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# Brain Tumor Molecular Pathways: The Most Important Examples and their Treatment

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## Abstract

The stem cells of a tumor lead to their various lesion and presentations. That's the importance of studying the tumor heterogeneity. The Glioblastoma Multiform (GBM) is the most aggressive and the most common brain tumor in adults. The surface markers of the tumor stem cells can be similar to the normal stem cells, such as the CD133, Nestin, Musashi, and Sox2. The GBM stem cells promote angiogenesis through the release of growth factors pro-angiogenic, such as the vascular endothelial growth factor (VEGF). Tumors that present CD133 as a surface marker are more likely to present necrosis and hemorrhage. Hypoxic areas usually express an increased resistance of the tumor and higher production rates of the CD133. Hypoxia is a stimulus for an increase production of VEGF. In the GBM the hypoxia inducible factor-2α (HIF-2α) is overexpressed, this determines an increase on the expression of CD133. The Notch proteins signalization regulates the progression of the tumor and the differentiation of the stem cells. Tyrosine kinase receptor signaling pathways are stimulated by cytokines and growth factors, like the epidermal and the fibroblasts growth factors and those pathways are directly correlated to the tumor degree. The sonic hedgehog protein is overactivated on GBM. The inflammation contributes and participates of the tumor development. The MB represents most of the brain tumors on children. The Notch protein, Sonic hedgehog and WNT proteins contribute for the establishment of the formation pathways of the MB. The most important treatments are also discussed in this article as well as new options.

***Keywords:*** *Brain Tumor; Heterogeneity; Epigenetic; Glioma and Stem Cells*

## Introduction

Different cells of a tumor can lead to various lesions. These lesions present specific cells morphology, genetic expression, metabolism and proliferation patterns. That's called tumor heterogeneity and this can happen due to the clonal evolution and the stem cell model. The first model indicates that every tumor cell is able to proliferate, modify and regenerate themselves due to mutations creating subgroups of cells inside the tumor. The stem cell model defends the idea of a single stem cell creating every cell of a tumor and the difference between those cells is the degree of differentiation. Those theories can coexist and explain the tumor heterogeneity. The brain tumors present

unsatisfactory results on its treatment, despite of the huge number of treatments options and much of that is due to their high rate of heterogeneity. The epigenetic that is the hereditary change on DNA that regulates the gene expression without changing the sequence of the DNA plays an important role on the tumor heterogeneity. This is an important compound when it comes glioblastomas [1,2].

## Methods

We performed a literature review using PUBMED and only articles published in English from 2002 to 2017 were used. Only one exception were made for the articles trial, one article published in Portuguese in a Brazilian journal was used due to its quality. We used Brain Tumor, Heterogeneity, Epigenetic, Glioma and Stem Cells as our key words. We raised a total of 75 articles, but only 21 had the data that interested us. We observed the factors involved in the genesis of the Glioblastoma Multiform and Medulloblastoma. Due to retrospective design of this literature review, we did not apply for ethics committee approval.

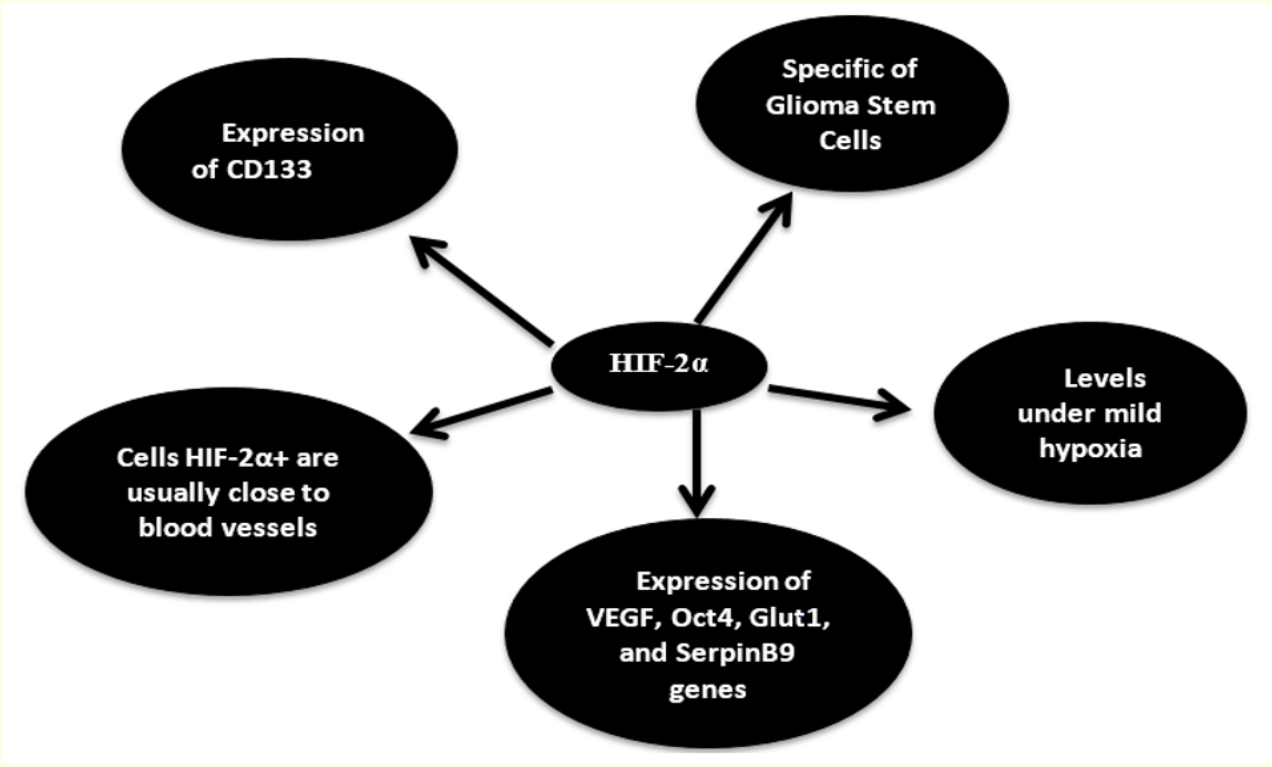
### GBM and its Markers

The glioblastoma multiform (GBM) is the most aggressive and the most common brain tumor in adults. The survival is usually of 4 to 6 months without treatment and 14 months with multimodal therapies. These kind of tumor has in the heterogeneity one of its most important characteristic. The GBM stem cells preserve many characteristics of the brain stem cells, such as self-renewal capability, long-term proliferation and the formation of neurospheres (what is important for the tumor proliferation). The surface markers of the tumor stem cells can be similar to the normal stem cells, such as the CD133, Nestin, Musashi, and Sox2 [1-4,12,19]. However the appearance frequency of pathological/unusual markers is higher in the tumor cells, such as the CD133 and others like A2B5, CD15, e CD171. The surface markers can vary from one patient to another. That's the reason for so many clinical and anatomical presentations of a tumor, once that the tumor stem cell determines the relation between the tumor and others structures, like adjacent cells, extracellular matrix and cytokines; those elements are crucial for the tumor proliferation and renovation [1,2].

### Hypoxia and angiogenesis creates the scenario for the GBM development

The GBM stem cells closely interact with the vascular niche and promote angiogenesis through the release of growth factors pro-angiogenic, such as the vascular endothelial growth factor (VEGF) and stromal-derived factor 1, besides endothelial migration [1-3,8]. So treat a GBM with a VEGF-neutralizing antibody, such as bevacizumab, decrease the tumor capacity to promote angiogenesis, which inhibits the tumorigenesis of glioma stem cells [12,17]. Although this drug has been presenting excellent rates of radiographic response and demonstrating a remarkable decrease in tumor enhancement and FLAIR hyperintensity, the long-term effects of it has been controversial as it's sad by Li., *et al* [14]. Tumors that present CD133 as a surface marker are more likely to present necrosis and hemorrhage, once that they are highly vascularized, probably because the GBM stem cells promote a stimulation of the pericyte. Those stem cells also express surface markers of pericytes, like the alpha smooth muscle actin, NG2, CD248 and CD146. However the vessels are disorganized and some areas of the tumor stay hypoxic, due to a low oxygen pressure. This justifies the necrosis areas. Those hypoxic areas usually express the gene MGMT and the methylation of its promoter leading to an increased resistance of the tumor and higher production rates of the CD133. Once the MGMT has the function of repair the DNA and remove alkyl groups, its presence leads to a resistance to temozolomide, as the drug adds an alkyl group in the tumor DNA stopping the tumor development. The hypoxic condition is a stimulus for the increase of the production of VEGF [1,2,10-12,16]. Physiologically the cells hydroxylate the hypoxia inducible factor (HIF) that is responsible for the cells survival, motility, metabolism and angiogenesis. There are different types of HIF. In the GBM the HIF-2α is overexpressed, this determines an increase on the expression of CD133 [1,2,10,11]. The HIF-2α is an attractive target once it is specific of brain tumor stem cells whereas is not expressed in other neural progenitor cells [11]. The HIF-1α also increases under hypoxic conditions. However this marker is not specific of the tumor and requests a severe hypoxic condition to present an increase on its levels whereas the HIF-2α increases its levels under mild hypoxia or even in physiological oxygen levels [11]. Most of the cells of a GBM that are HIF-2α+ are close to blood vessels [11]. There are other genes responsible for the induction of hypoxic state, such as Glut1, SerpinB9 and VEGF [1-3]. These pathways and

mechanisms allows the GBM to survive and grow in hypoxic conditions, this microenvironment created is associated with poor prognosis and resistance to radiation therapy [1,2,9-11]. Keith., *et al*. [10] proposed that HIF stabilization in hypoxic tumor cells would lead to the adoption of stem cell properties, such as self-renewal and pluripotency, by stimulating the expression and activity of Oct4, Notch protein, and other critical signaling pathways. Owing to that hypoxic tumor tissues would create an appropriate environment for GBM stem cells [10,11]. Li., *et al.* [11] reported that HIF2α induces the expression of VEGF, Oct4, Glut1, and SerpinB9 genes. Oct4 is an important regulator of stem cell self-renew and differentiation is already considered a cancer stem cell target. The glucose transporter Glut1 is usually over-expressed and overactivated in cancer cells to enable their accelerated metabolism. The SerpinB9 is a proteinase inhibitor that prevents TCD8 lymphocytes apoptosis actions and are also able to directly inhibit caspases. These data presented suggests that the upregulation of Oct4, Glut1, and SerpinB9 due to a HIF2α activity provides GBM stem cells with advantages in metabolism, proliferation, survival, and escape from immune responses [11]. Some of the most important features of the HIF2α are presented on scheme 1.

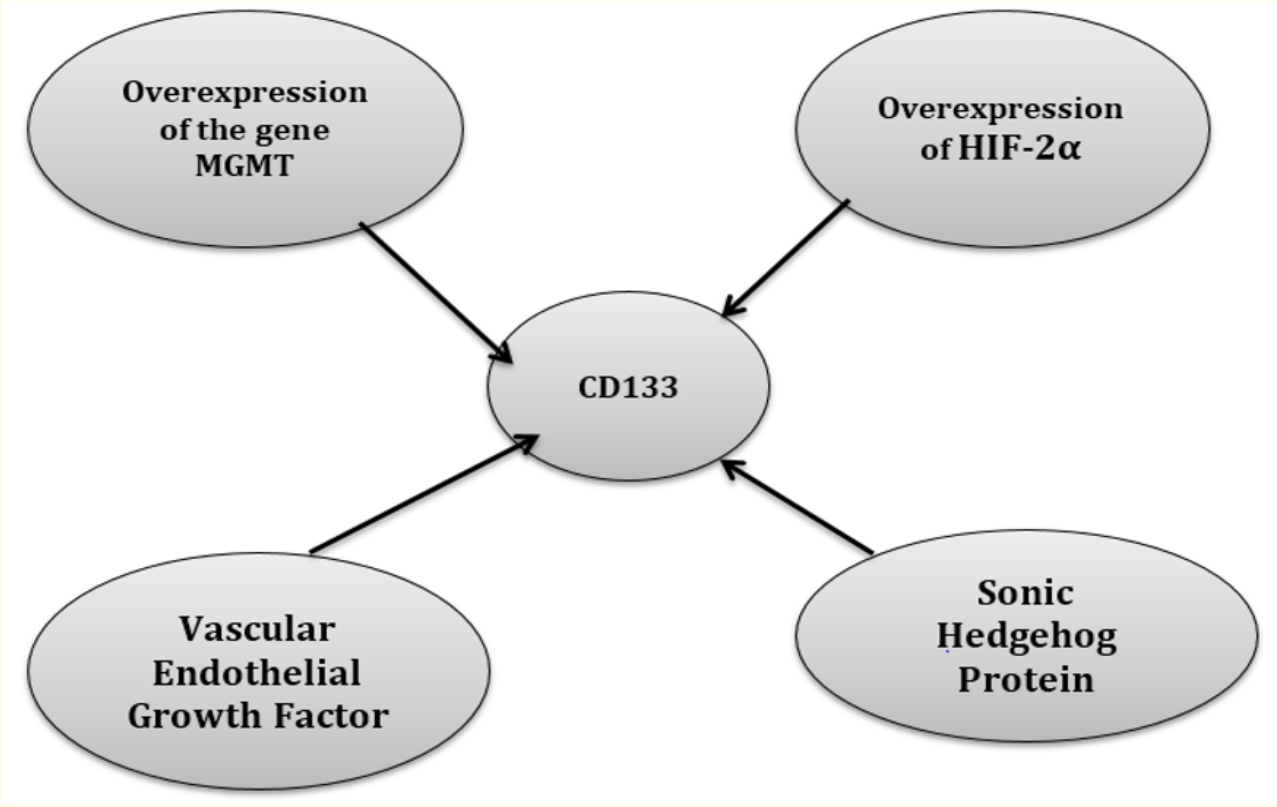



***Scheme 1:*** *Features and particularities of the HIF2α that play an important role for the GBM development.*

## Endothelial cells on the inside and the complex molecular signalization

The endothelial cells inside the tumor present markers that contribute for its growth, such as the epidermal growth factor receptor (EGFR) and an alteration on the chromosome 7. Those endothelial cells are recruited by GBM stem cells via SDF-1/CXCR4. The Notch proteins signalization also regulates the progression of the tumor and the differentiation of the stem cells, once the Notch proteins are transmembrane receptors that mediate interactions and function of cells and their proliferation, differentiation, and apoptosis [1,2,12]. The Notch signaling also increases the expression of the Nestin, a GBM stem cell marker. The activation of Notch in GBM cells leads to the

formation of neurospheres [12]. Owing to that the Notch pathway blockade by γ-secretase inhibitors slows GBM neurospheres growth, once they reduce the expression of glioma stem cell markers, like CD133 and Nestin [15-17]. Tyrosine kinase receptor signaling pathways are stimulated by cytokines and growth factors, like the epidermal and the fibroblasts growth factors. One of those pathways is the PI3K-Akt-mTOR that is found on GBM, once it's overexpressed on the tumor stem cells. This pathway activates the VEGF, what increases the tumor growth, also translate many tumor stem cells surface markers, such as the CD133 and stimulates the angiogenesis. This marker contributes with the increase of the Akt pathway and is directly correlated to the tumor degree [1,2,12]. The pharmacologic inhibitors of Akt decrease the GBM neurosphere formation, also leading to apoptosis, and the impairment of the tumor development. Owing to these data, the hypothesis that Akt inhibition specifically targets the GBM stem cells population, reducing tumor malignancy is valid [12]. The sonic hedgehog protein is overactivated on GBM. This protein is also related to tumor stem cells gene and surface markers expressions, like the CD133, promoting the growth of the tumor, due to that hedgehog pathway inhibition blocks the GBM stem cell growth [1,2,12]. The cyclopamine treatment (a hedgehog inhibitor) also provokes the impairment of the viability of GBM stem cells, so the tumor fails in its propagation and this treatment also improves the radiation effects on GBM treatment [12,13,18]. Bone morphogenetic proteins (BMPs) are growth factors that interact with receptor kinases to regulate proliferation, apoptosis, and differentiation of neural stem cells. In GBM stem cells this growth factor induces differentiation of the tumor cells into astroglial and neuron-like cells, leading to a delay tumor growth. So the development capability of the GBM increases when the BMP receptor is silenced by the epigenetic [2,12]. The factors that increase the expression of CD133 on the tumor cells are shown on scheme 2.




***Scheme 2:*** *Factors that increase the expression of CD133 on the tumor cells.*

There are transcription factors that extremely important for the regulation of the tumor stem cells, such as the Oct4, Sox2, Nanog, c-Myc and Olig2. The Oct4 and Sox2 increase the tumor stem cells and the tumor activity [1,2,12]. The Oct4 is also a factor that contributes to the generation of inducible pluripotent stem cells. This transcription factor is correlated to the glioma grade too [12]. The Oct4 inhibition sensitizes the tumor to the temozolomide [19]. The c-Myc factor induces a pluripotency of the fibroblasts. This factor is correlated to the tumor degree, being more expressed in tumor cells that present the CD133 [1,2,12,20]. This factor is also required for the maintenance of gliomas and for its tumorigenic capacity [12,20]. Olig2 is a factor very present on GBM and on its stem cells, especially when it contains CD133. This factor can control the proliferation of the tumor stem cells [1,2]. However Olig2 seems to be needed for different brain tumors initiation [12].

The isocitrate dehydrogenase 1 (IDH-1) is an enzyme that suffers mutations particularly in GBM. Those mutant enzymes generate an onco metabolite known as D-2- hydroxyglutarate (D-2-HG) instead of formatting α-ketoglutarate (α-KG) in the citric acid cycle. This metabolite (D-2-HG) promotes an increase on the tumor cells proliferation and on the angiogenesis, due to the activation of the HIF and also leads to a hypermethylation of histones. The methylation of H3K4 causes the opening of the chromatin for its transcription. The chromatin close is due to H3k27, what stops the transcription. The methylation of histones is stimulated in hypoxic tumor stem cells, supporting the expression of HIF-2 and the tumor proliferation. The microRNAs (miRNAs) are important in the genesis of the GBM, playing an important role on the pluripotency, on the reprogramming and on the pathways of the tumor stem cells. The miRNA-124, o miRNA-146a and the miRNA-34a contribute for the tumor genesis, whereas the miRNA-125b and the miRNA-9 regulate the resistance to chemotherapy and radiotherapy [1,2]. However Li., *et al.* [12] reports that the levels of miR-124 and miR-137 are reduced in GBM. Besides that the overexpression of both of these miRNAs inhibit the proliferation and induce the differentiation of glioma stem cells, leading to a tumor suppression [12]. In GBM the miRNA-21 are usually overexpressed and its inhibition leads to apoptosis. In GBM cells that are CD133+ the levels of miRNA-451 are lower, probably because this miRNA inhibits the growth of glioma stem cells and impairs the formation of neurospheres [12].

## Inflammation makes the microenvironment for the GBM growth

The inflammation contributes and participates of the tumor development. There are two pathways for the establishment of the tumor inflammation, the intrinsic and extrinsic. The intrinsic pathway is responsible for the chronic inflammatory microenvironment of the tumor due to the integration of genetic events. The extrinsic pathway is responsible for repetitive inflammation. Once that the tumor is always in an inflammatory milieu, immunosuppressive and inhibitory cytokines are secreted and the cells of the immune response that invades the tumor secrete more inflammatory mediators. The microglia and macrophages at the central nervous system are responsible for this process when it comes to brain tumors. They secrete cytokines and growth factors crating an appropriate microenvironment for the tumor growth and invasion [1,2,21].

The cyclooxygenase enzyme (COX) has an important role at the chronic inflammation, once they are responsible for an increase on the levels of prostaglandins, prostacyclin and thromboxane. The levels of the COX-2 is directly linked with the malignancy level of the brain tumors [1,2].

The changes on the signal transducer and activator of transcription proteins (STAT) are important for the immune deregulation of the tumor. Those proteins are transcription factors that regulate the signalization of the tyrosine kinase, growth factors and cytoplasmic enzymes. The STAT-3 is overactivated on many brain tumors enhancing the inflammatory process due to the interleukin 6 (IL-6) and IL-10, what decrease neutrophils and other cells of the immune system activity [1,2,21].

The inflammatory cytokines activate the NF-κB. This transcription factor codifies anti-apoptotic proteins, pro-inflammatory cytokines, chemokines, adhesion molecules, proteases and DNA repair proteins, like the MGMT that leads to an increase on the CD133 levels [1,2,21].

Owing to all this process and factors the chronic inflammation causes an oxidative stress releasing reactive oxygen and nitrogen specimens, which deregulate DNA mismatch repair, base excision repair, repair by excision of nucleotides, the cell cycle and homologous recombination [1,2,21].

The Treatments of GBM presented are showed in table 1.

| GBM Treatment Options | |
|---|---|
| **Drug** | **Action** |
| Bevacizumab | VEGF-neutralizing antibody |
| Temozolamide | Adds an alkyl group in the tumor DNA |
| ***γ*-secretase inhibitors** | Notch protein pathway blockade |
| Inhibitors of Akt decrease | Impairs the GBM neurosphere formation |
| Cyclopamine | Hedgehog pathway inhibition |

***Table 1:*** *Treatments of GBM presented.*

### The MB is ruled by similar molecular pathways

The brain tumors are the main cause of children death due to cancer. The medulloblastoma (MB) represents most of them. Kool., *et al.* [5] analyzed 7 studies studying a total of 550 patients and related that MB affects more man than woman (1,5:1); 88% of the patients that presented a MB were under 16 years old; most of the patients (44%) studied were between 4 and 9 years old. The histology distribution also showed to be dependent of the age; infants (0 - 3 years) presented a higher frequency of desmoplastic tumors (presenting dense fibrosis around the tumor). However in children (10 - 16 years) the desmoplastic presentation was lower than 9%. The large cell-anaplastic histology showed the lower rates of occurrence and in adults (> 16 years) the rates were especially low (3%). Most of the tumors reported presented a classic histological presentation [5].

Some studies are showing various molecular subgroups of MB, leading to the establishment of different genetic manifestations and of the pathogenesis of the tumor [1]. The MB may present the CD133 as a marker and nestin that is a neuronal stem cell protein, this protein can participate on the formation of the neurospheres on many brain tumors, like the MB. This protein was found in stem cells on the perivascular region of the tumor and also determined radioresistance, once it activates the Akt/PI3K and p53 signaling pathways [2,4,12]. The nestin determines the proliferation of the tumor cells [4]. The Notch protein can activate the nestin promoter [4,12]. This is one of the reasons why the inhibition of Notch-1 signaling via a γ-secretase inhibitor induces MB stem cell apoptosis, differentiation and reduces tumor progression [2]. In the MB the Sonic hedgehog is overexpressed, what contributes for an increase of the levels of CD133 [2,4,6,7,12]. The Notch protein, Sonic hedgehog and WNT proteins contribute for the establishment of the formation pathways of the MB, once they control the proliferation and differentiation of cerebellar granular cells and mutations/disturbances on those cells are probably the genesis of the MB stem cells [6,7].

## Conclusion

The stem cells of a tumor lead to their various lesion and presentations. That's the importance of studying the tumor heterogeneity. Some models try to explain this, they mark the need of a tumor cell be able to proliferate, modify and regenerate themselves. One theory says the tumor initiates due to one stem cell and this cell creates all the other and other hypothesize that different cells participates on the tumor genesis. The epigenetic is an important feature on the tumor genesis. The GBM is the most aggressive and the most common brain tumor in adults. The GBM stem cells preserve many characteristics of the brain stem cells, such as self-renewal capability, long-term

proliferation and the formation of neurospheres. The surface markers of the tumor stem cells can be similar to the normal stem cells, such as the CD133, Nestin, Musashi, and Sox2. The GBM stem cells promote angiogenesis through the release of growth factors pro-angiogenic, such as the VEGF. So treat a GBM with bevacizumab impairs the tumor development. Tumors that present CD133 as a surface marker are more likely to present necrosis and hemorrhage. Hypoxic areas usually express the gene MGMT leading to an increased resistance of the tumor and higher production rates of the CD133; its presence leads to a resistance to temozolomide. Hypoxia is a stimulus for an increase production of VEGF. In the GBM the HIF-2α is overexpressed, this determines an increase on the expression of CD133. Specific pathways and mechanisms allows the GBM to survive and grow in hypoxic conditions, this microenvironment created is associated with poor prognosis and resistance to radiation therapy. The endothelial cells inside the tumor present markers that contribute for its growth, such as the EGFR. The Notch proteins signalization regulates the progression of the tumor and the differentiation of the stem cells, once the Notch proteins mediate interactions and function of cells and their proliferation, differentiation, and apoptosis. The Notch signaling also increases the expression of the Nestin, a GBM stem cell marker. The activation of Notch in GBM cells leads to the formation of neurospheres. Owing to that the Notch pathway blockade by *γ*-secretase inhibitors slows GBM neurospheres growth. Tyrosine kinase receptor signaling pathways are stimulated by cytokines and growth factors, like the epidermal and the fibroblasts growth factors and those pathways are directly correlated to the tumor degree. The pharmacologic inhibitors of Akt decrease the GBM neurosphere formation, also leading to apoptosis, and the impairment of the tumor development. The sonic hedgehog protein is overactivated on GBM. This protein is also related to tumor stem cells gene and surface markers expressions, like the CD133, promoting the growth of the tumor, due to that the cyclopamine blocks the GBM stem cell growth. This cyclopamine treatment provokes the impairment of the viability of GBM stem cells, so the tumor fails in its propagation and also improves the radiation effects on GBM treatment. The development capability of the GBM increases when the BMP receptor is silenced by the epigenetic. There are transcription factors that extremely important for the regulation of the tumor stem cells, such as the Oct4, Sox2, Nanog, c-Myc and Olig2. The Oct4 inhibition sensitizes the tumor to the temozolomide. D-2-HG (an onco metabolite generated by IDH-1) promotes an increase on the tumor cells proliferation and on the angiogenesis, due to the activation of the HIF. The miRNAs are important in the genesis of the GBM, playing an important role on the pluripotency, on the reprogramming and on the pathways of the tumor stem cells. The inflammation contributes and participates of the tumor development. The chronic inflammatory processes and factors causes an oxidative stress releasing reactive oxygen and nitrogen specimens, which deregulate DNA mismatch repair, base excision repair, repair by excision of nucleotides, the cell cycle and homologous recombination.

The MB represents most of the brain tumors on children. Most of the patients are under 16 years old and the classic histological presentation is the most common, followed by the dysplasia. The MB may present the CD133 and nestin as markers. The Notch protein can activate the nestin promoter. This is one of the reasons why the inhibition of Notch-1 signaling via a γ-secretase inhibitor induces MB stem cell apoptosis, differentiation and reduces tumor progression. In the MB the Sonic hedgehog is overexpressed. The Notch protein, Sonic hedgehog and WNT proteins contribute for the establishment of the formation pathways of the MB, once they control the proliferation and differentiation of cerebellar granular cells and mutations/disturbances on those cells are probably the genesis of the MB stem cells.

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