Examining the Crucial Role of Myeloid Derived Suppressor Cells in Glioblastoma

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Glioblastoma (GBM) is a prominent brain cancer that has a tumor microenvironment (TME) promoting immunosuppressive factors, which support its growth and survival. With myeloid-derived suppressor cells (MDSCs) in the TME and in the peripheral blood, there are many immunosuppressive effects that occur, all of which allow the tumors to progress in the body. Understanding the role of MDSCs in GBM, particularly their interactions with other TME components, is crucial. This literature review analyzes a variety of sources to emphasize important interconnected relationships within GBM, and the true significance of MDSCs in the TME.

Keywords: MDSCs, glioblastoma, tumor microenvironment, TAMs, hypoxia, T cells, NK cells, chemokines, cytokines

Introduction

Myeloid Derived Suppressor Cells

Myeloid derived suppressor cells (MDSCs) are a heterogeneous population of cells derived from monocytes that create an immunosuppressive environment in which tumors can thrive (Yu & Quail, 2021; Lakshmanachetty et al., 2021)[1,2]. They make up around 30%-50% of tumor-promoting in the TME. In cases in which pathological diseases are not present, immature myeloid cells would typically differentiate into macrophages, neutrophils, NK cells, and dendritic cells.

However, with pathological diseases, this maturation is blocked by the expression of cytokines such as IL-10, IFN-γ, IL-6, GM-CSF, and G-CSF; which then leads to the development of MDSCs. These cells are created to combat immune cells, such as T cells and NK cells. The environment in which the tumor survives is essential to the functions that MDSCs carry out. These tasks being carried out contribute to the GBM being a malignant tumor, and grants the survival of cells that suppress the immune response.

MDSCs Role in Glioblastoma

Glioblastoma (GBM) is the most common primary, malignant brain cancer (Yu & Quail, 2021)[1 1]. Prognosis is poor, with median survival rates being less than 15 months (Lakshmanachetty et al., 2021)[2]. Standard treatment involves surgical debulking followed by radiation and chemotherapy with temozolomide (Yu & Quail, 2021; Richard, 2020)[1,3,4]. However, these treatments often fail due to the blood-brain barrier, diffuse tumor margins, and the immunosuppressive effects of protumoral myeloid cells (Alban et al., 2020)[5].

The TME of GBM is highly heterogeneous, and is comprised of tumor-associated macrophages (TAMs), regulatory T cells (Tregs), NK cells, T cells, and importantly MDSCs (Zhang et al., 2022)[6]. MDSCs relationship with these cells is major for performing its own functions and aiding with other cells in the GBM TME. This is a huge area of interest with MDSCs and GBM due to the similarity of sex playing a key role in its functionality (Bayik et al., 2020)[7]. MDSCs in GBM has a unique place, and is an area of knowledge that should be better understood.

Subsets of MDSCs in Glioblastoma

MDSCs can be separated into two subsets: granulocytic (gMDSCs) and monocytic (mMDSCs). They are expressed as CD11b+CD14+CD66b+ and CD11b+CD14+CD15-, respectively (Lakshmanachetty et al., 2021; Alban et al., 2020)[2,5]. The subsets are associated by gender and their different functions from each other. Bayik et al. (2020)[7], has found typically, male patients have a higher quantity of mMDSCs, while female patients would have a higher quantity in gMDSCs. gMDSCs are found to be similar to neutrophils and are present in the peripheral blood when a tumor is.

Their main function is to keep systemic immunosuppression up. mMDSCs are localized at the tumor microenvironment and instead support tumor growth and progression. They are more similar to inflammatory monocytes. This difference has been shown to be important in tailoring treatments for cancer patients (Bayik et al., 2020)[7].

MDSCs can be further classified by their CD45

Table 1 An overview of the differences between the two main subsets in MDSCs: granulocytic and monocytic. These subsets have different functions with GBM, subsequently different concentrations in the TME. (Lakshmanachetty et al., 2021; Richard, 2020; Gieryng & Kaminska, 2016)[2–4,8]

G-MDSCs	M-MDSCs
Higher quantity in women patients	Higher quantities in male patients
Reactive Oxygen Species produced to eliminate T cells	Nitric oxide synthase 2 (NOS2) & arginase 1 (Arg1) produced to eliminate T cells
Less conducive in hypoxic environment	Hypoxia preferentially recruit into TME
Strengthen immunosuppressive environment	Support tumor growth

expression: CD11b+CD45^{high} and CD11B+CD45^{low}. CD11B+CD45^{low}cells are microglia, while CD11b+CD45^{high} cells are found to be peripheral macrophages. The latter are found to be more reactive in the glioblastoma microenvironment (Richard, 2020)[4]. This is significant because it shows the importance of macrophages in the TME. These cells promote cell inflammation, aiding in immune suppression, and facilitating tumor survival. Lectin-type oxidized receptor 1 (LOX-1) plays a critical role in mediating endoplasmic reticulum stress and lipid metabolism, which is implicated in promoting immunosuppressive functions within the TME.

With the help of LOX-1, MDSCs are able to keep an immune suppressed tumor microenvironment (Lakshmanachetty et al., 2021)[2]. Their activity being prominent is through the work of cytokines, chemokines, and other expressions, which otherwise benefit the tumor progression and growth. MDSCs are used for three main functions: depletion of essential amino acids, block immunity, and support tumor growth. The main targets are immune cells such as T cells and NK cells. A blockage of T cells and NK cells occurs through various different mechanisms (Richard, 2020; Zhang et al., 2022)[4,6].

Another notable subset of MDSCs that has been identified is the CD11b+GR1+ phenotype. This subtype is responsible for blocking immune responses to the tumor and speeding tumor growth and progression. CD11b+GR1+^{high} cells are found mostly at the primary tumor in the tumor microenvironment. CD11b+GR1+^{low} cells are known to be the cause of the upregulation of IL-4Rα in the TME; which aids in enabling monocytes, upregulating macrophages, and preventing T cell activation (Richard, 2020)[4].

MDSCs & T cells/Tregs

Immune surveillance is the critical function that immunosuppressive cells and molecules have to overcome to continue tumor survival. Immune surveillance is a process in which T cells survey the immune system for foreign pathogens and attack them, which makes these cells vital for immune responses. Similar to MDSCs, T cells can be put into two subsets: cytotoxic T cells (CD8+ T cells) and helper T cells (CD4+ T cells). CD8+ T cells' responsibility is to directly destroy tumor cells, while CD4+ T cells provide support for other immune cells in an anti-tumor response against GBM. Depending on the subset, T cells will recognize MHC Class I molecules or MHC Class II, respectively. When an Antigen Presenting Cell (APC), such as a dendritic cell, recognizes these antigens, T cells will be activated. These activated cells will attack the glial cells that present those antigens in the tumor (Brown et al., 2018)[9]. Regulatory T cells (Tregs) are a type of CD4+ T cells, regulating immune tolerance and suppressing excessive immune responses. Tregs are an important cell type in autoimmune diseases, however in cancer they contribute to tumor growth (Zhang et al., 2022)[6]. These cells inhibit T cell function by suppressing responses to APCs, and subsequently, T cells cannot provide an effective anti-tumor response.

One of the main functions that MDSCs perform is the depletion of essential amino acids, specifically in T cells. Without these amino acids, T cells are not able to be activated, and therefore will be rendered useless (Zhang et al., 2022)[6]. The activation of mMDSCs results in a blockade of CD4+ T cells, which subsequently promotes the expansion of mMDSCs, causing a cycle to persist in the TME (Richard, 2020)[4]. gMDSCs generate reactive oxygen species (ROS), while mMDSCs produce nitric oxide synthase 2 (NOS2) & arginase 1 (Arg1), which inhibits T cell function and induces apoptosis (Lakshmanachetty et al., 2021; Richard, 2020; Gieryng & Kaminska, 2016)[2,4,8].

Through the downregulation of granulocyte colony-stimulating factor (GM-CSF) from the microbiota, MDSCs have an increased expression of ROS, which then affects T cell functions (Zhang et al., 2022)[6]. The stimulation of Tregs through factors such as TGF-β and IL-10 is a result of the functions MDSCs carry out (Richard, 2020)[4]. With the secretion of IFN-γ, MDSCs are able to express TGF-β and IL-10, and inhibit T cell function. This interferon can also replace chemokines expressed by T cells and replace them with immunosuppressive ones that MDSCs secrete. They also could lead to a more effective connection between PD-1 and its ligand PD-L1 (Richard, 2020)[4]. With T cells and many other elements in the GBM, it is evident that there are several ways that chemokines and cytokines are used with MDSCs to manipulate immune responses to have an immunosuppressive environment.

MDSCs & Essential chemokines and cytokines

MDSCs secrete a variety of cytokines and chemokines to perform their functions. The chemokine CCL2 and its receptor CCR2 plays a critical role in recruiting MDSCs into the TME of GBM. STAT3 is a protein heavily involved with immature myeloid cells and their development into MDSCs in pathological diseases. Evidence suggests that STAT3 is also important in immunosuppression caused by MDSCs (Richard, 2020)[4]. IL-10 and TGF-β are important cytokines also involved in the immunosuppression activities of MDSCs, by inhibiting anti-tumor immune responses (Lakshmanachetty et al., 2021)[2]. IL-10 is an essential cytokine that frequently mediates interactions between MDSCs and the other elements in the TME, which fosters an immunosuppressed environment. Tregs use factors like IL-10 to promote their immunosuppressive factors. IL-10 is also used to upregulate immune checkpoint molecules such as B7-H4 and PD-L1 (Zhang et al., 2022)[6]. TGF-β is another cytokine that expedites the expansion of regulatory immune cells such as Tregs and Bregs, which contributes to a protumor environment. Secreted by MDSCs, TGF-β stimulates the body to upregulate these cells, which then in turn continue to produce these cytokines: creating a cycle (Lakshmanachetty et al., 2021; Zhang et al., 2022)[2,6].

The secretion of chemokines such as CCL3, CC14, and CCL5 by MDSCs are salient in the recruitment of Tregs into the TME, which then plays a crucial role of maintaining the suppression of an anti-tumor response. With these two cells in abundance, consequently apoptosis is promoted (Lakshmanachetty et al., 2021)[2]. Through metabolism, M-CSF and G-CSF are cytokines that bind to MDSCs, and upregulation of glycolysis and ATP production is shown: which supports the immunosuppressive functions of MDSCs (Lakshmanachetty et al., 2021)[2]. With the production and secretion levels of chemokines and cytokines, it creates a cardinal view for future treatments, especially when regarding MDSCs.

MDSCs and NK Cells

Natural Killer (NK) cells are paramount for the innate immune system, similar to T cells, and are associated with a more favorable prognosis in glioblastoma. Research for NK cells has been limited, despite their tumoricidal potential (Yu & Quail, 2021)[1]. NK cells are impaired throughout the body in the presence of GBM. Through the gut microbiota imbalance that occurs when this brain cancer is present, NK cells are damaged. The connection between PD-1 and PD-L1 from tumor cells and NK cells respectively leads to a significant reduction in the functions of NK cells, rendering them ineffective in targeting glioma cells (Zhang et al., 2022)[6].

MDSCs share similar functional characteristics with NK cells, and significant potential to counteract MDSC-mediated immunosuppression is highlighted due to the similarities (Lakshmanachetty et al., 2021)[2]. However, MDSCs inhibit NK cells through various mechanisms, including the production of nitric oxide (NO), and subsequently their cytotoxic functions are hindered. TGFβ1, produced by MDSCs, diminishes NK cell cytotoxicity, which contributes to an immunosuppressive TME (Lakshmanachetty et al., 2021; Zhang et al., 2022)[2,6]. The specific subset CD11b+GR1+ is able to suppress the production of perforin, which creates pores in cell membranes, and channels are constructed to target the cell. This production of perforin occurs by NK cells, and this suppression actively counteracts the functions of these immune cells (Lakshmanachetty et al., 2021; Osińska et al., 2014)[2,10]. The suppression of these cytokines by MDSCs is important as there is a significant loss in the effort against the tumor. With the blockage of the CCL2/CCR2 signaling pathway, MDSCs are impaired and they can not suppress NK cells easily, highlighting a potential therapeutic target (Zhang et al., 2022)[6]. NK cells are shown to be vital to the immune response, and this is an area of possible treatments that can be explored further.

MDSCs and TAMs

MDSCs are an essential part of suppressing the immune response, and this function is enhanced with their interactions with Tumor-Associated Macrophages (TAMs) (Noy & Pollard, 2014)[11]. Macrophages can be polarized into two categories: M1 macrophages and M2 macrophages. M1 macrophages contribute to the immune system's response through their proinflammatory and tumoricidal activities. In comparison, M2 macrophages are anti-inflammatory in nature and support tumor progression (Noy & Pollard, 2014)[11]. Through the process of polarization, where the macrophage switches between the two phenotypes, TAMs are switched from M1 phenotype to the M2 phenotype from cytokines such as IFN-γ and TGF-β, even if originally the cell was tumoricidal (Noy & Pollard, 2014)[11]. The secretion of cytokines from TAMs recruits more immune cells to the GBM tumor microenvironment, creating a cycle of immune cell infiltration which ultimately supports the tumor. TAMs work in all areas of glioblastoma, from the tumor microenvironment to metastasis.

TAMs and MDSCs take up a quantifiable percentage, 30-50%, of the cellular population in the glioblastoma TME, with MDSCs being a prominent focus of research due to their well known role with immune suppression (Lakshmanachetty et al., 2021)[2]. MDSCs have the ability to downregulate the MHC Class II Expression, inhibiting the production of M1 macrophages, and upregulating the protumoral M2 macrophages (Lakshmanachetty et al., 2021)[2]. TAMs share functional similarities to MDSCs, which includes their expression of immunosuppressive markers, their existence in both primary and secondary tumors, and shaping an immunosuppressive microenvironment that supports the tumor (Richard, 2020)[4].

MDSCs and Hypoxia

The hypoxic regions in GBM are essential for sustaining the tumor and promoting the aggressiveness of gliomas. Certain factors and exosomes are secreted by hypoxic tumor cells for active recruitment of MDSCs to the TME, as exemplified by RYu & Quail, 2021; Richard, (2020)[1,4]. Hypoxia leads to the upregulation of factors such as vascular endothelial growth factor-A (VEGF) and Hypoxia inducible factor 1-α (HIF-1α), which sustains the tumor, and the amplification of CCL26 to recruit CX3CR1 MDSCs into the GBM microenvironment.

Another main function of MDSCs is metabolic reprogramming, where tumor cells tend to rely on glycolysis for energy and metabolic processes (Lakshmanachetty et al., 2021; Richard, 2020)[2,4]. Hypoxia takes control of oxidation with pyruvate, which starts a chain reaction. With the hypoxic conditions, tumor cells have excessive glycolysis, which leads to an increased lactate production. This metabolic shift upregulates and recruits more MDSCs; enabling an immunosuppressive environment. This increases the expression of the immune checkpoint molecule, programmed death one and its ligand (PD-1 & PD-L1), with cytotoxic T lymphocyte-antigen associated protein 4 (CTLA-4) (Lakshmanachetty et al., 2021)[2], to promote the suppression of T cell immunity.

As proven by Gieryang & Kaminska (2016)[8], mMDSCs and hypoxia are important to perform each other's respective tasks successfully. However, evidence suggests gMDSCs are not sustainable within the GBM microenvironment because of the hypoxic environment, and due to their metabolic differences (Gieryng & Kaminska, 2016)[8]. Furthermore, the TME secrete specific chemokines to preferentially recruit mMDSCs specifically, while the hypoxic environment is less conducive to the survival of gMDSCs. mMDSCs have a different set of functions: to support tumor growth and progression, while gMDSCs give strength towards immunosuppression.

Hypoxia and MDSCs have complementary roles in the GBM microenvironment, with both working to support tumor progression and inhibit immune cell infiltration. This crucial partnership between MDSCs and hypoxia is essential for the tumor to strive and continue to grow. Knowing this, it is important to continue to study MDSCs and hypoxia to gain a better understanding of how their relationship influences the TME and tailor treatments for it.

Treatments Targeting MDSCs

MDSCs are known to be resistant to many targeted therapies, which presents the persistent challenge against treatments for GBM (Yu & Quail, 2021)[1]. Because of this, there is a limited selection of clinical trials that have been conducted, nevertheless successful. Currently, there are no treatments against MDSCs specifically that are successful, but in combination with other therapies; there are promising results. There are significant discoveries from the experiments that have been conducted however. Fludarabine and anti IL-β are therapies that have been explored as potential treatment options for mMDSCs and gMDSCs, respectively. Fludarabine has shown efficacy in increasing the quantity of effective CD8+ T cells in both female and male GL261 mice and male SB28 mice. However, fludarabine did not produce a remarkable difference in SB28 female mice in GBM, highlighting a potential difference in treatment response when it comes to efficacy (Bayik et al., 2020)[7]. Likewise, anti-IL-β therapy demonstrated efficacy in GL261 mice, although responses varied depending on the sex of the mouse (Bayik et al., 2020)[7]. These findings indicate gMDSCs and mMDSCs may respond differently with the same treatments, which further demonstrates the need for targeted therapies that are tailored for MDSC subsets. This implication also shows how treatments will affect people differently because of their sex, as gMDSCs and mMDSCs are prominent in females and males, respectively. Currently, there are no treatments that are tailored towards gMDSCs or mMDSCs in a gendered manner in clinical trials. Another therapeutic approach that has promising results against MDSCs include blocking the chemokine CCL2/CCR2, which is preeminent for the recruitment of MDSCs to the tumor site and peripheral blood. This chemical is required to recruit MDSCs to the tumor or peripheral blood (Zhang et al., 2022)[6]. Another strategy involves the modification of MDSCs to reduce the binding of TCR to CD8+ T cells, which lowers the amount of T cells that interact with antigens and get rendered useless (Richard, 2020)[4].

However there are options that indirectly affect MDSCs and target the results of them performing their functions. An example of this, Ablative hypofractionated RT (AHFRT), can reduce hypoxia in the TME, thereby impairing the function of mMDSCs (Lakshmanachetty et al., 2021)[2]. TK/Flt3L gene therapy, in combination with PD-1 and CTLA-4 therapy, is effective in increasing T cells while also interfering with MDSCs and their immunosuppressive factors (Zhang et al., 2022)[6]. Other therapies have promising potential with glioblastoma, including immune checkpoint inhibitors and chimeric antigen receptor (CAR)-T cell therapy. These therapies are very promising with fighting GBM because of their pattern of being successful in other aggressive cancers. ICIs prevent the bonds of molecules such as PD-1/PD-L1, and CTLA-4, and the thwarting of these elements eliminates the support that the tumor obtains (Yu & Quail, 2021)[1]. CAR-T cell therapy uses genetically modified T cells to destroy tumor cells more effectively (Zhang et al., 2022)[6]. The integration of therapies in GBM, with MDSCs, can have a greater impact in understanding the mechanisms that follow with these cells. They have the potential to create an environment that the body can not fight, so further research conducted should focus on their strengths in the TME, and their effects on the body. This can be conducted by combining ther-

Table 2 Treatment Options/Strategies against MDSCs with descriptions. This table summarizes the treatments that are useful and could be used in a defense against MDSCs.

Treatment/Strategy	Description
Fludarabine	Increase of CD8+ T cells (GL261 mice & SB28 male mice)
Anti IL-β	GL261 mice, however results varied
Blockage of CCL2/CCR2	Reduces recruitment of MDSCs
Modification of MDSCs	Lowers quantity of interactions between APCs and T cells
AHFRT	Reduction of hypoxia: impairing MDSCs
TK/Flt3L with PD-1 & CTLA-4 therapy	Increasing in T cells with interference of MDSCs
CAR T-Cell therapy	Genetically modified T cells to destroy tumor cells
ICIs	Prevent the bond between immunosuppressive molecules and their respective ligands.

apies, such as depletion while also inducing MDSC apoptosis (Tang et. al)[12]. As presented by Mehdizadeh et. al, MDSCs that are depleted with immunotherapies result in less tumor cells and dormancy for the tumor (Mehdizadeh et. al)[13]. However, even with these crucial findings, it is important to note that it is difficult to get a proper understanding of these treatments in mice and for them to be translated into humans. Clinical trials are significant, and it is crucial for MDSC treatments to be tested in humans to understand their full effects.

Conclusion

MDSCs play a vital role in the progression of GBM. Their unique subsets, granolycytic which keeps an immunosuppressive environment, and monocytic which supports tumor growth, and enable a tumor to persist in its environment. These cells attract several cells into the tumor microenvironment (TME) under the regulation of cytokines and chemokines, which then promotes the conditions that MDSCs create in their respective spaces. With their strong immunosuppressive functions, these cells are resistant to many therapies, and further research should be conducted to create more effective treatments that encompass all facets of glioblastoma. This research should not focus solely on treatments, but for a broader understanding of these vital components of glioblastoma, and cancer in general; as understanding MDSCs in GBM also creates space for research in other cancers.

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