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BRAIN T CELL SUBSETS POTENTIALLY PARTICIPATE DYNAMICALLY IN NEUROINFLAMMATION AND NEURODEGENERATION

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ABSTRACT

T cells play a crucial role in the immune response by producing soluble mediators, including cytokines. Mature and activated T cells are effector cells and present different phenotypes. T cells have a certain plasticity that allows them to adapt to different antigens. They are distinguished by their different differentiation and production of molecules and intervene both in modulating the immune system and in brain inflammation. T cells are divided into various subsets including T helper cells (Th), cytotoxic T cells (Tc), and regulatory T cells (Treg). Their activation leads to the production of specific transcription factors that regulate the expression of specific genes. CD4+ T cells are helper cells that aid in the production of antibodies, while CD8+ Tc cells are killer cells that act against infected or abnormal cells and mediate neuroinflammation. CD8+ cells mediate neurodegeneration in neuroinflammatory diseases such as Alzheimer's disease (AD) and Parkinson's disease (PD). Treg cells are immune regulators and regulate inflammation. Dysregulation of T cells mediates many neurological disorders such as depression and schizophrenia. The in-depth study of T cells and their subsets helps to better understand their mechanism of action and their function in neurological diseases.

KEYWORDS: *T cell, subset, neuroinflammation, neurodegeneration, immune response*

INTRODUCTION

T cells play a crucial role in the immune response and act by producing soluble mediators and by cell-to-cell contact (1). Many T cell subsets have been characterized, and terminally differentiated subtypes are considered effector cells. Data suggests that the phenotype of all existing T cells has not yet been defined (2). T cells can have mixed phenotypes that interconvert from one subset phenotype to another that, through specific signals, can produce molecules with memory. T cells have a certain plasticity to adapt to the immune response and various microenvironments (3). They are particularly important for the defense against pathogens that invade tissues (4). T cell subsets are distinguished by their differentiation and identified by the expressed cell surface markers but can also be classified by the molecules that they produce (5). It is important to understand the markers of T cell subsets, transcriptional regulators, effector molecules, and the function of the subsets in the immune response (6). Understanding these T cell subsets and their regulation can be an important tool in the therapy against immune diseases. T cells and their subsets play an important role in both immune system modulation, neuroinflammation, and neurodegeneration in the brain (7) (Table I).

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Table I. *Some T-cell subset receptors (surface phenotype).*

Cell type	Receptors
Naive	IL-7R, CD3, TCR, CD62L, CCR7
Cytotoxic	CD3, TCR, CD8
Exhausted	CD3, CD8, PD1, TIM3, 1B11, LAG3
Anergic	CD3, TRC, BTLA
Helper	Cytokine receptor, CD3, TCR, CD4, Chemokine receptor
Regulatory	GITR, CD3, TCR, IL7R, CCR7
Memory	CD44, CD3, TCR, IL7R, CCR7
NKT	NK1.1, SLAMF1, TCR, SLAMF6, TGFβR
γδ T cell	CD3, γδ TCR
CD8αα	CD3, TCR, CD8αα, B220

T cell subsets are part of the adaptive immune system and are classified based on their function and surface markers. Transcription factors are critical in determining T-cell subset differentiation and function (8). T cells are categorized into various subtypes, including T helper cells (Th), cytotoxic T cells (Tc), and regulatory T cells (Treg), amongst others (9). Each subtype's differentiation is driven by specific transcription factors that regulate the expression of lineage-specific genes (Table II).

Table II. *T helper (Th) cell transcription factors*.

Th1	T-bet, STAT4, STAT1
Th2	GATA3, STAT6, DEC2, MAF
Th9	PU.1
Th17	RORγt, STAT3, RORα
Th22	AHR
TFH	BCL-6, STAT3

DISCUSSION

CD4+ cells have various subtypes such as Th1, Th2, Th17, and Treg (10). These cells act through the release of cytokines and are classified based on their function and surface markers.

CD8+ Tc cells are killer cells and act against infected or damaged cells, causing inflammation (11). These cells also act against abnormal neurons, causing neuroinflammation (12). CD8+ T cells can act against myelin and neuronal antigens, causing damage at the axonal level (13).

Tregs are immune T cells that regulate homeostasis and the immune response when it is too high. Tregs may also help maintain brain health and regulate inflammation (14). Treg cells suppress excessive inflammation and, when reduced, contribute to the progression of brain disease. T cells are found in the brain and cerebrospinal fluid in limited numbers due to the blood-brain barrier (BBB) limiting their entry (15). T cell subsets play a dual role in neuroprotection and neuroinflammation. Neuroinflammation is a pathological effect that occurs in many brain diseases including Alzheimer's disease (AD), multiple sclerosis (MS), and Parkinson's disease (PD) (16). Activated innate Th1 cells in the brain produce interferon-gamma (IFN-γ), which causes inflammation and neuronal damage, while Th17 cells produce IL-17, a cytokine that participates in the breakdown of the BBB, allowing inflammatory cells to enter the brain (17).

In neurodegenerative diseases such as AD and PD, T cells are found to be infiltrated in brain regions with amyloid plaques (AD) or Lewy bodies (PD) (18). In these diseases, inflammatory cytokines play a fundamental role in neurodegeneration. In addition, dysregulation of T cells and their subsets mediates many psychiatric disorders such as depression and schizophrenia by activating inflammation (15). In fact, T cells enter the brain after BBB breakdown caused

by systemic inflammation. Cytokines released into brain tissue alter the physiology of neurons and microglia (19). These effects provide the basis for promising therapeutic advancement that may involve enhancing Treg cells or inhibiting pro-inflammatory cytokines such as IL-1, TNF, IL-6, and IL-17 (20).

Naive T cells are crucial elements of our immune system and participate in the pathophysiology of the brain (21). Naive T cells are T lymphocytes that have not yet encountered their specific antigen which are called “virgin cells” and are ready to be activated by a specific antigen presented by antigen-presenting cells (APCs). These cells originate in the bone marrow, mature in the thymus, and then circulate in the blood and lymph nodes, waiting to be activated (22). Once activated, they differentiate into effector T cells or memory T cells. Naive T cells can affect the brain directly or indirectly through several mechanisms. Naive T cells do not normally cross the BBB, but in the case of neurodegenerative disease where the BBB is dysregulated, T cells can enter the brain (23).

“T cell exhaustion in the brain” refers to the phenomenon in which T cells lose their functional capacity after prolonged activation in response to chronic infections, tumors, or autoimmune conditions (24). Prolonged immune activation leads to T cell exhaustion, a reaction which may be particularly important in the context of neuroinflammatory or neurodegenerative diseases (25). Exhausted T cells have reduced cytokine production, proliferation, and cytotoxicity, impairing their ability to fight infections or tumors.

Anergic T cells in the brain play a role in the immune system's regulation to maintain balance and prevent excessive inflammation or autoimmunity (26). T cell anergy is a state of functional unresponsiveness in T cells, where they are alive but fail to proliferate or produce cytokines upon stimulation (27). This occurs when T cells receive signal 1 (antigen recognition via the T-cell receptor) without signal 2 (costimulatory signals, e.g., CD28 interaction with B7 molecules on APCs). T cells infiltrating the brain in certain conditions such as neuroinflammation, infection, or autoimmunity, may encounter signals capable of producing immunological tolerance that leads to anergy (28).

Memory T cells are a subset of T lymphocytes that are primarily associated with the immune system (21). There is growing interest in how they might interact with or influence the brain. Memory T cells can cross the BBB under certain conditions, such as during neuroinflammation (29). In diseases such as MS, memory T cells target myelin, leading to neurodegeneration.

Natural Killer T (NKT) cells are a subset of immune cells that bridge the innate and adaptive immune systems (30). They are known for their role in recognizing lipid antigens presented by the CD1d molecule and producing large amounts of cytokines (31). Their relationship to the brain and neurological functions is a growing area of research. NKT cells are primarily studied in the context of the immune system but they are also involved in neuroinflammation and brain homeostasis. NKT cells are known to secrete cytokines such as IFN-γ and IL-4, which influence inflammation (32).

Gamma delta (γδ) T cells are a unique subset of T cells that play a role in immune surveillance and tissue homeostasis, including in the brain (33). Unlike the more common alpha-beta (αβ) T cells, γδ T cells have a distinct T cell receptor (TCR) composed of γ and δ chains. These cells are involved in both innate and adaptive immunity and are notable for their ability to respond to non-peptide antigens without the need for antigen presentation by major histocompatibility complex (MHC) molecules (34). γδ T cells are implicated in neuroinflammatory conditions, such as MS and other autoimmune diseases, and are thought to contribute to the breakdown of the BBB and the recruitment of other inflammatory cells into the central nervous system (CNS) (35).

CD8αα T cells express a homodimer of the CD8α chain, unlike conventional CD8αβ T cells, which express a heterodimer of CD8α and CD8β (36). CD8αα T cells often express TCRs with limited diversity, such as γδ TCRs or invariant αβ TCRs, which are associated with innate-like immune responses. These cells are involved in immune regulation, tissue repair, and maintaining homeostasis, and they are generally less cytotoxic than CD8αβ T cells (37).

CONCLUSIONS

Today we know that T cells can infiltrate the CNS in both physiological and pathological conditions and their presence is tightly regulated by the BBB. Th1 cells release IFN-γ, which activates microglia and astrocytes, exacerbating neuroinflammation, while TH17 cells produce IL-17, which disrupts the BBB, allowing further immune infiltration. T cell subtypes have been implicated in MS, AD, and PD. CD8+ cells can directly target neurons, contributing to neurodegeneration, while Treg cells suppress excessive inflammation. It is interesting to understand which T cell subtypes mediate the pathophysiological state of the brain and their functions.

Modulating T cell responses using immune inhibitors, Treg-based therapies, or cytokine blockade could offer potential treatment strategies for neurodegenerative diseases.

Conflict of interest

The authors declare that they have no conflict of interest.

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