Transactions on Cancer (2023)
Clausius Scientific Press, Canada

DOI: 10.23977/tranc.2023.040118
ISSN 2523-6482 Vol. 4 Num. 1

Regulation of Macrophage Polarization and Tumor Immunosuppression in Glioblastoma

Yixuan Li[1,a,*]

[1]*Beijing 101 Middle School, Beijing, 100000, China*
[a]*lyr20050418@outlook.com*
[*]*Corresponding author*

Keywords: Glioblastoma, Macrophage, Polarization regulation, Tumor Immunosuppression

Abstract: Macrophage polarization is the polarization of a series of functional states after activation of monocytes, and different microenvironmental stimuli can regulate their differentiation. Macrophage is not only an important component of the tumor microenvironment, but also an essential part of it. By interacting with various factors, it regulates the growth, invasion, metastasis, and lymphangiogenesis of the tumor. The increase in the number and density of macrophages such as glioblastoma is closely related to the malignancy of the tumor. Nearly 80% of studies have shown that the number of macrophages in tumor tissues is associated with poor prognosis. Exploring the molecular mechanism of macrophage polarization regulation can contribute to a deeper understanding of the pathogenesis of related diseases and provide new ideas for the development of novel anti-tumor drugs.

1. Introduction

Glioblastoma is one of the most common lethal malignant tumors in the central nervous system. Glioblastoma is common in older individuals, often occurring over the age of 60, and has a slightly higher incidence in males than females. At present, tumor immunotherapy has become a new field for treating glioblastoma. Although clinical trials are actively being conducted, it also faces many challenges and difficulties.

In recent years, research on polarization regulation of macrophages has received widespread attention. Macrophages are an important class of white blood cells in the immune system, belonging to the monocyte series. They are one of the earliest immune cells to reach the site of infection or injury, playing important functions such as phagocytosing pathogens, clearing cell debris, producing inflammatory mediators, and participating in immune regulation. Macrophage is one of the important immune cell components in the tumor microenvironment of glioblastoma. Macrophage is abundant in glioma tissue, accounting for about 40% of the tumor tissue and playing a significant role in the development of glioblastoma. At the same time, macrophage may also be influenced by the tumor immunosuppression mechanism. Different microenvironments and stimulation conditions can affect the polarization state of macrophage, thereby affecting immune response and disease development.

2. Related Work

Currently, significant progress has been made in the study of glioma related macrophages, providing more research directions for the treatment of glioblastoma. Fang Xiang antagonized glioblastoma's radiation resistance by inhibiting key enzymes involved in DNA damage repair, thereby improving the patient's immune system after treatment [1]. Zhang Jinhao conducted a study using bioinformatics analysis and samples from the China Glioma Genomics Database, combined with potential drug therapy options for ACT001. His research showed that ACT001 can not only inhibit the proliferation of U87 glioma cells, but also improve the immunosuppression microenvironment of glioblastoma by inhibiting the phosphorylation and nuclear translocation of P65, thereby inhibiting the progression of glioblastoma [2]. Yang Pei and other researchers used Cibersort deconvolution algorithm and semi quantitative method to analyze and judge the correlation between the expression of vesicular amine transporter 1 (VAT 1) and the immune microenvironment of glioblastoma (GBM). Through preliminary research, they found that high expression of VAT1 in GBM patients may affect the tumor immune response and may affect the infiltration of tumor immune cells by regulating the NF-kB signaling pathway [3]. Li S et al. investigated the molecular mechanisms underlying the anti glioma effects of liposomes and magnolol (Lip HNK) using qRT-PCR, immunoblotting, co-culture, and in vivo animal experiments. Their research results indicated that Lip-HNK inhibited the growth of glioblastoma by upregulating M1 macrophage and limiting M2 phenotype macrophage [4]. Ma J stated that with the identification of more and more key factors, the main group in various immune spectra is tumor related macrophages, and microglia are their localization homologs. Many new treatment methods can be explored to break the ominous cycle, improve tumor sensitivity to treatment, and improve the prognosis of glioblastoma patients [5]. Kuntzel T suggested reactivating two very unique pathological compounds that target macrophage and microglial polarization: multiple sclerosis and glioblastoma, which may be a method to limit and reduce tumor progression [6].

Yan T stated that the immunosuppression tumor microenvironment is a key factor hindering the success of tumor immunotherapy, and tumor associated macrophages (TAMs) are crucial for the formation of tumor immunosuppression microenvironment. Hyaluronic acid (HA) is an important component of the glioblastoma microenvironment, and it plays a crucial role in macrophage polarization and CD47/SIRPα signaling between glioblastoma cells and macrophage. Inhibiting the HA pathway may be a new immunotherapy approach for glioblastoma [7].

Through numerous research literature, it can be found that studying the polarization regulation of macrophage and the tumor immunosuppression of glioblastoma is important for understanding tumor immunotherapy [8]. This not only provides new breakthroughs for the treatment of glioblastoma, but also has guiding significance for other types of tumor immunotherapy [9-10]. Therefore, this article explores the relationship between macrophage polarization regulation and glioblastoma, and investigates the influence of macrophage polarization state on glioblastoma immune suppression. This article utilizes macrophage polarization regulation to reveal the intrinsic immunosuppression mechanism of glioblastoma and explore new avenues for tumor immunotherapy.

Macrophage polarization regulation plays an important role in tumor immunosuppression. Macrophage can polarize into two different phenotypic states, namely M1 and M2, with different functions and secretions [11]. This polarization regulation can affect multiple aspects of tumor immune antigen presentation, cytotoxicity, and immune regulation. M1 macrophage can promote immune antigen presentation, increase cytotoxicity, and promote anti tumor immune response. M2 macrophage mainly suppresses immune response and promotes tumor growth and escape by producing anti-inflammatory factors and regulating the activity of other immune cells [12-13].

3. Methods

3.1 Immunosuppression Mechanism of Glioblastoma

For glioblastoma, the activation of immune evasion mechanisms is of great significance for its development and progression. Immune evasion is a series of strategies adopted by the tumor to avoid being recognized and attacked by the immune system. A typical mechanism of glioblastoma immune evasion is to evade recognition by the immune system by altering the expression of surface molecules [14-15].

In glioblastoma, tumor cells downregulate the expression of tumor antigens or major histocompatibility complex (MHC) molecules, making it difficult for the immune system to recognize these tumor cells as abnormal and harmful [16].

A specific case is the expression of PD-L1 (Programmed cell death protein-1) in glioblastoma. PD-L1 is an immunosuppressive molecule that binds to the PD-1 (Programmed Death-1) receptor on T cells, inhibiting T cell activation and function. Studies have found that many glioblastoma patients express high levels of PD-L1 in their tumor cells, which enables tumor cells to utilize the PD-L1 or PD-1 signaling pathway to suppress immune system attacks [17].

Further analysis revealed that high expression of PD-L1 in glioblastoma is associated with poor immune evasion and prognosis. A clinical trial using glioblastoma as the research object showed that inhibiting the PD-L1 or PD-1 pathway can restore the immune cell's ability to attack the tumor, thereby achieving the effect of inhibiting tumor growth.

3.2 Macrophage Polarization Regulation

Macrophage is the most important part of the host defense system, whose main function is to eliminate invading foreign microorganisms through phagocytosis, forming the first line of natural immunity. At the same time, it can also regulate the host's acquired immune response through antigen processing, presentation, and other methods. Macrophage (Mφ) is a heterogeneous and multifunctional cell that changes in function with changes in the external environment. It can be divided into two subtypes: pro-inflammatory subtype (M1) and non activated anti-inflammatory subtype (M2). During this process, M1 macrophage secretes a large amount of IL-1b and L-6. Pro-inflammatory factors such as carbon monoxide synthase have pro-inflammatory functions and can eliminate bacteria. M2 macrophage, characterized mainly by CD206Arg-1JIL-13, plays an important role in the resolution of inflammatory responses after tissue injury.

3.3 Relationship between Macrophage Polarization and Glioblastoma

GAM can be divided into intrinsic microglia in the brain and myeloid macrophages. Under normal circumstances, microglia (MG) residing in the brain are inherent immune active cells, with a quantity of 10-20%, and are inherent immune active cells in the brain. Previous studies have shown that under normal circumstances, intrinsic microglia in the brain are replaced by endogenous microglia. After the formation of gliomas, the blood-brain barrier is broken, and a large number of chemokines secreted by them can migrate to the brain parenchyma. GAM can be divided into two activation subtypes based on its effects: inflammatory M1 and anti-inflammatory M2. M1 type microglia express high levels of differentiation clusters CD80, CD86, and major histocompatibility complex II (MHCII) molecules, and secrete high levels of tumor necrosis factor a, interleukin-12, etc., playing an anti tumor role. M2 cells express high levels of CD163, CD204 and CD14, as well as low levels of CD80 and MHCI, and secrete cytokines such as IL-10, chemokine C-C ligand 20 (CCL20), CCL22, and prostaglandin-E2.5, which mediate the immunosuppression response and

promote the tumor response. In most high-grade gliomas, the anti-inflammatory phenotype M2 is predominant.

3.4 Polarization Control of M1 and M2 Macrophage

The polarization of macrophage is regulated by various signaling molecules and their pathways. At present, there are mainly clear signaling pathways and transcription factors, such as phosphoinositide 3-kina ses (PI3K)/Akt signaling pathway, Notch signaling pathway, janus kinase (JAK)-signal transducers and ac-tivators of transeription (STAT) signaling pathway, TGF-B signaling pathway, and TLR4/NF-KB signaling pathway.

3.5 PI3K/Akt Signaling Pathway

PI3K generates three subtypes of activated protein kinase Akt, namely phosphatidylinositol-3,4,5 triphosphate, Akt1, Akt2, and Akt3. After Aktl knockout, iNOSTNF cu and IL-6 increase, while Akt2 knockout results in high expression of Fizzl and IL-10. Aktl can regulate M2 polarization and inhibit M1 polarization, but Akt2 can regulate M1/M2 polarization. MiR-155 and C/EBPβ are key molecules that regulate the Akt signaling pathway. Previous studies have found that Akt2 can upregulate miR-155, which in turn can inhibit C/EBP β, thus promoting the conversion of Mφ to M1. Aktl upregulates C/EBP by downregulating miR-155 β, and Mφ and M2 polarization can be promoted.

3.6 Notch

There are four types of Notch receptors in mammalian signaling pathways: Notch1, Notch2, Notch3, and Notch4, which are expressed in various tissues and organs. The expression of Notchl is more extensive, and Notch ligands can be divided into two categories: Dela-like and Jagged. The former includes Dela-like1, Dela-like3, and Dela-like4 (DIl1, DII3, DII4), while the latter includes Jag-gedl and Jagged. These ligands bind to the same or different Notch receptors, and the Notch receptors are activated. Through the dissociation of proteins of the adisintegrin and mealloproteinase do-main (ADAM) type and the action of the r-secretase complex, a portion of the Notch intracellulardomain (NICD) of the Notch receptor is released from the inner side of the cell membrane into the human nucleus. Through the interaction between the RAM domain and the transcription factor RBP-J, the transcription of promoters containing RBP-J recognition sites is activated, thereby activating the Notch signaling pathway and participating in the regulation of the growth and development of many organs, tissues, and cells. Research has shown that the ligand DII4 binds to the Notch1 receptor to form a complex that activates downstream ADAM protease and secretase regulation γ, leading to NICD entering the nucleus and interacting with RBP-J, ultimately promoting MI polarization.

4. Results and Discussion

4.1 Latest Research Progress

Different stimuli can produce different subtypes of M2, which can be classified into M2a, M2b, and M2d. IL-4 and IL-13 stimulation induce the M2a subtype, while immune complexes, TLR, and IL-1ra stimulation induce the M2b subtype. These cells have the function of immune regulation and driving Th2 cell responses. IL-10 stimulation induces the M2c subtype, which plays an important role in suppressing immune responses and promoting tissue remodeling. Therefore, compared with

M1 type, M2 type has greater heterogeneity and can exert different inhibitory effects on inflammatory reactions based on different activation states, enhance phagocytic ability, promote tissue repair, and eliminate pathogens.

Although activation is crucial for inducing effective immune responses, inappropriate and sustained macrophage activation and polarization can lead to tissue damage, immune dysfunction, or pathological changes. For example, although M1 type plays an important role in resisting acute viral and mycobacterial infections, it can also induce the occurrence of autoimmune diseases. M2 type, although playing an important role in controlling worm infections, can also lead to asthma and allergic reactions. M2 type can secrete IL-10 and tumor growth factor (TGF)-β, which can promote tumor growth. Functional and transcriptome sequence analysis shows that tumor associated macrophages (TAMs) are very similar to M2 type. Drug intervention to shift TAMs from M2 type to M1 type is beneficial for protecting anti-tumor activity. For example, co induction of TAMs from M2 to M1 by CpG and LI-10R antibodies can quickly reduce the size of the tumor.

4.2 Control Trials

40 female experimental rats with a weight of (200 ± 20)g are selected. The rats are randomly divided into a blank control group and an experimental group, with 20 rats in each group. Two groups of experiments are subjected to live detection analysis for 24 and 48 hours, followed by analysis of biomarker data for macrophage, as well as analysis of polarization status and clinical parameters related to immunosuppression in macrophage. The experiments are shown in the following figure 1:

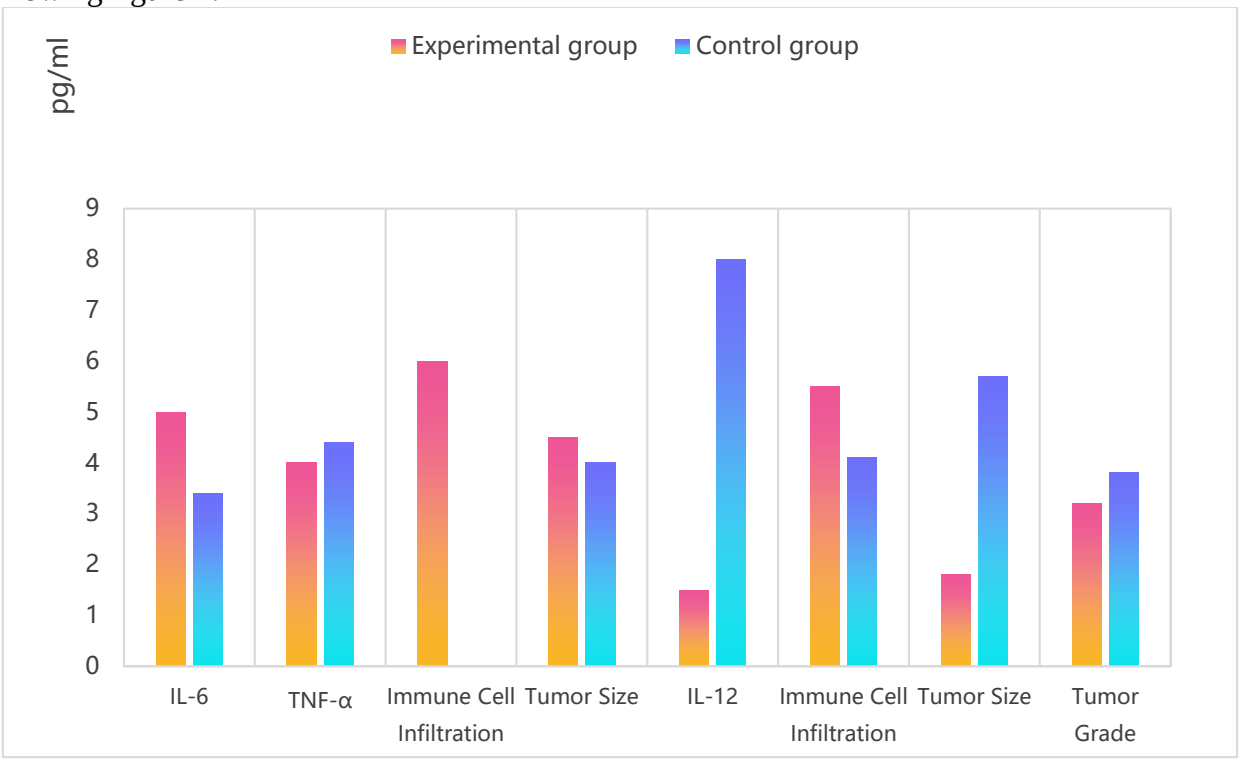

Figure 1: Experimental results

From the Figure 1, it can be seen that the clinical data in the experimental group showed high levels of cytokines and immune cell infiltration, indicating a significant correlation between the appearance of macrophage polarization and patient survival rate. This provides useful information for further exploration of tumor immunotherapy.

5. Conclusion

The regulation of macrophage polarization is closely related to the tumor immunosuppression in glioblastoma, and understanding and intervening in macrophage polarization status is of great significance for the treatment of glioblastoma. Further research can contribute to the development of new treatment strategies, improve the therapeutic efficacy of glioblastoma, and provide new ideas and directions for other types of immunotherapy for Tumors.

References

[1] Fang Xiang, Tian Guopeng, Bai Shengwei, Luo Yusong, Pan Yawen. The role and prospects of DNA-PKcs inhibitors in the treatment of glioblastoma. Journal of International Neurology and Neurosurgery, 2023, 50(1):64-68.

[2] Zhang Jinhao, Liu Peidong, Zhang Chen, Li Jiabo, Ren Xiao, Chen Lulu, et al.ACT001 reduces the expression of programmed cell death protein ligand 1 in glioblastoma cells by inhibiting P65 phosphorylation. Chinese Journal of Contemporary Neurology and Neurosurgery, 2021, 21(6):9-9

[3] Yang Pei, Liu Qi, Tao Rui, Wang Jiangfei. The correlation between the expression of vesicular amine transporter 1 and the immune microenvironment of glioblastoma. Chinese Journal of Neurosurgery, 2022, 38(3):6-6.

[4] Li S, Li L, Chen J, Fan Y, Wang C, Du Y, et al. Liposomal honokiol inhibits glioblastoma growth through regulating macrophage polarization. Annals of Translational Medicine, 2021, 9(22).1644-1644.

[5] Ma J, Chen C C, Li M. Macrophages/microglia in the glioblastoma tumor microenvironment. International journal of molecular sciences, 2021, 22(11): 5775-5775.

[6] Kuntzel T, Bagnard D. Manipulating macrophage/microglia polarization to treat glioblastoma or multiple sclerosis. Pharmaceutics, 2022, 14(2): 344-344.

[7] Yan T, Wang K, Li J, Hu H, Yang H, Cai M, et al. Suppression of the hyaluronic acid pathway induces M1 macrophages polarization via STAT1 in glioblastoma. Cell Death Discovery, 2022, 8(1): 193-193.

[8] Li J, Stanger B Z. Cell cycle regulation meets tumor immunosuppression. Trends in Immunology, 2020, 41(10): 859-863.

[9] Ma H, Kang Z, Foo T K, et al. Disrupted BRCA1-PALB2 interaction induces tumor immunosuppression and T-lymphocyte infiltration in HCC through cGAS-STING pathway. Hepatology, 2023, 77(1): 33-47.

[10] Gao J, Wu Z, Zhao M, et al. Allosteric inhibition reveals SHP2-mediated tumor immunosuppression in colon cancer by single-cell transcriptomics. Acta Pharmaceutica Sinica B, 2022, 12(1): 149-166.

[11] McKay Z P, Brown M C, Gromeier M. Aryl hydrocarbon receptor signaling controls CD155 expression on macrophages and mediates tumor immunosuppression. The Journal of Immunology, 2021, 206(6): 1385-1394.

[12] Luo Y, Li L, Chen X, et al. Effects of lactate in immunosuppression and inflammation: Progress and prospects. International Reviews of Immunology, 2022, 41(1): 19-29.

[13] Xu Y, Yan J, Tao Y, et al. Pituitary hormone α-MSH promotes tumor-induced myelopoiesis and immunosuppression. Science, 2022, 377(6610): 1085-1091.

[14] Cao X, Wang Y, Zhang W, et al. Targeting macrophages for enhancing CD47 blockade–elicited lymphoma clearance and overcoming tumor-induced immunosuppression. The Journal of the American Society of Hematology, 2022, 139(22): 3290-3302.

[15] Bae J, Accardi F, Hideshima T, et al. Targeting LAG3/GAL-3 to overcome immunosuppression and enhance anti-tumor immune responses in multiple myeloma. Leukemia, 2022, 36(1): 138-154.

[16] Tao N, Li H, Deng L, et al. A cascade nanozyme with amplified sonodynamic therapeutic effects through comodulation of hypoxia and immunosuppression against cancer. ACS nano, 2021, 16(1): 485-501.

[17] Zhang H, Yu P, Tomar V S, et al. Targeting PARP11 to avert immunosuppression and improve CAR T therapy in solid tumors. Nature cancer, 2022, 3(7): 808-820.