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Perspective

Medulloblastoma stem cell programs: Molecular roadmaps of disease progression

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SUMMARY

Over the last decade, an unprecedented number of sequencing studies have characterized the molecular landscape of pediatric brain cancers, including the highly heterogeneous tumor medulloblastoma (MB). Extensive MB profiling has enabled a much deeper understanding of the primitive neurodevelopmental programs that are hijacked during tumor progression. However, we have yet to successfully target and fully eradicate the putative stem and early progenitor cells that drive MB tumorigenesis. This goal will require better human models that faithfully recapitulate oncogenic events, a deeper understanding of the mechanisms governing cell fate decisions in the primary and metastatic compartments, and comprehensive validation studies of MB stem/progenitor cell molecular signatures extracted from bioinformatics datasets. In this perspective, we summarize the current knowledge of the developmental origins of MB and highlight the unmet needs pertaining to tumor modeling, characterization of molecular programs driving metastatic cells, and post-transcriptional regulation of cell fate.

INTRODUCTION

Recent comparative transcriptomic studies have provided remarkable insight into the origins of the embryonal brain tumor medulloblastoma (MB).[1–4] Historically considered a single disease, sequencing technologies have revealed extensive MB heterogeneity, leading to the classification of molecular subgroups that exhibit different genomic alterations, gene expression profiles, and responses to treatment: Wingless (WNT), Sonic Hedgehog (SHH), Group 3, and Group 4 MB.[5] Further categorization of the subgroups into distinct subtypes based on molecular and clinical features has informed patient risk stratification.[6] Despite these molecular insights, most targeted therapies are still in the development and testing phases. Following the identification of the putative stem and progenitor MB cells of origin,[1–4] research efforts must now shift toward elucidating the biological mechanisms driving tumor progression to successfully target and eradicate these cells. Achieving this will require the generation of robust human models that consistently recapitulate the oncogenic events driving MB from the primitive cells of origin. While the wealth of available sequencing data has implicated numerous genes and pathways in MB pathogenesis, functional validation of these findings, particularly in the stem/progenitor cell context, is considerably lacking. Moreover, the post-transcriptional landscape, including alternative splicing (AS) signatures, is a critical, yet largely ignored, regulator of MB progression and represents an underexplored source of therapeutic targets and potential biomarkers. MB metastasis, the most significant contributor to patient mortality, is also understudied at all regulatory levels. A deeper understanding of the mechanisms that regulate MB cell fate decisions and leptomeningeal spread will inform therapeutic strategies to treat the primary and metastatic tumor compartments, improving outcomes in these young patients. In this perspective, we will discuss these considerations, from the study of stem cell programs in MB, the generation of faithful human models, the functional analysis of candidate genes and pathways within and beyond the transcriptome, and the extension of these findings to metastatic disease.

MB STEM CELL ORIGINS

Over the past two decades, the cancer stem cell (CSC) model of tumor heterogeneity has evolved significantly. Driven by pioneering studies in hematopoietic malignancies, CSCs were originally isolated by fluorescence-activated cell sorting technologies to enrich for a rare population of undifferentiated cells bearing specific cell surface markers.[7,8] These cells exhibited tumor-initiating capacity, forming new tumors when transplanted into immunodeficient mice.[7,8] Indeed, CSCs are operationally defined by their self-renewal capacity, confirmed in serial transplantation assays that reconstitute a xenograft mirroring the original tumor.[9] Progenitor cells generated by CSCs are highly proliferative but exhibit limited capacity for self-renewal in the long term.

Following the work in hematopoietic tumors, CSCs with similar characteristics were identified in brain cancers, including MB.[10–12] This early work demonstrated that self-renewing stem cells were found in a CD133+ population. However, controversies surrounding the exclusivity of this marker, its non-specific expression, and the variable results depending on culture

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conditions prompted researchers to search for more consistent alternatives.[13–19] Studies in mouse models of SHH MB have shown that tumors could be propagated by CD15^{+} progenitor cells co-expressing the transcription factor atonal homolog 1 (*Atoh1*).[20] By contrast, Ward et al.[21] demonstrated that CD15+ stem-like cells, rather than progenitors, exhibit tumor-initiating capacity. These studies were further refined by Vanner et al. who showed that a rare, quiescent, SOX2+ cell subset within the CD15+ population drives tumor propagation and drug resistance.[22] Moreover, our laboratory has shown that the low-affinity CD271/p75 neurotrophin receptor (p75NTR) is nearly exclusive to tumors from patients with SHH MB and is associated with stem/progenitor cells that are sensitive to mitogen-activated protein kinase (MAPK) pathway inhibition.[23–25] While not an exhaustive list (see Werbowetski-Ogilvie[12] for a more detailed historical perspective), these cancer stem/progenitor cell studies underscored the complexities of MB tumors and the technical challenges associated with deconstructing these heterogeneous cell populations. From the choice of animal model to disparities in representative cell surface markers and tumor-initiating cell frequency, the inconsistencies between studies have made it difficult to discern which markers best represent the MB-initiating cells. Characterizing the functional relevance of additional proteins and their downstream effectors will reveal combinations of markers that can be used to study this clinically relevant population in comprehensive therapeutic targeting studies across various models.

In parallel to MB stem cell sorting and lineage tracing studies, molecular profiling was being used to classify MB tumors into 4 subgroups: WNT, SHH, Group 3, and Group 4 MB.[26–30] WNT and SHH MB are aptly named for the pathways that drive oncogenesis in these subgroups. While Group 3 MB and Group 4 MB collectively account for most MB cases, these subgroups remain less defined. Further molecular characterization using DNA methylation profiling and/or transcriptomics revealed distinct subtypes within the core subgroups.[31–33] Large-scale multiomic studies have provided essential information to guide further characterization of the molecular programs driving MB pathogenesis. However, "bulk tumor" sequencing approaches dilute the molecular profiles of rare cells such as tumor-initiating stem cells, skewing the data toward more abundant cell populations, particularly the actively cycling progenitors. Single-cell RNA sequencing (scRNA-seq) approaches remedy this, allowing for complex analysis of intratumoral cellular heterogeneity. A series of scRNA-seq studies in 2019 compared primary MB tumor expression profiles from patients to murine cerebellar transcriptomes across several developmental stages to investigate MB cellular origins.[34–36] However, shortly thereafter, landmark findings in human cerebellar development highlighted critical divergent characteristics between mouse and human rhombic lip (RL) biology,[37] requiring a refinement of previously defined putative MB cells of origin for multiple subgroups. The human cerebellar RL (also known as the upper rhombic lip [URL]) persists for months, in contrast to its brief existence in mice. Moreover, the human RL progenitor niche is both spatially and molecularly more complex than that of the mouse. The human cerebellar RL emerges around 30 post-conception days as a simple neuroepithelial structure. As development progresses from embryonic to fetal stages, the human cerebellar RL undergoes significant morphological changes not observed in mice. By approximately 8 post-conception weeks (8 PCW), the RL extends into a tail-like structure, which subsequently develops an internal substructure (Figure 1A). Around 11 PCWs, the human RL expands and splits into two molecularly and structurally distinct domains, separated by a prominent vascular plexus: the stem cell-enriched SOX2+ RL ventricular zone (RL^{VZ}) and subventricular zone (RL^{SVZ}) that exhibit a more persistent proliferative progenitor state[37,38] (Figure 1B). Around 14 PCW, the RL becomes internalized into the developing nodulus, where it persists as a pool of proliferating cells until birth. This progenitor population remains active during the third trimester,[37] a period marked by substantial growth in cerebellar size and volume, leaving this proliferative region more vulnerable to adverse genetic events and cerebellar disease.

Studies investigating the human-specific developmental origins of MB soon followed and focused on comparing MB transcriptomes to human fetal cerebellar RL signatures.[1–4] SHH MB mapped to the granule neuron precursors (GNPs),[1,2] consistent with previous mouse modeling and transcriptomic analyses, while Group 3 and Group 4 MB were proposed to originate from the stem cell/progenitor-rich, human-specific RL^{VZ}/RL^{SVZ} and RL^{SVZ}, respectively[1,2,39] (Figure 1C). WNT tumors are believed to originate from human lower RL (LRL) progenitor cells,[36,40] although evidence supporting this is based on mouse data (Figure 1A). Multiple studies have suggested that the most primitive and deadly *MYC*-amplified subset of Group 3 MBs[31] aligns with the stem cell-enriched RL^{VZ} and is associated with high expression of protogenin (PRTG).[1,39] However, other groups contend that Group 3 and Group 4 MB share a lineage trajectory along the RL^{SVZ}.[2] Although the precise developmental origin of these Group 3 MBs remains unresolved, the presence of persistent CSC populations in established Group 3 tumors is clear, and the molecular signatures that govern these caricatures of normal development represent oncogenic vulnerabilities.

Collectively, the past two decades of brain tumor stem cell research support the notion that primitive stem/progenitor cells give rise to MB. Significant advances in sequencing technologies have enabled more precise assessments of genomic, epigenomic, transcriptomic, and, to a lesser extent, post-transcriptomic and proteomic disruptions in MBs (Figure 2). Even though these large-scale MB omics data have identified candidate genes, proteins, and pathways that contribute to MB pathogenesis, functional validation studies are still lacking, particularly in relevant stem cell-enriched conditions that are predicted to mimic MB origins. Tumor cells that retain aberrant stem/progenitor cell signatures represent distortions of early cerebellar development and are linked with tumor propagation, metastasis, and drug resistance.[41] Further characterization and targeting of these most primitive MB cells will lead to treatments that have fewer toxic effects on the nervous systems of young patients. For example, Zhang et al.[42] used an integrated approach in mouse models of SHH MB to demonstrate that OLIG2+ cells drive tumor initiation and then re-emerge upon relapse. This subpopulation is dependent on HIPPO-YAP and AURORA-A/MYCN signaling, and concurrent targeting of both pathways improved survival in animal models.[42] More recent findings demonstrate that direct inhibition of OLIG2 using CD-179, a small molecule inhibitor, increases differentiation and limits the ability to

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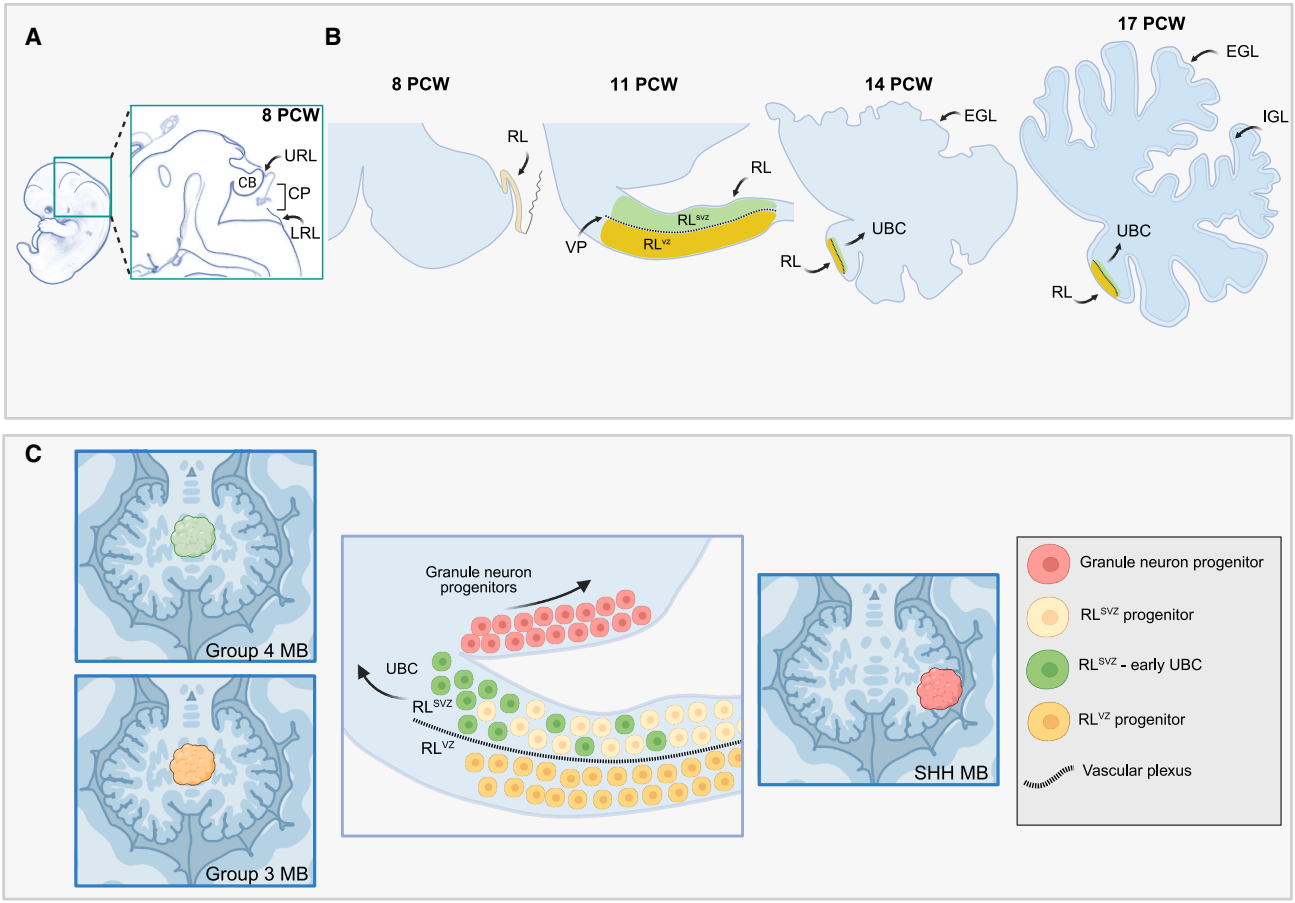

Figure 1. Schematics of early human cerebellar development and MB developmental origins

(A) Schematic of a human embryo at 8 post-conception weeks (8 pcw). Mid-sagittal section highlighting the hindbrain, with the cerebellum (CB), upper RL (URL), lower RL (LRL) of the brainstem, and the intervening developing choroid plexus (CP).

(B) The cerebellar RL at 8 pcw is a simple structure with limited substructure. By 11 pcw, the RL has expanded into a compartmentalized ventricular zone (RL^{VZ}) and subventricular zone (RL^{SVZ}), separated by a vascular plexus (VP). By 14 pcw, significant development has occurred, including initial cerebellar foliation, and the cerebellar RL becomes incorporated into the posterior lobule. The RL is the source of highly proliferative granule cell progenitors, which migrate over the developing CB to form the external granule cell layer (EGL) and differentiate, migrating inward to form the mature granule neurons in the internal granule cell layer (IGL) of the mature CB. The RL also produces differentiating unipolar brush cells (UBCs).

(C) SHH MBs are derived from granule neuron progenitors and localized to the cerebellar hemispheres. Progenitor cells of the RL^{VZ}/RL^{SVZ} are the putative Group 3 MB cells of origin, while Group 4 MB tumors are proposed to be derived from the early UBC lineage within the RL^{SVZ}. Both Group 3 MB and Group 4 MBs are localized to the midline.

activate quiescent SOX2+ stem cells to generate proliferating progenitors.[43,44] However, the clinical relevance of these subpopulations will need to be further explored in human models of the disease.

HUMAN-SPECIFIC MODELING OF MB

Characterization of the primitive cells driving MB tumorigenesis will require the development of faithful human models that recapitulate disease progression.[45] Cross-species differences in cerebellar development[37,38] and the more recent identification of the putative human-specific origins of Group 3 and Group 4 MB[1,2] highlight the limitations of current mouse models and underscore why previous attempts to generate genetically engineered Group 3 and Group 4 MB mouse models have largely failed. Indeed, mouse models[40,46–51] only partially recapitulate human MB subgroup biology. In addition, many existing human cellular MB models also poorly reflect their counterparts in patients.[52,53] However, the identification of putative human MB cells of origin has catalyzed attempts to generate more reproducible models that better capture tumor initiation and heterogeneity. While the field awaits these much-needed upgrades, we continue to utilize currently available human models to answer mechanistic questions.

Patient-derived MB cells and established cell lines are valuable tools for rapid functional validation of genes and pathways that may regulate tumor progression. Despite their utility, MB cell lines are often, and perhaps unfairly, dismissed. In line with the stem/progenitor cell of origin, these cells can be grown as tumorspheres or organoids[54] in defined, stem cell-enriching media to assess cancer hallmarks as well as potential therapeutics in a high-throughput manner. Brain tumor cells grown as 3D structures better mimic the phenotypic and genotypic alterations, as well as the cellular heterogeneity observed in primary tumors,

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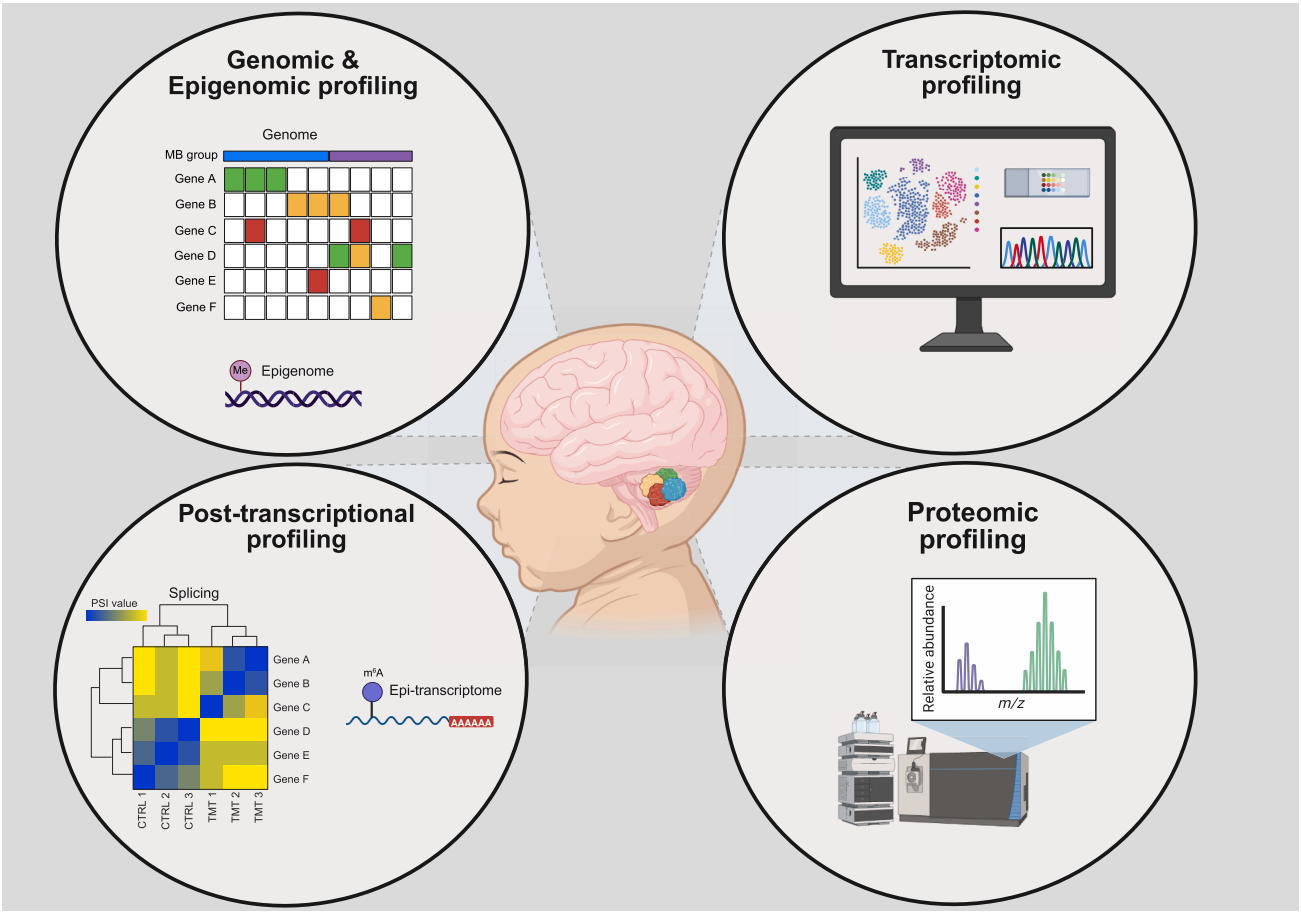

Figure 2. A snapshot of MB omics

Over the past two decades, genomic, epigenomic, and transcriptomic characterization of MB patient samples has provided insights into the genes and pathways implicated in tumor progression. However, functional validation of the molecular mechanisms driving tumorigenesis is often lacking and must be more comprehensively assessed using biologically relevant, human-specific MB models. The post-transcriptional landscape, which includes, but is not limited to, AS, RNA stability, translation regulation, and post-translational modifications, remains to be studied in-depth. AS contributes to MB cell fate and tumor growth. This gene regulatory layer represents an underexplored resource for the development of therapies and biomarkers.

compared with cells grown in serum-containing adherent culture.[55] Unfortunately, reproducibility remains a challenge due to inconsistent cell culture conditions across laboratories, yielding different results in downstream molecular assays. As patient-derived MB tumor cells are particularly difficult to sustain long-term, greater attention to cell culture nuances, including media components, plating conditions, and cell density, would benefit the field.

However, the inability of patient-derived and established cell lines to model tumor initiation is an obvious limitation. Most available human cell lines are derived from Group 3 MB and, to a lesser extent, SHH MB.[53] WNT and Group 4 MB models are scarce, creating challenges when attempting functional and mechanistic assessments in these underrepresented subgroups. Xenograft mouse models will continue to be essential to evaluate tumorigenic properties of relevant genes and pathways and for preclinical testing of therapeutics in an *in vivo* setting, regardless of whether the cells are newly derived or established MB lines.

In vitro differentiation of human pluripotent stem cells to cerebellar fates using 2D[56,57] cultures or 3D cerebellar organoids[58–64] has emerged as a powerful tool to study human cerebellar development and early molecular events that divert normal cerebellar trajectories toward oncogenic transformation. SHH MB can be partially recapitulated in human *PTCH1* mutant cerebellar organoids.[65] Additionally, SHH MB cells have been co-cultured with cerebellar organoids to examine the contribution of the tumor microenvironment toward tumor progression.[66] Optimization of human cerebellar cultures will be particularly important for Group 3 and Group 4 MB, as pathways that drive oncogenic transformation from the putative stem/progenitor cells of origin are still poorly understood and will require validation. Some 3D cerebellar organoid protocols appear to generate the human-specific progenitor cell population of the RL^{SVZ},[58,59] although most are not well characterized. The plethora of genes, pathways, and post-transcriptional events identified in large-scale genomic studies that contribute to MB progression may also be functionally assessed in these models to determine their role in tumor initiation and progression. For example, Ballabio et al. utilized human cerebellar organoids to model Group 3 MB and to test the effect of specific gene combinations (*GFI1/MYC* and *OTX2/MYC*) in regulating tumor properties.[67,68] These organoids displayed a

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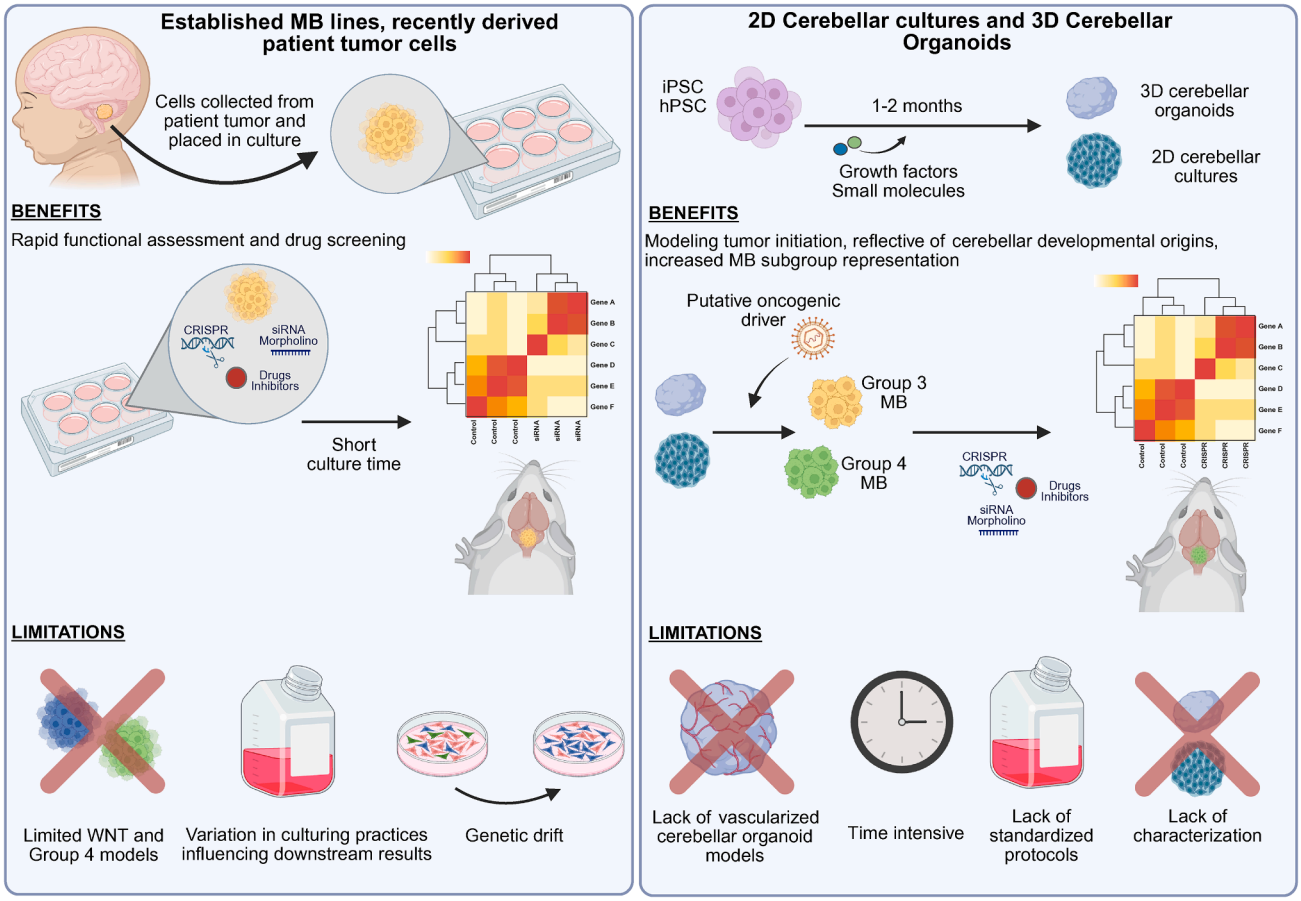

Figure 3. Human-specific models of MB

Every human MB model has unique benefits and limitations. Established and recently derived cell lines from patients allow for rapid functional assessments and high-throughput drug testing. When grown in appropriate culture conditions, the molecular profiles of these cells also overlap with patient tumor profiles. Limitations of these models include limited subgroup representation, variation in culturing practices altering downstream results, and genetic drift. Cerebellar models (2D and 3D) enable the modeling of tumor initiation from cells of origin and increase MB subgroup representation. Limitations include the lack of vascularized cerebellar organoids, the length of protocols, extensive variation between protocols, and the lack of organoid characterization against human cerebellar tissues.

DNA methylation profile that clustered with Group 3 MB patient tumors when transplanted into nude mice. While human cerebellar organoid models may provide insight into disease states and the molecular drivers of MB, they are not without challenges. Compared with 3D tumorsphere models from MB cell lines that enable rapid functional assessments, generation of 2D and 3D cerebellar cultures is time intensive, requiring up to 2 months for the emergence of the RL^{SVZ} in 3D models.[58] Similar to MB cell culturing techniques, no standard 3D cerebellar organoid protocol exists, and the organoids are not well characterized against native normal human developmental cerebellar tissue. This limitation leads to extensive variability between models and laboratories (Figure 3). Furthermore, vascularized cerebellar organoid models are currently unavailable. This has implications for Group 3 MB modeling, as the vasculature may contribute to tumor initiation.[39] Comprehensive analyses of cerebellar organoid cellular diversity across a greater number of human pluripotent stem cell lines will also be essential, as cell line variability will inevitably require further protocol optimization.[58] Nevertheless, continued refinement of these technologies will enhance reproducibility and enable large-scale analyses of gene and pathway alterations that are predicted to initiate MB formation. These studies will be important, particularly for understanding the biological complexities of Group 3 and Group 4 MB tumor progression.

In addition to 2D and 3D cerebellar models, neural precursors derived from transformed human embryonic stem cells,[69] as previously demonstrated by our group, and induced pluripotent stem cell (iPSC)-derived neuroepithelial stem cell (NES) models[70,71] are additional tools for studying the mechanisms driving MB progression. Human somatic cells containing mutations in known MB molecular drivers or cells that are genetically manipulated to recapitulate oncogenic molecular events can be reprogrammed into a more primitive state for evaluation of MB initiation and progression. Several studies have shown that iPSCs derived from Gorlin syndrome patients with germline *PTCH* mutations successfully model SHH MB growth.[71–74]

Human models of MB have several advantages. However, they do come with limitations (Figure 3). Improved protocol standardization will enhance reproducibility between labs and enable

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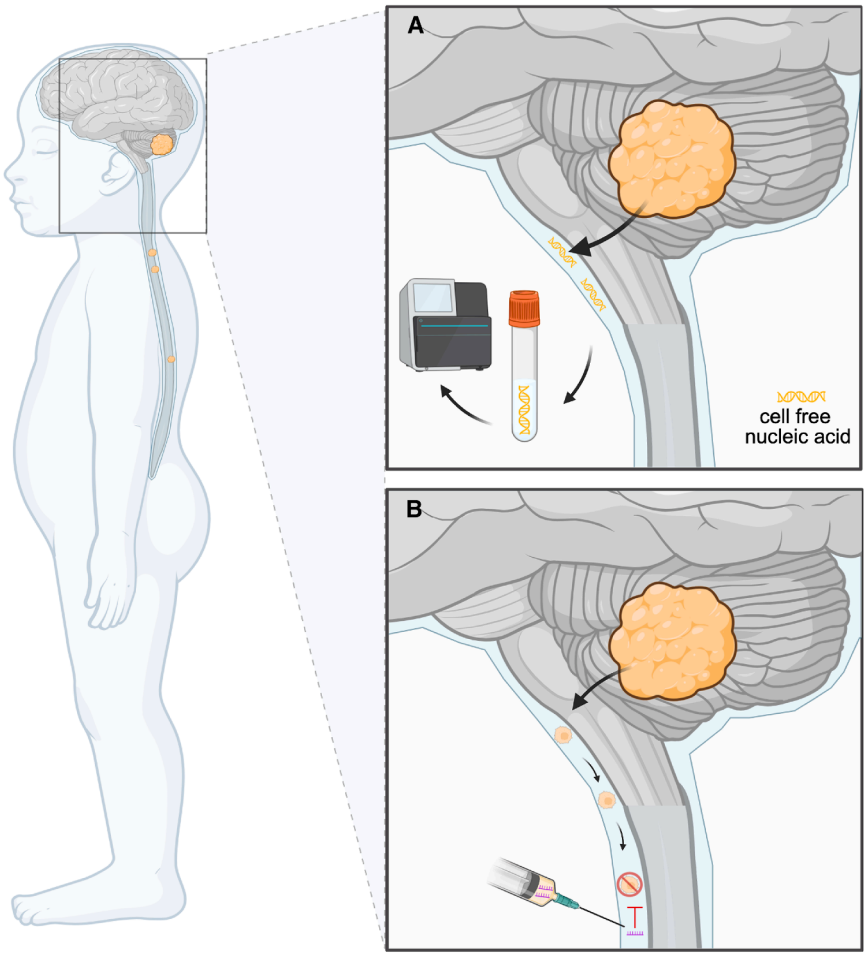

Figure 4. Potential treatment strategies and surveillance of MB metastasis

(A) A CSF liquid biopsy may detect tumor-specific nucleic acids, with sequencing revealing splice variants that may serve as biomarkers and therapeutic targets against primary and metastatic MB cells.

(B) Splice-altering therapies and other small molecular inhibitors may target migrating metastatic cells before they colonize the distal metastatic site.

more comprehensive analyses of the mechanisms regulating tumor initiation and progression. These improvements will ultimately lead to the development of therapeutic interventions targeting MB stem and progenitor cells.

POST-TRANSCRIPTIONAL MB SIGNATURES

Most MB molecular profiling studies have focused on representative genomic, epigenomic, and transcriptomic signatures. Only a subset of studies have investigated the contribution of the proteome to MB subgroup biology (Figure 2) and how subgroup-specific protein profiles could be integrated into existing MB classifications.[75–78] Investigations included a characterization of the MB phospho-proteome[75,76] and the N-gylcome,[77] along with the identification of putative biomarkers and actionable targets. Importantly, these studies also demonstrated the discordance between the transcriptome and the proteome in MB subgroups, particularly for Group 3 and Group 4 tumors.[75] Indeed, genomic alterations and gene expression profiles are often poor predictors of drug responses,[79] further underscoring that functional validation of putative targets in faithful human models is essential at all "omics" levels to advance therapeutic discovery.

Given the discordance between mRNA and protein levels in Group 3 and Group 4 MB tumors,[75,76] post-transcriptional regulation appears to play a key role in the biology of these subgroups. We reported a non-canonical role for the transcription factor OTX2 in regulating AS to maintain the primitive stem cell state in Group 3 MB.[80] Interestingly, OTX2-mediated transcription and splicing effects are mostly independent.[80] If candidate genes had been selected based on transcriptional profiling alone, several viable targets would have been overlooked.

In addition to aberrant AS in Group 3 tumors, recurrent non-coding mutations in U1 spliceosomal small nuclear RNAs have also been identified in SHH MB, leading to excess cryptic splicing events.[81] The post-transcriptional landscape represents an untapped source of therapeutic targets in MB (Figure 2). Targeting splicing involves a broad range of existing and emerging strategies, which include, but are not limited to, inhibiting the core spliceosome, inhibiting splicing factors, targeting of neoantigens derived from AS, and using splice-altering morpholinos or other antisense oligonucleotides (ASOs) with similar chemistries. These approaches remain largely untested in MB tumors. However, splicing-targeting modalities, including nusinersen and eteplirsen, have received FDA approval for treatment of neuromuscular diseases,[82–85] underscoring a plausible therapeutic path, especially in MB where mutational burden is low, and splicing dysregulation may be a tractable vulnerability.

In addition to serving as therapeutic targets, alternatively spliced oncogenic transcript variants also represent potential biomarkers that may be surveilled through liquid biopsy (Figure 4A). Cell-free DNA extracted from the cerebrospinal fluid (CSF) showed the presence of disease in MB patient samples.[86] Methods to identify cell-free RNA (cfRNA) from tumor cells have also been developed from blood samples,[87,88] and splice variants from plasma-isolated cfRNA can be detected.[87] Combined, these findings underscore the intriguing possibility of extracting cfRNA from the CSF of an MB patient, which can then be examined for oncogenic splice variants. This strategy could enable patient stratification and treatment strategies aimed at targeting the post-transcriptional landscape and associated downstream targets.

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The epi-transcriptome represents an additional post-transcriptional regulatory layer that contributes to MB tumorigenesis.[89,90] In SHH MB, hypermethylation of *PTCH1* and *GLI2* transcripts driven by elevated expression of the m^{6}A methyltransferase methyltransferase-like 3 (METTL3) leads to constitutive activation of SHH signaling, promoting tumor progression.[89] Moreover, elevated METTL3 correlates with poorer prognosis in patients with SHH MB. Inhibition of *METTL3* expression in both SHH and Group 3 MBs reduced tumorigenesis, suggesting a potential therapeutic avenue for these subgroups.[89,90] By contrast, METTL3 appears to exert tumor-suppressive effects in Group 4 MB, underscoring subgroup-specific functional differences that warrant further investigation.[89]

MB AND METASTASIS

Up to 30% of patients with MB present with universally fatal metastatic disease at diagnosis. Yet, fewer than 10% of MB publications focus on this aspect of tumor progression. Leptomeningeal spread in MB occurs when tumor cells seed the meninges or subarachnoid space containing CSF, which then extends to the spinal cord. MB can also spread through the blood to the leptomeningeal space.[91] Although some studies have shown that metastatic MBs exhibit molecular distinctions relative to primary tumors,[92] few definitive molecular drivers have been identified. Further examination of the molecular signatures of putative stem and progenitor cells in the metastatic compartment is needed to develop more effective treatment strategies.

MB metastasis varies by subgroup, with WNT MB exhibiting low rates of leptomeningeal spread.[93,94] SHH MB typically recurs in the post-surgical cavity[94,95]; however, the SHHβ subtype affecting infants ≤3 years old has high rates (30%–35%) of metastatic dissemination at diagnosis.[31,96] Group 3 and Group 4 MBs exhibit elevated rates of metastasis at diagnosis, with Group 3 MB displaying the highest frequency of leptomeningeal disease, comprising up to 45% of cases.[29,30,94,97]

Several molecular pathways driving SHH MB metastasis have been characterized. A PDGFR-GRK6-CXCR4 signaling axis promotes migration in SHH MB cells, where PDGFR increases C-X-C motif chemokine receptor 4 (CXCR4) signaling through the suppression of G protein-coupled receptor kinase 6 (GRK6) expression.[98–100] Furthermore, *PDGFRB* expression is elevated in metastatic MB and drives migration through PDGFRB/ERK-mediated activation of p21 (RAC1) activated kinase 1 (PAK1).[98,100–102] In humanized stem cell models of SHH MB, elevated OCT4 activatesmTOR signaling, promoting leptomeningeal spread.[70,98,100] Inhibition of mTOR signaling improves survival and reduces metastasis *in vivo*. Additionally, AMP-activated kinase (AMPK)-mediated restriction of mTOR signaling regulates SHH MB cell fate decisions and reduces tumor growth.[103] AMPK also inhibits SHH MB cell migration through suppression of nuclear factor κB (NF-κB) signaling.[98,104]

Aberrant Notch pathway signaling has also been implicated in metastatic MB. Overexpression of the Notch pathway transcription factor *Atoh7* in a *Ptch*$^{+/-}$ SHH MB mouse model background promotes metastatic spread.[105] In Group 3 MB, elevated NOTCH1 expression was observed in spinal cord metastases from xenograft models.[106] Furthermore, cerebellar transplantation of sorted NOTCH1+ cells from primary xenografts resulted in significant metastasis, which was absent from the NOTCH1− cell counterparts.

A few additional molecular drivers have been evaluated in Group 3 MB metastasis. SOX9-mediated MYC suppression increased epithelial-mesenchymal transition (EMT) and leptomeningeal disease in Group 3 MB.[107] Inhibition of the tumor suppressor PTEN through elevated PRUNE1/transforming growth factor β (TGF-β) signaling promoted EMT and metastasis in Group 3 MB and could be attenuated by treatment with anti-PRUNE1 compounds *in vivo*.[108] Interestingly, the chromatin remodeling protein SWI/SNF related BAF chromatin remodeling complex subunit D3 (SMARCD3) also contributes to Group 3 MB metastasis, decreasing or increasing the incidence of metastasis when silenced or overexpressed, respectively.[109]

The tumor microenvironment has also undergone investigation for its contribution toward leptomeningeal spread. To survive in the nutrient-poor CSF, metastatic MB cells upregulate GABA transaminase (ABAT) expression to enable utilization of GABA as an energy source.[110] In addition, ABAT expression is significantly upregulated in metastatic tumor cells relative to primary tumors and is required for MB cells to colonize the leptomeninges. Indeed, niche-specific metabolic dependencies require further consideration. While metabolic vulnerabilities have been exploited to inhibit primary tumor growth in the most aggressive stem cell-enriched *MYC*-amplified Group 3 MBs,[111–113] further assessments in the metastatic compartment are necessary.

Recently, a PDGF-BMP signaling axis between metastatic MB cells and the tumor microenvironment was described.[114] PDGF ligands were secreted by metastatic MB tumor cells to attract meningeal fibroblasts to the leptomeninges. These fibroblasts were reprogrammed to become metastasis-associated meningeal fibroblasts, which, in turn, drive tumor propagation and metastatic tumor colonization through BMP4/7 signaling. Additionally, a pro-inflammatory tumor microenvironment generated following radiation-induced MB tumor cell death promoted blood-brain-barrier disruption and leptomeningeal dissemination.[115]

Limited studies have identified distinct molecular events between primary and recurrent MB tumors.[116] While conservation of subgroup classification is observed,[95] a 5-fold increase in mutational burden accompanies tumor recurrence.[116] However, the paucity of available recurrent/metastatic patient tumor samples has hampered more extensive investigations. To comprehensively profile molecular signatures in primary tumors relative to the metastatic compartment at transcriptional and post-transcriptional levels, the latter of which has never been explored, relevant *in vivo* models will be essential. These models include orthotopic xenografts of patient-derived and human MB cell lines, orthotopic transplantation of transformed 2D/3D cerebellar cells, and relevant genetically engineered mouse models that demonstrate leptomeningeal spread.[114,115] Comparative expression profiling in the primary and metastatic tumor compartments *in vivo* will identify niche-specific molecular vulnerabilities. Pathways can subsequently be targeted with combinatorial treatment strategies aimed at reducing both primary and metastatic tumor burden while improving survival outcomes. Additionally, single-cell/single-nuclei approaches combined with long-read sequencing technologies[117] would capture

complex splicing patterns at an unprecedented resolution in the metastatic compartment. These analyses would also determine whether stem/progenitor molecular programs are preserved in the metastatic space and influenced by the tumor microenvironment. An AS atlas in metastatic MB would facilitate functional validation using ASO technologies *in vitro* and *in vivo*. ASOs that induce splice-switching of self-renewal-promoting events or even small molecule inhibitors that target the splicing machinery may provide viable strategies to treat leptomeningeal spread. Furthermore, intrathecal CSF administration of these therapies could influence metastasizing tumor cells that have left the primary tumor as well as recolonized cells (Figure 4B). As metastasis is identified through traditional magnetic resonance imaging at relapse,[114,118,119] combining CSF-based biomarker surveillance with therapeutic delivery also warrants further investigation.

CONCLUDING REMARKS

In the past two decades, the characterization of MB stem cell programs has relied on an ever-expanding toolbox, ranging from cell sorting assays combined with serial transplantation to single-cell/nuclei technologies that can compare tumor cells to the developing human fetal cerebellum. However, open questions pertaining to tumor modeling, stem cell programs in primary and metastatic cells, and the post-transcriptional regulation of cell fate decisions still need to be addressed. Metastatic MBs display uniformly poor outcomes, yet there are no available therapies targeting these highly drug-resistant cells. The development of effective treatment for MB requires a more comprehensive understanding of the molecular mechanisms that drive tumor progression and metastasis across all gene regulatory layers. This process already begins with the generation and use of robust human models that faithfully recapitulate oncogenic events. Importantly, future efforts must continue to evolve beyond the passive accumulation of sequencing data and prioritize functional validation of candidate targets. Without mechanistic insights into how these candidate drivers contribute to MB progression and metastasis, therapeutic innovation will stall. Future studies must also investigate the entire tumor ecosystem and consider the bidirectional relationships between MB stem/progenitor cells and their microenvironment, which includes cells of the normal central nervous system, the immune system, and the vasculature[120] across the primary and metastatic compartments. Although the inherent plasticity of MB CSCs presents unique challenges, more comprehensive foundational studies that move beyond the transcriptome will guide the next generation of combinatorial targeted therapies that aim to abrogate both MB growth and leptomeningeal spread in future clinical trials.

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DECLARATION OF INTERESTS

The authors declare no competing interests.

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