

Review

Cancer Stem Cell Biomarkers in the Nervous System

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Abstract

Cancer stem cells (CSCs) have been increasingly recognized in recent years. CSCs from human neural tumors are one of the root causes of metastatic tumor progression, therapeutic resistance and recurrence. However, there is a lack of comprehensive literature that systematically consolidates the biomarkers specific to CSCs in neurological cancers. Therefore, this review provides a comprehensive summary of cancer stem cell (CSC) biomarkers for neurological tumors such as glioma, meningioma, medulloblastoma and neurofibroma. It also points out the possible functions of these biomarkers in diagnosis, treatment and prognosis, providing a broader perspective. First, we quantitatively screened key words such as CSCs, biomarkers, and expression by bibliometric analysis and clarified the intrinsic connections between the key words. Then, we describe the CSC biomarkers of major neurological tumors and their pathway mechanisms, and provide an in-depth analysis of the commonalities and differences with the biomarkers of non-CSCs. In addition, many studies have shown that antipsychotic drugs can inhibit tumor growth and reduce the expression of CSC biomarkers, which facilitates targeted therapy against tumors in the nervous system. Therefore, this study will focus on the biomarkers of CSCs in the nervous system, hoping to provide guidance for future in-depth exploration and monitoring of neurological tumors for clinical applications.

Keywords: cancer stem cell; neurological tumors; biomarker; nervous system

1. Introduction

Cancer is still one of the major causes of death worldwide, with cancer stem cells (CSCs) being a particularly complex component [1,2]. In the WHO Classification of Tumors of the Central Nervous System 2021, the tumors covered include glioma, meningioma, medulloblastoma and pituitary tumors [3]. However, tumors related to the peripheral nervous system include neurofibromas and schwannomas [4]. The incidence of each tumor in the nervous system varies widely depending on the histology. Incidence rates were highest for neurofibroma (1/3000), meningioma (7.44 per 100,000), glioblastomas (3.19 per 100,000) and medulloblastoma (0.71 per 100,000) [5,6]. As one of the major tumor types, glioma is highly malignant and has a poor prognosis even after the application of comprehensive treatment. Recent studies have shown that glioblastoma has surpassed pancreatic cancer and liver cancer as the most difficult to treat tumors [7]. Therefore, it is of great interest to investigate CSCs in the nervous system.

Stem cells are able to differentiate into any cell of an organism and have the ability of self-renewal [8]. Among them, CSCs are a small population of stem cells, and are one of the underlying causes of highly metastatic, recurrence-prone and untreatable cancers. Not only can they give rise to all cell types present in the tumor tissue from which they originate through cell differentiation, they can also drive tumorigenesis and cause recurrence [9–11]. CSC biomarkers

can indicate the malignancy of tumors and respond to the development of tumors. Certain molecules are specifically expressed in CSCs or cancer stem cell-like cells [9]. These natural growth molecules can be detected in body fluids or tissues, thus acting as biomarkers to identify CSC and monitor treatment effectiveness, and used to isolate cell populations with CSC characteristics [12]. However, because CSC biomarkers are not universally expressed across tumor types, one marker cannot be used for all tumors [13]. The diagnosis, treatment and prognosis of the same tumor may also involve different biomarkers [12]. Therefore, classification studies on CSC biomarkers of different tumors are of great interest for monitoring and treating tumors.

A large number of biomarkers have been identified in the nervous system. However, there are relatively fewer CSC biomarkers. Moreover, most studies have concentrated on a single CSC biomarker rather than multiple biomarkers that may be more reliable for CSC identification. Furthermore, given the intrinsic connection between the nervous system and mental illness, there may be a potential function of drugs applied to mental illness on neurological CSCs [14]. To address the above three shortcomings, this research aims to review CSC biomarkers for their diagnostic and prognostic potential in several neurological tumors, including glioma, medulloblastoma, meningioma, and neurofibromas.



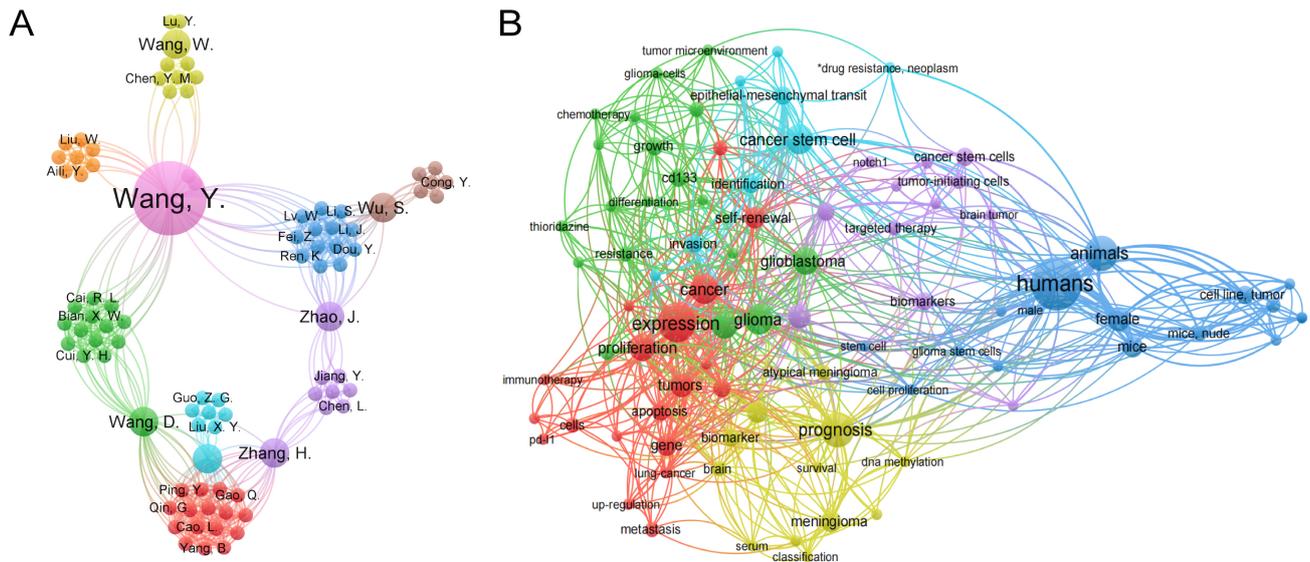


Fig. 1. Content of bibliometric analysis. (A) Authorship-based bibliometric map of the studies. (B) Co-occurrences of the keywords based on the full counting method. The strength of the links was normalized by the association strength method and the weight of keywords refers to the total link strength. Only the links with a minimum strength of three are displayed.

2. Bibliometric Analysis

An authorship-based bibliometric map showed that neurological CSC biomarker research tends to be in “small teams” (Fig. 1A). Meanwhile, each team formed a self-completeness academic community, and the mutual communication between each community was much less than that within the community. It can often be self-sufficient and has less interaction with the outside world. However, neurological CSC marker research involves a complicated process, which is difficult for an isolated group to generate systematic data. Team collaboration to achieve an aggregation effect on CSC biomarker research will be highly appreciated.

The word frequency analysis on neurological CSC (Fig. 1B) suggests that most of the literature focused on hotspot information about stem cells, such as expression, glioma, biomarker, and prognosis. Expression clustered with the words gene, proliferation, tumor, and overexpression, predicts that overexpression of biomarkers such as genes can inhibit tumor cell metastasis and proliferation. It also induces apoptosis and reduces the stemness of CSCs. The high association of CSCs with words such as recognition, invasion, and epithelial-mesenchymal transition (EMT) suggests that CSC formation is related to EMT and that identification and detection of CSCs by flow cytometry methods are also important. EMT is a key process in CSC formation. In this process, epithelial cells acquire the characteristics of mesenchymal cells, with enhanced cell invasion and migration ability, and allow the cells to acquire properties such as self-renewal. The co-occurrence of the terms glioma and glioblastoma, CD133, and growth indicates that most of the research on glioma, one of the major tumor species, has focused on glioblastoma. It also pre-

dicts a correlation between the formation of the biomarker CD133 and the growth of the tumor. A careful reading of the literature also confirms that glycosylation of CD133 maintains the self-renewal of CSCs and tumor growth and promotes the ability of glioma stem cells (GSCs) to resist chemotherapy. In addition, the words prognosis, meningioma, DNA methylation, and survival time were clustered into one category, indicating that the study of prognostic markers mainly focused on meningioma and that the expression level of prognostic markers correlated with postoperative survival time. Further studies showed that the differences in DNA methylation among meningioma patients led to different clinical prognostic characteristics. The expression levels of prognostic markers were significantly correlated with postoperative survival time. If the expression of markers was positively correlated with prognosis, increased markers indicated a good prognosis and a longer postoperative survival time for the patients. In conclusion, the primary subjects for most of the literature are humans versus animals. By constructing xenograft models derived from cell lines with biomarkers, the investigators found that they were more malignant and aggressive, exhibiting a strong stemness phenotype.

3. Functions and Pathways Involved in Stem Cell Biomarkers of Tumor Species

3.1 Characteristics of the Tumor Species

Glioma is the most common primary intracranial tumor, accounting for nearly 80% of malignant brain tumors, with a high mortality and malignancy rate [15]. According to the WHO 2007 pathological criteria, gliomas can be classified into four grades according to their malignancy:

grade I is Fibrillary astrocytoma, grade II is Diffuse astrocytoma, grade III is Anaplastic astrocytoma, and grade IV is Glioblastoma multiform (GBM) [16]. The WHO 2016 and 2021 pathology criteria are refined according to molecular typing and age stage. Among them, grade I and II gliomas are called low-grade malignant astrocytoma, grade III and IV gliomas are malignant glioma cells, and grade III gliomas are prone to progress to grade IV GBM [3,17,18]. As a more aggressive tumor, GBM is the most malignant, with a recurrence rate of 100% and an average survival time of less than 12 months in most cases [19,20]. Medulloblastoma (MB) is one of the most common malignant brain tumors in children, accounting for approximately 10% of all tumor deaths in young infants [21]. After standard treatment, approximately 1/3 of MB patients experience recurrence, and the probability of long-term survival after recurrence is low [22]. Current genetically-defined categories include WNT-activated, SHH-activated *TP53* wild-type, SHH-activated *TP53*-mutant, and non-WNT/non-SHH [23]. Meningioma (MG) is a common intracranial and intraspinal neoplasm accounting for 25–30% of all primary neurological tumors, and its postoperative recurrence rate often ranges from 13% to 40% [24,25]. The WHO classification system describes 15 different MG subtypes, 9 of which are allotted WHO grade I, 3 WHO grade II, and 1 WHO grade III. The risk of recurrence is relatively low for WHO grade I meningiomas, but WHO grade III meningiomas are characterized by rapid growth, early recurrence, and a risk of systemic metastasis [26]. There are three types of neurofibromas: neurofibromatosis type 1 (NF1), accounting for 96% of all cases; neurofibromatosis type 2 (NF2), accounting for 3%; and schwannomatosis, accounting for <1% [27]. NF1 is one of the most common human monogenic diseases, with a prevalence of 1 in 3000, and consists mainly of Schwann cells [28] (Table 1).

3.2 CSC Biomarkers

3.2.1 Glioma

Biomarkers for glioma CSC diagnosis include NADH (Table 2, Ref. [24,27,29–41]). Yuan *et al.* [29] found that glioma cells demonstrate stem cell-like properties characteristic of GSCs at NADH^{high} autofluorescence, so the autofluorescence of NADH can be an appropriate marker to sort GSCs. Biomarkers of glioma CSC treatment are CD133, ALDH1, KLF4, SOX2, NANOG, MYC, ABCG2, Nestin and Msi-1 [30–33]. Tian *et al.* [32] demonstrated that the BET inhibitor ZBC260 inhibits tumor growth and GSC-like properties through the Wnt/ β -linked protein pathway. The main biomarkers of stem cells such as aldehyde dehydrogenase 1 (ALDH1), KLF4, SOX2, NANOG, MYC and ABCG2 are significantly reduced with increasing levels of ZBC260 to achieve therapeutic effects. Moreover, Wei *et al.* [33] demonstrated that low expression of MAN1A1 results in the formation of a high-mannose type N-glycan on CD133 in GSCs. This interaction with DNMT1 facilitates

GSC self-renewal and tumorigenesis, suggesting a potential therapeutic approach. Several studies have identified key molecular targets for inhibiting GSC-like traits. These findings suggest promising avenues for developing therapies to combat GSC-like traits in glioma. The expression levels of CD133, IL6, TGF- β , BRAP, HOXB5 and GAS5 are prognostic biomarkers in glioma patients [31,34–36]. Liu *et al.* [31] found a positive correlation between the expression of CD133, a CSC biomarker for glioma, and WHO tumor grade. Conversely, CD133 expression is negatively correlated with prognosis. Its elevation in glioma tissues predicts poor prognosis in glioma patients, while regulatory T cells increase IL6 expression by secreting TGF- β to activate NF- κ B signaling, and IL6 then contributes to GSC stemness by activating the STAT3 signaling pathway. Wang *et al.* [34] discovered that the expression of BRAP is linked to favorable outcomes in individuals with glioma. BRAP hinders the proliferation and migration of glioma cells, as well as the self-renewal of GSCs, by targeting the TGF- β /PI3K/AKT/mTOR signaling pathway. These findings suggest that BRAP could serve as a prognostic marker for glioma patients. Wu *et al.* [35] showed that GAS5 overexpression reduces cell viability, inhibits the migration of GBM cells, and impairs the stemness of GSCs through miR-let-125e and miR-6a. Moreover, GAS5 expression levels are significantly correlated with postoperative survival time and reduced in high-grade glioma tissues and cells, making it a prognostic biomarker. Zhao *et al.* [36] found that HOXB5 is overexpressed in gliomas, which correlates with poor patient survival and regulates the proliferation of GSCs. Functionally, they confirmed that HOXB5 promoted the proliferation of GSCs by activating IL6-mediated JAK2/STAT3 signaling (Fig. 2).

3.2.2 Medulloblastoma

Medulloblastoma (MB) comprises a subpopulation of CSCs, and the key properties of CSCs depend on phosphatidylinositol 3 kinase (PI3K). Thus, activation of the PI3K/AKT pathway contributes to the development of MB [37]. Biomarkers for the diagnosis of MB CSC include CD133, Nestin, SOX2, CD24 and CD15 [38,39]. Dietl *et al.* [39] demonstrated that MB3W1 cells, which exhibit high ALDH activity, also express high levels of CD133 and CD15, suggesting that they possess characteristics commonly associated with CSCs. Biomarkers for the treatment of MB CSC include CD133, CD15, OCT4, NANOG, *Sox2*, *Klf4*, *Nestin* and *Bmi1* [37,40]. Eckerdt *et al.* [37] mentioned that PIK3CA expression correlates positively with the expression of several stem cell/pluripotency markers such as *Sox2*, *Klf4*, *Nestin* and *Bmi1*. Moreover, they observed a significant increase in *Nestin* expression, a CSC biomarker, and phosphorylation of AKT, which contributes to tumorigenesis and mediates survival and drug resistance in brain CSCs. Gong *et al.* [40] discovered that increased expression of the neuropilin-1 in cancer cells promotes the

Table 1. Overview of cancer stem cell (CSC) biomarkers for neurological tumors.

Tumors of the nervous system	Morbidity	Recurrence rate	Gene expression	Protein expression	Pathway(s)
Glioma	6.02/100,000	100% (in Glioblastoma)		NADH, CD133, KLF4, SOX2, ALDH1, NANOG, MYC, ABCG2, HOXB5, BRAP	Wnt/ β -linked protein, TGF β /PI3K/AKT/mTOR, STAT3, NF- κ B
Medulloblastoma	0.71/100,000	1/3	<i>Sox2, Klf4, Nestin, Bmi1</i>	CD133, CD15, Nestin, CD24, SOX2	PI3K/AKT, MAPK
Meningioma	7.44/100,000	13% to 40%		NANOG, SOX2	
Neurofibroma	1/3000		<i>PROM1, NKX2-2</i>	CD68, OCT3/4, NANOG, SOX2	PI3K/AKT/GSK3 β , Wnt

Notes: Proteins are in normal font, genes are in italics.

Table 2. CSC biomarkers for neurological tumors.

	Diagnostic biomarker	Pathway(s)	Prognostic biomarker	Pathway(s)	Treatment biomarker	Pathway(s)	References
Glioma	NADH (+)		CD133, IL6, TGF- β (-) GAS5 (-) HOXB5 (-) BRAP (+)	TGF- β -NF- κ B -IL6-STAT3 IL-6/IL-6R/STAT3 TGF β /PI3K/AKT/mTOR	CD133 (+) ALDH1, KLF4, SOX2, NANOG, MYC, ABCG2 (+)	Wnt/ β -linked protein	[29–36]
Medulloblastoma	CD133, CD15, Nestin, CD24, SOX2 (+)				CD133, CD15 (+) <i>Sox2, Klf4, Nestin, Bmi1</i> (+)	PI3K/AKT, MAPK PI3K/AKT	[37–40]
Meningioma	NANOG (+)		SOX2 (-)				[24,41]
Neurofibroma	<i>PROM1, NKX2-2</i> (+)	Wnt			CD68, NANOG, OCT3/4, SOX2 (+)	PI3K/AKT/GSK3 β	[27,41]

Notes: tumor growth, prognostic effect and marker content were positively correlated as (+); Proteins are in normal font, genes are in italics.

Table 3. Non-CSC biomarkers for neurological tumors.

	Diagnostic biomarker	Prognostic biomarker	Pathway(s)	Treatment biomarker	References
Glioma	APRP (+)	PD-L1 (-) VASH1 (-) TP73 mRNA (-) HOXB5 (+)		Methyladenizine DNA modifications (-)	[43–45,47–49]
Medulloblastoma	CADH1, FGFR4, FIBB (+)	miR-137 (-) <i>PBK</i> (-) UBE2G1 (+)			[50–53]
Meningioma	miR-497 (+) VIMENTIN (+)	DVL1 (+) GSKIP (-) DNA methylation (+)	Wnt Wnt		[54–58]
Neurofibroma	miR-204 (+)			PD-L1 (+)	[59,60]

Notes: tumor growth, prognostic effect and marker content were positively correlated as (+); Proteins are in normal font, genes are in italics.

development of CSC features. However, MR438, when used in conjunction with the neuropilin-1, effectively suppresses the activation of PI3K/AKT and MAPK pathways, reducing the expression of CSC biomarkers like CD133 and CD15, thus limiting the progression of MB (Fig. 3).

3.2.3 Meningioma

The CSC Biomarkers for the diagnosis of intracranial meningioma (MG) include KLF4, MYC, CD133, SOX2, OCT4, NANOG, NESTIN and VIMENTIN [24]. The CSC biomarker of prognosis for intracranial MG is SOX2. Clinical studies by Di Bonaventura *et al.* [41] have shown a close correlation between SOX2 expression and MG grading, with prognostic implications for both overall survival and recurrence-free survival. Therefore, the assessment of SOX2 can be a valuable tool in guiding adjuvant treatment for MG patients.

3.2.4 Neurofibroma

Biomarkers for the diagnosis of neurofibroma CSC are *PROM1* and *NKX2-2*. A recent study by Luscan *et al.* [28] found that *PROM1* and *NKX2-2* are overexpressed in malignant peripheral nerve sheath tumors (MPNSTs), suggesting a higher proportion of CSCs in this group. Additionally, the study demonstrated that activation of the Wnt signaling pathway can promote Schwann-mesenchymal transition, leading to the generation of CSCs during NF1 tumorigenesis. The biomarkers of neurofibroma CSC treatment are CD68, OCT3/4, NANOG and SOX2. Jia *et al.* [42] demonstrated that inhibiting PI3K/AKT signaling and GSK3 β , as well as macrophage-induced stem cell biomarkers, effectively suppressed the formation of spheres induced by CM. It offers a potential therapeutic approach for treating neurofibromas (Fig. 4).

4. Differences and Correlations between CSC Biomarkers and Non-CSC Biomarkers

Non-CSC diagnostic biomarkers in glioma include APRP protein. Ali *et al.* [43] reported that glioma patients with higher tumor grades had increased levels of positive APRP fibrinogen and reduced levels of negative APRP biomarker albumin. In glioma, non-CSC therapeutic biomarkers such as PD-L1, as well as methyladenine DNA modifications, can serve as potential targets for therapy [44,45]. Xie *et al.* [45] found that N6-methyladenine DNA modification was enriched in human glioblastoma. Reducing this modification, which can inhibit tumor growth, is an effective therapeutic strategy. The expression levels of VASH1, TP73 mRNA, HOXA5 and FMR1NB protein are prognostic biomarkers for glioma patients [46–49]. Aili *et al.* [46] showed that high VASH1 expression is associated with poor prognosis and that VASH1 affects tumor cell invasion and migration by influencing microtubule formation and immune infiltration in the tumor microenvironment. Ding *et al.* [49] found that HOXA5 was a prognos-

tic biomarker, and its overexpression could promote glioma progression by affecting glioma cell proliferation.

The non-CSC diagnostic biomarkers for MB are CADH1, FGFR4 and FIBB and other urinary proteins. Hao *et al.* [50] found that urinary proteins such as CADH1, FGFR4 and FIBB can be used to differentiate between MB patients and healthy individuals. The biomarkers of non-CSC prognosis in MB include miR-137, *PBK* and *UBE2G1* [51–53]. Ji *et al.* [53] demonstrated that upregulated miR-137 inhibited cell proliferation, migration, invasion and cell cycle progression, and induced apoptosis by targeting KDM1A. Thus, it was concluded that miR-137 downregulation was significantly associated with poor prognosis of MB.

The non-CSC diagnostic biomarkers for intracranial MG are miR-497 and VIMENTIN [54,55]. Abdelrahman *et al.* [54] found that serum miR-497 is a valid and easily measured biomarker for the diagnosis and classification of MG in clinical studies. Kim *et al.* [55] showed that all primary cell lines derived from both benign and atypical MG express high levels of the MG biomarker VIMENTIN, which is strongly associated with malignancy. The DVL1 protein is a biomarkers of non-CSC treatment in intracranial meningioma. Bukovac *et al.* [56] showed that higher nuclear expression of DVL1 protein and higher expression of active β -linked protein significantly correlated with higher MG grade. Therefore, DVL1 protein can be used as a biomarker for MG development and Wnt signaling pathway activation. Moreover, biomarkers associated with the prognosis of non-CSC in intracranial MG include total DNA methylation and GSKIP protein [57,58]. Barciszewska *et al.* [57] concluded that since 5-methylcytosine levels in peripheral blood can reflect graded levels in tumor tissue, changes in 5-methylcytosine can be used as a biomarker of DNA damage and tumor malignancy in intracranial MG. Cheng *et al.* [58] found that high GSKIP protein expression was associated with poor prognosis of MG. Moreover, the GSKIP protein is bound to protein kinase A and glycogen synthase kinase 3 β to regulate different biological processes and malignant tumorigenesis through the Wnt pathway.

For diagnostic biomarkers of neurofibromas, a study identified the downregulation of miR-204 as a novel diagnostic biomarker and potential therapeutic target for patients with NF1 with MPNSTs.16 [59]. Biomarkers for non-CSC treatment in neurofibromas include PD-L1 [60]. Farschtschi *et al.* [60] found that PD-L1 is upregulated in MPNST patients in a study and could be a potential biomarker for malignant transformation in NF1 patients.

Overall, there is some overlap between CSC and non-CSC type biomarkers in the nervous system, but these biomarkers may play different roles in different pathways. Ki67, for instance, serves as a biomarker for non-stem cell therapy in intracranial MG and as a diagnostic biomarker for stem cells in MB [38,61]. De Carvalho *et al.* [61] found that Ki67 observed in recurrent tumors of MG was higher

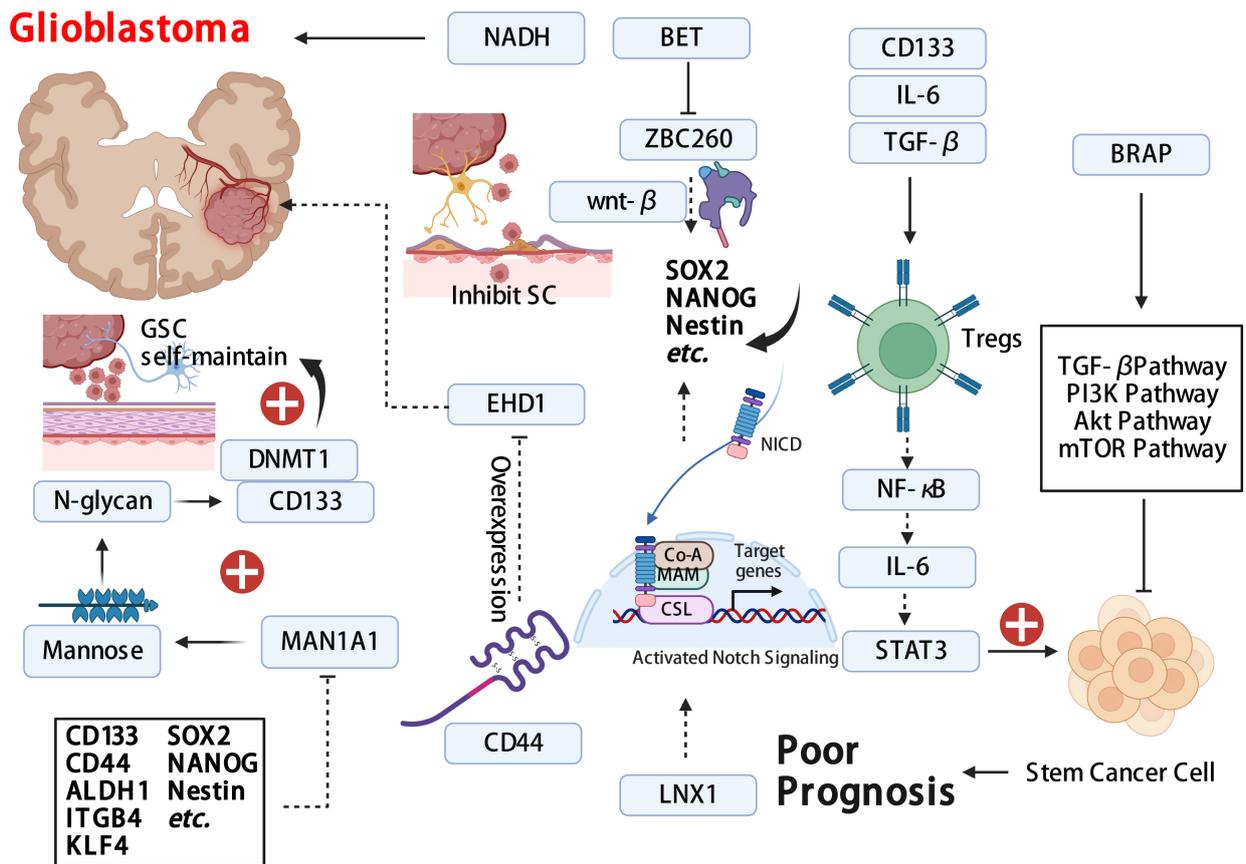


Fig. 2. Mechanisms of CSC biomarkers in glioma. GSC, glioma stem cell. Created with BioRender.com.

than in primary tumors and correlated with poor prognosis. Moreover, elevated Ki67 indicates larger recurrent tumors and more severe peritumor edema. These findings indicate that Ki67 plays multiple roles in diverse tumor types and holds potential as both a diagnostic indicator and a prognostic factor. However, HOXA5 is a prognostic biomarker for both glioma cells and GSCs, both of which are associated with poor patient survival and regulate the proliferation of GSCs [36,49].

Vimentin serves as a diagnostic biomarker for both CSCs and non-CSCs in intracranial MG [55,62]. In non-CSCs, strong expression of Vimentin is significantly associated with malignancy [55]. However, Vimentin is a CSC biomarker that regulates several signaling pathways, such as MAPK, PI3K/Akt, and Wnt/ β -catenin. This protein affects the proliferation, differentiation, and invasiveness of CSCs, contributing to the recurrence of rare and aggressive MG variants (Table 3, Ref. [43–45,47–60]).

5. Therapeutic Targets of CSCs

Because neurological tumors such as gliomas are resistant to conventional treatment and prone to recurrence, research to explore their precise molecular mechanisms and reliable therapeutic targets has received widespread attention [63]. Baisiwal demonstrated that overexpression of LNX1 activates the Notch1 signaling pathway and in-

creases the population of GSCs [20]. However, knocking down LNX1 modulates Notch1 activity, leading to downregulation of the Notch1. CSCs are significantly reduced after TMZ treatment, thereby improving patient survival. These results suggest that LNX1-regulated Notch1 signaling contributes to treatment resistance and is a possible therapeutic target. Moreover, Lu *et al.* [64] discovered that knockdown of EH Domain Containing 1 (EHD1) reduced CSC-like traits in glioma cells. EHD1 binding to CD44 enhances CD44 stability, whereas CD44 overexpression reduces the inhibitory effect of EHD1 knockdown on GSC-like traits. Thus, EHD1 is positively correlated with the expression of CSC biomarkers in glioma tissues and has the potential to be an effective target for glioma progression. Mazor *et al.* [65] showed that lncRNA TP73-AS1 is associated with the aggressiveness of glioblastoma, and its high expression is associated with poor patient prognosis. Meanwhile, TP73-AS1 downregulation resensitizes GBM cancer stem cells to TMZ treatment and may serve as a promising therapeutic target.

Eckerdt *et al.* [37,66] also found that signaling in the PI3K-AKT-mTOR axis was blocked by dual inhibition of PI3K α and mTOR. It also enhanced the inhibition of tumor growth in MB *in vivo*, contributing to the development of more effective therapeutic strategies. Wang *et al.* [67] showed that miR-222-3p is also a therapeutic target.

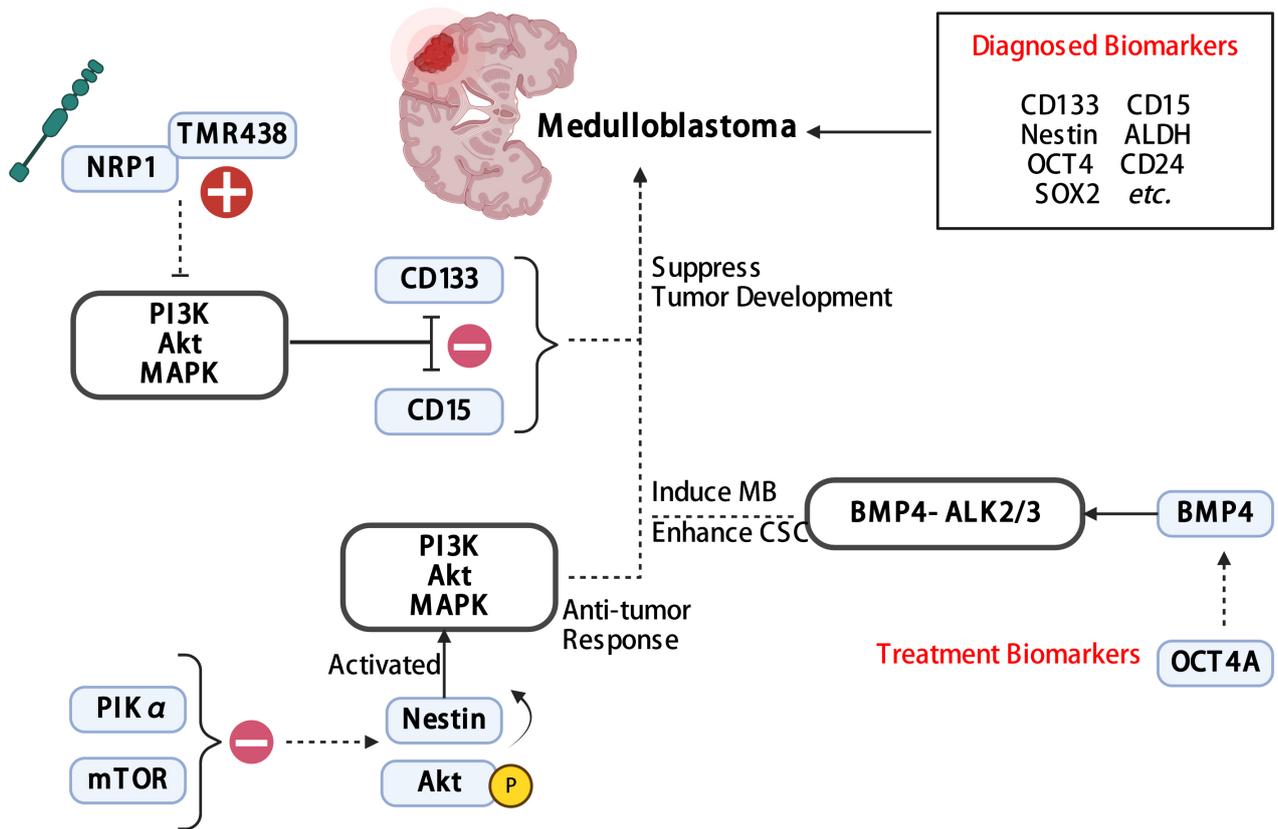


Fig. 3. Mechanisms of CSC biomarkers in medulloblastoma. Created with BioRender.com.

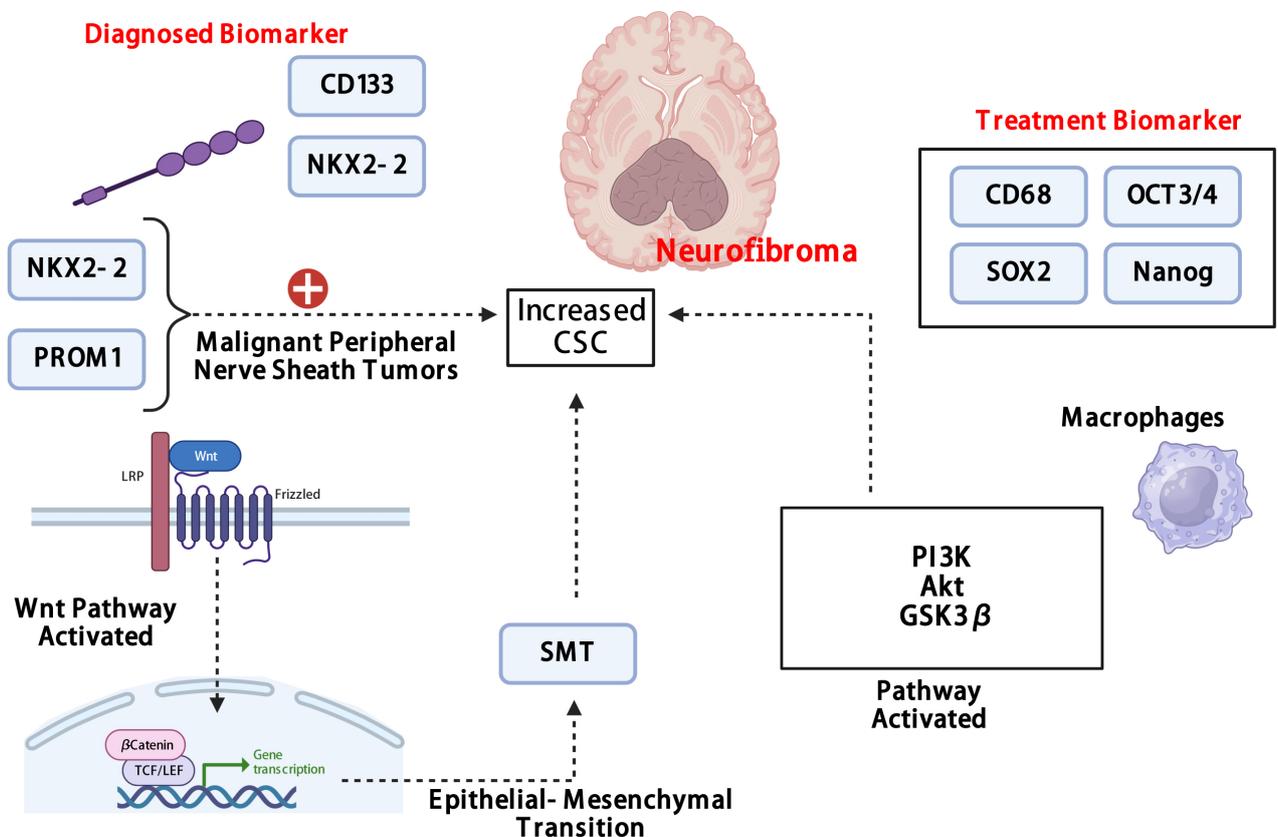


Fig. 4. Mechanisms of CSC biomarkers in neurofibroma. SMT, Schwann-mesenchymal transition. Created with BioRender.com.

It not only inhibits cell viability, but also suppresses MB stem cell-like cell formation via the Notch2/c-myc pathway. Filipponi *et al.* [68] discovered that OCT4 induces the BMP4 signaling pathway, which promotes both stem cell pluripotency and MB tumorigenesis. Conversely, inhibiting BMP4-ALK2/3 signaling reduces tumor-initiating cell (TIC) ability and CSC biomarker expression, suggesting potential implications for MB treatment.

Additionally, published research suggests that taking antipsychotic medication may reduce the risk of cancer development in patients. Many antipsychotic drugs can also treat tumors in the nervous system and inhibit tumor growth [14]. *SOX2-OT*, an evolutionarily conserved long non-coding RNA, contains *SOX2* in its intronic region, which can regulate *SOX2* expression [69]. *SOX2-OT* have been linked to several health conditions, including psychiatric disorders, cancer and diabetes complications. *SOX2* is a proven biomarker for CSCs in many nervous system tumors. Therefore, CSCs of the nervous system are associated with the occurrence of mental illness. Penflutidol is an FDA-approved antipsychotic drug specifically for schizophrenia that has potential anticancer effects against glioblastoma. Ranjan *et al.* [70] discovered that penflutidol inhibits the activation of Akt by blocking its phosphorylation at Ser473, thereby reducing Akt-mediated GLI1 expression. Furthermore, it directly regulates CSC biomarkers such as OCT4, Nanog and Sox2, decreasing CSC characteristics and inhibiting tumor growth. Dong *et al.* [71] found that the traditional antipsychotic drug fluspirilene can be utilized as a targeted treatment for GSCs. It works by inhibiting the STAT3-related signaling pathway, thereby reducing the proliferation of GSCs and their stemness, ultimately treating GBM. In addition, Cheng *et al.* [72] screened the antipsychotic drug thioridazine by public gene expression data. It was shown to have potent anti-GBM and anti-GSCs properties, inhibiting GBM tumorigenesis and inducing autophagy *in vivo*. And pimozide, which is used clinically for the treatment of schizophrenia, inhibits USP1 in GBM cells, resulting in decreased levels of ID1, Sox2, as well as inhibiting stem cell maintenance [73].

Apart from their medical applications, antipsychotic drugs have demonstrated additional pharmacological properties. They can regulate cell signaling pathways and participate in various intracellular functions, ultimately weakening the characteristics of CSCs and inhibiting cancer cell proliferation [74].

6. Detection of Neurological CSCs

The proportion of CSCs in tumor tissue is very low, typically only 0.01–2% of the total tumor mass. CSCs and normal stem cells also share similar biomarkers and signaling pathways [75]. Therefore, it is important to identify and detect CSCs in the nervous system. Many recent studies have focused on the pathological characteristics and detection methods of neurological CSCs.

CSCs can be identified by specific surface markers. For example, CD133 can be used to identify stem cells in normal and cancerous tissues and has been widely used as a marker to identify CSCs [76]. The assessment of the expression rate of relevant genes and protein markers in CSC reflects their density in the patient's tumor tissue [77]. However, as with non-CSC, most identification of molecular biomarkers for CSC is based on antibody recognition of specific proteins. Cell surface markers are usually detected using immunohistochemistry, western blot (WB), and flow cytometry (FCM) methods. For immunohistochemistry staining and WB, the avidin-biotin-peroxidase complex method can be used, where the expression level of biomarkers is assessed by the percentage of positively stained cells and the intensity of staining [34,78]. FCM involves incubating cells with a fluorescent dye. The expression of biomarkers can also be determined using a cell sorter by further incubation with labeled secondary antibodies [79].

Second, Hematoxylin and eosin is the most essential pathological staining technique when examining tissues and cells under the microscope. Sometimes, abdominal tumors are embedded in paraffin and then sectioned for Hematoxylin and eosin staining [37]. Moreover, microstructural characterization was performed with a high-resolution scanning electron microscope [80].

Detection tools for CSCs include fluorescence-activated cell sorter (FACS), magnetic-activated cell sorter (MACS), sphere formation assays, and techniques such as immunohistochemistry, FCM and WB for cell surface markers. For CSC characterization, FACS and MACS provide data for identifying individual CSCs in cell populations [81,82]. FACS selection is a strategy for isolating CSCs based on specific markers expressed by CSCs using flow cytometry. By labeling cells with fluorescent or magnetic bead-coupled antibodies, the CSC population can be separated from tumor cells by FACS or MACS. In practice, FACS selection is purer, more accurate and superior to MACS [83].

Alternatively, the colony-forming ability of CSCs was used for isolation and identification [75]. Sphere formation assays is an *in vitro* method that is commonly used to identify CSCs and study their properties [82]. *In vitro* formation of floating clone (from one cell) colonies, called different “glioma spheres” or errant “neurospheres”, is commonly used as an indicator of potential stem cells. These colonies themselves can generate new colonies and can give rise to a variety of cell types within the tumor [84].

7. Discussions

This review has established the credibility and repeatability of the research through strict literature screening standards in the early stage. However, most of the literature is one-sided in describing biomarkers of a single tumor and is not well-informed in terms of diagnosis, treatment and

prognosis. In contrast, this study comprehensively summarizes the sets of multiple CSC biomarkers, including neurological tumors such as glioma, MB, MG and neurofibroma, as a more accurate and reliable method to monitor the effects. The commonalities and differences in their functional pathways were also analyzed, providing a broader perspective. The bibliometric analysis we completed also remedied the shortcomings of other articles by obtaining more comprehensive information about CSC biomarkers in the nervous system. In addition, since most tumor recurrence and metastasis are caused by the promotion of CSCs, research addresses CSCs from the root cause to provide guidance for clinical application of CSC biomarkers in oncology.

However, CSCs with self-renewal and pluripotency capabilities are plastic and their plasticity is affected by the microenvironment [85,86]. Recent studies have revealed that infiltrating macrophages can regulate the PI3K/AKT/GSK3 β signaling pathway to induce stem cell-like characteristics and promote the growth of neurofibroma [42], so the tumor microenvironment plays an important role in regulating cell stemness. In addition, due to the heterogeneity of CSCs and the different specific signaling pathways they activate, a single CSC biomarker is incompetent to discriminate between CSC and non-CSC. The blockage of a single CSC-associated pathway may not effectively block the occurrence of cancers [85].

To date, the impact of CSC on mental illness in the nervous system has not been confirmed. Previous studies have reported that antipsychotic drugs might be able to treat CSC through pathways such as STAT3 and Akt, inhibiting the proliferation and spread of cancer cells [70,71]. However, the effects of these drugs on different types of tumors and CSCs may vary. Meanwhile, current research is relatively limited and not only does not directly point out that neurological CSC accelerates the degree of tumor progression but also does not provide a specific assessment of the change in the degree of progression. Therefore, further research on this issue is also necessary to address these concerns.

8. Conclusions

This review provides a comprehensive summary of CSC biomarkers for neurological tumors such as glioma, meningioma, medulloblastoma and neurofibroma. In glioma, the CSC diagnostic biomarkers include NADH. And biomarkers of CSC treatment are CD133, ALDH1, KLF4, SOX2, NANOG, MYC, ABCG2, Nestin and Msi-1. The expression levels of CD133, IL6, TGF- β , BRAP, HOXB5 and GAS5 are prognostic biomarkers in glioma patients. Also, the CSC diagnostic biomarkers of MB include CD133, Nestin, SOX2, CD24 and CD15. Biomarkers for the treatment of CSC include CD133, CD15, OCT4, NANOG, *Sox2*, *Klf4*, *Nestin* and *Bmi1*. Biomarkers for the diagnosis of intracranial MG CSC include KLF4, MYC, CD133, SOX2, OCT4, NANOG, NESTIN and VI-

MENTIN. And the biomarker of prognosis for intracranial MG CSC is SOX2. In neurofibroma, the CSC diagnostic biomarkers include *PROM1* and *NKX2-2*. The biomarkers of neurofibroma CSC treatment are CD68, OCT3/4, NANOG and SOX2. In addition, many antipsychotic drugs can also treat tumors in the nervous system and inhibit tumor growth. Therefore, this study hopes to provide guidance for future in-depth exploration and monitoring of tumors for clinical applications.

Abbreviations

CSC, cancer stem cell; EMT, epithelial-mesenchymal transition; GSC, glioma stem cell; GBM, glioblastoma multiform; MB, medulloblastoma; MG, meningioma; NF1, neurofibromatosis type 1; NF2, neurofibromatosis type 2; ALDH1, dehydrogenase 1; PI3K, phosphatidylinositol 3 kinase; MPNSTs, nerve sheath tumors; FACS, fluorescence-activated cell sorter; MACS, magnetic-activated cell sorter; FCM, flow cytometry; WB, western blot; EHD1, EH Domain Containing 1.

Author Contributions

HX, JF and XL conceived and designed the work. XL, JH, YK, XC, QY and LZ collected and summarized the literature. XL, YK, HX and JF interpreted the content of the review, generated tables and figures and wrote the original manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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