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ABOUT COVER

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MINIREVIEWS

Immune microenvironment of medulloblastoma: The association between its molecular subgroups and potential targeted immunotherapeutic receptors

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Abstract

Medulloblastoma (MB) is considered the commonest malignant brain tumor in children. Multimodal treatments consisting of surgery, radiation, and chemotherapy have improved patients' survival. Nevertheless, the recurrence occurs in 30% of cases. The persistent mortality rates, the failure of current therapies to extend life expectancy, and the serious complications of non-targeted cytotoxic treatment indicate the need for more refined therapeutic approaches. Most MBs originating from the neurons of external granular layer line the outer surface of

neocerebellum and responsible for the afferent and efferent connections. Recently, MBs have been segregated into four molecular subgroups: Wingless-activated (WNT-MB) (Group 1); Sonic-hedgehog-activated (SHH-MB) (Group 2); Group 3 and 4 MBs. These molecular alterations follow specific gene mutations and disease-risk stratifications. The current treatment protocols and ongoing clinical trials against these molecular subgroups are still using common chemotherapeutic agents by which their efficacy have improved the progression-free survival but did not change the overall survival. However, the need to explore new therapies targeting specific receptors in MB microenvironment became essential. The immune microenvironment of MBs consists of distinctive cellular heterogeneities including immune cells and none-immune cells. Tumour associate macrophage and tumour infiltrating lymphocyte are considered the main principal cells in tumour microenvironment, and their role are still under investigation. In this review, we discuss the mechanism of interaction between MB cells and immune cells in the microenvironment, with an overview of the recent investigations and clinical trials

Key Words: Medulloblastoma; Tumour microenvironment; Tumour associated macrophages; Tumour infiltrating lymphocyte; Immunotherapies

Core Tip: Medulloblastoma (MB) is the most common malignant childhood tumor of the brain. Multimodal treatments consisting of surgery, radiation, and chemotherapy have reduced the cumulative incidence of late mortality. Nevertheless, the recurrence rate remains high. In this review, we discuss the mechanism of interaction between tumour cells of MB and immune cells in the microenvironment, with an overview of the recent investigations and clinical trials.

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INTRODUCTION

Brain tumors are the leading cause of oncological death during childhood, and medulloblastoma (MB) is the commonest malignant tumor of the brain, accounting for 20%-30% of all central nervous system (CNS) tumors[1]. Diverse treatment modalities consisting of surgery and chemoradiotherapy have improved the patient's survival. Nevertheless, more than 1/3 of children with MB die within 5-years after diagnosis[2]. Late mortality remains a significant problem in disease consequences, which is attributed to tumour recurrence[3]. The persistent mortality, the failure of current drug therapies to extend life expectancy, and the serious complications of cytotoxic therapies indicate the necessity to explore new targeted treatments. Over the past decades, several tumor-centric studies have identified mutant genes and signaling pathways dysfunction that encourage MB growth. Most of MBs originate from the granular layer of cerebellum, which reside in the external granular layer and line the neocerebellum of newborns[4]. The existence of irregular biological signaling pathways created signaling dysregulation and genetic mutations affecting cerebellar development. Hence, the anatomical and cellular complexity of developing human tissues within the rhombic lip germinal zone produces glutamatergic neuronal lineages before its centralization. Molecular signatures encoded within a human rhombic-lip-derived lineage trajectory aligned with photoreceptor and unipolar cell profiles that are maintained in some medulloblastomas, suggesting a convergent basis. The advanced genomic studies over decades led to the assemblage of large amount of genetic information which resulted in four distinguishing molecular subgroups of MB including (Group 1) Wingless-activated (WNT-MB); (Group 2) Sonic-hedgehog-activated (SHH-MB); and Group 3 and Group 4[5] (Figure 1). Each group is characterized by distinct genetic abnormalities, methylation profiles, and clinical outcome. WNT- and SHH-type MBs are clearly detached from the other groups with lack of signaling pathway dysregulation identified in Group 3 and 4[5].

Molecular subgroups of MB

WNT-MB is the least common type, accounting for about 10%-15% of all MB patients. They are classically absent in infants and are seen more among children above 10 years of age[6-8] (Figure 1). The

Molecular subtype	WNT	SHH	Group 3	Group 4
Prevalence	10- 15 %	25%	25%	35%
Age	10-12 years old	< 16 years old	< 3 years old	Children
Gender	1:1	1:1	2:1	3:1
Location	Midline 4th ventricle	Cerebellar vermis	Midline 4th ventricle	Midline 4th ventricle
Pathology	Classic, rare LCA	DN, classic, LCA	Classic, rarely LCA	Classic, rarely LCA
Metastasis	5 - 10%	15-20%	45%	30-40%
Recurrence	Rare	Local	Metastatic	Metastatic
Common driver genetic mutation	1.CTNNB1 (90%)-WNT 2.DDX3X (50 %) 3.SMARCA4 (25%) 4.TP53 (<20 %)	1.TERT (83%) 2.PTCH1 (45%) -SHH 3.TP53 (15%) 4.SUFU (10 %) 5.SMO (rare) 6.MYCN (rare) 7.GLI2 (very rare)	1.GFI1(30 %) 2.MYC (10-20 %) 3.PVT1 (10 %) 4.SMARCA4 (rare) 5.OTX2 (very rare)	1. KDM6A (15 %) 2.SNCAIP (10%) 3.MYCN (5%) 4.CDK6 (rare) 5.GFI1 (very rare)
Chromosome alteration	Monosomy 6	Loss of 9q (PTCH1)	Isochromosome 17q	Isochromosome 17q
MYC status	+	+	+++	-
5-year survival	>90%	70%	40%	70-80%

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Figure 1 Molecular subgroups of medulloblastoma based on 2021 World Health Organization classification of central nervous system tumours. SHH: Sonic-hedgehog; MYC: Myelocytomatosis oncogene; LCA: Life cycle assessment; WNT: Wingless.

clinical outcome of the disease under 16-years of age is usually good, with 90% 5-year survival[8]. The genetic mutation of the Catenin Beta-1 (*CTNNB1*) gene is the most common genetic alteration accounting for 85% of all WNT-MBs[9,10]. A gene expression with methylation profiling performed on several MB cases in 2016 has divided WNT- MBs into two variants: WNT-α, which consists of patients with chromosome 6 monosomy and WNT-β, that occurs in adults with chromosomal diploidy[11,12]. *CTNNB1* mutation usually occurs with other chromatin remodeling mutations such as Cyclic Adenosine Monophosphate Response Element Binding Protein (*CREBBP*), Mediator Complex Subunit 13 (*MED13*) and subunits of the nucleosome-remodeling complex such as SWI Matrix Associated, Actin Dependent Regulator of Chromatin, Subfamily A, Member 4 (*SMARCA4*), At-rich interaction Domain 1A (*ARID1A*) [9,10,13]. Most of WNT-MBs carries DEAD-Box Helicase 3 X-Linked (*DDX3X*) mutations, which participates in mRNA translation[12,14]. The germline mutation of antigen presenting cells (APC) on chromosome 5 as inherited Turcot syndrome and Anaplastic Lymphoma Kinase (*ALK*) gene also contribute to the development of WNT-MBs[9,15].

SHH-MB accounts for about 25% of all MBs with a 70% 5-years overall survival (OS). It is frequently seen in infants and adult patients[16,17]. The majority shows histologically nodular or desmoplastic morphology, which predicts a favourable prognosis[18]. *TP53* mutation segregates SHH-MBs into tumors with *TP53*-wildtype, often seen in young children and associated with favorable prognosis, and *TP53* mutant SHH-MB classically seen among older children and associated with poorer prognosis. SHH-MB with Protein Patch Homolog-1 (*PTCH1*) and Suppressor of Fused Homolog (*SUFU*) mutation are associated with Gorlin syndrome[19,20]. In children, *TP53* mutations frequently occurs with *GLI2* and *MYCN*-amplifications[9] (Figure 1).

Group 3 MB, a classical histological variant, accounts for 25% of all MBs and considered the deadliest subtype[7,21]. Tumours in this group with *MYC*-amplification carries a 20% risk of 5-years survival[22]. However, the most common cytogenetic abnormalities seen in Group 3 is the 17 ploss followed 16q and 9q losses[19]. Rare genetic variants in Group 3 MBs include Orthodenticle Homebox-2 (*OTX2*) and Enhancer of Zeste 2 Polycomb Repressive Complex 2 Subunit (*EZH2*) amplifications and *SMARCA4* mutations[23] (Figure 1).

Group 4 MB is the most frequent type among all MBs and often occurs in male more than females[6]. Isochromosome 17q is the most common cytogenetic aberration seen in this group. Other genetic variants include the loss of chromosome 8p, 10q, and the aberrations of 11p and 18q[2,17]. The clinical outcome is better in patients with chromosome 11 loss with an OS above 90%[19]. Zhou *et al*[24] reported that around 40% of Group 4 patients showed metastasis and treated as a high-risk disease. As we mentioned before, Group 3 and Group 4 MBs are genetically heterogeneous and not associated with germline mutations[25].

Current treatment options in MB

The magnitude of surgical resection in MB may not be as significant as earlier. After surgery, patients are treated with radiotherapy of the whole spinal axis with an additional boost targeting the tumor margins[26]. Radiotherapy usually starts 20-30 d after surgery however, delay of radiation may increase

risk of recurrence and is therefore not recommended for patients older than 3 years[27,28]. Post-operative radiotherapy for children less than 3 years of old may increase risk of cognitive dysfunction [18]. Postoperative chemotherapy in MB patients is essential strategy to reduce the radiation effects and improve the survival, particularly in young children. The treatment varies based on the risk of drug toxicity and recurrence rate. Both risks are correlated with MB molecular alterations and considered as prognostic factors prior treatment. The risk of toxicity should be taken carefully in infants and children younger than three years of age while the recurrence is usually high in metastatic cases or cases undergoing subtotal resection. Anaplastic and large cell variants may have poor response and worsening outcome[29] (Figure 2). The high-risk group consists of SHH-MBs with *MYCN*-amplification; SHH-MB with metastatic dissemination and wildtype *TP53*, and metastatic Group 4 MBs[7]. High-risk population includes mutant *TP53* SHH-MB patients and metastatic Group 3 MBs with *MYCN*-amplifications[7] (Figure 2).

Multi-modality treatments have been used in multiple clinical trials for ten years. The standard protocols included different chemotherapeutic agents with long-term or maintenance dose-related regime including ifosfamide, etoposide, methotrexate, cisplatin, and cytarabine, lomustine, and vincristine[30]. The maintenance regimen has improved the overall survival compared to the sandwich approach among patients with M0 or M1 disease[30,31]. Nonetheless, the most frequent and current treatment strategy includes risk-adapted radiotherapy followed by 4 cycles of cyclophosphamide, and a high dose of chemotherapy such as cisplatin, vincristine, followed by autologous stem cell transplantation. This protocol has improved the 5-year OS into 95%[16]. Additional clinical trials are ongoing to explore the efficacy of different treatment regimes in newly diagnosed MBs (Clinicaltrials.gov). The current treatment protocols and ongoing clinical trials are still using the same circulating chemotherapeutic agents but with different regimes. Multiple clinical trials have tested new therapies. Those trials were completed with positive and negative results (Clinicaltrials.gov). For example, a combined everolimus and ribociclib (cyclin D and CDK6 inhibitors) has been tested as a phase I trial (NCT03387020) in children with recurrent MBs. Some novel therapeutic strategies are currently recruiting, and their target are to reduce recurrence and to avoid the cytotoxic effects of chemoradiation (Table 1). For example, the usage of Entrectinib, a *TRK* inhibitor, and *ALK* inhibitor has been studied in a phase I/II trial (NCT02650401). There is a high tendency to discover the efficacy of molecularly targeted agents for MBs with dominant genetic alterations, regardless of the tumor subgroup. Patients with *FGFR*-gene mutation can be treated with erdafitinib (NCT03210714); MBs with *TSC*-gene mutations can be treated with samotolisib (NCT03213678); *SMARCA4*-gene mutations can be treated with tazemetostat, an *EZH2* inhibitor.

Immune microenvironment of MB

All the previously mentioned clinical trials are stratified based on disease risk, molecular subgroups, patients age, and all are targeting tumour cells. The necessity to explore MB microenvironment is encouraged to help discovering new targeted receptors. The immune microenvironment of any cancer represents all types of cells surrounding the tumour cells including immune and none-immune cells. The relationship between these cells is mechanical and heterogeneous, by which they can facilitate in promoting or inhibiting tumor growth[32]. Because some studies have indicated that MBs have fewer immune cells than glioblastoma[33,34], the role of immune microenvironment in promoting or suppressing MB progression was found to be difficult to understand. Some cellular factors in tumour microenvironment may act against immune reaction and can promote tumour growth progression and angiogenesis. The infiltration of immune cells in MB might be limited due to the blood–brain barrier (BBB), which acts as physical barrier for immune cells infiltration[35]. Despite of some immune cells bypass across BBB, there may be an increase in trafficking toward the brain under certain conditions due to destruction of the BBB[36]. Some experimental models showed that the reactive astrocytes surrounding the tumour microenvironment form perivascular barriers to restrict the immune cells infiltration to the brain through BBB[37].

The presence of inflammatory cells in the tumor microenvironment has been scientifically accepted as an essential element in tumour progression. A study done by Gururangan *et al*[38] found that treated MB patients exhibited more CD4+T-cell lymphopenia. We can also presume that pre-operative and post-operative steroid treatment may induce systemic immunosuppression which prevents antitumor immunity in MB patients. Tumours with a low mutational burden respond less efficiently to immune checkpoint inhibitor compared to tumors with a high mutational burden[39]. Moreover, the acidification of the tumour microenvironment causing glycolytic activity can encourage macrophages infiltration through G protein coupled receptor, which in turn enhances vascular endothelial growth factor, thus promoting M2-like features of tumor-associated macrophage (TAM)[40].

APC, the immune cells in microenvironment, were proven to infiltrate malignant brain tumours in children. APCs is expressed by Major Histocompatibility Complex (MHC) class-I on tumor cells to allow them to be identified and killed by CD8 cytotoxic T- cells. MBs and atypical teratoid/rhabdoid tumors showed the lowermost cellular infiltration of this type among all malignant brain tumors[34]. Microglia, resident macrophages in the brain, are the most dominant APCs in brain tumors[35]. It is not clear if microglia promote anti-MB immune response. Mundt *et al*[41] showed that microglia are dispensable for T-cell entry into the brain and for local reactivation of T-cells. The loss of MHC class-I expression on

Table 1 The most recent active and recruiting clinical trials of medulloblastoma that are targeting immune receptors or using different chemotherapeutic agents

Clinical Trial	Trial objective	Samples	Targeted subgroup	Completion date
NCT01878617	Clinical and molecular risk directed therapy of newly diagnosed MB	660	WNT, non-WNT, SHH	2028
NCT00089245	Intrathecal radioimmunotherapy using I-8H9	120	8H9 reactive MB confirmed by IHC	2024
NCT02905110	Simultaneous methotrexate/etoposide infusion	10	All MB subtypes	2023
NCT02962167	Modified measles virus (MV-NIS)	46	All MB subtypes	2024
NCT02271711	Expanded NK cells infusion with recurrent medulloblastoma	12	All MB subtypes	2023
NCT02359565	Pembrolizumab in patient with recurrent medulloblastoma	45	All MB subtypes	2023
NCT03389802	APX005M, a humanized IgG1κ monoclonal Ab that binds to CD40	45	MB with CD40 activity	2023
NCT03299309	PEP (CMV)-specific peptide vaccine in medulloblastoma	30	All MB subtypes	2024
NCT03598244	Volitinib, a small molecule inhibitor of c-Met in recurrent MB	50	All MB subtypes	2023
NCT03173950	Nivolumab, Immune check point inhibitor, in refractory MB	180	All MB subtypes	2024
NCT03500991	HER2-Specific CAR T-cell locoregional immunotherapy	48	Her-2 expressed medulloblastoma	2039
NCT01356290	Antiangiogenic therapy for recurrent medulloblastoma	100	All MB subtypes	2026
NCT03911388	G207, an oncolytic herpes simplex virus-1 (HSV)	15	All MB subtypes	2025
NCT03638167	EGFR806-specific CAR T-cell locoregional immunotherapy	36	EGFR positive tumours	2040
NCT03893487	Fimepinostat, a small molecule inhibitor in young MB	30	All MB subtypes	2027
NCT03709680	Palbociclib in combination with temozolomide and irinotecan	184	All MB subtypes	2028
NCT03904862	CX-4945 inhibitor of casein kinase II (CK2) tolerability	60	SHH-medulloblastoma	2028
NCT03936465	BMS-986158, a bromodomain inhibitor	66	MYCN amplification or BRD3 translocation MB	2024
NCT02650401	Entrectinib (RXDX-101), a TRKA/B/C, ROS1, and ALK inhibitor	68	MB harboring- NTRK1/2/3, ROS1, ALK fusions	2027
NCT03210714	Erdafitinib, an oral pan-FGFR inhibitor	49	Mutations in the FGFR1/2/3/4 pathway	2024
NCT03213678	Samotolisib, a PI3K/mTOR inhibitor	24	PI3K/MTOR activating mutations	2024
NCT03213704	Larotrectinib, NTRK fusion inhibitor for medulloblastoma	49	MB with NTRK fusions	2024
NCT03213665	Tazemetostat, a small molecule EZH2 inhibitor	20	EZH2, SMARCB1, or SMARCA4 mutations	2023
NCT03233204	Olaparib for refractory or aggressive medulloblastoma	29	Defects in DNA damage repair genes	2024
NCT04023669	LY2606368, a molecularly targeted CHK1/2 inhibitor	21	Group3/Group4; SHH; indeterminate types	2026
NCT03526250	Palbociclib (Pediatric MATCH treating trials	49	Rb positive solid tumours	2025
NCT02444546	Wild-Type Reovirus in Combination with Sargramostim	06	All MB subtypes	2026
NCT04185038	B7-H3-Specific CAR-T Cell Locoregional Immunotherapy	90	All MB subtypes	2041

NCT01601184	Vismodegib combined with Temozolomide	24	SHH-MB group	2023
NCT03155620	Targeted therapy directed by genetic testing	2316	All MB subtypes	2027
NCT00089245	Iodine I 131 monoclonal antibody 8H9	120	All MB subtypes	2025
NCT02271711	Natural killer cell therapy	12	All MB subtypes	
NCT04315064	Infusion of Panobinostat (MTX110)	5	All MB subtypes	2024
NCT04743661	131I-Omburtamab in recurrent medullo-blastoma	62	All MB subtypes	2030
NCT03257631	Pomalidomide onotherapy for recurrent or progressive MB	53	All MB subtypes	2023
NCT04320888	Selpercatinib for treatment of advanced medulloblastoma	49	Tumour with activating RET alteration	2027

ALK: Anaplastic Lymphoma Kinase; CMV: Cytomegalovirus; EGFR: Epidermal Growth Factor Receptor; MB: Medulloblastoma; PEP: Post-exposure prophylaxis; SHH: Sonic-hedgehog; IHC: Immunohistochemistry; RET: Rearranged in transfection; NK: Natural killer; WNT: Wingless.

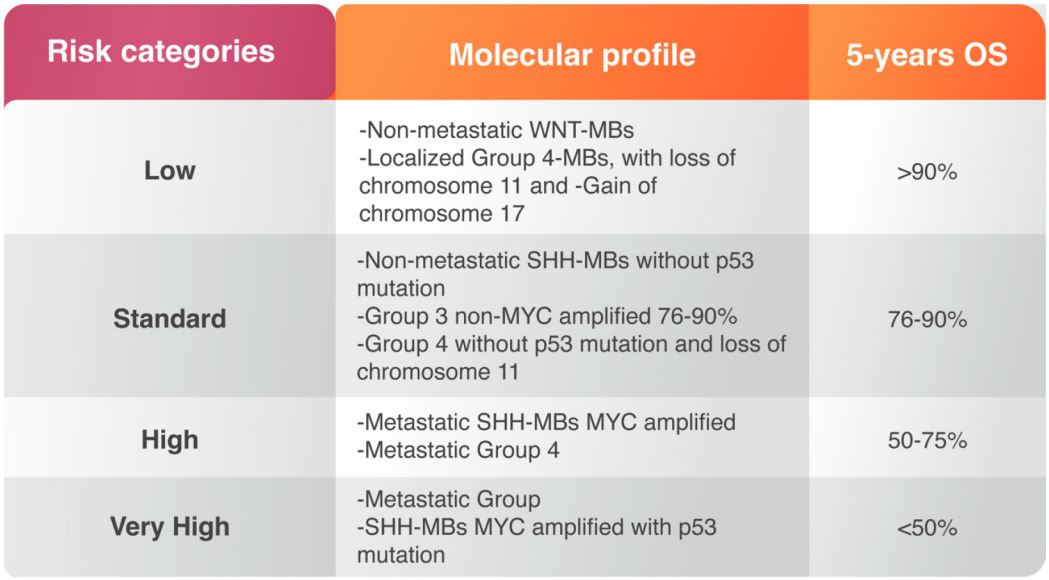

Figure 2 Risk groups and categories of medulloblastoma with their molecular profiles and the 5-years survival associated with each group. The information presented in this figure were taken with permission from the reference: Luzzi *et al*[91], 2020. SHH: Sonic-hedgehog; MB: Medulloblastoma; MYC: Myelocytomatosis oncogene; OS: Overall survival; WNT: Wingless.

tumor surface is also a common mechanism of immune escape in MB[42,43]. Because MHC class-I helps in the activation of CD8 cytotoxic T-cells, it acts as a passive regulator of natural killer (NK) cells. Thus, the loss of MHC-class I in tumor cells may increase tumour cell evasion[42,43].

Tumour associated macrophages in immune microenvironment

TAM is considered the major immune cell in the tumor microenvironment that can either support or inhibit tumor growth[44,45]. TAMs interact with tumour cells to promote tumour progression and invasion[46]. They are subclassified into two groups: (1) TAMs with M1 polarization, are induced by IFN-γ to release proinflammatory particles and are associated with some inflammatory response; and (2) TAMs with M2 polarization, are induced by interleukin-4 to release growth factors (*e.g.*, epidermal growth factor, fibroblast growth factor-1, vascular endothelial growth factor) and involved in tumour progression and immunosuppression[47-49]. Uncontrolled activation of M1-polarzed TAM can shift towards M2-polarization in long term. However, the M2-like macrophages, which mimic TAMs in the tumour microenvironment, can be stimulated by cytokines[50]. EGF released by TAMs stimulate carcinogenesis, while VEGF regulates angiogenesis. These processes emphasize the actual immune-suppressive function of TAMs[51]. TAMs infiltration in the tumour microenvironment was proven to be a poor prognostic factor[50]. Clinical data have indicated that a large number of M2-polarized TAMs expressing CD163 and CD204 were correlated with a poor outcome of several body cancers[47] (Figure 3). Moreover, the presence of TAMs, mainly M2- type, has been also noted in many adult malignancies including CNS tumors[52-54]. In response to hypoxia, TAMs overexpress the PD-1 ligands

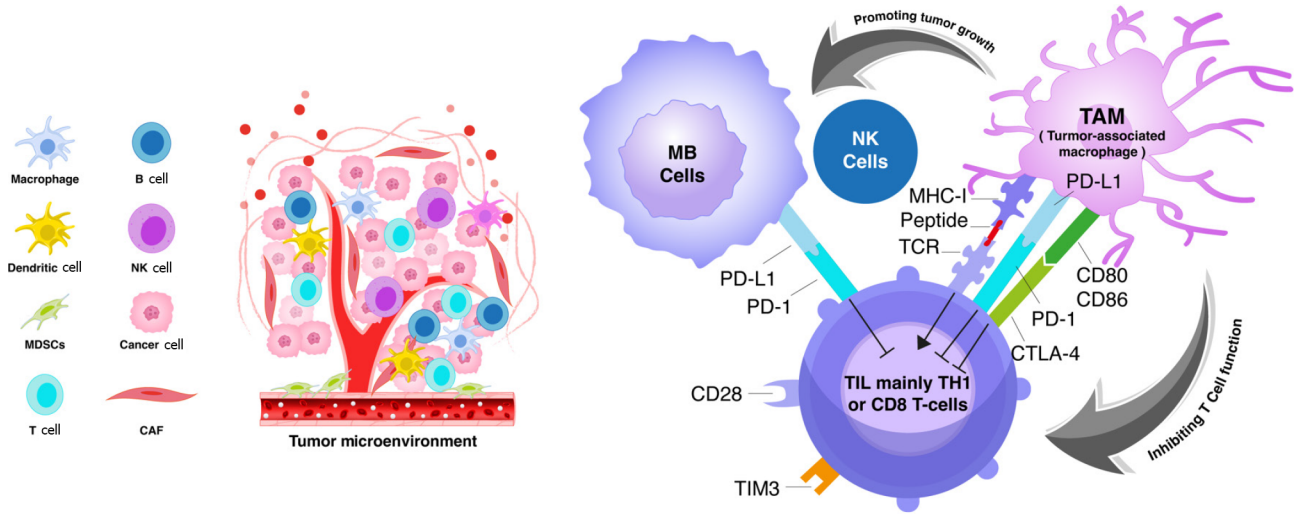

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Figure 3 The signaling interaction between tumour cells, tumor-associated macrophages, and tumour infiltrating lymphocytes in medulloblastoma microenvironment. Tumour microenvironment represents diverse cellular heterogeneities including immune and none-immune cells. The targeted receptors linked between immune cells represent a potential targeted therapy. CAF: Cancer-associated fibroblasts; MB: Medulloblastoma; NK: Natural killer; TAM: Tumor-associated macrophage; TIL: Tumour infiltrating lymphocytes.

[55]. PD-L1 overexpression in TAM has been reported in glioblastoma[56] but it has never been explored well in other brain tumours such as medulloblastoma.

The current role of TAMs in the prognosis of MB is still controversial. Despite of the molecular insights provided by MB subgroups, less information were reported about the role of TAMs in MBs[33]. The genetic alterations and the disease risk would make diverse effects on immune microenvironment [57]. Because TAMs are composed of variable amounts of microglia and macrophages, the composition of TAMs are different in all MB subgroups. Margol *et al*[58] and Zhang *et al*[59] reported that TAMs were significantly higher in SHH-MB compared to other MB subgroups. This may be due to the high expression of monocyte chemotactic protein-1 (MCP-1], which helps in TAM recruitment and M2 polarization[60]. Another possibility, SHH-MB may exhibit molecular signatures predictive for fibroblast, T-cells, and macrophage infiltration[34]. Nevertheless, the role of TAMs in this era is not clear and the previous reported studies did not reveal the prognostic connotations of TAMs in SHH-MBs[58].

CD163 expression was observed in the small number of SHH-MBs, which suggested that TAMs may play a dynamic role in SHH-MB formation[58,61]. Another study done by Crotty *et al*[62], revealed that less TAMs in microenvironment was associated with a low recurrence and low risk of metastasis. Lee *et al*[63] suggested that a large number of M1-polarized TAMs was associated with worsening outcome in SHH-MB patients. Lee and his group has also investigated the correlation between TAM recruitment and outcome, and they revealed that expressed M1-polarized TAMs predicted better progression-free survival but, TAMs showed no significant effect on OS[59]. Few studies showed that the immunoreactivity in MB microenvironment, regardless the subtype, is age-related[64]. In a study done by Zhang *et al*, they divided the patients into three age groups. They found that the group between 0-3 years of age and the group between 11-18 year of age had more TAMs than the group aged between 4-10 years. It implies that TAMs in MBs are crucial in different age groups[59]. Zhang *et al*[59] also found that TAMs, mainly M1-polarized type, are prevalent in MBs with metastatic disease.

Tumour recurrence and metastases are the major obstacle for treatment success, and the disease recurrence is responsible for 90% of MB mortality[65]. Group 3 and 4 patients develop spinal metastases regardless of the type of chemotherapy given after resection[2]. The presence of *TP53-MYCN*-alteration in these groups is associated with rapid tumour progression[66]. The ability of Group 3 and 4 to metastasize indicates that these tumor cells participate in the epithelial-to-mesenchymal transition (EMT), thus warranting additional investigations into EMT[67]. It is not yet known why tumor cells enter the EMT phase. A study done by Bonde *et al*[68] showed that TGFβ triggers the EMT phase, shifting the cancer cells to gain a mesenchymal phenotype. The lack of local nutrients, loss of supportive cells in microenvironment, and repeated mutations can all be reasons for this aggressive behavior. Funakoshi *et al*[69] found that loss of CDH1 allows tumour cells to detach from each other and can invade and metastasize.

Tumour infiltrating lymphocyte in immune microenvironment

Generally, increased T-cells trafficking in the brain has been reported in some neurological diseases. The activated T-cells have the role to alter the BBB, allowing for immune cells recruitment and entry to the brain parenchyma[70]. Tumour infiltrating lymphocytes (TIL) are considered signaling interacted cells

between TAMs and tumour cells in the tumour microenvironment (Figure 3). The number of T-cells present in MB was found to be not significantly high compared to other control tissues[33]. Small amount of CD8 cytotoxic T-cells and NK cells suggest a less antitumor activity in MB[34]. However, a small percentage of helper T-cells (Th17) cells was also found at the site of the tumor but with uncertain significance[11]. Some experimental trials revealed that MB cells stimulate the release of the T-cells attractant (RANTES) from the endothelium, causing T-cell immigration[71]. Hence, increasing numbers of T-helper lymphocytes correlate with favourable prognosis in MB patients receiving chemotherapy [44].

T-regulatory cells (Tregs) control the activity of immune cells by releasing some anti-inflammatory cytokines such interleukin-10 (IL-10), and CTLA4-mediated trogocytosis[44]. Treg infiltration in MB microenvironment has been described by Gate *et al*[44]. Consequently, TGFβ drives the CD4 helper T-cells to Tregs, which in turn releases high levels of TGFβ. This process generates a feeding circuit to support immunosuppression. Elevated Treg in MBs can be therapy-induced, as Treg has been detected in the peripheral blood of some treated patients[38].

Interaction between TAMs and TILs in MB microenvironment

The interaction between TAMs and TILs were not scientifically explored in MB microenvironment (Figure 3). Kurdi *et al*[54] has explained the crosstalk between tumour cells, TAM sand TILs in glioblastoma. TAMs encircle cancer cells and supresses the killing action of T-cell thus, T-cells will not be able to help tumour cells against immune evasion. The TAMs accumulate in the microenvironment with less T-cells evolution[54]. Salsman *et al*[71] revealed that MB cell lines can interact with tumor endothelium to recruit T-cells to MB microenvironment, in particular macrophage migration inhibitory factor (MIF). MIF is the key molecule released by MB to stimulate the endothelial cells in the microenvironment to release more potent T-lymphocyte attractants[71].

Current immunotherapy in MB and possible targeted receptors

Immune checkpoints represent a family of proteins on T-cells surface that interact with some ligands on APCs or tumour cells while they inhibit TCR-mediated ligands. Certain cancers (colorectal, ovarian and brain cancers) are resistant to immune checkpoint inhibitor[72]. The number of studies utilizing immunotherapy in the treatment approach of MB is limited. The approach had few selected options. Most of studies were observational and contained a small sample size. There are two clinical trials currently investigating the blockade of inhibitory checkpoint pathways in MB including pembrolizumab and nivolumab (NCT02359565) (NCT03173950). CD276, another immune check point inhibitor on T-cell, is also under investigation[73]. CD40 [a TNF receptor] expressed by antigen presenting cells and B-cells expresses cytokines, activates T-cells, and in turn timulate programmed cell death[74]. CD40 has a significant cytotoxic effect on tumor cells. APX005M, a humanized IgG1κ monoclonal antibody agonist of CD40 is currently evaluated in a phase I trial (NCT03389802) in patients with recurrent MBs. The recent actively recruiting clinical trials are summarized in (Table 1).

Numerous studies revealed that TAMs may interfere with some anti-tumor treatments such as chemotherapies and other antibody-based immunotherapies targeting some molecules such as PD-1/PD-1[50,72]. These findings emphasize that TAMs might be a promising target of novel anti-tumor treatment particularly in patient not responding to the standard treatment. The ability of TAMs to limit the efficacy of immune check point blockade has been previously investigated in several cancers[75,76]. TAMs express multiple ligands for checkpoint receptors, such as PD-L1/2, CD80/86, and CD204/CD206, and the current checkpoint inhibitors are different from the targeted receptors as they maintain a state of effective immunosuppression[77] (Figure 3). These legends, representing M2-polarized TAMs, have not been investigated in MB microenvironment. Martin *et al*[78] showed that MBs expressing reduced levels of PD-L1 can help tumour cells to evade from the immunity, suggesting that an inflamed tumor microenvironment is necessary for PD-1 pathway stimulation. However, the efficacy of PD-PD-L1 inhibitor has not been yet proven to be formally used in MB treatment.

Trogocytosis is a process involved in immune microenvironment concerned with the transfer of membrane fragments and cell surface proteins between cells. It is not known if induced iTregs can undergo trogocytosis. The trogocytosis of CD80/CD86 occurring in CTLA-4 or PDL1-independent approach plays a significant role in the immune suppression[79]. CD80/86 expression and trogocytosis have never been explored in MB microenvironment. As a key mechanism, Treg-linked CTLA-4 inhibits the CD80/CD86 molecules expression on APCs. Tekguc *et al*[80] revealed that blockade of CTLA-4 and PD-1/PD-L1 pathways may impede Treg-mediated immunosuppression, which in turn enhances anti tumour activity response. This novel exploration has not been investigated in MB. Several investigations have demonstrated that activation of PI3Kγ signaling in macrophages suppresses NF-κB, thereby stimulating immunosuppression. TAMs in cancers treated with chemotherapies are often responsible for chemoresistance as they are more susceptible to the cytotoxic effect of macrophages[81]. This process occurs when there is excessive recruitment of anti-apoptotic process in tumour microenvironment[82].

Understanding the molecular events in the mechanism of TAMs activation allows for the development of anti-tumor treatment strategies. TAMs can be targeted to inhibit their infiltration in microenvironment through direct killing or through a TAM-polarization reprogramming. TAMs accumulate in tumour microenvironment because of the continuous recruitment of monocytes from the blood

circulation to TAMs through multiple tumour derived mediators. These mediators play a connection role between macrophages and tumour cells. CCL2 has been described as the main mediator involved in TAM recruitment. Indeed, the blockage of this pathway would cause less TAMs accumulation in tumour microenvironment[83]. Another pathway involved in monocytic recruitment into TAMs is the CXCL12/CXCR4 pathway[84]. It has been used in different trials of different cancers such as myeloid leukemia but never been tried in brain cancers.

CSF-1, a colony stimulating factor involved in the proliferation and the recruitment of monocytes-macrophages, is an essential target against TAM in tumour microenvironment. The expression of CSF-1 in tumour microenvirment was proven to be a poor prognosticator in multiple body cancers[85]. After treatment with CSF-1 inhibitor in one of clinical trials, the number of TAMs have depleted and there was an infiltration of CD8 cytotoxic T-cells in the tumor[86,87].

Reprogramming of TAM is another possible strategy to inhibit TAM activity. Several approaches attempted to switch M2-polarized TAMs into antitumor M1-like macrophages through monoclonal antibody inhibitors and Toll-like receptor (TLR) blockers. Alvarez-Arellano *et al*[88] revealed that TLR7 is a prognostic factor of survival in MB. Resiquimod, an agonist to TLR7/8, has shown an attention couple years ago for its efficacy to reprogram macrophages[89]. The CD47–SIRPα, involved in the regulation of phagocytosis, has never been used to reprogram TAMs. CD47 is expressed by tumor cells and interacts with the signal regulatory protein-α. Substantial evidence assumed that overexpression of CD47 in many cancers had a role in the phagocytic resistance[90]. However, this investigation has never been investigated in MB patients. Promising results were obtained in lymphoma patients in a combination of anti-CD47 with anti-CD20. Despite these results, the *in vivo* application of CD47 for the treatment of cancer is still limited.

CONCLUSION

Medulloblastoma is the most common malignant pediatric tumour in CNS that are subclassified into four distinguishing molecular subgroups. The current treatments failed to improve the patient's survival significantly while the serious complications associated with these cytotoxic therapies warrant for exploring new therapeutic approaches targeting different immune receptors. The identification of tumour microenvironment has facilitated the scientists understanding how tumor growth and progression are regulated. TAMs and TILs, the main dominant immune cells in microenvironment, seem to have a major role in immune mechanism and tumor progression. Their infiltration in microenvironment has prompted researchers to evaluate the interaction of new targeted immune receptors with the current signaling pathways. Their infiltration in microenvironment may also be targeted through different reprogramming mechanisms. However, the ability of TAMs to limit the efficacy of immune check point blockade in MB requires further investigations. These strategic thoughts emphasize that TAMs might be a promising targeted treatment particularly in patients with recurrent or progressive MB. Further studies to explore new targeted receptors in tumour microenvironment and understanding the conventional relationship between TAMs, TILs and tumour cells are essential to develop new therapeutic approaches.

FOOTNOTES

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