Chapter 22

Brain Tumor Stemness

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Additional information is available at the end of the chapter

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1. Introduction

The incidence of primary tumors of the central nervous system (CNS) has been estimated in 15.8/100,000 and 17.2/100,000 individuals for men and women, respectively [1,2], which globally represents approximately 190,000 new cases per year. They represent the 3rd most common cause of death from cancer in middle-aged men, and the 4th most common in women between 15 and 34 years of age [3,4]. The most frequent tumors called gliomas exhibit glial characteristics on pathologic examination [1,3]. Despite advances in the knowledge of the molecular biology of gliomas, effective therapeutic strategies remain elusive. After multimodality treatment with surgery, radiation and chemotherapy, the overall survival (OS) of patients with Glioblastoma (GB), the most frequent glioma, is around 14.6 months and the survival at 2 years is 26% [5, 6, 7, 8]. Although it is recognized that there are progenitor cells that can differentiate into neuronal and glial cells, the concept of a brain tumor stem cells is more controversial. In 2002, Altman and colleagues proposed the theory of post-natal neurogenesis that, associated with the finding of progenitor cells in glial tumors, suggested that these cells could be targeted for more effective therapies[9]. One of the difficulties is that there are no specific phenotypic markers for these cancer stem cells, and, therefore, their identification is limited to a functional characterization.

Nonetheless, pluripotent cells obtained from human brain tumors that express the CD133 surface marker (or Prominin 1; PROM1 is the founding member of pentaspantransmembrane glycoproteins) have the ability for sustained self-renewal, proliferation and tumor initiation/propagation. Furthermore, this functionally defined glioma stem cells form a niche around the blood vessels, being highly pro- angiogenic; those are regulated by hypoxia and are resistant to conventional oncologic treatment like radiotherapy and/or chemotherapy [10, 11]. In addition, they have important migration and invasion capabilities while actively interacting with the immune system. Therefore, therapeutic opportunities include targeting of stem cell specific pathways, induction of differentiation of stem cells, blocking microen-

vironment signals (including angiogenesis factors), and harnessing the immune system to recognize and attack stem cells. Significant challenges continues since the presence of cancer stem cells within the tumor is highly heterogenous, they can remain quiescent for years, and they may share biological features with normal stem cells [12, 13].

We present here a detailed review of the published literature on cancer stem cells of gliomas and meduloblastomas, and their possible relationships with the response to chemo-radiotherapy and to future therapeutic interventions. Similarly, we discuss their role in the progression of the disease, and we provide an analysis of the functional properties of neuronal progenitor cells and of their tumor homologues that lose their regulatory capacity during the process of neurogenesis.

2. Identification of progenitor cells in the brain and the relationship with glial tumors

Cancer only develops after mutations occurs in a few cells. These abnormal cells lose the capacity for self -regulation and have the potential for uncontrolled proliferation [12]. Two hypothetical models have been invoked to explain this phenomenon. The first is the "stochastic" which predicts that all cells have a homogeneous capacity to initiate a neoplasm with areas in which the elements are activated in a synchronic and constitutive manner [12]. The second model is the "hierarchic" which assumes that only a sub-group of cells in the tumor has the potential to proliferate and to generate new neoplasic focus; the other cells act as support or representate well-differentiated or terminal tumor cells. This model explains the findings of the pluripotent progenitor cells in acute myeloid leukemia, in cerebral tumors, and in cancer of the breast, prostate and colon [13, 14]. Nevertheless, those two models are not exclusive and it is likely that there is a combination of both scenarios in most types of cancer. Fig. (1) Summarizes the principal molecular alterations of cerebral tumors of glial origin.

Early studies by Nottebohm et al. reported the discovery of neural embryonic tissue in the cerebral parenchyma of birds [15],followed by reports of similar findings in rodents, primates and humans [16]. As a consequence, it is generally accepted that neurogenesis persists during adulthood, particularly at the level of the dentate gyrus of the hippocampus (in the hilus and in several planes of the granular laminae) and in the upper region of the deep lateral ventricles, neighboring the striated body, as shown in Fig. (2).These cells constitute about 0.2% of the elements forming the encephalon, primitively associated with the telencephalon and generally expressing the glial fibrillary acidic protein (GFAP) [16, 17]. They have a putative role in, and are capable of regenerating the neurogenetic structure in vivo and in vitro; generally enjoying a state of relative quiescence with a cell cycle of about 28 days (type B cells or pluripotent astrocytes) [18].

Usually, the pluripotent progenitor cells have a capacity of generating other second-order progenitor elements that divide every 12 hours (rapid proliferation phase). These cells, termed type C (immature precursors), maintain multipotent capacity and generate other

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neuronal precursors with greater maturity, termed type A cells (migrant neuroblasts). This type A cells are capable of migrating in groups across the rostral portion of the lateral ventricle up to the olfactory bulb where they are integrated as new interneurons in different layers of the cortex (Fig. 2) [19].The subventricular stem cells are conserved in eutherian mammals, but only in man is the cellular displacement not grouped, but rather individual; and follow a destiny that, as-yet, has not been clarified [20]. Analogously to the subventricular zone, the hippocampus granular region amplifies some lesser-known precursor cells termed type D, which have limited migratory capacity (short distances) [20].

From the neurochemical perspective, the type B cells express intermediate filaments such as vimentin and nestin, and are characteristically negative for the neuronal markers PSA-NCAM (Poly-Sialated Neural Cell Adhesion Molecule) and TuJ1 (class III beta-tubulin) [21]. They frequently express PDGFR-α (platelet-derived growth factor receptor) which appears to act as a regulator of balance for the differentiation between the oligodendrocytes and neurons during the phase of asymmetric neurogenesis. The type B cells, while being highly sensitive to stimulation by epidermal growth factor (EGF) and FGF2 (fibroblast growth factor type 2) [20], show constitutive positivity for CD133.

The expression of CD133 marker has been observed in normal progenitor cells, glial tumors and central nervous system neoplasms (“neurosphere” model) [22, 23]. CD133 is a 130 KDa surface glycoprotein with 5 transmembrane domains [24]. There are several isoforms of CD133 regulated by methylation, but their specific regulatory roles in transcription are still unknown [24]. Some reports suggest that their position in the membrane has some relationship with the dynamic organization of cell structure and, as such, determines cell polarity, migration and interaction with other neighboring cells, especially with those belonging to the tumor endothelium [21, 25]. The CD133 positive (CD133+) cells have a series of mechanisms that contribute to preferential activation of regulatory points of the cell cycle, increasing its resistance to standard chemotherapy and radiation therapy. [26]. This finding and other routes of abnormal activation such as Wnt/β-catenin (Wnt was coined as a combination of Wg and Int and can be pronounced as 'wint'), Notch (The notch signaling pathway is a highly conserved cell signaling system present in most multicellular organism), SHh (sonic-hedgehog), PTEN (phosphatase and tensin homolog) and Bmi-1 (polycomb ring finger oncogene) explain, at least in part, why progenitor cells of glial tumors are resistant to radiotherapy [26, 27]. In addition, these cells exhibit primary resistance to chemotherapy agents like carboplatin, paclitaxel and etoposide [28, 29].

GB are remarkably heterogeneous tumors, both phenotypically and genetically, and it is very unlikely that a single antigen will selectively identify a single population of uniquely tumorigenic cells that is common to all GBs. It is important to note that CD133-negative brain tumor cells can also generate tumors in murine cancer models, and those new cells can express CD133 in celular membrane [30]. In human tissue, another investigation have shown that A2B5, a glial progenitor marker, is expressed in human gliomas, up to 61.7% of tumoral cells, viewed on flow cytometry [31]. It would be considered that the role of CD133+ cells, versus the rest of the cell population, in brain tumor initiation and progression is still

uncertain, but most of studies and models agree with the importance of CD133+ cells in tumorgenesis on the brain [16-29].

A study that evaluated the genetic expression of the BCRP1/ABCG2 (also known as Abcg2 murine/ABCG2 human) and MGMT (O-6-methylguanine-DNA methyltransferase) in glial progenitors found a significant increase in their activity, similar to various apoptosis suppressors such as Bcl-2 (B-cell lymphoma 2, apoptosis checkpoint), FLIP (inhibitory protein), BCL-XL ("B-cell lymphoma-extra large", involved in the signal transduction pathway of the FAS-L.) and of some inhibitors of pro-apoptosis proteins such as XIAP (Co-chaperone of The hsp90, immunophilin homolog XAP2), cIAP1 (cellular inhibitor of apoptosis 1), cIAP2 (cellular inhibitor of apoptosis 2), NAIP (neuronal apoptosis inhibitory protein) and survivin (baculoviral inhibitor of apoptosis repeat-containing 5 or BIRC5) [23]. Furthermore, the inhibition of the caspases 3, 7 and 9 is significantly higher in recurrent GB rich in CD133+ cells than in its counterpart in which lower counts are observed [32].

Nestin, an intermediate class IV filament that is produced in considerable quantities in normal and tumor progenitor cells during brain development and in glial neoplasms [33, 34], is a constituent part of the cytoskeleton, has the responsibility for the maintenance of the cell morphology and facilitates adhesion, proliferation and migration. In adults, nestin is expressed in the subventricular progenitor cells, in some remnants near the choroid plexus and in the prosencephalon [35]. As in high grade gliomas, nestin is re-expressed in multiple cell lines of the brain during other circumstances such as acute ischemia, trauma and meningo-encephalitis [36]. In neoplasms, the co-expression of nestin and vimentin is related to substantial increase in invasive capacity (associated with multifocality), the facility to repair external attack (nuclear nestin regulates chromatin), and motility. This combination of markers could be useful in assessing the prognosis, especially since its presence is associated to a more aggressive tumor phenotype, rich in progenitor cells [37].

The normal and tumor precursor cells share the expression of multiple markers, the capacity of unlimited regeneration, exponential proliferation and open differentiation. Additionally, they have similar telomerase activity and resistance to apoptosis, as well as a higher capacity to transport substances to membrane level [38]. The latter characteristic facilitates the exocyte of anti-neoplastic molecules via proteins of the ABC family, such as MDR-1 (Gene that encodes P-glycoprotein; ABCB1, ATP-binding cassette, sub-family B member 1), MRP-1 (human multidrug resistance protein or ABCC1), ABCA2, ABCA3 and ABCG2 (Genes that encodes the ATP-binding cassette sub-family A member 2 protein, sub-family A member 3 protein and sub-family G member 2 protein; respectively) [21, 38, 39].

3. Molecular changes that favor tumor progenitor cells

The progenitor cells of brain tumors have certain characteristics that differentiate them from their normal counterparts. By definition, the cancer stem cells need to have the capacity to develop tumors following orthotopic implantation (if the tumor is an identical phenotypic copy of the original tumor). They exhibit a sustained capacity for self-renewal and are capa-

ble of showing polyclonality [33]. Reilly et al. established a murine model that combined mutations in the p53 gene and in the gene specific for neurofibromatosis (Nf1, neurofibromin 11), capable of activating the Ras (a protein superfamily of small GTPases) pathway to favor the formation of astrocytomas. They found that the deletion of any tumor suppressor gene and/or the activation of oncogenes such as Ras and Akt (serine/threonine protein kinase) in the undifferentiated cells that express CD133 or nestin, resulted in the formation of glial tumors [40].

Another important alteration is view on PDGF. The effect of PDGF on the nestin-positive progenitor cells is equivalent to that which occurs when the loss of CDKN2A (cyclin-dependent kinase inhibitor 2A), which codes for the INK4a (tumour suppressor protein) and ARF (ADP-ribosylation factor 11) is combined with the increase in the expression of EGFR in the immature and in the mature cells [36,41]. Further, during embryogenesis neural progenitors have been shown to express the A isoform of the PDGFR, while its mature homologue (glia and neurons) is expressed on the PDGF surface. PDGFR-B is found in small quantities in pluriultipotent cells, but only increases as the cells differentiate and mature, especially into oligodendrocytes, and in the presence of phosphorylated PDGFR-A [42]. Infusion of PDGF-A in the subventricular region of certain rodents suppresses the production of neuroblasts and generates a hyperplasia of type B cells which frequently results in the development of astrocytomas and oligodendrogliomas. Additionally, activation, via the PDGF signaling, in the regions of the brain rich in precursor cells contributes to tumorigenesis, which seems to be favored by autocrine and paracrine stimulation of PDGF-A, PDGF-B and the OLIG2 (oligodendrocyte lineage transcription factor 2) transcription factors [42, 43].

Some of the signaling pathways included in the evolution of progenitor cells and in their differentiation are altered in the gliomas. The Notch pathway is essential for the maintenance of tumor cell architecture. It is expressed from embryogenesis and interacts, normally or abnormally, with multiple ligands such as DLL-1, 3 and 4 (delta-like 1, 3 and 4 respectively), together with the Jag-1 and Jag-2 proteins (jagged 1 and 2 respectively). The Notch signaling pathway controls neural differentiation and is known to maintain CNS character and to inhibit neurogenesis. The Notch–Hes (Hairy and enhancer of split) pathway is necessary for self-renewing cell division and, thus, maintenance of the neural precursor population [44-47]. Another recent studies have shown that Fbw7 acts as a molecular switch that antagonizes Notch activity and JNK/c-Jun signaling to enable neural stem cell differentiation and progenitor survival [48]. In tumor progenitors, the Notch receptors has been shown acting as a trigger for stimulation of differentiation [49] and, in preclinical studies, it has been shown experimental therapeutic implications [50]. Differentiation is mediated by tumor necrosis factor- α (TNF-α) activator enzyme and by the C-secretase, which is responsible for the signal transcription to the nucleus for unlinking responses via transcription factor CBF1/Su(H)/LAG1 (CSL) (homologous Drosophila gene Suppressor of Hairless /Longevity assurance gene 1 or cardiolipinsynthetase) [49]. This interaction results in the activation of target genes responsible for preempting differentiation and apopotosis [49] and gives the opportunity for developing therapeutic options [49, 50]. The Notch signaling pathway prevents the degradation and ubiquitous distribution of nestin in the progenitor cells, and cooperates

with K-Ras (v-Ki-ras2; Kirsten rat sarcoma viral oncogene homolog) in promoting colony formation [49-51].

A study demonstrated that the inhibition of the Notch-1 receptor induces apoptosis and inhibits the proliferation of glial cell tumors that express CD133 [52]. This provides an opportunity to modulate the pathways responsible of treatment resistance, since there are compounds available that act as decoys, as inhibitors of ϒ-secretase, as intracellular bait directed against MAML-1 (mastermind-like 1), or simply as inhibitors of the Ras pathway [53, 54].

Epithelial Growth Factor is another important issue in the molecular changes on progenitor cells. Using the model of the neurosphere [22], Singh et al. inoculated cells isolated from high grade glioma into the cranium of immuno-suppressed rodents and observed that the minimum number of cells required to produce a neoplasm was 1x105. However, when the experiment was repeated using CD133+ cells stimulated by EGF, the number required was reduced to 100-fold [25, 55]. It is important to note that CD133 expression occurs not only in the neural and neoplastic progenitor cells but also in endothelial stem cells that participate in blood vessel formation necessary for the development of normal brain and for tumorigenesis [55, 56]. In preclinical models, activated EGFR signaling induce behaviors characteristic of GB on stem cells, including enhanced proliferation, survival and migration, even in the absence of EGF ligand. wtEGFR block neuronal differentiation and is associated with a dramatic increase in chemotaxis in the presence of EGF. EGFRvIII expression lead to an increase in neural stem cells proliferation and survival, while it simultaneously blocked neuronal differentiation and promoted glial fate. It gives an opportunity for terapeutic development on this EGF field [57].

4. The micro-environment of progenitor cells and glial tumors

The presence of progenitor cells in Acute Myeloid Leukemia highlights the importance of the micro-environment in maintaining its function, and the quiescent state [9, 12, 14]. The perivascular niche of the glial tumor progenitor cells is highly specialized and depends, in great part, on the capillaries that are similar to those in the periventricular region of the human brain. At the proximity to the endothelial cells, enables inter-cellular communication that causes enrichment with brain derived neurotrophic factor (BDNF), vascular endothelial growth factor C (VEGF-C) and pigment factor derived from the endothelium (PEDF) [9]; molecules that facilitate, principally, migration and neoplasic proliferation. Even more, there is consistent evidence that the extra-cellular matrix is responsible for key points in the regulation of tumor precursors via the tenascin-C gene. Expression of this gene by the cells of the neural crest translates into anti-adhesive properties that block the interaction of fibronectin with the syndecans [58]. Further, chondroitin sulfate continues stimulating the progenitor cell to maintain its primitive state, and impedes evolution of its progeny.

Although the niche affects the biology of the progenitor cells in the tumor, the communication is not unidirectional. Several studies have demonstrated that the precursors are able to promote the replication of endothelial cells, including the necessary stimulus for the forma-

tion of complex neovascular structures [59, 60] by increasing the concentrations of VEGF and BDNF [9, 60, 61]. Complementing these data, Calabrese et al. found, using multi-photon laser scanning microscopy, that the CD133+/nestin+ cells were always found in the intimal layer proximal to the vascular endothelium of GB, medulloblastomas, ependymomas and oligodendrogliomas [61].

Classically, pathology of high-grade gliomas describes a disorganized and aberrant vascular growth randomly generated to supply the voracity of the tumor. However, several recently published reviews explain that this architecture is available in the altered form to serve as lodging for the tumor precursors and their vascular analogues [9, 14].

Glial progenitor cells and their descendants are capable of interfering with the blood vessels of the brain, using the effect known as "perivascular satellitosis". Nevertheless, it is infrequent to find extra-axial lesions. Clinically, the microvascular density of GB correlates with prognosis [62]; a factor that contributes to the response observed in anti-angiogenesis, possibly dependent on VEGF generated in elevated quantities by the CD133+ cells [63, 64]. Further, the observation that CD133+ GB cells lose their ability to recruit endothelial cells and form blood vessels after being exposed to low concentrations of bevacizumab suggests that this effect is controlled, at least in part, by the decrease in the expression of VEGF, VEGFR2 and angiopoietin-2 (Ang-2) [9].

Data from pre-clinical studies and clinical trials indicate that three drugs that block angiogenesis may be promising therapy for high-grade gliomas, due to their inhibitory potential on the niche of tumor progenitors. An estudy demonstrated that endothelial cells increase brain tumor stem cell survival and targeting the tumor vasculature with bevacizumab reduces the number of cancer stem cells in treated tumors [65]. Bevacizumab (humanized monoclonal antibody against VEGF receptors 1 and 2) and cediranib (AZD2171, potent inhibitor of VEGF receptor tyrosine kinases type 1, 2 and 3) are being evaluated currently in clinical trials. [65, 66, 67]Those are agents that act on the VEGF 1, 2 and 3 receptors, suggesting an improvement in progression- free survival (PFS) and OS in patients with recurrent high grade gliomas. Cilengitide blocks the $\alpha v\beta 6$, $\alpha v\beta 5$ y $\alpha v\beta 3$ integrins [68] and has been evaluated in clinical trials [69, 70]. As previously mentioned, the effect of these molecules is the normalization of the tumor vessels, or the depletion of the blood flow, that interferes with the maintenance and survival of the precursor and terminal cells of the tumor, thus, anti-angiogenic therapy may function as a therapy against Glioma Stem Cells. A further nuance has come from early studies that suggest that glioblastoma cells can form parts of the tumor vasculature [71]. It is likely that anti-angiogenic drugs might not only inhibit tumor vascularization to suppress GB growth, but also directly disrupt the niches for the maintenance of GSCs, therefore weakening the ''tumor roots''.

5. Role of progenitor cells in meduloblastomas

The two germinal epithelia of the cerebellum are found in the deep ventricular zone of the velum of the posterior medulla and in the outermost layer of the metencephalon [72]. The

matrix of the first of these regions gives rise to several neuronal and glial cell lines, and the second, only produces granular cells which are the most numerous elements in all of the prosencephalon [73]. In humans, peak growth of the cerebellum occurs later in comparison with the remainder of the CNS, and its principal stage of development is in the third trimester of gestation. In other more rudimentary mammalians this event occurs during the two weeks following birth [74]. Nevertheless, evolution of this neural structure is observed in children up to the end of the first year of life, and appears to be dependent on the presence of the CD133+ cells, which are concentrated principally in the white matter and in the rhombic lips [75].

The evidence that connects the pluripotent neural cells with the tumor elements of the meduloblastoma is merely correlative and is supported by the expression of the calbindin-D (calcium binding protein D) among the precursors of normal cerebellum and, as well as being found in 50% of the meduloblastomas, especially in those of the classical type. In contrast, nodular lesions or desmoplasias express the marker p75, which suggests a dual tumor origin. This hypothesis is supported by the behavior of the meduloblastomas induced in murine models that frequently express CD133+ but which have a specific dissimilar evolution such as, among other aspects, the aberrant activation of the Hedgehog (Hh) gene [76].

The Hh pathway regulates the development of the cerebellum in many species, but has cardinal importance among humans, where it promotes migration of precursors of granular cells, and their proliferation incited by the production of the Hh ligand in Purkinje cells. The mutation in the PTCH (patched homolog 1) receptor which results in constitutive activation of the Hh pathway is found in a great number of patients with sporadic meduloblastoma, as well as in those with Gorlin syndrome, an autosomal dominant entity characterized by coexistence of basal cell carcinomas and primitive neuroectodermal tumors [73, 75]. Approximately 14% of the mice heterozygous for the PTCH mutation develop medulobastomas, in which primary alterations of the precursors of the granular cells are frequently found, as well as changes in the SMO (smoothened) and SUFU (suppressor of fused homolog) genes, which are generators of this type of neoplasia in vivo [77]. Other animal models have demonstrated that meduloblastomas initiated by genetic changes in the different pathways of Hh also result in the activation of this signaling pathway; in particular, the inactivation of the CXCR6 (chemokine receptor CXCR6) that results in the expression of Gli1, Gli2 (GLI family zinc finger 1 and 2), Ptc2 (Hh receptor Patched type 2) and Sfrp1(secreted frizzled-related protein 1) proteins evident in the meduloblastomas, and which are susceptible to inhibition of Hh with molecules such as cyclopamine, or with specific inhibitors such as Hh-antagonist [78].

Another signaling pathway altered in sporadic and inherited meduloblastomas is the Wingless/Wnt (wingless-type MMTV integration site family member) that regulates the proliferation of progenitor cells in the deep ventricular region and in the hippocampus [9]. The loss of Wnt1, a key effector of β-catenin, causes several abnormalities in the midbrain and in the cerebellum, and is found over-expressed in classical meduloblastomas [79, 80]. Although its role in the regulation of the pluripotent progenitors of the cerebellum is not clear, it appears to depend on similar mutations to those identified in the patients with Turcot syndrome; an

autosomal recessive condition caused by the loss of function of the adenomatous polyposis gene, and which is present in 5% of medulloblastomas [80]. The mutations have also been observed in a small subgroup of patients with primitive neuroectoderm tumors and results in the decrease in expression of Axin-2 (plays an important role in the regulation of the stability of beta-catenin in the Wnt signaling pathway); the gene that acts as negative regulator of Wnt and which has been detected in a small group of patients with medulloblastoma [81].

The nuclear translocation of the β-catenin resulting in the activation of the Wnt pathway is observed in 25% of the patients with medulloblastoma and, usually, corresponds to an elevated presence of the CD133 cells. Paradoxically, and in contrary to what occurs in high-grade gliomas, their presence is associated with a favorable clinical evolution, related to the absence of alterations in Hh and aberrations in chromosome 17 [82].

The Notch signaling pathway is observed to be active in the progenitor cells of the deep ventricular region and in the rhombic region. It promotes proliferation and survival and inhibits cellular differentiation. The four isoforms of the receptor do not result in the same changes in the cerebellum. For example, Notch-2 stimulates the proliferation of progenitors of the granular neuromas, while Notch-1 is associated with their differentiation; a consistent finding in the classical forms of medulloblastomas [82]. Some primitive neuroectoderm tumors show increase in the Notch-2 loci and in co-expression of the Hes1 pathway, that correlate clinically with adverse prognosis; while other studies have provided evidence for alternative and abnormal regulation Notch Hh pathway [72]. Finally, hypoxia and the protein products that this activity generates, promote the proliferation of progenitor cells of the cerebellum stimulated by the Notch pathway; a finding that has been confirmed in medulloblastomas [83]. Fig. (3) summarizes the principal signaling pathways of the neural precursors of the cerebellum and of medulloblastomas.

Several subordinate pathways can promote the generation of medulloblastomas from neural progenitor cells. The REN (renin) gene located on chromosome 17 promotes the differentiation of granular precursors, suppressing the Hh signals, an alteration that frequently results in medulloblastoma [73]. The N-myc oncogene (v-mycmyelocytomatosis viral related oncogene, neuroblastoma derived), which plays an essential role in cerebellum growth, is a primary constituent of white matter of the Hh pathway in medulloblastoma and is observed to be amplified in large cell variants, which favor a negative clinical outcome. Other transcription factors associated with the more primitive processes of progenitor cells of the cerebellum and tumor development are RE-1 (RE1-Silencing Transcription factor), OTX2 (orthodenticle homolog 2) and BMI1 (BMI1 polycomb ring finger oncogene) [72, 73]. A recent report described the substantial role of molecular alterations of CD15+/CD133− in the induction of primitive neuroectoderm brain tumors [84].

6. Therapeutic implications of tumor progenitors

The prognostic implications of the presence of stem cells in gliomas has been examined in a few clinical trials. A study that included 44 patients with GB treated surgically followed by

radiotherapy and temozolamide (TMZ), evaluated the prognostic value of CD133 expression and of the capacity of the tumor to generate CD133+ cells in culture. The CD133 status, as determined by immunohistochemistry, had no prognostic value, but the in vitro capacity to generate precursors was associated to a significant reduction in OS (HR: 2.50; 95%CI: 1.04-6.06; P = 0.004) of 8 (95%CI: 4.0-11.5) and 15 months (95%CI: 11.0-19.0) for tumors with higher and lower quantity of CD133+ cells, respectively (P = 0.0002). Similarly, the PFS was also associated to the ability to generate precursors from the tumor (3.5 months for high versus 9.0 months for low grade; P = 0.0001). The CD133+ count was also associated with a higher mortality risk (HR: 1.65; 95%CI: 1.05-2.60; P = 0.0285) [85]. A similar study examining high grade oligodendrogliomas found that tumors without CD133+ cells had an improved prognosis, and this marker predicted clinical outcome better than histological assessment [86]. Another immunohistochemical analysis for nestin and CD133 of both, low grade and high grade gliomas, revealed that their expression correlates with survival, with tumors that co-express nestin+/CD133+ carrying a shorter survival [87]. These findings have stimulated the active search for new therapeutic strategies directed against the precursors of cerebral tumors, and their microenvironment.

Therapeutic interventions directed against cerebral tumor progenitor cells can be divided into three groups: firstly, directed towards provoking differentiation of the precursors; secondly, designed to eliminate the progenitor cells inhibiting their multi-potentiality and quiescence; thirdly, directed towards attacking the tumor microenvironment [88, 89].

The therapies that provoke differentiation of the progenitors focus on the capacity to reverse the malignant state and, essentially, to recover the auto-regenerative property [90]. To-date, two groups of medications affect differentiation: derivatives of retinoic acid and compounds directed against epigenetic changes (histone deacetylators).

Among the compounds directed towards eliminating progenitor cells, the therapies of note are those that are directed against tumor markers of progenitor cells expressed in cellular membrane (antibodies against CD133+) [9], the inhibitors of the Hh pathway (cyclopamine, NBT-272) [91], PPAR-γ agonists [92], TMZ [93], inhibitors of mTOR (sirolimus, everolimus, temsirolimus, deforolimus) [94], derivatives of bone morphogenetic protein (BMP) [95], target molecules directed against check-points that avoid damage induced by radiotherapy in the progenitors (Chk1 and Chk2, checkpoint homolog type 1 and 2) [15], imatinib [96, 97] and inhibitors of the ABCB super-family [98]. Similarly, it is important to mention the drugs that modify the micro-environment, among which are the angiogenesis blocking drugs such as bevacizumab [65], cediranib [67] and cilengitide [68, 69] and, equally, the inhibitors of PI3K (phosphoinositide-3-kinase) that could act turning the medulloblastoma progenitors closest to the vascular niche more sensitive to irradiation, as in vitro studies show for human endothelial cells precursors [99]. Fig. (4) highlights some strategies directed against the cell precursors of brain tumors.

The effect of retinoic acid on the CD133+ cells appears to be related to the repression of the Wnt/β-catenin pathway that slows the proliferation accompanying over-expression of Axin [100]. The same strategy is used in a preclinical model to test the effectiveness of combining 13-cis-retenoic acid with vorinostat (SAHA) in medulloblastoma cells in culture. Retinoic

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acid acts on the transcriptional activation of BMP-2 (Bone morphogenetic protein 2), and SA-HA facilitates the apopotosis controlling chromatin; effects that lead to an increase in the sensitivity to cisplatin and etoposide [101]. Heat shock protein 90 (HSP90) operates as a supplier of β-catenin during its conformational maturation phase. The inhibitor 17-allylamino-17-demethoxygeldanamycin (17-AAG) modifies the HSP90 phenotype and affects the aberrant expression of the β-catenin. This enables the inhibition (in vivo and in vitro) of the growth of several cell lines of glioma and their progenitors CD133+, and translates into an increase in the effect of radiation on the GB; a finding that is more evident during exposure to TMZ [102].

With respect to the preponderant role of Hh in the development of normal and tumor progenitor cells, Bar et al explored the effectiveness of cyclopamine in a subpopulation of primordial GB cells [103]. In the study, 26% of the samples showed Gli (transcription factors mediating the Hh pathway isolated from Glioblastoma) over-expression, a target function of this pathway that was inhibited satisfactorily in 60% of the cases. The outcome was a significant decrease in the CD133+ progenitor growth. In parallel, the administration of cyclopamine on neurospheres inhibited the generation of new colonies, suggesting a regression of the clonogenic capacity of the glioma progenitors.

Beier et al. demonstrated that TMZ is incapable of inducing death of the CD133+ cells. Proliferation was effectively inhibited by reducing its metabolism in vitro by 72% following 7 days of incubation [93]. Depending on the subtype of cells, TMZ induces arrest in the G2-M transition or delay in the cell cycle at G2. However, in all the cultures, the cells at sub-G0 peak of apopotosis, was <8%. Genetical analysis shows that the pattern of presentation of the promoter of the MGMT gene was greater among the negative cells, which does not explain the susceptibility of the progenitors to the alkylating agent [93].

Glial progenitors and their progeny conserve a mechanism of homogeneous differentiation promoted by BMP (bone morphogenetic protein) and its ligands, reducing slightly the quantity of CD133+ cells and favoring the increase in the astroglia and of the cellular elements, similar to neurons. An study observed in some in vivo models that the therapeutic stimulus of the different isoforms of BMP delays tumor growth and the potential for vascular invasion of the GB [104].

Cancer stem cells from GB specimens seems to be immune suppressive as they inhibit mitogen T cell proliferation from normal donors [105].Therefore targeting specifically cancer stem cells may revert the immune suppressive microenvironment induced by these cells, allowing a synergistic effect when combined with immune therapy. On the other hand GB derived stem cells may be a source of unique antigens that can be used for dendritic cell vaccination, as has been demonstrated in the animal model [106].

As previously mentioned, the use of bevacizumab attenuates the capacity of the tumor progenitors to promote angiogenesis, and it will be seen not only following the regulation of acidosis and hypoxia but also by the activation of oncogenes such as PTEN and EGFR [64, 107]. Cediranib, a pan-inhibitor of VEGF receptor, normalizes the blood vessels of the tumor in patients with recurrent GB; the perilesional edema is alleviated and the capacity for pre-

production of the CD133+ progenitors and the endothelium precursor cells is reduced [66]. Cilengitide reduces the expression of $\alpha v\beta 3$ integrin in the tumor micro-environment. The migratory and proliferative capacity of the precursors is reduced by up to 60%; an effect that appears to be dependent on the dose and on the co-expression of other surface antigens of the endothelial cells (CD144 and von Willebrand factor) [68-70].

Aldehyde dehydrogenase function is used by cancer stem cells to repopulate a tumor mass after chemotherapy cytoreduction. As in hematopoyetic stem cells, it would be spected that inhibition of Aldehyde dehydrogenase helps differentiate cells. With the inhibition of aldehyde dehydrogenase, stem cell division to non-stem daughter cells tends to become blocked. Exist potent aldehyde dehydrogenase inhibitors on the market: chloral hydrate, chloramphenicol, and disulfiram, that could be useful [108].

7. Conclusion

Our understanding about cancer and the relationship with the theory of stem cells is growing up as the tumoral incidence around the world does.

Advances in molecular cell biology will give to the oncology physicians and scientist the tools for understanding the processes underlying tumorgenesis and intracelullar processes for viability, serving as possible targets in oncotherapy, diagnosis and prognosis.

Molecular characteristics that give susceptibility for brain tumors to some therapies encourage the clinicians to become experts for giving the best therapeutic choices according to molecular guidance for radio/chemotherapy or other alternatives, like biological therapy, immunotherapy and experimental treatment options.

Future about stem cells as a chapter of brain tumors is on the road for establish individualized treatment profiles, depending on clinical, pathological and molecular characteristics of patients and tumors, a traslational analysis from the molecules to the patients.

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