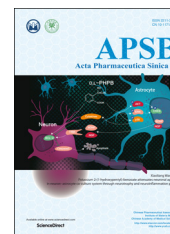




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REVIEW

Remodeling the blood–brain barrier microenvironment by natural products for brain tumor therapy



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Abstract Brain tumor incidence shows an upward trend in recent years; brain tumors account for 5% of adult tumors, while in children, this figure has increased to 70%. Moreover, 20%–30% of malignant tumors will eventually metastasize into the brain. Both benign and malignant tumors can cause an increase in intracranial pressure and brain tissue compression, leading to central nervous system (CNS) damage which endangers the patients' lives. Despite the many approaches to treating brain tumors and the progress that has been made, only modest gains in survival time of brain tumor patients have been achieved. At present, chemotherapy is the treatment of choice for many cancers, but the special structure of the blood–brain barrier (BBB) limits most chemotherapeutic agents from passing through the BBB and penetrating into tumors in the brain. The BBB microenvironment contains numerous cell types, including endothelial cells, astrocytes, peripheral cells and microglia, and extracellular matrix (ECM). Many chemical components of natural products are reported to regulate the BBB microenvironment near brain tumors and assist in their treatment. This review focuses on the composition and function of the BBB microenvironment under both physiological and pathological conditions, and the current research progress in regulating the BBB microenvironment by natural products to promote the treatment of brain tumors.

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1. Introduction

Brain and central nervous system (CNS) tumors are the most common neoplasm among those 0–19 years old, with an average annual age-adjusted incidence rate of 5.42 per 100,000¹. The annual incidence of adult glioblastoma is 7.2 per 100,000, making it the most common adult primary intrinsic brain tumor². The BBB excludes drugs from entering the brain, due to the special structure of the microvasculature. Despite many methods of surgical resection, radiotherapy, and chemotherapy for treatment, outcomes have remained dismal³. Recently, remodeling the tumor microenvironment has become a promising way of enhancing tumor therapy for various advanced cancers; however, research on the effects of BBB microenvironment on brain tumor therapy is still in its infancy. The BBB microenvironment includes endothelial cells, astrocytes, peripheral cells, microglia, and extracellular matrix (ECM). These cells also play a key role in controlling the formation and morphology of brain tumors. Regulation of the BBB microenvironment by natural products shows increasing potential for assisting in the treatment of brain tumors. Natural products affect a number of factors secreted by some tumor-associated cells and influence tumor biology. In this review, we describe the composition and function of the BBB microenvironment and highlight the effects of natural products on regulating the brain tumor BBB microenvironment to treat brain tumors. The signaling pathways, factors, interactions described in this review provide a perspective on regulating the BBB microenvironment for brain tumor therapy.

2. The composition and function of the BBB microenvironment

The BBB is an important structure which maintains the balance of the CNS microenvironment and maintains the normal functioning of the brain⁴. The BBB microenvironment (Fig. 1) is constituted of endothelial cells, astrocytes, pericytes, macrophage, fibroblasts, neuronal cells, basal membranes, microglia, and other cell types⁵. In addition, there are many transporters on the BBB, including

P-glycoprotein (P-gp) and other multidrug resistance-related proteins^{6,7}, which can reduce the apparent distribution of drugs in the brain.

Astrocytes are involved in nerve signal transmission, nutrient transport, maintaining the balance of brain microenvironment and ECM ion balance buffering. Astrocytes also participate in the inflammatory response of the CNS^{8,9} and maintain the integrity of the BBB¹⁰.

Peripheral cells are multifunctional cells, with immune function in the CNS neurovascular unit¹¹. Peripheral cells surround the endothelial cells and play an important role in the BBB microenvironment and in maintaining the BBB function by secreting growth factors and ECM.

Microglia are a kind of long-standing immune cell in the human brain. They can stimulate the opening of BBB, leukocyte extravasation, and angiogenesis¹². Fibroblasts, when co-cultured with glioblastoma cells, can induce production and activation of matrix metalloproteinase MMP2, and its activators membrane type 1 metalloprotease (MT1-MMP) and MT2-MMP¹³, which affect the growth progression of gliomas¹⁴.

Other cells like endothelial cells in the BBB microenvironment maintain the normal function and integrity of the BBB by forming tight junctions that limit transcytosis⁴. CNS neurons bind chemicals and convey electrical signals. They can regulate the ionic microenvironment of the synaptic and axonal regions of the nerve cell, which are essential to the nerve signal transduction¹⁵. The basement membrane is attached as a support tissue to the neurovascular unit cells, forming a substrate for cellular differentiation and gene expression⁹.

3. The formation, morphology and classification of brain tumors

Benign tumors are nodular, lobulated or cystic with a clear border and often with an envelope. Brain tumors are usually solitary. Under electron microscopy, the orthotopic brain gliomas have mitochondria with dense matrix cohesive structures, indicating an active state. The mitochondria extend and tightly connect to the

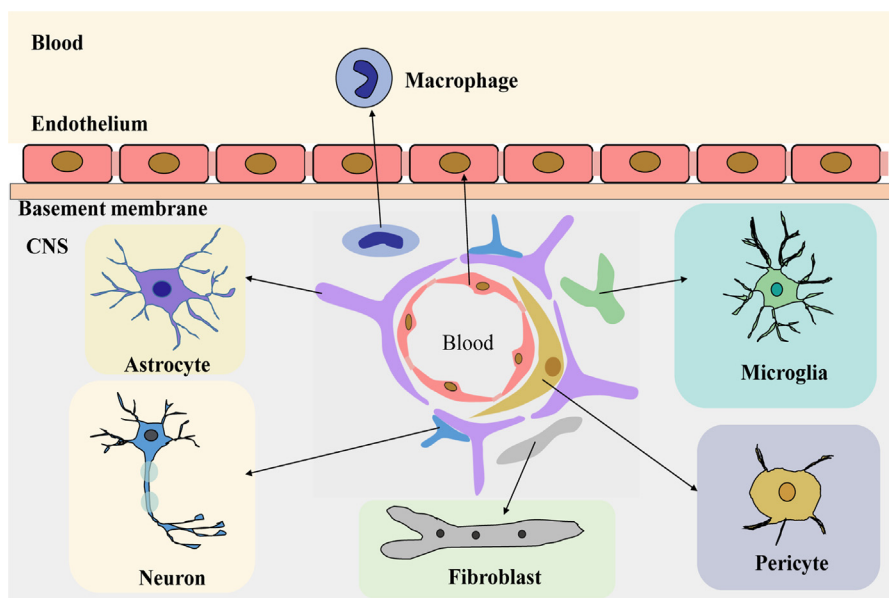


Figure 1 The composition of the blood–brain barrier microenvironment.

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