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Review

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

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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

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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 has 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 TNFα. 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 TGFβ, 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

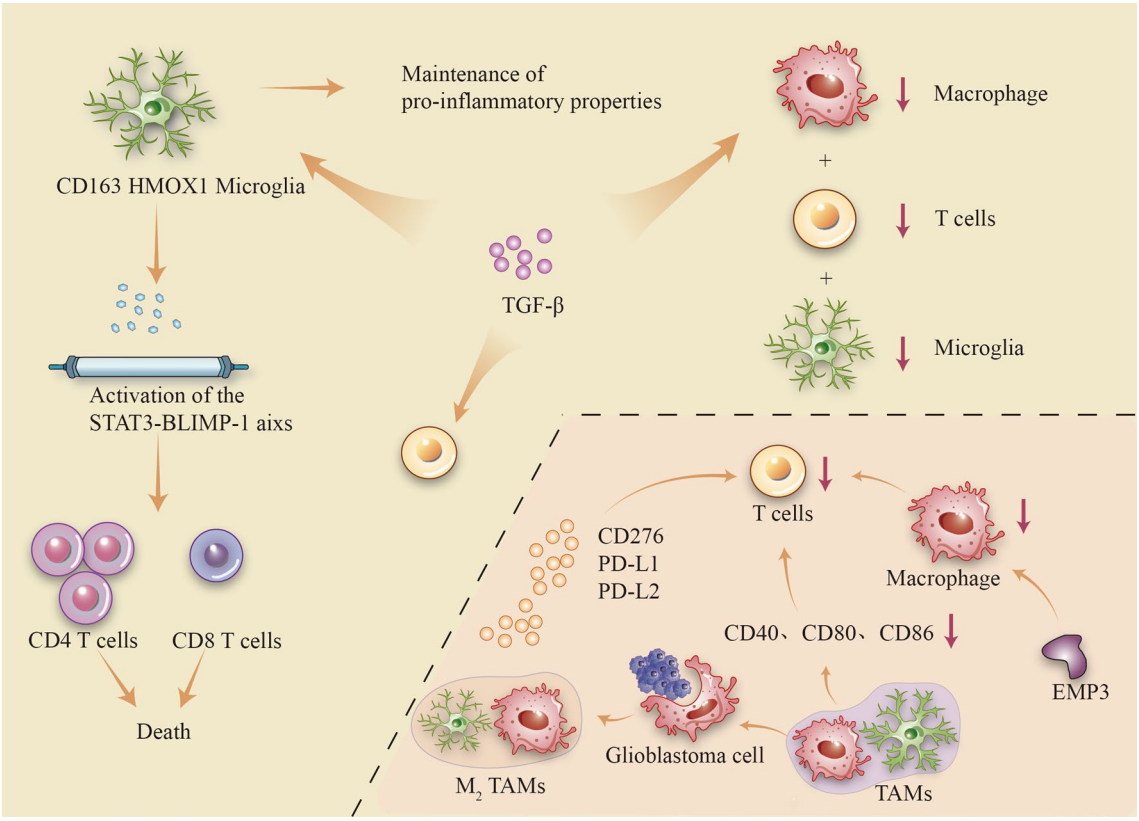


Fig. 1 CD163HMOX1 microglia in mesenchymal GBMs promote T-cell depletion through IL-10 and maintain inflammation via TGF-β, which also inhibits microglial proliferation. TGF-β supports tumor progression and immunosuppression. TAMs with M2 characteristics, including CD276, PD-L1, and PD-L2, suppress T 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-β1, 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

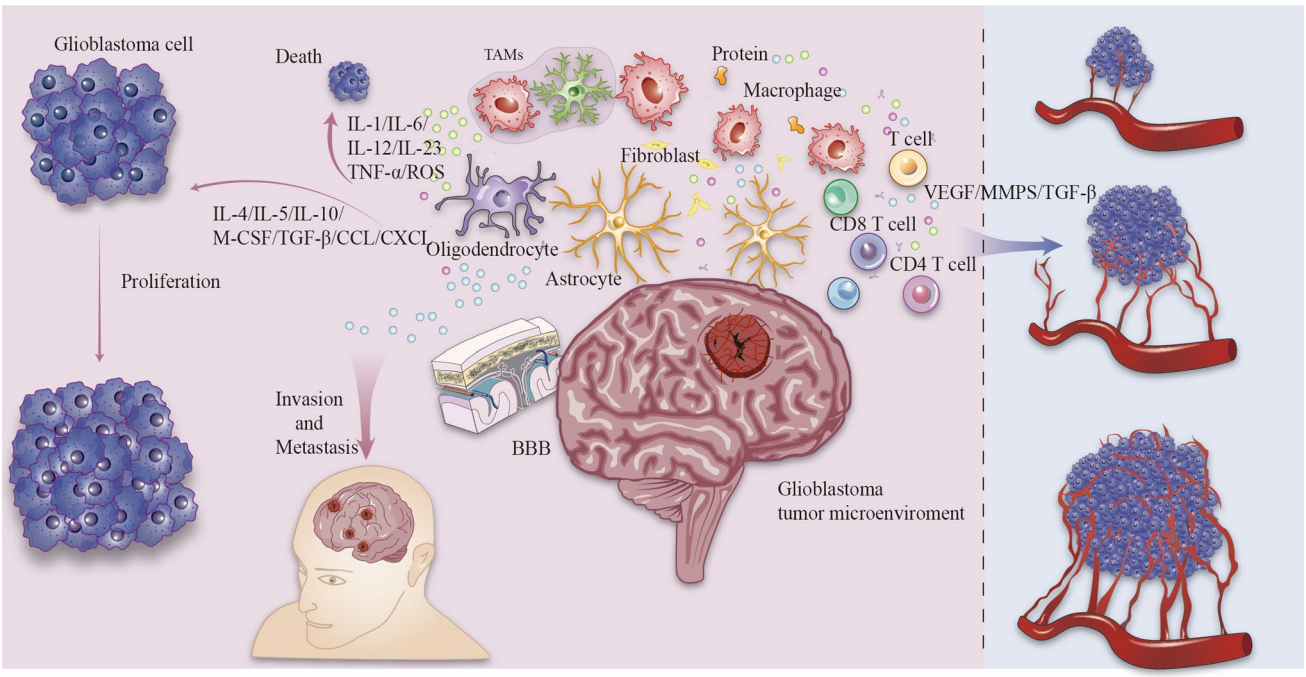
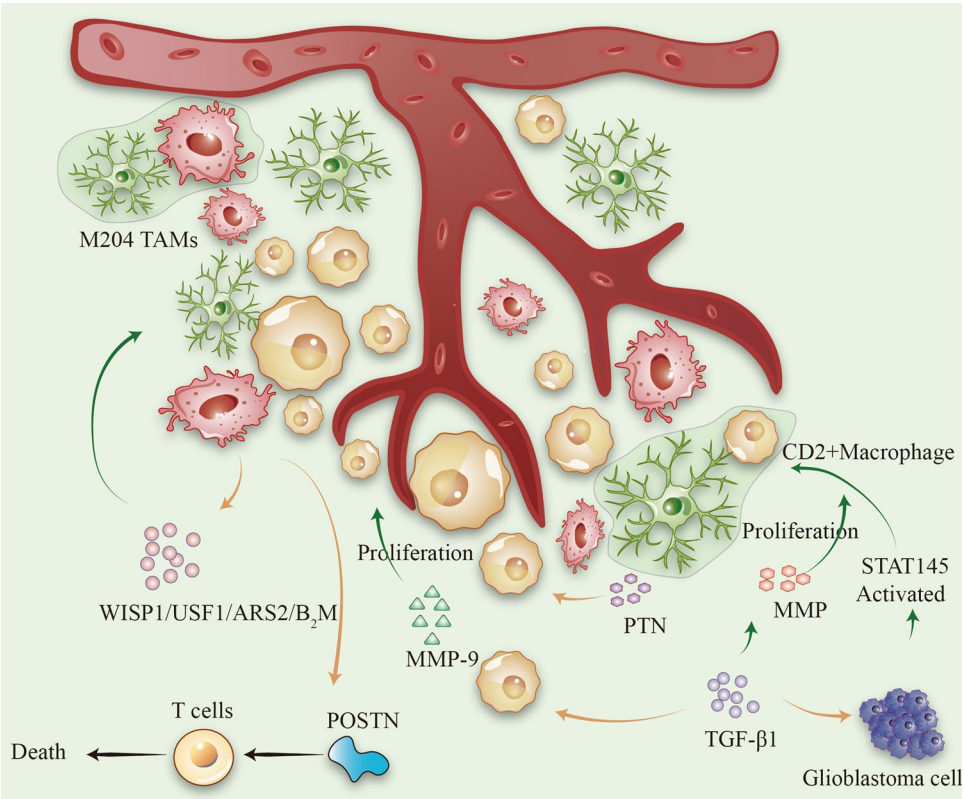


Fig. 2 This figure illustrates the key features of TAMs in the tumor microenvironment and their dynamic interactions. The figure first shows the components of the glioblastoma tumor microenvironment, in which tumor cells are constantly dividing and expanding, accompanied by the formation of neovascularization 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-β1 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 α6β1-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 β2-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-3β (GSK-3β) is able to modulate the inflammatory response in microglia [89]. The inhibition of GBM by GSK-3β 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-3β 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-3β 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 mice	B2M	PIP5K1A and PI1K/AKT/mTOR	GSCs renewal and tumour growth	[83]
In vivo	4-week-old NU/NU nude mice	TGFBI	Integrin αvβ5-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-κB 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-κB/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 SIRPα inhibits immunophagocytosis [106, 107]. Disrupting the CD47-SIRPα 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-κB and inducing CCL16 production, converting TAMs to M1 anti-tumor phenotype [114]. NF-κB, crucial for TAM transcription [115], is typically activated through IKKβ-mediated IκBα phosphorylation [116]. In ovarian cancer-derived TAMs, inhibiting IKKβ enhances antitumor potential, shifting from M2 to M1 state [117]. Notably, Alantolactone (ATL) in glioblastoma multiforme targets IKKβ's ATP-binding site, potentially inhibiting NF-κB, downregulating cyclooxygenase-2 (a pro-tumor signal) [118]. Although not confirmed, this may involve elevating M1 TAMs, emphasizing the importance of IKKβ/NF-κB 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 trabedersen in phase II trials [119] suggests that other pathways of TGF-β origin may exhibit potent pro-tumourigenic 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.

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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.

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

Declarations

Competing interests The authors declare no competing interests.

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