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What underlies the diversity of brain tumors?

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Abstract

Glioma and medulloblastoma represent the most commonly occurring malignant brain tumors in adults and in children respectively. Recent genomic and transcriptional approaches present a complex group of diseases, and delineate a number of molecular subgroups within tumors that share a common histopathology. Differences in cells of origin, regional niches, developmental timing and genetic events all contribute to this heterogeneity. In an attempt to recapitulate the diversity of brain tumors, an increasing array of genetically engineered mouse models (GEMMs) has been developed. These models often utilize promoters and genetic drivers from normal brain development, and can provide insight into specific cells from which these tumors originate. GEMMs show promise in both developmental biology and developmental therapeutics. This review describes numerous murine brain tumor models in the context of normal brain development, and the potential for these animals to impact brain tumor research.

Keywords

development; medulloblastoma; glioma; murine model; transgene

1. Introduction

Human brain tumors comprise a multitude of various different tumors that can be distinguished at both a histological and a molecular level. This review summarizes use of genetically engineered mice to model glioma and the embryonal tumors medulloblastoma (MB) and primitive neuroectodermal tumors (PNETs), focused on developmental aspects and molecular pathways.

2. Normal Brain Development and Brain Tumor Development

The brain is formed during embryogenesis and continues to develop after birth. The central nervous system (CNS) arises from the neural plate on day 19 in human embryos. As the plate folds along its anteroposterior axis (primary neurulation), it develops into a tube with vesicles that are the anlagen of fore- mid- and hindbrain [1]. More posteriorly the narrow tube develops into the spinal cord, which forms both from primary and secondary neurulation, the latter process referring to tube formation arising through canalization of a solid cylindrical neural structure. Neural tube closure begins at Embryonic Day (E) 8.5 and

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finishes at E10.5 in mice. Proper neurulation of the CNS relies on the inhibition of bone morphogenetic protein (BMP) signaling [2].

2.1 Developing forebrain and cellular origin of gliomas

Cortical neurogenesis begins around E9-E10 in the mouse where Fibroblast Growth Factor (FGF)-driven neuroepithelial cells line the forebrain ventricles and spinal canal giving rise to radial glial cells [3]. Radial glial cells are primary progenitor cells that eventually give rise to mature neurons as well as oligodendrocytes, astrocytes and ependymal cells [4] (Figure 1). The differentiation of these mature cells starts from radial glia-derived progenitors and are driven by specific developmental morphogens which promote brain patterning and give rise to the complex brain structure [1]. Radial glia or neural stem cells (NSCs) are bipolar, and divide asymmetrically to enable both self-renewal, and to generate progenitors and more differentiated brain cells that form the adult brain. In humans (and to a lesser degree in rodents), a group of unipolar radial glia-like cells arising from the outer subventricular zone (so-called ORG cells) have been shown recently to contribute to both neural migration and the expanded numbers of neurons in human cortex [5].

Progenitors, including oligodendrocyte precursor cells (OPCs) and ependymal cells arise from radial glia and NSCs. These cells become regionally restricted depending on intrinsic maturation, and on cues from developmental organizing pathways like Sonic Hedgehog (SHH), Wingless proteins (WNTs), BMPs and FGFs. Brain lipid-binding protein (BLBP) is expressed by radial glia cells in brain and spinal cord [6–8]. When the *Blbp* promoter was used to drive Cre/loxP to follow cellular fate using the Rosa26 reporter, it was evident that neurons in almost all brain regions were labeled [9] suggesting they all originate from these BLBP-positive cells. OPCs are presumably also derived from the radial glia. OPCs express NG2 and continue to produce myelin-producing oligodendrocytes [10]. Adult OPCs are also born and are presumably derived from NSCs [11] that reside in the adult forebrain in lateral regions of the lateral ventricles and in the dentate gyrus in the hippocampus. Such NSCs are termed “type B” cells, slowly dividing subventricular zone (SVZ) astrocytes or subgranular zone (SGZ) astrocytes [12,13]. During neurogenesis, type B NSCs give rise to transit amplifying progenitors (type C cells) that later give rise to immature neuroblasts (type A cells). Type A cells in rodents migrate to the olfactory bulb where they differentiate into olfactory neurons [14]. Ependymal cells also originate from radial glia, are born in the embryonic and early postnatal brain and do not divide after differentiation [15]. As discussed in detail below, cells of origin for glioma are probably heterogeneous, as both NSCs and OPCs that are both derived from a neuroepithelial cell could generate brain tumors in mouse models (Figure 1).

2.2. Developing hindbrain and cellular origin of MB

Segmentation plays a prominent role in the developing hindbrain. One area of segmentation, the isthmic region, lies at the midbrain-hindbrain boundary of the neural tube. During E9.5 in mice the so-called isthmic organizer secretes FGFs and WNTs, which provide regional identity and pattern proliferation along the anterior/posterior axis [16]. Abrogation of *Otx2* and *Gbx2* in mice indicated these proteins were essential for regionalization of the midbrain and rostral hindbrain [17]. The region where transcription factors like *En1*, *Pax2*, and *Otx2* are expressed acquires midbrain identity, while FGF8 also expressed in the isthmus, produces a strong local signal associated to cerebellum fate determination [18].

The cerebellum is in control of balance control and motor coordination but also shares with the cerebrum some role in cognitive functions, speech and spatial memory [19], functions that may be affected in children with brain tumors, or after surgical resection [20]. Two distinct germinal zones give rise to the cells of the cerebellum [21] that arise from

rhombomere 1. After E10 in mice, the ventricular zone (VZ), the primary germinal zone, forms along the fourth ventricle. The VZ of the cerebellar anlage contains primitive cells like neuroepithelial cells and radial glia. These PTF1A-positive progenitors exit the cell cycle, migrate radially into the cerebellum and give rise to all GABAergic cells [22], Purkinje neurons and interneurons including Basket and Stellate cells. Interestingly, deleting *Ptf1a* leads to failure of VZ cells to generate GABAergic neuronal cell types. [23]. This GABAergic linage could be traced through E18 when these embryos died. Some radial glias from VZ convert into Bergmann glial cells [24]. Precursors of Bergmann glia are found after E15, and they keep their processes once made by their radial predecessors [25].

The second cerebellar germinal zone forms along the anterior aspect of the rhombic lip (RL) structure and give rise to glutamatergic neurons [26] including cerebellar granule neurons [27,28], the most abundant cell type in the entire CNS. Cells exiting the anterior RL migrate over the cerebellar anlage forming the external germinal layer (EGL). The EGL consists of MATH1-positive granule cell progenitors (GCPs) that continue to proliferate. The peak of this proliferation occurs at P7 [29] in response to SHH produced by Purkinje neurons [30,31]. However, SHH that prevents differentiation and promotes proliferation of granule neuron precursors is also present in the embryonic cerebrospinal fluid, that circulates within the cerebellar VZ by E12.5-E15 [32].

Whether the RL is the sole source of SHH-dependent granule cells remains unclear. When *Math1* is depleted there is a failure to produce granule cells but the RL still forms [28]. Fate mapping has suggested that Math1-positive cells are not the definite RL stem cells. Instead, another yet undefined RL stem cell population may actually give rise to Math1-positive cells [33,34]. Since the RL and EGL cells are both derived from GFAP-positive cells [35] both populations could conceivably give rise to SHH-driven MB [36,37]. This suggests GFAP-positive VZ cells are certainly a major contributor to both these germinal zones. For example, if the VZ marker PTF1A is deleted, some mutant VZ progenitor cells aberrantly migrate to express RL markers like MATH1 and ZIC1/2 [38].

The cerebellum is structurally complete by 3 weeks of age in mice and at ~2 years of age in human [39]. The fully developed cerebellar cortex consists of molecular, Purkinje cell, and internal granule cell layers. The development of VZ and RL are regulated by NOTCH activity in the VZ, and BMPs that signal from the roof plate. Early, during embryonic cerebellar development BMPs stimulate production of RL-derived neurons and expression of MATH1 [40–42]. Later on, during postnatal periods BMPs instead inhibit MATH1, SHH-induced GCP proliferation and MB development [43,44]. Loss of *Notch1* in the cerebellar primordium leads to severe hypoplasia and an increased RL neurogenesis [41,45] while overexpression of *Notch2* activity postnatally inhibits GCP differentiation [46]. Thus NOTCH signaling like SHH signaling acts to arrest the differentiation state of cerebellar precursors at different developmental stages.

As for glioma, the cells of origin for MB are not clearly identified, and it is likely that more than one type of cell can generate these tumors (Figure 1). In fact, neural stem cells, granule precursor cells and progenitor cells from the lower RL of the developing dorsal spinal cord all give rise to MB in mouse models, as further discussed below.

3 Glioma

3.1 Classification and prognosis

Gliomas are the most common tumors in the central nervous system (CNS). They are classified histopathologically as astrocytomas, oligodendrogliomas, mixed oligo-astrocytomas and ependymomas, and graded with regard to malignancy as I- IV according

to the World Health Organization (WHO) classification system. Grade I and II tumors are slowly growing, while high-grade gliomas (of grade III and IV) are malignant tumors with a high proliferation rate. In addition, grade IV gliomas, also called glioblastoma multiform (GBM), show areas of necrotic pathology and of vascular proliferation.

The vast majority of grade IV gliomas present *de novo* as primary GBM, however rarely, secondary GBM progresses from lower grade gliomas. Although the primary and secondary GBM display the same histopathologic features, they have different underlying genetic mutations and molecular characteristics. The prognosis for GBM is unfortunately dismal, with grade rather than stage typically the main prognostic stratifier. The alkylating agent temozolomide in combination with radiation and chemotherapy results in a 5-year overall survival of less than 10% after diagnosis [47]. Lower-grade astrocytomas, and oligodendroglioma patients have a better prognosis where oligodendroglioma with a combination of LOH (loss of heterozygosity) on Chromosome 1p/19q often respond better to chemotherapy [48].

3.2 Molecular characterization

There has been great progress in the characterization of gliomas at both genomic and transcriptional levels. Several large-scale genomic efforts, including the Cancer Genome Atlas Research network have focused on GBM and in fact, the TCGA database now includes over 500 GBMs (http://cancergenome.nih.gov) [49]. Three key signaling pathways commonly disrupted in a majority of GBMs include the receptor tyrosine kinase (RTK) signaling pathways as well as the tumor suppressor pathways of RB and p53 (Figure 2). In addition to the identification of mutations affecting these pathways, new genes have been implicated as key players in gliomagenesis, and new subgroups of GBM have been identified on the basis of these genetic aberrations and gene expression profiles.

Analysis of high-grade glioma (WHO grade III and IV) gene expression patterns initially identified three subgroups, named Proneural, Mesenchymal and Proliferative types. These groups displayed features of neuronal progenitors, mesenchymal cells and proliferating cells, respectively [50]. A larger set of GBM patient samples from the TCGA were later analyzed to identify four separate groups; Classical, Mesenchymal, Proneural and Neural [51]. The tumors of the Classical group are characterized by *EGFR* amplification and loss of *PTEN* and *CDKN2A*. Mutations in *TP53* are rarely found in this group. Activation of SHH and Notch are relatively common. The Mesenchymal group of GBM is characterized by mutation or loss of *NF1*, *PTEN* and *TP53*. They display an angiogenic or mesenchymal gene expression profile with activated TNF and NFkB pathways. The Neural group of GBM often shows overexpression and amplification of *EGFR,* and displays a gene expression profile resembling normal brain.

The Proneural subtype of GBM often shows *PDGFRA* amplifications and loss of *TP53*, *CDKN2A* and *PTEN*. The Proneural tumors also commonly have mutations in *IDH1* and in genes encoding PI3K. The gene expression profiles of Proneural tumors resemble neuronal and oligodendrocyte progenitor cells. The genetic aberrations of secondary GBMs mostly resemble the Proneural subtype, with *TP53* and IDH mutations and overexpression of *PDGFRA*. These genetic aberrations are emerging early in the tumor progression from low- to high grade astrocytic glioma. Analysis of IDH1 mutation status in human glioma samples showed an association of mutated IDH1 with frontal lobe location, Proneural gene expression signature, altered methylation pattern and a better prognosis [52].

Oligodendrogliomas are grade II-III gliomas with oligodendroglia-like histology, often displaying LOH on chromosome 1p and 19q as well as loss of IDH1 and overexpression of *EGFR* and *PDGFRA*. Pilocytic astrocytomas are benign (Grade I) tumors often carrying

activating mutations in *BRAF* [53,54], and activation of the MAPK signaling pathway. Roughly 15% of Neurofibromatosis Type 1 (NF1) patients also have pilocytic astrocytomas, particularly in the optic pathway [55].

GBM is also a lethal brain tumor in children where DNA copy number and gene expression signatures indicate some differences. Interestingly, mutations in regulatory Histone 3.3 and chromatin remodeling genes are highly prevalent in pediatric GBMs but also in adult GBMs [56].

Ependymomas are glial tumors with many different genetic aberrations, including loss of *CDKN2A*, *PTEN* and overexpression of *NOTCH1* and *EPHB2*. Ependymomas are a heterogeneous group of tumors that probably consists of several subgroups, arising in different locations in the CNS [57].

3.3 Mouse models of gliomas

Genetically engineered mouse models (GEMMs) have been extensively used to model human gliomas. Mutations and genetic aberrations found in human gliomas have been introduced into both germ-line cells and somatic cells by various methods (Table I). The use of inducible gene-expression constructs and tissue-specific promoters allows for the targeting of a specific cell type at a specific time point or developmental stage. GEMMs have provided means to study both the mechanisms of tumor initiation and progression as well as to find new potential targets for treatment.

3.4 Models using RTKs or growth factors

Excessive growth factor signaling is one crucial component in the glioma development. Genetic analysis of high-grade tumors reveals a high frequency of aberrations affecting the RTK/RAS/PI3K signaling pathways. The most commonly mutated RTK is EGFR, which is found mutated or amplified in 45% of GBMs. Activating mutations or amplifications are also found in PDGFRA (13%), ERBB2 (8%) and MET (4%) [49].

The most commonly constitutively activated form of EGFR in glioma is EGFRvIII that has lost parts of its extracellular domain and signals independent of ligand binding [58,59]. Constitutively activated forms of EGFR have been used in combination with other genetic aberrations such as loss of tumor suppressors *Ink4a/Arf*, *p53* or *Pten*, to induce both low- and high grade gliomas in mice [60-63]. The Classical subgroup of GBM is characterized by EGFR signaling together with loss of *CDKN2A*. GEMMs with this combination of genetic aberrations have been generated in several ways.

Low-grade gliomas formed when an active form of EGFR was expressed in Nestin-positive progenitor cells of newborn *Ink4a/Arf*$^{-/-}$ mice. Active EGFR was introduced into Nestin-expressing cells or GFAP-expressing cells by the avian retroviral RCAS/tv-a system. In this model, tumors/glioma-like lesions formed more frequently from Nestin-positive cells, than GFAP-positive cells [60]. In a transplantation mouse model system using newborn EGFRvIII overexpressing *Ink4a/Arf*$^{-/-}$ primary cells, both NSCs and mature astrocytes were shown to induce high grade gliomas when orthotopically transplanted into recipient mouse brain [64].

Excessive EGFR signaling together with loss of *Ink4a/Arf* has also been targeted in cells of oligodendroglial lineage. Transgenic expression of active EGFR in the form of the transforming avian allele *v-erbB,* in S100β-positive oligodendrocytes of mice resulted in low grade oligodendrogliomas [61]. When combined with either loss of p53 or loss of *Ink4a/Arf*, misexpression of *v-erbB* gave high grade oligodendrogliomas with a reduced latency. This model was used to demonstrate that tumors originated from an expanded pool of

oligodendrocyte precursor cells [63], an observation also demonstrated in human oligodendroglioma

GBMs have been generated in mice by combining *EGFRvIII* with loss of both *Pten* and *Ink4a/Arf*. The expression of *EGFRvIII* was induced in adult mouse striatum by adenoviral Cre [65]. Recently, another inducible mouse model showed that overexpression of wild-type *EGFR* together with the ligand transforming growth factor alpha (TGFα), could also induce GBM. In this model, lentiviruses were used to introduce TGFα together with Cre to the striatum of *Ink4a/Arf*$^{-/-}$ mice resulting in oncogene dependent, high grade gliomas [66].

Analysis of human glioma tissue show that overexpression of *PDGFRA* is found in both low-and high-grade tumors [67]. The activating ligands (PDGF-A, -B, -C and -D) are also expressed in human gliomas, and the expression patterns of PDGF ligands and receptors PDGFRA and PDGFRB in glioma tissue suggest the presence of autocrine and paracrine loops stimulating tumor growth [68]. Ectopic expression of the PDGF ligands, and PDGFB in particular, has been used extensively to model different glioma subtypes in mice. Retroviral expression of *PDGFB* has been shown to cause malignant oligodendroglial tumors, when injected into embryonic [69] or newborn mouse brain [70]. Experiments on newborn rat brains show that retroviral *PDGFB* can cause a shift in the differentiation of NSCs, producing more PDGFRA/NG2/OLIG2-expressing OPCs [71].

A targeted approach using the RCAS/tv-a system, induced expression of *PDGFB* specifically in GFAP-, Nestin- or CNP-expressing cells, resulting in oligodendrogliomas and some mixed oligoastrocytomas [72,73]. The gliomas induced by *PDGFB* with the RCAS/tv-a system were altered to a more malignant tumor phenotype when combined with a second genetic aberration such as loss of p53 or Ink4a/Arf [74,75].

In contrast to the retroviral models, transgenic expression of *PDGFB* from the GFAP promoter only resulted in gliomas when combined with loss of p53. Mice over-expressing *PDGFB* on a *Trp53* null background developed GBM-like tumors with high expression of *PDGFRA* on tumor cells and *PDGFRB* on tumor vessels [76]. In comparison, the same human GFAP promoter was also used to overexpress the long form of *PDGFA*. In contrast to the high-grade astrocytic gliomas formed by *PDGFB* in *Trp53* null mice, transgenic expression of $PDGFA_L$ instead led to rapid expansion of oligodendrocyte progenitor cells and oligoastrocytomas in a *Trp53* wild-type background [77].

Retroviral expression of *PDGFB* together with Cre has been used to generate high-grade astrocytic tumors in subcortical white matter regions of adult *Pten*$^{-/-}$ as well as *Pten*$^{-/-}$*Trp53*$^{-/-}$ mice. Gene expression profiling of the resulting tumors revealed a strong similarity to the human Proneural GBM subtype [78].

3.5 Models using other oncogenes

Several glioma models target the downstream signaling pathways activated by growth factor signaling. Activated RTKs signal via many pathways, including the RAS/MAPK and PI3K/AKT pathways, to promote cell proliferation and survival. Activation of different components in these pathways promotes glioma formation in mice (Figure 2).

Transgenic mice overexpressing a constitutively active form of *RAS* (*V*^{12}*Ha-ras*) under the GFAP promoter develop astrocytic gliomas. Increasing the expression levels of the transgene resulted in progression of the tumors from low- to high-grade gliomas [79]. Adding overexpression of activated *EGFRvIII* to the model turned the gliomas to a more oligodendrocytic pathology [62]. On the other hand, when the RCAS/tv-a system was used to somatically introduce an activated form of *K-Ras* into newborn mice, transduction of

activated *Akt* was also needed for tumor formation. High grade gliomas formed only when the activated *Akt* and *K-Ras* genes were introduced together into Nestin-expressing neural progenitors, and tumors did not form from GFAP-expressing cells [80]. The same activated variant of *K-Ras* in combination with loss of the tumor suppressor locus *Ink4a/Arf* resulted in glioma formation from both GFAP- and Nestin-positive cells, some with a sarcoma-like phenotype [81].

In adult mouse brain, lentiviral vectors carrying *H-Ras* and *Akt* induced high-grade astrocytomas when introduced to GFAP-expressing cells of both SVZ and hippocampus. On a *Trp53* null background, the developing gliomas became more malignant, and cortical tumors also formed in addition to the SVZ and hippocampal tumors [82].

3.6 Models using tumor suppressor genes

The signaling activity of Ras is regulated by NF1, which has been found to be mutated in 18% of human GBM [49]. Loss of *Nf1* has been used to model gliomas in mice in combination with loss of other tumor suppressors such as *Trp53*, *Rb* or *Ink4a/Arf*.

The tumor suppressor genes *Trp53* and *Nf1* are located on the same chromosome, allowing for an easy way for targeting the two genes at once. Mice heterozygous for both *Trp53* and *Nf1* genes develop low and high grade astrocytomas displaying loss of heterozygosity (LOH) for the remaining *Trp53* and *Nf1* allele [83]. More restricted approaches where *Trp53* and *Nf1* were mutated or deleted only in GFAP-expressing cells also resulted in high grade astrocytomas [84,85]. Gliomas formed only when *Trp53* was deleted before or simultaneously as *Nf1*, indicating that loss of *Trp53* is crucial for the initiation of gliomagenesis [85]. Loss of p53 is indeed an early event in human gliomagenesis, and mutations in *TP53*, and LOH at chromosomal region 17p containing the *TP53* gene are commonly found in both low- and high grade gliomas [86].

A tumor suppressor gene commonly found inactivated in human high-grade gliomas, but not in low-grade tumors is *PTEN*. Loss of *PTEN* leads to hyperactivation of AKT and increased proliferation and migration. Adding heterozygosity for *Pten* to a mouse model with deleted *Nf1* and *Trp53* in GFAP-expressing cells resulted in a more malignant tumor phenotype, and frequent LOH of the remaining allele of *Pten* in progressed grade IV tumors [87]. Conditional mouse models have further been utilized to study the tumor suppressing roles of p53, NF1 and PTEN in different cell types and in different areas of the brain. Conditional loss of *Nf1* and *Trp53* in Nestin-expressing cells resulted in high grade astrocytomas when targeting both newborn and adult SVZ. However, no tumors were formed by targeting cortical Nestin-expressing cells with the same genetic aberrations [88]. Another study showed that combined loss of *Trp53* and *Pten* in GFAP-expressing cells of adult SVZ resulted in high grade astrocytic gliomas, while loss of *Trp53* and *Pten* in GFAP-expressing cells in other regions failed to generate tumors. Mice carrying conditional alleles of *Trp53*, *Pten* and *Rb* were also generated. Mice with loss of all three genes developed high grade tumors, with reduced latency, and in some cases a PNET-like phenotype [89]. Gliomas induced by the combined loss of *Trp53* and *Pten* or *Trp53*, *Pten* and *Rb* showed gene expression profiles similar to human GBM, including Proneural, Mesenchymal and Proliferative subgroups [90]. The RB signaling pathway is one of the three critical pathways often mutated in human GBM, [49]. RB signaling was found altered in 78% of primary GBMs. The most common aberrations were deletions and mutations in *CDKN2A* and *CDKN2B* [49]. Many genetically engineered mouse models of glioma include loss of the *Cdkn2a* or *Ink4a/Arf* locus, coding for both *Ink4a* and *Arf*. Targeted deletion of this locus thus affects both p53 and RB pathways.

3.7 Models for other glioma subgroups

Pediatric gliomas are histologically similar to adult gliomas, although they arise in different anatomic locations and show differences in signaling. Grade I pilocytic astrocytomas are more common in children than adults. These benign tumors are characterized by an active MAPK signaling pathway defined by gene fusions involving BRAF [54] that results in constitutive activation of BRAF kinase activity. Pilocytic astrocytoma has recently been modeled in mice by introducing a mutated active form (V600E) of BRAF into Nestin-expressing cells using the RCAS/tv-a system [91].

Pediatric gliomas of grade II-IV are often located in the brain stem. These brain stem gliomas or DIPGs (diffuse intrinsic pontine gliomas) are often driven by excessive PDGF signaling. The RCAS/tv-a system was used to overexpress *PDGFB* specifically in Nestin-positive cells of newborn mouse brain stem, located adjacent to the fourth ventricle. *PDGFB* expression in these cells resulted in low-grade brain stem gliomas, and when *PDGFB* was introduced into *Ink4a/Arf*$^{-/-}$ mice, more malignant, high grade brain stem gliomas developed [92]. Low-grade, diffusely growing brain stem gliomas were also occasionally found in the transgenic *PDGFB*/*Trp53*$^{-/-}$ model, where GFAP was used to direct transgene expression [76].

Transgenic overexpression of *PDGFB* in GFAP-expressing cells has also been used to model spinal glioma with a mixed oligoastrocytic phenotype. Over-expressing *PDGFB* on a *Trp53* heterozygous background reduced the tumor latency in this model [93].

3.8 Cells of origin for glioma

Mouse models for glioma are commonly generated by introducing genetic aberrations found in human tumors into mouse brain. The genes have been targeted in putative cells of origin at different developmental stages with the help of specific promoters. Inducible systems have revealed early steps in tumorigenesis in adult mouse brain; however a paucity of specific markers has made it difficult to identify cells of origin. Sophisticated methods to target genes somatically in specific brain areas have reduced the number of manipulated cells in the mouse brain, narrowing the search for the origins of glioma.

Early steps of tumorigenesis have been studied in mouse models, to provide insights about the origin of tumors. In transgenic mice with activated alleles of EGFR (*v-erbB*), under control of the human S100β promoter, analysis of tumor location by MRI, followed by identification of dividing cells in the same area, revealed NG2+ OPCs as cells of origin for oligodendroglial tumors [63]. Retroviral transfer of *PDGFB* to myelinating OPCs expressing *Cnp* using the RCAS/tv-a system also suggested OPCs a cell of origin for PDGF-driven oligodendrogliomas [73]. Early steps of tumor formation have also been analyzed in a mouse model for astrocytic GBM. Here, constitutive transgenic expression of GFAP-Cre was used to knock-out *Trp53* in *Nf1* heterozygous mice. Tumor progenitor cells with mutated p53 were tracked during early tumor formation and were found to migrate from SVZ to other brain regions along the corpus callosum, a large white matter structure that connects the two hemispheres [84]. A mosaic mouse model, also with targeted deletions of *Nf1* and *Trp53*, was used recently to show that, although the combined genetic aberrations were induced in the NSC compartment of SVZ, the actual tumorigenesis occurred in the developing OPCs [94].

Another strategy to pin point origin has been to reduce the number of targeted cells. The promoters used to direct gene expression are typically active in many different cell types at several developmental stages. Local injections of virally expressed Cre have been used in combination with specific promoters to target cells selectively in a small area. Comparison of tumor forming abilities in different brain areas showed that both Nestin-positive and

GFAP-positive cells residing in neurogenic niches were more easily transformed than cells in differentiated areas [82,88]. On the other hand, results from RCAS/tv-a glioma models indicate no difference in the tumor forming ability of cells residing in different brain areas [95]. These studies illustrate the necessity for the right cellular context in modeling tumor formation, as the same genetic alterations may give completely different outcomes depending on cell type.

An alternative approach to elucidate cell of origin has been to compare the gene expression profiles of human tumors with the expression profiles of different normal cell types in the brain. This has proven to be very successful in the case of ependymomas, where gene expression profiling proved the cell of origin of ependymomas to be radial glia [96]. The same type of comparison of gene expression profiles was then further used to identify putative cell types to target when developing relevant mouse models for different subtypes of ependymoma [57].

4 Embryonal brain tumors

4.1 Classification and prognosis

Medulloblastoma (MB) is the most common malignant brain tumor of childhood accounting for 20% of pediatric CNS tumors [110]. Surgical resection, radiation and chemotherapy have led to an improvement in overall survival of 70–80% in MB patients [111]. However, the quality of life for survivors is often compromised by treatment-related side effects. MB are also the largest group under embryonal brain tumors followed by primitive neuroectodermal tumors (PNETs), pineal gland tumors, ependymoblastomas and atypical teratoid/rhabdoid tumors (ATRTs) [112]. Embryonal tumors like MB are thought to originate from cerebellar or even spinal cord structures while PNETs form in other structures of the CNS most commonly in the forebrain, cerebrum. A rare and highly lethal embryonal tumor with abundant neuropil and true rosettes (ETANTR), has also been described recently as a variety of PNET [113].

4.2 Molecular characterization of MB

An international consensus panel has now agreed on dividing human MB into four major molecular subgroups [114], WNT, SHH, Group 3 and Group 4 (Figure 3). This followed after a number of large sample gene expression studies of human MB confirmed very different expression patterns in these tumors [115–118]. The first two groups are characterized for expressing SHH and WNT pathway markers while Group 3 shows a photoreceptor/GABAergic profile and Group 4 presents a neuronal/glutamatergic profile [116]. Further, Group 3 MB has a subset of MYC-amplified tumors and SHH, WNT and group 4 MB all have subsets of MYCN-amplified tumors [114,119].

4.3 Mouse models of MB

Mouse models for MB can be divided into developmental pathways that are important in cerebellar development. While early reports focused on the SHH pathway (SHH models), recent reports describe non-SHH models that depend on WNT signaling, as well as models for Group 3 MB and Group 4 MB, that are not so clearly correlated with any given developmental pathway (Table II).

4.4 MB models for SHH pathway

The Hedgehog gene was first identified in Drosophila melanogaster [150] and is highly conserved between invertebrates and mammalians. Sonic Hedgehog (SHH) promotes neurogenesis of granule cell precursors in the developing cerebellum [30,31]. Purkinje

neurons secrete this mitogen, promoting proliferation of GCPs. The gradient of SHH also drives migration of GCPs from external germinal layer to the internal granule layer [151].

SHH acts as a ligand for its receptor Patched, the 12-pass transmembrane protein (PTCH). PTCH in the absence of ligand, suppresses Smoothened (SMO), a 7-pass transmembrane protein. When SHH binds PTCH, SMO is derepressed, leading to the activation of GLI family transcription factors (Figure 3). The activation of GLI is in part regulated by a complex inhibitory protein complex that includes suppressor of fused (SUFU).

Germline mutations in PTCH lead to Gorlin's syndrome, characterized by increasing incidence of basal cell carcinoma, MB and rhabdomyosarcoma [152]. The first transgenic model for this syndrome and for SHH-driven MB was the *Ptch* knock-out mouse, described more than 15 years ago [120]. When knocked out constitutively, the model is embryonic lethal, however mice heterozygous for $Ptch^{+/-}$ develop MB at 14% incidence after 5 weeks. The incidence of SHH-driven tumors is dramatically increased with radiation [121] or when p53 is additionally mutated [122]. Constitutively active Smo, *SmoA*, can drive MB at a high incidence (48%) from the NeuroD2 promoter in GCPs [130]. Homozygous *SmoA* (Smo/Smo) further increase incidence and also promote leptomeningeal spread [131]. Another model drives another active Smo, *SmoM2*, ubiquitously using either sporadic leakage or global induction after birth giving rise to MB [132] and also other types of tumors like those described in Gorlin's syndrome above.

The primary cilium, a non-motile single organelle on the cell membrane, often referred to as the cells antenna, is essential for the SHH pathway [153] as SMO and PTCH are both localized to this structure [154,155]. During SHH stimulation SMO is recruited to replace PTCH at this structure leading to downstream activation of GLI proteins. It is therefore not surprising that primary cilia are required for SHH-driven MB formation, as shown when *Kif3a* null or *Ift88* null mice, which lack primary cilia [156] were crossed with the SmoM2 model.

Shh itself drives MB using in utero injection of a *Shh*-containing retrovirus [134] or when it is restricted to Nestin-expressing progenitors using the RCAS/tv-a system [135]. Further, different combinations of SHH with oncogenes like c-myc, IGF or AKT increases MB penetrance in the latter system [136]. Similarly, *N-myc* or *Bcl-2* increases MB penetrance together with *Shh* [137]. N-MYC is a downstream target of the SHH pathway and actually essential for driving SHH-driven tumors. In normal GPCs [157] as well as in MBs driven conditionally from Math1-directed Ptch loss [158], pre-tumorigenic GPCs required *N-myc* in order to generate tumors. Interestingly, downstream SHH-pathway members like the transcription factor GLI1 cannot alone (or together with oncogenes like *N-myc*) give rise to MB, at least not in nestin-expressing cells [159,137]. By contrast, SHH is tumorigenic without GLI1 expression, as SHH-driven MB were formed also in *Gli1* null mutants [134]. However, SHH still required MATH1 for its tumorigenic capacity [160].

The negative regulator *Sufu* induces SHH-like MB, but only when p53 is also depleted [133]. Interestingly, as p53 mutations are prevalent in human SHH MB [161] it is not surprising to find *Trp53* null mice driving SHH-driven MB in different combinations. Besides driving more tumors in *Ptch* mutants [122] *Trp53* loss promotes tumorigenesis when combined with *Rb* loss in GCPs [127]. Similarly, when critical components of the DNA repair machinery are suppressed, p53 further drives SHH-positive MB. This is true when *Trp53* null mice are crossed with mice that lost the DNA-repair gene Poly-(ADP-ribose) polymerase (*Parp*) [142] or when crossed with mice depleted in critical non-homogenous end joining proteins like LIG4 [143], XRCC2 [140] or XRCC4 [141].

4.5 MB models for WNT pathway

Wnt was initially discovered in forward genomic screens in the early eighties when Nusse and Varmus observed that mouse mammary tumor virus integrations in a novel *Int* target gene could promote breast tumor development in mice [162]. Fly homologues with a wingless (Wg) phenotype were identified subsequently, with WNT representing a hybrid between Wg and Int. In the activated canonical WNT pathway WNT proteins bind to cell-surface receptors of the Frizzled family (FZD) that cause the receptors to activate Dishevelled family proteins (DSH) which results in an increased amount of β-catenin that reaches the nucleus (Figure 3). WNT proteins are like SHH proteins morphogens important for brain patterning. About 10–15% of MBs are associated with aberrant WNT signaling and of generally good prognosis with mutations in the β-catenin gene, *CTNNB1* often found in this subgroup [163]. Further, mutations in adenomatous polyposis coli (*APC*) a scaffolding protein critical to this pathway, are often identified in patients with Turcot's syndrome, with APC mutant pedigrees occasionally generating MB. The origin of these tumors was recently directed to a region of the lower RL structure in BLBP-positive, *Ctnnb1* mutated, *Trp53* defective mice [149]. Here, cells of origin were targeted embryonically, where CTNNB1 was transduced via electroporation into OLIG3/ZIC1-positive cells of origin. Such tumors, formed in the brain stem, could recapitulate human WNT MB that also localize to this structure by MRI.

4.6 Models for Group 3 and Group 4 MB

Group 3 and Group 4 constitute more than 60% of human MB and are also the groups that correlate strongest with worst prognosis [119]. MYC is amplified in a subset of Group 3 tumors [114], whereas MYCN is amplified in a subset of Group 4 MB [164]. A transgenic mouse was generated driving human MYCN in hindbrain NSCs, the GTML model [147]. This mouse used a Tet-Off model to drive classic or LC/A tumors from the Glutamate transporter 1 (Glt1) promoter, and is regulatable, where expression of MYCN could be turned off using doxycycline, leading to tumor regression through senescence. This is today the only transgenic model that can be used to follow non-SHH MB formation and also model disseminated tumors via leptomeningeal spread.

More other recent models used wild-type or mutationally stabilized T58A versions of MYC or MYCN to generate non-SHH tumors. Two different labs used MYC in combination with p53 loss to drive anaplastic MB from P7 cerebellar stem cells, following orthotopic transplantation [145,146]. Expression profiles from these tumors correlated with of human Group 3 MB and expressed the Group 3 signature marker, NPR3 [118,114]. Interestingly, while MYCN drove GCPs to become SHH tumors, MYC apparently reprogrammed these same cells to a SHH-independent lineage [146]. While these data suggest that MYC and MYCN sub serve distinct functions in transformation and reprogramming, the basis for these differences remains unexplained.

Another model investigated MYCN biology in a time and space-dependent matter by driving it from distinct populations of NSCs. Here, prenatal NSCs generated SHH-driven MBs in response to N-MYC expression. In contrast, N-MYC generated non-SHH MB from postnatal cerebellar stem cells [148]. These postnatal tumors expressed markers for Group 4 MB, like KCNA1 [118,114]. These MYC/MYCN models described are the first that could be used to recapitulate MYC and MYCN-amplified Group 3 and Group 4 MB, respectively; brain tumors that have a very poor prognosis [119]. These non-SHH models, including the majority of the GTML tumors, showed insensitivity to SMO inhibitors, like cyclopamine, that inhibits the SHH-pathway. Interestingly, inhibitors of PI3K/mTOR proved effective in MYC-generated MB [145] suggesting a role for this pathway in maintenance.

4.7 Models for metastatic MB

MB can disseminate through the cerebrospinal fluid into the leptomenigeal space. Metastases mark poor prognosis, are found in up to 30–40% of children at diagnosis, and are frequently observed in recurrent MB [165,166]. All molecular subgroups of human MB except the WNT group present this feature. Mouse models that show leptomeningeal spread include the Smo/Smo model [131] and the GTML model [147]. The mechanisms of dissemination have recently been studied in SHH-driven Ptch1 heterozygous and p53 mutant MB models, that were combined with a Sleeping Beauty system [144] for functional cancer gene discovery. Interestingly, metastases in MB from mice and patients lost MYCN amplification (but not MYC amplification) when these were found in the primary tumor [144]. Interestingly, metastases from the SB screen present higher expression of PDGFRα both in primary tumors and metastases [144], (metastases in human MBs also show high levels of PDGFRα [167].) suggesting a therapeutic target.

4.8 Other embryonal brain tumor models

Retrovirus-mediated transfer of SV40 virus large T antigen generates a large percentage of PNETs in animals [168–170]. Further, RCAS/tv-a viruses containing *c-myc* generated PNETs from GFAP-expressing forebrain cells in p53-deficient mice [171]. Beta-catenin activation enhanced tumor progression in this model. Malignant glioma with PNET characteristics (MG-PNET) is a rare forebrain tumor described with MYCN amplified in 40% of human cases [172]. Such tumors were modeled using N-MYC overexpressed in GFAP-positive NSCs isolated from forebrain VZ regions followed by orthotopic transplantation [148]. While these first brain tumor models used perinatal NSCs, brain tumors could also be generated from adult NSCs in another model that followed PNET formation after orthotopic transplantation.

Recombination of PTEN/p53 in adult NSCs gave rise to gliomas, whereas deletion of Rb/p53 or Rb/p53/PTEN generated PNETs, indicating an important role of an early Rb loss in driving the PNET phenotype [89]. Germ line mutations of INI1 (SNF5) have been identified in 78% of children with atypic theratoid/rhabdoid tumors (ATRTs) [173], indicating that INI1 is the mayor tumor suppressor in this disease. INI1 loss has recently been found to promote an aberrant activation of the SHH/GLI pathway [174]. Mouse models that recapitulate ATRTs are still missing. While homozygous deletion of *Ini1*/*Snf5* results in early embryonic lethality heterozygotes develop primitive sarcomas but not ATRTs [175,176]. Finally, adult MB comprises three molecular variants [177] with SHH tumors being the most common and with Group 3 MB missing. Whether mouse models better recapitulate these adult or childhood MB is not clear, especially as the timing of tumor formation in mice cannot be compared to that of human tumors.

4.9 Cell of origin for embryonal brain tumor development

Many labs have suggested a putative cell of origin for their MB model. Importantly, as MB at the transcriptome level is not just one but at least four different types of tumors [114], one might suggest different types of originating cell for these molecularly distinct brain tumors. The most studied candidate for MB is the granule neuron precursor that has been shown to give rise to MB in SHH-models [36,37]. The SmoM2 model described above was used to carefully study cell of origin for MB when it was further refined to give rise to MB only [36]. This was achieved by using specific promoters expressed in distinct cell types including the *Tlx3* promoter for GPCs in the EGL of Lobes VI-IX and the *Math1* promoter for all types of GCPs. The authors also used the *Olig2* promoter and the human *GFAP* promoter for cells expressed in various parts of the RL, two promoters that drive expression of SmoM2 in cells that later give rise to GPCs as well as cerebellar astrocytes and interneurons. Similarly, *Ptch* loss could be driven conditionally and restrict Cre using

promoters like *Math1* and *GFAP* to target the cerebellar cell types we just described [37]. Importantly, these two models confirm that SHH-driven MB could be generated from primitive NSCs as well as more restricted GCPs, with MBs developing spatially and coupled to the cell of origin that expressed the specific promoter.

Surprisingly, WNT-driven MBs were recently shown to emanate from Olig3-positive lower RL progenitors in the developing dorsal brain stem [149]. Other types of brain stem cells, particularly GCPs of the cochlear nuclei, a derivative of the auditory lower RL, have recently been shown to generate SHH-driven tumors [178]. Math1-postive GCPs do not generate MYC-driven MB. It is rather Math1-negative NSCs that generate such tumors that correlate with molecular profiles of human Group 3 MB [146,145]. Interestingly, the age at transformation might determine the type of tumor generated. While GFAP-positive NSCs isolated from embryonic cerebellum give rise to SHH MB following N-MYC transduction, GFAP-positive NSCs isolated at postnatal ages generates a KCNA1-positive N-MYC-driven MB characteristic of a human Group 4 MB lacking SHH-dependence [148]. This clearly demonstrates the importance of intrinsic differences in distinct NSC populations. However, a detailed analysis of cells of origin in MYC/MYCN-driven tumors in models in vivo would reveal what specific cells that really respond to transformation and produce these Group 3 and Group 4 tumors. Moreover, what types of cells generate those subgroups of Group 3 and Group 4 MB that do not express MYC proteins, or that show MYC/MYCN amplification?

5. Improved mouse models for human brain tumors

5.1 Current models recapitulate human brain tumor histology

A prominent feature of glioma is the ability to diffusely invade into surrounding normal parenchyma which makes complete removal difficult upon resection. Grade III gliomas (anaplastic astrocytoma, anaplastic oligodendroglioma and anaplastic oligoastrocytoma) are characterized by increased cellularity, nuclear atypia, and proliferative activity. Grade IV GBMs also contain areas of microvascular proliferation and necrosis often surrounded by pseudopalisading cells [179].

MB typically presents with poorly differentiated cells. MB has histologically been classified into five variants: classic, desmoplastic/nodular, MB with extensive nodularity, large cell MB and anaplastic MB [180].

PNETs occur predominantly in children and adolescents and show aggressive clinical behavior. They may be phenotypically undifferentiated, or present differentiation along neuronal, astrocytic and ependymal lines. CNS PNETs include supratentorial PNETs but also similar tumors located in the brain stem and spinal cord [112].

Many of the models described in this review present histological characteristics and close pathological similarities/hallmarks of the human brain tumor they model. Three examples of transgenic models that present such features are presented in Figure 4.

5.2 New models targeting different brain tumor subtypes

There is a need for new models to recapitulate those cancer genes frequently altered in brain tumors. This is evident when studying the identified cancer genes in high-throughput expression data (as described above) but also from identified gene alterations in recent whole genome sequencing efforts for brain tumors [181,182,161]. As sequencing technology improves and gets cheaper, it is likely that whole genome sequencing will be the method to use to find important mutations that drive or promote these brain tumors. Large scale sequencing of each major cancer is ongoing through the International Cancer Genome Consortium [183]. Of course, mutations found in these screens needs to be validated

functionally, like using GEMMs. Valuable features for existing brain tumor models are listed in Figure 5. Also included are needs for new models to recapitulate all currently understood subtypes and clinically relevant pathways.

5.3 Forward genetics in mice: Retroviral and Sleeping Beauty strategies in brain tumors

Retroviral tagging as an instrument to find novel tumor-initiating genes has been used in murine glioma models driven by a Moloney Murine Leukemia Virus containing human PDGFB [184–186]. Here, over 60 common insertion sites (CIS) were identified that contained genes that could collaborate in PDGF-driven brain tumor formation. Several candidate genes in these CIS have been functionally evaluated as having a clear role in gliomagenesis [187–191] suggesting such retroviral screens are useful tools in understanding and identifying brain tumor initiating events. Several sleeping beauty transposon-based techniques have also been used to drive glioma [192–194] and MB [195] in mice and identified genetic drivers in the genesis of these brain tumors. Forward genetics using sleeping beauty has successfully been able to drive SHH-driven MB to disseminate along the leptomenigeal space to form metastases [144]. Additional Sleeping Beauty systems promise to identify novel cancer genes and to identify and validate candidate drivers for brain tumors.

6. Conclusion and future perspectives

Numerous mouse models exist that have been helpful in recapitulating diverse brain tumors that occur in humans, especially glioma and MB. A further refinement of mouse-to-human transcriptome/genome correlation will clarify how well these models recapitulate clinically relevant subtypes. The origin of brain tumors is almost certainly diverse. After several decades of brain tumor modeling in animals, a view of how to manipulate mouse brain tumors is now beginning to emerge. A challenge for future research is to build better parallels with human brain and brain tumor development. A major need is for markers that are better and more specific markers than the broadly expressed markers commonly used in the models described in this review.

Many of the models employ the most clinically relevant (most frequently altered) genes found in human brain tumors. Some of these gene alterations function solely in initiation while others are specifically involved in progression or dissemination of the disease. GEMMs have been useful for, and could further clarify how particular cancer genes contribute to the biology of brain tumors. GEMMs could further be used to identify those cancer proteins that are essential for maintenance of brain tumors; proteins that represent promising therapeutic targets. Hopefully, existing and future GEMMs for human brain tumor subtypes can help us find cures for diverse brain tumors with dismal prognoses like GBM, and can guide us to select more effective and more precise compounds that could replace the damaging and long-lasting effects of radiation and chemotherapy, especially in children with MB.

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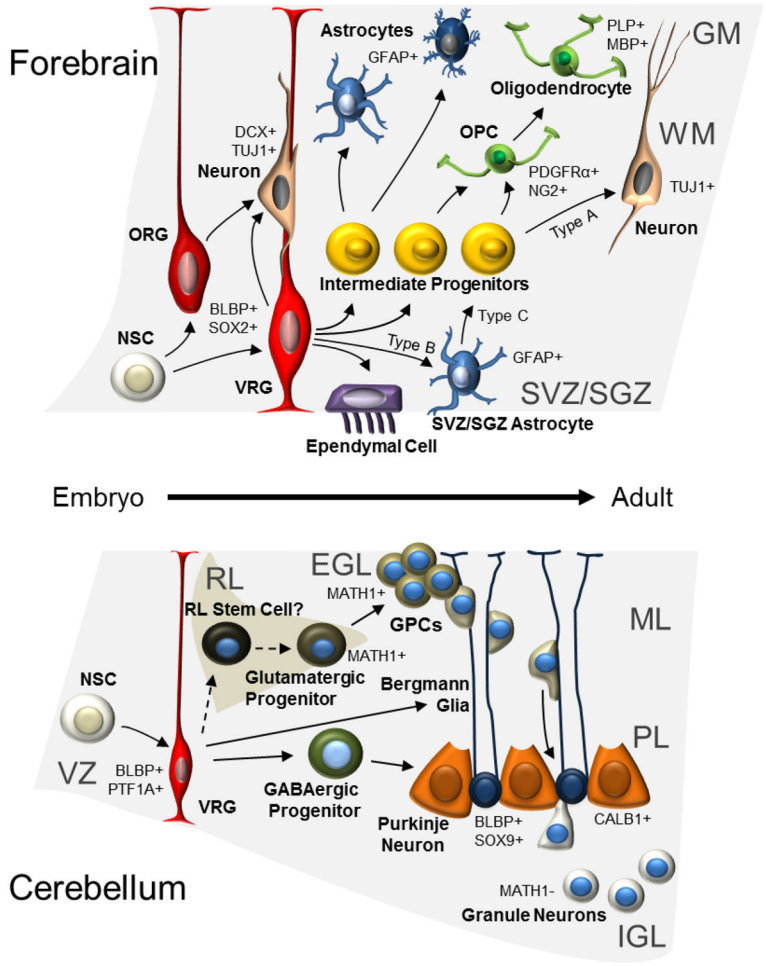

Figure 1. Cells involved in normal brain development from embryo to adult

The schematic figure shows regions and cells of origin for glioma (in forebrain, above) and MB (in cerebellum, below). Processes of the radial glia (RG) serve as guides for migrating more immature neurons [196,197]. RG born from neuroepithelial stem cells could give rise to basically all other cell types including ependymal cells that line the ventricles. However, they first give rise to more restricted intermediate progenitors that determine the path for astrocytes (protoplasmic (in GM) or fibrous (in WM)), oligodendrocytes and neurons. Radial glia cells form neural stem cells, specifically called type B cells (SVZ astrocytes) that reside in the subventricular zone (SVZ) even in the adult forebrain [12]. Similar adult neural stem cells also exist in the dentate gyrus granule cell layer in the hippocampus [13]. Radial glia form neural stem cells that can give rise to multiple cerebellar cell types, and also more directly (around birth) convert into Bergmann glia that keep their extended processes even in adult brain. In cerebellum, granule precursor cells are also formed and divide in the external germinal layer (EGL) from the boost of SHH-producing large Purkinje neurons. Before the cerebellar EGL layer disappears (around three weeks of age in mice) the GPCs that constitute EGL migrate down the Bergmann glial processes and pass Purkinje neurons before they settle down as more differentiated granule neurons in the IGL. GM: Grey matter; WM: White matter; NSC: Neuroepithelial stem cell; ORG: Outer SVZ radial glia-like cells; VRG: ventricular epithelium radial glia; OPC: Oligodendrocyte precursor cell; SVZ: Subventricular zone; SGZ: Subgranular zone; VZ; Ventricular zone at 4th ventricle; RL: Rhombic lip; EGL: External germinal layer; GPC: Granule cell progenitor; ML: Molecular

layer; PL: Purkinje cell layer; IGL: Internal granular layer. Examples of markers that are expressed, or not expressed, in the various cell types are shown followed by + or −, respectively.

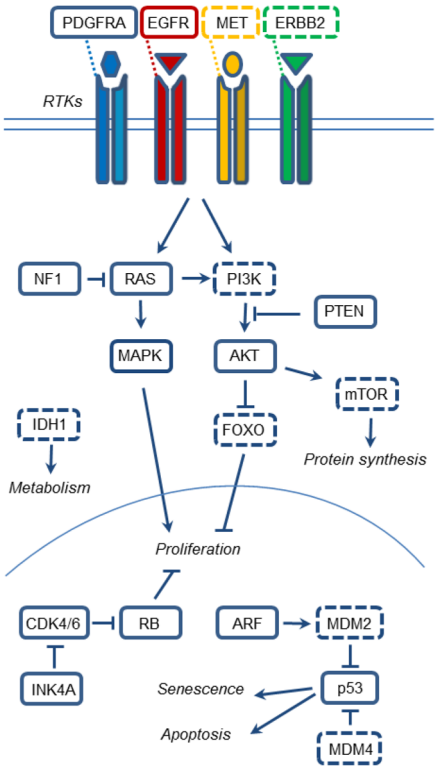

Figure 2. Common molecular pathways of glioma

Major molecular pathways altered in glioma, starting with receptor tyrosine kinases (RTKs) on the cell surface, cytosolic proteins and nuclear proteins/transcription factors. Shown are also the relationship between these brain cancer proteins and their mechanisms of action. Proteins surrounded by broken lines identify glioma pathways that are not yet modeled in mice or described in this review.

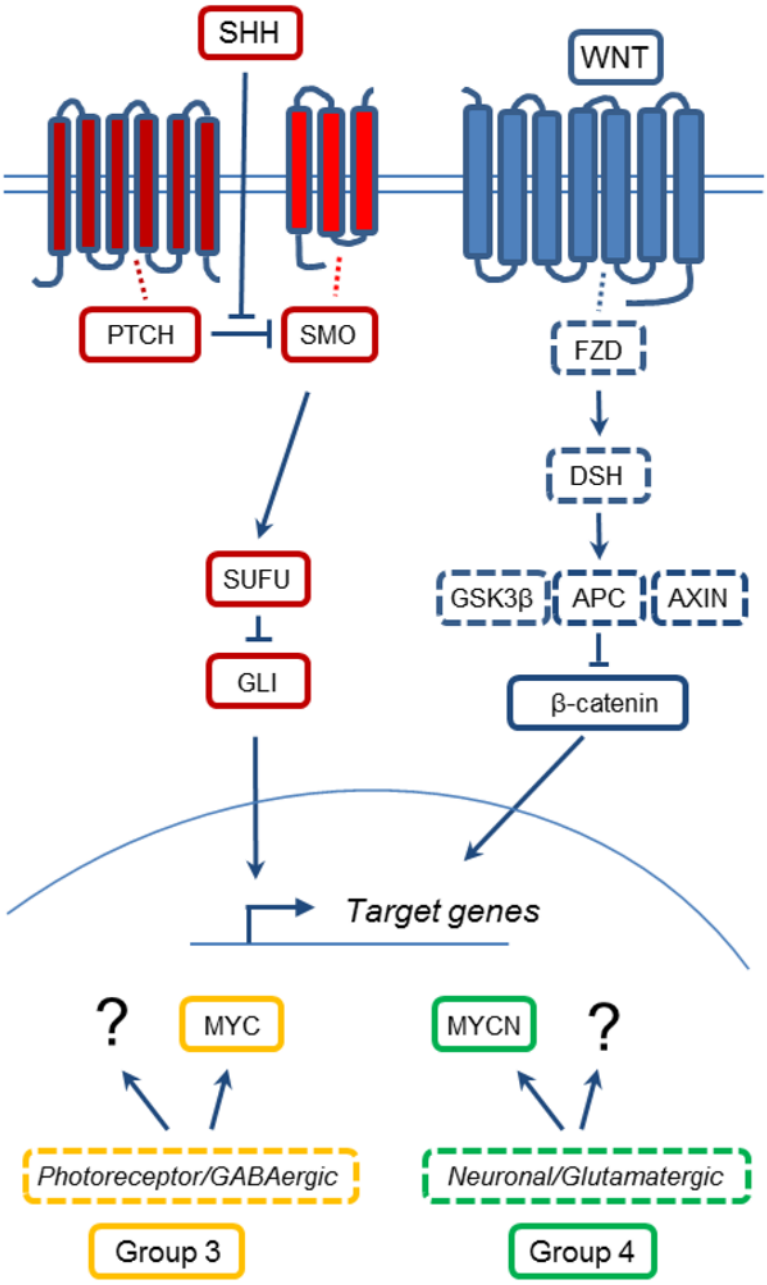

Figure 3. Molecular pathways in four MB subgroups

The four major molecular pathways altered in MB. Shown are two simplified versions of the SHH and the WNT pathway that represent two of the MB subgroups. MB of Group 3 and Group 4 present some degree of MYC and MYCN alterations, respectively. Group 3 and Group 4 further present a profile of not yet identified Photoreceptor/GABAergic and Neuronal/Glutamatergic pathways, respectively. Proteins surrounded by broken lines identify MB pathways that are not yet modeled in mice or described in this review. ?: unknown pathway/mechanism.

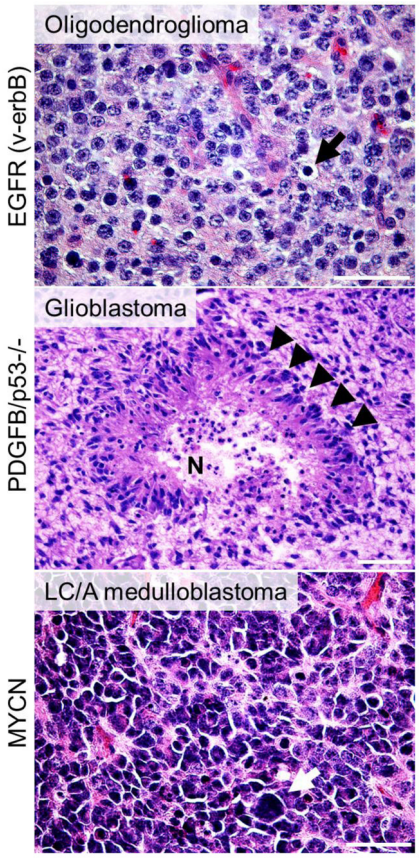

Figure 4. Transgenic brain tumor models that recapitulate human brain tumors

Three examples of models where different types of brain tumors are generated from specific promoters that targets a distinct population of cells in the brain with three clinically relevant cancer genes, *v-erbB* (activated EGFR), *PDGFB* (that activates PDGFRα), *Trp53* as well as *MYCN*. **A)** Tumor cells from an S100β-*v-erbB*-driven oligodendroglioma with typical round nuclei and perinuclear cytoplasmic retraction (black arrows). [61] **B)** A GFAP-*PDGFB*-driven *Trp53* null GBM with characteristic pseudopalisadation (black arrowheads) surrounding a necrotic area (N) [76]. **C)** A Glt1-*MYCN*-driven LC/A MB with atypical large cells (white arrow) [147].

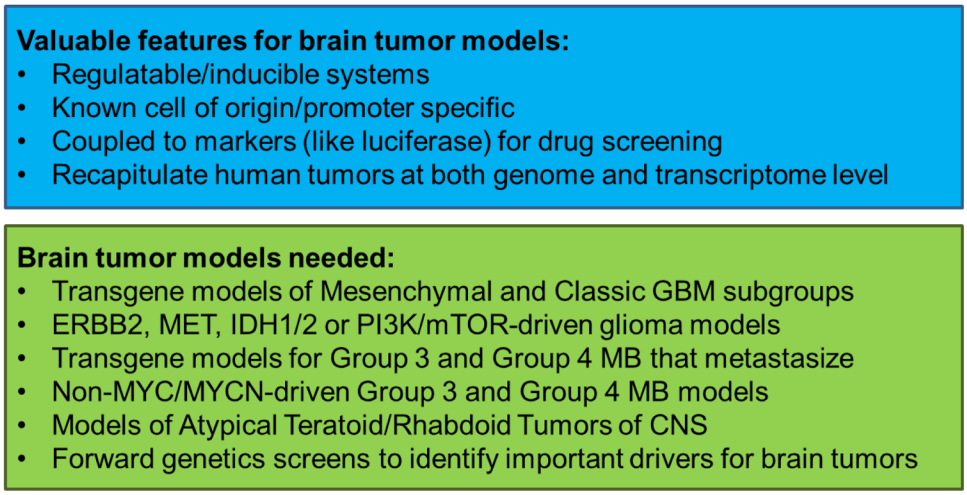

Figure 5. New animal models for human brain tumors

Useful features for great brain tumor models and models that are still missing or ongoing.

Table I

Mouse models of glioma divided after classification and WHO grade with driving cancer gene, putative targeted cell of origin (Targeted cell) and the mechanism of the model as indicated.

Cancer genes	Targeted cell	Mechanism	Reference
Ependymoma models			
EphB2/Ink4a/Arf$^{-/-}$	NSCs	Transplant	[57]
Pilocytic astrocytoma models (I)			
BRAF^{V600E}	Nestin	RCAS	[91]
Astrocytoma models (II-III)			
v-src	GFAP	Transgenic	[97]
Arf$^{-/-}$	-	Transgenic	[98]
c-myc	GFAP	Transgenic	[99]
K-ras	GFAP	Cre	[100]
H-Ras	GFAP	Transgenic	[101]
H-Ras/Pten$^{loxp/loxp}$	GFAP	Cre	[102]
^{T}*121*$^{/Pten+/-}$	GFAP	Cre	[103]
EGFR/Ink4a/Arf$^{-/-}$	Nestin	RCAS	[60]
Oligodendroglioma models (II-III)			
H-ras	GFAP	Transgenic	[79]
H-ras/EGFRvIII	GFAP	Transgenic	[62]
v-ErbB/Ink4a/Arf$^{+/-}$	S100β	Transgenic	[61]
v-ErbB/Trp53$^{-/-}$	S100β	Transgenic	[63]
PDGFB/Ink4a/Arf$^{-/-}$	-	Retroviral	[104]
PDGFB/Ink4a/Arf$^{-/-}$	Nestin	RCAS	[72]
PDGFB/Akt	Nestin	RCAS	[105]
PDGFB	CNP	RCAS	[73]
PDGFB	Embryo	Retroviral	[69]
$PDGFA_L$	GFAP	Transgenic	[77]
Glioblastoma (GBM) models (IV)			
Nf1$^{+/-}$*/Trp53*$^{+/-}$	-	Transgenic	[83]
PDGFB	-	Retroviral	[70]
PDGFB	Nestin	RCAS	[106]
PDGFB/Trp53$^{-/-}$	GFAP	Transgenic	[76]
K-Ras/Akt	Nestin	RCAS	[80]
K-Ras/Ink4a/Arf$^{-/-}$	GFAP, Nestin	RCAS	[81]
K-Ras/Akt/Pten$^{loxp/loxp}$	Nestin	RCAS/Cre	[107]
Nf1$^{loxp/+}$*/Trp53*$^{+/-}$	GFAP	Cre	[85]
Pten$^{loxp/+}$*/Trp53*$^{loxp/loxp}$	GFAP	Cre	[108]
Pten$^{loxp/+}$*/Nf1*$^{loxp/+}$*/Trp53*$^{loxp/-}$	GFAP	Cre	[87]
p53$^{-/-}$	Embryo	Mutagen	[109]
Pten$^{loxp/+}$*/Nf1*$^{loxp/+}$*/Trp53*$^{loxp/loxp}$	SVZ, Nestin	CreER	[88]

Cancer genes	Targeted cell	Mechanism	Reference
Akt/H-Ras/Trp53$^{+/-}$	SVZ, HC, GFAP	Lentiviral/Cre	[82]
Pten$^{loxp/loxp}$*/Trp53*$^{loxp/loxp}$*/Rb*$^{loxp/loxp}$	SVZ, GFAP	Adenoviral/Cre	[89]
Nf1$^{+/-}$*/Trp53*$^{loxp/loxp}$	GFAP	Transgenic/Cre	[84]
PDGFB/Pten$^{loxp/loxp}$*/Trp53*$^{loxp/loxp}$	Subcortical WM	Retroviral/Cre	[78]
Pten$^{loxp/loxp}$*/Trp53*$^{loxp/loxp}$*/Rb1*$^{loxp/loxp}$	Astrocyte (GFAP) OPC (NG2), NSCs (GFAP/Nestin)	CreER	[90]
Nf1$^{-/-}$*/Trp53*$^{-/-}$		MADM/Cre	[94]
EGFRvIII/Ink4a/Arf$^{-/-}$	NSC, Astrocyte	Transplant	[64]
Pten$^{-/-}$*/EGFRvIII/ Ink4a/Arf*$^{-/-}$	Striatum	Adenoviral/Cre	[65]
TGFa/EGFRwt/Ink4a/Arf$^{-/-}$	Striatum	Lentiviral/Cre	[66]

NSCs: neural stem cells; SVZ: Subventricular zone ;OPC: Oligodendrocyte precursor cell; WM: White matter. HC: Hippocampus.

Table II

Mouse models of MB with suggested molecular subtype (MB profile), dissemination/metastasis (Mets), mechanism of the model and putative cell of origin.

Genes/pathway	MB profile; Mets	Mechanism; Putative origin	Reference
SHH models			
Ptch$^{+/-}$	SHH; -	KO; GPC	[120]
Ptch$^{+/-}$;	SHH; -	KO, irradiation; GPC	[121]
Ptch$^{+/-}$; *Trp53*$^{-/-}$	SHH; -	KO; GPC	[122]
Ptch$^{+/-}$; [a]*Ink4c*$^{+/-}$	SHH; -	KO; GPC	[123]
Ptch$^{+/-}$; *Ptc2*$^{+/-}$	SHH; -	KO; GPC	[124]
Ptch$^{+/-}$; [a]*Kip1*$^{+/-}$	SHH; -	KO; GPC	[125]
Ptch+/−; Hic1$^{-/-}$	SHH; -	KO; GPC	[126]
Math1-CreE; Ptch$^{C/C}$	SHH; -	CKO; GPC	[37]
GFAP-Cre; Ptch$^{C/C}$	SHH; -	CKO; GFAP-positive cell	[37]
GFAP-Cre; Rb$^{loxp/loxp}$; [a]*Trp53*$^{loxp/loxp}$	SHH; -	CKO; GFAP-positive cell	[127]
GFAP-Cre; Rb$^{loxp/loxp}$; [a]*Trp53*$^{loxp/loxp}$	SHH; -	OM; GFAP-positive cell	[128]
Nestin-Cre: Ptch$^{C/C}$	SHH; -	CKO; Nestin-positive cell	[129]
ND2-SmoA^{hemizygous}	SHH; -	CTG; GPC	[130]
ND2-SmoA/SmoA	SHH; Mets	CTG; GPC	[131]
SmoM2	SHH; -	CTG; GPC	[132]
GFAP-Cre or *Math1-Cre* or *Olig2-Cre* or *Tlx-Cre; SmoM2;*	SHH; -	CTG; NSC, GPC or Olig2- positive cell	[36]
Sufu$^{+/-}$; *Trp53*$^{-/-}$	SHH; -	KO; GPC	[133]
Shh	SHH; -	Ectopic; GPC	[134]
Nestin-tva-Shh	SHH; -	RCAS; Nestin-positive cell	[135]
Nestin-tva-Shh; c-myc; Akt; IGF2	SHH; -	RCAS; Nestin-positive cell	[136]
Nestin-tva-Shh; Mycn	SHH; -	RCAS; Nestin-positive cell	[137]
Nestin-tva-Shh; Bcl-2	SHH; -	RCAS; Nestin-positive cell	[138]
Nestin-Cre;Brca2	SHH; -	CTG; Nestin-positive cell	[139]
Nestin-Cre;Lig4	SHH; -	CTG; Nestin-positive cell	[140]
Nestin-Cre;Xrcc2	SHH; -	CTG; Nestin-positive cell	[140]
Nestin-Cre;Xrcc4	SHH; -	CTG; Nestin-positive cell	[141]
Parp1$^{-/-}$; *Trp53*$^{-/-}$	SHH; -	KO; GPC	[142]
Lig4$^{-/-}$; *Trp53*$^{-/-}$	SHH; -	KO; GPC	[143]
SB11; Ptch$^{+/-}$	SHH; Mets	SB/KO; GPC	[144]
SB11; Trp53^{mut}	SHH; Mets	SB/KO; GPC	[144]
Non-SHH models			
[b]*Prom1*$^{+}$*Lin* -sorted; [c]*Myc; DNp53*$^{-/-}$	Group 3	OM/RV/KO; NSC	[145]
Atoh1-GFP-sorted*; Myc* or *Mycn;* [d]*Trp53*$^{-/-}$;	Group 3 or SHH	OM/RV/KO; NSC or GPC	[146]
Glt1-tTA; TRE-MYCN	Group 3/4; Mets	TG; Glt1-positive cell	[147]
GFAP-tva-Mycn^{T58A} from P0 or E16 NSCs	Group 4 or SHH	OM/RCAS; GFAP-postive NSC	[148]

Genes/pathway	MB profile; Mets	Mechanism; Putative origin	Reference
Blbp-Cre;Ctnnb1;Trp53$^{loxp/loxp}$	WNT	CTG; LRL precursor	[149]

[a] or $-/-$;

[b] or *Math1-GFP*-sorted;

[c] WT or T58A mutant;

[d] with or without Cdkn2c$^{-/-}$;

KO: knock-out; CKO: conditional knock-out; CTG: conditional transgenic model; GPC: granule cell precursor; NSC: neural stem cell; OM: orthotopic model; RV: retroviral; SB: Sleeping Beauty; DN: dominant-negative.