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T LYMPHOCYTE INTERACTION IN THE CENTRAL NERVOUS SYSTEM

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ABSTRACT

Physical and mental health are inextricably intertwined. Neuroimmunology seeks to define and characterize the physiological relevance, the pathological significance, and the cytological and biochemical mechanisms of the communication between the nervous and the immune systems. The migration of lymphocytes to and from lymphoid organs is essential to the physiological regulation of the immune response, and the efficiency of cellular immune processes depends largely upon the distribution and trafficking of T lymphocytes in the CNS, a mechanism that is fundamental for the pathogenesis of various neurological disorders, including autoimmune diseases. Immune cells, including lymphocytes, are activated and mediate brain disease, such as multiple sclerosis (MS), in which myelin-reactive T cells attack the central nervous system (CNS) and cause demyelination. T lymphocytes infiltrate the brain and the interaction of CD4+ and CD8+ cells with adhesion molecules mediates neuroinflammation, contributing to CNS pathology. T regulatory cells (Tregs) are found both in lymphoid tissues and non-lymphoid tissue and differentiate after activation with antigen and specific cytokines, generating anti-inflammatory cytokines that are involved in immune regulation, cellular homeostasis, and the immune response. In tumors of the CNS, the infiltration of lymphocytes has important effects on tumor progression and immunosuppression.

KEYWORDS: *lymphocyte, T cell, CNS, inflammation, autoimmunity, cancer, lymphocyte migration*

INTRODUCTION

Both T and B lymphocytes are generated by bone marrow and are responsible for cellular and humoral responses respectively (1). B (bursal) lymphocytes are immune cells responsible for producing antibodies against specific antigens. T (thymus) lymphocytes participate in the immune response by producing cytokines and other molecules. The immune system plays an important role in the pathophysiological processes of the brain. Immune cells, including lymphocytes, are activated and mediate brain disease. Lymphocytes are developed in the primary lymphoid organs, the thymus and bone marrow, and include B Cells, T cells, and natural killer (NK) cells. When immune cells are activated, they cause inflammation that may result in neuronal necrosis, disruption of the blood-brain barrier (BBB), microglia activation, and the release of inflammatory molecules. T regulatory cells (Tregs) are lymphocyte cells that play an immunosuppressive and anti-inflammatory role in various diseases (Table I). For example, in the autoimmune disease multiple sclerosis (MS), myelin-reactive T cells, in addition to other immune cells, attack the central nervous system (CNS), causing progressive

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demyelination. The infiltration of lymphocytes into tumors of the CNS has important effects on tumor progression and immunosuppression. Tregs, which are naïve CD4+ T cells, differentiate after activation with antigen and some specific cytokines, such as IL-2 and transforming growth factor-β (TGF-β) (2). Tregs generate anti-inflammatory cytokines such as IL-10 and TGF-β that are involved in immune regulation, cellular homeostasis, and the immune response (3). These cells are found both in lymphoid tissues and in non-lymphoid tissues such as lung, adipose and muscle tissue, skin, and brain tissues.

Table I. *Different functions of lymphocytes activated by antigen in the immune system. In addition, T cells also participate in cellular immunity by killing bacteria.*

Activation of lymphocytes			
Lymphocytes + antigen	→ Effector cells + phagocytes + complement	→ Elimination of antigen	
	→ Memory cells		
	→ Cell death		
Cellular immunity			
Bacteria →	Phagocytes and killing →	T lymphocyte activation →	Macrophage activation and bacteria killing

Lymphocytes in the central nervous system

It is known that lymphocytes participate in neuroinflammation. Furthermore, in neurological diseases, there is a dramatic influx of T cells and other inflammatory cells including macrophages and mast cells (MCs). The chemoattraction of lymphocytes in the CNS is mediated by some cytokines and chemokines. When T lymphocytes are activated by antigen in the CNS, they release several cytokines including T cell growth factor (IL-2) which activates IL-1 and tumor necrosis factor (TNF), inducing inflammation (4) (Fig.1). The knowledge of these latter molecules has made it possible to better understand neuropathological phenomena and cerebral inflammation.

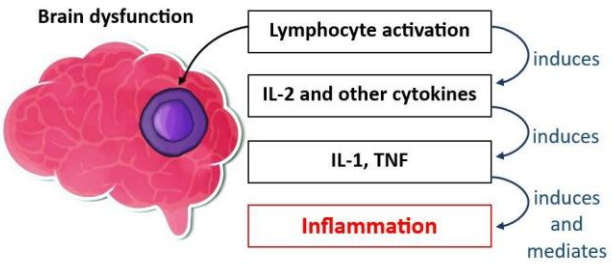

Fig. 1. *Lymphocytes infiltrate the brain, where they are activated by damage to the central nervous system (CNS) and secrete T-cell growth factor (IL-2) and other cytokines, which induce the secretion of IL-1 and TNF that mediate inflammation.*

CD4+ cells infiltrating the CNS mediate the immune response and inflammation. Th1, Th17 cells, and various cytokines and chemokines participate in these pathophysiological processes, mediating the inflammatory reaction. Conversely, Th2 and Treg cells act as immune mediators and are found to be anti-inflammatory. Lymphocyte entry into the CNS is limited by the BBB and glial cells which are abundant and control various biological aspects through communication with macrophages, T cells, NK cells, and other cells.

The meninges are formed by the pia mater, arachnoid mater, and dura mater which surround the CNS. The meninges also contain various immune cells including lymphocytes that participate in brain immunity and immune surveillance of the CNS. Meninges are made up of meningeal lymphatic vessels which drain the brain and are important in health and diseases. In the CNS, B lymphocytes represent a small cellular population that participates in the pathogenesis of some neurological diseases through the production of antibodies, antigen presentation, and secretion of inflammatory and anti-inflammatory molecules (5).

MS is an autoimmune disease that affects the CNS, in which lymphocytes play a crucial role. MS is characterized by chronic inflammation, demyelination, the loss of neurons, and gliosis, and although the exact etiology is unknown, T and B lymphocytes appear to be involved in the processes of demyelination and axonal damage that occur in the CNS. The most well-known hypothesis is that certain CD4+ T cells, with activation by environmental factors, differentiate into Th cell subsets, such as Th1 and Th17 cells, responsible for the activation of other inflammatory immune cells and the generation of cytokines (6). In the animal MS model, experimental allergic encephalomyelitis (EAE), B cells were seen to produce IL-10 that modulates the immune response and IL-10 and Foxp3 expression was enhanced in non-encephalitogenic T cells of the CNS (7).

Lymphocytes in tumors of the central nervous system

Over the last twenty years, the subject of tumor immunity has been increasingly investigated with many scientific publications, particularly regarding the functions of lymphocytes (8-12). This has allowed for improved diagnosis, treatment, and care for cancer patients, although there is much more that remains to be discovered (13). Tumor tissue is made up of different types of cells, such as fibroblasts, pericytes, endothelial cells, and immune cells. Neurons, microglia, astrocytes, and other cells play an important role in neurodegenerative disorders and in brain tumors (14).

T lymphocytes are responsible for cell-mediated immunity and are generally classified into T helper lymphocytes (or CD4+ lymphocytes) and cytotoxic T lymphocytes (also called killer lymphocytes) or CTLs (also called CD8+ lymphocytes). T lymphocytes, such as NK cells, can directly kill tumor cells, while CD4+ T helper cells produce IL-4 that helps to release antibodies by B cells. Treg cells, which are regulatory lymphocytes, generate cytokines and participate in the immunological network. Treg lymphocytes exert tolerance to the antigen and suppress effector T lymphocytes.

It has been observed that in tumor tissue, there are immune cells, such as tumor infiltrating lymphocytes (TILs), that probably have not undergone the immunosuppression that usually occurs in cancer and can respond to tumor antigens (15). This phenomenon occurs in all types of cancer, including brain tumors. These immune cells infiltrate the tumor tissue and should act as effector cells, but the tumor microenvironment inhibits their defensive action. The immunotherapy adopted in brain tumors is increasingly assuming a fundamental importance and the use of TIL lymphocytes has aroused great expectations in both *in vitro* and *in vivo* experiments (16-19).

The immune system is very important in brain diseases, including CNS tumors. In some tumors, such as gliomas, for example, the infiltration of TILs (albeit in low concentrations), has aroused much interest in the scientific community (20). In gliomas, some TILs colonize the perivascular tissue and invade the external parts of the tumor. Various types of lymphocytes have been identified in these tumors including CD45R0+, CD8+, CD4+, and FOXP3+ (21). The presence of these lymphocytes in gliomas serve as biomarkers that indicate both the pathological state of the patient and the therapy to be adopted, although further research in this field is still needed. Lymphocytic infiltration is also found in meningiomas where the rare intratumoral T lymphocytes, also present in the perivascular area, can indicate the severity of the disease (22). These lymphocytes are often represented by NK, CD4+, CD8+, CD45+, and CD20+ cells (23). Although the significance of the presence of these lymphocytes is not clear, it could be argued that their infiltration may represent a weak attempt at an immune response against the tumor.

T lymphocytes expressing CD3+ and CD8+ receptors with anti-tumor activity can infiltrate brain tumors (24,25). Treg lymphocytes expressing CD25, CD4+, and FOXP3 receptors, also present in the tumor microenvironment, inhibit anti-tumor lymphocytes (26). Th cells with CD3+, CD4+, CTLA4, and PD-1 receptors help B cells produce anti-tumor antibodies (27). Often, these reactions are rather mild and do not help to completely defeat the tumor.

Recent knowledge of tumor immunology has led to new immunotherapies including cytotoxic therapies with T lymphocytes and vaccines (28). Today, tumor immunotherapy researchers are studying a type of anti-tumor lymphocyte called chimeric antigen receptor T-cells (CAR-T), which are cells engineered to express chimeric antigen receptors (29). CAR-T cells are assembled by the fusion of a recognition domain, a single-chain antibody, and a T-cell stimulation domain. So far, this therapy has shown promising results in the treatment of hematologic cancers (30), but it is hoped that in the near future, it will find application for other tumors as well, including brain tumors.

CONCLUSIONS

The immune system defends the body against infections from microorganisms, protecting the individual and ensuring health. Innate and adaptive, or cell-mediated immunity, is the first classification of the immune system. Innate immunity acts non-specifically on all foreign microorganisms with the activation of phagocytic cells, including microglia in the brain. Humoral immunity is mediated by circulating antibodies responsible for specific antigen recognition, while cellular immunity is mediated by lymphocytes. Activation of the immune system leads to the production of cytokines, inducing

cell death and generating antibodies. Microbial agents coming from outside the body can break down the BBB, enter the CNS, and cause cerebral dysregulation with activation of myelomonocytic cells. T lymphocytes infiltrate the brain and the interaction of CD4+ and CD8+ cells with adhesion molecules mediates neuroinflammation, causing CNS pathology. Therefore, it is important to underline that the trafficking of T lymphocytes in the CNS is fundamental to the pathogenesis of various autoimmune diseases of the brain. Here, we summarized the aberrant function of T lymphocytes in the CNS, an effect that mediates neuroinflammation rather than protecting the brain from external stimulus.

Conflict of interest

The authors declare that they have no conflict of interest.

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