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# Insights of immune cell heterogeneity, tumor-initiated subtype transformation, drug resistance, treatment and detecting technologies in glioma microenvironment

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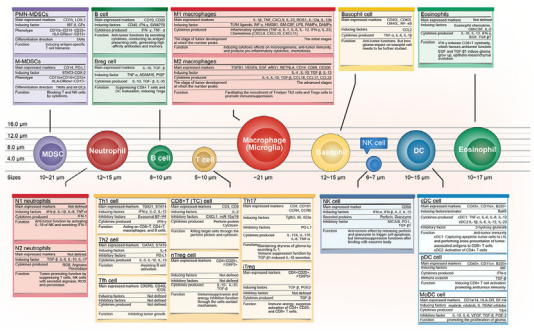
## HIGHLIGHTS

- The characteristics of immunocyte subtypes and the exact mechanism of glioma-induced subtypes transformation were summarized.
- The mechanism of chemotherapy resistance in glioma and prospective immunotherapy targets were analyzed.
- The progress of single cell sequencing in exploring immune cell subtypes in glioma was concluded.

## GRAPHICAL ABSTRACT

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## ABSTRACT

*Background:* With the gradual understanding of glioma development and the immune microenvironment, many immune cells have been discovered. Despite the growing comprehension of immune cell functions and the clinical application of immunotherapy, the precise roles and characteristics of immune cell subtypes, how glioma induces subtype transformation of immune cells and its impact on glioma progression have yet to be understood.

*Aim of the review:* In this review, we comprehensively center on the four major immune cells within the glioma microenvironment, particularly neutrophils, macrophages, lymphocytes, myeloid-derived suppressor cells (MDSCs), and other significant immune cells. We discuss (1) immune cell subtype markers, (2) glioma-induced immune cell subtype transformation, (3) the mechanisms of each subtype influencing chemotherapy resistance, (4) therapies targeting immune cells, and (5) immune cell-associated single-cell sequencing. Eventually, we identified the characteristics of immune cell subtypes in glioma, comprehensively summarized the exact mechanism of glioma-induced immune cell subtype transformation, and concluded the progress of single-cell sequencing in exploring immune cell subtypes in glioma.

*Key scientific concepts of review:* In conclusion, we have analyzed the mechanism of chemotherapy resistance detailly, and have discovered prospective immunotherapy targets, excavating the potential of novel immunotherapies approach that synergistically combines radiotherapy, chemotherapy, and surgery, thereby paving the way for improved immunotherapeutic strategies against glioma and enhanced patient outcomes.



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**Contents**

## Introduction

The immune microenvironment in glioma includes microglial cells, neuronal forerunner cells, fibroblasts, pericytes, neurons, astrocytes, immune cells and soluble cytokines secreted by various cells [1–3]. Immune cells contain tumor-associated macrophages (TAMs), dendritic cells (DCs), natural killer cells (NKs), MDSCs, neutrophils, lymphocytes, basophils, eosinophils and other immune cells [4]. The functions of usual immune cells include immune surveillance, immune response, and immune memory to help the mortal physique resist external incentives [5,6]. Recently, many new subtypes of immune cells in glioma have been discovered, for example, M1 macrophages, M2 macrophages, polymorphonuclear MDSCs (PMN-MDSCs) and monocytic MDSCs (M-MDSCs) [7]. Different subtypes of immune cells have distinct effects on glioma. For example, M1 macrophages may hinder the glioma and help enhance the therapeutic outcome. The proportions of M2 macrophages are associated with glioma multiplication and impoverished forecast [8]. The relationship between immune cell subtype transition and drug resistance has been well elucidated in glioma [9]. The discovery of potential therapeutic targeting pathways has been opened to seek to suppress glioma growth by modulating the immune system [10]. Even with flow treatment of glioma, containing maximal surgical excision followed by a mixture of radiotherapy and/or chemotherapy, the middle survival for patients with glioblastoma is only $\sim$ 14.6 months since the growing resistance of glioma to radiotherapy and chemotherapy [11]. The flow immunotherapy methods in glioma, which are popular research directions in recent years, mainly include DCs inoculations, peptide vaccines, immune checkpoint inhibitors and chimeric antigen receptor T (CAR-T) cells [12]. Immunotherapy drugs have been approved by the FDA for marketing and unemotional therapy, but overall, none of these drugs can cure glioma patients [13]. There is an imperative demand to find novel therapeutic targets for clinical therapy and prolong patient prognosis. In this article, we debate the four major immunocytes in the glioma microenvironment, including neutrophils, macrophages, MDSCs, and lymphocytes, as well as other immune cells, then mainly discuss each type of immune cells from the following aspects such as subtype classification, impact of glioma on immune subtype and subtype evolution, the application of single-cell sequencing (ScRNA-seq), drug resistance, the therapeutic targets and patients' prognosis. At last, we will discuss the possibility of a new immunotherapy method, which can be better combined with radiotherapy, chemotherapy, surgery and other treatments to maximize the curative effect, provide a set of reasonable treatment plans, and prolong the survival time of patients.

## MDSCs in glioma microenvironment

Under chronic inflammatory or neoplasia conditions, the immune system cannot keep up with the demand for neutralization as a result of deregulated myelopoiesis, one subpopulation of cells which expands prodigiously under such circumstances is named as MDSCs [14]. MDSCs are suppressor cells derived from medulla ossium that are forerunners of DCs, macrophages and granulocytes, and have the potent to suppress immune cell responses significantly [15]. Furthermore, MDSCs in glioma can also be derived directly from normal monocytes that have been subjected to immunosuppressive effects [16] (**Supplementary Table 1**).

### *The subtypes of MDSCs in glioma*

MDSCs express myeloid markers CD11b and CD33, but without markers of developed myeloid cells (MHC II molecules DP, DQ and HLA-DR) [17]. MDSCs in glioma are defined as two populations, regarding as M-MDSCs and PMN-MDSCs, by the statement of CD14 or CD15 individually [18].

M-MDSCs express the supernal degree of the macrophage migration inhibitory factor (MIF) cognate receptor CD74 and localize in the glioma microenvironment [19], and are characterized as CD11b + CD14 + CD33 + HLA-DR$^{low}$/− CD15− [20]. PMN-MDSCs express high proficiency of the MIF non-homologous receptor CXCR2 [19], and are observed as CD11b + CD14 − CD33 + HLA-DR$^{low}$/−CD15+ (or CD66+) in human gliomas [20].

An increasing number of markers are employed to identify subgroups of MDSCs. In a mouse model of glioma, MDSCs can be distinguished as M-MDSCs (CD11b + Ly6C$^{high}$Ly6G−) and PMN-MDSCs (CD11b + Ly6C$^{low}$Ly6G+) [21]. MDSCs can also be characterized by Gr1expression, and MDSCs from the monocyte population (CD11b + Gr1$^{low}$) are more infiltrated than those from granulocytes (CD11b + Gr1$^{High}$), especially from neutrophils [22]. Both PMN-MDSCs and M-MDSCs are capable of further dividing into B220- and B220 + subgroups, but tumors only induce amplification of B220- PMN-MDSCs and B220- M-MDSCs [23] (Fig. 1).

### *The MDSCs subtype transformation induced by glioma*

M-MDSCs are conversed from precursor cells by hypoxic conditions [24] and tumor-derived signals, such as STAT3-COX-2 signaling [25]. The expansion of M-MDSCs in tumors is regulated by miR-486 (a Sox2-induced miRNA regulating the degree of self-resumption in glioma stem cells), which is considered as a regulator of myeloid cell differentiation and apoptosis by marking CCAAT/enhancer binding protein alpha (C/EBP-α) [26,27]. Under hypoxic conditions (such as HIF1α stimulation) [24] and regulation of other factors (such as LIF, IL-6, and cFLIP, A1, ARG1 and IRF8 stimulation) [28,29], M-MDSCs are capable of differentiating into TAMs. NCOR2 controls M-MDSCs to differentiate into inf-DCs but not inflammatory macrophages [30]. There are also various conditions and factors in the tumor microenvironment that can contribute to M-MDSCs differentiation into inf-DCs, such as hypoxia, lactate accumulation, and adenosine accumulation [31].

The main factors of MDSCs differentiating into PMN-MDSCs include the interferon regulatory factor 8 (IRF-8) and the granulocyte progenitor cells (GPs) in the tumor microenvironment. The PMN-MDSCs generation is promoted by the IRF-8 loss GPs, as well as tumor-derived GPs [32]. PMN-MDSCs are also recognized as granulocytic MDSCs (G-MDSCs) [33], and might be further differentiated into tumor-associated neutrophils (TANs) through not-well-defined cytokines [34], as there is no method to distinguish between PMN-MDSCs and TANs [35] (Fig. 2**a**).

### *How MDSCs influence the chemotherapy resistance in glioma*

#### *The chemotherapy resistance is due to the recruitment and activation of MDSCs*

Chemoresistance in glioma is related to the induction, infiltration, and aggregation of MDSCs, producing an immunosuppressive microenvironment [14] and reducing the effectiveness of

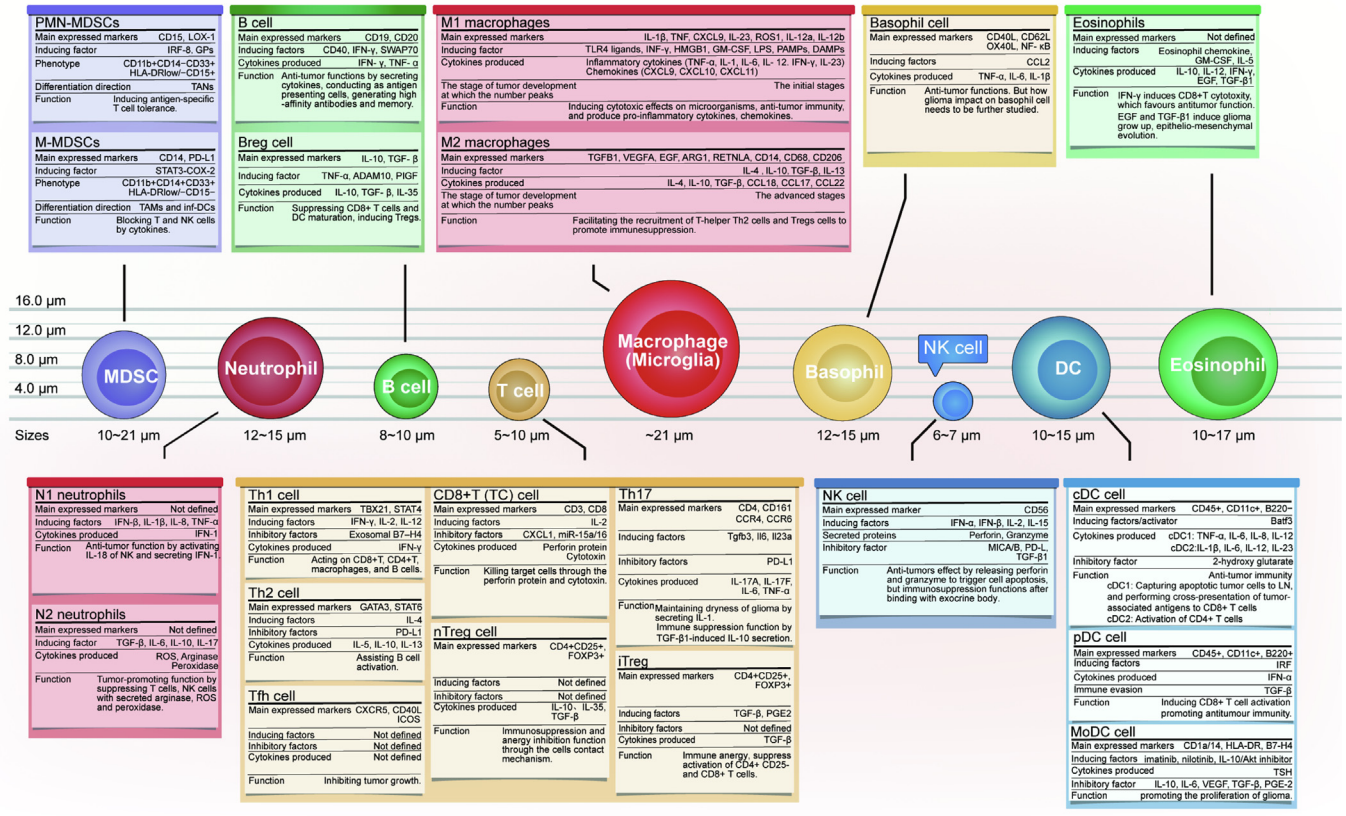



**Fig. 1. Immune cells subtype in glioma microenvironment.** The landscape of immune cells and the characteristics of different immune cell subtypes in glioma microenvironment. The characteristics of each immune cell subtype are described in detail, including main expressed markers, inducing factors, inhibitory factors, cytokines produced and function. Besides, the immune cells involved in the figure mainly include M1 macrophages, M2 macrophages, N1 neutrophils, N2 neutrophils, M-MDSCs, PMN-MDSCs, TH1, TH2, TH17, Tfh, CD8 + T, nTreg, iTreg, B cells, Breg, eosinophils, Basophils, NK cells, cDC, pDC and MoDC.

chemotherapy drugs [36]. For example, the itaconate secreted by MDSCs is mainly absorbed by CD8 + T, then itaconate blocks the biosynthesis of aspartic acid and serine/glycine in CD8 + T lymphocytes, thus hindering the multiplication and activation of CD8 + T lymphocytes [37].

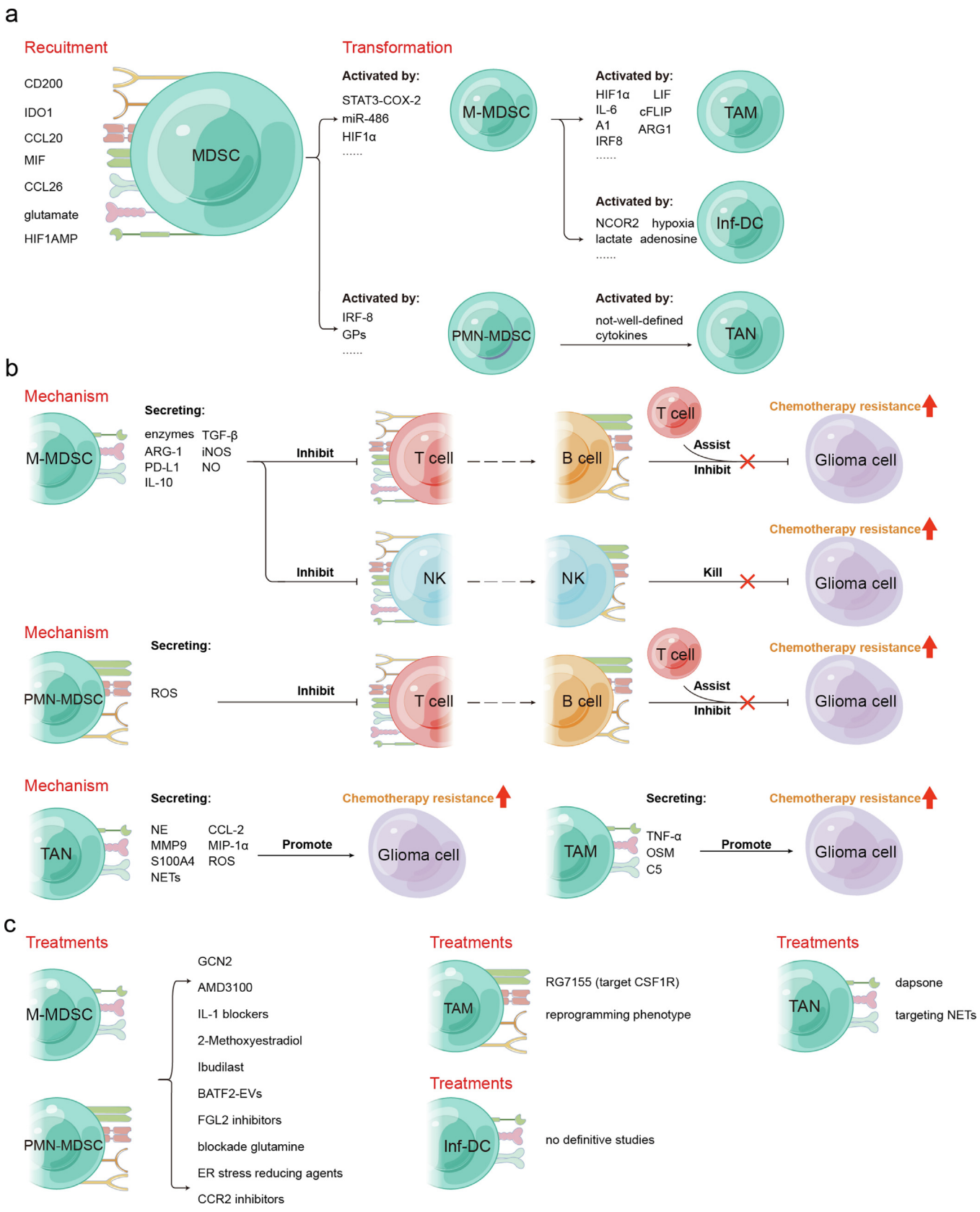
Glioma cells enlist MDSCs from the medulla ossium by overexpressing CD200 [14], MIF [19], indoleamine 2,3-dioxygenase (IDO1) [38], CC-chemokine-ligand-20 (CCL20) [39], and other growth factors. And hypoxia in the microenvironment congregates CX3CR1-expressing MDSCs by raising CCL26 expression [39], and upregulates the statement of VEGF and hypoxia-inducible factor-1α (HIF1AMP) in glioma cells, which in turn induces extracellular nucleoside diphosphate hydrolase 2 (ENTPD2), and induce the generation of 5′-AMP to help the accumulation of MDSCs [40]. Glioma stem cells metabolize and secrete high levels of glutamate into the TME to evade immunological surveillance, higher concentrations of glutamate enable MDSCs to mature and penetrate into glioma sites [41], then glutamine-derived α-ketoglutarate (α-KG) promotes the expansion of MDSCs via NDMA receptors [14].

Currently, the activation process of MDSCs is described mainly by using two-signal models. One group is primarily driven by tumor-derived growth cytokines, including not only INF-γ, STAT-3 [22], IL-6, IRF8, IL-10, and TGF-β but also other substances such as Phosphatidylinositol 3-kinase (PI3K), receptor tyrosinase kinase (RTK) and cyclooxygenase, CCAAT/enhancer-binding protein beta (C/EBP-β), Notch, adenosine receptor A2B signaling, vascular endothelial growth factor 2 (VEGF-2), NOD-like receptor thermal protein domain associated protein 3 (NLRP3), granulocyte–macrophage colony-stimulating factor (GM-CSF) [42–44]. Another set of signal models is mainly mediated by the tumor stroma cell-derived factors including the NF-κB pathway, STAT-1, STAT-6, PGE-2 and COX-2 [45]. Guo X. et al. accepted that the exosomes secreted by glioma cells could produce influential immunosuppressive effects by improving the proliferation and immunosuppressive capabilities of MDSCs in the microenvironment, and the hypoxic microenvironment in the tumor could further facilitate the above effects of glioma exosomes [46]. The above proofs prove that glioma cells are conscientious for rendering MDSCs with the capability to facilitate immune resistance and chemotherapy resistance [47].

### *The distinct mechanism of different subtypes of MDSCs regulating glioma chemotherapy resistance*

Immunosuppression generated by PMN-MDSCs and M-MDSCs in the glioma significantly contributes to tumor development and treatment resistance [48].

M-MDSCs migrate into the tumor microenvironment, which is mediated by glioma-derived CCL2 and CCL7 [49]. Then M-MDSCs activate the CD45 tyrosine phosphatase, which selectively obstructs the action of STAT3 that promotes MDSCs collection by hindering the ultimate differentiation of immature myeloid cells, then differentiate into TAMs and M2-like TAMs, which facilitates the immunological evasion of GBM cells [24]. M-MDSCs stamp out diverse immunologic functions by secreting a mass of immunosuppressive cytokines containing inducible nitric oxide synthase (iNOS), arginase-1 (ARG-1) [50], programmed death ligand 1 (PD-L1), NO, IL-10, and TGF-β [51], and suppress lymphocytes via the production of enzymes and free radicals and reprogram essential lymphocytes metabolites [49]. Specifically, M-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Recuitment
CD200
IDO1
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MIF
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glutamate
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Transformation
Activated by:
STAT3-COX-2
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HIF1α
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M-MDSC
Activated by:
HIF1α LIF
IL-6 cFLIP
A1 ARG1
IRF8
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TAM
Activated by:
NCOR2 hypoxia
lactate adenosine
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Inf-DC
Activated by:
IRF-8
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Secreting:
enzymes TGF-β
ARG-1 iNOS
PD-L1 NO
IL-10
Inhibit
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TNF-α
OSM
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Treatments
M-MDSC
PMN-MDSC
GCN2
AMD3100
IL-1 blockers
2-Methoxyestradiol
Ibudilast
BATF2-EVs
FGL2 inhibitors
blockade glutamine
ER stress reducing agents
CCR2 inhibitors
Treatments
TAM
RG7155 (target CSF1R)
reprogramming phenotype
Treatments
Inf-DC
no definitive studies
Treatments
TAN
dapsone
targeting NETs

MDSCs depend on cytokines to block T cells, NK cells and other immune responses in both antigen-particular and non-particular methods and hinder CD4 + T cell function by producing NOS2, ARG-1 and reactive nitrogen [52,53]. Furthermore, the inhibitory function of M-MDSCs requires IFN-γ or STAT1, of which nitric oxide (NO) is one of the mediators [54].

PMN-MDSCs chiefly act by inducing tolerable antigen-specific T cells and stamping down CD8 + T cells mainly via producing apathetic oxygen species (ROS) in glioma [14]. At the same time, IFN-γ is strictly obligatory for the suppressant function of PMN-MDSCs, which is reliant on STAT1 signaling or NO production [55].

The above effects render immune cells ineffective and immunosuppressive microenvironment, contributing to chemotherapy resistance (Fig. 2**b,** **Supplementary Table 1**).

*The advanced treatments targeting MDSCs subtypes in glioma*

There are four classical types of targeted therapy for MDSCs, including (1) the selective elimination of MDSCs with gemcitabine [56], (2) differentiation of MDSCs to mature uninhibited myeloid cells induced by ATRA, vitamin A or 1,25-(OH)2D3 [57,58], (3) the blocking function of MDSCs by application of Nitro-aspirin [59,60], COX-2 inhibitors, phosphodiesterase-5 inhibitors [61], (4) the inhibiting expansion of MDSCs by administration of VEGF-specific blocking antibodies [62,63]. However, there is more limited in gliomas thought mostly studied in other tumors.

At the same time, there is also other frontier research on targeting MDSCs or the function of MDSCs to restrain tumor malignant progression.

Firstly, the population of MDSCs in the GBM is reported to be reduced by the amino acid-deficient pressure sensor GCN2 [64], IL-1 receptor antagonists or blockers [65], and A CXCR4 antagonist (AMD3100) [66]. MDSCs can also be eliminated by the 2-Methoxyestradiol (inhibiting hypoxia-driven exosomes miR-1246 and PD-L1expression in glioma cells) [16], Ibudilast (a brain-penetrating MIF-CD74 interaction antagonist with augmented CD8 + T cell activity in the GBM) [19], EVs from the basic leucine zipper ATF-like transcription factor 2 (BATF2)-overexpressing glioma cell lines (BATF2-EVs) [67].

Gal-3 inhibition combined with aOX40, an MDSCs targeting drug, increases CD8 + T cell recruitment [68] preventing glioma development. FGL2 is found to enhance glioma immunosuppression by enhancing the quantity of CD39 + regulatory T cells and MDSCs, therefore FGL2 is an immunosuppressive modulator and is latent as an immunotherapy target for GBM [69].

Secondly, the stoppage of glutamine/glutamine catabolism prohibits the recruitment, generation and metabolic reprogramming of MDSCs by hindering the discharge of tumor-derived granulocyte colony-stimulating factor (G-CSF) and promotes the manufacture of antineoplastic provocative macrophages [70].

Thirdly, endoplasmic reticulum (ER) stress-reducing agents such as 4-PBA can resume antineoplastic immunoreaction by suppressing suppressive MDSCs aggravated by ER stress [71]. Prominent ER stress in tumor-carrying hosts could also induce enhanced MDSCs-mediated inhibition, leading to glioma growth [72], and ER has become a potential therapeutic target.

Fourthly, CCL2, an important MDSCs chemokine, is reduced after treatment with acetylsalicylic acid (ASA) in tumor-bearing mice to delay glioma development [73]. CCL2 is mainly produced by CD163-positive infiltrating macrophages and is a crucial chemokine for CCR2 + Ly-6C+monocyte-derived MDSCs, and tumors mature in CCL2-deficient mice are unsuccessful to develop to their maximum size with restricted generation of monocyte-derived MDSCs [39]. Therefore, targeting CCL2 has proved to be a prospective target for the therapy of glioma. The experiments showed that combined CCR2 and programmed cell death protein 1 (PD-1) blockade extended survival in a clinically relevant mouse model of glioma and provided the basis for advancing this combination therapy into early human trials [74].

Additionally, in mice, blocking MDSCs recruitment by CXCR2 antagonists reduced tumor volume [75]. Di Mitri et al. indicated that CXCR2 blockade reprograms TAMs to a pro-provocative subtype and that CXCR2 may be a significant contender for cancer remedy [76].

At last, Zhou, Q.F., et al. condition that the first proof that the elongated non-coding RNA (lncRNA) MALAT1 negatively modulates MDSCs in lung neoplasm [77]. On the horizon, delivering specific lncRNA that targets MDSCs could be used as an adjustable therapeutic treatment of glioma (Fig. 2**c**).

*The single-cell sequencing about detecting MDSCs in glioma*

MDSCs are hard to differentiate from traditional immune cells in terms of function, differentiation and activation [78]. Advanced reporter fate-mapping and high-dimensional single-cell assays can now approve more precise distinguisher of the cells comprising MDSCs in glioma [79].

Single-cell RNA sequencing (scRNA-seq) in the mainstream market consists of low-throughput sequencing (Smart-seq2, CEL-Seq2, et al.) and high-throughput sequencing methods (10X-Chromium, Drop-seq, Seq-Well, inDrops and sci-RNA-seq, et al.) [80] in glioma. For instance, Smart-seq2 can obtain more fragmented information about the gene through the insertion of Tn5, that is, the length of read mRNA is longer in glioma [81]. High throughput sequencing, such as 10X-Chromium, reads a certain length after reverse transcription, but more cells can be detected than Smart-seq2, so it can better detect new MDSCs subtypes [82]. Meanwhile, both 10X-Chromium and BD Rhapsody platforms are within 30 min, and the continuous procedure is unified containing library construction, sequencing, and data analysis [83].

**Fig. 2.** The MDSCs subtype transformation and treatments targeting subtypes in glioma microenvironment. (a) MDSCs could be recruited by multiple cytokines and glioma-secreted molecular (including CD200 [14], IDO1 [400], CCL20 [54], MIF [19], CCl26 [401], HIF1AMP [40] and glutamate [41]). According to specific activation of some signaling, MDSCs are typically characterized as M-MDSC (STAT3-COX2 signaling activity [25], miR-486 regulation [26,27], HIF1α stimulation [402], et al.) and PMN-MDSC (IRF-8 loss GPs [32], et al.). M-MDSC can be activated by HIF-1α [402] and other factors (such as LIF, IL-6, cFLIP, A1, ARG1, IRF8 [28,29]), and transformed into TAM, or can be activated by NCOR2 [30], hypoxia condition and lactate adenosine accumulation [31], and transformed into Inf-DC. PMN-MDSC might be further differentiate into TANs through not-well-defined cytokines [34], as there is no method to distinguish between PMN-MDSCs and TANs [35]. (b) M-MDSCs exert a role in promoting glioma growth and developing chemotherapy resistance by secreting a mass of immunosuppressive cytokines, containing iNOS, ARG-1 [50], PD-L1, NO, IL-10, and TGF-β [51], and enzymes, free radicals [49] to straight block T cell, NK cells and other immune responses. PMN-MDSCs exert chemotherapy resistance function chiefly by inhibiting the function of T cells via producing ROS in glioma [14]. In glioma cells, TAN secretes NE, MMP9 [128,129], S100A4 [124], NETs [122], CCL-2, MIP-1α [126], and ROS [14] to promote glioma growth and chemotherapy resistance, while TAM secretes TNF-α [288], OSM [286], and C5 [274] to promote glioma growth and chemotherapy resistance. (c) Depending on the working mechanisms, targeting treatments for different subtypes of MDSCs include administrating GCN2 [64], AMD3100 [66], IL-1 receptor blockers [65], TKI [403], 2-Methoxyestradiol [16], Ibudilast [19], BATF2-EVs [67], FGL2 [69], blockade of glutamine [70], ER stress [71,72], CCR2 inhibitors [74], RG7155 [326], reprogramming phenotype [70], dapsone [130], targeting NETs [139].

At present, scRNA-seq provides datum displaying transcriptional heterogeneity within MDSCs and may identify previously unreported or rare MDSCs populations in glioma [33], and subtypes of MDSCs such as M-MDSCs and PMN-MDSCs have been found by single-cell sequencing technology [17,28]. There are significant differences in gene expression (RNA) and surface phenotype (protein) among MDSCs subsets [84]. ScRNA-seq revealed that inflammation-driven MDSCs in glioma contain a series of myeloid precursors at various phases of differentiation, from promyelocytes to mature neutrophils. In addition, discriminative phenotypic immunomarkers excavated can be used to distinguish mature myeloid cells from immature MDSCs [85], and lectin-type oxidized LDL receptor-1 (LOX-1) differentiates PMN-MDSCs from neutrophils and M-MDSCs by scRNA-seq in glioblastoma [50]. At the same time LOX-1 has become a special marker of PMN-MDSCs [50], CD11b, CD14, CD15, and CD66b [50] are also included in the main marker of PMM-MDSCs in glioma and the main marker of M-MDSCs is PD-L1 in glioma [20], CD14, CD68, CD163, CD206 and S100A9 [86]. In addition, a comprehensive analysis of multiple RNA-sequencing datasets is performed to assess the effectiveness of targeted medication remedies, such as the antitumor activity of the novel EP4 antagonist YY001 in a mixture with an anti-PD-1 antitrope *in vitro* and *in vivo* [87].

Although the simultaneous sequencing of genetic and epigenetic bases in DNA is achieved in glioma [88], the application of DNA sequencing on MDSCs subtypes in glioma needs further promoted. It would be necessary to develop a more effective sequencing technology, including the Spactial transcriptomics, to observe the interaction between cells, and to understand the dynamic transformation process between MDSCs subtypes [89].

These investigations reveal that the differentiation status and function of TAMs can be influenced by therapeutic interventions, subsequently impacting glioma growth and treatment outcomes. For instance, specific immune modulators can induce a TAMs phenotype shift from immunosuppressive to immunostimulatory, hence enhancing the efficacy of immunotherapy. Some treatments, such as radiotherapy and chemotherapy, may induce subtype differentiation in TAMs, affecting the immune activity within the tumor microenvironment. Despite the considerable promise of single-cell technologies in elucidating the heterogeneity and adaptability of TAMs in GBM, several challenges persist in fully harnessing these technologies for clinical translation. Firstly, while single-cell techniques offer insights into TAM diversity, validating their functional roles *in vivo* is imperative to understand their interactions with GBM cells and other immune components. Secondly, limitations in characterizing key molecular states of TAMs, such as epigenomic and metabolic profiles, call for integration with complementary omics approaches to provide a more comprehensive view. Thirdly, the selection of clustering algorithms for TAM characterization from scRNA-Seq data remains ambiguous, necessitating further refinement. Additionally, the spatial distribution of TAMs introduces additional complexity, requiring a deeper understanding of the microenvironmental cues driving TAM activation and polarization. Addressing these challenges through interdisciplinary efforts and technological advancements will be pivotal in advancing TAM-targeted therapies for GBM patients. Overall, these studies provide valuable insights into the mechanisms of TAMs in glioma therapy and hold promise for the development of more effective treatment strategies.

## Neutrophils in glioma microenvironment

Neutrophils in glioma, the most abundant circulating leukocytes in humans, have expansive functions in immunoreaction [12]. High-grade glioma can be capable of inducing neutrophil infiltration and reticular formation [90], and most gliomas experience severe neutrophilia due to the high production of G-CSF by tumor cells [91]. LINC01116 facilitates neutrophil recruitment and tumor proliferation via DDX5-mediated IL-1β regulation in glioma [92]. Besides, IL-8 [93], CCL8, MIF [22], damage-associated molecular patterns (DAMPs) [94], PILRA [95] in glioma also recruit neutrophils (**Supplementary Table 2**).

### *The subtypes of neutrophils in glioma*

Neutrophils are divided into N1-neutrophils and N2-neutrophils during tumor progression [96], and are divided into N1/N2 neutrophils, TANs and PMN-MDSCs primarily defined by their functional phenotype [97].

In addition, in mouse glioma model, a unique subpopulation of granulocytes is recognized that is characterized by immature neutrophils, possesses neuroprotective possessions, and is able to promote CNS axonal regeneration *in vivo*, in part by secreting a cocktail of growth factors, such as immature $Ly6G^{low}$ neutrophils in the eye drive retinal ganglion cell (RGC) axon regeneration and spinal cord repair [98]. The crosstalk between TANs and the glioma microenvironment modulates heterogeneity toward N1/N2 neutrophils polarization [99]. However, few specific cell surface markers have been identified to define these populations of neutrophils [100] (Fig. 1).

### *The neutrophils subtype transformation induced by glioma*

Neutrophils infiltrating into tumors are called TANs in glioma [101]. TANs polarize to N1 through IFN-β, IL-1β, IL-8, TNF-α and other cytokines regulation [102,103]. TANs can be polarized to an N1-N2 phenotype, and TANs acquire N2 (tumor-promoting phenotype) driven by IL-6, IL-8, TGF-β, IL-10, IL-17, IFN-1 [102–105]. The transformation from N1 to N2 is associated with a series of cytokines, including prostaglandin E2 (PGE2) [22], TGF-β [73], matrix metallopeptidase 9 (MMP-9) [106], IL-10 [104], PD-L1 [107] in glioma microenvironment. While the transformation from the N2 phenotype to the N1 phenotype can be induced by IFN-β, TGF-β inhibitor [108].

The chief regulator of neutrophils generation and release from the medulla ossium is G-CSF, which downregulates CXCR4 and upregulates CXCR2 to promote the production of N2 neutrophils [105], while CXCR4 promotes TANs proliferation via the KLF5/BCL2L12 dependent pathway in glioma [109], and CXCR2 expressed by neutrophils [110] promotes proliferation, invasion and neurosphere formation of glioblastoma stem cells (GSCs) [111] (Fig. 3**a**).

### *How neutrophils influence the chemotherapy resistance in glioma*

#### *The chemotherapy resistance is due to the production of tumor-promoting neutrophils*

In contrast that N1-type neutrophils (the main neutrophils type in the early stage of tumorigenesis) have anti-tumor functions by secreting IFN-1 and activating IL18 of NK cells, N2-type neutrophils (predominantly acquire N2 phenotype as the activity of the N1 subtype of TANs is downregulated in glioma progresses [73]) secrete molecules such as ROS, arginase and peroxidase, which hinder the efficacy of T and NK cells and accomplish tumor-promoting belongings [112]. Under chemotherapy such as Temozolomide treatment, the progression of glioma is associated with filtration of CD11b+ /CD15 + granulocyte subsets in blood and tumor tissues [113]. To sum up, the increase of the N1 phenotype will be positive to chemotherapy, however, chemotherapy resistance is in the situation of an increase of the N2 phenotype [114].

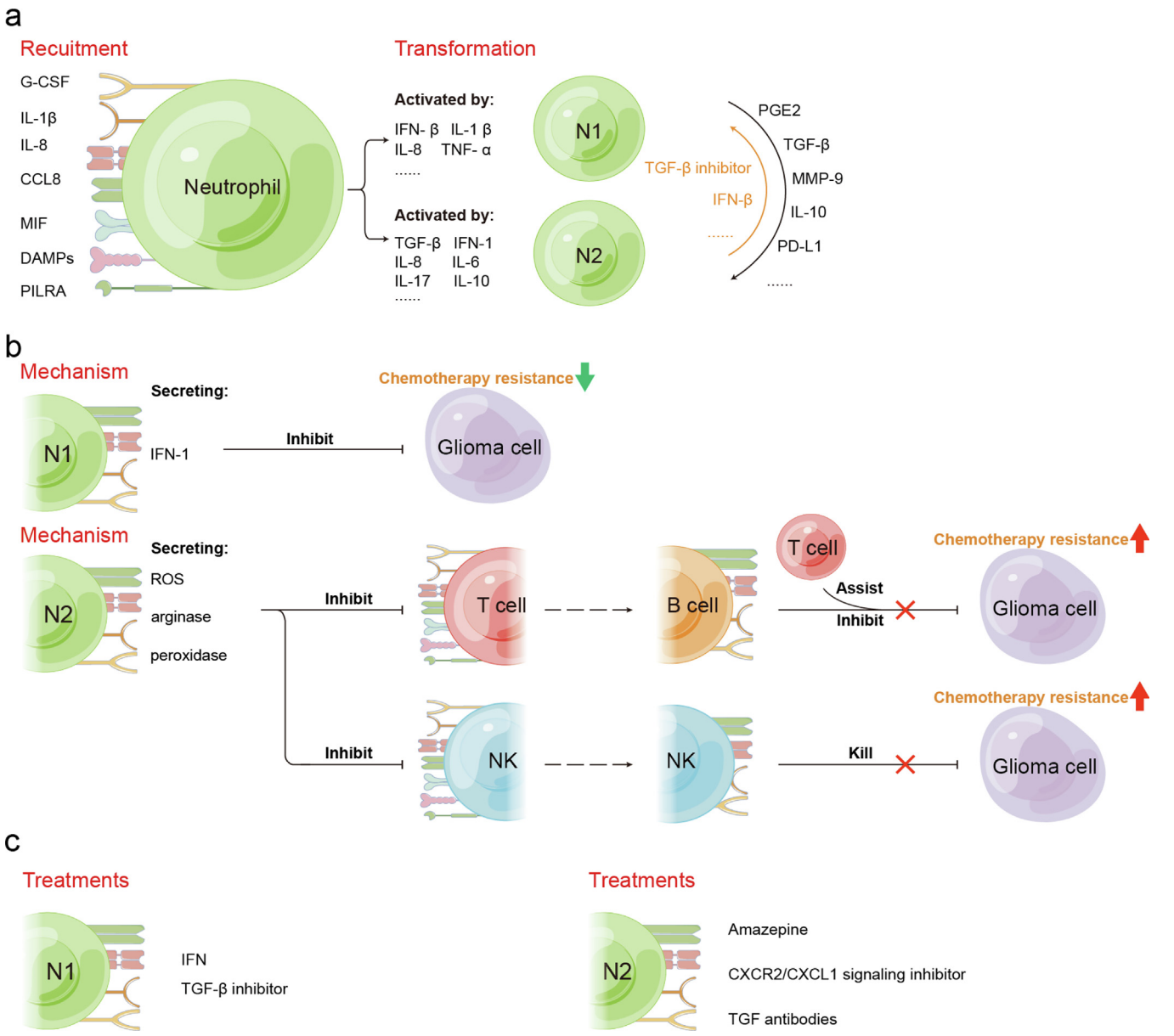



**Fig. 3.** The Neutrophil subtype transformation and treatments targeting subtypes in glioma microenvironment. (a) Neutrophil can be recruited by multiple cytokines (including G-CSF [91], IL-1β [92], IL-8 [93], CCL8, MIF [22], DAMPs [94] and PILRA [95]). Through variable stimulations, neutrophils are characterized as N1-neutrophils (IFN-β, IL-1β, IL-8, TNF-α and other cytokines regulation [102,103]) and N2-Neutrophils (TGF-β, IL-6, IL-8, IL-10, IL-17, IFN-1 [102–105]). The transformation from N1 to N2 is associated with cytokines such as PGE2 [404], TGF-β [22], MMP-9 [106], IL-10 [104], PD-L1 [405] in glioma microenvironment, while the transformation from N2 to N1 is induced by IFN-β, TGF-β inhibitor [108]. (b) N1 secretes IFN-1 to inhibit glioma growth and improve chemotherapy efficiency [73], while N2 secretes ROS, arginase, peroxidase to hinder the efficacy of T and NK cells and then promotes glioma growth and chemotherapy resistance [112]. (c) The potential strategies of N1 for immunotherapy are stimulating IFN and/or inhibiting TGF-β [22], and the potential strategies of N2 for immunotherapy are administrating Amazepine [131], CXCR2/CXCL1 signaling inhibitor [75] and TGF antibodies [133].

Studies have shown that mature Ly6G+neutrophils promote the occurrence and progression of glioma and cancer metastasis through two different mechanisms [115]. First, neutrophils hinder the function of NKs and significantly raise the survival time of tumor cells [116] as well as secreting IL-1β and matrix metalloproteinases, which help tumor cells spill over at metastatic sites [117]. Second, the infiltrated Ly6G+TANs cells transformed GBM tumor cells into a stem cell state through differentiation and nitrosative stress signaling [118]. This framework is further proved by Jeon et al., showing that nuclear factor kB (NF-kB) inhibitors and Ly6G neutralizing antibodies can reduce the number of GSCs with multidirectional differentiation potential [119], an important factor leading to the resistance to radiotherapy, chemotherapy, and recurrence [120].

Therefore, chemotherapy resistance is closely related to immunosuppressive microenvironment produced by tumor-promoting neutrophils [121].

*The chemotherapy resistance is due to the NETs released by neutrophils*

Neutrophil extracellular traps (NETs) are composed of DNA filaments in chromatin wrapped around granulin, which can be secreted by neutrophils to capture microorganisms [122]. NETs-derived HMGB1 binds to RAGE and activates NF-kB signaling pathway in glioblastoma, then NETs encourage it to facilitate glioblastoma secretion of IL-8 that recruits neutrophils through PI3K/AKT/ROS axis in TINs (TANs) and intervenes the establishment of NETs [93]. The DNA segments of NETs promote cancer metastasis

via interacting with membrane protein CCDC25 [123], which senses extracellular DNA and activates the ILK-β pathway to improve cellular movement [122]. NETs induced by tumor-infiltrated neutrophils are dedicated to being a carcinogenic marker of high-grade gliomas (HGGs) and to be conducive to tumor multiplication and assault, leading to chemotherapy resistance [93].

*The chemotherapy resistance is due to the cytokines secreted by neutrophils*

*In vitro* and in mouse models of GBM, infiltrating S100 calcium-binding protein A4 (S100A4) secreted by TANs promotes GSCs growth, malignant phenotypic transformation, and development of chemotherapy resistance [124]. S100A4 also contributes to GSCs activation and proliferation by resisting anti-VEGF therapy and generating immunosuppressive microenvironment [118], whereas inhibition of S100A4 enhances response to anti-VEGF therapy [125].

Besides, neutrophils are capable of releasing CCR2 ligands (CCL-2, MIP-1α), leading to the recruitment of inflammatory monocytes expressing CCR2 which facilitating *in vivo* glioma cell migration after biopsy [126], greatly increasing the difficulty of chemotherapy.

Additionally, the secretion of high-level proapoptotic ROS containing $H_2O_2$ and NO mainly by neutrophils can also result in early induced T cell death [7]. The establishment of a glioma immunosuppressive microenvironment lacking T cells increases chemotherapy resistance [127].

Last but not least, Neutrophils elastase (NE) and matrix metalloproteinase 9 (MMP9) (secreted by neutrophils) that cleave laminin triggers glioma cell proliferation via the activation of integrin signaling [128,129], which challenges chemotherapy for glioma. We can attempt to develop medications targeting NE and MMP9 amalgamating temozolomide for the treatment of glioma (Fig. 3**b**, **Supplementary Table 2**).

*Neutrophil-related treatment in glioma*

*The treatment targeting neutrophil subtypes*

Stimulating IFN and/or inhibiting TGF-β and other molecular mechanisms that promote the differentiation of TANs into an anti-tumor phenotype (N1) are potential targets for immunotherapy [22].

Besides, TANs are the major carriers of angiogenic factor VEGF, which has a significant effect on GBM progression. Suppression of the activity of TANs by dapsone (sulphone antibiotic) caused a diminution in the level of VEGF in GBM [130]. Dapsone inhibits glomerular basement membrane VEGF activity. In addition, Amazepine can inhibit the N2 neutrophils response of GBM cells mediated by the inflammatory factor IL-8, thereby limiting the migration of glioma cells [131].

At last, one of the most common targeting strategies is to block N2 neutrophil recruitment by targeting CXCR2/CXCL1 signaling [132]. Several studies have shown that tumor-promoting neutrophils can also be reprogrammed into anti-tumor neutrophils, where anti-transforming growth factor antibodies favor the secretion of inflammatory factors and the tumoricidal activity of neutrophils [133], which provides a new idea for immunotherapy in glioma (Fig. 3**c**).

*The potential treatments for neutrophils*

First of all, clinical trials of GM-CSF (Colony-stimulating factor, promotes differentiation into mature granulosa) in combination with EGFRvIII peptide inoculation and bevacizumab have indicated that this mixture therapy enhances progression-free survival in GBM patients compared to monomodal remedy [22]. Further evidence added that preliminary research findings from a Phase 2 clinical experiment of GM-CSF in combination with cyclophosphamide and bevacizumab, the results all showed that these treatments improved the survival rate of GBM patients [134].

Secondly, the research using human xenograft GBM displayed antineoplastic efficacy of anti-Ly6G antibody, with existing rebound effects and eventually resistant neutrophil [7]. In the experiment, although the availability of neutrophil depletion progressively disappears when TANs are detected in the cerebral tissue, partial elimination continues. At the terminal stage, TANs appeared to be largely depletion-resistant [94]. Applying anti-Ly6G for eliminating neutrophils improved the survival of mouse withstand IDH-wt tumors modestly but did not benefit Ntva Ink4a/Arf+/−mouse withstand IDH-mutant tumors [135]. At present, the results of anti-LY-6G are only in the experiment, and the clinical application of anti-LY-6G is still quite difficult.

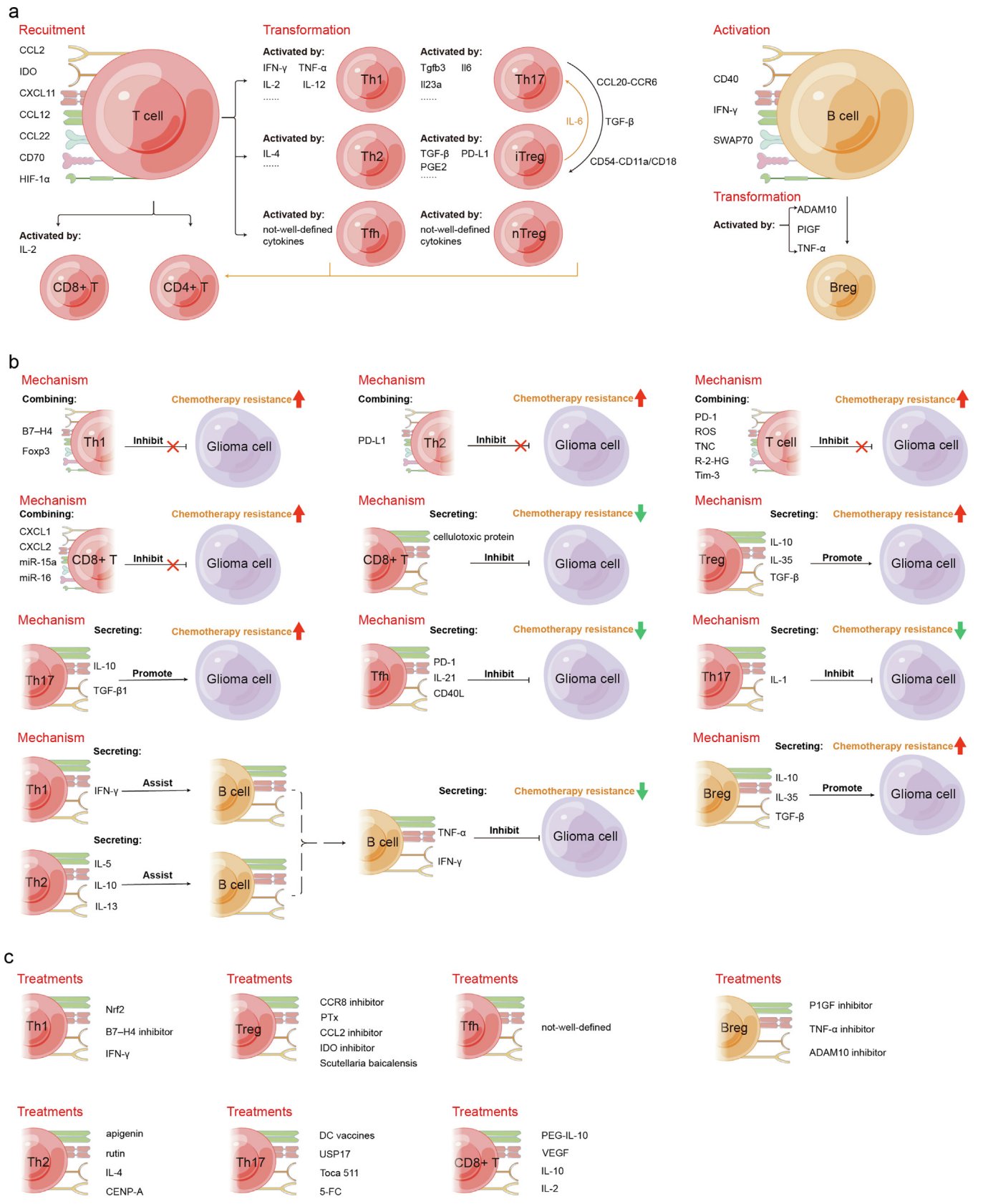
Thirdly, in recent years, glioma cell expresses extracellular vesicles (EVs) have been indicated to support angiogenesis, glioma growth in recipient cells and promote glioma cell migration and attack [136]. In addition, glioma EVs mediate reprogramming of metabolic activity and immunomodulation of TME [136]. However, the exact effect of glioma EVs on neutrophils is still unclear [136]. Therefore, studying the effect of EVs on neutrophils will contribute to the treatment of targeted neutrophil subtypes.

Fourthly, a novel role of neutrophils as cell-based drug delivery vehicles (CBDDV) as liposomes containing the anticancer drug paclitaxel in tumor-bearing mice has recently been elucidated. Studies have shown that the enlistment of neutrophils at neoplasm sites is higher in a provocative state. Inflammatory mediators stimulate neutrophils to release liposomal PTX and deliver PTX to remaining aggressive tumor cells, ultimately limiting glioma progression [137]. These findings can be further explored to curb the growth of GBM.

Lastly, targeting NETs released by neutrophils may also be an effective targeting strategy, but the mechanisms of NETs formation and tumor capture have only been studied in animal models; thus, its role in the pre-metastatic and metastatic niches of human cancers still not clear [138]. However, studies have shown that tumors bind to NETs through the CCDC25 transmembrane protein [139]. Resection of CCDC25 reduced metastasis and primary growth in several tumor models [140]. There is no doubt that this is a potentially promising therapeutic target.

*The single-cell sequencing about detecting neutrophils in glioma*

ScRNA-seq technology has contributed to the identification of neutrophil phenotypes in the tumor microenvironment [141], and can identify morphologically identical various granulocyte populations with differing transcriptomes, improve the understanding of the heterogeneity of mature granulocytes in glioma [142]. Also, scRNA-seq finds that different subtypes of the same cell can co-exist in tumors [141]. The expression of SMOC1 is adversely associated with levels of not only penetrating B cells, CD8 + T cells, CD4 + T cells, macrophages, neutrophils and dendritic cells, but also gene markers of most immune cells in Low-grade glioma. ScRNA-seq findings demonstrated that SMOC1 could be a potential biomarker to influence prognosis [143]. Inflammation drives new transcriptional activity in neutrophils that Grieshaber-Bouyer, et al. observed the expression of transcription factors such as Hmgb2 and Ncor1 under inflammatory conditions take marked changes [144], and reprograms the genetic structure of neutrophil populations, alters dynamic switching between subpopulations, and primes neutrophils for enhanced function without affecting overall heterogeneity [142]. We can try to sequence neutrophils in glioma immune microenvironment by high-throughput RNA sequencing, low-throughput RNA sequencing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Foxp3
Th1
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Glioma cell
Chemotherapy resistance
Mechanism
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PD-L1
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Glioma cell
Chemotherapy resistance
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PD-1
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IL-10
IL-35
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Assist
B cell
Secreting:
Th2
IL-5
IL-10
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CCL2 inhibitor
IDO inhibitor
Scutellaria baicalensis
Treatments
Tfh
not-well-defined
Treatments
Breg
P1GF inhibitor
TNF-α inhibitor
ADAM10 inhibitor
Treatments
Th2
apigenin
rutin
IL-4
CENP-A
Treatments
Th17
DC vaccines
USP17
Toca 511
5-FC
Treatments
CD8+ T
PEG-IL-10
VEGF
IL-10
IL-2

and immunoprecipitation to find new subtypes. This requires rigorous experiments and improvement of our existing technology.

The extensive investigation into the role of neutrophils in the glioma microenvironment reveals intricate mechanisms underlying tumor progression and treatment resistance. While the identification of neutrophil subtypes, containing N1 and N2 neutrophils, TANs, and PMN-MDSCs, provides worthy insights into the heterogeneity of the glioma milieu, challenges remain in precisely defining these populations due to the scarcity of specific cell immunomarkers. Moreover, the transformation of neutrophils induced by glioma, from tumor-suppressive N1 to tumor-promoting N2 phenotypes, underscores the dynamic interplay between cancer cells and the immune microenvironment. The significant contribution of neutrophil-derived factors, containing extracellular traps and cytokines, to chemotherapy resistance highlights the urgent need for targeted therapeutic interventions. While promising strategies, such as inhibiting TGF-β signaling and targeting CXCR2/CXCL1 signaling, show potential for immunotherapy, further clinical validation is required to translate these findings into effective treatments for glioma patients. Future research efforts should focus on elucidating the molecular mechanisms driving neutrophil polarization and identifying novel therapeutic targets to overcome chemotherapy resistance. Additionally, advancements in single-cell sequencing technologies offer exciting prospects for characterizing neutrophil heterogeneity and transcriptional dynamics in the glioma microenvironment. By integrating multidisciplinary approaches and leveraging innovative technologies, future studies hold promise for revolutionizing our understanding of neutrophil biology in glioma and developing more efficacious therapeutic strategies to improve patient outcomes.

## Lymphocytes in glioma microenvironment

In experimental murine representations of Low-grade gliomas (LGGs), T cell migrating into the tumor is intervened by neoplastic cell-producing chemokines (CCL2 and CCL12), whereas HGGs attract T cells by releasing IDO, CCL2, and CCL22 [145]. Besides, the oncolytic adenovirus with CXCL11 could enhance the recruitment of CAR-T cells [146]. CD70 on gliomas may help recruit T cells into the neoplasm [147]. HIF-1α facilitates Treg recruitment by modulating hypoxic T cell metabolism [148]. Helper T cells can polarize into several distinct subtypes, containing Th1 and Th2, Th3, Th17, Tfh and so on [149]. Regulatory T cells (Treg) are separated into natural regulatory T cells (nTreg), induced regulatory T cells (iTreg), and other regulatory T cells [150] (**Supplementary Table 3**).

### *The subtypes and secreted cytokines of lymphocytes in glioma*

#### *T lymphocytes*

Th1 cells in glioma, the main markers are TBX21, STAT1 and STAT4 [151], exert immune function by acting on the most important executive cells such as macrophages, IgG-producing B cells and IFN-producing CD4 + T cells, CD8 + T cells [152]. For example, its main executive cytokine is IFN-γ [153], IFN-γ activates macrophages to enhance Th1 mediated anti-tumor immunity [154]. While Th2 in glioma, the main marker is GATA3, STAT6, STAT5A [151], functions as assisting B cell activation and participating in immune answers by producing IL-4, IL-5, IL-10 and IL-13 [155–157]. In addition, Th17 cells, which are identified by the main markers such as CD4, CD161, CCR4, and CCR6 [158], have a promoting effect on maintaining the dryness of glioma cells by secreting IL-1 [159]. On the other hand, prevenient studies have confirmed that Th17 cells in the GBM microenvironment may be involved in immune suppression via TGF-β1-induced IL-10 expression [160]. Additionally, Tfh cells express PD-1, chemokine receptor 5 (CXCR5), inducible costimulatory molecules (ICOS), CD40L, IL-21 and transcription factors such as C-MAF and BATF, and can promote the formation of tertiary lymph structure to increase tumor immune infiltration and inhibit glioma growth [161]. Finally, in CD8 + T cells, the main markers are CD3 and CD8 [162], which kill target cells through neoplasm cellulotoxic proteins containing perforin, granzyme A/B, IFN-γ and first apoptosis signal ligand (FASL) [163]. Treg in glioma first consists of nTreg and iTreg based on the origin [164]. nTregs are mainly constituted of Foxp3 + CD25 + CD4 + Treg cells, which act through cell-to-cell communication [165], and iTregs are mainly characterized as the CD4 + CD25 + FOXP3+ [166] (Fig. 1).

#### *B lymphocytes*

In general, B cells with the common markers CD19 and CD20 [167], are shown to have anti-tumor functions by secreting cytokines(including IFN-γ, TNF-α) [168], conducting as antigen presenting cells, producing high-attractions antitropes and memory [169]. In addition, 4-1BBL+B cells express proinflammatory cytokines and activation markers (TNF-α, IFN-γ, CD69, and CD86) and have a superior ability to activate autologous CD8 + T compared with 4-1BBL–negative B cells [170].

Various subsets of Bregs in glioma have been identified including IL-10 + Bregs [171], TGF-β + Bregs [172], IL-35 + Bregs [173].

**Fig. 4.** The Lymphocytes subtype transformation and treatments targeting subtypes in glioma microenvironment. (a) There are two main types of lymphocytes: B cells and T cells. T cells can be recruited by variable cytokines and receptors associated with glioma (including IDO, CCL2, CCL12, CCL22 [145], CXCL11 [146], CD70 [147], HIF-1α [148]). CD8 + T cells require the action of cytokines such as IL-2 [188]. CD4 + T cells can differentiate into several distinct subtypes, including Th1 and Th2, Th17, Tfh [149] and nTreg [150]. Th1 is mainly induced by IL-12 [406], IFN-γ and IL-2 [181], TNF-α [183]. Th2 is mainly induced by IL-4 [182]. There is limited relevant studies about Tfh in glioma microenvironment [187]. Th17 cells is promoted by Tgfb3, Il6, and Il23a [192]. iTreg cell is induced by cytokines such as TGF-β, PGE2 and PD-L1/PD-1 [196]. The cytokines or stimulator inducing nTreg are not well defined. (b) Suppression of normal immune cell function can lead to glioma chemotherapy resistance. For example, the binding of ROS [191], TNC [205], R-2-HG [207], PD-1, Tim-3, CTLA-4 [209], and exosomes [184] to T lymphocytes promotes chemotherapy resistance in gliomas. Similarly, the combination of B7-H4, Foxp3 and Th1 inhibits the normal immune function of Th1 and promotes chemotherapy resistance in glioma [185]. The binding of PD-L1 to Th2 inhibits the normal immune function of Th2 and promotes chemotherapy resistance in glioma [193]. The high statement of CXCL1/CXCL2 interrupters the accumulation of CD8 + T cells [189], and miR-15a/16 downregulates the activation of CD8 + T cells [190], which promotes glioma chemotherapy resistance. Tfh, Th17, Treg and Breg secrete some cytokines to exert tumor-promoting effects. For example, PD-1, IL-21 and CD40L secreted by Tfh [161], TGF-β1 and IL-10 secreted by Th17 [160], TGF-β [172], IL-10 [171], IL-35 [173] secreted by Treg and Breg. Regarding anti-tumor effects, Th1, Th2, Th17, CD8 + T, B cells secrete cytokines to inhibit the growth and chemotherapy resistance of gliomas. For example, IL-1 secreted by Th17 [159], cellulotoxic proteins secreted by CD8 + T cells [163], and TNF-α, IFN-γ secreted by B cells [168], directly act on glioma cells and inhibits tumor growth. IFN-γ secreted by Th1 [153], and IL-5, IL-10 and IL-13 secreted by Th2 [155–157] assist in the activation of B cells and enhance the anti-tumor effect of B cells. (c) The targeting treatments for different subtypes of T cell include: (a) targeting Th1: Nrf2 inhibition [215], IFN-γ [216]; (b) targeting Th2: Apigenin, rutin [218], IL-4 [182], CENP-A [217]; (c) targeting Treg: inhibiting CCR8 [229], PTx [226], inhibiting CCL2 [39], IDO1 inhibitor [223] and Scutellaria baicalensis [227]; (d) targeting Th17: DC vaccines [192], USP17 [219], Toca 511 and 5-FC [220]; (e) targeting Tfh: treatments targeting Tfh are not-well defined [186]; (f) targeting CD8 + T cell: treatment of IL-10 and PEG-IL-10 [221], VEGF [191], IL-2 [188]. B cells can be activated by CD40, IFN-γ [170] and SWAP70 [200]. Breg can be induced by TNF-α [174], ADAM10 [175] and PIGF [202] secreted by glioma cells. The targeting treatments for Bregs include P1GF inhibitor [202], TNF-α inhibitor and ADAM10 inhibitor [233,234].

Bregs induced by glioma cells have strong immunosuppressive functions as repressing CD8 + T cells, inducing Tregs and inhibiting dendritic cell maturation in glioma [174,175]. In addition, A variety of soluble molecules (such as the anti-inflammatory cytokine TGF-β [172], IL-10 [171], IL-35 [173]) can also be secreted by Bregs in glioma, then trigger intracellular signaling cascades [176], regulate gene transcription and translation [177], and indirectly regulate the activity of immune cells by binding to cell surface receptors of adjoining immune cells [178]. However, there is no single marker that can identify all Bregs in glioma [179] (Fig. 1).

*The lymphocyte subtype transformation induced by glioma*

*T lymphocytes*

Th1 is mainly induced by IL-12 [180], IFN-γ and IL-2 [181], while the differentiation of Th2 cells in glioma needs to be induced by IL-4 [182]. Phosphoantigen stimulation of Vγ9Vδ2 T cells differentiates them into Th1-like subtype with IFN-γ and TNF-α in glioma [183]. GSCs-derived exosomes hinder T cell activation [184]. For example, exosomes B7–H4 secreted by glioblastoma cells induce Foxp3 expression, which inhibits Th1 cell differentiation [185].

Although current results also show that Tfh cells are significantly decreased in gliomas [186], there are no relevant specific studies about Tfh in glioma microenvironment [187].

CD8 + T cells in glioma proliferation and differentiation require the action of cytokines (such as IL-2) [188]. The high statement of CXCL1/CXCL2 interrupted the accumulation of CD8 + T cells in the tumor microenvironment [189], and miR-15a/16 downregulates the activation of CD8 + T cells [190]. The expression of inhibitory particles on T lymphocytes is promoted by VEGF [191].

The differentiation and establishment of Th17 in glioma are facilitated by the expression of Tgfb3, Il6, and Il23a that is DCs genes products [192]. Generally speaking, for Th cells, studies have indicated that the using up of Th cell is expected to the binding of PD-L1 secreted by glioma to Th cell receptor PD-1 [193].

At present, it is believed that natural Treg which accounts for most of the brain-tumor inhabitant Tregs is derived from the thymus [3], and mainly exerts its inhibitive function through the cell communication mechanism [194], and IL-10, IL-35 and TGF-β secreted by nTregs hinder effector T cell response [195]. Acquired Treg (induced regulatory T cells) is induced by peripheral mature T cells under the condition of continuous antigen stimulation and cytokines such as TGF-β, PGE2 and the communication PD-L1/PD-1 [196]. Then iTregs in return release TGF-β transformed conventional T cells into iTregs [196]. Th17 and iTregs share common features, whose formation is highly dependent on the levels of IL-6 and TGF-β ratio respectively [192], and isochronously increase with the development of GBM as Tregs are capable of affecting the Th17 cells [197]. Th17 are transformed into Tregs cells via Mesenchymal stem cells (MSCs) by achieving a direct cellular contact via CD54-CD11a/CD18 and CCL20-CCR6, triggering PGE2 secretion and trimethylation at K4me3 of histone H3 in the FoxP3 gene locus promoter [198] (Fig. 4**a**).

*B lymphocytes*

The activation of B cells in glioma requires both antigen-stimulatory signals and costimulatory signals [199] such as CD40, IFN-γ [170] and SWAP70 [200].

The exact origin of these Bregs in glioma remains unclear, and any immature B cell can be induced into a regulatory phenotype [201]. TNF-α [174], ADAM10 [175] and PlGF [202] secreted by glioma cells have been identified as Breg-antileptic cytokines in the glioma microenvironment. In addition, GBM-associated MDSCs strengthen regulatory B cell function by delivering PD-L1 microvesicles that can be taken up by tumor B cells. Delivering functional PD-L1 via micro-vesicles ensures Bregs have the potential to inhibit CD8 + T cell activation [203] (Fig. 4**a**).

*How lymphocytes influence the chemotherapy resistance in glioma*

*The chemotherapy resistance is due to the inhibition of anti-tumor lymphocyte production*

Glioma cells not only shift the immunocytes phenotype and function from a potential glioma suppressor to a glioma-promoting state, but also regulate the recruitment and expansion of immunosuppressive cell [51], and specifically, the expression of immunoregulation ligands on the tumor surface hinders the activation of T cells and the implement of their functions [204].

Human GBM cells secrete Ganglioside, which increases ROS generation and acceleratively induces activated caspase-mediated T cell apoptosis [191]. Also, Tenascin C (TNC) is produced by cerebrum tumor-initiating cells (BTICs), which hinders the proliferation and activity of T cells by interacting with α5β1 and αvβ6 integrin on T cells [205]. Another research demonstrated that the GBM cell-derived kynurenine can inhibit T cell immunoreaction by binding to the aromatic hydrocarbon receptor (AHR) in TAMs [206].

On the one hand, the metabolite R-2-hydroxyglutarate (R-2-HG) generated by mutations in isocitrate dehydrogenase (IDH) facilitates glioma genesis through DNA and histone methylation. Tumor cell-derived R-2-HG is absorbed by T cells, after which it induces a nuclear factor perturbation between activated T cell transcriptional activity and polyamine biosynthesis, resulting in inhibition of T cell activity [207]. T cell immunoreactions are also stamped out by glioma-derived exosomes not straightly interacting with T cells [184]. On the other hand, glioma-induced T cell senescence confers tumor cell resistance to immunotherapy, declined expression of the CD28, a costimulatory molecule, is a hallmark of senescent T cells, and the increase of CD8 + CD28 − T Cells might impose a strong obstacle to immunotherapy in glioblastoma [208].

Finally, immunosuppressive checkpoints expressed by infiltrating T cells in GBM, such as PD-1, Tim-3, cytotoxic T-lymphocytes-associated protein 4 (CTLA-4) and IDO1, inhibit T cell activation, proliferation and immunoreaction [209], thus reducing the effectiveness of GBM chemotherapy.

*The chemotherapy resistance is due to the production of regulatory lymphocytes*

The expression of lncRNA HOXA-AS2 is abnormally up-regulated in glioma cells, and lncRNA HOXA-AS2 facilitates the expression of KDM2A/JAG1 by binding to miR-302a, subsequently immune tolerance and promoting proliferation of Treg, whose degree of infiltration is higher in samples with higher interferon-gamma-inducible protein 30 (IFI30) expression [210]. Then, local Treg-mediated improvement of immunosuppression and direct elimination of T cells via IDO, create a tolerant surrounding in tumors [211]. Unfortunately, Tregs and TAMs, the immunosuppressive properties, can antagonize the effectiveness of CAR-T and enhance T cell exhaustion [212]. Temozolomide reduces the accumulation of MDSCs, whereas temozolomide irradiation increases intratumoral granzyme B+CD8 + T cells and also increases CD4 + Treg [141].

In addition to this, Bregs negatively regulate immune responses by producing anti-provocative cytokines such as IL-10, IL-35 and TGF-β [213]. All in all, the antagonist of Treg and Breg produces an immunosuppressive microenvironment, which brings new challenges to chemotherapy such as temozolomide [214]. In the case of chemotherapy resistance, we must consider the treatment for lymphocyte suppression subtypes (Fig. 4**b**, **Supplementary Table 3**).

*Lymphocytes-related treatment in glioma*

*The treatment targeting lymphocyte subtypes*

Nuclear factor erythroid 2–related factor 2 (NRF2) inhibition in DCs accelerates T cell proliferation and Th1 cell immunoreaction in glioma [215]. IFN-γ produced by T cells is considered fundamental for the induction of Th1 polarization-based antineoplastic immunity [216].

Elevated centromere protein (CENP-A) expression may induce Th2 cell infiltration, exerting immune anti-tumor function in glioma [217]. Apigenin and rutin induce apoptosis and increase TNF-α in mice glioma cells while reducing IL-10, indicating a transition from the immunosuppressive Th2 cell to Th1 cell spectrum, which further inspires that apigenin and rutin could be administrated in glioma therapy [218].

Additionally, improving glioma therapy by employing immunogenic cell death (ICD) and photosens-based photodynamic therapy (PS-PDT)-based DCs vaccines to induce Th17 immunity [192]. Ubiquitin-specific protease 17 (USP17) could regulate Th17 function indicating its potential to be associated with glioma immunity and further targeted therapy [219]. Several mouse models have indicated that IL-17 secreted by Th17 can cement MDSCs in the tumor microenvironment, which is further corroboration for the benefits of reducing Th17 with Toca 511 and 5-FC [220].

IL-10 and PEG-IL-10 can initiate the proliferation and cellulotoxic of CD8 + T cells. In animal models, the increasing serum IL-10 concentration produced by PEG-IL-10 (Pegilodecali) enhances the cytotoxicity and expansion of tumor-specific CD8 + T cells, and ultimately treats tumors [221].

CCL2 produced by glioma cells is a key chemokine for CCR4 + Tregs, and tumor growth in CCL2-deficient mice fails to maximize Tregs production, making CCL2 a potential therapeutic target [39]. Research evidence suggests that exercise may reduce tumor progression and thus control tumor development. For example, it appears that rodent exercise triggers tumor-infiltrating changes in macrophages, neutrophils, NK cells, cytotoxic and Treg lymphocytes leading to tumor suppression [222]. The upregulation of IDO is confirmed to be a mechanism for achieving tumor tolerance, in which the tightly coupled positive feedback system between IDO and Tregs is considered as an important function. The strategies blocking IDO improve the competence of tumor immunotherapy [211]. For example, GDC-0919 (IDO1 inhibitor) attenuated RT-induced Tregs and improved T cell activation [223]. Targeting the critical T-cell transcription factor NFAT, which intermediates the expression of anergy-related genes in the cancer circumstances [224], the function of NFAT in Treg reactions is still uncertain and needs to be explained [225]. PTx as an immunotherapy adjuvant can diminish CD4+ /CD25+ /FoxP3 + Treg cells in glioma, and PTx can be used as an immunotherapy adjuvant for the overall treatment of glioma [226]. TGF-β1 induces Treg activity in malignant gliomas, and Scutellaria baicalensis can potentially reverse tumor-mediated immunosuppression by inhibiting TGF-β1 secretion and Treg responses to TGF-β1 [227]. FOXp3 + CCR8 + Treg cells are recruited to infiltrate into tumor tissues and perform immunosuppressive functions by the chemokine CCL1 [228]. Diminish tumor-infiltrating FOXp3 + CCR8 + Treg cells and enhance antitumor immunity by blocking of the CCL1/CCR8 pathway through drugs targeting CCR8 [229]. Different inoculations and antibodies are also developed by targeting the Treg transcriptional regulator FOXp3, Treg-associated cell surface molecules CD25, CTLA-4 and GITR [230]. The immunocyte activation is derived from CD3 and costimulatory receptors CD28 or TNFRSF9/4-1BB [231,232], Which might be a new treatment by stimulating them.

P1GF released by glioma cells can induce Bregs to inhibit CD8 + T cell activity [202]. Targeting P1GF becomes a researchable strategy for the treatment of glioma. We can also block the action of glioma-derived ADAM10, TNF-α inducing Bregs to treat glioma [233,234] (Fig. 4**c**).

*The other treatments for lymphocytes*

Firstly, the glioma-derived EVs carry a broad spectrum of tumor antigens, which can induce idiosyncrasy B-cell and T-cell immunoreactions and effectively activate antigen-presenting cells, thereby inhibiting tumor recurrence and metastasis [235].

Secondly, an increased rate of T cell apoptosis in PTEN-lacking glioblastoma cells in human glioblastoma cells could be detected, and a new method that replaces PTEN and then increasing the proportion of T cells is found by studying cytokines in the PTEN pathway [236].

Thirdly, CD161 whose ligand is CLEC2D, exerts a critical function in hindering the cytotoxicity of T cells in glioma patients [237]. Therefore, CD161 is a novel valuable target for immunotherapeutic in glioma.

Fourthly, oncolytic viruses (OVs) are biotherapeutics used to contaminate and selectively slay cancer cells. OVs are able to recruit T cells and induce sustained immunoreactions against viruses and tumors [238]. HSV-1 mutant dlsptk, the first genetically edited on HSV carried the deletion of the thymidine kinase gene, which destroyed gliomas progression, can be used for the treatment of malignant gliomas [239]. But to fully exploit the therapeutic potential of OVs and HSV-1, there are still many issues such as spreading and penetration that need to be addressed despite improvements [240].

Fifthly, glioma-derived exosomes suppress T cell immune responses by performing on monocyte maturation instead of directly interacting with T cells, therefore targeting exosomes is already a hot spot in immunotherapy [184,241]. In experiments in humanized dKO-NOG (NOG-MHCI/II-2 KO) mice, the STAT3 inhibitor STX-0119 is investigated for its antitumor activity by promoting the accumulation of tumor-infiltrating lymphocytes at tumor sites [242].

Lastly, glioblastoma cells induce PD-L1 secretion by activating versatile receptors such as toll-like receptor (TLR), epidermal growth factor receptor (EGFR), interferon alpha receptor (IFNAR), interferon-gamma receptor (IFNGR) [243]. The combination of the PD-L1 to the PD-1 receptor activates the protein tyrosine phosphatase SHP-2, which dephosphorylates Zap 70 and hinders T cell multiplication and downregulates lymphocytes cytotoxicity [243]. Furthermore, PD-L1 can weaken antineoplastic immunoreactions mediated by CAR-T cells. For this feature of therapy, the combination of anti-PD-L1 with CAR-T cells, and the editing of the PD-L1 gene of CAR-T cells have been proposed to intrude this inhibitory axis [244]. Treatment with CAR-T cells gathers allogeneic T cells in peripheral blood and genetically edits the cells *in vitro* to express specific tumor-associated antigens. CAR-T can target tumor antigens without antigen treatment, and are separated from HLA-mediated antigen presentation. Several early clinical experiments of glioma-targeted CAR-T cells have been completed, targeting various tumor antigens in gliomas, such as EGFR III, HER2, and IL13 [232,245,246]. By injecting CAR-T into the resection cavity to prevent GBM recurrence, or by direct stereotaxic injection of CAR-T to suppress inoperable or recurring tumors [247]. Four CAR-T cell products are already on the market, Kymriah, Yescarta, Tecartus and Breyanzi [248]. The biggest problem is the treatment resistance caused by antigen loss. More advanced CARs therapies are being examined to avoid antigen loss, using precise gene insertions to prevent graft-versus-host disease (GvHD), or using dual-targeting approaches and adaptive CARs [249]. Researchers have discovered that irradiation increases IL-8 secretion by tumors. Thus, constructed IL-8 receptor-modified CD70CAR-T cells migrate into the neoplasm and induce an enhanced antineoplastic immunoreaction in GBM [250]. However, the significant and dur-

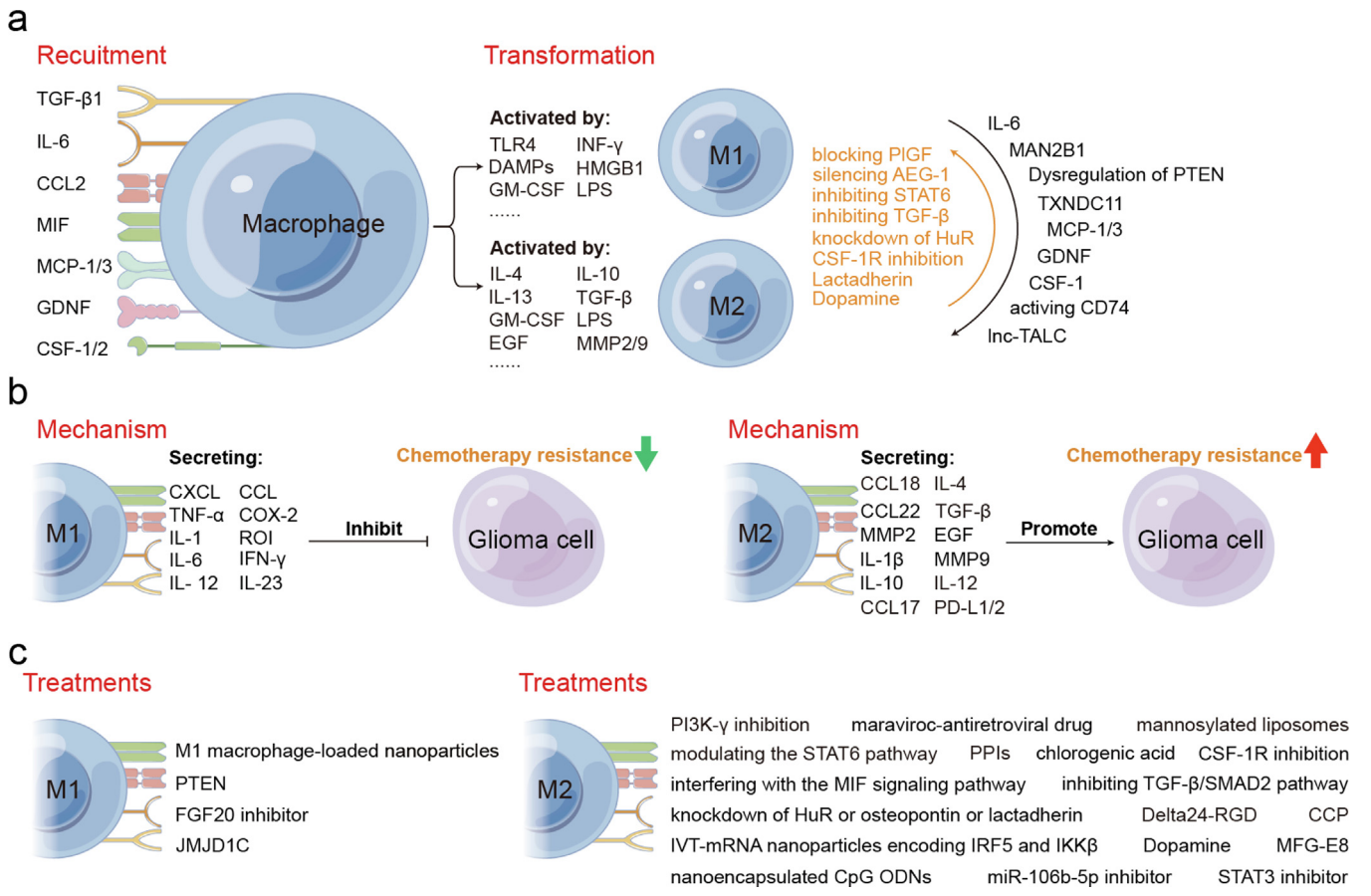



**Fig. 5.** The macrophages subtype transformation and treatments targeting subtype in glioma microenvironment. (a) Macrophages can be recruited by multiple cytokines (including TGF-β1, IL-6, CCL2 [275], MIF [276], MCP-1/3, GDNF, CSF-1/2) [278,279]. Through variable cytokines regulation, macrophages are defined as M1-macrophages through TLR4, IFN-γ [269], HMGB1 [271], DAMPs, GM-CSF, LPS [270] and other cytokines and M2-macrophages are activated through cytokines such as IL-4, IL-10, IL-13 [269], TGF-β [272], GM-CSF [260], LPS [314], EGF, MMP2/9 [292]. Also, M1 macrophages can transform into M2 macrophages through cytokine (IL-6 [275], Dysregulation of PTEN [278], MAN2B1, TXNDC11 [283], MCP-1/3, GDNF, CSF-1 [278,279], activing CD74 [276]. and Inc-TALC [274]) regulation. At the same times, M2 macrophages can transform into M1 macrophages through cytokine and inhibitor (blocking PlGF [318], silencing AEG-1 [296], inhibiting TGF-β [306], knockdown of HuR [309], CSF-1R inhibition [273], Lactadherin [311] and Dopamine [312]) regulation. (b) M1 macrophages can secrete chemokines (CXCL9, CXCL10, CXCL11, CXCL12, CXCL16, CCL2, CCL3 and CCL5), TNF-α, IL-1, IL-6, IL-12, IFN-γ IL-23, COX-2 [73] and ROI [272] to exert anti-tumor function. While activated M2 macrophages secrete large quantities of cytokines such as IL-4, IL-10, TGF-β, CCL18, CCL17, CCL22 [272], TGF-β, EGF, MMP2, MMP9, IL-10 [292] and PD-L1/2 promote glioma development, progression, angiogenesis and chemotherapy resistance. (c) Depending on the working mechanisms, targeting treatments for M1 subtypes of macrophage include administrating M1 macrophage-loaded nanoparticles [315], PTEN [318], FGF20 inhibitor[330] and JMJD1C [331]. At the same times, targeting treatments for M2 subtypes of macrophage include administrating PI3K-γ inhibition [300], Delta24-RGD [301], CCP [302], mannosylated liposomes[303], modulating the STAT6 pathway [304], PPIs [305], chlorogenic acid [299], TGF-β/SMAD2 signaling pathway [306], interfering with the MIF signaling pathway [308], IVT-mRNA nanoparticles encoding interferon Regulatory Factor 5 (IRF5) and IKKβ [307], knockdown of HuR (an RNA regulator) [309] or osteopontin [310] or lactadherin [311], Dopamine [312], CSF-1R inhibition [273], nanoencapsulated CpG ODNs [313], maraviroc-antiretroviral drug [323], MFG-E8 [314], STAT3 inhibitor [321].

able survival benefit of PD-1 and CAR-T on GBM patients is not obvious [251]. Treatment of GBM-specific IL13CAR-T cells with the serine/threonine kinase glycogen synthase kinase-3 (GSK-3) inhibitor SB216763 resulted in reduced PD-1 expression due to T-bet upregulation, and facilitated T cell subsistence and proliferation, efficient in murdering glioma cells [252].

*The single-cell sequencing about detecting lymphocytes in glioma*

Single-cell transcriptomics revealed that both tumor cells and hematopoietic cells in GBM express multiple immune avoidance negotiators to suppress immune cell immunization [253]. ScRNA-seq finds that the main transcription factors of Th1 are STAT4 and T-bet and so on [254], and reveals that CD8 + T cells can differentiate into distinct CXCR5 + PD-1 + Tfh cell subsets, which have semblable genetic characteristics to CD4 + Tfh cells and regulate B cell autoimmunity and autoantibodies generation [255]. Tfhs participate in the information transmission during B cell differentiation and favor the B cells activation [256]. The combination of single-cell T-cell receptor (TCR) sequencing and ScRNA-seq results in paired TCRs-α and TCR-β is measured by high-throughput analysis under single-cell resolution. The advantage of this approach is that it can characterize the clonal expansion of T cells in steady-state and disease, and track the transcriptome changes of the same clone during illness and treatment [257]. We can directly use RNA sequencing technology to further sequence the lymphocytes in the immune microenvironment of glioma and try to find new subtypes. Our focus is to improve the existing technology so that a large number of cells and full-length RNA can be measured simultaneously.

The exploration of lymphocytes within the glioma microenvironment presents a complex interplay between tumor-induced immune responses and potential therapeutic targets. In experimental murine models, distinct subtypes of T lymphocyte cells, such as Th1, Th2, Th17, Tfh, and CD8 + T, exhibit differential recruitment and cytokine secretion patterns orchestrated by the glioma cells. Notably, the regulatory role of hypoxia-inducible factor 1-alpha (HIF-1α) in facilitating regulatory T cell (Treg) recruit-

ment highlights the intricate mechanisms at play. However, despite their potential anti-tumor functions, such as IFN-γ-mediated macrophage activation by Th1 cells, gliomas exploit various strategies to evade immune surveillance, including inducting T cell apoptosis and senescence, the promotion of Treg and Breg immunosuppressive phenotypes. These findings underscore the urgent need for therapeutic interventions targeting lymphocyte subtypes to enhance anti-tumor immunity. Strategies such as NRF2 inhibition to promote Th1 responses, modulation of Th2 polarization through agents like apigenin and rutin, and blockade of immunosuppressive checkpoints hold promise for bolstering anti-glioma immune responses. Moreover, advancements in single-cell sequencing technologies offer unprecedented insights into the heterogeneity and dynamics of lymphocyte populations within the glioma microenvironment, paving the way for the development of personalized immunotherapeutic approaches. Future research endeavors should focus on elucidating novel lymphocyte subtypes, unraveling the intricate signaling pathways driving immune evasion, and refining therapeutic interventions to overcome chemotherapy resistance and improve patient outcomes in glioma treatment.

## Macrophages in glioma microenvironment

Macrophages are derived from monocytes and occupant microglia in the glioma microenvironment [258]. And glioma-associated macrophages including M1 and M2 macrophages [259] are activated by CSF-1, CCL2 [181], M-CSF and GM-CSF [260] (**Supplementary Table 4**).

### *The subtypes of macrophages in glioma*

Glioma-bearing mice display a raised expression of M1 macrophages in the initial stages of tumor progression, whereas the M2 phenotype is observed in the sophisticated stages of glioma [261]. Both tissue-retaining macrophages and derived macrophages have M1 and M2 phenotypes [262]. Cytokine-rich tumor e surroundings can allow macrophages to differentiate from one phenotype to another, and macrophages are divided into classically activated (M1, antitumor) and alternatively activated (M2, pro-tumor) macrophages [263]. M0 is an intermediate state between the M1 and M2 in other phenotypes categorization [264].

M1 markers are IL-1β, TNF, CXCL9, IL-23, ROS1, IL-12a and IL-12b, while M2 markers include TGFB1, VEGFA, EGF, ARG1, CD14, CD68, CD206, RETNLA, CCL22, IL-6 and IL-10 in glioma [265]. Concretely, M2 status markers such as CD14 and CD68 levels are positively associated with the glioma grade [266,267]. Glioma-derived MCP-3 promotes TAMs recruitment in human GBM cells [268] (Fig. 1).

### *The macrophage subtype transformation induced by glioma*

M1 macrophages are activated by TLR4 ligands, INF-γ [269], GM-CSF, LPS, or PAMPs/ DAMPs [270], high mobility group box 1 (HMGB1) [271],while macrophages M2 phenotype are activated by TGF-β [272], IL-4, IL-10 and IL-13 [269] in glioma microenvironment, and exosomes from the hypoxic glioma cells foster M2 polarization [273,274].

Research has indicated that the gliomas are capable of releasing inflammatory mediators/chemotactic factors such as TGF-β1, IL-6, CCL2 [275], MIF [276], PTPRZ1-MET signaling [277], monocyte chemoattractant proteins-1/3 (MCP-1/3), glial cell-derived neurotrophic factor (GDNF), and colony-stimulating factor-1 (CSF-1), CSF-2 [278,279], which are responsible for recruiting TAMs to the tumor site and for the polarization of TAMs from M1 to M2 phenotypes, thereby inducing tumorigenesis. For example, IL-6 released from gliomas [280] can lead to a phenotype shift from M1 macrophages to M2 macrophages by STAT3 activation [281]. Gliomas evade the pro-inflammatory M1 transition of macrophage by activating CD74 by secreting MIF, which go in front to the M2 transition of macrophage [276].

On the other hand, polarization of M2 to M1 macrophages is through inhibition of M2 state, blockade of PlGF inducing vessel normalization or reprogramming of NO in combination with other signals [263,282].

The expression of Mannosidase Alpha Class 2B Member 1 (MAN2B1) is strongly related to M2 macrophages and weakly related to M1 macrophages. At the same time, it is established that the expression of thioredoxin domain-containing protein 11 (TXNDC11) is definitely related to the infiltration of M2 macrophages, and passively corresponds with the infiltration of M0 and M1 macrophages [283]. Therefore, MAN2B1 and TXNDC11 can be used as markers of macrophage subtype transition [284] (Fig. 5**a**).

### *How macrophages influence the chemotherapy resistance in glioma*

#### *The chemotherapy resistance is due to TAMs' inhibition*

EGFR and EGFRvIII synergistically elevate the chemokine CCL2 to induce TAMs infiltration [285]. The recent research by Hara et al. indicates that Oncostatin M (OSM) secreted by macrophages induces GBM towards the mesenchymal state through the receptor activation of OSMR/LIFR-GP130 and STAT3 signaling [286]. TAMs promote dysmorphic and aberrant tumor angiogenesis induced by GBM progression, which is characterized as aberrantly dilated blood vessels with perfusion defects, reduced branch points, and increased vessel leakage [287]. For instance, TNF-α released by glioma-associated macrophages enhance endothelial activation and chemoresistance against anti-angiogenic treatment [288]. On the other hand, glioblastoma cell–released exosomes containing lncRNA induce TAMs to generate complement C5, which promotes the repair of TMZ-induced DNA damage, promoting chemotherapy resistance [274].

#### *The chemotherapy resistance is due to the immunosuppressive microenvironment directly generated by M2 macrophage*

Activated M1 macrophages can induce cytotoxic effects, antitumor exemption, and produce chemokines (CXCL9, CXCL10, CXCL11, CXCL12, CXCL16, CCL2, CCL3 and CCL5), pro-inflammatory cytokines (TNF-α, IL-1, IL-6, IL-12, IFN-γ and IL-23), apathetic oxygen/nitrogen species and COX-2 [73] and ROI [272], while activated M2 macrophages characterized by discharge of large quantities of IL-4, IL-10, TGF-β, CCL18, CCL17 and CCL22 [272] promote glioma development, progression, angiogenesis and immunosuppression by facilitating the recruitment of Th2 cells and Tregs [289–291]. Recent consequence recommends that exosomes derived from GBM cells are conducive to a more malignant phenotype of GBM by transferring lnc-TALC to microglia, intensifying M2 polarization and the production of an immunosuppressive microenvironment [274].

The transition of TAMs to M2 macrophages in gliomas releases large amounts of TGF-β, EGF, MMP2, MMP9, and IL-10, thereby promoting tumor angiogenesis and invasion, as well as an immunosuppressive microenvironment [292]. What's more, IL-1β secreted from M2 macrophage can induce glioma cell migration. Thereafter, IL-1β activates the PI3K pathway by phosphorylating the glycolytic enzyme glycerol-3-phosphate dehydrogenase (GPD2), thereby supporting tumor cell survival and growth [73]. On the other side of the shield, gliomas improve the interactive connection between macrophages and MDSCs, and MDSCs inhibit macrophage secretion of IL-12 and tilt macrophages toward an M2-type macrophage phenotype by IL-10 secretion and cell

contact-dependent mechanisms, thus creating an immunosuppressive environment [14]. Importantly, M2 macrophages express immune checkpoint ligands such as PD-L1 and PD-L2 [293], which decisively modulate T cell activation, proliferation, and immune evasion by human neoplasms [294]. Clinical experiments of PD-1/PD-L1 suppressants are in progress in glioma patients. CheckMate143 (NCT02017717), a randomized controlled clinical trial contrasting Nivolumab (PD-1 antibody) with Bevacizumab in periodic glioblastoma patients, is the first trial launched in the United States [295].

At the same time, silencing astrocyte-elevated gene-1 (AEG-1) attenuates the polarization of M2 macrophages and sensitizes glioma cells to temozolomide in glioma [296].

In a word, M2, which promotes glioma growth, is not conducive to the efficacy of temozolomide, and even makes the chemotherapeutic drug temozolomide resistant [297] (Fig. 5**b**, **Supplementary Table 4**).

*Macrophages-related treatment in glioma*

*The treatment by reprograming M2 macrophages to M1 macrophages*

TAMs exert a crucial influence on the incident and development of GBM, and advocate their significance as latent therapeutic targets for the treatment of GBM and other malignancies [73]. Therefore, targeting macrophage and reprogramming it to an antineoplastic phenotype have become a more desirable therapy than systemic elimination [298]. For example, A series of studies showed that chlorogenic acid [299], PI3K-γ inhibition with AZD3458 [300], topical Delta24-RGD (replicative oncolytic adenovirus) therapy [301], curcumin phytosome (CCP) caused NK cells [302], mannosylated liposomes in designing rational delivery systems [303], lactoferrin nanoparticles modulating the STAT6 pathway [304], proton pump inhibitors (PPIs) [305] inhibited the growth of glioblastoma by repolarizing the macrophages phenotype from M2 to M1. In addition, biomimetic nanoparticles which inhibit the STAT6 pathway and TGF-β/SMAD2 signaling pathway [306], and IVT-mRNA nanoparticles encoding interferon Regulatory Factor 5 (IRF5) and IKKβ [307], interfering with the MIF signaling pathway [308], knockdown of HuR (an RNA regulator) [309] or osteopontin [310] or lactadherin [311], Dopamine (DA) [312], CSF-1 receptor inhibition immunotherapy [273] can also repolarize TAMs from the M2 phenotype to the M1 phenotype. Recent trends in drug delivery research reveal nanoencapsulated CpG ODNs as key players in polarizing M2 clearance to the much-needed pro-inflammatory type M1, establishing the applicability of nanoformulation-carrying CpG ODNs as emerging therapeutic interventions for GBM [313]. In addition, forced expression of MFG-E8 in BV-2 microglia not only enhanced IL-4-induced M2 polarization, but also hindered LPS-induced M1 phenotype polarization [314]. At the same time, *in vitro* cell assays demonstrated that M1 macrophages maintained excellent cerebrum tropism after particle loading and could efficiently convey particles across the endothelial obstacle into tumor tissue. While M1-NPs (M1 macrophage-loaded nanoparticles) exhibited higher cerebrum tumor delivery than complimentary nanoparticles *in vivo* imaging. This result provides a new strategy to utilize M1 macrophages as drug delivery vehicles [315]. Research Team fused macrophage exosomes with liposomes to obtain new nanostructures, which not only withhold the biological function of the macrophages, but also improved the capability of medication carrier, then successfully delivering cargo to the brain through the BBB for treatment [316]. In addition, the PTEN gene encrypts a protein phosphatase and a Ten-SIN homolog [317], and dysregulation of this gene has been implicated in glioma, for not expressing PTEN manifested as a significant reduction in LOX (lysyl oxidase), macrophage infiltration and tumor progression in glioblastoma cells [318] (Fig. 5**c**).

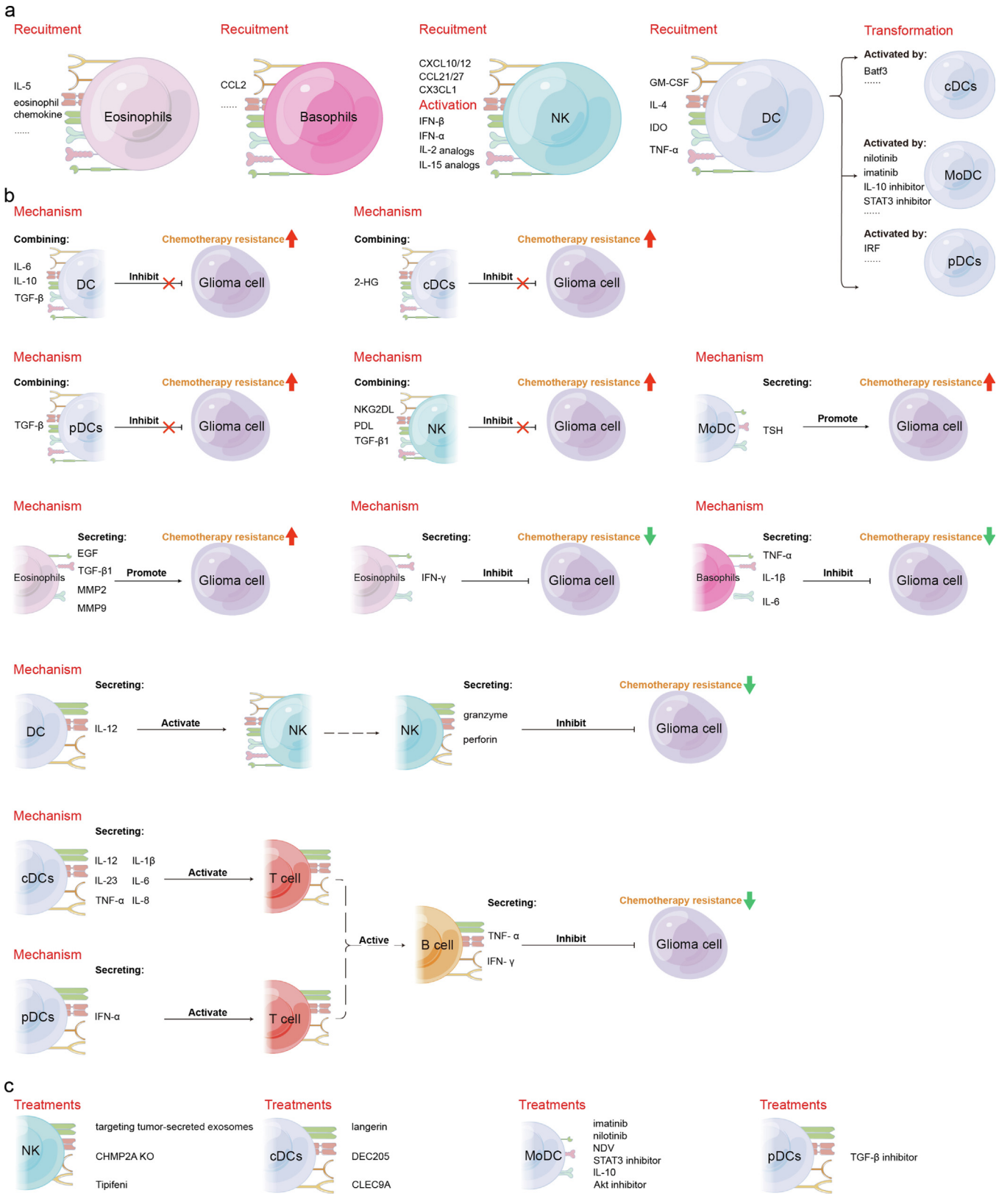
*The existing other research on the treatment of macrophage subtypes*

There is a range of studies showing that ibuprofen and diclofenac have been discovered to decrease the phosphorylation of STAT3 in glioma cells, slowing glioma progression [319,320] and the STAT3 antagonist Pacritinib conquers temozolomide resistance by negatively regulating miR-21-rich exosomes in M2 macrophages in glioma [321]. Duloxetine (a serotonin-norepinephrine reuptake inhibitor) presented a significant reduction in the level of chemokine CCL2 and prohibited TAMs infiltration into the tumor mass [322], antagonist (maraviroc-antiretroviral medication)'s inhibition of CC5R-mediatedactivity caused a decrease in the expression of M2 marker genes (Arg-1 and IL-10) and the M2 population mediated by the downregulation of the Akt signaling pathway [323], CDX-LIPO (brain-targeted liposome and disulfiram/copper synergistic delivery system) significantly triggers tumor cell autophagy, induces immunogenic cell dying, and simultaneously activates tumor-penetrating macrophages and DC cells, T and NK cells manufacturing anti-tumor exemption and tumor regression, promoted mTOR-mediated macrophage reprogramming glucose metabolism in gliomas [324]. Also, blockade of macrophage transcription via targeting the CSF1R (macrophage/-monocyte lineage-specific receptor) is the most commonly targeted strategy for suppressing immunosuppression and metastasis [325], for example, a monoclonal antibody, RG7155 (target CSF1R), inhibits the penetration of TAMs in mouse models and clinical samples [326]. Although RG7155 has recently entered a phase I clinical trial in combination with immune checkpoint antagonist target the ligand of PD-1, PD-L1 [188], in glioma models, despite initial strong efficacy, long-term inhibition of CSF1R leads to medicine resistance and tumor recurrence [327].

*The potential research on the treatment of macrophage subtypes*

AHR [328], the combination of macrophage reprogramming and PD-L1/PD-1 blockade [329], targeting of FGF20 [330], JMJD1C (Jumonji domain containing 1C) [331], miR-106b-5p [332] and TGF-β [333], circBTG2 [334], SYK [335] can be considered as promising targets for enhancing immunity against glioma [328].

The reasons for each are as follows: (1) A recent research revealed an essential function for the GBM cell-derived kynurenine-activated AHR (aryl hydrocarbon receptor) in TAMs and cellular immunity, AHR promotes CCR2 expression-mediated TAMs recruitment and exo nucleotidase CD39-mediated CD8 + T cell dysfunction by co-stimulating adenosine with CD73 [336], however, targets classical monocytes through the CCR2/CCL2 passage, which plays a key role in tumor metastasis, has given controversial results because of rebound phenomena and side effects [337]. (2) PD-L1 is expressed on both M1 and M2 macrophages [338]. The reprogramming of phenotype from M2 to M1 might improve the expression of PD-L1, which can be transcriptionally activated by STAT3 [339,340]. And PD-L1/PD-1 blockade could compensate for the deficiency in macrophage reprogramming [329]. (3) FGF20 binds to the FGF receptor 1 subtype of macrophages and subsequently increases the stability of β-catenin by phosphorylating GSK-3β, thereby inhibiting the polarization of M1 macrophages [330]. (4) JMJD1C promotes M1 phenotype polarization and hinders glioma xenograft growth through the miR-302a/METTL3/SOCS2 axis both *in vivo* and *in vitro* [331]. (5) miR-142-3p is the most down-regulated miRNA in glioblastoma-infiltrating macrophages. M2 macrophages had lower expression of miR-142-3p compared to the M1 phenotype, and miR-142-3p adjusts M2 macrophages through TGF-β signaling [341]. miR-106b-5p hinders IRFI/IFN-β signaling to facilitate M2 macrophage polarization of glioblastoma [332]. (6) Exo-circBTG2 produced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langerin
DEC205
CLEC9A
Treatments
MoDC
imatinib
nilotinib
NDV
STAT3 inhibitor
IL-10
Akt inhibitor
Treatments
pDCs
TGF-β inhibitor

from RBP-J OE macrophages hinders neoplasm progression through the circBTG2/miR-25-3p/PTEN pathway [334]. (7) SYK participates in remodeling the immunosuppressive microenvironment and is an encouraging biomarker and immunotherapy target for diffuse glioma [335].

*The single-cell sequencing about detecting macrophage in glioma*

In the scRNA-seq dataset, the average radiosensitivity index (RSI) of neoplastic cells is positively connected with high M2 macrophages, and high M2 macrophage proportions may be involved in radioresistant glioblastoma [342]. Another scRNA-seq discovers that the levels of TGF-β1 and M-CSF are significantly higher in 1p/19q non-codeletion LGGs than in 1p/19q codeletion LGGs, indicating that M-CSF and TGF-β1 may exert a critical function in regulating the TAMs phenotype in glioma [343]. ScRNA-seq analysis also shows that BTB domain and CNC homology 1 (BACH1) are expressed at higher levels in TAMs than in other cell types in GBMs, and overexpression of BACH1 can upregulate the expression of TAMs chemokines and ICs in glioma *in vitro*. Meanwhile, GBM with high BACH1 expression has a stronger immunosuppressive tumor microenvironment [344]. In addition, TAMs and malignant cells in GBM express a high level of PYGL and difference analysis verify that the expression level of PYGL is definitely associated with the malignant degree of glioma by the single-cell sequencing data analysis [345]. RNA sequencing of macrophages keeping apart from primary tumor specimens made known that both diffuse pontine glioma-associated (DIPG-associated) and adult GBM-associated macrophages express gene programs associated with extracellular matrix remodeling and angiogenesis [346]. Through M1/M2 gene analysis, not only do M1 and M2 gene expression profiles differ, but we also illuminate that the expression of Gpnmb and Spp1 is highly upregulated in both mouse and human glioma-associated microglia/macrophages [308]. MicroRNA sequencing analysis identified miR-1246 as the most enriched microRNA in hypoxic glioma-derived exosomes (H-GDEs) [347]. Interestingly, analyses of single-cell RNA-seq from human glioma samples reveal that Fn14 is equally expressed by tumor-infiltrating macrophages [348]. This finding can potentially be leveraged to deliver novel immunomodulatory agents to the glioma microenvironment via the Fn14-directed DART NP platform [349].

The intricate interplay between macrophages and the glioma microenvironment profoundly influences tumor progression and treatment outcomes. In the glioma microenvironment, there is a dominance of M1 macrophages in early tumor stages, transitioning to an M2 phenotype in advanced gliomas, with both tissue-resident and derived macrophages displaying these subtypes. This phenotypic plasticity is modulated by the cytokine milieu, with M1 macrophages characterized by pro-inflammatory markers like IL-1β and TNF, while M2 macrophages express immunosuppressive markers such as TGF-β and IL-10. Notably, the transition between M1 and M2 states is influenced by various factors including MCP-3 and IL-6 released by gliomas. Mechanistically, gliomas manipulate macrophage polarization through intricate signaling pathways involving molecules like CD74 and MAN2B1. Such phenotypic shifts have significant implications for glioma progression and chemotherapy resistance. Indeed, M2 macrophages foster an immunosuppressive microenvironment, impeding cytotoxic effects and promoting angiogenesis and tumor growth. Targeting macrophage polarization emerges as a promising therapeutic strategy. Reprogramming M2 macrophages to an anti-tumor M1 phenotype using agents like chlorogenic acid or PI3K-γ inhibitors presents a viable approach. Moreover, blocking pathways like FGF20 or JMJD1C show the potential to inhibit M2 polarization and glioma progression. Notably, ongoing research explores novel targets including AHR and miRNAs like miR-106b-5p, promising avenues for enhancing anti-tumor immunity. Single-cell sequencing studies further elucidate the heterogeneity of macrophage populations and their dynamic roles in glioma, offering insights into potential therapeutic targets and precision medicine approaches. Collectively, understanding macrophage dynamics in the glioma microenvironment holds great promise for improving treatment efficacy and patient outcomes in this challenging disease landscape.

## Other immune cells

Eosinophils, basophils, NKs and DCs may produce an immunosuppressive microenvironment, which greatly reduces the efficacy of the chemotherapeutic drug temozolomide in the immunosuppressive microenvironment [350]. Eosinophils, basophils, NKs and DCs are very few in the immune microenvironment of glioma. ScRNA-seq and other means are very promising for finding new subtypes, and are also significant for finding new targets for the treatment of glioma (**Supplementary Table 5**).

*Eosinophils' drug resistance and potential research value in glioma microenvironment*

Eosinophils in glioma with no defined expression markers [351] are associated with the tumor grade of glioma, and it is assumed that eosinophils could be a prognostic indicator of glioma [352]. Cytokines such as IL-5 and eosinophils chemokine produced by glioma cells allure eosinophils [156] and IL-4 can counteract eosinophilic percolation [156]. Then glioma cells secrete GM-CSF to induce oxidative excitability of eosinophils [50] (Fig. 6**a**). Eosinophils may inhibit glioma tumorigenesis, which is worth exploring in the future and may provide some new approaches for glioma treatment [353]. IL-12 and IL-10 derived from eosinophils can improve the sticking of tumors by enhancing the expression of E-cadherin on tumor cells, thereby diminishing metastasis and

**Fig. 6.** The eosinophils, basophils, NK cells and DCs subtype transformation and treatments targeting subtype in glioma microenvironment. The cytokines regulate the recruitment of eosinophils, basophils, NK cells and DCs, for example: IL-5, eosinophils chemokine for eosinophils [156], CCL2 for basophils [356], CXCL10/12, CCL21/27 and CX3CL1for NK cells [367], GM-CSF, IL-4 [377], IDO [180] and TNF-α [161] for DCs. DCs are then gradually activated and differentiated into cDCs through cytokine (Batf3 [386]), MoDCs through cytokine (STAT3 inhibitor [385], IL-10 inhibitor [393], nilotinib and imatinib [393]) and pDCs through cytokine (IRF [391]) regulation. (b) Glioma-derived factors inhibit anti-tumor immunity of immune cells, for example, IL-6, IL-10 and TGF-β could hinder DCs maturation [375], 2-HG impairs the differentiation of cDCs [387]. TGF-β can contribute to immune evasion by pDCs [391], NKG2DL, PDL and TGF-β1 appear on exosomes, these exosomes can bind to cognate receptors on NK cells to inhibit their antitumor activity leading to drug resistance [370]. At the same time, MoDCs and eosinophils secrete some cytokines to exert tumor-promoting effects. For example, TSH secreted by MoDCs [392], EGF, TGF-β1, MMP2 and MMP9 [354] secreted by eosinophils, act on glioma cells to cause chemotherapy resistance. However, basophils and eosinophils secrete some cytokines to exert anti-tumor effects. For example, basophils secreting TNF-α, IL-1β and IL-6 [360], and eosinophils secreting IFN-γ [354], which act on glioma cells to inhibit glioma growth. DC cells secrete IL-12 to activate NK cells, and the activated NK cells secrete granzyme and perforin, which have the effect of killing glioma cells [161]. Inflammatory cytokines such as TNF-α, IL-1β, IL-6, IL-8, IL-12 and IL-23 secreted by cDCs [384], IFN-α secreted by pDCs [390], which are significant in activating T cells and facilitate a wide range of immunoreactions to exert anti-tumor effect. (c) The targeting treatments for different subtypes include: (a) targeting NKs: targeting tumor-secreted exosomes [372], CHMP2A KO and Tipifeni [371]; (b) targeting cDCs: langerin, DEC205 and CLEC9A [390]; (c) targeting MoDCs: imatinib, nilotinib [393], NDV [394], STAT3 inhibitor [385], IL-10 inhibitor and Akt inhibitor [393]; (d) targeting pDCs: TGF-β inhibitor [391].

migration [354]. At the same time, indirectly, IFN-γ produced by eosinophils or IFN-γ derived from CD8 + T co-induce CD8 + T cells migration and subsequent cytotoxicity to promote anti-tumor immunity [354]. Eosinophils granule ontogeny transcript, a long noncoding RNA, hinders glioma cell multiplication and migration and elevates cell apoptosis in mortal glioma [355]. However, eosinophils can synthesize and release EGF and TGF-β1 and they can induce neoplasm cellular growth and epithelial-mesenchymal evolution respectively leading to drug resistance [354] (Fig. 6**b**). In addition, eosinophils could secret matrix metalloproteinases containing MMP2 and MMP9 to induce matrix remodeling, which can also promote the generation of metastasis and dissemination, thus drug resistance [354] (Fig. 1). ScRNA-seq of eosinophils in glioma is less studied, which can be a promising research direction, not only to improve sequencing technology but also to find new subtypes of eosinophils in glioma.

*Basophils' drug resistance and potential research value in glioma microenvironment*

Basophils, attracted by CCL2 [356] (Fig. 6**a**), express different markers on their surfaces, such as Mcpt8 [357] CD40L, CD62L, OX40L, NF-κB to stimulate adjacent cells [358,359]. Basophils release inflammatory cytokines (TNF-α, IL-6 and IL-1β) to apply direct antineoplastic functions and could induce the apoptosis of tumor cells [360]. Increasing proof shows that basophils may not only get involved in the crossfire between immunocytes and cancer cells but also in the initiation of other types of cells, especially in cancer [361]. Mikael J Pittet reported that basophils can enhance the recruitment of specific CD8 + T cells in tumors by secreting the chemokines CCL3 and CCL4 in glioblastoma [362]. These clarify that similarly to other immunocytes, basophils may take effect in an anti-tumor effect in glioma microenvironments. However, how glioma affects the function of basophils remains to be further studied [363] (Fig. 6**b**). Research identifies that basophils retain their capability to be activated in glioma and may participate in the induction of hypersensitivity to anticancer medicines by IgE [364]. However, the assessment of the security of IgE is still lacking, and further work is required to gain a clearer understanding of basophils and their contributions to anti-glioma immunity [364]. Histamine in basophils increases the permeability in brain tumor tissue without affecting normal cerebrum permeability [365], which can enhance the effectiveness of antitumor medications (Fig. 1). ScRNA-seq is crucial for discovering new basophils subtypes in glioma, and will be a hot field in the future. Epigenetics can be used to further study the role of basophils in glioma. Uncover the influence of DNA methylation and Chromatin conformation on this phenomenon.

*NK cells heterogeneity, drug resistance, treatment and detecting technologies in glioma microenvironment*

CD56 is the universal immune marker for NK cells, and at least two major populations of NK cells have been identified: CD56Dim (low expression level of CD56) and CD56bright (high expression level of CD56) [366]. The cytokines of chemotactic NK cells are CXCL10/12, CCL21/27, and CX3CL1 [367], and Castriconi et al. found that glioblastoma-derived glioma stem cells are highly sensitive to lysates mediated by NK cells [368] activated by IFN-α and IFN-β secreted by glioma[181]. IL-2 analogs such as ANV419 selectively activate T cells and NK cells, and IL-15 analogs such as Anktiva (one of the cytokines expected to replace IL-2 function) can stimulate NK and CD8 + T cells, but not Treg cells [369]. However, tumor-secreted cytokines such as NK cells activating receptor NKG2D ligand (NKG2DL), PDL, and TGF-β1 appear on exosomes. These exosomes can bind to cognate receptors on NK cells to induce downstream signaling and inhibit their antitumor activity leading to drug resistance [370]. NKs have a prominent function in antitumor T-cell immunity as they upregulate the expression of MHCI in neoplasm cells and APCs and promote the differentiation of effector CD4 + T cells [204], and once NK cells encounter tumor cells, they will release perforin and granzyme, which respectively penetrate the plasma membrane and trigger cell apoptosis [161] (Fig. 6**b**). ScRNA-seq finds that CHMP2A can induce the death of NK cells by promoting the secretion of EVs by tumors. CHMP2A KO or the use of the inhibitor Tipifeni (a kind of farnesyltransferase inhibitor) can lessen the secretion of EV, thus improving the killing effectiveness of NK cells against tumors [371]. The anti-tumor efficiency of NK cells might be reinstated by targeting tumor-secreted exosomes that are conveyed to NK cells by fusion with cell membranes [372] (Fig. 6**c**).

*DC cells heterogeneity, glioma-initiated subtype transformation, drug resistance, treatment, detecting technologies in glioma microenvironment*

*The maturation and drug resistance of DCs in glioma*

DC cells in glioma express CD11c, MHC II markers [373] and secrete multifunctional pro-inflammatory cytokines, such as IL-12, which irritate the differentiation of primitive T cells into effector T cells and irritate the activation of NK cells [374]. Simultaneously, Immature DCs express a low frequency of maturation markers, containing CD40, CD80, CD83, CD86 and MHC-II [375].

DCs are recruited to the TME through the use of CCL5 and XCLI [376]. The four most important cytokines that induce DCs generation are GM-CSF, IL-4 [377], IDO [180] and TNF-α [161]. For example, GM-CSF enhances DCs generation and IL-4 hinders the differentiation of DCs precursor cells into CD14 + macrophages, but differentiates into CD14- CD1a- immature DCs [377], then DC precursor cells differentiated into mature phenotype CD1a+/CD83 + DCs Through TNF-α [161]. However, glioma-derived factors such as IL-6, IL-10 and TGF-β could hinder DCs maturation [375] to evade immune control [378]. For example, glioma releases IL-6, which inhibits the differentiation of CD34 + T cells into DCs and promotes their commitment toward monocytic lineage with poor APC function [379]. It is further demonstrated that IL-4 and IL-13 reverse the inhibitory effect of tumor cells on DCs differentiation [379].

The ligation of specific cell surface molecules on DCs can result in antigen presentation to T cells [380]. For example, in tumor-carrying parasitifers, the differentiation and the function of DCs are compromised, increasing immature DCs are generated and then infiltrated into the glioma microenvironment, which suppresses antineoplastic T cell immunity due to deactivation of T cells by lack of multiple co-stimulatory molecules [204], thus leading to the immunosuppressive microenvironment and chemotherapy resistance. However, mature DCs could activate glioma-specific CD8 + T and are able to kill glioma cells *in vitro* [381].

*The subtypes, transformation and treatment of DCs in glioma*

DCs are categorized into conventional or classical DCs (cDCs), plasmacytoid DCs (pDCs) and monocyte-derived DCs (moDCs) [382]. cDCs cells are identified as CD45+/CD11c+/B220 – and pDCs are identified as CD45+/CD11c+/B220+ [383]. cDCs can be subdivided into at least two distinct subpopulations, according to their functional characteristic: cDC1 (BDCA3, CD141$^{high}$, XCR1, CLEC9A and DNGR1) and cDC2 (CD11b, CD1c (BDCA1), CD115 (M-CSFR) and CD172a (SIRPα)) [384]. The markers of MoDC are CD1a, CD14, CD40, HLA-DR and B7-H4 [385] (Fig. 1).

Studies in gliomas demonstrated that Batf3-dependent cDCs are critical for cross-presentation antigen [386]. cDCs exert effective anti-tumor immunity, 2-hydroxy glutarate (2-HG) impairs the dif-

ferentiation of monocytes into cDCs with unknown specific mechanism in glioma [387].

cDC1 secret inflammatory cytokines such as TNF-α, IL-6, IL-8 and IL-12 upon activation [384], and are decisive antigen-presenting DCs heterogeneity for the production of antineoplastic, which entrapment apoptotic tumor cells to migrate into draining lymph nodes, and perform cross-presentation of tumor-associated antigens to CD8 + T cells [388,389]. At the same time, cDC2 secrete abundant cytokines such as IL-1β, IL-6, IL-12 and IL-23 and are significant in activating CD4 + T cells and facilitate a wide range of immunoreactions including Th1, Th2, and Th17 in specific circumstances [384]. Targeting antigens and adjuvants to tumor-tolerant DCs *in vivo* can improve antitumor immunity, and the C-type lectin receptor (CLR) exhibits diverse expression patterns on DCs and has been used as a preferential target receptor (such as using DEC205, CLEC9A, and langerin to target cDC1) to stimulate T cell responses [390].

pDCs, whose differentiation is through the involvement of transcription factors like IRF [391], naturally derived blood, induce CD8 + T cell activation and promote antitumor immunity through production of IFN-α [390]. TGF-β derived by glioblastoma can contribute to immune evasion by pDCs [391]. Therefore, TGF-β inhibitors may mitigate the immune evasion effect of MoDCs.

MoDCs-secreting thyroid-stimulating hormone (TSH) could promote the proliferation of glioma [392], and the differentiation of MoDCs is inhibited by glioma-derived factors IL-10, IL-6, VEGF, TGF-β and PGE-2 [385]. At the same time, phosphorylated MITF translocates into the nucleus upon therapy of MoDCs with imatinib, nilotinib, IL-10 inhibitor, or Akt inhibitor, which promotes the generation of MoDCs [393]. Also, tumor-inducing inhibitory signaling in MoDC precursors is interrupted by the amalgamated STAT3 and p38 MAPK signaling pathways, which may support clinical immunotherapy strategies [385]. However, STAT3 inhibition only obstructs IL-6 effects [385]. Besides, human MoDCs treated with NDV show a remarkable curative effect in glioma [394] (Fig. 6**b**).

*The other research on DCs*

DCs can interact with DCs to convert them into tolerable DCs [395], and tumors can induce DCs tolerance. *In vitro* cryoablation restores the function of tumor-tolerant DCs [396]. The immunosuppressive in glioma remodeled by GSCs may curtail the clinical curative outcome of the modified DCs vaccines, indicating the necessity of exploring a new strategy of targeting transformed DCs (t-DCs) to improve patients' prognosis on the basis of clarifying the exact mechanisms of mutual interactions between GSCs and DCs [397]. At the same time, JAK1 signaling in DCs promotes peripheral tolerance in autoimmunity through PD-L1-mediated Treg induction [398]. We can apply this research to gliomas. ScRNA-seq finds that peripheral blood DCs (PBDCs) are reduced in newly diagnosed adult-type diffuse glioma patients compared to tumor-infiltrating DCs (TIDCs), and that all subsets of DCs are recruited in the core lesions of glioma but they are functionally impaired [399]. Using recent advances in single-cell sequencing technologies and reference-based mapping, we show that the biological function of DCs is not confined to priming peripheral T cells in glioma [379].

The exploration of other immune cell subtypes, including eosinophils, basophils, NK cells, and DCs, in the glioma microenvironment presents avenues for further investigation and potential therapeutic targeting. Eosinophils, despite their limited presence in gliomas, exhibit complex interactions with the tumor milieu. While they may initially inhibit tumorigenesis through cytokine release and the promotion of anti-tumor immunity, eosinophils can also contribute to drug resistance and tumor progression via the secretion of growth factors and matrix remodeling enzymes. Future research should aim to elucidate the precise role of eosinophils in glioma progression and explore strategies to harness their anti-tumor potential while mitigating their pro-tumorigenic effects. Similarly, basophils exhibit potential anti-tumor functions mediated by inflammatory cytokine release, yet their interactions with glioma cells remain poorly understood. Investigating the mechanisms underlying basophil-mediated anti-tumor immunity and drug resistance could unveil novel therapeutic targets for glioma treatment. Additionally, the heterogeneity of NK cells and DCs in the glioma microenvironment presents opportunities for targeted therapies. Understanding the distinct roles of NK cell subsets in anti-tumor immunity and the mechanisms driving their activation and inhibition by glioma-derived factors is crucial for developing effective immunotherapeutic strategies. Similarly, delineating the subtypes and functional specialization of DCs, as well as their interactions with other immune cells in gliomas, holds promise for enhancing anti-tumor immunity. ScRNA-seq offers a powerful strategy to uncover the transcriptional heterogeneity and functional diversity of these immune cell populations, promoting the development of precision immunotherapies tailored to individual patients. Future research efforts should focus on elucidating the molecular mechanisms regulating the activity of these immune cell subsets in the glioma microenvironment and identifying novel therapeutic targets to overcome immunosuppression and enhance anti-tumor immunity.

## Conclusion

Gliomas create a profound immunosuppressive surrounding within the tumor due to the dysfunction of glioma-induced T and NK cells, DC cells, expansion of Tregs, Bregs and MDSCs, macrophages (tumor-promoting phenotype), neutrophils (tumor-promoting phenotype), upregulation of cytokines secreted by glioma cells and immunosuppressive immune cells. To address the above issues, we have explored the markers of immune cell subtypes, the causation of chemotherapy resistance, and the current and potential immune-targeted therapy. This review describes the impact of glioma cells on each immune cell subtype, and also analyzes how gliomas affect immune cell subtype transformation and lead to chemotherapy tolerance, lists the similarities and differences such as immune markers of immune cell subtypes, integrates the previous single-cell sequencing technology to explore various subtypes of immune cells, at the same time, proposed current immunotherapy measures and potential targeted therapy targets. Further, gliomas can influence the differentiation of MDSCs, neutrophils, T cells, B cells, macrophages, eosinophils, basophils, NK cells and dendritic cells through cytokines. Therefore, its function becomes immunosuppressive and drug treatment develops tolerance. Changing the inhibitory state of immune cells by targeting cytokines in the signaling pathway can be used as a strategy for the treatment of glioma, and some drugs have achieved well-targeted efficacy. However, although the therapeutic efficacy of some targeted drugs has been verified in other tumors, glioma cannot be used for the treatment due to blood–brain barrier, ‘‘cold tumor” and other reasons. At the same time, some targeted therapies can target systemic organs, resulting in systemic adverse reactions that limit their application in gliomas. The most important of all is that many targeted therapeutic drugs need gene detection before application, and targeted therapy can only be carried out if appropriate therapeutic targets are found through gene detection. Consequently, the number of patients who can really adapt to targeted therapy and benefit from targeted therapy is relatively limited. This review provided perceptions on how to improve current treatment strategies, as well as theoretical guidance for medication development and medication enhancement. We provided a

table of molecular markers for M1/M2 macrophages, N1/N2 neutrophils, Treg, MDSCs and other immune cells. These molecular markers provided a theoretical foundation for predicting the progress of immune cells and selecting specific targeted drugs according to the immunosuppressive environment. However, this study did not address the impact of different grades of gliomas on immune cell transformation, for example, how high-grade glioma and low-grade glioma influence the differentiation of macrophages respectively. In addition, further classification of intratumoral heterogeneity and immune cell subtypes in GBM using single-cell sequencing technology is required to obtain a more complete and precise classification of cell subtypes. It is also necessary to study the differential expression of DNA, mRNA, lncRNA, and proteins in different cell subtypes, and analyze the level at which the transformation of immune cells mainly functions. Through these molecular-level studies, we can further improve molecular detection methods, guide targeted therapy based on molecular classification, and form a set of precise GBM molecular treatment manuals to improve patient outcomes.

## Ethical approval and consent to participate

Not applicable.

## Consent for publication

Not applicable.

## Availability of data and materials

Data and materials related to this work are available upon request.

## Credit author statement

T.C. and W.M. wrote the article. C.J. conducted cutting-edge searches and modifications. X.M. and J.C. provided critical perspectives on the article ideas. T.C., Q.Y., X.H., Y.W., X.W. and Y.S. participated in the figure design and article revision. All authors contributed to the article and approved the submission version

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## Compliance with Ethics requirements

*No ethical approval is needed.*

## Declaration of competing interest

*The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.*

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## Appendix A. Supplementary data

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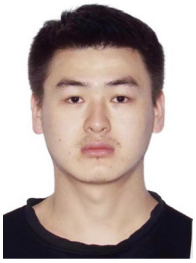

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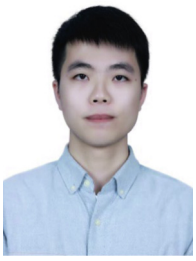

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