Medulloblastoma cancer stem cells: molecular signatures and therapeutic targets

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ABSTRACT

Medulloblastoma (MB) is the most common malignant primary intracranial neoplasm diagnosed in childhood. Although numerous efforts have been made during the past few years to exploit novel targeted therapies for this aggressive neoplasm, there still exist substantial hurdles hindering successful management of MB. Lately, progress in cancer biology has shown evidence that a subpopulation of cells within the tumour, namely cancer stem cells (CSCs), are thought to be responsible for the resistance to most chemotherapeutic agents and radiation therapy, accounting for cancer recurrence. Hence, it is crucial to identify the molecular signatures and genetic aberrations that characterise those CSCs and develop therapies that specifically target them. In this review, we aim to give an overview of the main genetic and molecular cues that depict MB-CSCs and provide a synopsis of the novel therapeutic approaches that specifically target this population of cells to attain enhanced antitumorous effects and therefore overcome resistance to therapy.

INTRODUCTION

Medulloblastoma (MB) is the most common malignant primary intracranial neoplasm in children, accounting for around 20% of all paediatric brain tumours.¹ It is a primitive neuroectodermal malignancy of the central nervous system that is believed to arise from neural stem cell precursors in the granular cell layer of the cerebellum.² Specifically, many studies demonstrate that it originates from the remnants of the primitive neuroectoderm in the germinal matrix of the fourth ventricle roof,^{3,4} while other studies have reported a different origin for this invasive neoplasm: the external granular layer precursor cells.^{5,6} MB is subdivided into four major entities at the molecular level⁷: MB^{WNT-activated}, MB^{SHH-activated,TP53-mutant}, MB^{SHH-activated,TP53-wildtype} and MB^{non-WNT/non-SHH} (includes MB^{non-WNT/non-SHH, Group3} and MB^{non-WNT/non-SHH, Group4}).

The incidence of MB ranges from 0.53 (children aged 0–4 years) to 0.16 (adolescents aged 15–19 years) per 100 000 population in patients up to 19 years old, and affects males more than females (1.7 times more frequently in the age group 0–14 years)⁸ and white people more than black (1.7 times).⁹ The incidence continues to decline with age, reaching 0.06 per 100 000 person-years by 55–64 years of age.⁹ The peak age at diagnosis of MB is 7 years, with more than 70% of all cases observed among children younger than 16 years of age,^{10,11} and 10%–15% of patients diagnosed in infancy.⁹ Although aggressive, the 10-year survival

for patients with MB in the USA was found to be 64.9%.⁸ This could be attributable to the multimodality treatment approach including surgical intervention, radiation therapy (RT) and chemotherapy.³

During the past decade, increased interest in understanding the molecular basis of MB has revealed new insights into the different molecular and signalling pathways that might contribute to the tumour's formation, progression and recurrence. In this regard, many articles have been published in the last few years tackling the role of cancer stem cells (CSCs) as principal drivers in MB initiation and relapse, and subsequently as potential therapeutic targets for this malignant neoplasm.¹² Indeed, the CSC concept has become increasingly prominent ever since it was first proposed four decades ago, based on their self-renewal ability, potential to differentiate into the different types of cells and uninhibited growth pattern contributing to resistance to conventional therapies.^{13,14}

CSCs were first identified in leukaemias in 1973 as a distinguished population of cells, embracing specific pro-oncogenic genetic signatures, that are capable of generating malignant haematopoietic colonies.¹⁵ With time, CSCs have been gradually identified in dedicated niches of many other tumours,¹⁴ including MB in 2003.¹⁶ Indeed, CSCs had been isolated from human and mouse MBs¹⁷ and were shown to reside in a perivascular niche (PVN).¹⁸ The stem cell niche is referred to the microenvironment surrounding cancer cells, and is composed of supportive cells, extracellular matrix and factors needed to maintain cancer stemness.¹⁹ Although the niche in MB tumours is still largely undefined,²⁰ a recent report by Calabrese *et al*¹⁸ revealed that CD133-positive MB-CSCs reside near endothelial cells and small vessels, and might function as a niche.

Highly tumourigenic MB cells have been shown to display features imitating those of neural stem and progenitor cells, such as upregulation of CD133, *Nestin* and *Musashi* (*MSI1*)²¹ (*MSI1*²² and *Nestin* are evolutionally conserved markers for central nervous system (CNS) progenitor cells and neuronal stem cells), as well as developmentally related genes, such as *Ebfs*.²³ Here, we discuss the latest discoveries related to MB-CSC genetic signatures and the novel therapies that specifically target those cells based on the molecular cues they harbour.

METHODOLOGY

This review was conducted using the 'Preferred Reporting Items for Systematic Reviews and Meta-Analyses' (PRISMA) 2009 guidelines. We performed

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a comprehensive search using two databases, namely OVID/Medline and PubMed, for mesh terms, keywords and combinations related to 'cancer stem cells' and 'medulloblastoma'. Complete search strategy is provided in online supplementary appendix S1. In total, 248 articles were retrieved through database search from inception to 15 September 2019. We inserted all articles into EndNote V.X8 referencing program, and excluded duplicates, abstracts, case reports, non-English articles, reviews, commentaries and editorials. As a result, a total of 105 articles were considered for full-text qualitative analysis and inclusion in the final review. Online supplementary appendix S2 illustrates the study flow chart of the review process according to PRISMA 2009 flow diagram guidelines.

MB CLASSIFICATIONS AND CSCS

Histologically, MB is classified into four main WHO-defined subsets²⁴: classic MB, large-cell anaplastic, desmoplastic MB and MB with extensive nodularity (other variants such as medulloblastoma and melanotic do exist but are extremely rare).² At a molecular level, and according to the latest consensus nomenclature, MB is subdivided into four major entities⁷: (1) MB^{WNT-activated} (thought to originate from the lower rhombic lip),^{25 26} (2) MB^{SHH-activated, TP53-mutant} and (3) MB^{SHH-activated, TP53-wildtype} (sonic hedgehog (SHH); arises from granular neuron progenitors in the external germinal layer),^{27 28} and (4) MB^{non-WNT/non-SHH} which comprises MB^{non-WNT/non-SHH, Group3} (develops from cerebellar stem cells with high levels of MYC amplification and is considered the most aggressive among all subgroups)^{29 30} and MB^{non-WNT/non-SHH, Group4} (the most prevalent yet still of unknown origin).^{31 32}

Noteworthy, genes that are mainly deregulated in MB, such as *WNT*, *SHH* and *Notch*, as well as the proto-oncogenes *RTK* (receptor tyrosine kinase) and *MYC*, are central to molecular pathways controlling cell cycle and growth of CSCs.^{33–35} Moreover, reports from retrospective studies reveal that several molecular and genetic aberrations that correlate with MB prognosis and outcome^{36–41} are also involved in the control of CSC stemness,^{42–47} including *neurotrophin-3 receptor*,⁴⁸ *CD15*,^{49–51} *PTEN*,⁵² *MYC*,^{53–55} *ErbB2*,⁵⁶ *β-catenin*,^{57 58} *survivin*^{59 60} and *p53*.⁶¹

Further exploration showed that other markers linked to CSCs might have a pivotal role in MB tumour formation and progression.⁶² For instance, Singh *et al*¹⁷ were the first to reveal a role of CSC markers in MB, where they found that injecting a small number as low as 100 *CD133*+ cells into immunodeficient mice could yield MB tumour formation in vivo, whereas tumour failed to develop with *CD133*– cells even on increasing the number of injected cells to 100 000 cells. In this regard, high mRNA levels of *CD133* had been correlated with poor prognosis and increased likelihood of metastases in paediatric MB.⁶³ This demonstrates the importance of identifying novel CSC biomarkers and genetic signals and incorporating them altogether with the currently available parameters to create new stratification schemes for MB.⁶⁴ Such schemes may help to refine the management approaches for the different histological and molecular entities of this tumour.^{65–68} We will elaborate more on the various studied molecular signatures and therapeutic targets pertaining to MB-CSCs.

MB-CSCS: FROM GENES TO THERAPIES

Ever since the first MB-CSCs were isolated from human tissues in 2003 (*CD133*+*Nestin*+) showing improved proliferation, self-renewal and differentiation in vitro,¹⁶ subsequent research has elucidated the genetic aberrations and molecular signatures

pertaining to those CSCs, paving the way for novel therapeutic targets in this aggressive intracranial tumour.

CD133 and its relation to other molecular signatures

CD133 (prominin-1) is the most common cell surface antigen used to detect and isolate CSCs from various solid tumours.⁶⁹ Physiologically, it induces WNT/β-catenin signalling^{70–73} and has also been described as an important regulator of PI3K/Akt signalling in CSCs.^{74 75} The use of this marker to identify MB-CSCs in paediatric tissue samples was first described by Singh *et al*,^{16 17} and the isolated *CD133*+ cells were termed brain tumour stem cells. These cells had the ability to grow into neurosphere-like clusters in vitro and to produce massive tumours on intracranial transplantation into NOD-SCID mice forebrains in vivo, expressing neural stem cell markers such as nestin.¹⁶ An alternative method for culturing MB-CSCs, other than the three-dimensional (3D) neurospheres technique, has been proposed by de la Rosa *et al*⁷⁶ using laminin-precoated flasks that enable dedifferentiation of cells and enrich the stem-like cell population. Based on their high expression of *CD133*, CSCs possess the ability to resist apoptosis as well as RT⁷⁷ and chemotherapeutic drugs.⁷⁸

A study by Annabi *et al*⁷⁹ demonstrated that members of the low-density lipoprotein receptor-related protein (LRP) family, including LRP-1, LRP-1b, LRP-5 and LRP-8, regulate the adaptive phenotype associated with *CD133*+ MB-CSCs. Another study by the same research group revealed that matrix metalloproteinase 9 and membrane type I-matrix metalloproteinase, which are major players in cancer cell invasion, metastasis and resistance to therapy, have crucial roles in maintaining the invasive phenotype of *CD133*+ neurosphere-derived MB cells, while targeting those two molecules may reduce the formation of brain tumour stem cells.⁸⁰

Inflammatory mediators such as cyclooxygenase-2 (COX-2), an enzyme that converts arachidonic acid to prostaglandins, have been shown to be overexpressed in a variety of tumours,^{81 82} including MB.⁸³ COX-2-derived prostaglandins have also been implicated in tumour growth and angiogenesis.⁸⁴ Henceforth, the role of anti-inflammatory drugs in targeting MB-CSCs has recently been assessed, whereby a study was conducted by Chen *et al*⁸⁵ and Yang *et al*⁸⁶ to assess the enhancing effects of celecoxib on ionising radiotherapy (IR) of *CD133*+ MB cells. Results demonstrated that celecoxib significantly enhanced radiosensitivity of those MB cells in vitro and in vivo.^{85 86} In the same milieu, resveratrol, a natural polyphenol derived from red wine, has been shown to inhibit proliferation and tumorigenicity of MB-CSCs and enhance radiosensitivity in treated MB-CSCs.⁸⁷

One of the mechanisms contributing to chemotherapeutic resistance in many tumours is upregulation of X linked inhibitor of apoptosis protein and cellular inhibitor of apoptosis 1/2.⁸⁸ This applies to *CD133*+ MB-CSCs, which displayed higher levels of both proteins and demonstrated hypersensitivity to treatment with small-molecule inhibitors of apoptosis proteins (IAP) inhibitors LCL161 and LBW242.⁸⁸ Another pathway that plays a role in the maintenance of *CD133*+ MB-CSCs was described by Chang *et al*,⁸⁹ who treated those cells with a potent STAT3 inhibitor, cucurbitacin I. Results revealed that the latter treatment suppressed the CSC-like properties and stemness of MB-derived *CD133*+ cells and increased the apoptotic sensitivity of those cells to RT and chemotherapeutic drugs.⁸⁹ Similarly, Garg *et al* and others showed that signal transducers and activators of the STAT3

pathway are activated in *CD133*+ MB-CSCs through regulation of *c-MYC*, a key genetic driver of MB^{non-WNT/non-SHH, Group3}.^{90 91}

An orthotopic xenograft model, named MB3W1, was established using cells derived from the malignant pleural effusions from a child with MB^{non-WNT/non-SHH, Group3}.⁹² This model displayed CSC characteristics such as the ability to form neurospheres, high aldehyde dehydrogenase (ALDH) activity, expression of *CD133/CD15* stem cell markers and high tumorigenicity in NOD-SCID mice.⁹² In a similar study by Friedman *et al*,⁹³ four human paediatric MB xenografts, mainly representing group 3 tumours, were used to prove that hypoxia increases *CD133* as well as primary HSV-1 (herpes simplex virus) entry molecule nectin-1 (*CD111*) expression. Interestingly, MB cells expressing *CD111* were also found to be highly sensitive to killing by clinically relevant oncolytic HSVs (G207 and M002) in vitro and in vivo.⁹³

In a study by Lim *et al*,⁹⁴ polymeric nanoparticle formulation of curcumin was used to assess its effect as a potential therapy for MB-CSCs. This compound is derived from the Indian spice turmeric and has been proven to harbour diverse effects on human diseases: proapoptotic, antiangiogenic, anti-inflammatory, immunomodulatory and antimetabolic effects.^{95 96} Treating MB cells with curcumin decreased anchorage-independent clonogenic growth, reduced the *CD133*+ stem-like population, attenuated insulin-like growth factor and STAT3 pathways, and blocked SHH signalling, but did not affect Notch signalling.⁹⁴

Hedgehog (SHH) pathway

The SHH entity of MB accounts for approximately 30% of all cases. It is driven by hedgehog ligands that undergo covalent modification by cholesterol^{97 98} and bind to the Patched (PTCH1) transmembrane receptor⁹⁹ to maintain tumour growth and stemness.^{100–102} In a recent study by Bell *et al*,¹⁰⁰ the authors used biomimetic high-density lipoprotein (HDL) nanoparticles to deplete cholesterol from hedgehog-driven MB and Ewing sarcoma cancer cells, via binding to the HDL receptor, scavenger receptor type B-1, and thereby targeting the CSC populations in those tumours.

Among the other drivers of the SHH pathway is the protein patched homolog 1 (Ptc).^{103–105} A single tumour mouse model, namely the *Ptc*^{+/-} model, has long been used to study the molecular and cellular mechanisms involved in MB formation, particularly MB^{SHH}.^{106 107} Chow *et al*¹⁰³ provided evidence that although MBs that form in *Ptc*^{+/-} MB mice are composed of three entities, all of them contain long-term, self-renewing stem cell-like cells that are responsible for tumour initiation on serial in vivo transplantations. Other studies were also published confirming this.^{107 108} Notably, high expression levels of *PTCH2* were observed in human MB tissues and correlated with a worse prognosis³⁴; although *PTCH2* is a tumour suppressor gene that inhibits SHH activity,¹⁰⁹ its role in MB might not necessarily be related to SHH pathway inhibition but to *GLI1* expression.^{34 110} This finding was further confirmed in a study by Po *et al*,¹⁰⁵ where *GLI1* and *GLI2*, the downstream effectors of SHH, were shown to bind to Nanog-specific cis-regulatory sequences in stem cells. In this regard, SHH signalling was linked to two distinct MB entities: wild-type *TP53* (MB^{SHH-activated,TP53-wildtype}) and *TP53* loss (MB^{SHH-activated,TP53-mutant}), a central event in promoting stemness, which contributes to Nanog upregulation in stem cells derived from both postnatal cerebellum and MB.¹⁰⁵

Notch pathway

Like the SHH pathway, Notch signalling is required for controlling growth and proliferation of neural stem/progenitor cells as well as embryonal brain tumours,¹¹¹ such as MB.^{20 112–115} Fan *et al*¹¹⁶ showed that MB stem-like cells exhibit higher levels of Notch signalling, which makes them more sensitive to this pathway inhibition. Indeed, Notch blockade with γ -secretase totally abolished *CD133*+ MB-CSCs, leading to loss of tumour-forming capacity (due to depletion of stem-like cells).¹¹⁶ Another study by Pistollato *et al*¹¹⁷ revealed that hypoxic conditions promote *Notch1* activation with its ligand Dll4 and lead to expansion of *CD133*+ and *Nestin*+ MB precursors.

PI3K pathway

The phosphoinositide-3-kinase (PI3K)/AKT signalling pathway has been reported to play an important role in the renewal of embryonic stem cells.^{118 119} Recent studies also referred to the role of PI3K/AKT/mTOR pathway in growth and maintenance of CSCs in solid tumours, such as breast and prostate cancers.^{75 120} In MB, Frasson *et al*¹¹⁹ revealed that PI3K/AKT inhibition with LY294002 yielded increased cell death of *CD133*+ MB-CSCs and spared the more differentiated cells via activation of the mitochondrial apoptotic cascade. In another study by Hambarzumyan *et al*,^{121 122} the authors demonstrated that PI3K pathway plays a crucial role in regulating survival of nestin-expressing MB-CSCs residing in the PVN, and inhibition of AKT signalling sensitises PVN cells to radiation-induced apoptosis.

MYC pathway

MYC proteins have been associated with several cancers, including MB tumours^{31 123} that harbour *MYC*, *MYCN* and *MYCL1* amplifications.¹¹⁸ In this regard, somatic mutations of *TP53* had been mostly found in WNT-MB and SHH-MB and are associated with *MYCN* rather than *MYC* amplification.¹²⁴

A study from the Chesler's group reported a genetically engineered mouse model of *MYCN*-driven MB (the GTML mouse model: *Glt1-tTA* (glutamate transporter 1-tetracycline transactivator), (*TRE*)-*MYCN* (tetracycline response element) and *Luc* (luciferase)),³¹ and later used this model to establish neurosphere lines.³² Those spheres demonstrated robust proliferation and expressed neuronal markers such as *Ng2*, *Syp*, *Olig2* and *Sox9*.¹²⁵ Besides, when transplanted orthotopically into the brains of nude mice, the neurosphere lines were able to form massive tumours with morphology that mimicked human MB, including Homer Wright (neuroblastic) rosettes.³²

Venkataraman *et al*¹²⁶ conducted a study concluding that inhibition of a member of the bromodomain and extraterminal domain family, namely BRD4, effectively suppresses *MYC*-driven MB through attenuating cancer cells self-renewal, stem cell signalling and induction of senescence in vitro and in vivo.¹²⁶

Polycomb repressive complexes

Polycomb repressive complexes 1 and 2 (PRC1 and PRC2) are evolutionarily conserved epigenetic regulators¹²⁷ implicated in cancer.¹²⁸ *BMI1* (B cell-specific Moloney murine leukaemia virus integration site), the best studied *PRC1* gene in oncology,^{129 130} is often overexpressed in cancer and has been implicated in maintaining tumour stemness by serving as a key CSC regulatory gene.^{131 132} In MB, *BMI1* is overexpressed across all subgroups, particularly MB^{non-WNT/non-SHH, Group3}.^{133 134} A study by Wang *et al*¹³⁴ revealed that SHH modulates *BMI1* to maintain MB-CSCs. Another study by Bakhshinyan *et al* used a small-molecule inhibitor to target *BMI1* in MB^{non-WNT/non-SHH, Group3} cell lines,

namely PTC-028, exemplifying significant reduction in stem cell properties in vitro and in vivo. BMI1 has also been shown to downregulate p53 in embryonal cancer precursor cells, such as neuroblastoma and MB, and subsequently promote MycN oncoprotein overexpression in those cells.¹³⁵ Manoranjan *et al*¹³⁶ studied the stem cell data gathered from genomic platforms and demonstrated that *FoxG1* interacts with *Bmi1* in MB^{non-WNT/non-SHH, Group3} to mediate stem cell self-renewal and tumour initiation.

Another protein that represents the catalytically active component of the PRC2 is enhancer of zeste homologue 2 (EZH2). This protein causes chromatin compaction and contributes to several biological processes, including differentiation, maintaining cell identity and proliferation.¹³⁷ It is shown to be highly expressed (more than twofold) in primary MB tissues and cell lines.¹³⁸ Since it was proven that EZH2 maintains glioblastoma CSCs,¹³⁹ Alimova *et al* evaluated the effects of knocking down *EZH2* expression on MB-CSCs. Results showed that neurosphere formation was attenuated after *EZH2* knockdown along with a significant decrease in Myc and Sox2 activities and G2 cell cycle arrest.¹³⁸ The authors concluded that EZH2 might be a potential therapeutic target for MB and is important for MB cell growth and transformation of neural stem cells.¹³⁸ In another study, an interaction between maternal embryonic leucine-zipper kinase and EZH2 was found in MB stem-like cells, representing an attractive therapeutic target and potential candidate for the diagnosis of MB.¹⁴⁰

Other genetic aberrations

Urokinase-type plasminogen activator receptor (uPAR) is a cell surface protein that drives directed extracellular proteolysis on the surface of invading cancer cells promoting invasion, migration and metastasis.¹⁴¹ It is overexpressed in the tumour-stromal invasive microenvironment in many human cancers, including MB.¹⁴² Asuthkar *et al*¹⁴³ showed that IR induces the expression of uPAR and other CSC markers, such as *MSI1* and *CD44*, and triggers WNT-7a- β -catenin signalling, which in turn promotes cancer stemness in MB. Overexpression of uPAR post-IR also negatively regulates Hand-1 activity, promoting angiogenesis via hypoxia-inducible factor-1a upregulation.¹⁴² Henceforth, targeting uPAR in patients with MB undergoing IR might overcome potential therapy resistance and prevent IR-induced tumour angiogenesis.^{142 143}

It is believed that in many tumours, drug resistance might be attributed to the efflux of chemotherapeutic drugs by key members of the ATP-binding cassette (ABC) transporter superfamily.¹⁴⁴ Since a subpopulation of cells within tumours, namely CSCs, underlie tumour progression and relapse, those cells must express ABC transporters.¹⁴⁵ Interestingly, in MB, significant correlation was found between ABCB1 expression and high-risk tumours among patients with poorer overall survival.¹⁴⁶

Polo-like kinase 1 (PLK1), a protein kinase that promotes mitosis via phosphorylating cyclin B1 and CDK1,¹⁴⁷ is shown to be overexpressed in a wide variety of cancers, including MB.¹⁴⁸ Inhibiting PLK1 by small-molecule inhibitor BI 2536 potently increased MB cellular apoptosis and sensitised cells to IR. It also reduced MB cell growth and CSC formation through decreasing the expression of SRY (sex determining region Y)-box 2 (SOX2).¹⁴⁸

Lastly, accumulating evidence demonstrates a crucial role of microRNAs in regulating and maintaining CSCs within different tumours. In MB, low expression of miR-466f-3p was found to sustain epithelial-to-mesenchymal transition in MB^{SHH-activated}

CSCs via Vegfa-Nrp2 signalling pathway.¹⁴⁹ Also, Kaid *et al*¹⁵⁰ found that miR-367 enhances stemness features of MB cells, such as proliferation, 3D tumour spheroid cell invasion and the ability to generate CD133-expressing neurosphere-like structures. Other studied microRNAs included miR-135a,¹⁵¹ miR-142-3p,¹⁵² miR-218^{153 154} and miR-34a.¹⁵⁵

CONCLUSIONS

The key for effective eradication of MB tumours and overcoming aggravating therapy resistance is the isolation of the MB-CSCs and identification of their specific molecular signatures and genetic aberrations. This eventually will lead to the development of novel therapeutic interventions and combinations to target aggressive MB stem cell-specific dysregulations.

Take home messages

- Subpopulation of cells within the tumor, named cancer stem cells, are thought to be responsible for cancer recurrence in medulloblastoma.
- The key for effective eradication of medulloblastoma tumors and overcoming aggravating therapy resistance is isolation of cancer stem cells.
- Highly tumorigenic medulloblastoma cells display features imitating those of neural stem and progenitor cells, such as upregulation of CD133 and Nestin.

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