

The two-sided battlefield of tumour-associated macrophages in glioblastoma: unravelling their therapeutic potential

Jingwen Xiong¹ · Xuancheng Zhou² · Lanqian Su² · Lai Jiang² · Ziwei Ming¹ · Can Pang³ · Claire Fuller⁴ · Ke Xu⁵ · Hao Chi² · Xiaomei Zheng⁶

Received: 9 August 2024 / Accepted: 15 October 2024

Published online: 25 October 2024

© The Author(s) 2024 **OPEN**

Abstract

Gliomas are the most common primary malignant tumours of the central nervous system (CNS), which are highly aggressive, with increasing morbidity and mortality rates year after year, posing a serious threat to the quality and expected survival time of patients. The treatment of gliomas is a major challenge in the field of neuro-oncology, especially high-grade gliomas such as glioblastomas (GBMs). Despite considerable progress in recent years in the study of the molecular and cellular mechanisms of GBMs, their prognosis remains bleak. Tumour-associated macrophages (TAMs) account for up to 50% of GBMs, and they are a highly heterogeneous cell population whose role cannot be ignored. Here, we focus on reviewing the contribution of classically activated M1-phenotype TAMs and alternatively activated M2-phenotype TAMs to GBMs, and exploring the research progress in reprogramming M1 TAMs into M2 TAMs.

Keywords GBM · TAM · Reprogramming · Immunotherapy · Phenotypic transition · TME

1 Introduction

The increasing prevalence of brain and other neurological cancers is a serious threat to human life and health [1]. Notably, GBMs, which constitute up to 33% of such cases, are the most aggressive and deadly [2, 3]. Their 5-year survival rate stands at a mere 4–7% [4]. GBMs are challenging because they are highly heterogeneous. GBM is categorized into three subtypes based on gene expression: preneural, mesenchymal, and classical, each subtype exhibits distinct heterogeneity in the tumor microenvironment (TME) [5]. While immunotherapy has shown effective anti-tumor outcomes in various cancers, its benefits in GBMs have been limited, largely because of the tumor's immunosuppressive microenvironment, partly due to the presence of a tumour immunosuppressive microenvironment [6]. The TME has a multifaceted composition, encompassing astrocytes, oligodendrocytes, fibroblasts, and microglia, as well as both adaptive and innate immune

Jingwen Xiong and Xuancheng Zhou have contributed equally to this work.

✉ Ke Xu, cqghxuke@cqu.edu.cn; ✉ Hao Chi, chihao7511@163.com; ✉ Xiaomei Zheng, zxmlst@163.com; Jingwen Xiong, xiongjingwen13@163.com; Xuancheng Zhou, zhouxuancheng04@163.com; Lanqian Su, qianlansu23@gmail.com; Lai Jiang, jianglai3232@163.com; Ziwei Ming, mingziwei1219@163.com; Can Pang, pangc21@lzu.edu.cn; Claire Fuller, Claire.fuller9@gmail.com | ¹Department of Sports Rehabilitation, Affiliated Hospital of Southwest Medical University, Luzhou 646000, China. ²Clinical Medical College, Affiliated Hospital of Southwest Medical University, Luzhou 646000, China. ³School of Public Health, Lanzhou University, Lanzhou 730000, China. ⁴Whiting School of Engineering, Johns Hopkins University, Baltimore, MD 21224, USA. ⁵Department of Oncology, Chongqing General Hospital, Chongqing University, Chongqing 401147, China. ⁶Department of Neurology, Affiliated Hospital of Southwest Medical University, Luzhou 646000, China.



cells [7]. Additionally, non-protein entities like diverse proteins, polysaccharides, and hormones are integral components of the TME [8]. TAMs in gliomas consist of microglia derived from yolk sac progenitor cells and bone marrow-derived macrophages/monocytes (BMDMs) [9, 10], which are the major members of the TME leading to immunosuppression, accounting for 30% of all cell types [11]. Under typical physiological circumstances, TAMs play roles in organogenesis, tissue equilibrium, and organism defense [12]. Within the brain, TAMs are responsible for synaptic pruning, phagocytizing apoptotic cells, modulating neuronal plasticity, and overseeing immunosurveillance [13–15]. Most studies have concluded that the number of TAMs correlates with tumour growth, low survival, poor patient prognosis and high recurrence rates [16–18]. However, TAMs are highly heterogeneous cell populations with not only pro-inflammatory M1 and anti-inflammatory M2 phenotypes, but also a wide range of other phenotypes [19–21]. Conventionally, the pro-inflammatory M1 phenotype is pivotal in causing tissue damage, while the anti-inflammatory M2 phenotype aids in tissue repair [22, 23]. In GBMs, M1 TAMs have been shown to be effective in eliminating cancer cells [24] and the M2 phenotype is usually associated with poor patient prognosis [17]. These phenotypic roles are transformed into each other due to changes in environmental factors, which results in their extreme instability during the development of GBMs. Therefore, it is an essential task to explore the factors and mechanisms of phenotypic transformation in TAMs.

2 Origin, localisation and phenotypic characterisation of TAMs

In the past, microglia were thought to be derived from bone marrow cells of the haematopoietic system [25]. However, recent studies have found that microglia are actually the progeny of CD45⁺ c-kit⁺ stem cells with erythroid and myeloid potential within the embryonic yolk sac [26], which together with the BMDM, constitute TAMs. Microglia and BMDMs are macrophage populations with distinct ontogenetic origins, with microglia originating from the embryonic yolk sac and BMDMs deriving from the bone marrow [27]. BMDM originates from hematopoietic progenitor cells, whereas microglia, post-birth, are not replenished by hematopoietic cells [9]. Microglia are dispersed throughout the tumor region in GBMs, while BMDMs are predominantly situated near vascular structures surrounding metastatic tumors in the brain, as well as within GBMs [28]. Notably, BMDMs constitute a greater fraction within the tumor's core, whereas microglia predominantly occupy the periphery of the tumor nucleus [10]. Currently, distinguishing microglia from BMDMs in excised GBM samples remains challenging due to their substantially overlapping labeling profiles [29]. However, this issue is somewhat mitigated by their distinct ontogeny and functional roles. Certain substances [30, 31] remain capable of effectively distinguishing between these two macrophage populations. These markers are undoubtedly useful in facilitating the exploration of their function in GBMs. Pathologically, TAMs assume a pro-inflammatory phenotype, releasing inflammatory cytokines to elicit a cytotoxic response. Initially serving a tumor-surveillance function, they are subsequently superseded by anti-inflammatory cells, which facilitate tissue repair, remodeling, and angiogenesis [32]. In GBMs, M1-type TAMs secrete IL-1, IL-6, IL-12, IL-23, TNF- α , and reactive oxygen species (ROS), triggering a pro-inflammatory response characterized by increased acute phase proteins, enhanced leukocyte migration to the site of infection, and enhanced antigen presentation and cytotoxicity [33]. In addition, they also release ROS, which damage cell membranes and DNA through oxidation, enhance the release of inflammatory factors, and regulate inflammatory responses [34]. Conversely, M2 TAMs manifest anti-inflammatory traits alongside pro-tumor proliferation and metastatic attributes. These cells release IL-4, IL-5, and VEGF, reduce MHCII expression [35], promote the polarization of macrophages towards M2 type and inhibit the production of pro-inflammatory cytokines. They also elevate levels of IL-10, M-CSF, CXCL14, CCL22, and CCL17 [36, 37]. M-CSF promotes macrophage proliferation and survival, CXCL14 regulates immune cell migration, and CCL22 and CCL17 inhibit inflammation by attracting regulatory T cells (Tregs). In addition, Luo et al. showed that cytokines secreted by cancer stem cells can also promote the polarization of macrophages towards M2 type [38]. This suite of factors contributes to immunosuppression and stimulates the release of transforming growth factor beta (TGF- β) [39].

3 Regulatory pathways of TAMs isoforms in the tumour microenvironment

The TME and cancer evolution within GBMs maintain a reciprocal relationship. TAMs modulate cancer proliferation, migration, angiogenesis, and immunosurveillance, orchestrating the TME to facilitate GBM progression [40, 41]. Conversely, cancer cells influence the composition and functionality of the TME via diverse signaling pathways [42–44]. Indeed, TAM infiltration in interstitial GBMs is attributed to notable mutations or deletions in PTEN, NF1, and EGFR genes [45–47]. Mutation or deletion of PTEN leads to overactivation of the PI3K/Akt signaling pathway, which promotes cancer cell

proliferation and thus suppresses immune cell function [48]. NF1 defects in tumor cells increase the infiltration of tumor-associated macrophages and microglia, thereby exacerbating the immunosuppression of the tumor microenvironment [46]. EGFR mutations activate KRAS, and active KRAS leads to increased CCL2 expression levels [49]. Following infiltration of TAMs, multiple signalling pathways within the TME are able to regulate polarisation between TAMs subtypes, resulting in a complex microenvironment centred on TAMs. TAMs are classified into M1 and M2 phenotypes, which is an extremely simplified classification. Both microglia and macrophages adhere to a common schema: the M1 phenotype represents classical activation, while the M2 phenotype is indicative of alternative activation [50, 51]. The M1 pro-inflammatory phenotype is activated by agents like lipopolysaccharide (LPS), IFN- γ , and TNF α . In contrast, the M2 anti-inflammatory phenotype is stimulated by interleukins, notably IL-4, IL-10, and IL-13 [47, 52]. M1-associated macrophages express markers such as CD40, CD74, MHC-II, and phosphorylated STAT1, while M2-aligned cells exhibit markers including CD163, CD204, arginase-1 (ARG1), and phosphorylated STAT3 [53].

The M2 phenotype has been subdivided into M2a, M2b, and M2c types based on their functions and properties. The M2a subtype is stimulated by IL-4 and IL-13 [54], while the M2b subtype responds to agonists of immune complexes, toll-like receptors (TLRs) [55], and IL-1R ligands. In contrast, TAMs exposed to TGF β , glucocorticosteroids and IL-10 manifest the M2c isoform [56]. In the complex TME of GBM, chromatin modification is influenced by the activity of metabolic enzymes, metabolites, and cofactors. Epigenetics and metabolic reprogramming play key roles in macrophage polarization, and metabolic reprogramming further influences the functional status of macrophages by regulating glycolysis, oxidative phosphorylation, and fatty acid oxidation [57]. In addition to the classical immunosuppressive and proangiogenic effects through cytokine production, TAMs produce other abundant activities in the TME.

3.1 Tumour-promoting functions of TAMs

3.1.1 Immunosuppression

Studies have shown that CD68 and CD163 positive M2 macrophages inhibit the anti-tumour function of T cells (Fig. 1), aid immune escape and reduce patient survival [58]. Liu and colleagues employed single-cell RNA sequencing (scRNA-seq) to uncover novel microglial subtypes displaying pro-inflammatory and proliferative characteristics. Among these, they identified CD163HMOX1 microglia, which promote T-cell depletion by secreting IL-10 while simultaneously sustaining their pro-inflammatory properties via TGF- β [59]. In the presence of IL-10, CD4 T cells are more susceptible to modulation than CD8 T cells, potentially owing to the activation of signaling pathways downstream of the STAT3-BLIMP-1 axis [60]. The presence of CD163 HMOX1 microglia and macrophages has exclusively been observed in mesenchymal GBMs [59, 61]. TAMs have the capability to prompt glioma stem cells into adopting a mesenchymal phenotype, consequently fostering an immunosuppressive microenvironment [61]. Nevertheless, it remains imperative to gather substantial evidence to establish whether the recently identified CD163HMOX1 microglia population also harbors this potential. In vitro experiments have convincingly shown that TGF- β exerts a substantial inhibitory effect on microglial proliferation and activation, impacting their cytokine production [62]. Subsequent investigations have also elucidated the role of TGF- β in regulating the differentiation and proliferation of T cells and macrophages [63]. This area of study is particularly captivating due to the dual autocrine and paracrine production of TGF- β within these cell types. TGF- β facilitates tumor progression by upregulating VEGF expression and inducing immunosuppressive effects [64, 65]. Nevertheless, there remains a scarcity of comprehensive experiments to establish the self-inhibitory actions of TGF- β produced by TAMs and its effects on tumors. Nonetheless, the prevailing consensus in the majority of studies suggests that TGF- β exhibits pro-tumorigenic properties, implying that its inhibitory impact on TAMs themselves may be less pronounced compared to its tumor-promoting effects.

The aggregation of macrophages led to the suppression of patients' helper T-cell type 1 (Th1) lymphocytes [66]. This suppression can be attributed to the increased levels of TGF- β [39]. TAMs undergo activation toward the M2 phenotype when stimulated by IL-4 and/or IL-13, and this activation is associated with the promotion of Th2 cell production [20]. Furthermore, the M2 phenotype attracts regulatory T cells (Tregs) by expressing chemokines such as CCL2 [39, 67]. Human primary TAMs exert suppression of T-cell immune function by disrupting the antigen-presentation process through downregulation of essential molecules like CD40, CD80, and CD86 [68]. However, when the colony-stimulating factor-1 receptor (CSF-1R) is inhibited and CD40 is upregulated, TAMs can undergo reprogramming [69], resulting in their capacity to initiate a protective T-cell response [70].

Remarkably, in vitro experiments revealed that BMDMs phagocytose glioma cells, resulting in the formation of double-positive TAMs, resembling the properties of TAMs found within the GBM tumor microenvironment [71]. These TAMs

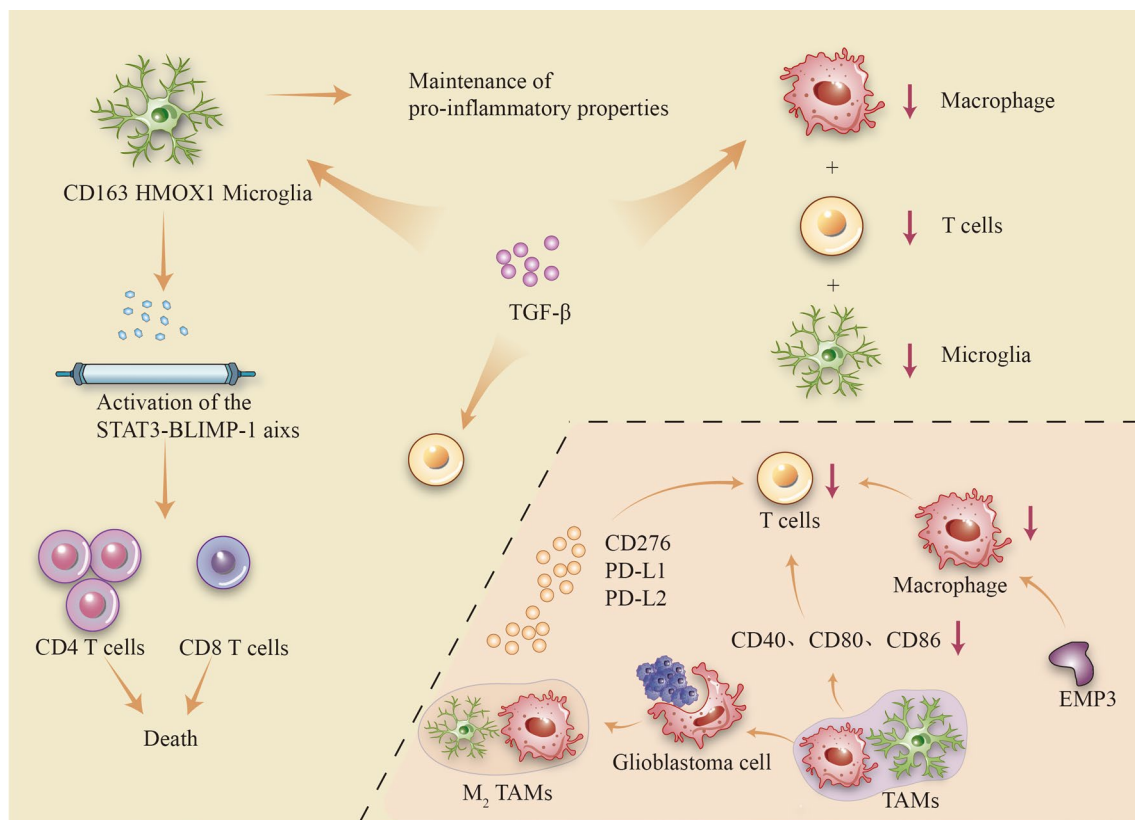


Fig. 1 CD163HMOX1 microglia in mesenchymal GBMs promote T-cell depletion through IL-10 and maintain inflammation via TGF- β , which also inhibits microglial proliferation. TGF- β supports tumor progression and immunosuppression. TAMs with M2 characteristics, including CD276, PD-L1, and PD-L2, suppress T cell expansion and response in the GBM microenvironment

exhibit M2 phenotypic characteristics and exert inhibitory effects on T cell expansion by expressing CD276, PD-L1, and PD-L2 [71]. Additionally, the expression of epithelial membrane protein 3 (EMP3), which promotes M2 TAMs polarization, negatively regulates T cell responses in GBMs by impairing the ability of macrophages to secrete CXCL9 and CXCL10 [72].

3.1.2 Involvement in tumour microenvironment remodelling

Complex signalling exists between TAMs and tumours in different regions of the TME [73]. An important function of TAMs is their ability to interact with GSCs, which together remodel the TME and create favourable conditions for tumour cell growth and metastasis (Fig. 2). Recent studies have found that GSCs can differentiate into endothelial cells [74] and then safely multiply in the perivascular niche (PVN) to form a glioma stem cell bank [75, 76]. Such GSCs are very hardy, attributed to their reduced proliferation rate and heightened ability to respond to DNA damage. Consequently, they display limited sensitivity to treatment-induced DNA damage, enabling them to evade treatment-related cell death and mitigate mitotic abnormalities [77]. M204-like TAMs marked by CD2+ macrophages was mainly distributed near blood vessels and necrotic areas, this observation suggests that these specific areas may engage in pre-tumor interactions with glioma stem cells [78].

In the experimental samples, there was co-localization observed between TAMs and CD133-positive glioma stem cell-like cells (GSLCs) within the marginal zone of GBMs [79] (Fig. 3). These TAMs exhibited elevated levels of TGF- β 1, leading to the upregulation of matrix metalloproteinase-9 (MMP-9) expression in GSLCs and consequently enhancing the aggressiveness of these GSLCs [79].

Moreover, recent research has uncovered that the activation of STAT145 in GBM cells, triggered by TGF- β released by M2 TAMs, facilitates persistent growth and self-renewal of GSCs. This pathway is regarded as the primary mechanism driving tumor expansion [39]. MMP is thought to be associated with the promotion of proliferation and migration of GBMs [64] and correlates with the M2 phenotype. Down-regulation of MMP-14 significantly improves the survival rate

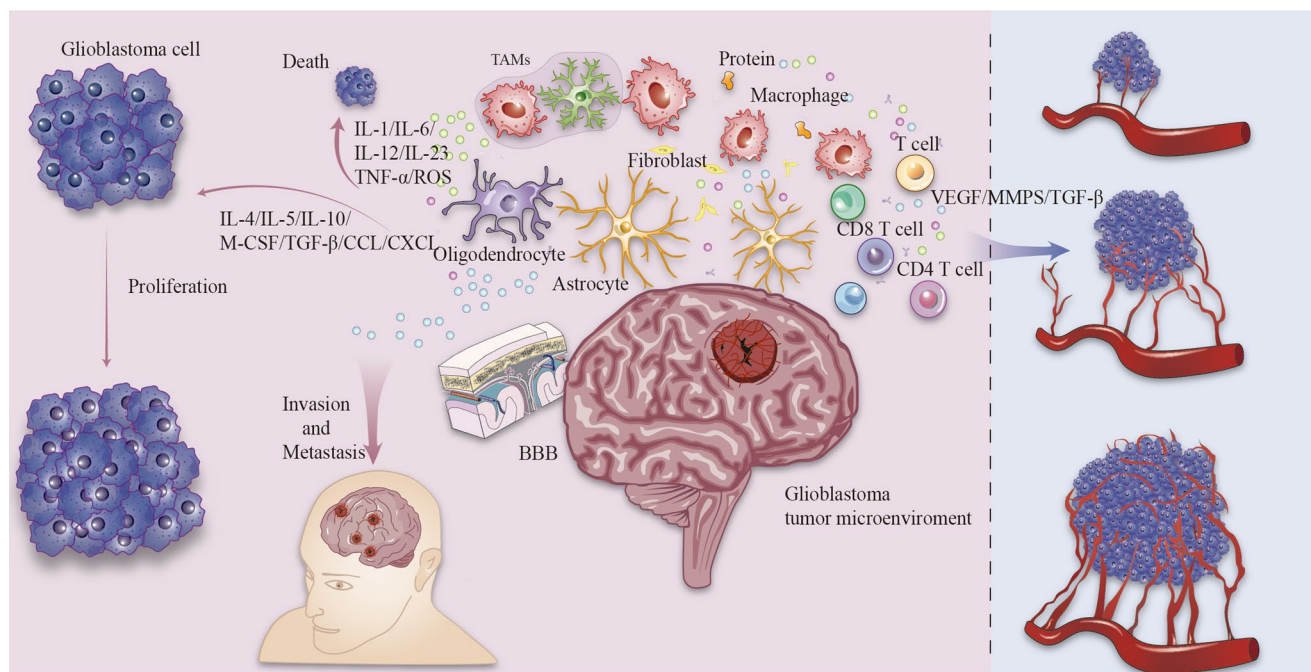
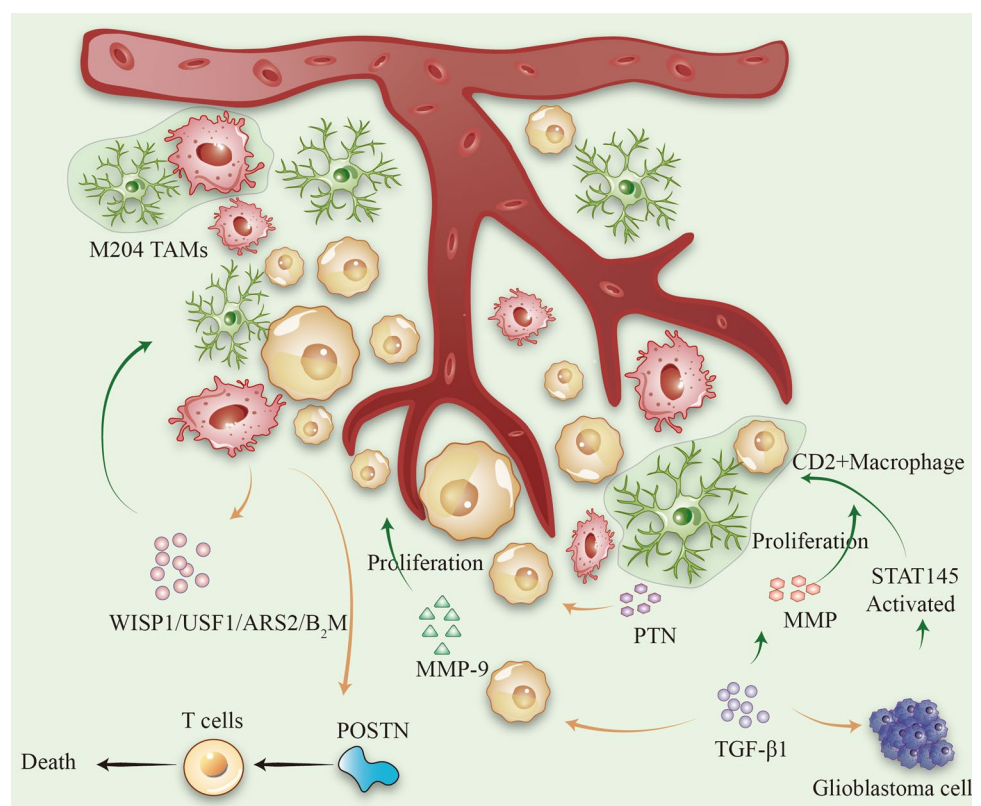


Fig. 2 This figure illustrates the key features of TAMs in the tumor microenvironment and their dynamic interactions. The figure first shows the components of the glioblastoma tumor microenvironment, in which tumor cells are constantly dividing and expanding, accompanied by the formation of neovascularization around the tumor. In addition, the figure highlights the role of TAMs in the tumor microenvironment, including their regulatory mechanisms in tumor development and their classical immunosuppressive role

Fig. 3 In the GBM marginal zone, elevated TGF- β 1 in TAMs upregulates MMP-9, enhancing tumor aggressiveness. TGF- β activation of STAT145 promotes tumor growth, while M2 TAMs sustain their phenotype and support tumor cells through the CXCR2-JAK2/STAT3 axis and Wnt signaling. POSTN recruitment of M2 TAMs contributes to an immunosuppressive environment



of GBM experimental mice [80]. Theoretically, inhibition of MMP-9 may have the same effect, which may be a promising therapeutic target.

Another important pathway is the maintenance of GSCs through Wnt signalling induction. GSCs initially release and express Wnt-induced signaling protein 1 (WISP1). Subsequently, WISP1 utilizes the $\alpha 6 \beta 1$ -Akt integrin pathway in an autocrine manner to enhance GSC stability. Additionally, it employs a paracrine mechanism to support M2 TAMs [81]. TAMs secrete pro-polypeptides (PTNs) that activate GSCs via PTPRZ1 receivers, thereby accelerating pathological growth of GBM [81]. Nonetheless, a significant hurdle in targeting Wnt signaling within glioblastomas lies in the internal and external heterogeneity of these tumors, particularly the presence of GSCs. These cells are resistant to therapy and could potentially be accountable for tumor recurrence [52]. M2 TAMs additionally sustain their phenotype via a paracrine mechanism involving the CXCR2-JAK2/STAT3 axis. This axis is activated by CXCL8, which also contributes to the maintenance of mesenchymal GSCs [82]. Other predisposing factors involved in the maintenance of GSCs and/or M2 TAMs through the paracrine pathway include $\beta 2$ -microglobulin (B2M) [83], upstream stimulatory factor 1 (USF1) [84], and arsenite resistance protein 2 (ARS2) [85]. In addition, periosteal protein (POSTN) secreted by GSCs efficiently recruited M2 TAMs [86] and GSCs induced T cell death and recruited Treg, which was largely associated with the recruitment of M2 TAMs.

3.2 Anti-tumour function of TAMs

TAMs are usually considered to be pro-tumourigenic because most cytokine production is associated with the M2 phenotype. Unfortunately, a minority of TAMs exist in the form of the M1 phenotype. Typical activation of anti-tumour M1 TAMs is activated by toll-like receptors (TLRs), which are partially activated by microorganisms [87]. The M1 phenotype of microglia becomes activated and can either engage in direct phagocytosis or eliminate microorganisms by releasing ROS or NO. Additionally, they secrete inflammatory cytokines such as tumor necrosis factor α (TNF- α), IL-6, IL-10, and IL-12 [88]. Glycogen synthase kinase-3 β (GSK-3 β) is able to modulate the inflammatory response in microglia [89]. The inhibition of GBM by GSK-3 β was found to correlate with the inhibition of molecular axes related to adhesion kinase, guanine nucleotide exchange factor/Rac1 and c-Jun N-terminal kinase [90]. GSK-3 β is involved in the Wnt/STOP signalling pathway, but its activation of microglia has not been characterised [52]. However, it is not clear whether these responses are triggered by activation of the M1 phenotype, but this study demonstrates the potential of GSK-3 β as a therapeutic target. Remarkably, macrophages are also involved in active immune responses. CD169 macrophages from human and mouse GBM recruit T cells and NK cells and promote specific T cell responses [91]. This is in contrast to classical T cell suppression [91].

4 Treatment of GBM: reprogramming of TAMs

There are many therapeutic options for targeting GBMs. In general, surgery is often difficult to completely remove the tumour mass, and conventional radiotherapy leads to normal tissue involvement [92]. In addition, most therapies targeting GBMs have failed [93]. One strategy has been to reprogram TAMs from a tumour-promoting M2 phenotype to an M1 phenotype, as M1 TAMs and M2 TAMs are very active in the TME. In addition to TLRs, cytokines and chemokines such as interferon gamma (IFN- γ), LPS and TNF- α can increase M1 phenotypic polarisation [94], which have been mentioned many times in previous reports and will no longer be the focus of our discussion, and in addition we have collated the latest advances in reprogramming TAMs (Table 1).

Classical STAT-3 activation is generally associated with M2 phenotypic polarization, while STAT-1 activation promotes M1 phenotypic polarization. More in-depth exploration of how these pathways interact and regulate TAM phenotypes is crucial for understanding their role in GBMs. One possible approach is to inhibit STAT-3 activation, downregulate M2 TAMs and/or increase M1 phenotypic polarisation. Zhang et al. showed that the use of the STAT-3 inhibitors CPA-3 and STAT261 siRNA induced reprogramming of TAMs and elimination of GBM cells in in vitro medium [103].

Moreover, a novel small-molecule STAT-3 inhibitor, WP1066, has been shown to elevate the expression of immune co-stimulatory molecules, including CD86, CD80, and CD40, which are essential for T-cell activation [97]. This outcome may be linked to the down-regulation of M2 TAMs. However, it's worth noting that another activator of M1 TAMs, granulocyte macrophage colony-stimulating factor (GM-CSF), can activate the PI3K-AKT pathway by means of STAT5 [104]. Regarding STAT-1, there is currently insufficient experimental data to confirm the stability and effectiveness of its activation of the M1 phenotype.

Table 1 Reprogramming of TAMs in glioblastomas

From the M1 phenotype to the M2 phenotype					
Evaluate	Experimental body	Key substance	Pathway/axis of action	Results	Ref.
In vivo	6–8 weeks old thymus-free mouse	B2M	PI3K/AKT and PI1K/AKT/mTOR	GSCs renewal and tumour growth	[83]
In vivo	4-week-old NU/NU nude mice	TGFBI	Integrin $\alpha\beta 5$ -Src-Stat3	Promotes maintenance of GSCs and growth of glioblastomas	[95]
In vivo	5-week-old female C57BL/6 mice	ARS2	ARS2-MAGL	Stimulation of β -catenin activation in GSCs	[85]
In vivo	C57BL/6N mice	FTL	Inhibition of iPLA expression	Promoting iron death and glioblastomas angiogenesis	[96]
In vivo	Orthotopic xenograft-bearing mice	CXCL8	PI3K/AKT, NF- κ B and CXCR2-JAK2/STAT3	Maintains GSCs proliferation, survival and self-renewal	[82]
From the M2 phenotype to the M1 phenotype					
Evaluate	Experimental body	therapeutic agents	Pathway/axis of action	Results	Ref.
In vivo	Nude mice	WP1066	Enhanced phosphorylation of Syk (Tyr352) in monocytes and ZAP-70 (Tyr319) in T cells	Effector T-cell proliferation	[97]
In vitro	–	Hu5F9-G4	CD47-SIRPa	Tumour growth inhibition of ATRT and PNET xenografts	[98]
In vivo	2–6 months Adult C57BL/6 male mice	CCP	P-STAT1 and IL12/iNOS/NO	Activation of NK cells and elimination of cysteinyl asparaginase 3 activation in CD133(+) GBM stem cells and GBM cells	[99]
In vivo	2–4 months old Adult C57BL/6 male mice	TriCurin (TrLp) liposomal formulation	C/NF- κ B/p300-HAT/p53/Cystathionase 3	Recruitment of NK cells, inhibition of GBM stem cells and triggering of GBM apoptosis	[100]
In vivo	6–8 weeks old female ICR mice	CHA	Promotes LPS, IFN and STAT1 activation and inhibits IL-2 and STAT6 activation	Inhibition of glioblastomas growth	[101]
In vivo	Nude mice	DT-GM1/DOX	PTN-PTPRZ1 signal axis	DT-GM1 micelle can cross BBB and targeting GBM microenvironment and exhibit effective therapeutic efficacy	[102]

CD47 has been identified on tumour cells as the “don’t eat me” signal [105]. At the tumour cell membrane, CD47 binding to SIRP α inhibits immunophagocytosis [106, 107]. Disrupting the CD47-SIRP α axis boosts the M1 phenotype, enhancing macrophage-mediated phagocytosis of glioma cells and GSCs [108, 109]. CD47 inhibitors, including Hu5F9-G4, TTI-621, ALX148, and the small molecule RRx-001, have been employed in clinical trials [110]. Gholamin et al. used Hu5F9-G4 in a study of pediatric brain tumors, demonstrating its safety and efficacy [98], with good tolerability. However, there are still limitations as it is uncertain whether it is associated with peripheral M1 macrophage recruitment. Although this reprogramming role has been demonstrated in breast, liver and bladder cancer species [107].

Interestingly, in a mouse model, curcumin (CC) was able to re-educate M2 TAMs into NO-producing M1 TAMs, and low levels of CC were also sufficient to elicit this reprogramming response [111]. This NO production was induced by inducible NOS (iNOS) induced macrophages [112]. Within TME, cancer cells release cytokines and STAT-3 transcription factors, leading to the increased expression of Arg1 in TAMs. Arg1, in turn, breaks down L-arginine, reducing the capacity of iNOS to utilize this substrate for NO production [111]. A synergistic strategy (TriCurin), in which CC was mixed with two natural polyphenols and then encapsulated in liposomes (TrLp), showed potent antitumor effects in a mouse model of GBM, where TrLp shifted M2 TAMs to a tumor-killing M1-like state, mobilizing NK cells for an immune response [100]. In addition, TriCurin inhibited STAT-3 signalling in GBMs [113]. We speculate that iNOS may be the main regulator and CC may be involved in STAT-3 signalling.

CpG, a TLR9 ligand, binds to the IL-10 receptor antibody, activating NF- κ B and inducing CCL16 production, converting TAMs to M1 anti-tumor phenotype [114]. NF- κ B, crucial for TAM transcription [115], is typically activated through IKK β -mediated I κ B α phosphorylation [116]. In ovarian cancer-derived TAMs, inhibiting IKK β enhances anti-tumor potential, shifting from M2 to M1 state [117]. Notably, Alantolactone (ATL) in glioblastoma multiforme targets IKK β 's ATP-binding site, potentially inhibiting NF- κ B, downregulating cyclooxygenase-2 (a pro-tumor signal) [118]. Although not confirmed, this may involve elevating M1 TAMs, emphasizing the importance of IKK β /NF- κ B inhibition in maintaining TAMs' M1 phenotype in tumors.

5 Discussion

With the introduction of TAMs reprogramming technology, new possibilities for tumour therapy have opened up. This technology not only targets tumour cells, but also regulates their growth microenvironment. Combined with immunotherapy, it provides a powerful tool to deeply regulate the tumour microenvironment, heralding the emergence of more precise treatments.

However, this does not mean that TAMs reprogramming is flawless. In GBM TME, TGF- β is a key factor in the regulation of TAM inflammation. Unfortunately, the multiple sources and targets of action of TGF- β make it a very difficult cytokine to control. For example, the disappointing performance of a TGF- β inhibitor called trabectedin in phase II trials [119] suggests that other pathways of TGF- β origin may exhibit potent pro-tumorigenic effects, which also creates difficulties for reprogramming TAMs. Although these reprogramming-related therapeutic agents are considered safe and effective [98], M1 TAMs still release some factors such as IL-1- β at the TME that may promote tumour cell growth rather than inhibit it, and it is not yet certain that this reprogramming effect is long-lasting and stable.

While TAMs reprogramming holds significant theoretical potential, its clinical application presents numerous challenges. Accurate assessment and monitoring of TAMs phenotype conversion, management of potential side effects, and optimization of these strategies for personalized treatment are crucial areas that need to be addressed. Long-term use of reprogramming therapies may also introduce new challenges, such as the impact on the patient's immune system over time, which necessitates further investigation.

As we mentioned earlier, disruption of the CD47-SIRP- α axis can significantly increase the M1 phenotype. We suggest that researchers could develop and evaluate the effectiveness of different types of CD47 inhibitors in inducing M1 phenotypes. For example, different strategies such as monoclonal antibodies, small molecule inhibitors or CAR T cell therapy may bring significant clinical application potential.

Therefore, when performing TAM reprogramming, we must find an appropriate balance between therapeutic efficacy and potential risks. With in-depth basic research and extensive clinical validation, the true potential and possible limitations of this approach will gradually become clearer.

Acknowledgements We express our deep gratitude to the Science and Technology Development Fund, Macau SAR, for their generous financial support under file No. 0098/2021/A2. This funding played a pivotal role in facilitating the research and preparation of this review. The insights and outcomes presented in this article were significantly enhanced by the resources and opportunities provided through this support.

Author contributions Conceptualization: JX, HC, and XZ jointly conceived the study's framework and set its overall direction. Manuscript writing: the manuscript was written collaboratively by JX, XZ, LS, ZM, CP, LJ and CF, with each author contributing significant sections and content. Literature review and data collection: the review of literature and the collection of relevant data were carried out by JX and XZ. Data analysis and visualization: the analysis and visualization of data were primarily handled by JX, XZ, and LS. Final revision: the final revision of the manuscript was undertaken by JX, HC, KX, and XZ, ensuring the accuracy and coherence of the final draft. All authors have read and approved the final manuscript.

Funding This study was supported by grants from Scientific research projects of Sichuan Provincial Medical Association (2018SHD5-10), Sichuan Provincial Department of Education Project (14ZB0167) and Sichuan Provincial Medical Association Subjects (S17074).

Data availability No datasets were generated or analysed during the current study.

Declarations

Competing interests The authors declare no competing interests.

Open Access This article is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License, which permits any non-commercial use, sharing, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if you modified the licensed material. You do not have permission under this licence to share adapted material derived from this article or parts of it. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by-nc-nd/4.0/>.

References

1. Khazaei Z, et al. The association between incidence and mortality of brain cancer and human development index (HDI): an ecological study. *BMC Public Health*. 2020;20:1696. <https://doi.org/10.1186/s12889-020-09838-4>.
2. Roda E, Bottone MG. Editorial: Brain cancers: new perspectives and therapies. *Front Neurosci*. 2022;16: 857408. <https://doi.org/10.3389/fnins.2022.857408>.
3. Geraldo LHM, et al. Glioblastoma therapy in the age of molecular medicine. *Trends Cancer*. 2019;5:46–65. <https://doi.org/10.1016/j.trecan.2018.11.002>.
4. Miller KD, et al. Brain and other central nervous system tumor statistics, 2021. *CA Cancer J Clin*. 2021;71:381–406. <https://doi.org/10.3322/caac.21693>.
5. Doucette T, et al. Immune heterogeneity of glioblastoma subtypes: extrapolation from the cancer genome atlas. *Cancer Immunol Res*. 2013;1:112–22. <https://doi.org/10.1158/2326-6066.Cir-13-0028>.
6. de Groot J, et al. Window-of-opportunity clinical trial of pembrolizumab in patients with recurrent glioblastoma reveals predominance of immune-suppressive macrophages. *Neuro Oncol*. 2020;22:539–49. <https://doi.org/10.1093/neuonc/noz185>.
7. Quail DF, Joyce JA. The microenvironmental landscape of brain tumors. *Cancer Cell*. 2017;31:326–41. <https://doi.org/10.1016/j.ccell.2017.02.009>.
8. Lathia JD, Mack SC, Mulkearns-Hubert EE, Valentim CL, Rich JN. Cancer stem cells in glioblastoma. *Genes Dev*. 2015;29:1203–17. <https://doi.org/10.1101/gad.261982.115>.
9. Gomez Perdiguero E, et al. Tissue-resident macrophages originate from yolk-sac-derived erythro-myeloid progenitors. *Nature*. 2015;518:547–51. <https://doi.org/10.1038/nature13989>.
10. Chen Z, et al. Cellular and molecular identity of tumor-associated macrophages in glioblastoma. *Cancer Res*. 2017;77:2266–78. <https://doi.org/10.1158/0008-5472.Can-16-2310>.
11. Graeber MB, Scheithauer BW, Kreutzberg GW. Microglia in brain tumors. *Glia*. 2002;40:252–9. <https://doi.org/10.1002/glia.10147>.
12. Sica A, Erreni M, Allavena P, Porta C. Macrophage polarization in pathology. *Cell Mol Life Sci*. 2015;72:4111–26. <https://doi.org/10.1007/s00018-015-1995-y>.
13. Tremblay M, et al. The role of microglia in the healthy brain. *J Neurosci*. 2011;31:16064–9. <https://doi.org/10.1523/jneurosci.4158-11.2011>.
14. Salter MW, Stevens B. Microglia emerge as central players in brain disease. *Nat Med*. 2017;23:1018–27. <https://doi.org/10.1038/nm.4397>.
15. Colonna M, Butovsky O. Microglia function in the central nervous system during health and neurodegeneration. *Annu Rev Immunol*. 2017;35:441–68. <https://doi.org/10.1146/annurev-immunol-051116-052358>.
16. Andersen BM, et al. Glial and myeloid heterogeneity in the brain tumour microenvironment. *Nat Rev Cancer*. 2021;21:786–802. <https://doi.org/10.1038/s41568-021-00397-3>.

17. Sørensen MD, Dahlrot RH, Boldt HB, Hansen S, Kristensen BW. Tumour-associated microglia/macrophages predict poor prognosis in high-grade gliomas and correlate with an aggressive tumour subtype. *Neuropathol Appl Neurobiol*. 2018;44:185–206. <https://doi.org/10.1111/nan.12428>.
18. Akkari L, et al. Dynamic changes in glioma macrophage populations after radiotherapy reveal CSF-1R inhibition as a strategy to overcome resistance. *Sci Transl Med*. 2020;12: eaaw7843. <https://doi.org/10.1126/scitranslmed.aaw7843>.
19. Mantovani A, et al. The chemokine system in diverse forms of macrophage activation and polarization. *Trends Immunol*. 2004;25:677–86. <https://doi.org/10.1016/j.it.2004.09.015>.
20. Murray PJ, et al. Macrophage activation and polarization: nomenclature and experimental guidelines. *Immunity*. 2014;41:14–20. <https://doi.org/10.1016/j.immuni.2014.06.008>.
21. Mosser DM, Edwards JP. Exploring the full spectrum of macrophage activation. *Nat Rev Immunol*. 2008;8:958–69. <https://doi.org/10.1038/nri2448>.
22. Hambardzumyan D, Gutmann DH, Kettenmann H. The role of microglia and macrophages in glioma maintenance and progression. *Nat Neurosci*. 2016;19:20–7. <https://doi.org/10.1038/nn.4185>.
23. da Fonseca AC, et al. Microglia in cancer: for good or for bad? *Adv Exp Med Biol*. 2016;949:245–61. https://doi.org/10.1007/978-3-319-40764-7_12.
24. Aminin D, Wang YM. Macrophages as a “weapon” in anticancer cellular immunotherapy. *Kaohsiung J Med Sci*. 2021;37:749–58. <https://doi.org/10.1002/kjm2.12405>.
25. Eglitis MA, Mezey E. Hematopoietic cells differentiate into both microglia and macroglia in the brains of adult mice. *Proc Natl Acad Sci USA*. 1997;94:4080–5. <https://doi.org/10.1073/pnas.94.8.4080>.
26. Kierdorf K, et al. Microglia emerge from erythromyeloid precursors via Pu.1- and Irf8-dependent pathways. *Nat Neurosci*. 2013;16:273–80. <https://doi.org/10.1155/2013/285246>.
27. Bowman RL, et al. Macrophage ontogeny underlies differences in tumor-specific education in brain malignancies. *Cell Rep*. 2016;17:2445–59. <https://doi.org/10.1016/j.celrep.2016.10.052>.
28. Friebe E, et al. Single-cell mapping of human brain cancer reveals tumor-specific instruction of tissue-invading leukocytes. *Cell*. 2020;181:1626–1642.e1620. <https://doi.org/10.1016/j.cell.2020.04.055>.
29. Wei J, Gabrusiewicz K, Heimberger A. The controversial role of microglia in malignant gliomas. *Clin Dev Immunol*. 2013;2013: 285246. <https://doi.org/10.1155/2013/285246>.
30. Saederup N, et al. Selective chemokine receptor usage by central nervous system myeloid cells in CCR2-red fluorescent protein knock-in mice. *PLoS ONE*. 2010;5: e13693. <https://doi.org/10.1371/journal.pone.0013693>.
31. Zhu H, et al. Surgical debulking promotes recruitment of macrophages and triggers glioblastoma phagocytosis in combination with CD47 blocking immunotherapy. *Oncotarget*. 2017;8:12145–57. <https://doi.org/10.18632/oncotarget.14553>.
32. Poon CC, Sarkar S, Yong VW, Kelly JJP. Glioblastoma-associated microglia and macrophages: targets for therapies to improve prognosis. *Brain*. 2017;140:1548–60. <https://doi.org/10.1093/brain/aww355>.
33. Dantzer R, O'Connor JC, Freund GG, Johnson RW, Kelley KW. From inflammation to sickness and depression: when the immune system subjugates the brain. *Nat Rev Neurosci*. 2008;9:46–56. <https://doi.org/10.1038/nrn2297>.
34. Holmdahl R, Sareila O, Olsson LM, Bäckdahl L, Wing K. Ncf1 polymorphism reveals oxidative regulation of autoimmune chronic inflammation. *Immunol Rev*. 2016;269:228–47. <https://doi.org/10.1111/imr.12378>.
35. Schartner JM, et al. Impaired capacity for upregulation of MHC class II in tumor-associated microglia. *Glia*. 2005;51:279–85. <https://doi.org/10.1002/glia.20201>.
36. Gabrusiewicz K, et al. Characteristics of the alternative phenotype of microglia/macrophages and its modulation in experimental gliomas. *PLoS ONE*. 2011;6: e23902. <https://doi.org/10.1371/journal.pone.0023902>.
37. Shapouri-Moghaddam A, et al. Macrophage plasticity, polarization, and function in health and disease. *J Cell Physiol*. 2018;233:6425–40. <https://doi.org/10.1002/jcp.26429>.
38. Luo S, et al. Macrophages are a double-edged sword: molecular crosstalk between tumor-associated macrophages and cancer stem cells. *Biomolecules*. 2022;12:850. <https://doi.org/10.3390/biom12060850>.
39. Caverzán MD, et al. Exploring monocytes-macrophages in immune microenvironment of glioblastoma for the design of novel therapeutic strategies. *Brain Sci*. 2023;13:542. <https://doi.org/10.3390/brainsci13040542>.
40. Hambardzumyan D, Bergers G. Glioblastoma: defining tumor niches. *Trends Cancer*. 2015;1:252–65. <https://doi.org/10.1016/j.trecan.2015.10.009>.
41. Li Y, et al. Glioma-derived LRIG3 interacts with NETO2 in tumor-associated macrophages to modulate microenvironment and suppress tumor growth. *Cell Death Dis*. 2023;14:28. <https://doi.org/10.1038/s41419-023-05555-z>.
42. Quail DF, Joyce JA. Microenvironmental regulation of tumor progression and metastasis. *Nat Med*. 2013;19:1423–37. <https://doi.org/10.1038/nm.3394>.
43. Parsa AT, et al. Loss of tumor suppressor PTEN function increases B7-H1 expression and immunoresistance in glioma. *Nat Med*. 2007;13:84–8. <https://doi.org/10.1038/nm1517>.
44. Zerrouqi A, Pyrzynska B, Febbraio M, Brat DJ, Van Meir EG. P14ARF inhibits human glioblastoma-induced angiogenesis by upregulating the expression of TIMP3. *J Clin Invest*. 2012;122:1283–95. <https://doi.org/10.1172/jci38596>.
45. Chen P, et al. Symbiotic macrophage-glioma cell interactions reveal synthetic lethality in PTEN-null glioma. *Cancer Cell*. 2019;35:868–884.e866. <https://doi.org/10.1016/j.ccell.2019.05.003>.
46. Wang Q, et al. Tumor evolution of glioma-intrinsic gene expression subtypes associates with immunological changes in the microenvironment. *Cancer Cell*. 2017;32:42–56.e46. <https://doi.org/10.1016/j.ccell.2017.06.003>.
47. Xuan W, Lesniak MS, James CD, Heimberger AB, Chen P. Context-dependent glioblastoma-macrophage/microglia symbiosis and associated mechanisms. *Trends Immunol*. 2021;42:280–92. <https://doi.org/10.1016/j.it.2021.02.004>.
48. Xu Z, Stokoe D, Kane LP, Weiss A. The inducible expression of the tumor suppressor gene PTEN promotes apoptosis and decreases cell size by inhibiting the PI3K/Akt pathway in Jurkat T cells. *Cell Growth Differ*. 2002;13:285–96.

49. An Z, et al. EGFR cooperates with EGFRVIII to recruit macrophages in glioblastoma. *Cancer Res.* 2018;78:6785–94. <https://doi.org/10.1158/0008-5472.Can-17-3551>.
50. Kober C, et al. Microglia and astrocytes attenuate the replication of the oncolytic vaccinia virus LIVP 1.1.1 in murine GL261 gliomas by acting as vaccinia virus traps. *J Transl Med.* 2015;13:216. <https://doi.org/10.1186/s12967-015-0586-x>.
51. Han Z, et al. TOPK promotes microglia/macrophage polarization towards M2 phenotype via inhibition of HDAC1 and HDAC2 activity after transient cerebral ischemia. *Aging Dis.* 2018;9:235–48. <https://doi.org/10.14336/ad.2017.0328>.
52. Matias D, et al. Microglia-glioblastoma interactions: new role for Wnt signaling. *Biochim Biophys Acta Rev Cancer.* 1868;333–340:2017. <https://doi.org/10.1016/j.bbcan.2017.05.007>.
53. Roesch S, Rapp C, Dettling S, Herold-Mende C. When immune cells turn bad-tumor-associated microglia/macrophages in glioma. *Int J Mol Sci.* 2018;19:436. <https://doi.org/10.3390/ijms19020436>.
54. Sun JX, Xu XH, Jin L. Effects of metabolism on macrophage polarization under different disease backgrounds. *Front Immunol.* 2022;13: 880286. <https://doi.org/10.3389/fimmu.2022.880286>.
55. Tian F, Chen H, Zhang J, He W. Reprogramming metabolism of macrophages as a target for kidney dysfunction treatment in autoimmune diseases. *Int J Mol Sci.* 2022;23:8024. <https://doi.org/10.3390/ijms23148024>.
56. Eldahshan W, Fagan SC, Ergul A. Inflammation within the neurovascular unit: focus on microglia for stroke injury and recovery. *Pharmacol Res.* 2019;147: 104349. <https://doi.org/10.1016/j.phrs.2019.104349>.
57. Torrisi F, et al. Epigenetics and metabolism reprogramming interplay into glioblastoma: novel insights on immunosuppressive mechanisms. *Antioxidants.* 2023;12:220. <https://doi.org/10.3390/antiox12020220>.
58. Vidyarthi A, et al. Predominance of M2 macrophages in gliomas leads to the suppression of local and systemic immunity. *Cancer Immunol Immunother.* 2019;68:1995–2004. <https://doi.org/10.1007/s00262-019-02423-8>.
59. Liu H, et al. Pro-inflammatory and proliferative microglia drive progression of glioblastoma. *Cell Rep.* 2021;36: 109718. <https://doi.org/10.1016/j.celrep.2021.109718>.
60. Ravi VM, et al. T-cell dysfunction in the glioblastoma microenvironment is mediated by myeloid cells releasing interleukin-10. *Nat Commun.* 2022;13:925. <https://doi.org/10.1038/s41467-022-28523-1>.
61. Sa JK, et al. Transcriptional regulatory networks of tumor-associated macrophages that drive malignancy in mesenchymal glioblastoma. *Genome Biol.* 2020;21:216. <https://doi.org/10.1186/s13059-020-02140-x>.
62. Suzumura A, Sawada M, Yamamoto H, Marunouchi T. Transforming growth factor-beta suppresses activation and proliferation of microglia in vitro. *J Immunol.* 1993;151:2150–8.
63. Letterio JJ, Roberts AB. Regulation of immune responses by TGF-beta. *Annu Rev Immunol.* 1998;16:137–61. <https://doi.org/10.1146/annurev.immunol.16.1.137>.
64. Watters JJ, Schartner JM, Badie B. Microglia function in brain tumors. *J Neurosci Res.* 2005;81:447–55. <https://doi.org/10.1002/jnr.20485>.
65. Sainz B Jr, Carron E, Vallespinós M, Machado HL. Cancer stem cells and macrophages: implications in tumor biology and therapeutic strategies. *Mediat Inflamm.* 2016;2016:9012369. <https://doi.org/10.1155/2016/9012369>.
66. Pires-Afonso Y, Niclou SP, Michelucci A. Revealing and harnessing tumour-associated microglia/macrophage heterogeneity in glioblastoma. *Int J Mol Sci.* 2020;21:689. <https://doi.org/10.3390/ijms21030689>.
67. Chang AL, et al. CCL2 produced by the glioma microenvironment is essential for the recruitment of regulatory T cells and myeloid-derived suppressor cells. *Cancer Res.* 2016;76:5671–82. <https://doi.org/10.1158/0008-5472.Can-16-0144>.
68. Hussain SF, et al. The role of human glioma-infiltrating microglia/macrophages in mediating antitumor immune responses. *Neuro Oncol.* 2006;8:261–79. <https://doi.org/10.1215/15228517-2006-008>.
69. Hoves S, et al. Rapid activation of tumor-associated macrophages boosts preexisting tumor immunity. *J Exp Med.* 2018;215:859–76. <https://doi.org/10.1084/jem.20171440>.
70. Perry CJ, et al. Myeloid-targeted immunotherapies act in synergy to induce inflammation and antitumor immunity. *J Exp Med.* 2018;215:877–93. <https://doi.org/10.1084/jem.20171435>.
71. Wu M, et al. Phagocytosis of glioma cells enhances the immunosuppressive phenotype of bone marrow-derived macrophages. *Cancer Res.* 2023;83:771–85. <https://doi.org/10.1158/0008-5472.Can-22-1570>.
72. Chen Q, et al. EMP3 mediates glioblastoma-associated macrophage infiltration to drive T cell exclusion. *J Exp Clin Cancer Res.* 2021;40:160. <https://doi.org/10.1186/s13046-021-01954-2>.
73. Zadeh Shirazi A, et al. A deep convolutional neural network for segmentation of whole-slide pathology images identifies novel tumour cell-perivascular niche interactions that are associated with poor survival in glioblastoma. *Br J Cancer.* 2021;125:337–50. <https://doi.org/10.1038/s41416-021-01394-x>.
74. Ricci-Vitiani L, et al. Tumour vascularization via endothelial differentiation of glioblastoma stem-like cells. *Nature.* 2010;468:824–8. <https://doi.org/10.1038/nature09557>.
75. Pietras A, et al. Osteopontin-CD44 signaling in the glioma perivascular niche enhances cancer stem cell phenotypes and promotes aggressive tumor growth. *Cell Stem Cell.* 2014;14:357–69. <https://doi.org/10.1016/j.stem.2014.01.005>.
76. Charles N, Holland EC. The perivascular niche microenvironment in brain tumor progression. *Cell Cycle.* 2010;9:3012–21. <https://doi.org/10.4161/cc.9.15.12710>.
77. Jung E, et al. Tumor cell plasticity, heterogeneity, and resistance in crucial microenvironmental niches in glioma. *Nat Commun.* 2021;12:1014. <https://doi.org/10.1038/s41467-021-21117-3>.
78. Sørensen MD, Kristensen BW. Tumour-associated CD204(+) microglia/macrophages accumulate in perivascular and perinecrotic niches and correlate with an interleukin-6-enriched inflammatory profile in glioblastoma. *Neuropathol Appl Neurobiol.* 2022;48: e12772. <https://doi.org/10.1111/nan.12772>.
79. Ye XZ, et al. Tumor-associated microglia/macrophages enhance the invasion of glioma stem-like cells via TGF-β1 signaling pathway. *J Immunol.* 2012;189:444–53. <https://doi.org/10.4049/jimmunol.1103248>.
80. Ulasov IV, et al. TMZ regulates GBM stemness via MMP14-DLL4-Notch3 pathway. *Int J Cancer.* 2020;146:2218–28. <https://doi.org/10.1002/ijc.32636>.

81. Shi Y, et al. Tumour-associated macrophages secrete pleiotrophin to promote PTPRZ1 signalling in glioblastoma stem cells for tumour growth. *Nat Commun.* 2017;8:15080. <https://doi.org/10.1038/ncomms15080>.
82. Yuan W, et al. Dual role of CXCL8 in maintaining the mesenchymal state of glioblastoma stem cells and M2-like tumor-associated macrophages. *Clin Cancer Res.* 2023;29:3779–92. <https://doi.org/10.1158/1078-0432.Ccr-22-3273>.
83. Li D, et al. β 2-Microglobulin maintains glioblastoma stem cells and induces M2-like polarization of tumor-associated macrophages. *Cancer Res.* 2022;82:3321–34. <https://doi.org/10.1158/0008-5472.Can-22-0507>.
84. Zhou Y, et al. USF1/CD90 signaling in maintaining glioblastoma stem cells and tumor-associated macrophages adhesion. *Neuro Oncol.* 2022;24:1482–93. <https://doi.org/10.1093/neuonc/noac063>.
85. Yin J, et al. ARS2/MAGL signaling in glioblastoma stem cells promotes self-renewal and M2-like polarization of tumor-associated macrophages. *Nat Commun.* 2020;11:2978. <https://doi.org/10.1038/s41467-020-16789-2>.
86. Zhou W, et al. Periostin secreted by glioblastoma stem cells recruits M2 tumour-associated macrophages and promotes malignant growth. *Nat Cell Biol.* 2015;17:170–82. <https://doi.org/10.1038/ncb3090>.
87. Feng Y, et al. A toll-like receptor agonist mimicking microbial signal to generate tumor-suppressive macrophages. *Nat Commun.* 2019;10:2272. <https://doi.org/10.1038/s41467-019-10354-2>.
88. Glass R, Synowitz M. CNS macrophages and peripheral myeloid cells in brain tumours. *Acta Neuropathol.* 2014;128:347–62. <https://doi.org/10.1007/s00401-014-1274-2>.
89. Li B, et al. GSK-3 β inhibition attenuates LPS-induced death but aggravates radiation-induced death via down-regulation of IL-6. *Cell Physiol Biochem.* 2013;32:1720–8. <https://doi.org/10.1159/000356606>.
90. Chikano Y, et al. Glycogen synthase kinase 3 β sustains invasion of glioblastoma via the focal adhesion kinase, Rac1, and c-Jun N-terminal kinase-mediated pathway. *Mol Cancer Ther.* 2015;14:564–74. <https://doi.org/10.1158/1535-7163.Mct-14-0479>.
91. Kim HJ, et al. Blood monocyte-derived CD169(+) macrophages contribute to antitumor immunity against glioblastoma. *Nat Commun.* 2022;13:6211. <https://doi.org/10.1038/s41467-022-34001-5>.
92. Xiao L, Zhang Y, Zhang M, Gao J. Editorial: Engineered cell-originated biomimetic materials for cancer therapy. *Front Bioeng Biotechnol.* 2023;11:125959. <https://doi.org/10.3389/fbioe.2023.125959>.
93. Pyonteck SM, et al. CSF-1R inhibition alters macrophage polarization and blocks glioma progression. *Nat Med.* 2013;19:1264–72. <https://doi.org/10.1038/nm.3337>.
94. Xu C, et al. Origin, activation, and targeted therapy of glioma-associated macrophages. *Front Immunol.* 2022;13: 974996. <https://doi.org/10.3389/fimmu.2022.974996>.
95. Peng P, et al. TGFBI secreted by tumor-associated macrophages promotes glioblastoma stem cell-driven tumor growth via integrin α v β 5-*Src*-Stat3 signaling. *Theranostics.* 2022;12:4221–36. <https://doi.org/10.7150/thno.69605>.
96. Li H, et al. Ferritin light chain promotes the reprogramming of glioma immune microenvironment and facilitates glioma progression. *Theranostics.* 2023;13:3794–813. <https://doi.org/10.7150/thno.82975>.
97. Hussain SF, et al. A novel small molecule inhibitor of signal transducers and activators of transcription 3 reverses immune tolerance in malignant glioma patients. *Cancer Res.* 2007;67:9630–6. <https://doi.org/10.1158/0008-5472.Can-07-1243>.
98. Gholamin S, et al. Disrupting the CD47-SIRP α anti-phagocytic axis by a humanized anti-CD47 antibody is an efficacious treatment for malignant pediatric brain tumors. *Sci Transl Med.* 2017;9:e2968. <https://doi.org/10.1126/scitranslmed.aaf2968>.
99. Mukherjee S, et al. Phytosomal curcumin causes natural killer cell-dependent repolarization of glioblastoma (GBM) tumor-associated microglia/macrophages and elimination of GBM and GBM stem cells. *J Exp Clin Cancer Res.* 2018;37:168. <https://doi.org/10.1186/s13046-018-0792-5>.
100. Mukherjee S, et al. Liposomal TriCurin, a synergistic combination of curcumin, epicatechin gallate and resveratrol, repolarizes tumor-associated microglia/macrophages, and eliminates glioblastoma (GBM) and GBM stem cells. *Molecules.* 2018;23:201. <https://doi.org/10.3390/molecules23010201>.
101. Xue N, et al. Chlorogenic acid inhibits glioblastoma growth through repolarizing macrophage from M2 to M1 phenotype. *Sci Rep.* 2017;7:39011. <https://doi.org/10.1038/srep39011>.
102. Yang M, et al. PTN-PTPRZ1 signaling axis blocking mediates tumor microenvironment remodeling for enhanced glioblastoma treatment. *J Control Release.* 2023;353:63–76. <https://doi.org/10.1016/j.jconrel.2022.11.025>.
103. Zhang L, et al. Stat3 inhibition activates tumor macrophages and abrogates glioma growth in mice. *Glia.* 2009;57:1458–67. <https://doi.org/10.1002/glia.20863>.
104. Jeannin P, Paolini L, Adam C, Delneste Y. The roles of CSFs on the functional polarization of tumor-associated macrophages. *FEBS J.* 2018;285:680–99. <https://doi.org/10.1111/febs.14343>.
105. Jaiswal S, et al. CD47 is upregulated on circulating hematopoietic stem cells and leukemia cells to avoid phagocytosis. *Cell.* 2009;138:271–85. <https://doi.org/10.1016/j.cell.2009.05.046>.
106. Zen K, et al. Inflammation-induced proteolytic processing of the SIRP α cytoplasmic ITIM in neutrophils propagates a proinflammatory state. *Nat Commun.* 2013;4:2436. <https://doi.org/10.1038/ncomms3436>.
107. Willingham SB, et al. The CD47-signal regulatory protein α (SIRP α) interaction is a therapeutic target for human solid tumors. *Proc Natl Acad Sci USA.* 2012;109:6662–7. <https://doi.org/10.1073/pnas.1121623109>.
108. Zhang M, et al. Anti-CD47 treatment stimulates phagocytosis of glioblastoma by M1 and M2 polarized macrophages and promotes M1 polarized macrophages in vivo. *PLoS ONE.* 2016;11:e0153550. <https://doi.org/10.1371/journal.pone.0153550>.
109. Li F, et al. Blocking the CD47-SIRP α axis by delivery of anti-CD47 antibody induces antitumor effects in glioma and glioma stem cells. *Oncoimmunology.* 2018;7:e1391973. <https://doi.org/10.1080/2162402x.2017.1391973>.
110. Oronsky B, Carter C, Reid T, Brinkhaus F, Knox SJ. Just eat it: a review of CD47 and SIRP- α antagonism. *Semin Oncol.* 2020;47:117–24. <https://doi.org/10.1053/j.seminoncol.2020.05.009>.
111. Baidoo JNE, Mukherjee S, Kashfi K, Banerjee P. A new perspective on cancer therapy: changing the treaded path? *Int J Mol Sci.* 2021;22:9836. <https://doi.org/10.3390/ijms22189836>.
112. Förstermann U, Sessa WC. Nitric oxide synthases: regulation and function. *Eur Heart J.* 2012;33: 829–37, 837a–37d. <https://doi.org/10.1093/eurheartj/ehr304>.

113. Mohapatra S, Cafiero J, Kashfi K, Mehta P, Banerjee P. Why don't the mutant cells that evade DNA repair cause cancer more frequently? Importance of the innate immune system in the tumor microenvironment. *Int J Mol Sci.* 2023;24:5026. <https://doi.org/10.3390/ijms24055026>.
114. Mancino A, Lawrence T. Nuclear factor-kappaB and tumor-associated macrophages. *Clin Cancer Res.* 2010;16:784–9. <https://doi.org/10.1158/1078-0432.Ccr-09-1015>.
115. Hagemann T, Biswas SK, Lawrence T, Sica A, Lewis CE. Regulation of macrophage function in tumors: the multifaceted role of NF-kappaB. *Blood.* 2009;113:3139–46. <https://doi.org/10.1182/blood-2008-12-172825>.
116. Novack DV, et al. The IkappaB function of NF-kappaB2 p100 controls stimulated osteoclastogenesis. *J Exp Med.* 2003;198:771–81. <https://doi.org/10.1084/jem.20030116>.
117. Hagemann T, et al. "Re-educating" tumor-associated macrophages by targeting NF-kappaB. *J Exp Med.* 2008;205:1261–8. <https://doi.org/10.1084/jem.20080108>.
118. Wang X, et al. Alantolactone, a natural sesquiterpene lactone, has potent antitumor activity against glioblastoma by targeting IKK β kinase activity and interrupting NF- κ B/COX-2-mediated signaling cascades. *J Exp Clin Cancer Res.* 2017;36:93. <https://doi.org/10.1186/s13046-017-0563-8>.
119. Bogdahn U, et al. Targeted therapy for high-grade glioma with the TGF- β 2 inhibitor trabedersen: results of a randomized and controlled phase IIb study. *Neuro Oncol.* 2011;13:132–42. <https://doi.org/10.1093/neuonc/noq142>.

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.