

Review Article

On the Genesis of Neuroblastoma and Glioma

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As the emergence of cancer is most frequent in proliferating tissues, replication errors are considered to be at the base of this disease. This review concentrates mainly on two neural cancers, neuroblastoma and glioma, with completely different backgrounds that are well documented with respect to their ontogeny. Although clinical data on other cancers of the nervous system are available, usually little can be said about their origins. Neuroblastoma is initiated in the embryo at a moment when the nervous system (NS) is in full expansion and occasionally genomic damage can lead to neoplasia. Glioma, to the contrary, occurs in the adult brain supposed to be mostly in a postmitotic state. According to current consensus, neural stem cells located in the subventricular zone (SVZ) in the adult are thought to accumulate enough genomic mutations to diverge on a carcinogenic course leading to diverse forms of glioma. After weighing the pros and cons of this current hypothesis in this review, it will be argued that this may be improbable, yielding to the original old concept of glial origin of glioma.

1. The Origins of Neural Cancers

Several hypotheses on the origin of cancers in general and those of the nervous system in particular have been proposed in the last century [1]. Currently, most hypotheses are based on the idea that a cancer is the result of the accumulation of several mutations, estimated at about 6 [2]. For this accumulation to occur, the precancer cell must be a cell that divides regularly such as those that form the nervous system during embryogenesis. Neuroblastoma is a childhood cancer of the nervous system in which the N-myc protooncogene transcription factor (N-myc) is often overexpressed [3]. This transcription factor is essential during neurogenesis for the rapid expansion of progenitor cell populations. It is encoded by the neuroblastoma-derived myelocytomatosis oncogene (MYCN). Overexpression of MYCN in transgenic mice indeed causes neuroblastoma in their pups [4]. It has been speculated that glioma and glioblastoma might arise from astrocytes with appropriate genetic abnormalities because astrocytes and their progenitors were, for long, the only cell types known to be capable of replication in the adult NS [5–7]. Expression of a mutated, constitutively active, epidermal growth factor receptor (EGFR) gene in mice

brain causes glioblastoma-like lesions [8] and infection with the viral oncogene v-ERB, a homologue of EGFR, initiates oligodendroglioma in mice [9].

Glial tumours are generally of a heterogeneous composition, containing cells with astrocytic, oligodendrocytic, and neuronal properties [10–13], indicating the presence of multipotent cells within the tumour. These multipotent cells might be the result of progenitor cell dedifferentiation in an abnormal environment [14, 15] or by oncogenic mutation [11]. Since the discovery of neural multipotent cells in the adult NS [16], the hypothesis that mutations accumulated in stem cells and their more committed progenitor offspring are at the origin of tumours of the NS meets almost general consensus [2].

During the life of an organism, many cells are created and many chromosome copies are made, which are almost inevitably accompanied by error. Evolution has put into place four mechanisms to limit the propagation of DNA damage and the risk of mutation-driven, uncontrolled proliferation.

First, only a few trustworthy stem cells are allowed to maintain the potential to divide during all of the organism's life span. This trustworthiness is achieved by dividing only rarely and by retaining the template copy of DNA at each

(asymmetrical) division [17, 18]. Hence, because the original DNA is retained by the stem cell, no telomere erosion takes place and, with the exception of double strand breaks, no copy errors can occur. It is the daughter progenitor cell that receives the possibly faulty copy.

Second, a stem cell generates progenitor cells by asymmetrical division that subsequently divide a limited number of times (they have their telomeres eroded) and that progressively lose the potential to differentiate into more than one phenotype. Their differentiated offspring becomes senescent and eventually dies, preventing genomic errors that possibly occurred in the course of its existence to spread and to develop into malignancy.

Third, if important DNA damage occurs that cannot be repaired, interleukins are secreted invoking an immune response and removal of the deficient cell. When telomeres become too short, a similar DNA damage response is elicited which implies increased activity of the tumour suppressor p53/p21 pathway. Natural killers, macrophages, and T-cells contribute to clearance of deficient cells [19].

Fourth, stem cells in the adult reside in niches that exert constant control over these stem cells. Stem cells need signals from the niche, in particular, endothelial cells, for proliferation and the generation of progenitor cells [20, 21].

In a perfect world, the stem cell population in adults would never need to expand by symmetrical division, and cancer would probably not exist. However, even though stem cells have taken antiapoptotic measures [22], they sometimes need to be replenished by symmetrical division, presumably to compensate for losses due to disease or other stresses [23, 24] or because stem cells might give rise to two daughter progenitor cells every now and then, thus eliminating themselves [23].

The rare symmetrical divisions necessary to replenish the stem cell store are nevertheless often designated as the principal source of carcinogenesis. Six arguments sustaining this hypothesis have been advanced as follows.

One, it is clear that postmitotic cells such as neurones cannot accumulate the number of required mutations to become a cancer cell. Cells in proliferating tissue stop proliferating after a number of cycles and are often removed. This mechanism to prevent aberrant proliferation seems to work rather well since cancer is mostly an aged man's disease [25, 26] even though several neural cancers are more frequent in early childhood than at adulthood [27]. It is likely that stem cells live long enough to accumulate the required number of mutations.

Two, stem cells are less apt to defend themselves against cytotoxic stress (of extracellular origin), because they use an error-prone DNA repair mechanism shared by quiescent cells, called nonhomologous end joining, as opposed to the more reliable homologous recombination used by proliferating cells [28].

Three, it has been shown experimentally that proliferating cells mutate more likely than senescent cells [2].

Four, cancers are clonal [29] and yet heterogeneous (e.g., neuron-, oligodendrocyte-, and astrocyte-like cells are present in GBM). Glioblastoma, pilocytic astrocytoma, and medulloblastoma give rise to these three cell types when put

in culture [10–13]. This suggests stem cell properties for at least a subpopulation in the cancer [10, 13, 29, 30].

Five, several authors suggest that the SVZ, where an important niche for adult neural stem cells is located, is the origin of glioma. Malignant glioma rarely occurs in the temporal lobe and the spinal cord [28]. It has been shown that subventricular zone cells cultured in neurobasal medium with EGF and bFGF spontaneously develop into cancer cells [31].

Six, with the exception of haematopoietic progenitors [32, 33], only germ and stem cells express telomerase, an enzyme that is also upregulated in a subpopulation of cancer cells [34].

Although several cancers may appear to result from the accumulation of mutations in stem cells, another set is likely due to mutations having occurred in more or less committed progenitors.

Firstly, Progenitor cells transfected with oncogenes such as myc and ras can develop into cancer cells [35]. A mutation that enhances β -catenin in granulocyte-macrophage progenitor cells causes chronic myeloid leukaemia [20].

Secondly, it has been observed that not all brain cancers are identical and that some appear to have limited differentiation potential: oligoastrocytoma and oligodendroglioma only give offspring that resemble oligodendrocytes and astrocytes. Neuroblastoma cells only display neuronal characteristics and do not differentiate into glial cells [4]. This suggests that the original cancer cells were not stem cells but mono- or bipotential progenitor cells that acquired self-renewal capacity [2].

2. Neuro- and Gliogenesis in the Embryo and the Neonate

As mentioned above, it seems most likely that transformation of a normal cell into a cancer cell occurs in proliferating tissues. For this reason, a period in life that should be especially cancer-prone is embryogenesis in which a single zygote evolves into an organism consisting of billions of cells. Indeed, several neural cancers are more frequent in newborn and children than in the adult, such as medulloblastoma [36], brainstem glioma [37, 38], ependymoma [39], retinoblastoma, and neuroblastoma [27, 40]. Low-grade glioma is a frequent CNS tumour in children. Other low-grade paediatric CNS tumours are pilocytic astrocytoma, pleomorphic xanthoastrocytoma, ganglioglioma, dysembryoplastic neuroepithelial tumour (DNET), desmoplastic infantile ganglioglioma, and oligodendroglioma [41].

Upon fertilisation, the mammalian egg divides forming a 32-cell morula, which then differentiates into a blastula. The outer cells will connect to the placenta and form the amniotic sac, while the inner cell mass will form the embryo (Figure 1). During gastrulation the mesoderm is formed from the ectoderm by invagination through the primitive streak. FGF signalling is required for the induction of the axial mesoderm, which then forms the notochord [42]. The notochord secretes Noggin and Chordin. Ectodermal cells express both bone morphogenetic protein 4 (Bmp4) and its receptor. Bmp4 signalling suppresses the expression of neural

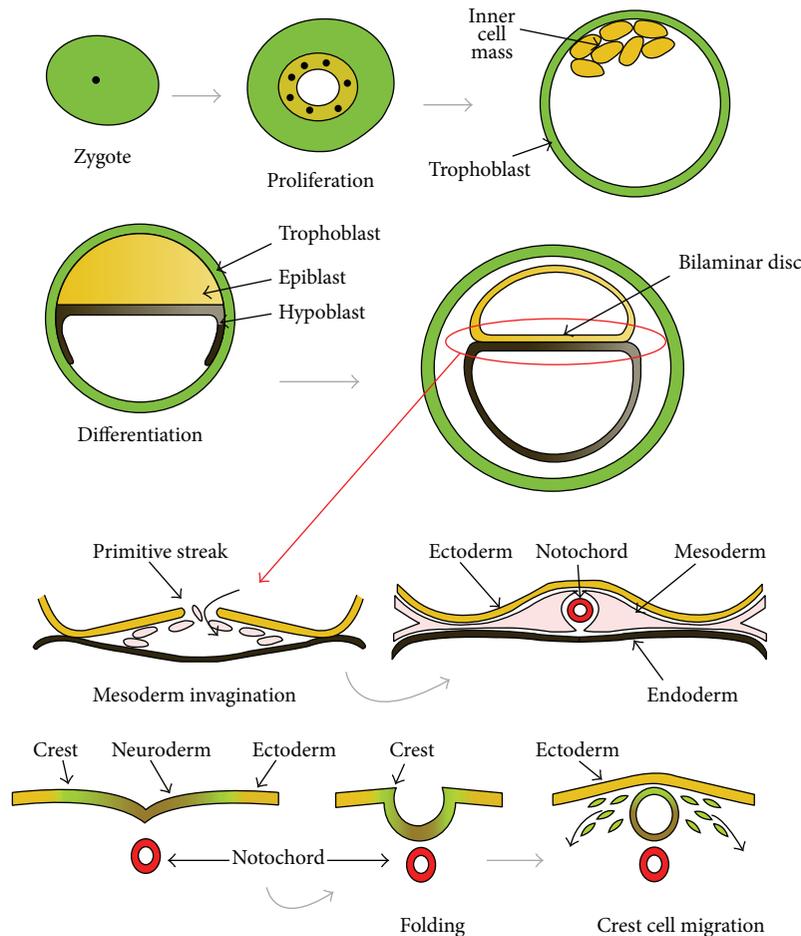


FIGURE 1: From zygote to neural tube. After a number of symmetric divisions, the (mammalian) zygote differentiates into a blastocyst. The outer cells contribute to the placenta and the inner cell mass forms the embryo. The blastocyst then implants itself in the uterus wall and proliferates to form epiblast and hypoblast cells. The former form ectoderm and the amniotic sac, while the latter give rise to the endoderm and the yolk sac. The embryo then elongates after which epiblast cells enter the space between the two layers of the bilaminar disc through an invagination called the primitive streak. These cells then form both mesoderm and, soon thereafter, the neural tube. The mesoderm induces the formation of the notochord, which in its turn induces neuroderm by secreting Chordin. After folding of the neural ridge, the ectoderm closes over the neural tube and neural crest cells migrate to distant locations.

genes. Noggin and Chordin are capable of binding to Bmp4, which then fails to bind to its receptor. This then leads to the transcription of neural progenitor genes in the ectoderm [43] and the formation of the neural groove. Chordin is necessary for forebrain development. In mammals, Noggin plays a role in neural tube fusion and has relatively mild effects on neural development. After induction, the neural groove folds in, creating the neural tube. The neural groove borders are at the origin of migrating neural crest cells that later form the peripheral nervous system (PNS).

After its formation, the neural tube takes on dorsal-ventral polarity due to sonic hedgehog (Shh) signalling. Shh is secreted by the notochord and induces the formation of the floor plate in the neural tube, which in its turn also commences to secrete Shh. The Shh gradient defines in a ventral to dorsal manner the fates of the neuronal tube cells. The neural crest fate is determined by low Shh in conjunction with high Bmp2&4 secreted by the close by ectoderm. The neural crest

cells express, amongst others, Slug and Snail. FGF, secreted by the mesoderm, and Wnt signalling are also implicated in crest cell determination [44]. Those from the trunk give rise to the peripheral autonomic ganglia, neurones, glia cells, and Schwann cells. They also form the adrenal medulla, melanocytes, thyroid parafollicular cells, and smooth muscle cells. Crest cells from the head form teeth, bones of the skull, and the visceral skeleton (i.e., bones other than those of legs and arms). Together with the cranial placode cells, they form the cranial ganglia. A subset of neural crest cells within the trunk region, the sympathoadrenal lineage, contributes to the sympathetic ganglia and medullary region of the adrenal gland. This lineage of cells, also called committed sympathoadrenal progenitors (SAPs), is thought to be the origin of neuroblastoma. SAPs undergo an epithelial to mesenchymal transition (EMT). Snail and Slug are transcription factors that are at the base of EMT induction. They are also implied in the adoption of stem cell properties and metastasis of cancer

cells [45, 46]. This EMT transition results in acquisition of enhanced migratory abilities, which allow the crest cells to leave the dorsal neural tube. Remarkably, DNA repair genes are downregulated during SAP migration, increasing the risk of genomic alterations [47]. At this time SAPs lose part of their multipotency, becoming restricted neural or melanocyte precursors [48]. Upon arrival of trunk SAPs in the mesenchyme lateral of the dorsal aorta, Bmp/Notch signals induce differentiation of these cells, which results in the creation of the primary sympathetic ganglion chain. Bmp-2, 4, and 7 induce the expression of *Ascl1*, a transcription factor transiently expressed throughout the autonomic progeny [49]. Shortly thereafter, *Phox2a* and *b* expression occurs in sympathoadrenal lineage cells. *Phox2a* is required for the production of enzymes in catecholamine biosynthesis (dopamine, (nor)adrenaline). Induction and differentiation of SAPs are due to a complex interplay of transcription factors and signalling pathways including FGF, Notch, Wnt, *Ascl1*, *Phox2a*, and *Phox2b* [48]. *Phox2b* mutations cause the congenital central hypoventilation syndrome [50]. The patients of this disease are predisposed to have neuroblastoma, ganglioneuroma, and ganglioneuroblastoma.

The early germinal zone of the NS consists of a single neuroepithelium layer that first expands by symmetrical division. The cells in this layer, the subventricular zone (SVZ), then transform into radial glia that by asymmetric division produce neurones in early embryogenesis and restricted progenitor daughter cells that produce up to six neurones each during later embryogenesis [51–53]. Radial glia cells express RC2, Nestin, Blbp, and the glial markers Vimentin and GFAP [54–56]. They remain in this state during neurogenesis by CBF1-mediated Notch signalling stimulated by reelin in the extracellular matrix [56] and by Delta1 expressed by migrating neurones as well as by ErbB and FGF signalling [1, 57]. Notch target genes prevent offspring from becoming neurones [58]. Notch signalling in the neuroepithelium is modulated by Numb protein that is asymmetrically distributed during radial glia division. Numb interacts with cytosolic ACBD3 during mitosis to temporarily suppress Notch signalling and to determine radial glia phenotype. After mitosis and retention of ACBD3 in the Golgi system, the young neuron synthesizes its own Numb, which, then, in the absence of cytosolic ACBD3, suppresses Notch signalling and thus enables neuronal differentiation [59]. Migration of young neurones to the pial face requires reelin secreted by Cajal-Retzius cells and doublecortin (*Dcx*) expressed by the young neurones. Around birth, SVZ radial glia cells mostly transform into astrocytes but also give rise to ependymal cells and oligodendrocytes [51, 60]. As mentioned before, the interplay between Bmp and Shh gradients determines the kind of daughter cell that will be produced. Regionalisation not only occurs to determine neuronal traits but has also been proposed to determine glial properties [53, 61]. At least two clearly distinct glial precursor cell types coexist at around E14 mouse embryonic stage. (1) The glial restricted precursor (GRP) which is negative for platelet-derived growth factor alpha (PDGF α) and NG2 and gives rise to GalC⁺ oligodendrocytes, A2B5⁻/GFAP⁺ type1 astrocytes, and A2B5⁺/GFAP⁺ type 2 astrocytes.

(2) The second precursor is the O-2A cell that stains positive for NG2, PDGF α , and O4 and that, possibly via a not yet identified progenitor cell, generates GalC⁺/O4⁺/MBP⁺ oligodendrocytes and type 2 astrocytes [61, 62]. After birth, the radial glia cell transforms into a tripotent (stem) cell that generates neurones, oligodendrocytes, and astrocytes [53]. In the early postnatal period, glial progenitors from the SVZ migrate to different places of the brain including neocortex, striatum, and hippocampus where most of them differentiate into astrocytes and oligodendrocytes [63], leaving small dispersed populations of immature glial cells that persist in adulthood [62, 64, 65]. Glial progenitors migrate radially or follow the white matter [63], very akin to the mode of migration of glioma cells [60]. In the peri- and early postnatal period, when angiogenesis is elevated, most progenitors differentiate into astrocytes upon blood vessel contact [66]. This is followed later by a wave of oligodendrocyte differentiation.

Similar to the generation of neocortex neurones in the SVZ, hippocampal neurones are born in the subgranular zone (SGZ) via the generation of progenitor cells by SGZ radial astrocytes. They possibly also furnish oligodendrocyte and astrocyte progenitors [53].

Cerebellar neurone precursors (GNPCs) continue to proliferate after birth and give rise to granule neurones that express the Notch ligand *Jagged1* [54]. They, too, migrate along radial glia from the SVZ to form a layer at the surface of the cerebellum that is called the external granular layer (EGL). The Purkinje cells in the EGL control the proliferation of the GNPCs through the release of sonic hedgehog (Shh). GNPCs from the upper rhombic lip of the SVZ are the source of Shh type of medulloblastoma, while GNPCs from the lower rhombic lip, which form brainstem nuclei, cause the Wnt type of medulloblastoma [67].

It has been shown that SVZ stem cells obtained from 8-day-old mice, maintained in vitro in the presence of EGF and bFGF, paradoxically increase in number by the formation of more committed progeny upon withdrawal of these mitogenic signals [68, 69]. Remarkably, this progeny transiently becomes hyperploid and shows other similarities with tumour cells such as changes in cell cycle genes and lack of contact inhibition of proliferation.

3. Neuro- and Gliogenesis in the Adult

Neural proliferation continues to take place in the adult SVZ, SGZ, and a zone lining the corpus callosum, named the subcallosal zone (SCZ) [70, 71] (Figure 2). Cells taken from the SCZ and grown in the presence of EGF and FGF form neurospheres containing self-renewing cells. They differentiate into neurones, astrocytes, and oligodendrocytes upon withdrawal of the mitogens. The presence of dormant neural stem cells in other parts of the adult cortex may be suspected [72].

In contrast to the situation in the embryonic neuroepithelium where Notch promotes abundant NSC proliferation, Notch signalling in the adult SVZ, in conjunction with EGF and FGF signalling, keeps stem cells in a slowly proliferate state and also promotes astrocyte differentiation [52, 58].

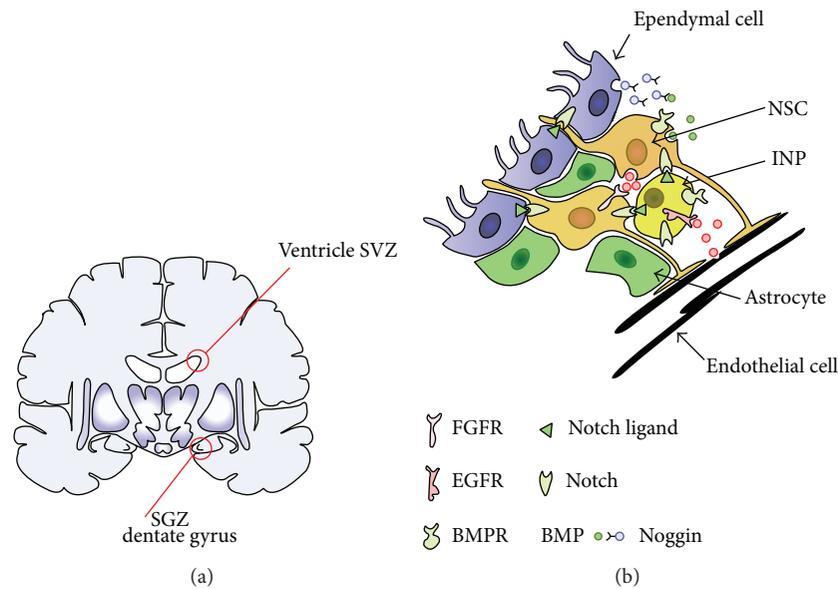


FIGURE 2: The neural stem cell niche in the subventricular zone. (a) Localization of the canonical germinative zones in the brain, the subventricular zone (SVZ), and the subgranular zone (SGZ). (b) NSC proliferation in the SVZ is stimulated by autocrine bFGF signalling and inhibited by CBF1-dependent Notch signalling. Noggin, secreted by ependymal cells, may inhibit Bmp signalling via Bmp receptors on NSCs and intermediate neural progenitors (INPs). Endothelial cells provide for regulatory factors including VEGF that stimulate INP proliferation. INP proliferation is inhibited by Bmps and CBF1-independent Notch signalling.

Adult SVZ NSCs express markers such as Sox2, GFAP, and Nestin [73]. They do no longer stain for RC2 [74] and do not stain for CD133, an often acclaimed marker of stem cells [75]. A dozen splice variants of CD133 exist; two of which, s1 and s3, are present in the brain. The 115 kD s1 variant partakes in myelination in mature oligodendrocytes, while ependymal cells and a subpopulation of astrocytes express the 100 kD s3 form [76]. Adult SVZ NSCs are thought to reside in a special environment or stem cell niche that provides for their maintenance [21, 70, 73, 77–79]. NSCs are surrounded by ependymal cells, a structure that is not present in nonneurogenic regions [80]. The NSCs contact both the ventricle and blood vessels, thus receiving signals from both sides. Vascular endothelial cells contribute soluble factors to the NSC niche, that is, pigment epithelium-derived factor, BDNF, erythropoietin, and vascular endothelial growth factor (VEGF). Ependymal cells produce Noggin, which, by blocking Bmps secreted by NSCs, augments proliferation of NSCs and progenitors and stimulates neuronal differentiation at the expense of (also Bmp-induced) glial differentiation [81]. Autocrine bFGF signalling via tyrosine kinase receptors on SVZ NSCs stimulates the proliferation of these stem cells [54, 82, 83], while Notch signalling mediated by intermediate neural progenitor (INP) cells inhibits it. Hence, Notch signalling in the adult SVZ promotes stem cell dormancy rather than proliferation [84–86]. The Number of INPs in the SVZ is positively regulated by stimulation of EGF receptors present on these cells that, via upregulation of Numb, antagonise Notch signalling. It has been shown that EGF-induced INP proliferation indirectly inhibits NSC proliferation [86]. Sonic hedgehog (Shh) signalling is upregulated in secondary glioblastoma, medulloblastoma, and ependymoma [30, 87], particularly in

so-called “neural cancer stem cells” [88]. The precise role of Shh signalling in normal SVZ proliferation is not very clear yet. Astrocytes taken from the SVZ and the SGZ of adult mice secrete Shh [72, 89] and neuroblast proliferation in the SVZ can be reduced by blocking Shh signalling or by ablation of the primary cilium, the centre of command of hedgehog-mediated signalling [90]. Shh plays a role in the migration of neuroblasts since it stimulates the secretion of Slit from INPs and astrocytes in the SVZ, which is a chemorepellent for migrating neuroblasts [60]. The patched receptor is present on migrating rostral stream neuroblasts [89] and on cells of the CA1-CA3 region of the hippocampus [91]. Rostral stream neuroblasts express Dcx as well [60].

Glia cells of the adult are born in dispersed gliogenic niches or from reactive astrocytes that are not restricted to the SVZ [64, 65]. Glial progenitors express PDGFR α and A2B2 or NG2. They differentiate into astrocytes upon blood vessel contact or into oligodendrocytes in the absence thereof [66]. When they assume oligodendrocyte lineage, they express O4 [92–94]. By retroviral labelling, it was shown that proliferating SCZ cells in vivo only give rise to oligodendrocytes and a few astrocytes but not to neurones [71]. However, after injury, GLAST+ cells from possibly the same region proliferate and generate β tubulin III+ cells [95]. Astrocytes in damaged areas release Shh, IL-6, neuregulins, VEGF, and bFGF thus amplifying glial progenitor proliferation [62, 92] and their dedifferentiation into tripotent progenitors [96]. Neurogenesis and INP proliferation in the adult SVZ can be induced by stroke. It has been shown that occlusion of the middle cerebral artery, causing substantial damage and neuronal death in the striatum and parietal cortex, induces birth of neuroblasts and astrocytes in the SVZ [84, 97].

The Dcx+ neuroblasts subsequently repopulate the striatum and parietal cortex. Young neurones normally follow the rostral migratory stream to meet their destination in the olfactory bulb, but they were found to leave the stream after a brain lesion due to the upregulation of reelin in the damaged area [85, 98, 99]. Ectopic expression of reelin in the cortex in the absence of injury had the same effect [98]. Since reelin does not have chemoattractant properties, other soluble factors should be supposed to intervene such as Shh released by reactive astrocytes [100], hepatocyte growth factor, stromal-derived factor 1 α , or stem cell factor, all of which have been shown to induce progenitor/neuroblast tropism [85, 89, 99].

4. Neural Stem Cells In Vitro

Neural cells with stem cell-like properties can be maintained in vitro using defined media containing EGF, bFGF, or both [16, 101]. They may be grown for some time on an adhesive substrate [69, 102], but most often culture dishes are treated so as to prevent adhesion. This causes cells to adhere to each other and to grow in neurospheres. Neurospheres contain multiple cell types amongst which cells that after isolation proliferate to give new, secondary neurospheres containing neurones, astrocytes, and oligodendrocytes. These multipotent, self-renewing cells are thought to be NSCs [70, 71, 101, 103, 104]. However, INPs give rise to neurospheres too [53] which can amount up to 90% of the spheres formed when starting from fresh SVZ tissue [103], but these are smaller and tend to have difficulties to form secondary and tertiary spheres [105]. In accordance with the notion that EGF promotes INP proliferation [86], neurospheres derived from EGF-infused mice ventricular zones give rise to more small spheres when compared to controls [105].

The neurosphere cell culture constitutes a relatively well-defined method to obtain a constant source of stem cells. Moreover, the lack of reliable and generally accepted NSC markers has made the neurosphere assay an important and often used tool to demonstrate stem cell properties. However, two potential drawbacks of this assay may lead to false negative and false positive NSC identifications. On the one hand, the neurosphere culture has been established initially using tissue from the striatum [16] and is not necessarily adapted for the maintenance of NSCs of other brain regions. So it has been argued that, since adult hippocampal tissue is unable to self-renew in the neurosphere assay, NSCs are absent in the hippocampus [106]. The adult CA1-CA3 region and dentate gyrus stain positive for patched [91] and astrocytes taken from the SGZ secrete Shh [72]. If cultured in the presence of Shh, adult hippocampal cells were shown to self-renew, giving offspring containing oligodendrocytes, astrocytes, and neurones [72, 91]. Similarly, the absence of cancer stem cells in secondary glioblastoma was deduced based on negative results with the neurosphere assay. These results were obtained in the absence of Shh in the culture medium [107], while it has been shown that Shh signalling is required for maintenance in low-grade glioma and secondary glioma [108, 109]. On the other hand, NSCs reside in niches,

special environments that may be partially responsible for the stemness of cells that, otherwise, would not be as remarkable as that. Cells in the neurosphere culture are exposed to important levels of the growth factors EGF and FGF (10–20 ng/mL) that might entice cells to dedifferentiate and proliferate. So it was shown that cells behaving as astrocyte and oligodendrocyte progenitors at E14 in vivo are reprogrammed to become tripotent stem cells in the neurosphere assay in vitro [110]. Similar results were obtained with P6 oligodendrocyte progenitor cells from the optic nerve [14]. Genetic and epigenetic transformations were observed in SVZ neurospheres after prolonged neurosphere culture, some clones adopting haematopoietic stem cell properties [111]. Reprogramming can even take on pathological traits, as SVZ cells cultured as neurospheres develop several chromosomal aberrations reminiscent of cancer cells and grow as tumours if transplanted into rodent brain [31]. Moreover, the presence of growth factors such as EGF and FGF tends to induce the epithelial to mesenchymal transition (EMT), dedifferentiation, and proliferation, important prerequisites for the development of cancer [44, 45, 112]. Even so, carcinogenesis in neurospheres does not appear to be very frequent, since another research group showed that NSCs could be maintained over 120 neurosphere passages without changes in karyotype [113, 114].

5. Neuroblastoma

Phox2b mutations cause the congenital central hypoventilation syndrome [50] which predisposes patients of this disease to develop ganglioneuroma, ganglioneuroblastoma, and neuroblastoma (NB) proper. The former two forms of neuroblastoma are morphologically more differentiated and are lower grade with more favourable outcome. Hence, not all NBs are identical. It is thought that mortality depends on the stage of the sympathoadrenal progenitor (SAP) development, the more differentiated stages causing less lethal tumours.

Sometimes a NB spontaneously regresses. Perhaps regression occurs more often than thought. Since most NBs secrete catecholamines, the presence of catecholamines in baby's urine indicates the presence of a NB. It has been found that high levels of catecholamines in baby urine occur at a much higher frequency than the diagnosis of NB [115, 116]. Hence, many NBs regress spontaneously before being diagnosed [4]. The International Neuroblastoma Staging System (INSS) differentiates NB into 5 "stages" that correspond in inverse order to embryonic developmental stages (see Table 1). SAPs are the common progenitors of melanocyte precursors and neural precursors [50] sometimes referred to as peripheral neural progenitors (PNPs). After migration and neuronal proliferation PNPs finally differentiate into glial cells [117]. Interestingly, both extracranial glioma and melanoma are infrequent in neonates [27, 118] suggesting that mutations in these progenitors are either infrequent or that beginning tumours regress.

Stage 4S is the NB type that often regresses and happens mostly in young children. Crest cells undergo an epithelial to mesenchymal transition (EMT). This EMT transition allows

TABLE 1: International Neuroblastoma Staging System (INSS).

1	Localized tumour with complete gross excision, with or without microscopic residual disease; representative ipsilateral lymph nodes negative for tumour microscopically (nodes attached to and removed with primary tumour may be positive)
2A	Localized tumour with incomplete gross excision; representative ipsilateral nonadherent lymph nodes negative for tumour microscopically
2B	Localized tumour with or without complete gross excision, with ipsilateral nonadherent lymph nodes positive for tumour; enlarged contralateral lymph nodes must be negative microscopically
3	Unresectable unilateral tumour infiltrating across the midline, with or without regional lymph node involvement; localized unilateral tumour with contralateral regional lymph node involvement; or midline tumour with bilateral extension by infiltration (unresectable) or by lymph node involvement
4	Any primary tumour with dissemination to distant lymph nodes, bone marrow, bone, liver, skin, and/or other organs (except as defined for stage 4S)
4S	Localized primary tumour (as defined for stage 1, 2A, or 2B), with dissemination limited to skin, liver, and/or bone marrow (limited to infants less than 1 year of age)

the neural crest cells to leave the dorsal neural tube. EMT is characterized by (1) loss of epithelial morphology, (2) downregulation of junctional complexes (E-cadherin, cytokeratin, occludins, and claudins), (3) upregulation of intracellular migratory proteins (RhoB), (4) increased expression of matrix modulators (collagenase, matrilysin, urokinase, heparanase, and matrix metalloproteinases), and (5) upregulation of matrix recognition molecules (N-cadherin). Metastatic neuroblastoma cells, INSS stages 3 and 4, exhibit many of these features [4]. More than 50% of all neuroblastoma patients are diagnosed with metastasis [119]. These tumours with unfavourable outcome most often overexpress the MYCN gene, which codes for a transcription factor that downregulates four “N-myc downregulated genes” [3, 120]. The latter genes play a role in differentiation of various tissues. Neuroblastoma of this stage generates cancer stem cells that are self-renewing and multipotent and that are able to produce neurones, Schwann-like cells, and melanocytes [121, 122]. Once the PNPs have reached their final destination, they stop migrating and differentiate into neurones. NBs evolving at this stage are more differentiated and belong to INSS stages 1 and 2. Glial differentiation occurs after neuronal differentiation, despite the continued presence of neurogenic Bmp2. The switch is due to Notch signalling by newly formed neuroblasts expressing Delta and Jagged to undifferentiated PNPs [117]. These glial cells form satellite cells, ensheathing neurone cell bodies, in the PNS ganglia and Schwann cells that myelinate axons. Schwannoma is a benign form of tumour that is rare in children [123]. It is not a multipotent cancer, producing Schwann-like cells only.

6. Glioma

The World Health Organization has classified the rather heterogeneous ensemble of CNS neoplasms into grades 1 through 4 [124]. This classification also applies to CNS tumours with a (suspected) glial component, that is, glioma (see Table 2). Low-grade gliomas grow slowly for many years before manifestation of symptoms (grade 1 or pilocytic astrocytoma and grade 2 or diffuse astrocytoma). Anaplastic

astrocytoma is grade 3. Glioblastomas, which are grade 4, grow rapidly and are highly vascularized and infiltrate. In the centre of the glioblastoma, necrosis and hypoxia typically occur. Once diagnosed, the life expectancies of grade 1 glioma and grade 4 glioblastoma patients are 10 years and 1.5 year, respectively. Extensive resection significantly increases 5-year survival rates of low-grade glioma patients, but degrades faculties. A surgical technique known as “intraoperative stimulation mapping” spares these faculties but then gives only very limited results on 5-year survival rates [125, 126].

The genesis of glioma appears to obey a certain sequence of events. P53, a gene implicated in the induction of senescence after DNA damage [19] and cell death by apoptosis, is mutated early in the development of low-grade glioma [127, 128]. These low-grade gliomas and secondary glioblastomas, that is, glioblastomas derived from low-grade gliomas, also carry a mutation in either the IDH1 or IDH2 gene [129]. In patients from whom multiple biopsies were made, the IDH mutation never occurred after p53 mutation, suggesting that IDH mutation necessarily precedes p53 mutation [130, 131]. Mutation of the PTEN gene and hyperexpression of the EGFR gene are late events [131]. IDH mutation causes hypoxia-induced factor (HIF) overexpression [132, 133]. Sonic hedgehog signalling is upregulated in low-grade glioma and secondary glioblastoma but downregulated in primary glioblastoma [108, 109]. The latter also lacks mutations in the IDH genes, almost never expressing mutated p53 [132], but carries often PTEN mutations and overexpresses the epithelial growth factor receptor [134, 135]. Chromosome 10 is lost in primary glioblastoma and 19q is lost in secondary glioblastoma [130].

The subventricular zone is an important niche for neural stem cells and is thought to be the origin of most if not all gliomas [28]. After having acquired the necessary number of mutations and undergone epithelial to mesenchymal transition (EMT), the mutated stem cell migrates and expands in the frontal (40%), temporal (29%), parietal (14%), and occipital (3%) lobes of the neocortex [136]. The EMT, required to adopt a migratory phenotype [44, 45, 137], is also a requirement for metastasis [46, 137–139]. In contrast to the low-stage neuroblastoma discussed above, for which migration and

TABLE 2: WHO classification of glial tumours of the CNS.

1	Subependymal giant cell astrocytoma Subependymoma Myxopapillary ependymoma Pilocytic astrocytoma Gangliocytoma Ganglioglioma Paraganglioma of the spinal cord Rosette-forming glioneuronal tumour of the fourth ventricle	Low proliferative potential and the possibility of cure by surgical resection
2	Ependymoma Pilomyxoid astrocytoma Diffuse astrocytoma Pleomorphic xanthoastrocytoma Oligodendroglioma Choroid glioma of the third ventricle	Diffusely infiltrative glial tumours with cytological atypia, often recurrent
3	Anaplastic astrocytoma Anaplastic oligodendroglioma Anaplastic oligoastrocytoma Anaplastic ependymoma Anaplastic ganglioglioma	As grade 2 plus anaplasia (i.e., dedifferentiation, pleomorphism, and hyperploidy) and mitotic activity
4	Glioblastoma Gliosarcoma Giant cell glioblastoma	As grade 3 plus microvascular proliferation and/or necrosis, virtually incurable

metastasis are intimately linked [4, 119], there is no indication whatsoever that gliomas in the early phases of their genesis and expansion are metastatic. The same argument argues against SVZ intermediate progenitors (INP) as the source of glioma, because they too need to migrate over long distances before expanding. Moreover, it seems odd that hardly a single cancer INP would reach the olfactory epithelium by the rostral migratory stream to form a tumour there, given that nasal glioma in the adult has never been reported and that olfactory neuroblastoma is extremely rare [140–142]. In addition, it has been demonstrated that human glioblastoma cells injected in the striatum of healthy mice tend to migrate towards the SVZ and olfactory bulbs rather than away from those structures [143]. The only cancers that actually originate in the SVZ are ependymoma [144], glioneuronal tumour [145], and neurocytoma [146, 147]. Hence, it seems more probable that gliomas originate elsewhere in the CNS and start to infiltrate (and eventually enter into metastasis) only after initial expansion. Indeed, Snail and Slug, key transcription factors in EMT, are more upregulated in glioma the more they attain higher WHO grade [148, 149].

The source of the glioma could then be either local dormant stem cells [72], progenitors recruited from the SVZ after traumatic [150] or age-related brain damage [84, 97], or glia cells that are activated upon brain damage or inflammation. After injury, microglia cells are the first to be activated and migrate to the site of damage. This is followed by proliferation of NG2+ glia cells and finally astrogliosis [93]. Normally, astrocytes are maintained in a senescent state by contact inhibition in which cadherins of one astrocyte retain β -catenin of neighbour astrocytes at the plasma membrane. Upon disruption of the cadherin bond, β -catenin is released, moves to the nucleus, and initiates the transcription of genes implied in migration, proliferation, and differentiation, thus initiating

the phenotype of reactive astrocytes [151]. Beside migration and proliferation, glioma cells share many features with reactive astrocytes such as growth factor expression (VEGF, EGFR), NG2, Nestin, Vimentin, CD133, and Sox2 expression and upregulation of IL-6, Stat3, Shh, and β -catenin signalling [100, 151–153]. Downregulation of β -catenin in glioma suppresses its growth [154]. Just as in glioma, HIF-associated signalling is important in astrocyte activation upon ischaemia [155]. Remarkably, like glioblastoma-initiating cells, activated astrocytes exhibit anchorage-independent growth; that is, they can grow in neurospheres without being eliminated by anoikis [156]. In vitro, they may take on tripotent properties [72, 157, 158] and give rise to β tubulin III+ cells in vivo [95].

The hypothesis that proliferating (NG2+) glial cells develop into glial tumours [5–7] appears most tempting as it explains many of the properties of these tumours, such as the absence of metastasis in the early stages of growth. However, it requires astrocyte activation. A correlation between brain damage and glioma incidence should therefore exist. Unfortunately, very little evidence for such a correlation has been established, as epidemiological studies on head injury, infections, and the use of cell phones on glioma incidence have not yielded clear-cut results [159–161]. Seizures are often associated with glioma but reasonably assumed to be the result rather than the cause of the tumour [162, 163]. Even so, the incidence of glial brain tumours increases sharply with age, the incidence in the elderly being 5 times as high as in young adults [164]. At that age (60+), many other diseases manifest themselves such as impaired blood circulation, transient ischaemic attack (TIA), and (generalised) chronic inflammation that might lead to repetitive minor brain damage, thus increasing the necessity of repair and the risk of neoplasia.

7. Conclusion

The fate of neural crest cells is determined while they still reside in the neuroepithelium. After having gone through the EMT and while migrating to their destination, these cells continue to multiply. Proliferation comes to an end when they reach their targets. The progenitors, that form the sympathetic ganglia, differentiate into neurones or Schwann cells. At every stage from neuroepithelium to ganglion, the crest cell progenitor may adopt malignant traits. As outlined above, malignancy and phenotype of neuroblastomas correlate well with the different stages of the crest cell's expedition, even if malignant cells acquire more phenotypical plasticity. Here, the theory is easy to comprehend and is appealing. In the case of glial tumours of the adult CNS, the theory used to be just as simple: glial cells are at the origin of glial tumours. The ideas changed around the turn of the century in favour of the hypothesis that the neural stem cell in the SVZ is the source of glioma. The reasons for this choice have been outlined in this review and lie mostly in the premise that the adult brain possesses very few cycling cells with multipotent properties that are similar to those found in gliomas. However, this hypothesis seems untenable in the light of several observations. Glioma cells, which do not give rise to metastasis in the early phases of their genesis, are nevertheless assumed to migrate throughout the brain before expansion. This is in contrast to other brain cancers, which are known to originate in the SVZ such as ependymoma, glioneuronal tumour, and neurocytoma which remain there until becoming metastatic. The ensemble of glioma markers is more akin to reactive astrocytes than to neuronal stem cells of the SVZ. The alternative hypothesis, that is, gliomas originate in situ from locally present tripotent stem cells, from glial progenitors, or from reactive astrocytes, still shows some weaknesses. For one, the existence of a widespread distribution of stem cells within the brain is not quite established. Hence, given the glial nature of glial tumours, a glial origin seems more likely. But this needs glial activation to occur and a relation between glioma incidence and brain repair is, for the moment, lacking.

Abbreviations

Bllp:	Brain lipid binding protein (a.k.a, fabp7: fatty acid binding protein 7)
Bmp:	Bone morphogenic protein
CNS:	Central nervous system
Dcx:	Doublecortin
DNET:	Dysembryoplastic neuroepithelial tumour
EGF:	Epidermal growth factor
EGFR:	Epidermal growth factor receptor
EGL:	External granular layer
EMT:	Epithelial to mesenchymal transition
ERK:	Extracellular signal-regulated kinase
FGF:	Fibroblast growth factor
GalC:	Galactosylceramidase
GBM:	Glioblastoma multiforme
GFAP:	Glial fibrillary acidic protein

GNPC:	Cerebellar neurone precursor
GRP:	Glial restricted precursor
IDH:	Isocitrate dehydrogenase
INP:	Intermediate neural progenitor
INSS:	International Neuroblastoma Staging System
Ascl:	Achaete-scute homolog
MYCN:	Neuroblastoma-derived myelocytomatosis oncogene
NB:	Neuroblastoma
NG2:	Neuroglycan 2
N-myc:	Transcription factor coded by MYCN
NS:	Nervous system
NSC:	Neural stem cell
O-2A:	Oligodendrocyte and type 2 astrocyte bipotent progenitor
PDGF:	Platelet-derived growth factor
PNP:	Peripheral neural progenitor
PNS:	Peripheral nervous system
SAP:	Sympathoadrenal progenitor
SCZ:	Subcallosal zone
SGZ:	Subgranular zone
Shh:	Sonic hedgehog
SVZ:	Subventricular zone
TIA:	Transient ischaemic attack
VEGF:	Vascular endothelial growth factor
Wnt:	Wingless integration site.

Conflict of Interests

The author declares that there is no conflict of interests regarding the publication of this paper.

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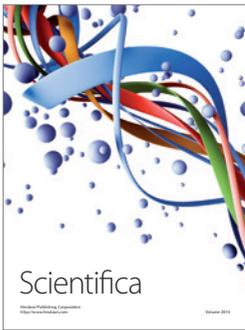
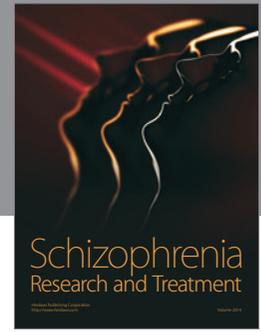
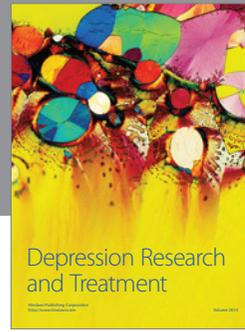
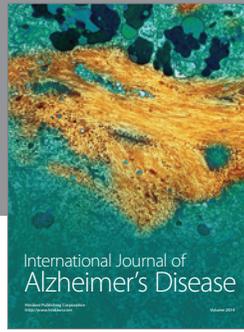
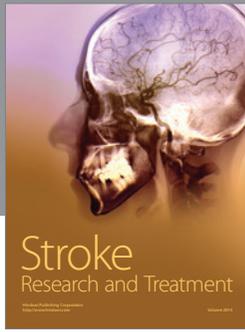
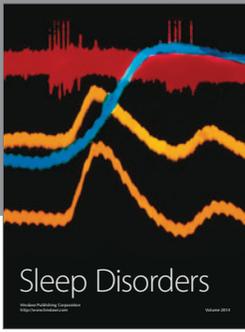
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