RGC). Currently, the consensus of opinion is that most brain tumors also originate from the so-called “brain tumor stem cells” (of which RGCs are a subtype).<sup>1</sup>

Stem cells may be found in the embryo, placenta, fetal blood and fetus, and in adults. Adult stem cell lines are predominantly located in muscle, skin, bone marrow, liver, blood, eyes, and brain. Normally, brain stem cells differentiate into different types, giving origin to neurons, astrocytes, oligodendrocytes, and ependymal cells (the traditional “no new neuron” theory is incorrect and no longer accepted; neurogenesis is thought to be a constant activity throughout life).<sup>2</sup> Neural stem cells have specific functional, molecular, and antigenic properties. Because stem cells are perennial, their functional integrity is at risk for malignant degeneration, but because brain stem cells are needed throughout our lifespan, they also tend to be inherently resistant to drugs and toxins.<sup>3</sup> Brain stem cells have a large rate of proliferation, particularly those located in the subventricular zones (SVZ), and we know rapid proliferation may lead to genetic errors.<sup>4</sup>

When brain tumor stem cells mutate (4–7 mutations are needed before degeneration occurs), they can generate phenotypically diverse tumors. Within a specific tumor, brain tumor stem cells constitute only a small fraction of the total malignant cells.<sup>2</sup> Mutations may be induced by intrinsic cell factors (“fragile” DNA) or extrinsic ones (viruses, carcinogens). A function of brain tumor stem cells is to maintain the bulk of differentiated tumor cells, as they harbor properties of self-renewal (they maintain their number through life), extensive proliferation, and an ability to change into different lines (at this phase they are called “tumor progenitor cells”), following a hierarchic rather than a stochastic model of growth.<sup>2</sup> For example, mutated brain tumor stem cells stimulated by epidermal and fibroblast growth factors express neural markers such as nestin and CD133 (a cell surface protein), committing them to a neural lineage (conversely leukemia tumor stem cells express CD34 and are CD133-negative).

However, some stem neural tumor cells may be also CD133-negative.<sup>1</sup> A practical difference is that CD133-positive cells tend to repair their DNA damage earlier and better and thus tend to be more resistant to radiation and chemotherapy; as such, glioblastomas respond very differently to treatment, depending on their CD133 status.<sup>1</sup> Tumor stem cells responsible for medulloblastoma express *BMI1* and sonic

hedgehog effectors (*GLI1–3*), which positively regulate cell renewal and proliferation, thus making them more resistant to conventional treatments.<sup>1–4</sup> Another important tumor suppressor is PTEN, which controls proliferation of brain stem cells. Glioblastomas with inactivation of PTEN have a more favorable prognosis.

As stated before, stem cells become tumor progenitor cells and, in turn, become differentiated tumor cells (1 or more distinct tumor cell pools may form).<sup>5</sup> Stem cells may bypass this sequence to produce tumors with single and multiple cell lineages (ie, tumors arise directly from stem cells). If differentiated, tumor cells tend to give origin to brain tumors with a single lineage, but they may undergo dedifferentiation and produce tumors with multiple cell lineages.<sup>1,2</sup> Most aggressive brain tumors harbor morphologically different cell types, suggesting that differentiation into multiple cellular lines occurs preferentially in them, whereas most benign tumors contain cells that are similar in shape and size.

It is interesting to note that in the human brain, most stem cells are located in the SVZ. Both supra- and infratentorially and when stimulated with carcinogens, cells in the SVZ become tumorigenic faster than those located elsewhere. In the SVZ, stem cells exist in the form of RGCs. RGCs remain quiescent until they receive transformational signals. It is not clear if RGCs, after receiving transformation signals, return to their initial stem cell configuration and then become tumorigenic or if they transform to tumor progenitor cells directly.<sup>1–4</sup> In the cerebellum, depending upon the signals received, RGCs and stem cells may give origin to either ependymoma or medulloblastoma. Abnormal stem cells are also responsible for glioblastomas. Tumors with the highest incidence in humans—medulloblastomas and glioblastomas—both originate from abnormal brain stem cells. Not surprising, both of these tumors are CD133-positive (as they contain neuronal differentiation), which makes them prone to be diffuse and resistant to treatment. Their RGCs are thought to be genetically abnormal and harbor oncogenes that lead to production of transformative factors. Because abnormal RGCs generate tumor cells that migrate, glioblastomas tend to multifocality (the eventual geographic fate of normal RGCs is not known). In the rest of this editorial, I will concentrate on the role of the RGC in the genesis of ependymoma and its implications.

We know that there are 3 types of ependymoma based on location: cerebellar, supratentorial, and spinal (all occurring along the walls of ependymal-lined cavities). Except for the myxopapillary type, all 3 types have similar initial histology but different prognoses and sex predilections, occur at different ages (posterior fossa ones are found in the youngest patients), and have distinct clinical behaviors suggesting they are separate diseases (cerebral and cerebellar ones may become anaplastic, whereas spinal ones almost never do). Nowadays, these 3 tumor types are recognized as being different. Ependymomas arising in the cerebral hemispheres (nearly always outside but adjacent to the lateral ventricles in the region of the RGCs) express *EPHB-EPHRIN* and *NOTCH* signaling systems and show an abnormality in 9p21.3.<sup>1</sup> Spinal cord ones express *HOX* (homeobox) genes and have an abnormal 22q12 (they arise around the central spinal canal in the ventral cord, as *HOX* genes are involved in the ventral/dorsal modeling of the cord), whereas those in the posterior fossa express *AQP1*, tend

to have a balanced karyotype, and always arise in the SVZ, projecting in or outside of the fourth ventricle.<sup>1</sup> Experiments have determined that the tumor progenitor cells in ependymoma correspond to RGCs.<sup>1</sup> Transplantation of these RGC-like cancer stem cells into the brains of rats produces ependymomas. It is also interesting to note that RGCs exposed to *EMX2* give origin to supratentorial ependymoma in childhood but not in adults (*EMX2* is called a “negative regulator”). As neuroradiologists, we not uncommonly see protruberances of tissue of normal signal intensities along the walls of the lateral ventricles. These generally correspond to hyperplastic astrocytic polyps. Meddling with the function of *EPHB-EPHRIN* in the SVZ interrupts neuroblast migration resulting in astrocytic proliferation and formation of polyps.

What are the clinical implications of these discoveries? Normally, the human body defends its stem cells very well, so if brain tumors originate from these cells, it is safe to assume that the new lineages will be resistant to the damage induced by conventional radiation and chemotherapies. Emphasis is being placed on targeting the pathways that regulate the life cycles of cancer stem cells. For example, cells from ependymomas and certain leukemias produce a substance called  $\gamma$ -secretase, which is involved in aberrant cancer cell renewal via activation of *NOTCH* signaling. Inhibitors of this secretase are being tried in patients with leukemia and are being considered for treatment of children with advanced ependymoma within the US Pediatric Brain Tumor Consortium.<sup>1-5</sup> Conventional therapies tend to kill normal and tumor cells but not the resistant brain tumor stem cells that eventually regenerate the tumor (this is the reason why glioblastomas always recur). In addition, the effect of conventional therapies on tumor cells is limited as they cannot effectively target all of the different cell lineages.

It is clear what we have historically called ependymomas comprise at least 3 tumors that are developmentally and molecularly distinct, and new and different treatments will be needed for each subgroup. Similarly, glioblastomas and medulloblastomas comprise different subtypes that determine patients' outcomes (at least 2 different glioblastoma subtypes are clearly recognizable). In the future, cultivation of individual brain tumor cells may lead to identification of specific molecular markers, which, in turn, may be used to prescribe personalized treatment protocols. Stem cells can also be engineered to produce substances (interleukins, metalloproteinases) that may induce tumor regression. Immortalized stem cells given through intravascular delivery migrate toward tumors. The use of stem cells as Trojan horses is currently experimental and it is possible that as they pass through the lung capillaries their migration towards the brain may be interrupted.

This topic is of enormous complexity, and I have attempted to simplify it. I have based—and extensively quoted—most of the information expressed here on the 5 references cited below. Anyone who is interested in this topic is encouraged to read these articles.

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DOI 10.3174/ajnr.A1674

## EDITORIAL

### Dirty-Appearing White Matter: A Disregarded Entity in Multiple Sclerosis

In patients with multiple sclerosis (MS), the term *dirty-appearing white matter* (DAWM) refers to brain regions of intermediate signal intensity between those of focal lesions and normal-appearing white matter (NAWM) on T2-weighted and proton attenuation-weighted images.<sup>1-4</sup> Such an abnormality tends to affect more frequently the deep WM, especially that around the ventricles. Defining the extent of DAWM is, however, a challenging task, because signal intensity changes associated with it are difficult to clearly separate from those of the surrounding tissues. As a consequence, DAWM abnormalities have been disregarded by most MR imaging studies of MS.

The pathology of MS lesions has been studied extensively, and it has been shown that focal areas of increased signal intensity on T2-weighted images are characterized by the presence of heterogeneous substrates, including edema, inflammation, demyelination, remyelination, gliosis, and axonal loss.<sup>5,6</sup> In contrast, the pathologic substrates of DAWM abnormalities have been investigated only recently.<sup>1,4</sup> Moore et al<sup>1</sup> demonstrated a loss of myelin phospholipids as well as axonal reduction whose extents are intermediate between those of discrete lesions and NAWM. In a similar setting, Seewann et al<sup>4</sup> detected axonal loss, reduced myelin attenuation, and chronic fibrillary gliosis in the DAWM of 10 patients with chronic MS. It is intriguing to note that the chronic nature of the process occurring in the DAWM was supported by the absence of acute axonal pathologic features, remyelination, and blood-brain barrier leakage. These findings support the notion that DAWM pathology might result from a secondary degenerative process remote from focal lesions. However, other seminal MR studies<sup>2,3</sup> suggested that DAWM abnormalities may represent early microscopic lesions that have the potential to evolve subsequently to discrete T2-visible changes. If this is the case, the use of high-field strength magnets should have allowed the detection of such tiny lesions, but a study conducted at 4.7T was unable to resolve focal abnormalities in the DAWM of patients with MS.<sup>4</sup>

During the past 2 decades, the application of quantitative MR-based techniques has partially contributed to overcome