Immune Microenvironment and Novel Immunotherapeutic Strategies in Medulloblastoma

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Abstract. Medulloblastoma (MB) is a primary malignant tumor of the central nervous system (CNS) commonly found in children, with an approximate 5-year overall survival (OS) rate of 70%. Currently, the standard treatment regimen for MB involves surgical resection of the tumor combined with postoperative radiotherapy and chemotherapy. Despite the fact that this treatment regimen has notably extended the survival time of patients, the associated adverse reactions impact the prognosis of life of patients, and the recurrence rate after treatment remains relatively high. The tumor microenvironment (TME), which includes tumor cells, non-tumor cells, extracellular matrix, and various signaling molecules, refers to the biological environment in which tumor cells reside. Immune checkpoint molecules are negative immunoregulatory molecules located on the surface of tumor cells. They directly bind to the corresponding receptors on the surface of T cells, which can inhibit the activation, proliferation, cytokine secretion, and cytotoxic reactions of T cells, and subsequently reduce the attack of the immune system on tumor cells. In recent years, immune checkpoint inhibitors (ICIs) have emerged as a vital approach in the immunotherapy of malignant tumors. These medications can impede the binding of immune checkpoint molecules to their ligands, relieve the inhibitory effect on immune cells, and restore the anti-tumor activity of immune cells. This article presents an overview of the immune microenvironment of medulloblastoma and discusses the potential application of immune checkpoint inhibitors, offering a certain reference for the immunotherapy of medulloblastoma.

Keywords: Medulloblastoma, Tumor Immune Microenvironment, T cell, Immunotherapy, Immune Checkpoint Inhibitor

1 Introduction

Medulloblastoma (MB) is a primary malignant tumor of the central nervous system (CNS) commonly found in children, accounting for approximately 25%-30% of central nervous system tumors in children [1]. It is mostly located in the cerebellar vermis and the fourth ventricle of the posterior cranial fossa. The clinical manifestations of MB patients are often associated with tumor occupation, increased intracranial pressure

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caused by the obstruction of cerebrospinal fluid circulation, and distant metastasis. Currently, the commonly used treatment modalities for MB include surgical resection of the tumor, followed by postoperative craniospinal irradiation (CSI) combined with intensified radiotherapy of the posterior cranial fossa, along with chemotherapy [2]. However, the prognosis of MB remains poor, and the adverse reactions caused by these treatment modalities, such as neurological damage from surgery, cognitive impairment from radiotherapy, and bone marrow suppression from chemotherapy, cannot be ignored. Therefore, improving the treatment strategies is an urgent priority. Previous research has indicated that immune checkpoint molecules are vital in the tumor microenvironment (TME) of MB [3]. In recent years, immune checkpoint inhibitors (ICIs) have exhibited favorable therapeutic effects in the clinical treatment of various malignant tumors, accompanied by relatively fewer side-effects on the body [4]. To further prolong the survival period of patients with medulloblastoma (MB) and improve their quality of life, it is imperative to better understand the TME of MB and develop safe and effective immunotherapy methods.

2 Clinical Characteristics of MB

The clinical manifestations of MB typically depend on the patient's age and the growth characteristics of the tumor. MB predominantly originates from the cerebellar vermis and grows in various directions into the fourth ventricle, obstructing the cerebrospinal fluid (CSF) circulation pathway and leading to hydrocephalus and CSF extravasation [5]. The mass effect of MB and secondary hydrocephalus can give rise to symptoms related to elevated intracranial pressure, such as headache, vomiting, and papilledema. In infant patients, irritability, feeding difficulties, decreased energy, developmental delay, and bulging of the anterior fontanelle may occur. When the tumor invades different regions of the central nervous system, various clinical symptoms will arise. Compression of the cerebellum can result in cerebellar dysfunction. When the tumor is located in the midline, it presents as truncal ataxia, such as a positive Romberg sign and abnormal gait. When it is located in the cerebellar hemisphere, it manifests as ipsilateral limb ataxia. When MB compresses the brainstem anteriorly, it can lead to sudden respiratory arrest, endangering the patient's life. MB can also invade the cranial nerves, resulting in corresponding clinical manifestations. Meanwhile, MB can spread and metastasize along with the CSF. When MB metastasizes to the surface of the brain, symptomatic epileptic seizures occur. Also, when it metastasizes to the spinal canal and involves the spinal cord and spinal nerves, pain and weakness in the back and extremities appear. In a small number of cases, MB can metastasize distantly to lymph nodes, bones, lungs, and the liver, etc., leading to symptoms in various systems.

3 Classification and Staging of MB

MB exhibits significant histological heterogeneity and can be classified into classic, nodular, medulloblastoma with extensive nodularity (MBEN), and anaplastic subtypes [6]. Among them, the classic subtype is the most common, accounting for

approximately 60%-70%. The tumor cells in this subtype are small and uniform in size, closely arranged in sheets or short bundles. They show less nuclear atypia, more mitotic figures, and no obvious neuronal differentiation. The nodular subtype accounts for about 15%-25%. The characteristic of this pathological subtype is the nodular arrangement of tumor cells. The tumor cells in the nodular areas show neuronal differentiation and are surrounded by a neuropil matrix. MBEN is commonly found in infants and young children. It has larger nodular areas compared to the nodular subtype, and the tumor cells also show neuronal differentiation. The anaplastic subtype accounts for approximately 10%. It is highly invasive and has a poor prognosis. The tumor cells in this subtype display obvious anaplastic features, including marked nuclear atypia, prominent nucleoli, numerous mitotic figures, cell wrapping, active mitosis, and extensive areas of apoptosis and necrosis.

4 Traditional Management of MB

Currently, the primary treatment modalities for MB encompass surgical resection of the tumor, followed by postoperative craniospinal irradiation (CSI) combined with intensified radiotherapy of the posterior cranial fossa, and chemotherapy [7]. Surgical resection of the tumor is the most crucial treatment modality for MB, which can minimize the tumor burden to the greatest extent, relieve tumor compression, and unblock the obstruction of the cerebrospinal fluid circulation. Some studies have indicated that, compared with near-total resection (tumor residual < 1.5 cm2 after surgery), gross-total resection (no residual tumor after surgery) offers no significant benefit. Therefore, when the tumor is significantly adherent to the brainstem, the surgical objective should be to protect the brain tissue as much as possible and keep the tumor residual < 1.5 cm2. Radiotherapy is generally carried out about 3-4 weeks after surgery, and the common regimen is 23.4 Gy of craniospinal irradiation combined with 55 Gy of posterior cranial fossa irradiation. However, radiation can cause severe adverse reactions, such as endocrine dysfunction, cognitive impairment, secondary tumors, and growth and development disorders in children, which are more prominent in children under 3 years old. Thus, radiotherapy should be avoided or postponed for such children. Chemotherapy can improve the survival rate of patients and reduce the radiotherapy dose as much as possible on the premise of not affecting the prognosis. Nevertheless, chemotherapy can also lead to a series of adverse reactions, such as nausea and vomiting, bone marrow suppression, and impairment of hearing and organ function. For patients aged ≥ 3 years who receive radiotherapy, the chemotherapy regimen usually consists of a combination of cisplatin, vincristine, and cyclophosphamide. For patients under 3 years old who cannot undergo radiotherapy, have a tumor residual > 1.5 cm2 after surgery, or have cerebrospinal fluid dissemination and metastasis, intrathecal injection of methotrexate can be administered.

5 Novel Therapeutic Strategy of MB

Although the standard treatment regimen for MB has significantly improved patients' survival rates, the associated neurotoxicity and long-term sequelae can affect patients' prognosis, and the incidence of disease progression after treatment remains relatively high [8]. Immunotherapy has achieved favorable therapeutic outcomes in multiple types of tumors, and many studies have indicated that the heterogeneity of MB and the immunosuppressive TME play crucial roles in tumor development and treatment resistance [9]. The TME encompasses tumor cells, the extracellular matrix and a rich array of peritumoral cellular components, such as immune cells including T cells, tumor-associated macrophages, natural killer (NK) cells, B cells, and neutrophils, as well as tumor-associated astrocytes and environmental molecules (e.g., growth factors, cytokines, chemokines, and exosomes). These components interact with tumor cells, influencing not only the survival, proliferation, invasion, and metastasis of tumor cells but also regulating their responses to the immune system and treatment. In recent years, the TME has been regarded as a crucial factor in tumor progression and the development of drug resistance, and it has emerged as a potential target for the treatment of malignant tumors.

5.1 Immune Characteristics of the Central Nervous System

In the past, the CNS has been regarded as an immune-privileged area. This immune privilege is mainly attributed to the existence of the blood-brain barrier (BBB), the low expression of major histocompatibility complex (MHC) molecules, and the absence of a traditional lymphatic drainage system [10]. As shown in Figure 1, the BBB is composed of basement membranes, endothelial cells, astrocyte foot processes, etc. Under normal physiological conditions, the BBB highly selectively regulates the entry and exit of substances, protecting it from external pathogens and immune responses, and also influencing the entry of drugs. Although the CNS is protected by the BBB, there are still a certain number of immune cells, including microglia, astrocytes, B lymphocytes, regulatory T cells (Tregs), and a small quantity of effector T cells (Teffs). Recent studies have found that the CNS actually has active immune surveillance and regulatory capabilities, and there is bidirectional communication between it and the peripheral immune system [11]. This characteristic plays a vital role in neuroinflammation, infectious diseases, and autoimmune diseases.

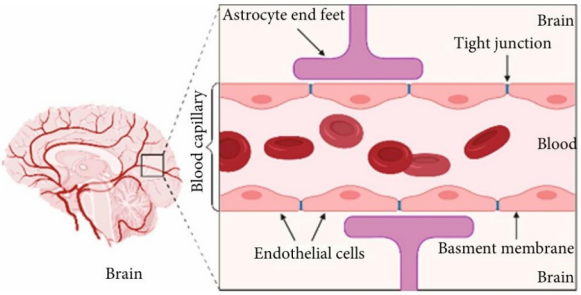

Fig. 1. Structure of the blood-brain barrier (BBB) [12].

5.2 Composition of Immune Microenvironment of Central Nervous System

Microglial cells are the primary resident immune cells within the CNS. Their functions are highly diverse, encompassing multiple aspects ranging from immune responses to neuroprotection and repair [13]. Microglia are responsible for monitoring and eliminating foreign pathogens, dead cells, and other harmful substances. When the CNS is damaged or affected by neuropathy, microglia play crucial protective and reparative roles. They can promote nerve repair and tissue reconstruction by releasing cytokines, chemokines, and participating in the clearance process after neuronal death. Meanwhile, microglia possess a powerful phagocytic function, capable of removing dead neurons, waste materials, tumor cells, and pathogens such as bacteria and viruses. Through phagocytosis, microglia contribute to maintaining the homeostasis of the CNS and facilitate the clearance and repair of damaged areas after nerve injury. Astrocytes, as the most abundant type of glial cells in the CNS, provide structural support to neurons [14]. Astrocytes not only assist in the formation and development of synaptic connections, but also regulate synaptic function and strength. In addition, astrocytes modulate neural activity by processing neurotransmitters (such as glutamate). Simultaneously, astrocytes regulate the inflammatory response by secreting cytokines (such as IL-1β, TNF-α, etc.). In neurodegenerative diseases such as Parkinson's disease and Alzheimer's disease, the over-activation of astrocytes may lead to the exacerbation of neuroinflammation, thereby impairing neuronal function [15]. Astrocytes also participate in holding the integrity of the BBB by wrapping around cerebral blood vessels with their end-feet. After CNS damage, astrocytes become activated and form glial scars. They promote the recovery of damaged areas by secreting cytokines and repair molecules. The quantity of other immune cells in the CNS is relatively low. However, their roles in the central nervous system are increasingly gaining attention. In disease conditions like immune activation, tumors, or infections, T cells can be recruited to the CNS, and B cells can also mediate immune responses in the form of antibodies, especially when the CNS is infected or damaged [16, 17].

5.3 Immunotherapy for Medulloblastoma

MB is composed of multiple tumor cell populations, including progenitor cells originating from cerebellar granule cell precursors and differentiated cells. Tumor cells at different differentiation stages determine the invasiveness of MB, and cells with a low degree of differentiation are often associated with poor prognosis. Tumor cells can express immune checkpoint molecules on their surface. Immune checkpoint molecules are a class of negative immune regulatory molecules, such as programmed death-ligand 1 (PD-L1), cytotoxic T-lymphocyte antigen 4 (CTLA-4), and V-domain Ig Suppressor of T-cell Activation (VISTA) [18]. They directly bind to the corresponding receptors on the surface of T cells, inhibiting the activation, proliferation, cytokine secretion, and cytotoxic responses of T cells. Consequently, this reduces the attack of the immune system on tumor cells. Other immune checkpoint molecules, such as CD47, inhibit the macrophages' phagocytosis of tumor cells through binding to the SIRPα receptor on macrophages [19]. In recent years, ICIs have emerged as a vital approach in the immunotherapy of malignant tumors. These drugs are capable of blocking the binding between immune checkpoint molecules and their ligands, relieving the inhibition on immune cells, and restoring the anti-tumor activity of immune cells. A large study by Allison M. Martin et al. reported that in some MB cases, particularly the sonic hedgehog (SHH) subtype with low MYC expression, PD-1 and its ligand PD-L1 demonstrated robust focal expression, which means they might be the key factors in the immune escape of MB [20]. Tumor cells upregulate the expression of PD-L1 to activate PD-1, thereby inhibiting T cell response (TCR) signal transduction, reducing T-cell activity, and avoiding the attack of the immune system. PD-1/PD-L1 inhibitors (anti-PD-1), such as Nivolumab and Pembrolizumab, can block immune inhibitory signals, re-activate T cells, and enhance their killing effect on tumor cells. In addition, these inhibitors can also affect immunosuppressive components such as Treg cells, MDSCs, and tumor-associated macrophages, thereby improving the tumor immune microenvironment. Currently, PD-1/PD-L1 inhibitors have been widely utilized as a standard treatment modality in the management of various tumors, such as melanoma and non-small cell lung cancer [21]. CTLA-4 is similar to CD28, both being co-stimulatory receptors on the surface of T cells. CD28 activates T cells by binding to B7-1 (CD80) or B7-2 (CD86), while CTLA-4 competes with B7-1/B7-2 for binding, inhibiting T-cell activation [22]. This mechanism makes CTLA-4 an important site for preventing excessive immune responses in the body. However, tumor cells use this mechanism to inhibit immune responses and evade immune surveillance. CTLA-4 inhibitors (anti-CTLA-4), such as Ipilimumab, are the first approved anti-CTLA-4 antibodies for clinical use [23]. It has the capacity to relieve the suppression state of T cells and restore the immune system's ability to attack tumors. Ipilimumab has been approved for the clinical treatment of melanoma and has also demonstrated efficacy in the treatment of various other cancers, such as lung cancer and kidney cancer. A study by J. Louise Lines established that VISTA as a negative checkpoint regulator that suppresses T-cell activation, induces Foxp3 expression through binding to its ligand, and is highly expressed within the tumor microenvironment [24]. Its mechanism of action is different from that of B7 family members (such as PD-1). VISTA promotes tumor immune

escape by maintaining T cells in a "quiescent state" to avoid excessive immune responses. VISTA inhibitors can relieve this negative regulation and restore the anti-tumor activity of T cells, becoming a potential new strategy in cancer treatment. Currently, inhibitors targeting VISTA are being actively developed, especially monoclonal antibodies and small-molecule inhibitors. For example, CA-170, the first small-molecule VISTA antagonist that entered clinical trials, has shown potential in the treatment of solid tumors and Hodgkin lymphoma [25]. While developing new immune checkpoint inhibitors, researchers are also exploring their combined application with other immunotherapies. Currently, more and more clinical trials indicate that combination immunotherapy (such as the combined application of immune checkpoint inhibitors and cytokine inhibitors) has demonstrated enhanced anti-tumor immune responses in some cancer models, which is expected to improve the treatment effect and shows good prospects in clinical practice [26].

6 Conclusion

Currently, the commonly adopted treatment regimen for MB involves surgical resection of the tumor, followed by postoperative radiotherapy and chemotherapy. Although this approach has notably improved patient survival rates, the associated neurotoxicity and long-term sequelae can impact patients' prognosis and quality of life to varying degrees, and the post-treatment recurrence rate remains relatively high. The surface of MB cells can express immune checkpoint molecules that directly bind to the corresponding receptors on the surface of T cells, thereby inhibiting the activation, proliferation, cytokine secretion, and cytotoxic responses of T cells. Consequently, this reduces the attack of the immune system on tumor cells. Therefore, the development of immune checkpoint inhibitors holds promise for enhancing the treatment efficacy of MB. In recent years, PD-1/PD-L1 inhibitors, CTLA-4 inhibitors, and inhibitors targeting VISTA have been successfully applied in the treatment of various types of tumor. It is believed that with in-depth research on the TME of MB and its immune checkpoints, MB immunotherapy can be applied in clinical practice at an early date.

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