Journal of Neuroimmunology 407 (2025) 578713

Contents lists available at ScienceDirect

Journal of Neuroimmunology

journal homepage: www.elsevier.com/locate/jneuroim

Full Length Article

Harnessing the innate immune system for glioblastoma therapeutics

Hamish McLean [a], Matthew Drill [a], Richard Sequeira [a], Padmakrishnan Chorakode Jayakrishnan [a], Rosalind L. Jeffree [a,b], Martin Hunn [a,b], Terence J. O'Brien [a,c], John Hamilton [d], Mastura Monif [a,c,*]

[a] Department of Neuroscience, School of Translational Medicine, Monash University, Melbourne, Australia
[b] Department of Neurosurgery, Alfred Health, Melbourne, Australia
[c] Department of Neurology, Alfred Health, Melbourne, Australia
[d] Department of Medicine, The University of Melbourne, Melbourne, Australia

ARTICLE INFO

Keywords:
Glioblastoma
Tumour microenvironment
Innate immunity
Immunotherapy
Anticancer therapy

ABSTRACT

Glioblastoma is the most common primary malignant brain cancer and is associated with significant mortality and resistance to treatment. One of the major barriers to successful treatment of this cancer is the highly immunosuppressive tumour microenvironment. This tumour microenvironment is comprised of a complex mixture of cancerous cells, neurons, astrocytes, and a variety of immune cells. Microglia, macrophages and monocytes make up a significant proportion of the cells present in the glioblastoma tumour microenvironment. These innate immune cells normally act to maintain homeostasis, though following exposure to cancer cells are signalled to support glioblastoma cancer cell proliferation and treatment resistance. This review provides detailed insights into the role of innate immunity on glioblastoma cell proliferation and glioblastoma pathogenesis. It discusses ways of harnessing the anti-tumour potential of innate immune cells and documents the current preclinical and clinical trials focusing on innate immunity in glioblastoma. The work presented showcases how the anti-tumour capacity of innate immune cells could be utilised to provide novel treatment strategies to combat glioblastoma.

1. Glioblastoma overview

Glioblastoma (GBM) is the most common type of primary malignant brain cancer globally with an incidence rate of 3.23 per 100,000 (Ostrom et al., 2021; Miller et al., 2021). Importantly, GBM is characterised by its incredibly poor survival rate (Ostrom et al., 2021; Miller et al., 2021; Xiao et al., 2023; Sharifian et al., 2024), high infiltrative capacity and resistance to treatment (Seker-Polat et al., 2022). GBM comprises 49.1 % of all malignant brain tumours (Ostrom et al., 2021) with a 5 year survival rate of ~6.8 % (Ostrom et al., 2021; Marenco-Hillembrand et al., 2020). This survival rate has only improved marginally in the last 2 decades, since standard treatment was changed to include temozolomide with the existing surgery and cranial radiation treatment (Marenco-Hillembrand et al., 2020). This change was shown to increase the median survival rate by just 3 months (12.5 to 15.6 months) (Marenco-Hillembrand et al., 2020). A recent meta-analysis further highlights this lack of significant improvement in long term survival; it showed 2-year survival increased from 9 % to 18 %, after 2005, but 5 year survival only improved by 1 % (Poon et al., 2020).

The WHO classification of GBMs has recently undergone several changes to reflect improved understanding of not just the disease histology but also, genetic and molecular markers (Louis et al., 2021). Importantly, following the 2021 updated WHO classifications, the grading system for gliomas now refers to expected clinical outcome rather than to different tumour types, meaning the same tumour type may be given one of multiple different grades depending on disease severity (eg. astrocytomas may be designated grade 2, 3 or 4, with grade 4 being reserved for the most severe cases) (Louis et al., 2021). GBM is still solely termed grade 4 to reflect its aggressive malignant nature and poor expected clinical outcomes (Louis et al., 2021). Additionally, to be considered GBM, cancer cells must be isocitrate dehydrogenase (IDH) wild-type. Previously diagnosed IDH-mutant GBMs are now considered astrocytomas. This reclassification was chosen to reflect the significant improvements in survival rate/outcomes conferred by IDH mutant status (Louis et al., 2021). This is significant as a study by Tesileanu et al. (Tesileanu et al., 2022) found no significant clinical benefit from the

* Corresponding author at: Department of Neuroscience, Level 6, The Alfred Centre, 99 Commercial Rd, Melbourne, VIC 3004, Australia.
E-mail address: Mastura.Monif@Monash.edu (M. Monif).

https://doi.org/10.1016/j.jneuroim.2025.578713
Received 3 March 2025; Received in revised form 27 July 2025; Accepted 2 August 2025
Available online 5 August 2025

addition of temozolomide to the treatment regime of GBM patients with IDH-wild type GBM, indicating temozolomide may not confer any benefit for GBM under this new classification. Additionally, Tesileanu et al. (Tesileanu et al., 2022) reported no significant effect of O6-methylguanine-DNA methyltransferase (MGMT) promoter methylation status on temozolomide response, though MGMT methylation status remained a significant determinant of overall survival. This conflicts with previous research which suggested MGMT promoter methylation status improved patient survival via promoting response to DNA-alkylating agents, such as temozolomide, a relationship extensively studied in GBM (Esteller et al., 2000; Hegi et al., 2004; Hegi Monika et al., 2005; Kitange et al., 2009; Weller et al., 2015). The recent changes in GBM classification may potentially add difficulties in comparing historical data to modern research results, but more accurately represents the current scientific understanding and confers more clinically relevant information at diagnosis (Wen and Packer, 2021).

The risk factors for GBM include: male sex, increasing age, white ethnicity, and inherited predisposition (Ostrom et al., 2021; Miller et al., 2021; Xiao et al., 2023; Sharifian et al., 2024; Miyakoshi et al., 2024; Colopi et al., 2023). Clinically, GBM typically presents with a range of neurological symptoms including focal motor deficits, headaches, cognitive changes, sensory impairments and seizures (Rasmussen et al., 2017; Chris et al., 2021). In addition, several systemic symptoms can also be present including nausea, lethargy and fatigue (Chris et al., 2021). These symptoms are largely non-specific and are present in a range of other brain tumours and non-tumour related neurological

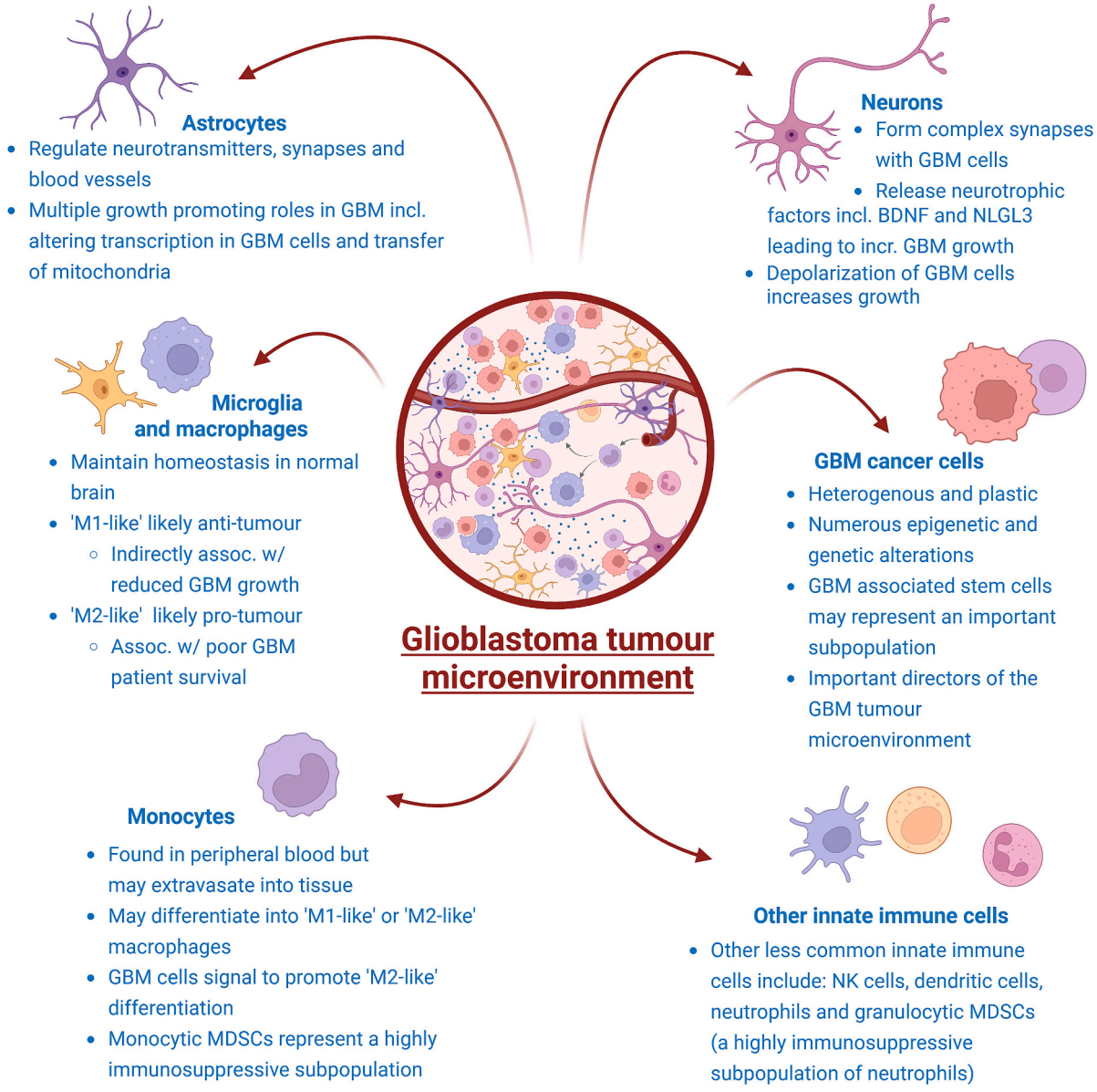

Fig. 1. Cells of the glioblastoma tumour microenvironment. The glioblastoma tumour microenvironment includes numerous cell types, with glioblastoma cancer cells, immune cells, neurons and astrocytes all present. This is a diverse, complex and dynamic system with glioblastoma cancer cells acting to manipulate and aberrantly regulate the normal homeostatic functions of these cell types. Astrocytes and neurons normally present in the central nervous system form unique interactions with glioblastoma cancer cells and support their proliferation through the release of growth factors and mitochondria, in addition to numerous other mechanisms. Microglia, macrophages and monocytes are particularly abundant in this environment and are signalled by glioblastoma cancer cells to assume a 'M2-like' phenotype, which is thought to support tumour growth and thus is associated with worsening patient outcomes. Other innate immune cells are also present and contribute to either promote or reduce glioblastoma cancer cell proliferation through a variety of mechanisms. Abbreviations used: GBM = glioblastoma, assoc. = associated, incr. = increased, BDNF = brain derived neurotrophic factor, NLGN3 = neuroligin-3, MDSC = myeloid-derived suppressor cell, NK = natural killer. Figure created with BioRender.com.

conditions (Chris et al., 2021). The standard treatment regimen for GBM is maximally safe surgical resection followed by cranial radiotherapy with adjuvant chemotherapy utilising temozolomide (Chris et al., 2021; Delgado-Martín and Medina, 2020). However, as previously mentioned this treatment combination results in only minor improvements in patient survival. GBM represents a significant burden to both the community and individual patients, highlighting the need for further research to improve understanding of the factors that govern GBM pathogenesis. Of particular interest is the complex GBM tumour microenvironment (TME) and the innate immune cells found within. Harnessing the functions of these innate immune cells may represent important novel therapeutic pathways in the treatment of GBM.

2. Innate immune cells of the tumour microenvironment

2.1. Tumour microenvironment overview

The role of the highly immunosuppressive TME within solid tumours has been a recently expanding field of interest in cancer research (Bertolaso and Dieli, 2017). Specifically, it seeks to explain the high percentage of non-cancerous cells within a solid tumour and how cancer cells may exploit the natural functions of innate immune cells to the cancer's benefit (Bertolaso and Dieli, 2017). Within the TME some of the most common cells are those of immune origin, constituting up to 70 % of cells present (Musca et al., 2023). However, estimates of immune cell number vary significantly between patients and cell counting techniques with others reporting values as low as 6 % (González-Tablas Pimenta et al., 2021). Of the immune cells present, the majority of cells reported are macrophages, monocytes, and microglia (Klemm et al., 2020; Friebel et al., 2020; Pombo Antunes et al., 2021) (Fig. 1.). Various members of the adaptive immune system such as cytotoxic T lymphocytes (CTLs), T helper, Tregs and B cells are also found in the GBM TME, though to a smaller extent (Klemm et al., 2020). Despite their proportion, and the growing body of evidence suggesting the importance of non-cancerous immune cells in tumour biology and treatment response, many of the specific roles of immune cells within GBM remain elusive. Inherently, immune cells perform a positive function in maintaining homeostasis with the evolutionary purpose of counteracting disease pathology. In the context of GBM, these functions are instead manipulated and aberrantly regulated, leading to deleterious effects to the benefit of the cancer. Previous research into artificially controlling these non-cancerous immune cells led to the discovery of multiple novel cancer immunotherapies. Such discoveries focus on two key factors of cancer biology: 1) The immune system's natural ability to target and kill cancer cells, and 2) the propensity for cancer cells to evade this immunological attack by generating immunosuppressive signals (Baumeister et al., 2016). Immunotherapies built upon these understandings have shown significant and meaningful results in other malignancies, particularly, metastatic melanoma (Schadendorf et al., 2015), Hodgkin's lymphoma (Ansell et al., 2015) and multiple haematological cancers (Pan et al., 2019). In these contexts, immunotherapies have harnessed the anti-tumour properties of the immune system to reduce tumour cell proliferation. Whilst immunotherapies have been trialled in GBM, none have progressed to routine clinical implementation. For example, immune checkpoint inhibitors including, nivolumab, pembrolizumab, durvalumab and atezolizumab have all been trialled in GBM (Stylli, 2020). These specific checkpoint inhibitors act to inhibit either the programmed cell death protein 1 (PD-1) receptor, which may be found on CTLs and other cells (Zhao et al., 2019), or its associated ligand which may be found on tumour cells (Nduom et al., 2016). Unfortunately, whilst these therapeutics have proven effective in other cancer types, they have shown limited efficacy in improving patient responses in GBM (Zhao et al., 2019). The PD-1/PD-L1 pathway is not the only target of immune checkpoint inhibitors however, with Cytotoxic-T-Lymphocyte associated protein 4 (CTLA-4) blockade being another alternative goal. CTLA-4 may be targeted by the monoclonal antibody ipilimumab, though this has had mixed and conflicting results in GBM (Duerinck et al., 2021; Omuro et al., 2017; Chen et al., 2023).

In addition to immune cells, common central nervous system (CNS) resident cells are also found within the GBM TME, including neurons and astrocytes (Broekman et al., 2018). Astrocytes have been shown to exhibit a myriad of functions in GBM including, altering transcription in the GBM cells and transferring mitochondria to these cells (Kim et al., 2019; Mega et al., 2020; Watson et al., 2023) (Fig. 1.). Additionally, as abundant cells in the CNS, astrocytes constitute a significant proportion of the cells present in the GBM TME (Karimi et al., 2023) and may be further subdivided into a number of unique subpopulations (John Lin et al., 2017). These subpopulations differ in their immunological actions, either promoting or suppressing inflammation following interaction with other members of the GBM TME, such as microglia and GBM cancer cells (Andersen et al., 2021; Perelroizen et al., 2022; Henrik Heiland et al., 2019; Faust Akl et al., 2025). Due to the potential shared lineage of astrocytes and GBM tumour cells, it has been suggested that GBM cancer cells can transform astrocytes into a tumour-like state through the release of various messengers, including extracellular vesicles and microribonucleic acids (Zeng et al., 2020). These extracellular vesicles can be found in the peripheral circulation and, in addition to other circulating markers such as circulating tumour cells, are being studied for their potential diagnostic and/or prognostic value (Qi et al., 2023). Furthermore, it has been shown that these extracellular vesicles are able to cross the blood-brain barrier (BBB) into the periphery even when the BBB remains intact (García-Romero et al., 2017), though the BBB is frequently compromised in GBM tumours (Watkins et al., 2014). This compromise in the BBB is at least in part due to the extensive neovascularisation seen in GBM and the formation of the 'blood-tumour barrier' (Arvanitis et al., 2020). Control of the vasculature within the GBM TME is multifaceted and dynamic, but has been shown to be coordinated by GBM cancer cells through changes in the extracellular matrix and release of angiogenic factors (Mammoto et al., 2013). Neurons are another crucial member of the GBM TME, and have been demonstrated to have numerous complex roles (Fig. 1.) (Venkatesh Humsa et al., 2015; Venkatesh et al., 2019; Taylor et al., 2023). This follows the discovery of the bidirectional cross talk which occurs between neurons and cancer cells (Venkatesh et al., 2019), where GBM cells increase the excitability of neurons and the resultant electrical stimuli from neurons increases cancer cell proliferation (Venkatesh et al., 2019). Additionally, GBM cells have been shown to stimulate the release of numerous growth factors from neurons including neuroligin-3 (NLGL3) (Venkatesh Humsa et al., 2015) and brain-derived neurotrophic factor (BDNF) (Taylor et al., 2023), which both act to further increase tumour cell growth.

2.2. Glioblastoma cancer cells

GBM cancer cells have extensive heterogeneity, are highly plastic and are able to adopt varied phenotypes in response to different stimuli (Yabo et al., 2021). Despite these barriers many genetic and molecular markers of these cancer cells have been identified including: TERT promoter region mutations, EGFR amplification and + 7/−10 chromosome alterations. Additionally, numerous epigenetic and metabolic alterations have been associated with GBM that can predispose the cancer cells to increased or decreased proliferative capacity (Kozono et al., 2015; He et al., 2023). The heterogeneity characteristic of GBM cancer cells results in the presence of multiple subpopulations with different phenotypes and ranging maturity (Schmitt et al., 2021). Previous studies have divided GBM cancer cells into 4 main cellular states: neural progenitor-like, oligodendrocyte-like, astrocyte-like and mesenchymal-like (Neftel et al., 2019). Individual GBM tumours vary in the proportion of each of these cell types, though the broader tissue architecture appears to be organised around sites of hypoxia and necrosis (Greenwald et al., 2024; Lv et al., 2024), and immune cell interactions (Ravi et al., 2022).

Novel research is increasingly demonstrating the importance of a specific subpopulation of GBM cells termed GBM associated stem cells (GSCs), important for both patient outcomes and their role in tumour proliferation (Sharifzad et al., 2019; Stoyanov et al., 2018; Vollmann-Zwerenz et al., 2020; Alves et al., 2021). These cells are marked by a characteristic stemness (high proliferative potential, ability to self-renew and pluripotency), which is important for treatment resistance, disease initiation, cellular heterogeneity and disease recurrence (Sharifzad et al., 2019). These four factors all represent key problems impeding the successful treatment of this highly invasive cancer. GSCs are identified by the following markers: CD133, CD44, CD15, Sex determined region Y-box 2 (SOX2) and L1 cell adhesion molecule (L1CAM) (Sharifzad et al., 2019; Rodriguez et al., 2022). Almost all of these markers have origins in neural or haematopoietic stem and progenitor cells (Rodriguez et al., 2022). The specific origin of GSCs is an ongoing area of debate and research. Common hypotheses suggest that these cells may either originate from normal mature and differentiated neural cells through a process of dedifferentiation, or through oncogenesis in existing neural stem cells (Sharifzad et al., 2019). To add further complications to the study of GSCs, distinctions between these stem cells and more differentiated cancer cells are not always clear with studies reporting GBM tumours containing a spectrum of cells existing between the two states (Neftel et al., 2019; Wang et al., 2019). Additionally, the features characteristic of GSCs (high proliferative potential, self-renewal and pluripotency) are debatably characteristic of all GBM cancer cells. This, coupled with the inherent plasticity of GBM cancer cells, makes defining this cell type as a distinct subpopulation in the GBM TME difficult. Regardless of their origin or distinction as a unique cell type, studies have demonstrated that increasing proportions of CD133 positive GBM cancer cells (proposed GSCs) correlate with a worsening patient survival rate (Pallini et al., 2008; Zeppernick et al., 2008).

GSCs are considered significant coordinators of the TME, releasing numerous immunomodulatory factors at increased rates compared to non-stem cancer cells. These factors include: Wnt-induced signalling protein 1, periostin, macrophage colony stimulating factor (M-CSF), Transforming growth factor β (TGF-β), macrophage inhibitory cytokine 1, CCL2, CCL5 and CCL7 (Tao et al., 2020; Zhou et al., 2015; Wu et al., 2010; Yi et al., 2011). Interestingly, many of these factors have been shown to not only recruit monocytes, macrophages and microglia, but also instruct these immune cells to release immunosuppressive cytokines and support GBM cancer cell growth (Tao et al., 2020; Zhou et al., 2015; Wu et al., 2010). Future therapeutic developments will therefore need to take into account the activity of the target on GSCs, in addition to mature cancer cells.

2.3. Microglia and macrophages

Microglia were first conceptualised by Pio del Rio-Hortega in 1932 (Kettenmann et al., 2011) and, as the CNS-resident 'macrophages', have since been proposed to be involved in the development of both neuronal and non-neuronal cells (Andoh and Koyama, 2021; Li and Barres, 2018; Touil et al., 2023; Lloyd et al., 2019; Parkhurst Christopher et al., 2013; Frost and Schafer, 2016), along with an extensive variety of CNS pathology (Lier et al., 2021). Of note, these cells are distinct from the embryonically-derived tissue-resident macrophages found at the borders of the CNS which represent a unique population (Mrdjen et al., 2018; Goldmann et al., 2016). Following their discovery, several distinct microglial phenotypes have been identified. These phenotypes include: resting or ramified, activated, amoeboid and dystrophic (Lier et al., 2021). Ramified microglia, are defined by long complex branching processes, small soma (Jinno et al., 2007) and a highly dynamic nature (Kamei and Okabe, 2023). Ramified microglia use these processes to survey the microenvironment and assist with maintenance of neuronal and synaptic integrity (Li et al., 2023). In contrast, activated microglia have a larger cell body, with the presence of lamellipodia (Lier et al., 2021; Vidal-Itriago et al., 2022). Once activated, microglia and macrophages may be further characterised on the gradient of 'activation states' which lies between the 'M1' and 'M2' poles (Guo et al., 2022). This activation gradient is similarly observed in both blood-derived macrophages and monocytes (Jurga et al., 2020). It is important to note that the terms 'M1' and 'M2' are antiquated and suggest binary activation states rather than the gradient of activation states and plasticity seen in vivo. In order to better capture this increasing complexity, this review will refer to these activation states as either 'M1-like' or 'M2-like'.

The 'M1-like' state or classical activation is marked, for example, by the expression of major histocompatibility complex (MHC) II, inducible nitric oxide synthase, CD11b and CD11c, and costimulatory molecules such as CD36 and Fc receptors (Guo et al., 2022; Jurga et al., 2020; Ghosh et al., 2016; Lisi et al., 2017). Furthermore, it is typically referred to as being highly 'pro-inflammatory' and is associated with cytokines such as IL-1β and tumour necrosis factor α (TNFα), as well as production of reactive oxidative species (ROS) and nitric oxide (Ghosh et al., 2016). The exact effects of 'M1-like' polarized macrophages/microglia on GBM growth are complex and incompletely defined, however, are typically expected to reduce tumour growth and increase patient survival, as seen in other tumours (Honkanen et al., 2019). This hypothesis would be in line with a recent study which found that blocking the PD-1 axis both promoted an 'M1-like' phenotype in microglia and blocked the growth of a glioma cell line (Wang et al., 2024). There are a number of different stimuli which may promote the maturation of ramified microglia or macrophages into an 'M1-like' polarized state, including: granulocyte-macrophage colony-stimulating factor (GM-CSF) (Kim and Son, 2021), TNFα and interferon-γ (IFNγ) (Guo et al., 2022; Jurga et al., 2020; Ghosh et al., 2016; Kim and Son, 2021). Use of these stimuli to promote 'M1-like' polarisation in GBM or other cancers may prove beneficial for the reasons outlined above but this is yet to be definitively determined (Lazarus et al., 2021). However, whilst evidence from other cancer types suggests that 'M1-like' microglia/macrophages could have potent anti-tumour activity, in the context of GBM, many of the inflammatory cytokines released by these microglia/macrophages have been associated with tumour growth. These include TNFα and IL-6, cytokines which are tightly linked with the 'M1-like' activation state, yet have been shown to support GBM tumour growth and proliferation (Strizova et al., 2023; Zhang et al., 2020a; Wei et al., 2021; Saidi et al., 2009).

The 'M2-like' state or alternative activation is considered to be characteristically 'anti-inflammatory' and associated primarily with tissue repair (Jurga et al., 2020). The identification of this subtype of activated microglia/macrophages is typically done using, for example: Arg-1, CD163 (Ghosh et al., 2016; Lisi et al., 2017), IL-10 and CD206 expression (Laffer et al., 2019). The conversion of microglia from a primarily inflammatory state to this primarily 'anti-inflammatory' reparative state is the subject of intense interest within the neuroimmunology community (Cui et al., 2020; Li et al., 2021; He et al., 2020; Du et al., 2018). Better understanding of mechanisms controlling 'M2-like' conversion may represent opportunities to not only halt inflammation-induced tissue damage but potentially promote repair. In the context of GBM specifically, increased numbers of 'M2-like' microglia likely contribute to increased tumour growth, highlighted by the association of poorer prognosis in GBM patients with increased expression of 'M2-like' microglia/macrophages (Xiao et al., 2022). The 'anti-inflammatory' and neuroprotective actions characteristic of this activation state are mediated by the expression of a number of key cytokines and growth factors, such as nerve growth factor (NGF), BDNF, IL-10 and TGF-β (Jurga et al., 2020). These factors are likely important contributors to the characteristically immunosuppressive GBM TME though also likely protect against overly injurious neuroinflammation. Importantly, 'M2-like' polarisation may be achieved through exposure to IL-4, IL-13, IL-10 (Kim and Son, 2021) or M-CSF, which are all commonly found in the GBM TME (Chen et al., 2021). However, many of the stimulators of the 'M1-like' polarisation state discussed above are also up-regulated in

GBM (Jarmuzek et al., 2023a). Ultimately, just as there is no true 'M1-M2' dichotomy seen in vivo, these activation states should be considered with nuance and as neither purely beneficial nor deleterious in GBM. Therefore, an optimal therapeutic strategy is likely less associated with promoting specific activation states ('M1-like' vs 'M2-like') but rather should focus on promoting specific anti-tumour actions in microglia and macrophages, e.g. reducing antigen presentation by tumour associated macrophages, which could reduce T cell exhaustion and improve response to immunotherapy (Polania et al., 2025).

2.4. Monocytes

Another key immune cell type which regulates and influences the TME are monocytes. These cells may act directly, or indirectly, via differentiation into blood-derived macrophages. In humans, 3 monocyte phenotypes have been defined, including: classical (marked by $CD14^{+}CD16^{+}$), non-classical ($CD14^{Dim}CD16^{+}$) and intermediate monocytes (intermediate for CD14 and CD16) (Kapellos et al., 2019). The functional distinctions between these phenotypes are less well defined when compared to 'M1-like' and 'M2-like' macrophages; however nonclassical monocytes are marked by a reduction in inflammatory markers (Gjelstrup et al., 2018). It was initially proposed that non-classical monocytes specifically gave rise to 'M2-like' polarized macrophages, while the same was true for classical monocytes and 'M1-like' macrophages; however this relationship remains uncertain (Orekhov et al., 2019). The capacity of monocytes to differentiate into 'M2-like' macrophages appears to be exploited by GBM cancer cells, which have been shown to signal for this differentiation by the release of factors such as extracellular vesicles (de Vrij et al., 2015). The importance of monocytes and their conversion to 'M2-like' macrophages is further highlighted by their putative prognostic value, where increases in monocytes or 'M2-like' macrophages is associated with worsening glioma patient survival (Zhang et al., 2021).

2.5. Neutrophils

Neutrophils, or polymorphonuclear cells, are the most common circulating immune cells in humans and are quickly recruited to sites of infection or tumours (Lin et al., 2021). Research has both shown their potential prognostic/predictive value and explored their effects within the GBM TME. While absolute neutrophil counts have not been found to be predictive of GBM prognosis (Lopes et al., 2018), the ratio of neutrophils-to-lymphocytes has been found to be predictive of overall survival, where increases in this ratio is associated with a worsening prognosis (Jarmuzek et al., 2023b). This ratio has also been associated with response to novel treatment modalities such as longer overall survival seen in low neutrophil-to-lymphocyte ratio patients treated with a combination of bevacizumab and irinotecan (Haksoyler et al., 2021). Similarly, an increased proportion of neutrophils in the brain has been associated with IDH wild-type gliomas compared to IDH mutant (Maas et al., 2023). 'Pro-tumour' neutrophils are known to contribute to immune suppression and angiogenesis whilst 'anti-tumour' neutrophils can induce apoptosis and cytotoxicity in GBM cancer cells (Khan et al., 2020). However, neutrophils associated with the GBM TME typically assume a pro-tumour phenotype with reduced ROS production, prolonged survival, increased immunosuppression and increased promotion of angiogenesis (Maas et al., 2023). These phenotypic changes were induced following interactions with the myeloid cells of the GBM TME (Maas et al., 2023). Conversely, following exposure to GBM cancer cells, neutrophils have been shown to adopt an antigen presenting cell-like appearance, involving an upregulation of MHC II (Lad et al., 2024). This change was shown to result in an increase in T cell recruitment to the tumour and decrease in tumour growth in a GBM mouse model (Lad et al., 2024).

2.6. Myeloid-derived suppressor cells

Myeloid-derived suppressor cells (MDSCs) are a recently defined cell type divided into either the monocytic and polymorphonuclear subsets, depending on the cell lineage from which they were derived (Veglia et al., 2021). It has been hypothesised that these cell types develop following the pathological activation of the myeloid component of the bone marrow, where there is chronic expression of myeloid growth factors and inflammatory signals (Veglia et al., 2021). This mechanism likely explains the notable increase in MDSCs seen in the cancer setting, as increased expression of these growth factors and inflammatory signals are a common feature of tumour development (Umansky et al., 2016). Importantly, distinguishing between these cells and other polymorphonuclear/monocytic cells is difficult, with no single marker being sufficient (Damuzzo et al., 2015). The main feature which separates these MDSCS is their potent immunosuppressive actions (Khan et al., 2020; Veglia et al., 2021). MDSCs produce factors such as IL-10 and have increased expression of immune checkpoint proteins, such as Programmed death ligand 1 (PD-L1) and Fas ligand (FasL) to inhibit the actions of T cells and NK cells (Krishnamoorthy et al., 2021). Importantly, both polymorphonuclear and monocytic MDSC subsets have been found to be increased in the periphery of GBM patients compared to lower grade gliomas and healthy controls (Alban et al., 2018; Gielen et al., 2016), and are associated with worsening overall survival (Alban et al., 2018). In addition to their immunosuppressive actions, MDSCs have been shown to play other complex pro-tumour roles including promoting angiogenesis, through the release of vascular endothelial growth factor (VEGF) (Yang et al., 2004), and promoting invasion, through the release of matrix metalloproteinases (Du et al., 2008). A final recently suggested role of MDSCs is the production of growth factors to support the growth of GSCs. In a recent publication, Jackson et al. (Jackson et al., 2025) identifies a unique subset of MDSCs termed early MDSCs, which is strongly associated with GBM. This compares to other glioma types including grade 4 IDH-mutant astrocytomas, where very few early MDSCs were present (Jackson et al., 2025). These early MDSCs were shown to be recruited to, and cluster around, GSCs (Jackson et al., 2025). Once recruited, early MDSCs likely support the growth of the GSCs leading to the dramatic reduction in overall survival reported in patients with high early MDSC expression (Jackson et al., 2025).

2.7. Natural killer cells

Natural killer (NK) cells are cytotoxic innate lymphoid cells that act with a similar function to CTLs, releasing pro-inflammatory cytokines and chemokines and releasing lytic vesicles (containing perforin and granzyme) to specifically lyse virally infected or cancerous cells (Wolf et al., 2023). Unlike CTLs, which are activated by specific antigens presented on MHC I, NK cells are coordinated by a complex series of activating and inhibitory signals expressed by host cells (Wolf et al., 2023). These activating signals are upregulated during times of cellular stress such as during the transformation into a cancer cell, making NK cells a potent defence against tumour development (Wolf et al., 2023). A notable inhibitory signal for NK cells is the MHC I molecule which is frequently downregulated on cancer cells (Cornel et al., 2020), enabling removal of cancer cells which may otherwise evade CTL detection. Due to these actions, the increased presence of NK cells have been positively associated with overall survival in a range of cancer types, such as colorectal cancer (Tang et al., 2020), hepatocellular carcinoma, and a range of other solid tumour types (Zhang et al., 2020b). However, the prognostic value of NK cell presence has not been shown in gliomas (Zhang et al., 2020b). NK cells have been shown to have a strong protective effect against systemic GBM metastases, which are rarely seen without NK cell suppression (Lee et al., 2015). Importantly, extracranial metastases in GBM are very uncommon, constituting just 0.2–2 % of GBM cases (Wu et al., 2021). One possible explanation for this is the difference between tumour associated NK cells and peripheral NK cells.

Shaim et al. (Shaim et al., 2021) have shown healthy allogeneic NK cells to specifically target GBM cancer cells over astrocytes. This lytic function was reduced in tumour associated NK cells compared to their peripheral or healthy allogeneic counterparts (Shaim et al., 2021). Certain NK cell-related gene signatures have also been associated with favourable GBM prognosis, such as low expression of ULBP1 (Li et al., 2022a) and CD73 (Wang and Matosevic, 2019). These associations suggest that NK cells alone may not be sufficient to significantly impact GBM tumour development but with optimisation (limiting inhibitory signals and increasing activating signals) they may represent crucial therapeutic targets in GBM.

2.8. Dendritic cells

Dendritic cells (DCs) represent the bridge between the innate and adaptive immune system, specialising in antigen presentation and priming of naïve T lymphocytes (Del Prete et al., 2023). These cells can be largely divided into three subgroups: conventional DC1s (cDC1s), cDC2s and plasmacytoid DCs (pDCs) (Del Prete et al., 2023). Specifically, cDC1s specialise in promoting CTL responses (by presenting antigens on MHC I) while cDC2s specialise in promoting CD4+ T responses (by presenting antigens on MHC II), though both are capable of presenting to either CD4+ or CD8+ T cells (Del Prete et al., 2023). pDCs are known to be the major producers of type I interferons (Del Prete et al., 2023). Type I interferons are especially notable in cancer due to their key functions in reducing tumour cell proliferation and increasing immune responses (e.g. increasing NK cell and DC activation whilst decreasing MDSC activity) (Yu et al., 2022; Lim et al., 2023). In the context of GBM, type I interferons have been shown to decrease the proliferation of both mature GBM cancer cells and GSCs (Du et al., 2017). cDC1s represent a potentially key immune cell type in cancer due to their promotion of CTL and Th1 type responses and recruitment of these T cell types to the tumour location (Srivastava et al., 2019). Decreased cDC1 numbers has consequently been associated with decreased overall survival in a number of cancer types, including breast cancer and head and neck squamous cell carcinoma (Broz Miranda et al., 2014). Similarly, knock out of cDC1s has been associated with an inability to reject transplanted tumours in mouse models (Spranger et al., 2017). Expansion of cDC1s has also been shown to improve the efficacy of immunotherapies, such as anti-PD-L1, in promoting anti-tumour responses (Salmon et al., 2016). Promotion of cDC1s may therefore represent a novel therapeutic strategy to act as an adjuvant with existing immunotherapies in GBM. cDC2s, in contrast, are less well characterised in cancer and GBM more specifically (Srivastava et al., 2019; Hu et al., 2023), though have been shown to be more numerous in GBM tumours compared to cDC1s (Friedrich et al., 2022).

3. Harnessing innate immune cells for GBM treatment

The many roles innate immune cells have been shown to play in the GBM discussed above, highlight the incredible potential of targeting these cell types for the treatment of GBM. The potential importance of targeting innate immune cells is further highlighted by the lack of success in treating GBM with immunotherapies which target the adaptive immune system more directly, eg. anti-CTLA4 and anti-PD-L1. In line with this a number of new techniques and drug targets have come under investigation (Fig. 2.). These novel therapies have investigated modifying the innate immune system at every step of its activity, including targeting: innate immune cytokines, cell surface and endosomal receptors, biochemical pathways, and exogenously modifying the cells themselves.

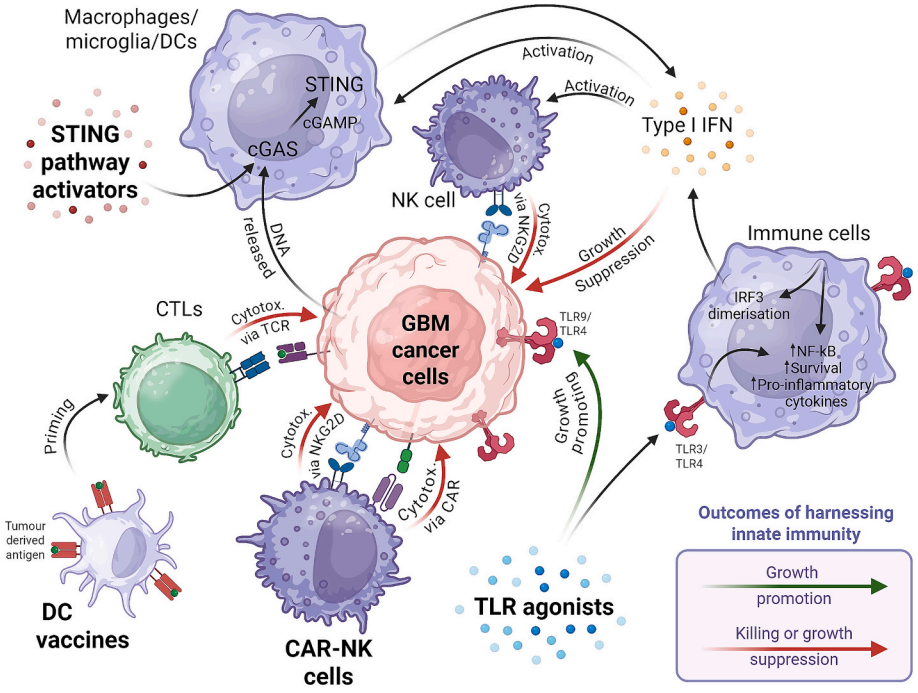

Fig. 2. Techniques for harnessing the innate immune system to treat glioblastoma. Numerous techniques for harnessing the innate immune system of the glioblastoma tumour microenvironment are under investigation. These include DC vaccines which prime CTLs enabling killing of tumour cells, CAR-NK cells which express chimeric antigen receptors (CARs) to recognise tumour cells, and finally TLR agonists and STING pathway activators which both stimulate the production of type I interferon and promote immune cell activation. The outcomes of harnessing innate immune cells with these therapies are highlighted, including: inducing cytotoxicity downstream of a number of different recognition pathways (TCR, CAR and NKG2D) and suppressing growth via actions of type I interferons. TLRs may also be found on glioblastoma cancer cells and as such TLR agonists may inadvertently promote cancer cell growth. Abbreviations used: GBM = glioblastoma, Cytotox. = cytotoxicity, DC = dendritic cells, NK cells = natural killer cells, CTLs = cytotoxic T lymphocytes, TCR = T cell receptor, CAR = chimeric antigen receptor, IFN = interferon, TLR = toll-like receptor, IRF3 = interferon regulating factor 3, NKG2D = natural killer group 2D, cGAS = cyclic GMP-AMP synthase, cGAMP = 2′3′ cyclic GMP-AMP, and STING = stimulator of interferon genes. Figure created with BioRender.com.

3.1. Targeting cytokines, growth factors and cell signalling molecules

Targeting the various cytokines and growth factors produced by the cancer cells and immune cells present within the TME represents a promising therapeutic strategy. Their inhibition may result in dual synergistic effects by both limiting their growth promoting effects on cancer cells and the influence they exert on the immune cells of the TME. One already approved drug for treatment of GBM is bevacizumab, a monoclonal antibody which targets and inhibits VEGF leading to reduced angiogenesis and cerebral oedema (Narita, 2015). This has been shown to lead to a significant reduction in GBM growth rate in murine models with high VEGF expressing GBM tumours (García-Romero et al., 2020). Importantly, bevacizumab was not been shown to have a cytotoxic effect on GBM cancer cell lines in vitro (Simon et al., 2014), suggesting the reduced growth seen in vivo in GBM mouse models is a downstream effect of reduced angiogenesis rather than direct cytotoxic effects. In GBM patients, the use of bevacizumab is only associated with increased progression-free survival and is not significantly associated with increased overall patient survival (Kaka et al., 2019). Despite the successful translation of this antibody, others have failed to translate into clinical practice. Numerous antibodies have been shown to cross the BBB and enter the tumour (Mariani et al., 1997; Rades et al., 2010; Ulaner et al., 2018), though this penetrance may not be sufficient to produce a therapeutic effect. Therefore, a number of small molecule inhibitors are being investigated in the hope that these have a further improved penetrance and biodistribution. These small molecule inhibitors include galunisertib, a small molecule inhibitor of TGF-β receptor I, which was shown to be well tolerated but did not lead to significant improvements in overall survival in a phase II clinical trial (Brandes et al., 2016). This failure comes despite previous studies showing inhibition of TGF-β signalling with galunisertib increased NK cell activity and overall survival in a GBM mouse model (Shaim et al., 2021).

Colony stimulating factor 1 receptor (CSF1R), which is important for macrophage and microglia survival and activity (Chitu et al., 2016), is another target of interest. Interestingly, despite its role in macrophage survival, inhibition of the CSF1R in a transgenic GBM mouse model was not shown to reduce macrophage numbers (Pyonteck et al., 2013). Instead, inhibition of CSF1R was shown to 're-educate' macrophages, where a reduction in 'M2-like' polarisation and promotion of 'M1-like' polarisation was identified (Pyonteck et al., 2013). Additionally, inhibition of the CSF1R was shown to reduce tumour size in both transgenic and xenograft preclinical mouse models (Pyonteck et al., 2013). However, these successes have not been replicated in clinical trials where small molecule inhibitors of CSF1R, such as pexidartinib, have been well tolerated but are yet to demonstrate improvements in patient's progression-free survival or overall survival (Butowski et al., 2014; Colman et al., 2018). Another molecule of interest is GM-CSF, which has complex roles in promoting GBM cancer cell growth and coordinating immune response (Curran et al., 2011). GM-CSF has previously been utilised as an adjuvant for vaccines in other cancer types, where it has been shown to promote inflammation and immune responses (Soiffer et al., 1998). Similarly, a number of ongoing clinical trials have begun investigating the use of GM-CSF as an adjuvant in combination with dendritic cell vaccines for the treatment of GBM (NCT01480479, NCT03615404, NCT02078648). However, in the context of GBM TMEs, GM-CSF is frequently upregulated and has been demonstrated to promote the immunosuppressive activity of MDSCs (Kohanbash et al., 2013). Additionally, GM-CSF produced by GBM cancer cells has been shown to promote eosinophil activity and viability (Curran et al., 2011). These eosinophils in turn release growth factors to support GBM cancer cell growth (Curran et al., 2011).

3.2. Toll-like receptor agonists

An important first step in the immune response against almost any pathogen or tumour cell is the activation of pattern recognition receptors (PRRs) on innate immune cells by pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs) (Li and Wu, 2021). PAMPs are molecular patterns which are generally only produced by pathogens and foreign bodies and therefore aid the body in distinguishing 'self' from 'non-self' (Li and Wu, 2021). Conversely, DAMPs are proteins and metabolites naturally produced and released by host cells during times of stress, inflammation, cellular damage or cell death (Li and Wu, 2021). These factors are strongly associated with tumour development and therefore highlight the importance of DAMPs and PRRs in initiating and propagating anti-tumour immune responses. Toll-like receptors (TLRs) represent some of the first discovered PRRs (Li and Wu, 2021) and have since been extensively studied in the context of cancer. TLRs are widely expressed on both innate and adaptive immune cells, including monocytes, macrophages, microglia, neutrophils, DCs, NK cells and T cells (Iwasaki and Medzhitov, 2004; Fiebich et al., 2018; Prince et al., 2011). Their activation can promote multiple anti-tumour responses in these cell types, depending on the specific TLR activated (Gillard et al., 2024). These anti-tumour responses include: activation of the NF-κB pathway, leading to increased survival, proliferation and production of pro-inflammatory cytokines in these immune cells; increases in the expression of co-stimulatory molecules necessary for activation of T cells; and type I interferon production, in the case of TLR3 and TLR4 activation (Kaczanowska et al., 2013). Activation of these anti-tumour mechanisms highlights the potential of TLR agonists as a novel therapeutic strategy, either to be used alone or concomitantly with other treatments.

Several recent trials have investigated the potential of TLR agonists in the treatment of GBM. Due to the wide expression of TLRs and highly immunogenic nature of TLR agonists, these drugs are frequently investigated as an adjuvant in combination with cancer vaccines. Here TLR agonists can work synergistically with cancer vaccines by increasing the immunogenicity, whilst the cancer vaccine can improve the specificity of the response. In orthotopic GL261/CT-2A murine glioma models this combination (of glioma antigens and intracranially injected TLR agonists) led to the promotion of tertiary lymphoid structures in the tumour and increased animal survival (Shen et al., 2024). Similarly, a phase II clinical trial found the addition of TLR agonists significantly improved interferon response to a DC vaccine and led to improved progression-free survival in GBM and improved overall survival in grade III glioma patients (Everson et al., 2024). Conversely, expression of multiple TLR subtypes has also been reported on glioma and GBM cancer cells (Xun et al., 2021), with increased expression of TLR9 being associated with worsening patient prognosis (Mu et al., 2017). Similarly, TLR4 knock out in a U-87 MG xenograft GBM mouse model significantly reduced tumour volume and increased cellular apoptosis (Casili et al., 2018). This study utilised an immunodeficient mouse model however, meaning it does not include the potential effects TLR4 knock out may have on immune cells in the GBM TME. In line with this, increased TLR4 expression has also been associated with increased median survival in GBM patients (Alvarado et al., 2017). This suggests that TLR agonists should be carefully investigated to ensure accurate TLR subtype activation is achieved.

3.3. STING/cGAS pathway activators

The cyclic GMP-AMP synthase (cGAS)/stimulator of interferon genes (STING) pathway represents another important PRR in the recognition of cancer (Decout et al., 2021). cGAS recognises double stranded DNA (dsDNA), leading to the formation of 2′3' cyclic GMP-AMP (cGAMP), which in turn binds to STING leading to increased production type I interferons and pro-inflammatory mediators (Decout et al., 2021). Recognition of dsDNA in the cytosol represents an important defence against viral infection but also enables the early detection of cancer, where extensive DNA damage leads to dsDNA accumulation in the cytosol of tumour cells and leakage during tumour cell turnover and

death (Gan et al., 2021). This extracellular dsDNA is then taken up by innate immune cells, notably macrophages and DCs, leading to their activation, initiation of an anti-tumour response, and presentation of tumour antigens to adaptive immune cells (Gan et al., 2021). Missense mutations in the STING gene in a GL261 mouse model of glioma have been associated with reductions in interferon production and CTL number (Ohkuri et al., 2014). Additionally, increases in the number of MDSCs and Tregs was observed, which (when combined with the decreases in interferon production and CTL number) may explain the decrease in overall survival observed in this model (Ohkuri et al., 2014). Conversely, STING agonism (with *c*-di-GMP, a cyclic dinucleotide and STING agonist) led to significant reductions in tumour volume and increases in brain infiltrating $CD8^+$ CTLs (Ohkuri et al., 2014). STING agonism with ADU-S100, a cyclic dinucleotide and STING agonist, has been shown to significantly increase NK cell infiltration in a CT-2A mouse model of glioma and improve survival in an NK cell dependent manner (Berger et al., 2022). Despite the preclinical efficacy, when translating these studies into human clinical trials, only a small subset of cancer patients were shown to respond (Low et al., 2024). It's possible that this limited response is due to the relatively short half-life of STING agonists. For example, ADU-S100 demonstrated a half-life of just 24 min in a recent phase I clinical trial (Meric-Bernstam et al., 2022). Similarly, rapid tumour extravasation of the cyclic dinucleotides used as STING agonists may also contribute to limited translatability (Jang et al., 2021). With pharmacodynamic and pharmacokinetic optimisation, STING agonists may represent potent novel therapies for the treatment of GBM.

3.4. Dendritic cell vaccines and cell-derived antigens

DCs are a critical link between the innate and adaptive immune systems, and are significant activators of T cell responses. DC vaccines seek to specifically amplify this pathway in the cancer setting. To produce DC vaccines, DCs are derived from a patient's own monocytes and are exposed to tumour associated antigens, and are then infused back into the patient (Datsi and Sorg, 2021). These infused DCs then migrate to the lymph nodes with the goal of driving a specific anti-tumour response and immunological memory (Datsi and Sorg, 2021). This technique has proven highly effective in animal models, providing sustained protection against primary glioma tumours and tumour rechallenges up to 50 days later (Heimberger et al., 2000). Additionally, a recent meta-analysis into phase II clinical trials found DC vaccines, in combinational with convention therapy, was well tolerated and led to a significant increase in overall survival (Lv et al., 2020). Despite these promising outcomes, phase III studies have historically been met with mixed results (Li et al., 2022b). Liau et al. (Liau et al., 2023) published a recent phase III study into both recurrent and newly diagnosed GBM patients which is perhaps the first study of its kind to report significant improvements in overall survival (~2.8 month improvement in median overall survival in newly diagnosed GBM patients compared to control groups and ~ 5.4 month improvement in median overall survival in recurrent GBM patients). Further, this DC vaccine was well tolerated, with only 5 serious adverse events being reported by the 296 total patients which received a vaccine dose (Liau et al., 2023).

However, this study has been criticised for its methodological design including selection bias, a change in primary end-point, cross-over design and the use of historical or external control groups (Gatto et al., 2023). Beyond these methodological challenges are also barriers intrinsic to basic GBM biology, namely: a highly immunosuppressive microenvironment and the relatively low mutation rate of GBM compared to other cancer types (Datsi and Sorg, 2021). This low mutation rate results in only a small number of neoantigens being produced for T cells to be effectively primed against (Nejo et al., 2019), potentially explaining the variable responses previously reported. However, therapies that are targeting the immunosuppressive microenvironment characteristic of GBM are also in development. For example, the combination of DC vaccines with TLR agonists or STING/cGAS pathway activators could lead to improved efficacy. Such combinations have led to promising phase II results in both GBM (Everson et al., 2024) and other cancer types (Wilgenhof et al., 2016), though to our knowledge have not been reported in phase III trials thus far.

3.5. Chimeric antigen receptor NK cells

Recently, there has been several successes in the use of chimeric antigen receptor (CAR) T cells for the treatment of haematological cancers, with several now approved for use by the Federal Drug Administration (Sengsayadeth et al., 2022). CAR-T cells are developed by adding a synthetically developed antigen receptor which can direct patient's own T cells towards a specific clinical target (eg. CD19 in B cell malignancies) (Sterner and Sterner, 2021). In the setting of GBM, CAR-T cells have produced promising pre-clinical results (Prapa et al., 2021; Choe et al., 2021), however, clinical trial results have been limited (Maggs et al., 2021). These limited results may in part be explained by the GBM cellular heterogeneity and antigenic shift (Sterner and Sterner, 2021). CAR-NK cells are a recent development which seek to alleviate these limitations. Notably, CAR-NK cells have multiple mechanisms for activating cellular cytotoxicity, via both the CAR and the normal mechanisms of NK cell activation. This is especially relevant in GBM where the characteristic heterogeneity and cellular plasticity add difficulties in CAR target selection. CAR-T cells are also associated with high rates of cytokine release syndrome (Xie et al., 2020), neurotoxicity and acquired resistance to therapy (Maggs et al., 2021). In comparison CAR-NK cells are thought to have less side effects, due to NK cells having a less inflammatory cytokine profile compared to CTLs (Xie et al., 2020). CAR-NK cells have the additional benefit of potential 'off-the-shelf' applications (Xie et al., 2020), where less strict HLA matching is required to avoid graft-versus-host disease (Siegler et al., 2018). Research into CAR-NK cells for treatment of cancer and GBM more specifically is still in its infancy, though current preclinical, phase I and phase II results are promising. Injection of EGFRvIII targeting CAR-NK cells resulted in a significant improvement in survival in an immunocompetent GBM mouse model compared to mice injected with NK cells lacking the CAR (Ma et al., 2021). This improvement in survival was further increased when CAR-NK cells were co-administered with an oncolytic virus expressing the IL-15 cytokine (Ma et al., 2021). Other preclinical studies on CAR-NK cells targeting either HER2 or B7-H3 have reported similar increases in survival compared to placebo mice (Tachi et al., 2024; Strecker et al., 2022; Zhang et al., 2016). A recent phase I study into intracranially injected CAR-NK cells targeting HER2-positive GBM demonstrated effective safety profiles, with none of the participants developing cytokine release syndrome or dose-limiting toxicities (Burger et al., 2023). If proven effective in future phase III trials, the improved safety profile and multiple mechanisms of cellular cytotoxicity of CAR-NK cells may therefore be especially significant in the treatment of GBM.

4. Future considerations

As understanding of the complex and varied roles the innate immune system plays in the GBM TME continues to grow, the importance of these cells in GBM treatment is only further highlighted. Whilst previously overlooked in favour of immunotherapies which targeted the adaptive immune system, novel research is revealing potential mechanisms for targeting the innate. Many of these techniques discussed above have proven highly effective in both cell culture and animal models, though are yet to demonstrate significant effects in larger clinical trials. These failings highlight that the greatest utility for harnessing the innate immune system in GBM is unlikely to come from using these techniques in isolation, but from using them in combination with other therapies. As innate immune cells are frequently the effector cells downstream of adaptive immune cells, utilising immunotherapies which target both the

adaptive and innate are likely to demonstrate synergistic effects. This is especially relevant in the context of GBM, where the extensive heterogeneity and highly immunosuppressive TME limit the efficacy of any one single treatment alone.

Other unique barriers in the treatment of GBM include its location within the brain. Future studies will need to investigate not only the effectiveness of a drug on its target but also its specificity for the tumour, ability to cross the BBB (despite the BBB frequently being compromised in GBM) and its overall pharmacokinetic and pharmacodynamic profile. The innate immune system functions normally systemically, with the aberrant behaviour demonstrated in GBM, largely concentrated with the tumour region of the brain. Furthermore, the "immune privileged" nature of the CNS often results in the innate immune system present behaving uniquely compared to other areas of the body. An emphasis should therefore be placed on localising treatment effects to the GBM TME, in order to avoid unexpected systemic side effects which may be produced by these innate immune cell modifying therapies. Furthermore, the location within the brain makes extensive neuroinflammation highly undesirable, potentially resulting in high levels of neurotoxicity. Rather than promoting 'M1-like' responses or highly pro-inflammatory response, effective therapies should specifically limit pro-tumour functions of tumour-associated macrophages, microglia, neutrophils, MDSCs and other innate immune cells, whilst simultaneously avoiding affecting otherwise beneficial functions of these cell types.

CAR-NK cells represent a particularly promising therapeutic strategy, with a high degree of specificity for the tumour and a potentially improved safety profile compared to the existing CAR-T cells. Whether this technique can effectively overcome the highly immunosuppressive GBM TME and whether suitable neoantigen targets can be identified still remains to be determined. Similarly, DC vaccines promise a high degree of specificity, yet have frequently been shown to be insufficiently immunogenic. The most optimal therapeutic strategy is therefore likely to come from combining these highly specific treatments with those that could alleviate the immunosuppressive GBM TME, eg. TLR agonists, STING/cGAS pathway activators or inhibitors of immunosuppressive cytokines and growth factors.

5. Conclusion

GBM is characterised by its extremely poor prognosis, which has not dramatically improved in the past two decades. Furthermore, previous drug trials have been largely unsuccessful. The innate immune cells of the TME represent a crucial target, demonstrating vast proposed roles in GBM proliferation and patient survival, though their exact mechanisms and roles remain unknown. GSCs and innate immune cells make up the majority of cells within the GBM TME. Increased study into the complex relationships which exist between these cells and mature GBM tumour cells are a key area of research for developing novel therapeutic targets. This review has outlined a number of novel techniques for harnessing the innate immune system currently under investigation, though few have yet made it to phase II-IV clinical trials, leaving much about their behaviour and effectiveness still uncertain. The large number of innate immune cells present in the body and tumour specifically, and the many functions they display, highlight their potential utility. Often these cell types are simultaneously beneficial and deleterious to a patient's overall health. Therefore, with increased understanding of the highly interconnected relationship which exists between innate immune cells and GBM, and by harnessing the anti-tumour potential of these crucial cells, we may be able to discover a much-needed therapy for this devastating cancer.

CRediT authorship contribution statement

Hamish McLean: Writing – original draft, Visualization, Conceptualization. **Matthew Drill:** Writing – review & editing, Supervision, Conceptualization. **Richard Sequeira:** Writing – review & editing. **Padmakrishnan Chorakode Jayakrishnan:** Writing – review & editing. **Rosalind L. Jeffree:** Writing – review & editing. **Martin Hunn:** Writing – review & editing. **Terence J. O'Brien:** Writing – review & editing, Supervision. **John Hamilton:** Writing – review & editing. **Mastura Monif:** Writing – review & editing, Supervision, Resources, Project administration, Funding acquisition, Conceptualization.

Funding

This research was funded by NHMRC Grant 2011590.

Declaration of competing interest

Prof. O'Brien's institution has received research funding for his research and consultancies.

from Chiesi, Eisai, Biogen, ES Therapeutics, Epidarex, LivaNova, Novartis, Supernus and.

UCB Pharma, outside the submitted work.

Dr. Mastura Monif has served on advisory board for Merck, has received speaker honoraria.

from Merck, Biogen, and Roche. Her institution receives funding from Merck, Australian.

National Health and Medical Research Council, Brain Foundation, Charles and Sylvia Viertel.

Foundation, Bethlehem Griffith Foundation and MS research.

Data availability

No data was used for the research described in the article.

References

Alban, T.J., Alvarado, A.G., Sorensen, M.D., Bayik, D., Volovetz, J., Serbinowski, E., et al., 2018. Global immune fingerprinting in glioblastoma patient peripheral blood reveals immune-suppression signatures associated with prognosis. JCI Insight 3 (21).

Alvarado, A.G., Thiagarajan, P.S., Mulkearns-Hubert, E.E., Silver, D.J., Hale, J.S., Alban, T.J., et al., 2017. Glioblastoma cancer stem cells evade innate immune suppression of self-renewal through reduced TLR4 expression. Cell Stem Cell 20 (4), 450–461 e4.

Alves, A.L.V., Gomes, I.N.F., Carloni, A.C., Rosa, M.N., da Silva, L.S., Evangelista, A.F., et al., 2021. Role of glioblastoma stem cells in cancer therapeutic resistance: a perspective on antineoplastic agents from natural sources and chemical derivatives. Stem Cell Res Ther 12 (1), 206.

Andersen, B.M., Faust Akl, C., Wheeler, M.A., Chiocca, E.A., Reardon, D.A., Quintana, F. J., 2021. Glial and myeloid heterogeneity in the brain tumour microenvironment. Nat. Rev. Cancer 21 (12), 786–802.

Andoh, M., Koyama, R., 2021. Comparative review of microglia and monocytes in CNS phagocytosis. Cells 10 (10), 2555.

Ansell, S.M., Lesokhin, A.M., Borrello, I., Halwani, A., Scott, E.C., Gutierrez, M., et al., 2015. PD-1 blockade with nivolumab in relapsed or refractory Hodgkin's lymphoma. N. Engl. J. Med. 372 (4), 311–319.

Arvanitis, C.D., Ferraro, G.B., Jain, R.K., 2020. The blood–brain barrier and blood–tumour barrier in brain tumours and metastases. Nat. Rev. Cancer 20 (1), 26–41.

Baumeister, S.H., Freeman, G.J., Dranoff, G., Sharpe, A.H., 2016. Coinhibitory pathways in immunotherapy for cancer. Annu. Rev. Immunol. 34, 539–573.

Berger, G., Knelson, E.H., Jimenez-Macias, J.L., Nowicki, M.O., Han, S., Panagioti, E., et al., 2022. STING activation promotes robust immune response and NK cell–mediated tumor regression in glioblastoma models. Proc. Natl. Acad. Sci. 119 (28), e2111003119.

Bertolaso, M., Dieli, A.M., 2017. Cancer and intercellular cooperation. R. Soc. Open Sci. 4 (10), 170470.

Brandes, A.A., Carpentier, A.F., Kesari, S., Sepulveda-Sanchez, J.M., Wheeler, H.R., Chinot, O., et al., 2016. A phase II randomized study of galunisertib monotherapy or galunisertib plus lomustine compared with lomustine monotherapy in patients with recurrent glioblastoma. Neuro-Oncology 18 (8), 1146–1156.

Broekman, M.L., Maas, S.L.N., Abels, E.R., Mempel, T.R., Krichevsky, A.M., Breakefield, X.O., 2018. Multidimensional communication in the microenvirons of glioblastoma. Nat. Rev. Neurol. 14 (8), 482–495.

Broz Miranda, L., Binnewies, M., Boldajipour, B., Nelson Amanda, E., Pollack Joshua, L., Erle David, J., et al., 2014. Dissecting the tumor myeloid compartment reveals rare activating antigen-presenting cells critical for T cell immunity. Cancer Cell 26 (5), 638–652.

Burger, M.C., Forster, M.-T., Romanski, A., Straßheimer, F., Macas, J., Zeiner, P.S., et al., 2023. Intracranial injection of natural killer cells engineered with a HER2-targeted

chimeric antigen receptor in patients with recurrent glioblastoma. Neuro-Oncology 25 (11), 2058–2071.
Butowski, N.A., Colman, H., Groot, J.F.D., Omuro, A.M.P., Nayak, L., Cloughesy, T.F., et al., 2014. A phase 2 study of orally administered PLX3397 in patients with recurrent glioblastoma. J. Clin. Oncol. 32 (15_suppl), 2023.
Casili, G., Caffo, M., Campolo, M., Barresi, V., Caruso, G., Cardali, S.M., et al., 2018. TLR-4/Wnt modulation as new therapeutic strategy in the treatment of glioblastomas. Oncotarget 9 (101), 37564–37580.
Chen, Y.C., Lai, Y.S., Hsuuw, Y.D., Chang, K.T., 2021. Withholding of M-CSF supplement reprograms macrophages to M2-like via endogenous CSF-1 activation. Int. J. Mol. Sci. 22 (7).
Chen, D., Varanasi, S.K., Hara, T., Traina, K., Sun, M., McDonald, B., et al., 2023. CTLA-4 blockade induces a microglia-Th1 cell partnership that stimulates microglia phagocytosis and anti-tumor function in glioblastoma. Immunity 56 (9), 2086–2104 e8.
Chitu, V., Gokhan, Ş., Nandi, S., Mehler, M.F., Stanley, E.R., 2016. Emerging roles for CSF-1 receptor and its ligands in the nervous system. Trends Neurosci. 39 (6), 378–393.
Choe, J.H., Watchmaker, P.B., Simic, M.S., Gilbert, R.D., Li, A.W., Krasnow, N.A., et al., 2021. SynNotch-CAR T cells overcome challenges of specificity, heterogeneity, and persistence in treating glioblastoma. Sci. Transl. Med. 13 (591).
Chris, M., Meera, N., Scott, A.M., Puneet, P., 2021. Glioblastoma: clinical presentation, diagnosis, and management. BMJ 374, n1560.
Colman, H., Raizer, J.J., Walbert, T., Plotkin, S.R., Chamberlain, M.C., Wong, E.T., et al., 2018. Phase 1b/2 study of pexidartinib (PEX) in combination with radiation therapy (XRT) and temozolomide (TMZ) in newly diagnosed glioblastoma. J. Clin. Oncol. 36 (15_suppl), 2015.
Colopi, A., Fuda, S., Santi, S., Onorato, A., Cesarini, V., Salvati, M., et al., 2023. Impact of age and gender on glioblastoma onset, progression, and management. Mech. Ageing Dev. 211, 111801.
Cornel, A.M., Mimpen, I.L., Nierkens, S., 2020. MHC class I downregulation in cancer: underlying mechanisms and potential targets for cancer immunotherapy. Cancers (Basel) 12 (7), 1760.
Cui, W., Sun, C., Ma, Y., Wang, S., Wang, X., Zhang, Y., 2020. Inhibition of TLR4 induces M2 microglial polarization and provides neuroprotection via the NLRP3 inflammasome in Alzheimer's disease. Front. Neurosci. 14.
Curran, C.S., Evans, M.D., Bertics, P.J., 2011. GM-CSF production by glioblastoma cells has a functional role in eosinophil survival, activation, and growth factor production for enhanced tumor cell proliferation. J. Immunol. 187 (3), 1254–1263.
Damuzzo, V., Pinton, L., Desantis, G., Solito, S., Marigo, I., Bronte, V., et al., 2015. Complexity and challenges in defining myeloid-derived suppressor cells. Cytometry B Clin. Cytom. 88 (2), 77–91.
Datsi, A., Sorg, R.V., 2021. Dendritic cell vaccination of glioblastoma: road to success or dead end. Front. Immunol. 12.
de Vrij, J., Maas, S.L.N., Kwappenberg, K.M.C., Schnoor, R., Kleijn, A., Dekker, L., et al., 2015. Glioblastoma-derived extracellular vesicles modify the phenotype of monocytic cells. Int. J. Cancer 137 (7), 1630–1642.
Decout, A., Katz, J.D., Venkatraman, S., Ablasser, A., 2021. The cGAS–STING pathway as a therapeutic target in inflammatory diseases. Nat. Rev. Immunol. 21 (9), 548–569.
Del Prete, A., Salvi, V., Soriani, A., Laffranchi, M., Sozio, F., Bosisio, D., et al., 2023. Dendritic cell subsets in cancer immunity and tumor antigen sensing. Cell. Mol. Immunol. 20 (5), 432–447.
Delgado-Martín, B., Medina, M.Á., 2020. Advances in the knowledge of the molecular biology of glioblastoma and its impact in patient diagnosis, stratification, and treatment. Adv. Sci. 7 (9), 1902971.
Du, R., Lu, K.V., Petritsch, C., Liu, P., Ganss, R., Passegué, E., et al., 2008. HIF1α induces the recruitment of bone marrow-derived vascular modulatory cells to regulate tumor angiogenesis and invasion. Cancer Cell 13 (3), 206–220.
Du, Z., Cai, C., Sims, M., Boop, F.A., Davidoff, A.M., Pfeffer, L.M., 2017. The effects of type I interferon on glioblastoma cancer stem cells. Biochem. Biophys. Res. Commun. 491 (2), 343–348.
Du, R.-H., Sun, H.-B., Hu, Z.-L., Lu, M., Ding, J.-H., Hu, G., 2018. Kir6.1/K-ATP channel modulates microglia phenotypes: implication in Parkinson's disease. Cell Death Dis. 9 (3), 404.
Duerinck, J., Schwarze, J.K., Awada, G., Tijtgat, J., Vaeyens, F., Bertels, C., et al., 2021. Intracerebral administration of CTLA-4 and PD-1 immune checkpoint blocking monoclonal antibodies in patients with recurrent glioblastoma: a phase I clinical trial. J. Immunother. Cancer 9 (6).
Esteller, M., Garcia-Foncillas, J., Andion, E., Goodman Steven, N., Hidalgo Oscar, F., Vanaclocha, V., et al., 2000. Inactivation of the DNA-repair gene MGMT and the clinical response of gliomas to alkylating agents. N. Engl. J. Med. 343 (19), 1350–1354.
Everson, R.G., Hugo, W., Sun, L., Antonios, J., Lee, A., Ding, L., et al., 2024. TLR agonists polarize interferon responses in conjunction with dendritic cell vaccination in malignant glioma: a randomized phase II trial. Nat. Commun. 15 (1), 3882.
Faust Akl, C., Andersen, B.M., Li, Z., Giovannoni, F., Diebold, M., Sanmarco, L.M., et al., 2025. Glioblastoma-instructed astrocytes suppress tumour-specific T cell immunity. Nature 643 (8070), 219–229.
Fiebich, B.L., Batista, C.R.A., Saliba, S.W., Yousif, N.M., de Oliveira, A.C.P., 2018. Role of microglia TLRs in neurodegeneration. Front. Cell. Neurosci. 12.
Friebel, E., Kapolou, K., Unger, S., Núñez, N.G., Utz, S., Rushing, E.J., et al., 2020. Single-cell mapping of human brain cancer reveals tumor-specific instruction of tissue-invading leukocytes. Cell 181 (7), 1626–1642 e20.
Friedrich, M., Hahn, M., Michel, J., Sankowski, R., Kilian, M., Kehl, N., et al., 2022. Dysfunctional dendritic cells limit antigen-specific T cell response in glioma. Neuro-Oncology 25 (2), 263–276.
Frost, J.L., Schafer, D.P., 2016. Microglia: architects of the developing nervous system. Trends Cell Biol. 26 (8), 587–597.
Gan, Y., Li, X., Han, S., Liang, Q., Ma, X., Rong, P., et al., 2021. The cGAS/STING pathway: a novel target for cancer therapy. Front. Immunol. 12, 795401.
García-Romero, N., Carrión-Navarro, J., Esteban-Rubio, S., Lázaro-Ibáñez, E., Peris-Celda, M., Alonso, M.M., et al., 2017. DNA sequences within glioma-derived extracellular vesicles can cross the intact blood-brain barrier and be detected in peripheral blood of patients. Oncotarget 8 (1), 1416–1428.
García-Romero, N., Palacín-Aliana, I., Madurga, R., Carrión-Navarro, J., Esteban-Rubio, S., Jiménez, B., et al., 2020. Bevacizumab dose adjustment to improve clinical outcomes of glioblastoma. BMC Med. 18 (1), 142.
Gatto, L., Di Nunno, V., Tosoni, A., Bartolini, S., Ranieri, L., Franceschi, E., 2023. DCVax-L vaccination in patients with glioblastoma: real promise or negative trial? The debate is open. Cancers (Basel) 15 (12), 3251.
Ghosh, M., Xu, Y., Pearse, D.D., 2016. Cyclic AMP is a key regulator of M1 to M2a phenotypic conversion of microglia in the presence of Th2 cytokines. J. Neuroinflammation 13 (1), 9.
Gielen, P.R., Schulte, B.M., Kers-Rebel, E.D., Verrijp, K., Bossman, S.A.J.F.H., ter Laan, M., et al., 2016. Elevated levels of polymorphonuclear myeloid-derived suppressor cells in patients with glioblastoma highly express S100A8/9 and arginase and suppress T cell function. Neuro-Oncology 18 (9), 1253–1264.
Gillard, A.G., Shin, D.H., Hampton, L.A., Lopez-Rivas, A., Parthasarathy, A., Fueyo, J., et al., 2024. Targeting innate immunity in glioma therapy. Int. J. Mol. Sci. 25 (2), 947.
Gjelstrup, M.C., Stilund, M., Petersen, T., Møller, H.J., Petersen, E.L., Christensen, T., 2018. Subsets of activated monocytes and markers of inflammation in incipient and progressed multiple sclerosis. Immunol. Cell Biol. 96 (2), 160–174.
Goldmann, T., Wieghofer, P., Jordão, M.J.C., Prutek, F., Hagemeyer, N., Frenzel, K., et al., 2016. Origin, fate and dynamics of macrophages at central nervous system interfaces. Nat. Immunol. 17 (7), 797–805.
González-Tablas Pimenta, M., Otero, Á., Arandia Guzman, D.A., Pascual-Argente, D., Ruíz Martín, L., Sousa-Casasnovas, P., et al., 2021. Tumor cell and immune cell profiles in primary human glioblastoma: impact on patient outcome. Brain Pathol. 31 (2), 365–380.
Greenwald, A.C., Darnell, N.G., Hoefflin, R., Simkin, D., Mount, C.W., Gonzalez Castro, L. N., et al., 2024. Integrative spatial analysis reveals a multi-layered organization of glioblastoma. Cell 187 (10), 2485–2501 e26.
Guo, S., Wang, H., Yin, Y., 2022. Microglia polarization from M1 to M2 in neurodegenerative diseases. Front. Aging Neurosci. 14.
Haksoyler, V., A Besen, A., Koseci, T., Olgun, P., Bayram, E., Topkan, E., 2021. Neutrophil-to-lymphocyte ratio is prognostic in recurrent glioblastoma multiforme treated with bevacizumab plus irinotecan. Biomark. Med 15 (11), 851–859.
He, Y., Gao, Y., Zhang, Q., Zhou, G., Cao, F., Yao, S., 2020. IL-4 switches microglia/macrophage M1/M2 polarization and alleviates neurological damage by modulating the JAK1/STAT6 pathway following ICH. Neuroscience 437, 161–171.
He, W., Edney, M.K., Paine, S.M.L., Griffiths, R.L., Scurr, D.J., Rahman, R., et al., 2023. Untargeted metabolomic characterization of glioblastoma intra-tumor heterogeneity using OrbiSIMS. Anal. Chem. 95 (14), 5994–6001.
Hegi Monika, E., Diserens, A.-C., Gorlia, T., Hamou, M.-F., de Tribolet, N., Weller, M., et al., 2005. MGMT gene silencing and benefit from temozolomide in glioblastoma. N. Engl. J. Med. 352 (10), 997–1003.
Hegi, M.E., Diserens, A.-C., Godard, S., Dietrich, P.-Y., Regli, L., Ostermann, S., et al., 2004. Clinical trial substantiates the predictive value of O-6-methylguanine-DNA methyltransferase promoter methylation in glioblastoma patients treated with temozolomide. Clin. Cancer Res. 10 (6), 1871–1874.
Heimberger, A.B., Crotty, L.E., Archer, G.E., McLendon, R.E., Friedman, A., Dranoff, G., et al., 2000. Bone marrow-derived dendritic cells pulsed with tumor homogenate induce immunity against syngeneic intracerebral glioma. J. Neuroimmunol. 103 (1), 16–25.
Henrik Heiland, D., Ravi, V.M., Behringer, S.P., Frenking, J.H., Wurm, J., Joseph, K., et al., 2019. Tumor-associated reactive astrocytes aid the evolution of immunosuppressive environment in glioblastoma. Nat. Commun. 10 (1), 2541.
Honkanen, T.J., Tikkanen, A., Karihtala, P., Mäkinen, M., Väyrynen, J.P., Koivunen, J.P., 2019. Prognostic and predictive role of tumour-associated macrophages in HER2 positive breast cancer. Sci. Rep. 9 (1), 10961.
Hu, X., Jiang, C., Gao, Y., Xue, X., 2023. Human dendritic cell subsets in the glioblastoma-associated microenvironment. J. Neuroimmunol. 383, 578147.
Iwasaki, A., Medzhitov, R., 2004. Toll-like receptor control of the adaptive immune responses. Nat. Immunol. 5 (10), 987–995.
Jackson, C., Cherry, C., Bom, S., Dykema, A.G., Wang, R., Thompson, E., et al., 2025. Distinct myeloid-derived suppressor cell populations in human glioblastoma. Science 387 (6731), eabm5214.
Jang, S.C., Economides, K.D., Moniz, R.J., Sia, C.L., Lewis, N., McCoy, C., et al., 2021. ExoSTING, an extracellular vesicle loaded with STING agonists, promotes tumor immune surveillance. Commun. Biol. 4 (1), 497.
Jarmuzek, P., Defort, P., Kot, M., Wawrzyniak-Gramacka, E., Morawin, B., Zembron-Lacny, A., 2023a. Cytokine profile in development of glioblastoma in relation to healthy individuals. Int. J. Mol. Sci. 24 (22).
Jarmuzek, P., Kozlowska, K., Defort, P., Kot, M., Zembron-Lacny, A., 2023b. Prognostic values of systemic inflammatory immunological markers in glioblastoma: a systematic review and meta-analysis. Cancers (Basel) 15 (13), 3339.
Jinno, S., Fleischer, F., Eckel, S., Schmidt, V., Kosaka, T., 2007. Spatial arrangement of microglia in the mouse hippocampus: a stereological study in comparison with astrocytes. Glia 55 (13), 1334–1347.

John Lin, C.-C., Yu, K., Hatcher, A., Huang, T.-W., Lee, H.K., Carlson, J., et al., 2017. Identification of diverse astrocyte populations and their malignant analogs. Nat. Neurosci. 20 (3), 396–405.
Jurga, A.M., Paleczna, M., Kuter, K.Z., 2020. Overview of general and discriminating markers of differential microglia phenotypes. Front. Cell. Neurosci. 14.
Kaczanowska, S., Joseph, A.M., Davila, E., 2013. TLR agonists: our best frenemy in cancer immunotherapy. J. Leukoc. Biol. 93 (6), 847–863.
Kaka, N., Hafazalla, K., Samawi, H., Simpkin, A., Perry, J., Sahgal, A., et al., 2019. Progression-free but no overall survival benefit for adult patients with bevacizumab therapy for the treatment of newly diagnosed glioblastoma: a systematic review and meta-analysis. Cancers (Basel) 11 (11), 1723.
Kamei, R., Okabe, S., 2023. In vivo imaging of the phagocytic dynamics underlying efficient clearance of adult-born hippocampal granule cells by ramified microglia. Glia 71 (8), 2005–2023.
Kapellos, T.S., Bonaguro, L., Gemünd, I., Reusch, N., Saglam, A., Hinkley, E.R., et al., 2019. Human monocyte subsets and phenotypes in major chronic inflammatory diseases. Front. Immunol. 10.
Karimi, E., Yu, M.W., Maritan, S.M., Perus, L.J.M., Rezanejad, M., Sorin, M., et al., 2023. Single-cell spatial immune landscapes of primary and metastatic brain tumours. Nature 614 (7948), 555–563.
Kettenmann, H., Hanisch, U.-K., Noda, M., Verkhratsky, A., 2011. Physiology of microglia. Physiol. Rev. 91 (2), 461–553.
Khan, S., Mittal, S., McGee, K., Alfaro-Munoz, K.D., Majd, N., Balasubramaniyan, V., et al., 2020. Role of neutrophils and myeloid-derived suppressor cells in glioma progression and treatment resistance. Int. J. Mol. Sci. 21 (6).
Kim, S., Son, Y., 2021. Astrocytes stimulate microglial proliferation and M2 polarization in vitro through crosstalk between astrocytes and microglia. Int. J. Mol. Sci. 22 (16), 8800.
Kim, Y., Park, J., Choi, Y.K., 2019. The role of astrocytes in the central nervous system focused on BK channel and heme oxygenase metabolites: a review. Antioxidants (Basel) 8 (5).
Kitange, G.J., Carlson, B.L., Schroeder, M.A., Grogan, P.T., Lamont, J.D., Decker, P.A., et al., 2009. Induction of MGMT expression is associated with temozolomide resistance in glioblastoma xenografts. Neuro-Oncology 11 (3), 281–291.
Klemm, F., Maas, R.R., Bowman, R.L., Kornete, M., Soukup, K., Nassiri, S., et al., 2020. Interrogation of the microenvironmental landscape in brain tumors reveals disease-specific alterations of immune cells. Cell 181 (7), 1643–1660 e17.
Kohanbash, G., McKaveney, K., Sakaki, M., Ueda, R., Mintz, A.H., Amankulor, N., et al., 2013. GM-CSF promotes the immunosuppressive activity of glioma-infiltrating myeloid cells through Interleukin-4 receptor-α. Cancer Res. 73 (21), 6413–6423.
Kozono, D., Li, J., Nitta, M., Sampetrean, O., Gonda, D., Kushwaha, D.S., et al., 2015. Dynamic epigenetic regulation of glioblastoma tumorigenicity through LSD1 modulation of MYC expression. Proc. Natl. Acad. Sci. 112 (30). E4055-E64.
Krishnamoorthy, M., Gerhardt, L., Maleki, Vareki S., 2021. Immunosuppressive effects of myeloid-derived suppressor cells in cancer and immunotherapy. Cells 10 (5).
Lad, M., Beniwal, A.S., Jain, S., Shukla, P., Kalistratova, V., Jung, J., et al., 2024. Glioblastoma induces the recruitment and differentiation of dendritic-like “hybrid” neutrophils from skull bone marrow. Cancer Cell 42 (9), 1549–1569 e16.
Laffer, B., Bauer, D., Wasmuth, S., Busch, M., Jalilvand, T.V., Thanos, S., et al., 2019. Loss of IL-10 promotes differentiation of microglia to a M1 phenotype. Front. Cell. Neurosci. 13, 430.
Lazarus, H.M., Ragsdale, C.E., Gale, R.P., Lyman, G.H., 2021. Sargramostim (rhu GM-CSF) as cancer therapy (systematic review) and an Immunomodulator. A drug before its time? Front. Immunol. 12.
Lee, S.J., Kang, W.Y., Yoon, Y., Jin, J.Y., Song, H.J., Her, J.H., et al., 2015. Natural killer (NK) cells inhibit systemic metastasis of glioblastoma cells and have therapeutic effects against glioblastomas in the brain. BMC Cancer 15 (1), 1011.
Li, Q., Barres, B.A., 2018. Microglia and macrophages in brain homeostasis and disease. Nat. Rev. Immunol. 18 (4), 225–242.
Li, D., Wu, M., 2021. Pattern recognition receptors in health and diseases. Signal Transduct. Target. Ther. 6 (1), 291.
Li, J., Dai, X., Zhou, L., Li, X., Pan, D., 2021. Edaravone plays protective effects on LPS-induced microglia by switching M1/M2 phenotypes and regulating NLRP3 inflammasome activation. Front. Pharmacol. 12.
Li, C., Liu, F., Sun, L., Liu, Z., Zeng, Y., 2022a. Natural killer cell-related gene signature predicts malignancy of glioma and the survival of patients. BMC Cancer 22 (1), 230.
Li, L., Zhou, J., Dong, X., Liao, Q., Zhou, D., Zhou, Y., 2022b. Dendritic cell vaccines for glioblastoma fail to complete clinical translation: bottlenecks and potential countermeasures. Int. Immunopharmacol. 109, 108929.
Li, H., Zhou, B., Liao, P., Liao, D., Yang, L., Wang, J., et al., 2023. Prolonged exposure of neonatal mice to sevoflurane leads to hyper-ramification in microglia, reduced contacts between microglia and synapses, and defects in adult behavior. Front. Neurol. 14.
Liau, L.M., Ashkan, K., Brem, S., Campian, J.L., Trusheim, J.E., Iwamoto, F.M., et al., 2023. Association of autologous tumor lysate-loaded dendritic cell vaccination with extension of survival among patients with newly diagnosed and recurrent glioblastoma: a phase 3 prospective externally controlled cohort trial. JAMA Oncol. 9 (1), 112–121.
Lier, J., Streit, W.J., Bechmann, I., 2021. Beyond activation: characterizing microglial functional phenotypes. Cells 10 (9), 2236.
Lim, J., Kang, I., La, J., Ku, K.B., Kang, B.H., Kim, Y., et al., 2023. Harnessing type I interferon-mediated immunity to target malignant brain tumors. Front. Immunol. 14.
Lin, Y.-J., Wei, K.-C., Chen, P.-Y., Lim, M., Hwang, T.-L., 2021. Roles of neutrophils in glioma and brain metastases. Front. Immunol. 12.
Lisi, L., Ciotti, G.M.P., Braun, D., Kalinin, S., Currò, D., Dello Russo, C., et al., 2017. Expression of iNOS, CD163 and ARG-1 taken as M1 and M2 markers of microglial polarization in human glioblastoma and the surrounding normal parenchyma. Neurosci. Lett. 645, 106–112.
Lloyd, A.F., Davies, C.L., Holloway, R.K., Labrak, Y., Ireland, G., Carradori, D., et al., 2019. Central nervous system regeneration is driven by microglia necroptosis and repopulation. Nat. Neurosci. 22 (7), 1046–1052.
Lopes, M., Carvalho, B., Vaz, R., Linhares, P., 2018. Influence of neutrophil–lymphocyte ratio in prognosis of glioblastoma multiforme. J. Neuro-Oncol. 136 (1), 173–180.
Louis, D.N., Perry, A., Wesseling, P., Brat, D.J., Cree, I.A., Figarella-Branger, D., et al., 2021. The 2021 WHO classification of tumors of the central nervous system: a summary. Neuro-Oncology 23 (8), 1231–1251.
Low, J.T., Brown, M.C., Reitman, Z.J., Bernstock, J.D., Markert, J.M., Friedman, G.K., et al., 2024. Understanding and therapeutically exploiting cGAS/STING signaling in glioblastoma. J. Clin. Invest. 134 (2).
Lv, L., Huang, J., Xi, H., Zhou, X., 2020. Efficacy and safety of dendritic cell vaccines for patients with glioblastoma: a meta-analysis of randomized controlled trials. Int. Immunopharmacol. 83, 106336.
Lv, X., Wang, B., Liu, K., Li, M.J., Yi, X., Wu, X., 2024. Decoding heterogeneous and coordinated tissue architecture in glioblastoma using spatial transcriptomics. iScience 27 (6).
Ma, R., Lu, T., Li, Z., Teng, K.-Y., Mansour, A.G., Yu, M., et al., 2021. An oncolytic virus expressing IL15/IL15Rα combined with off-the-shelf EGFR-CAR NK cells targets glioblastoma. Cancer Res. 81 (13), 3635–3648.
Maas, R.R., Soukup, K., Fournier, N., Massara, M., Galland, S., Kornete, M., et al., 2023. The local microenvironment drives activation of neutrophils in human brain tumors. Cell 186 (21), 4546–4566 (e27).
Maggs, L., Cattaneo, G., Dal, A.E., Moghaddam, A.S., Ferrone, S., 2021. CAR T cell-based immunotherapy for the treatment of glioblastoma. Front. Neurosci. 15.
Mammoto, T., Jiang, A., Jiang, E., Panigrahy, D., Kieran, M.W., Mammoto, A., 2013. Role of collagen matrix in tumor angiogenesis and glioblastoma multiforme progression. Am. J. Pathol. 183 (4), 1293–1305.
Marenco-Hillembrand, L., Wijesekera, O., Suarez-Meade, P., Mampre, D., Jackson, C., Peterson, J., et al., 2020. Trends in glioblastoma: outcomes over time and type of intervention: a systematic evidence based analysis. J. Neuro-Oncol. 147 (2), 297–307.
Mariani, G., Lasku, A., Pau, A., Villa, G., Motta, C., Calcagno, G., et al., 1997. A pilot pharmacokinetic and immunoscintigraphic study with the technetium-99m-labeled monoclonal antibody BC-1 directed against oncofetal fibronectin in patients with brain tumors. Cancer 80 (12 Suppl), 2484–2489.
Mega, A., Hartmark Nilsen, M., Leiss, L.W., Tobin, N.P., Miletic, H., Sleire, L., et al., 2020. Astrocytes enhance glioblastoma growth. Glia 68 (2), 316–327.
Meric-Bernstam, F., Sweis, R.F., Hodi, F.S., Messersmith, W.A., Andtbacka, R.H.I., Ingham, M., et al., 2022. Phase I dose-escalation trial of MIW815 (ADU-S100), an intratumoral STING agonist, in patients with advanced/metastatic solid tumors or lymphomas. Clin. Cancer Res. 28 (4), 677–688.
Miller, K.D., Ostrom, Q.T., Kruchko, C., Patil, N., Tihan, T., Cioffi, G., et al., 2021. Brain and other central nervous system tumor statistics, 2021. CA Cancer J. Clin. 71 (5), 381–406.
Miyakoshi, A., Ubukata, N., Miyake, H., Shoji-Asahina, A., Dote, H., Ohata, E., et al., 2024. Risk factors for glioblastoma in adults in Japan: an exploratory cohort study based on the Shizuoka Kokuho database, the Shizuoka study. J. Neuro-Oncol. 166 (2), 341–349.
Mrdjen, D., Pavlovic, A., Hartmann, F.J., Schreiner, B., Utz, S.G., Leung, B.P., et al., 2018. High-dimensional single-cell mapping of central nervous system immune cells reveals distinct myeloid subsets in health, aging, and disease. Immunity 48 (2), 380–395 (e6).
Mu, L., Wang, Y., Wang, Y., Zhang, H., Shang, D., Tan, F., et al., 2017. Tumor location and survival outcomes in adult patients with supratentorial glioblastoma by levels of toll-like receptor 9 expression. World Neurosurg. 97, 279–283.
Musca, B., Russo, M.G., Tushe, A., Magri, S., Battaggia, G., Pinton, L., et al., 2023. The immune cell landscape of glioblastoma patients highlights a myeloid-enriched and immune suppressed microenvironment compared to metastatic brain tumors. Front. Immunol. 14.
Narita, Y., 2015. Bevacizumab for glioblastoma. Ther. Clin. Risk Manag. 11 (null), 1759–1765.
Nduom, E.K., Wei, J., Yaghi, N.K., Huang, N., Kong, L.-Y., Gabrusiewicz, K., et al., 2016. PD-L1 expression and prognostic impact in glioblastoma. Neuro-Oncology 18 (2), 195–205.
Neftel, C., Laffy, J., Filbin, M.G., Hara, T., Shore, M.E., Rahme, G.J., et al., 2019. An integrative model of cellular states, plasticity, and genetics for glioblastoma. Cell 178 (4), 835–849 e21.
Nejo, T., Matsushita, H., Karasaki, T., Nomura, M., Saito, K., Tanaka, S., et al., 2019. Reduced neoantigen expression revealed by longitudinal multiomics as a possible immune evasion mechanism in glioma. Cancer Immunol. Res. 7 (7), 1148–1161.
Ohkuri, T., Ghosh, A., Kosaka, A., Zhu, J., Ikeura, M., David, M., et al., 2014. STING contributes to antiglioma immunity via triggering type I IFN signals in the tumor microenvironment. Cancer Immunol. Res. 2 (12), 1199–1208.
Omuro, A., Vlahovic, G., Lim, M., Sahebjam, S., Baehring, J., Cloughesy, T., et al., 2017. Nivolumab with or without ipilimumab in patients with recurrent glioblastoma: results from exploratory phase I cohorts of CheckMate 143. Neuro-Oncology 20 (5), 674–686.
Orekhov, A.N., Orekhova, V.A., Nikiforov, N.G., Myasoedova, V.A., Grechko, A.V., Romanenko, E.B., et al., 2019. Monocyte differentiation and macrophage polarization. Vessel Plus. 3, 10.

Ostrom, Q.T., Cioffi, G., Waite, K., Kruchko, C., Barnholtz-Sloan, J.S., 2021. CBTRUS statistical report: primary brain and other central nervous system tumors diagnosed in the United States in 2014–2018. Neuro-Oncology 23 (Supplement_3) iii1-iii105.
Pallini, R., Ricci-Vitiani, L., Banna, G.L., Signore, M., Lombardi, D., Todaro, M., et al., 2008. Cancer stem cell analysis and clinical outcome in patients with glioblastoma multiforme. Clin. Cancer Res. 14 (24), 8205–8212.
Pan, J., Niu, Q., Deng, B., Liu, S., Wu, T., Gao, Z., et al., 2019. CD22 CAR T-cell therapy in refractory or relapsed B acute lymphoblastic leukemia. Leukemia 33 (12), 2854–2866.
Parkhurst Christopher, N., Yang, G., Ninan, I., Savas Jeffrey, N., Yates John III, R., Lafaille Juan, J., et al., 2013. Microglia promote learning-dependent synapse formation through brain-derived neurotrophic factor. Cell 155 (7), 1596–1609.
Perelroizen, R., Philosof, B., Budick-Harmelin, N., Chernobylsky, T., Ron, A., Katzir, R., et al., 2022. Astrocyte immunometabolic regulation of the tumour microenvironment drives glioblastoma pathogenicity. Brain 145 (9), 3288–3307.
Polania, J.W., Hoyt-Miggelbrink, A., Tomaszewski, W.H., Wachsmuth, L.P., Lorrey, S.J., Wilkinson, D.S., et al., 2025. Antigen presentation by tumor-associated macrophages drives T cells from a progenitor exhaustion state to terminal exhaustion. Immunity 58 (1), 232–246 (e6).
Pombo Antunes, A.R., Scheyltjens, I., Lodi, F., Messiaen, J., Antoranz, A., Duerinck, J., et al., 2021. Single-cell profiling of myeloid cells in glioblastoma across species and disease stage reveals macrophage competition and specialization. Nat. Neurosci. 24 (4), 595–610.
Poon, M.T.C., Sudlow, C.L.M., Figueroa, J.D., Brennan, P.M., 2020. Longer-term (≥2 years) survival in patients with glioblastoma in population-based studies pre- and post-2005: a systematic review and meta-analysis. Sci. Rep. 10 (1), 11622.
Prapa, M., Chiavelli, C., Golinelli, G., Grisendi, G., Bestagno, M., Di Tinco, R., et al., 2021. GD2 CAR T cells against human glioblastoma. npj Precis. Oncol. 5 (1), 93.
Prince, L.R., Whyte, M.K., Sabroe, I., Parker, L.C., 2011. The role of TLRs in neutrophil activation. Curr. Opin. Pharmacol. 11 (4), 397–403.
Pyonteck, S.M., Akkari, L., Schuhmacher, A.J., Bowman, R.L., Sevenich, L., Quail, D.F., et al., 2013. CSF-1R inhibition alters macrophage polarization and blocks glioma progression. Nat. Med. 19 (10), 1264–1272.
Qi, D., Geng, Y., Cardenas, J., Gu, J., Yi, S.S., Huang, J.H., et al., 2023. Transcriptomic analyses of patient peripheral blood with hemoglobin depletion reveal glioblastoma biomarkers. npj Genom. Med. 8 (1), 2.
Rades, D., Nadrowitz, R., Buchmann, I., Hunold, P., Noack, F., Schild, S.E., et al., 2010. Radiolabeled cetuximab plus whole-brain irradiation (WBI) for the treatment of brain metastases from non-small cell lung cancer (NSCLC). Strahlenther. Onkol. 186 (8), 458–462.
Rasmussen, B.K., Hansen, S., Laursen, R.J., Kosteljanetz, M., Schultz, H., Nørgård, B.M., et al., 2017. Epidemiology of glioma: clinical characteristics, symptoms, and predictors of glioma patients grade I–IV in the the Danish Neuro-Oncology Registry. J. Neuro-Oncol. 135 (3), 571–579.
Ravi, V.M., Will, P., Kueckelhaus, J., Sun, N., Joseph, K., Salié, H., et al., 2022. Spatially resolved multi-omics deciphers bidirectional tumor-host interdependence in glioblastoma. Cancer Cell 40 (6), 639–655 (e13).
Rodriguez, S.M.B., Staicu, G.-A., Sevastre, A.-S., Baloi, C., Ciubotaru, V., Dricu, A., et al., 2022. Glioblastoma stem cells—useful tools in the battle against cancer. Int. J. Mol. Sci. 23 (9), 4602.
Saidi, A., Hagedorn, M., Allain, N., Verpelli, C., Sala, C., Bello, L., et al., 2009. Combined targeting of interleukin-6 and vascular endothelial growth factor potently inhibits glioma growth and invasiveness. Int. J. Cancer 125 (5), 1054–1064.
Salmon, H., Idoyaga, J., Rahman, A., Leboeuf, M., Remark, R., Jordan, S., et al., 2016. Expansion and activation of CD103⁺ dendritic cell progenitors at the tumor site enhances tumor responses to therapeutic PD-L1 and BRAF inhibition. Immunity 44 (4), 924–938.
Schadendorf, D., Hodi, F.S., Robert, C., Weber, J.S., Margolin, K., Hamid, O., et al., 2015. Pooled analysis of long-term survival data from phase II and phase III trials of ipilimumab in unresectable or metastatic melanoma. J. Clin. Oncol. 33 (17), 1889–1894.
Schmitt, M.J., Company, C., Dramaretska, Y., Barozzi, I., Göhrig, A., Kertalli, S., et al., 2021. Phenotypic mapping of pathologic cross-talk between glioblastoma and innate immune cells by synthetic genetic tracing. Cancer Discov. 11 (3), 754–777.
Seker-Polat, F., Pinarbasi Degirmenci, N., Solaroglu, I., Bagci-Onder, T., 2022. Tumor cell infiltration into the brain in glioblastoma: from mechanisms to clinical perspectives. Cancers (Basel) 14 (2), 443.
Sengsayadeth, S., Savani, B.N., Oluwole, O., Dholaria, B., 2022. Overview of approved CAR-T therapies, ongoing clinical trials, and its impact on clinical practice. eJHaem 3 (S1), 6–10.
Shaim, H., Shanley, M., Basar, R., Daher, M., Gumin, J., Zamler, D.B., et al., 2021. Targeting the αv integrin/TGF-β axis improves natural killer cell function against glioblastoma stem cells. J. Clin. Invest. 131 (14).
Sharifian, M.J., Igland, J., Klungsøyr, K., Engeland, A., Zhou, A., Bjørge, T., 2024. Incidence trends of adult glioma in Norway and its association with occupation and education: a registry-based cohort study. Cancer Epidemiol. 89, 102524.
Sharifzad, F., Ghavami, S., Verdi, J., Mardpour, S., Mollapour Sisakht, M., Azizi, Z., et al., 2019. Glioblastoma cancer stem cell biology: potential theranostic targets. Drug Resist. Updat. 42, 35–45.
Shen, S., Cui, Y., Li, M., Yu, K., Zhu, Q., Zhang, X., et al., 2024. Toll-like receptor agonists promote the formation of tertiary lymphoid structure and improve anti-glioma immunity. Neuro-Oncology. 27 (1), 140–154.
Siegler, E.L., Zhu, Y., Wang, P., Yang, L., 2018. Off-the-shelf CAR-NK cells for cancer immunotherapy. Cell Stem Cell. 23 (2), 160–161.
Simon, T., Coquerel, B., Petit, A., Kassim, Y., Demange, E., Le Cerf, D., et al., 2014. Direct effect of bevacizumab on glioblastoma cell lines in vitro. NeuroMolecular Med. 16 (4), 752–771.
Soiffer, R., Lynch, T., Mihm, M., Jung, K., Rhuda, C., Schmollinger, J.C., et al., 1998. Vaccination with irradiated autologous melanoma cells engineered to secrete human granulocyte–macrophage colony-stimulating factor generates potent antitumor immunity in patients with metastatic melanoma. Proc. Natl. Acad. Sci. 95 (22), 13141–13146.
Spranger, S., Dai, D., Horton, B., Gajewski, T.F., 2017. Tumor-residing Batf3 dendritic cells are required for effector T cell trafficking and adoptive T cell therapy. Cancer Cell 31 (5), 711–723 e4.
Srivastava, S., Jackson, C., Kim, T., Choi, J., Lim, M., 2019. A characterization of dendritic cells and their role in immunotherapy in glioblastoma: from preclinical studies to clinical trials. Cancers (Basel) 11 (4), 537.
Sterner, R.C., Sterner, R.M., 2021. CAR-T cell therapy: current limitations and potential strategies. Blood Cancer J. 11 (4), 69.
Stoyanov, G.S., Dzhenkov, D., Ghenev, P., Iliev, B., Enchev, Y., Tonchev, A.B., 2018. Cell biology of glioblastoma multiforme: from basic science to diagnosis and treatment. Med. Oncol. 35 (3), 27.
Strecker, M., Wlotzka, K., Strassheimer, F., Roller, B., Ludmirski, G., König, S., et al., 2022. AAV-mediated gene transfer of a checkpoint inhibitor in combination with HER2-targeted CAR-NK cells as experimental therapy for glioblastoma. Oncoimmunology 11 (1), 2127508.
Strizova, Z., Benesova, I., Bartolini, R., Novysedlak, R., Cecrdlova, E., Foley Lily, K., et al., 2023. M1/M2 macrophages and their overlaps – myth or reality? Clin. Sci. 137 (15), 1067–1093.
Stylli, S.S., 2020. Novel treatment strategies for glioblastoma. Cancers (Basel) 12 (10), 2883.
Tachi, T., Kijima, N., Kuroda, H., Ikeda, S., Murakami, K., Nakagawa, T., et al., 2024. Antitumor effects of intracranial injection of B7-H3-targeted Car-T and Car-Nk cells in a patient-derived glioblastoma xenograft model. Cancer Immunol. Immunother. 73 (12), 256.
Tang, Y.-p., Xie, M.-z., Li, K.-z., Li, J.-l., Cai, Z.-m., Hu, B.-l., 2020. Prognostic value of peripheral blood natural killer cells in colorectal cancer. BMC Gastroenterol. 20 (1), 31.
Tao, W., Chu, C., Zhou, W., Huang, Z., Zhai, K., Fang, X., et al., 2020. Dual role of WISP1 in maintaining glioma stem cells and tumor-supportive macrophages in glioblastoma. Nat. Commun. 11 (1), 3015.
Taylor, K.R., Barron, T., Hui, A., Spitzer, A., Yalçin, B., Ivec, A.E., et al., 2023. Glioma synapses recruit mechanisms of adaptive plasticity. Nature 623 (7986), 366–374.
Tesileanu, C.M.S., Sanson, M., Wick, W., Brandes, A.A., Clement, P.M., Erridge, S.C., et al., 2022. Temozolomide and radiotherapy versus radiotherapy alone in patients with glioblastoma, IDH-wildtype: post hoc analysis of the EORTC randomized phase III CATNON trial. Clin. Cancer Res. 28 (12), 2527–2535.
Touil, H., Li, R., Zuroff, L., Moore, C.S., Healy, L., Cignarella, F., et al., 2023. Cross-talk between B cells, microglia and macrophages, and implications to central nervous system compartmentalized inflammation and progressive multiple sclerosis. eBioMedicine 96.
Ulaner, G.A., Lyashchenko, S.K., Riedl, C., Ruan, S., Zanzonico, P.B., Lake, D., et al., 2018. First-in-human human epidermal growth factor receptor 2-targeted imaging using (89)Zr-Pertuzumab PET/CT: dosimetry and clinical application in patients with breast Cancer. J. Nucl. Med. 59 (6), 900–906.
Umansky, V., Blattner, C., Gebhardt, C., Utikal, J., 2016. The role of myeloid-derived suppressor cells (MDSC) in cancer progression. Vaccines 4 (4), 36.
Veglia, F., Sanseviero, E., Gabrilovich, D.I., 2021. Myeloid-derived suppressor cells in the era of increasing myeloid cell diversity. Nat. Rev. Immunol. 21 (8), 485–498.
Venkatesh Humsa, S., Johung Tessa, B., Caretti, V., Noll, A., Tang, Y., Nagaraja, S., et al., 2015. Neuronal activity promotes glioma growth through Neuroligin-3 secretion. Cell 161 (4), 803–816.
Venkatesh, H.S., Morishita, W., Geraghty, A.C., Silverbush, D., Gillespie, S.M., Arzt, M., et al., 2019. Electrical and synaptic integration of glioma into neural circuits. Nature 573 (7775), 539–545.
Vidal-Itriago, A., Radford, R.A.W., Aramideh, J.A., Maurel, C., Scherer, N.M., Don, E.K., et al., 2022. Microglia morphophysiological diversity and its implications for the CNS. Front. Immunol. 13, 997786.
Vollmann-Zwerenz, A., Leidgens, V., Feliciello, G., Klein, C.A., Hau, P., 2020. Tumor cell invasion in glioblastoma. Int. J. Mol. Sci. 21 (6), 1932.
Wang, J., Matosevic, S., 2019. NT5E/CD73 as correlative factor of patient survival and natural killer cell infiltration in glioblastoma. J. Clin. Med. 8 (10), 1526.
Wang, L., Babikir, H., Müller, S., Yagnik, G., Shamardani, K., Catalan, F., et al., 2019. The phenotypes of proliferating glioblastoma cells reside on a single axis of variation. Cancer Discov. 9 (12), 1708–1719.
Wang, X.-P., Guo, W., Chen, Y.-F., Hong, C., Ji, J., Zhang, X.-Y., et al., 2024. PD-1/PD-L1 axis is involved in the interaction between microglial polarization and glioma. Int. Immunopharmacol. 133, 112074.
Watkins, S., Robel, S., Kimbrough, I.F., Robert, S.M., Ellis-Davies, G., Sontheimer, H., 2014. Disruption of astrocyte–vascular coupling and the blood–brain barrier by invading glioma cells. Nat. Commun. 5 (1), 4196.
Watson, D.C., Bayik, D., Storevik, S., Moreino, S.S., Sprowls, S.A., Han, J., et al., 2023. GAP43-dependent mitochondria transfer from astrocytes enhances glioblastoma tumorigenicity. Nat. Can. 4 (5), 648–664.
Wei, Q., Singh, O., Ekinci, C., Gill, J., Li, M., Mamatjan, Y., et al., 2021. TNFα secreted by glioma associated macrophages promotes endothelial activation and resistance against anti-angiogenic therapy. Acta Neuropathol. Commun. 9, 1–19.
Weller, M., Tabatabai, G., Kästner, B., Felsberg, J., Steinbach, J.P., Wick, A., et al., 2015. MGMT promoter methylation is a strong prognostic biomarker for benefit from dose-

intensified temozolomide rechallenge in progressive glioblastoma: the DIRECTOR trial. Clin. Cancer Res. 21 (9), 2057–2064.
Wen, P.Y., Packer, R.J., 2021. The 2021 WHO classification of tumors of the central nervous system: clinical implications. Neuro-Oncology 23 (8), 1215–1217.
Wilgenhof, S., Corthals, J., Heirman, C., Nv, Baren, Lucas, S., Kvistborg, P., et al., 2016. Phase II study of autologous monocyte-derived mRNA electroporated dendritic cells (TriMixDC-MEL) plus Ipilimumab in patients with pretreated advanced melanoma. J. Clin. Oncol. 34 (12), 1330–1338.
Wolf, N.K., Kissiov, D.U., Raulet, D.H., 2023. Roles of natural killer cells in immunity to cancer, and applications to immunotherapy. Nat. Rev. Immunol. 23 (2), 90–105.
Wu, A., Wei, J., Kong, L.-Y., Wang, Y., Priebe, W., Qiao, W., et al., 2010. Glioma cancer stem cells induce immunosuppressive macrophages/microglia. Neuro-Oncology 12 (11), 1113–1125.
Wu, X., Wang, J., Wang, Y., 2021. Multiple intracranial and extracranial metastases from postoperative glioblastoma: a case report and review of the literature. Interdiscip. Neurosurg. 24, 101025.
Xiao, Y., Yang, K., Wang, Z., Zhao, M., Deng, Y., Ji, W., et al., 2022. CD44-mediated poor prognosis in glioma is associated with M2-polarization of tumor-associated macrophages and immunosuppression. Front. Surg. 8.
Xiao, D., Yan, C., Li, D., Xi, T., Liu, X., Zhu, D., et al., 2023. National Brain Tumour Registry of China (NBTRC) statistical report of primary brain tumours diagnosed in China in years 2019–2020. Lancet Regional Health – West. Pac. 34.
Xie, G., Dong, H., Liang, Y., Ham, J.D., Rizwan, R., Chen, J., 2020. CAR-NK cells: a promising cellular immunotherapy for cancer. eBioMedicine 59.
Xun, Y., Yang, H., Kaminska, B., You, H., 2021. Toll-like receptors and toll-like receptor-targeted immunotherapy against glioma. J. Hematol. Oncol. 14 (1), 176.
Yabo, Y.A., Niclou, S.P., Golebiewska, A., 2021. Cancer cell heterogeneity and plasticity: a paradigm shift in glioblastoma. Neuro-Oncology 24 (5), 669–682.
Yang, L., DeBusk, L.M., Fukuda, K., Fingleton, B., Green-Jarvis, B., Shyr, Y., et al., 2004. Expansion of myeloid immune suppressor Gr+CD11b+ cells in tumor-bearing host directly promotes tumor angiogenesis. Cancer Cell 6 (4), 409–421.
Yi, L., Xiao, H., Xu, M., Ye, X., Hu, J., Li, F., et al., 2011. Glioma-initiating cells: A predominant role in microglia/macrophages tropism to glioma. J. Neuroimmunol. 232 (1), 75–82.
Yu, R., Zhu, B., Chen, D., 2022. Type I interferon-mediated tumor immunity and its role in immunotherapy. Cell. Mol. Life Sci. 79 (3), 191.
Zeng, A., Wei, Z., Rabinovsky, R., Jun, H.J., El Fatimy, R., Deforzh, E., et al., 2020. Glioblastoma-derived extracellular vesicles facilitate transformation of astrocytes via reprogramming oncogenic metabolism. iScience 23 (8), 101420.
Zeppernick, F., Ahmadi, R., Campos, B., Dictus, C., Helmke, B.M., Becker, N., et al., 2008. Stem cell marker CD133 affects clinical outcome in glioma patients. Clin. Cancer Res. 14 (1), 123–129.
Zhang, C., Burger, M.C., Jennewein, L., Genßler, S., Schönfeld, K., Zeiner, P., et al., 2016. ErbB2/HER2-specific NK cells for targeted therapy of glioblastoma. J. Natl. Cancer Inst. 108 (5), djv375.
Zhang, G., Tanaka, S., Jiapaer, S., Sabit, H., Tamai, S., Kinoshita, M., et al., 2020a. RBPJ contributes to the malignancy of glioblastoma and induction of proneural-mesenchymal transition via IL-6-STAT3 pathway. Cancer Sci. 111 (11), 4166–4176.
Zhang, S., Liu, W., Hu, B., Wang, P., Lv, X., Chen, S., et al., 2020b. Prognostic significance of tumor-infiltrating natural killer cells in solid tumors: a systematic review and meta-analysis. Front. Immunol. 11.
Zhang, N., Dai, Z., Wu, W., Wang, Z., Cao, H., Zhang, Y., et al., 2021. The predictive value of monocytes in immune microenvironment and prognosis of glioma patients based on machine learning. Front. Immunol. 12.
Zhao, J., Chen, A.X., Gartrell, R.D., Silverman, A.M., Aparicio, L., Chu, T., et al., 2019. Immune and genomic correlates of response to anti-PD-1 immunotherapy in glioblastoma. Nat. Med. 25 (3), 462–469.
Zhou, W., Ke, S.Q., Huang, Z., Flavahan, W., Fang, X., Paul, J., et al., 2015. Periostin secreted by glioblastoma stem cells recruits M2 tumour-associated macrophages and promotes malignant growth. Nat. Cell Biol. 17 (2), 170–182.