

# A contemporary review of molecular candidates for the development and treatment of childhood medulloblastoma

N. Ceren Sümer-Turanlıgil · Emel Öykü Çetin · Yiğit Uyanıkgil

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## Abstract

**Introduction** Medulloblastoma is the most common pediatric central nervous system tumor; however, the causes are not well established. There has been some emphasis on mutations in developmental pathways and their impact on tumor pathology in hereditary diseases, but, in order to better understand the nature of diseases like medulloblastoma, other mechanisms also require attention.

**Purpose** The purpose of this review is to provide an overview of the main genes involved in neurodevelopment, their downstream targets, and modulatory links by growth factors. Occurrence of pediatric brain tumors including medulloblastoma are mostly sporadic, but some hereditary diseases like Li–Fraumeni syndrome, Gorlin’s syndrome, Turcot’s syndrome, and Rubenstein–Tarbi syndrome are known to contribute their development as consequences of germline mutations at specific points: DNA-repairing gene Tp53 for Li–Fraumeni syndrome or Patch for Gorlin’s, and apoptosis-related gene product adenomatous polyposis coli for Turcot’s disease.

**Conclusion** Intracellular relations at molecular level and future therapeutics that specifically target the corresponding pathways should be well understood in order to prevent and cure childhood medulloblastoma.

**Keywords** Medulloblastoma · Development · Cancer stem cells · Signaling · Chemotherapy

## Introduction

Medulloblastoma (MB) is the most frequent primary central nervous system (CNS) tumor which is observed in 20–30 % of children up to 10 years old and occurs in the posterior fossa and the fourth ventricle [24,41,61]. The most common location of the tumor is the cerebellum (94.4 %), usually in the midline (75 %) of the inferior vermis [18]. It is neuroectodermal in histology and origin, therefore considered as a member of primitive neuroectodermal embryogenic tumor (PNETs). Approximately 20 % of the children diagnosed with CNS malignancies have MB. Occurrence of pediatric brain tumors including medulloblastoma are mostly sporadic, but some hereditary diseases like Li–Fraumeni syndrome, Gorlin’s syndrome, Turcot’s syndrome, and Rubenstein–Tarbi syndrome are known to contribute their development as consequences of germline mutations at, for example, Tp53 (for Li–Fraumeni), adenomatous polyposis coli (APC, for Turcot), or Ptc (for Gorlin’s). The predispositions underlying MB development are related with developmental signaling pathways like *Shh*, *Wnt/β-catenin*, and *Notch* which are also affiliated to familial inheritance. In addition, aberrant regulation of insulin-like growth factor (IGF) and DNA repair signaling have been implicated in MB formation [11,24,40,42,45,48,65].

Definitive diagnosis of MB is dependent on tumor histology, and WHO classifies MB according to the histopathology of the tumor: subgroups are defined as classical, desmoplastic/nodular, extensive nodular, anaplastic, and large cell MB. A variant of MB named medullomyoblastoma may exist showing characteristics of rhabdomyoblastic differentiation. MBs display hypercellularity, variable enhancement, and necrotic areas in imaging studies [12,19,26,42,61].

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N. C. Sümer-Turanlıgil  
Department of Biophysics, School of Medicine, Ege University,  
İzmir, Turkey

E. Ö. Çetin  
Department of Pharmaceutical Technology, Department of  
Biopharmaceutics and Pharmacokinetics, Faculty of Pharmacy,  
Ege University, İzmir, Turkey

Y. Uyanıkgil (✉)  
Department of Histology and Embryology, School of Medicine,  
Ege University, İzmir, Turkey  
e-mail: yigit.uyanikgil@ege.edu.tr

## Similarity of cancer stem cells to developing cerebellum cells

Adult neural stem cells are responsible for self-renewal and differentiation into all kinds of neural cells including neurons, astrocytes, and oligodendrocytes. They are found in the subventricular zone of lateral ventricle and subgranular zone of the dentate gyrus [43]. Stem cells are described as self-renewing multipotent cells which display multilineage differentiation. Normal somatic stem cells should renew, and there should be a balance between self-renewal and differentiation in a context similar to cancer. Cancer may be defined as a disorder of unregulated self-renewal. MB arises as a result of dysregulations in differentiation. During these processes, neural stem cells and their progenitors seem to be responsible for transformation in the architecture of brain tumors. Microarray studies suggested a similarity of human MBs with the developing brain. MBs arise from the external granular layer (EGL) of a developing cerebellum. Since some types of human MB exhibit similar gene expression representations to murine EGL, a correlation between stem and progenitor cells, with disrupted or mutated signaling pathways which normally check self-renewal of stem cell such as *Shh* pathway, as a model of MB development is proposed [19,39,52].

The stem cell theory for carcinogenesis states that cancer cells are produced monoclonally from a stem cell or stem-like cell. Different than normal stem cells, they are supposed to undergo cell division without differentiating terminally [58]. Cancer stem cells were observed in the subgroup of cancer cells which expressed Cluster of Differentiation (CD) 133. When CD 133 (+) human glioma cells were transplanted into the brains of immunodeficient mice, glioma development started. On the other hand, transplantation of CD 133 (–) did not cause tumor formation. This is considered as a sign of self-renewal property [33,39]. But all the tumorigenic cells do not have to be CD 133 (+); they are rather thought to include a different subgroup of stem-like cells [37]. It is also a possibility that some MBs may arise from fully differentiated cells [19].

## Roles of developmental pathways in MB formation

### Hedgehog-Patch pathways

Oncogenic mutations of elements of Hedgehog-Patch pathway (*Hh*) has been defined in 20–25 % of human MBs. *Hh* pathway members are evolutionarily conserved among species varying from *Drosophila* to humans. The role of *Hh* pathway, in general, is patterning and developing different organs and, in particular, regulating proliferation of granule neuron precursors (GNPs). An imbalance between differentiation and proliferation of GNPs is enough to be considered

as a cause of MB formation. The cerebellum of mammals evolves from GNPs at the fetal rhombic lip. Those precursors migrate from the rhombic lip to create the EGL. The relevant *Hh* subtype is *Shh*. Interestingly, when downstream targets of *Hh* pathway are analyzed, it is observed that most of the tumors, which compromise mutated *Hh* signaling pathway genes, developed additional ways for that pathway activation [23,31,40,48,57].

Hedgehog-patched pathways control cerebellar EGL development. *Shh* is produced by Purkinje cells and is a target for *Patched 1* (Ptc 1). Ptc 1 is a tumor-suppressor gene which codes for a 12-cross occupying transmembrane surface receptor responsible for hedgehog proteins. The location of the chromosome mutated in Gorlin's syndrome is 9q22-31, which is a potential tumor-suppressor locus. MBs have been proved to evolve from mutated Ptc receptor and protein at about 15 % of sporadic human and mice MBs leading to activation of *Hh* pathway. Mutational analysis through this locus revealed exon 13 Y601X nonsense mutations in a 3-year-old patient. In the same context, Ptc 1 knockout transgenic mice models have been shown as useful tools to explore MB development [9,15,19,48].

Moreover, *Hh* signaling cascade is a regulator of DNA-damage response, which is supposed to be important in creating a tendency to medulloblastomagenesis in response to injuries of the genetic material, especially to double-strand breaks (DSBs) when it fails to work properly. The appropriate function of DSBs is to stimulate signaling on purpose to end the damage or the survival of cell [48].

### *Regulation of Patch expression and how this regulation can contribute to MB formation*

The mechanism responsible for related proliferation of GCPs is the inhibition of Smoothed (*Smo*) function and activation of *Gli* family of transcription factors including *Gli 1*, *Gli 2*, and *Gli 3* [11,26]. *Gli* proteins interact with a *cis*-element with the aid of a zinc-finger DNA-binding domain, resulting in the activation or inhibition of target genes among which Ptc 1 and *Gli* transcription factors themselves exist and, therefore, alter features of cells. *Gli 1* is always an activator, and its degradation is ubiquitin-mediated [13,36,48,63]. *Gli 1* and *Gli 2* are found to be more related with tumor development. Numb and Itch proteins mediate the activity of *Gli 1*. Itch itself is an ubiquitin ligase. *Hh/Gli* oncogenic potential is affected by the stability of *Gli* and its interaction with those mediators, Numb and Itch. Dysregulation of *Gli 1* by these factors determines the enhancement of *Gli 1*-dependent proliferation of MB. Negative regulators of the Hedgehog-Patched pathway include Suppressor of the Fused (*Sufu*), Rab 23, or Ren. Ren deletion at about 40 % of sporadic human MB has been shown to exist. Within sporadic MBs, Ptc 1 loss-of-function mutations are found at a range of 10–20 %. *Smo* and *Sufu* mutations

are observed in human MB though rare [13,26,48,57]. *Smo* is a heterotrimeric guanosine triphosphate-binding protein (G-protein)-coupled receptor and is a component of *Hh* pathway [6,48]. Degradation of *Sufu* is promoted by *Shh* via an ubiquitin–proteasome-dependent manner. It has been suggested to underlie to the decreased stability of *Sufu* in tumor cell lines [63].

Another transcription factor, Nanog, lies in the basis of self-renewal characteristics of embryonic stem cells and has been stressed in the literature by its activation reinitiated by cancer. Po and colleagues showed that the increased expression of Nanog and *Gli 1* in either mice or human MB stem cells may be *Hh*-dependent [46].

#### *ErbB receptor and Patch*

The Erb B receptor family has roles implicated for both tumorigenesis and developmental processes. The Erb B4 is highly expressed in human and mice cerebellum during embryogenesis. Its expression is lower during the lifetime of an adult. It has been shown that the expression of cytoplasmic isoforms of ErbB4, CYT 1, and CYT 2, localized in mouse GCPs in vitro and human MB cell lines, falls down by *Hh* signaling. Selective overexpression of ErbB4 CYT 1 has been observed during the *Ptch 1* single mutant studies, which led researchers to propose that there is an alternative tumorigenic pathway valid in the absence of *Hh*. This overexpression is a protective mechanism to escape from apoptosis [21]. A family of epidermal growth factor receptor ErbB 2, also named HER 2/neu, has been found to be overexpressed at about 80 % of MB specimens representing a bad prognosis [26].

#### *Other regulators of Hh pathway in MB*

A transcription factor named Atoh 1 or Math 1 is one of the regulators of *Shh* pathway having roles in GNP expansion. That transcription factor has been found to be associated with the aggressiveness of MB and bad prognosis. Flora and colleagues suggested that it is important in postpartum cerebellar physiology, which is the factor contributing to MB generation, and actor through activation of *Gli 2* [23].

#### Wnt pathway

*Wnt* pathway controls stem and progenitor cell proliferations in the early ventral zone (VZ) of the embryo and postpartum SVZ and hippocampus. APC is a gene involved in Wnt pathway which is mutated in Turcot's syndrome. APC is involved in a complex of proteins consisting  $\beta$ -catenin, glycogen synthase kinase 3- $\beta$  (GSK3- $\beta$ ), and Axin. Through a recent experiment, it has been revealed that GSK3- $\beta$  is the pivot molecule interconnecting PI3K/Akt and Wnt pathways for extension of MB

[62]; but targets of Wnt pathway are rather considered to be c-Myc, cyclin D1, and AXIN 2. Among them, cyclin D1 is essential in mediating CGCP proliferation and is a downstream target of *Shh*, Notch, and Wnt signaling. Gain of function mutations in Wnt pathway may also occur. Those mutations seem most likely to be in  $\beta$ -catenin gene but may also be observed in *APC* and *AXIN 2* genes. Axin 2 is defined as a negative loop in Wnt signaling. The APC-Axin complex is primarily responsible for targeting  $\beta$ -catenin to proteolysis by proteasome pathway. Wnt is not considered to control the way that EGL precursors behave [11,26].

#### Notch pathway

Notch is a transmembrane receptor which is highly conserved. It acts during pattern formation, proliferation, and survival of stem cells but at the meantime inhibits their differentiation. When Notch signaling is impaired, the whole cell field may turn to neurons. Notch signaling results in transcriptional activation of *Hes 1* and *Hes 5*, the helix-loop-helix transcription factors. Notch 2, which is predominantly expressed in proliferating CGNPs, is found to be overexpressed in MBs of about 15 % [11,12,17,26].

It has been demonstrated that inhibiting both Notch and *Shh* pathways in human primary and cultured cells and the xenografts resulted in more tumor loss than targeting only one of them. It has been declared that Notch signaling is essential for MB survival [28]. However, it has later been reported that Notch signaling is not essential for the pathology of *Shh*-driven, genetically engineered MB mouse models [30].

#### **Receptor tyrosine kinases and intracellular signaling mechanisms related to MB development**

Receptor tyrosine kinases (RTKs) have intrinsic tyrosine kinase activity. They are involved in a variety of cellular processes like cell proliferation and migration, metabolism, and survival, and are activated by either growth promoting factors or cytokines. IGF and cognate receptors (IGF-R) have been found to be responsible for malignancy of MB [26]. The IGF/PI3K signaling pathway enhances the *Shh*-related MB development. PI3K prevents the degradation of n-*Myc*; therefore, n-*Myc* is upregulated. PI3K inhibitors are used to prevent tumor resistance as therapeutic strategies. The function of *Myc* family of proto-oncogenes is to serve for the regulation of cellular proliferation, differentiation, or apoptosis. An augmentation in *Myc* transcription has been found to be correlated with decreased survival. Also, inhibition of IGF-1R signaling exhibited reduced MB growth. IGF-1R signaling is thought to activate AKT and PI3K and also Ras/mitogen-activated protein kinase (MAPK) signaling. Within MBs,

targets of Ras/MAPK pathways are upregulated. Among the targets of this pathway lies platelet-derived growth factor receptor-B (PDGFR-B) which is upregulated in metastatic MB [3,6,8,11,65].

It has been mentioned that PDGFR is overexpressed especially during metastatic conditions. They treated metastatic MB cells with PDGF and observed that extracellular signal-regulated kinase (ERK) phosphorylation is triggered and migration is advanced. ERK is a member of MAPK family that has been stated to be involved in many steps of tumor progression including regulations of apoptosis-related proteins and extracellular matrix proteins [35,62].

#### ERK signaling

Downstream targets of MAPK may include mammalian target of the rapamycin (mTOR). It is able to phosphorylate and activate Akt at serine 473. Protein translation that has been regulated by mTOR may lead to malignant growth in case of MBs [3,60].

Rac 1 is a previously defined GTPase belonging to the Rho family as participating in activation of three MAP kinase cascades: ERK, JNK, and p38. Inhibiting them, as a part of the group's study, revealed ERK and JNK, which are important for invasion and prohibition of growth despite the fact that the prohibitory effect of Rac 1 in one of these cell lines was not found to be intervened by either ERK or JNK. Three different human MB cell lines were tested to evaluate the role of *Rac 1* and related signaling molecules as candidates responsible for tumor invasion. They concluded that *Rac 1* depletion prevents invasive action but has no effect on cell survival. [64].

#### Akt signaling

The cascade of PI3K/Akt can be downregulated by PTEN whose homozygous deletions in mice are shown to exhibit dysplasia of primary granule cells at cerebellum [4].

#### Other RTKs

Impaired regulations of several other RTKs such as c-Met, ErbB 2 (also called *Her 2/neu*, a family of epidermal growth factor receptor), and vascular endothelial growth factor receptor have also been found to be in association with MB [28]. ErbB 2 has been found to be overexpressed at about 80 % of MB specimens representing a bad prognosis [12,50].

The proto-oncogene *kit* is a RTK subclass III family member. The amplification of *kit* is observed in correlation with poor prognosis at some medulloblastoma and cellular PNET species. However, methylation of *kit* promoter is searched experimentally to support the hypothesis which declares its contribution to tumor formation in MB. This hypothesis has not been proved [16].

#### Gap junctions in MB development

Gap junctions are channels spanning the cell membrane and are responsible for communication of neighbor cells via permission of direct transport of molecules smaller than 1 kDa. Human cancers are considered to have accumulation of gap junction disruptions, either by a decrease in the expression of channel protein connexin or by a dysfunction of channel creation. It has also been observed that healing the functions of gap junctions reveal a decline in carcinogenic potential [32]. Direct relation of any disruption with functions of gap junctions specifically contributing to MB development requires more experimental evidence.

#### Neurotrophins in MB development

NTs are members of neurotrophic factors that play important roles in proliferation, migration, and differentiation concerning both developing nervous system and functioning adult nervous system. Maintenance of neuronal activity and regeneration, structural stability, and neurogenesis all depend on normal actions of NTs. Their insufficiency or pathology might result in a disruption of neuronal maintenance, abnormalities within the structure of the brain, and a decrease in plasticity [14,38,51]. In particular, they serve as important modulators of synaptic transmission comprising neurotransmitter release and postsynaptic responses to neurotransmitters, facilitation of long-term potentiation, and survival. Four main NTs in mammals, named nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin 3 (NT 3), and NT 4/5, bind respectively to four receptors named pan 75 neurotrophin receptor (p75NTR), TrkA, TrkB, and TrkC. Trk symbolizes tropomyosin-related kinase family of RTKs. NGF specifically binds to TrkA, BDNF and NT 4 bind to TrkB, NT 3 binds to TrkC but is also able to bind to Trk A and B though with low affinity. When a neurotrophin binds to its receptor, Trk receptor dimerizes, and its intracellular tyrosine residues are phosphorylated. Intracellular signaling pathways are activated thereafter. On the other hand, entire NTs are capable of binding p75NTR [14,49,53,54].

NGF is a neurotrophin which is supposed to be a factor affecting the physical characteristics of MB. Concluding effects of NGF binding to receptor TrkA, like differentiation or proliferation, may involve different cascades depending on the type of cells. In MB cell cultures, NGF has been shown to induce apoptosis which is dependent to Ras activity but independent to MEK/ERK [38]. Also, affluence of *TrkC* mRNA expression has been correlated with an improved response to the treatment of childhood MB and 5-year survival; however, a study in 2004 has implicated that it had no effect on prognosis [7,12,26].

Similarly, BDNF/TrkB signaling components have been tested for vitality in human MB cells. They also

have been noted as possible mediators of durability of cells. Expressions of many microribonucleic acids have been found to be decreased in human MB primary specimens. Especially miR-9 and miR-125 seemed to contribute to growth blockage and promotion of apoptosis after recovery of their expression when the target is a preproliferative TrkC isoform [22,27,50].

### Other molecules and pathways related to MB development

#### c-Myc

Cellular-Myc (*c-Myc*) is a transcription factor organizing cellular growth and death. It is specifically important for MB because it stands for large-cell/anaplastic subtype and poor prognosis. It is also usually overexpressed or amplified. It has been suggested that pathogenesis of neuronal Myc (*n-Myc*) involves cooperation of both *Shh* and *c-Myc* [11,17,26,65]. Myc is described as an interconnecting agent which settles disarrayed activities of *Shh*, *Wnt*, and PI3K/Akt signalings. The transcription factor RE-1 silencing transcription factor is a blocker of neuronal differentiation and is greatly expressed in MB as well as neural stem cells. It is able to transform *c-myc*-immortalized GCPs towards MB [3,19].

#### Hippo

Hippo, which is a novel tumor suppressor, limits the organ size by blocking yes-associated protein (YAP 1) transcriptional coactivator activity. YAP 1 is able to cause transformation and proliferation. It acts as a regulator of expression of many transcription factors including RUNX 2, SMAD 7, p73, p53BP2, and TEA domain-associated transcription factor (TEAD) family members. It has been found that YAP 1 and its partner TEAD 1 are expressed in very large amounts in *Shh*-driven MBs in humans and mice. YAP 1 activity, in cooperation with TEAD 1, leads to proliferation of CGNPs. The YAP 1/TEAD 1 complex adjusts expression of *Gli 2*, which further translocates to the nucleus and arranges transcription of *Gli 1* and then regulates activity of elements of cell cycle machinery [20].

#### DNA repair mechanism

DNA damage repair or failure, such as deletion of DNA ligase IV, or cell cycle dysregulation influencing components like *Kip 1*, *Ink 4C*, *Ink 4D*, or even loss of genes related with poly (ADP-ribose) polymerase 1, XRCCA, *Brca 2*<sup>Nestin-cre</sup> (inactivation by Nestin-cre), have been shown to develop murine MB when combined with p53 deletions. But, in humans,

concurrent mutations within these pathways are not frequent [25,28,48]. When *Ptc1* heterozygous mice are exposed to a radiation-like environmental factor combined with loss of PARP 1, which is a part of DNA repair mechanism, an increased tendency to develop MB was observed [56].

#### Hox genes

Homeobox (*Hox*) complex have differential roles in regulating developmental anteroposterior axis formation which also compromises neuronal classification. This process requires expression of particular genes that belong to and represent the complex [1]. An overexpression and occasionally an amplification of a transcription factor named orthodenticle homeobox 2 (*Otx 2*) has previously been underlined for MBs. Investigations of the downstream components of *Otx 2* actions led people to mention about some cell cycle genes which demonstrate a requirement for participation of other oncogenic changes for MB formation [5].

#### Other genes and transcription factors

Within classical MBs, SOX gene family members, primarily Sox4 and Sox11, are shown to be overexpressed when compared with ependymoma and normal cerebellum [10,11]. Signal transducer and activator of transcription (STAT) is a transcription factor emphasized as both a downstream of IGF and an inducer of stem-like behavior in glioblastoma-like brain tumors [37].

### Role of primary cilia

The possibility of existence of primary cilia in few human MB subtypes has been reported in the literature. Interestingly, those having primary cilia were exhibiting high *Hh* signaling with defined mutations in pathway components like *Ptch1*. Experimental mutations using mouse models were performed, and it was concluded that primary cilia are able to activate or inhibit development of the tumors consistent with predisposing oncogenic circumstances [29].

### Viral etiology

Associations with viral infections, especially with human neurotrophic polyoma virus (JCV) in MB development have also been described. The viral early protein, T antigen, is thought to be responsible for tumorigenesis. It is observed that transgenic mice producing T antigen in relation with JCV early promoters/enhancers developed neuroblastomas and MBs [47].

## Novel chemotherapeutic agents as candidates to prevent MB development

Classical chemotherapeutic agents which are used in the treatment of childhood MB are reviewed before [8]. However, classical chemotherapy is toxic. Toxicity increases when classical drugs are combined with standard surgery and radiotherapy [55]. Basic candidate molecules for a better management of MB in the literature are updated below.

### Hedgehog inhibitors

Hedgehog inhibitors are on trial, but there is lack of evidence about their potential clinical use. Most of them target *Smo* and contribute to silencing of *Hh* signaling. Antagonizing *Smo* receptor is shown to inhibit *Hh* signaling and promote tumor regression within animal models of MB [6,8,26]. According to the cancer stem-cell approach, the cells inside a neoplasm are not equal in unlimited self-renewal potentials and long-term growth. In case of MB, a clinical phenotype is suggested to be affected from modulation of stem cell-like cells. *Hh* inhibition, for example via cyclopamine, seems to be a potential in vitro MB growth attenuator, but the involvement of stem-like cells in the tumor through this attenuation has not been proved [19]. Existence of studies showing that *Shh* cascade and errors derived from it does not make significant differences in the prognosis; a resistance to *Hh*-inhibiting therapies in the literature may require further attention, and understanding on the etiology of MB also regarding the interactions of developmental pathways to propose key downstream targets is needed [44,45].

### Wnt inhibitors

Interestingly, phenotypes of blastoma with positive mutations in  $\beta$ -catenin, a member of APC complex functioning at downstream Wnt, are shown to be related with overall survivals. Due to this fact and the suspicions regarding the importance of Wnt in cancer stem cells, it was previously proposed that targeting inhibition of Wnt pathway members may not be beneficial [26].

### Notch inhibitors

In MB stem cell lines and PNETs, blocking Notch resulted in suppression of transcription of its target *Hes 1* and therefore resulted in exiting from cell cycle, apoptosis, and differentiation. This finding correlated with poor consequences [19,26].

### Other inhibitors related with cell signaling

Cascades regulated by *Rac 1* have been suggested as potential targets for treatment of MB, but further experimentation

is necessary [64]. An ErbB 2-antibody, Trastuzumab, had promising effects to ErbB 2-receptor-positive MB cases, but its activity was limited due to low blood–brain barrier infiltration [26].

2-Amino-*N*-(4-[5-(2-phenanthrenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenyl)-acetamide (OSU03012) is the third generation cognate of celecoxib and has inhibitory impacts on phosphoinositide-dependent protein kinase 1, the downstream component of PI3K/Akt cascade. OSU03012 triggered apoptosis following interruption of cell division. It has been tested by various ways including combinations with standard chemotherapy agents and the mTOR inhibitors, CCI-779 or rapamycin. The results portrayed its aid in conveying cellular toxicity [4].

### Curcumin

An Indian spice product, curcumin, is a polyphenol which has antitumorigenic effects. It is still on the phase of human clinical trials, but its way of action is well proposed including IGF, Akt, MAPK, STAT 3, nuclear factor kappa B, and Notch as target molecules whose dysregulations contribute pathologies of malign brain tumors. Administration of curcumin nanoparticles to MB cell lines was revealed with 35 % inhibition of tumor growth which is further experimented to define potential responsible mechanisms and led to identify increases in apoptosis and cell cycle arrest. Although some MB cell lines display STAT 3 $\alpha$ -positive expression pattern, effects of nanocurcumin on STAT signaling has different conclusions depending on the type of lines, but other pathways like IGF are shown to be suppressed by it [37].

### PGE2

Prostaglandin E2 (PGE2) was shown to trigger MB growth; therefore, nonsteroid anti-inflammatory drugs and small interfering RNA aiming to inhibit cyclooxygenase 2, which is the producer of PGE2, were administered to human MB cell lines, and a reduction in MB tumor growth was observed. A combinatory treatment approach involving both *Shh*-like developmental inhibition and application of nonsteroid anti-inflammatory drugs has recently been proposed [2,3].

### Superoxide dismutase mimetics

A compound mimicking action of superoxide dismutase in mitochondria called ortho-isomer manganese (III) meso-tetrakis (*N*-n-hexylpyridinium-2-yl) porphyrin has recently been tested in brain tumors including MB. The results point this compound as a strong alternative chemotherapeutic candidate for increasing general survival ratio of 173 % in pediatric MB xenografted mice. The proposed ways of functions

include inhibitions of cellular radicals which then affect transcriptional activities and coupling of reductants with relevant signaling molecules [34].

### Retinoic acid

Experiments revealed prevention of MB growth by all Trans and 13-*cis* retinoic acids in vitro, proposing those candidates as drugs to be developed. Retinoids trigger apoptosis and differentiation in mice and cell cultures. Combination trials with other chemotherapeutics are on discussion [8,55,59].

### Conclusion

As known today, there are multiple pathways which are responsible for MB formation, most of which are developmental and make crosstalk at certain molecules. Causes of MB still need further investments and investigations. The better nature of the disease is understood, the more effective and lifesaving treatment strategies can be developed. Targeting, for example, elements of MAPK cascades does not seem to promote survival more than classical chemotherapeutics; they both have serious side effects. In case of *Shh* pathway, it looks a better approach to target and specifically inhibit it, since it may be less active in normal life than development; but at this point, patients are mostly children, who still develop. Again, side effects may prevent a complete cure. Also, tumors may activate alternative pathways to favor their proliferation as usually seen in escaping from the immune system and developing resistance to cytotoxic drugs. As described in the literature above, once the MBs develop, therapy should be personalized, relying on the nature of the tumor with appropriate markers screened. Therefore, the best approach could be the preventive one: by encouraging women to take as many precautions as possible during their pregnancy to at least decrease the frequency of MB.

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