UPDATE ON THE ROLE OF T CELLS IN COGNITIVE IMPAIRMENT

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Abstract

The central nervous system (CNS) has long been considered an immune-privileged site, with minimal interaction between immune cells, particularly of the adaptive immune system. Previously, the presence of immune cells in this organ was primarily linked to events involving disruption of the blood-brain barrier (BBB) or inflammation. However, current research has shown that immune cells are found patrolling CNS under homeostatic conditions. Specifically, T cells of the adaptive immune system are able to cross the BBB and are associated with aging and cognitive impairment. In addition, T-cell infiltration has been observed in pathological conditions, where inflammation correlates with poor prognosis. Despite ongoing research, the role of this population in the aging brain under both physiological and pathological conditions is not yet fully understood. In this review, we provide an overview of the interactions between T cells and other immune and CNS parenchymal cells, and examine the molecular mechanisms by which these interactions may contribute to normal brain function and the scenarios in which disruption of these connections lead to cognitive impairment. A comprehensive understanding of the role of T cells in the aging brain and the underlying molecular pathways under normal conditions could pave the way for new research to better understand brain disorders.

Update on the role of T cells in cognitive impairment

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Short summary: Exploring the Interactions Between T Cells and the Central Nervous System: Implications for Brain Function and Disease

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ABSTRACT

The central nervous system (CNS) has long been considered an immune-privileged site, with minimal interaction between immune cells, particularly of the adaptive immune system. Previously, the presence of immune cells in this organ was primarily linked to events involving disruption of the blood-brain barrier (BBB) or inflammation. However, current research has shown that immune cells are found patrolling CNS

under homeostatic conditions. Specifically, T cells of the adaptive immune system are able to cross the BBB and are associated with aging and cognitive impairment. In addition, T-cell infiltration has been observed in pathological conditions, where inflammation correlates with poor prognosis. Despite ongoing research, the role of this population in the aging brain under both physiological and pathological conditions is not yet fully understood. In this review, we provide an overview of the interactions between T cells and other immune and CNS parenchymal cells, and examine the molecular mechanisms by which these interactions may contribute to normal brain function and the scenarios in which disruption of these connections lead to cognitive impairment. A comprehensive understanding of the role of T cells in the aging brain and the underlying molecular pathways under normal conditions could pave the way for new research to better understand brain disorders.

ABBREVIATIONS

AD: Alzheimer's disease

AIS: acute ischemic stroke

APC: Antigen-presenting cell

ARD: Age-related disease

Aβ: β-amyloid

BBB: Blood-brain barrier

BCPB: Blood-chroroid plexus barrier

CNS: Central nervous system

CP: Choroid plexus

CSF: Cerebrospinal fluid

EAE: experimental autoimmune encephalomyelitis

IFNγ· Interferon gamma

IL: Interleukin

MS: Multiple sclerosis

PD: Parkinson's disease

SAS: Subarachinoid space

SASP: Senescence-associated secretory phenotype

Th1: T helper 1

Th17: T helper 17

Th2: T helper 2

TNFα: Tumor necrosis factor alpha

Treg: T regulatory cells

1. INTRODUCTION

For decades, the central nervous system (CNS) has been considered an immune-isolated organ, due to the lack of lymphatic vessels and the restriction of the blood-brain barrier (BBB), which limits the access of immune cells (Arcuri, Mecca, Giambanco & Donato, 2019; Mapunda, Tibar, Regragui & Engelhardt, 2022). However, recent studies have shown evidence of the presence of immune cells in both physiological and pathological conditions within the CNS (Arcuri, Mecca, Giambanco & Donato, 2019; Stephenson, Nutma, van der Valk & Amor, 2018). The use of lymphatic-cell-reporter mice has demonstrated the existence of

classic lymphatic vessels within the layers of the meninges and the presence of adaptive immune cells, such as T and B lymphocytes, in these vessels under homeostatic conditions (Buckley & McGavern, 2022; Louveau et al., 2015).

The meninges protect the brain and spinal cord and consist of three different layers. The outermost layer, the dura mater, is a collagenous membrane that is richly vascularized and innervated, and contains numerous lymphatic vessels (Mapunda, Tibar, Regragui & Engelhardt, 2022; Rua & McGavern, 2018). The middle layer, the arachnoid mater, primarily regulates molecules transport (Yasuda et al., 2013) and the innermost layer, the pia mater, surrounds the parenchyma of the CNS. Together, the arachnoid and pia maters are referred to as the leptomeninges (Decimo, Fumagalli, Berton, Krampera & Bifari, 2012). Between these two lies the subarachnoid space (SAS), composed of trabeculae and collagen fibers. The cerebrospinal fluid (CSF), produced by the ependymal cells of the choroid plexus (CP), flows through this space (Rua & McGavern, 2018). The dural lymphatic vessels reabsorb the CSF from the SAS through glymphatic system (Buckley & McGavern, 2022; Prinz & Priller, 2017) (Figure 1).

Dysregulation of the CNS immune response can lead to the development of autoimmune diseases, such as multiple sclerosis (MS) (Ransohoff, 2016). A thorough comprehension of the role of T cells in this scenario, as well as the molecular processes underlying age-related changes under normal conditions, could provide new opportunities for research on understanding the brain in autoimmune and neurodegenerative diseases.

2. T LYMPHOCYTES IN THE HEALTHY BRAIN

2.1. T cells and where to find them

In physiological conditions, the highest concentration of immune cells in the CNS can be found within the dura mater. These include T and B lymphocytes, macrophages and other myeloid cells (Buckley & McGavern, 2022; Louveau et al., 2015). T lymphocytes travel from CNS postcapillary venules to the meninges, specifically to dura mater and the SAS (Mrdjen et al., 2018; Ransohoff & Engelhardt, 2012). T cells exit via lymphatic vasculature and reach the draining cervical lymph nodes (Buckley & McGavern, 2022). Although the skull and vertebral bodies possess bone marrow pockets (Cugurra et al., 2021), the majority of T lymphocytes in the CNS comes from the blood (Rustenhoven et al., 2021).

The process of diapedesis requires several steps, starting with the capture of immune cells on the endothelium by selectins, which slows down their movement. The recognition of their G-protein coupled receptors (GPCRs) then allows the arrest and crawling of immune cells in an integrin-dependent manner, leading to the passage through the endothelium (Mapunda, Tibar, Regragui & Engelhardt, 2022). T lymphocytes diapedesis from CNS postcapillary venules is restricted to activated memory T cells, which are capable of expressing C-C chemokine receptor type 7 (CCR7) and recognizing C-C chemokine ligand type 19 (CCL19), which facilitates the migration of this subset of T cells through the BBB (Marchetti & Engelhardt, 2020). Moreover, the BBB endothelial cells constitutively express atypical chemokine receptor 1 (ACKR1), which, by transporting chemokines to the luminal side of the venular endothelium, restricts the crossing of this barrier to activated T cells (Marchetti et al., 2022). In steady state, $CD4^+$ T lymphocytes are able to cross the BBB through leukocyte function-associated antigen-1 (LFA-1)-dependent adhesive interactions (Castro Dias et al., 2021; Marchetti & Engelhardt, 2020). Different types of T helper cells may use different mechanisms and sites to perform the diapedesis process (Mundt, Greter, Flugel & Becher, 2019). For instance, T helper 17 (Th17) lymphocytes, which express CCR6 and CCR4, preferably enter via CP-associated blood-CP barrier (BCPB) by LFA-1. On the other hand, T helper 1 (Th1) pass the BBB in the spinal cord microvessels through VLA-4 (Glatigny, Duhen, Oukka & Bettelli, 2011; Rothhammer et al., 2011). In addition, $CD8^+$ T cells are more dependent on LFA-1 for diapedesis in the CNS and also require endothelial junctional adhesion molecule B (JAM-B) to pass through the BBB (Alvarez et al., 2015; Mapunda, Tibar, Regragui & Engelhardt, 2022).

The repertoire of immune cells in a non-neuroinflammatory state has been characterized by many authors. Analysis using single-cells techniques has revealed a wide variety of immune populations, such as border-associated macrophages (BAMs), monocytes, natural killer (NK) cells, dendritic cells, innate lymphoid cells,

B and T lymphocytes. In the healthy CNS, T cells could be found patrolling the meninges and the CP, but not in the brain parenchyma (Table 1) (Mundt, Greter, Flugel & Becher, 2019; Prinz & Priller, 2017). Due to the restrictions of the BBB, activated T cells with a memory phenotype and fewer tissue-resident antigen-presenting cells (APCs) can be found in the dura mater, as well as the SAS and CSF (de Graaf et al., 2011; Kawakami & Flugel, 2010; Kivisakk, Tucky, Wei, Campbell & Ransohoff, 2006). Moreover, these T lymphocytes upregulate genes and cytotoxicity-related markers that resemble tissue-resident T cells (Croese, Castellani & Schwartz, 2021; Norris & Kipnis, 2019). T cells constitute a significant portion of the immune environment within the CSF, making up as much as 84% of the total of immune cells. Among T cells, $CD4^+$ cells comprise 48.95%, $CD8^+$ cells represent 17.61%, double positive $CD4^+CD8^+$ cells represent 9.63%, regulatory T cells (Treg) constitute 2.49%, and natural killer (NK) cells make up 3.45%. The ratio of $CD4^+$ T cells to $CD8^+$ T cells is estimated to be around 3.1 to 1. (Piehl et al., 2022; Ransohoff & Engelhardt, 2012). .

2.2. T cell subsets and functions in brain homeostasis

The main functions of these T lymphocytes (Table 1) are modulating the phenotype of myeloid cells, preventing the actions of pathogens that may invade the CNS and orchestrating inflammatory environment in the brain and even modify neuronal activity (Croese, Castellani & Schwartz, 2021) (Norris & Kipnis, 2019). Interleukin (IL)-4 produced by T helper 2 cells (Th2) has been shown to play a critical role in memory and learning. This was demonstrated in experiments where cognitive impairment phenotype was rescued by passive transfer of IL-4 in T cells from *Il4* $^{-/-}$ mice (Derecki et al., 2010). Additionally, T lymphocyte-secreted interferon gamma (IFNγ) has also been shown to participate in social behaviour. The restoration of normal social behavior in *Ifng* $^{-/-}$ mice was achieved through repopulation with wild-type T cells. IFNγ directly affects receptors on inhibitory cortical interneurons, resulting in regulation of GABA production (Filiano et al., 2016). T lymphocytes also play a key role in fetal and adult neurogenesis. The transcriptional transition to mature microglia is demonstrated to be dependent of $CD4^+$ T cells (Prinz, Masuda, Wheeler & Quintana, 2021). Further characterization of this subset showed that Th2 lymphocytes produce cytokines which activate microglia, and subsequently, induce neurogenesis and oligodendrogenesis in adult neural progenitor cells (Arcuri, Mecca, Giambanco & Donato, 2019). All this data suggests that a well-proportioned T cell population is required to maintain proper neuronal activity.

Different types of T lymphocytes could be found in the CNS during homeostatic states (Table 1). Treg cells may be present in the meninges, CP, CSF and perivascular spaces. Their process of diapedesis is determined by chemokines CCL1 and CCL20, cytokines such as IL-2 and IL-33, and serotonin. CNS Tregs upregulate exclusive genes such as*Htr7* (Iellem, 2001; Ito et al., 2019). The main functions of Treg cells in the CNS are to control IFNγ and tumor necrosis factor alpha (TNFα) secretion by immune cells through their inactivation, and to moderate acute inflammation by secreting IL-10 (Liesz et al., 2009). γδ T lymphocytes can be seen in the meninges, CSF and brain parenchyma after brain injury. Two different subsets have been identified, either producing IFNγ or IL-17. After neuronal development, fetal γδ T cells persist in the meningeal spaces throughout life. These T cells mainly belong to the IL-17-producer subset. IL-17-secreting γδ T lymphocytes contribute to controlling synaptic plasticity in short-term memory tests and to encourage brain-derived neurotrophic factor (BDNF) secretion by glial cells. Moreover, IL-17 production has been linked to anxiety behaviours in mice (Alves de Lima et al., 2020; Ribeiro M, 2019). Th17 and IL-22-producing T helper cells can be found in perivascular spaces and SAS. Retinoid-related orphan receptor γt (RORγt) is differentially expressed in Th17 cells, while aryl hydrocarbon receptor (AhR) is the pivotal transcription factor of IL-22 producing cells (Sallusto et al., 2012). These subsets have a pivotal role in the initiation of inflammatory responses in the brain (Lee et al., 2022). Other immune cell types can influence T cell activity in the CNS. For example, NK cells produce IFNγ which induces the expression of TNF-related apoptosis-inducing ligand TRAIL on astrocytes. This limits autoimmune responses in the CNS by promoting T lymphocyte apoptosis (Sanmarco, Polonio, Wheeler & Quintana, 2021). Recent studies have shown that microbiota may play a role as an environmental driver in the IL-17 production by Th17 and γδ T lymphocytes in the brain (Fung, Olson & Hsiao, 2017). T cell-derived IL-17 can directly affect brain development by causing cortical malformations and distorted social behaviours, as well as cognitive dysfunction in the adult brain. On the

other hand, a conserved function through evolution of IL-17 has been described since this cytokine control neuronal chemosensation in *C.elegans*(Norris & Kipnis, 2019).

In addition to cytokines, $CD4^+$ T lymphocytes that produce neurotransmitters have been documented. For example, a specific subset secrets acetylcholine (ACh) to reduce the immune response and regulate blood pressure (Olofsson et al., 2016). This $CD4^+$ T cell subset is able to sense norepinephrine, which is secreted by white adipose tissue-resident macrophages (Norris & Kipnis, 2019).

3. INFLAMMAGING AND COGNITIVE IMPAIRMENT

3.1. Aging and age-related diseases

Throughout the lifespan of an organism, all cell types experience gradual changes that affect their performance either directly or indirectly. This process, known as aging, is a compendium of different cellular and molecular processes, such as DNA-related changes, mitochondrial dysfunction or epigenetic alterations (Lopez-Otin, Blasco, Partridge, Serrano & Kroemer, 2013) that result in morbidity and increased risk of chronic diseases referred to as age-related diseases (ARDs) (Franceschi et al., 2018). Among these, conditions that affect the CNS are frequent, including Alzheimer's disease (AD) or Parkinson's disease (PD).

The complex aging phenomenon is one of the most challenging questions for humanity to comprehend. It is important to differentiate between age-associated pathologies and the normal, steady aging process, if such distinction exists. This is a complex paradigm where the boundaries are difficult to stablish. One of the running hypotheses is the continuum hypothesis, which suggests that the aging process and age-related diseases exist on a spectrum, with some individuals experiencing accelerated aging and developing one or more ARDs and others experiencing slower aging and remaining healthy (Franceschi et al., 2018). Studies have found that even seemingly healthy individuals often shows signs of pathology upon *post-mortem* examination, such as Lewy bodies, β-amyloid (Aβ) plaques or microvascular brain injuries of their brains (Sonnen et al., 2011), leading to increased interest in understanding the molecular hallmarks of aging, prevent and treat ARDs (Franceschi et al., 2018).

However, some experts consider the aging process is just one of the susceptibility factors that contribute to ARD development. Other aspects such as genetic predisposition of age-unrelated genes or exposure to exogenous agents play important roles and the balance of those determine the outcome (Nelson et al., 2011). In this case, a "healthy way of aging" would potentially exist with no collateral ARDs but still different to the phenotype of young individuals. Until this topic is fully explored, this review considers homeostatic aging to be the absence of clinically noticeable pathologies.

3. 2. Inflammaging and immunosenescence

Recently, chronic inflammation has been identified as one of the hallmarks of aging (Schmauck-Medina et al., 2022) and a strong connection to most ARDs, including those involving cognitive decline. The term "inflammaging" has been coined to describe the low-grade systemic inflammation caused by modifications in the immune cells over time, known as immunosenescence. All immune cell subsets are affected, but T cells experience a significant impact. One notable change is a reduced responsiveness to new antigens, which is caused by the reduction in the naïve T cell pool. This reduction is caused by the combination of thymic involution and the increase in the memory compartment due to continuous exposure to a myriad of antigens since birth (Aiello et al., 2019; Mittelbrunn & Kroemer, 2021). The accumulation of terminally differentiated T cells leads to the loss of co-stimulatory molecules CD28 and CD27, which occurs upon clonal expansion, and upregulation of CD57 and killer cell lectin-like receptor subfamily G member 1 (KLRG1) cytotoxic markers (Aiello et al., 2019; Rodriguez et al., 2020). Altogether, this senescent T cell pool is antigen-independent and highly differentiated, which is the perfect trigger to the release of the pro-inflammatory cytokines (IFNγ, TNF-α, IL-2 and IL-6) that characterizes the inflammaging status (Mittelbrunn & Kroemer, 2021; Rodriguez et al., 2020). Moreover, the senescence-associated secretory phenotype (SASP) adopted by immune and non-immune cells in older organisms further promotes inflammation through the release of cytokines and chemokines such as IL-6, IL-8 or IL-1β, which boost the action of innate cells, and Th1 and

Th17 populations (Rea, Gibson, McGilligan, McNerlan, Alexander & Ross, 2018). Morover, exhausted T cells become poor cytokine producers, an extensive profiling study revealed the existence of a distinct age-related $CD8^+$ T cell secreting high levels of granzyme K. Such environment exacerbates the SASP from senescent cells, perpetuating the inflammaging status (Mogilenko et al., 2021).

3.3. T cells and age-related cognitive impairment

It is well stablished that age-related systemic inflammation and a decline in T cell function have a negative impact on cognitive function (Lin et al., 2018). To understand the connection between inflammaging and T cell aging in such an impenetrable system, it is important to analyze the different factors that can influence this scenario (Figure 1).

Some studies have suggested that there may be a disruption of the barriers that could result in the entry of immune cells into the CNS (Banks, Reed, Logsdon, Rhea & Erickson, 2021). However, the age-related disruption has mainly been studied in rodents, and there is still no consensus on whether leakiness is increased over time. Studies in humans are limited to post-mortem examinations and imaging, making it challenging to translate the findings (Banks, Reed, Logsdon, Rhea & Erickson, 2021). Despite the mixed evidence on passive BBB extravasation, the systemic inflammation combined with an inherent baseline inflammation within the CNS is known to prime the microglia and astrocytes to adopt an altered phenotype, triggering the recruitment of immune cells into the brain parenchyma via diapedesis (Erickson & Banks, 2019). This is also possible by the upregulation of adhesion molecules in the endothelium and the ependymal cells in the ventricles and SAS, which is triggered by cytokines such as IL-1β and TNFα, providing access to APCs and effector cells to further amplify the inflammatory cascade.

Once in the brain parenchyma, the presence of T cells in aged individuals has been linked to cognitive dysfunction in numerous ways. First, a murine model of accelerated T cell senescence revealed an increase leakage of T cells in the CNS and subsequent defects in neurological function (Desdin-Mico et al., 2020), supporting the fact that T cell immunosenescence is sufficient to induce this pro-inflammatory detrimental stage. Further, the association between age-related cognitive decay and T cell influx into the white matter was stablished in monkeys (Batterman, Cabrera, Moore & Rosene, 2021), but evidence in humans is still to be found.

One of the ways T cells can lead to defects in the CNS structure and function is prompting axon degeneration in a TCR and granzyme B-dependent manner, causing cognitive and motor impairments in the brain of aging mice (Groh et al, 2021). The role of cytotoxic T cells in cognitive decline is further supported by the observations of Piehl et al (2022), which found an increased expression of C-X-C motif chemokine receptor 6 (CXCR6) in the $CD8^+$ T cells within the CSF of cognitively impaired individuals, together with an accumulation of its ligand, C-X-C motif chemokine ligand 16 (CXCL16), suggesting that this damaging subset of T cells is being recruited in the brain.

The connection between T cell activity and loss of cognitive function can also be seen through the presence of IFNγ-expressing $CD8^+$ T cells compromising neural stem cells found in neurogenic niches of older mice (Dulken et al., 2019). Disrupting neurogenesis, which is crucial for maintaining brain function and plasticity, has a direct correlation with the decline in brain function in aging organisms. Therefore, targeting this T cell population might provide a promising therapeutic opportunity.

IL-17 has been suggested to negatively impact neurogenesis (Liu et al., 2014), but recent evidence also suggests that it can induce neuron regeneration in the gut barrier (Enamorado et al., 2023). *In vitro* studies have shown that Th17-derived IL-17 and IL-22 can penetrate the BBB and promote neuron death in (Kebir et al., 2007; Wojkowska, Szpakowski & Glabinski, 2017). Despite this role, Th17 lymphocytes and γδ T cells have mostly been related with a detrimental effect on cognitive function in ARDs (Komiyama et al., 2006; Lees, Iwakura & Russell, 2008). Studies in aged individuals are needed to assess the real impact of this cytokine on neuron viability and regeneration in the context of inflammaging.

The Treg cell population has been shown to undergo changes with age, with an increase in naturally occurring

Treg cells (nTregs) and a decline in inducible Treg (iTreg) in peripheral blood of both mice and humans. This increase is reported in both $CD4^+$ and $CD8^+$ Treg cells and correspond to a memory phenotype, similar to the effector subsets (Jagger, Shimojima, Goronzy & Weyand, 2014). While these suppressive cells have been shown to slow the progression of some ARDs (McGeachy, Stephens & Anderton, 2005; Tennakoon, Mehta, Ortega, Bhoj, Racke & Karandikar, 2006), their presence and activity in the aging brain, and their relationship with cognitive function in the absence of disease, have yet to be fully understood.

It is evident that T cells and inflammaging have a detrimental effect on cognitive function. However, many questions remain unanswered, such as the functional competence of Tregs or the composition of the cytokine milieu within the parenchyma. Further research is needed to elucidate and distinguish the different mechanisms playing a role, with the aim of identifying potential therapeutic strategies to slow down aging and decrease the risk to ARDs development.

4. BRAIN T CELLS IN NEURODEGENERATIVE DISEASES

4.1. T cells in Alzheimer's disease

AD is the most prevalent neurodegenerative disorder among elderly adults, often progressing to dementia. It primarily manifests as cognitive impairments, including memory loss, language difficulties, misidentifications, and behavioral disturbances. These symptoms are linked to two protein changes in the brain. The first is hyperphosphorylation of the Tau protein, resulting in the formation of intracellular neurofibrillary tangles. The second is the formation of extracellular Aβ-peptide deposits, leading to the creation of amyloid plaques. Both of these processes result in synaptic loss and damage to neurons, contributing to the decline in cognitive function.

T cells, as fundamental cells in the adaptive immune system, may have different roles in the progression of the disease and either may contribute to the aggravation of the pathology or have a protective function in other cases (Table 2). Aberrant T cells may indirectly influence the pathogenesis of AD by secreting proinflammatory cytokines that maintain a detrimental neuroinflammatory state. However, the multifactorial role of T cells in the pathogenesis of AD is also related to an immune response to disease risk factors: the apolipoprotein E (APOE), Aβ peptide, secretases or Tau protein.

The *APOE* gene plays a significant role in AD by influencing the Tau neurotoxicity (Kang et al., 2021), and regulating the levels of Th17 and Treg cells. The specific allele of the APOE protein is crucial, as individuals with the APOE4 allele have higher levels of T cell activation and a higher risk of developing AD (Bonacina et al., 2018). As a result, this gene may be considered a potential target for controlling abnormal T cell activation in AD (Dai & Shen, 2021).

The presence of Aβ-reactive T cells is a result of APCs presenting either the Aβ precursor protein (APP) or Aβ peptide, cleaved by β- and γ-secretases. Both APP and exogenous Aβ can directly modulate T cell function. Additionally, expression of the precursor by monocytes triggers the release of proinflammatory cytokines, which indirectly activate T cells (Dai & Shen, 2021). The role of Aβ-reactive T cells remains controversial, as some animal studies have shown them to be beneficial in clearing Aβ peptides through IFNγ-mediated activation of microglia (Fisher, Nemirovsky, Baron & Monsonego, 2010), while others suggest that these T cells can strongly activate proinflammatory cytokines such as IL-6, TNFα and IL-1β, contributing to a neuroinflammatory and neurotoxic environment (Mietelska-Porowska & Wojda, 2017).

T cells have the ability to control the enzymes responsible for APP processing. T cell-mediated biological changes regulate the expression and activity of β-secretase, and in turn, influence T cell function. Furthermore, the Notch family of receptors are substrates of γ-secretase, which releases the Notch intracellular domain (NICD) during proteolysis for translocation to the nucleus and activation of transcription factors involved in T cell development (Dai & Shen, 2021). Additionally, α-secretase, which promote a non-amyloidogenic cleavage of APP, is also involved in T cell function by processing various substrates, while T cells promote α-secretase activation.

The presence of T cells in the brain is correlated with Tau pathology and can result in excessive T cell

activation (Merlini, Kirabali, Kulic, Nitsch & Ferretti, 2018). In summary, T cells in AD may have a dual role. On the one hand, they can migrate into the CNS parenchyma and contribute to neuronal death during AD progression. However, T cell infiltration in the CNS parenchyma may also have a beneficial effect by promoting the restoration of glial function. In normal conditions, the T cell infiltrate in the CNS parenchyma has a neuroprotective role in spatial learning and preserving neurogenesis (Dai & Shen, 2021). Thus, it is important to thoroughly understand the immune response in AD in order to develop effective therapeutic strategies.

4.2. T cells and Parkinson's disease

PD is the second most prevalent neurodegenerative disorder that affects the motor system and causes symptoms like tremors, stiffness, bradykinesia, gait impairment and many non-motor symptoms. The symptoms are linked to α-synuclein inclusions and the loss of dopaminergic neurons. Inflammation in the brain, specifically the role of T-lymphocytes, can trigger a type 1 pro-inflammatory response, which may initially have a protective effect, but eventually, the inflammation becomes harmful and suppresses the type 2 anti-inflammatory response, leading to a dysregulated state of neuroinflammation and consequent dopaminergic neurodegeneration. Regulating the immune response is a promising approach for managing the disease's pathogenicity and improving the response to treatments (Baird, Bourdette, Meshul & Quinn, 2019).

In both AD and PD, it is important to identify an early immune response in peripheral blood, as this can be used as a diagnostic and prognostic tool, and even as a means to regulate the progression of both diseases through the use of immunomodulators., Increased levels of activated lymphocytes, apoptosis susceptible lymphocytes, central memory T cells, regulatory T and B cells have been found in both diseases. Characteristic immune cells in AD and PD include $CD4^+CD38^+$ and $CD8^+CD38^+$ T lymphocytes, and $CD4^+CD69^+$ and $CD8^+CD69^+$ T cells in PD. Regulatory T cells, such as $CD19^+$ $CD5^+$ $IL10^+$in PD and AD, and $CD19^+$ $CD5^+IL10^+$ $FoxP3^+$, $CD4^+FoxP3^+$ $CD25^+CD45RO^+$ in PD, are also found to play a role in both diseases. In AD, an increase of effector $CD4^+$lymphocytes have been found in the early stages of the disease, while a decrease of $CD4^+$ $CD38^+CD38^+$ lymphocytes occur as the disease progresses (Garfias et al., 2019).

4.3. Autoimmunity in the brain: Multiple sclerosis

It is known that deregulation of the immune system plays a crucial role in neurological disorders. This is particularly evident in diseases where the underlying pathology is autoimmune-related. MS is a chronic autoimmune disease in which self-reactive T cell clones attack the myelin component of the CNS. In early MS, active lesions are characterized by focal demyelination of white matter accompanied by perivenular infiltrates of immune cells such as $CD8^+$ T cells, $CD20^+$ B cells, plasmablasts, and macrophages that form a typical perivascular cuff. This demyelination disrupts the BBB and causes progressive loss of neurological function due to damage to the myelin sheath around the neuronal axons (Frischer et al., 2009).

Genetic predisposition to MS is linked to specific HLA class II haplotypes (HLA-DR15 and HLA-DQ6), which are thought to present autoantigens to the adaptive immune system. Other immune-related genes have also been implicated in the development of MS, such as those encoding for IL-17 and IL-2. In addition to genetics, various environmental factors, such as lifestyle, vitamin deficiencies, and infections such as EBV, have been identified as risk factors for MS. Studying the immune response in the experimental autoimmune encephalomyelitis (EAE) model has provided insight into the role of T cell phenotypes and their effector mechanisms in the pathology of MS (Pilli, Zou, Tea, Dale & Brilot, 2017).

4.3.1. Effector $CD4^+$ T cells in MS

The onset of MS is caused by the activation of specific myelin-specific T lymphocytes in the peripheral compartment, which gain access to the CNS through the expression of appropriate adhesion molecules and receptors in the BBB. Once inside the brain, T cells are reactivated by self-antigens presented by resident APCs, leading to the manifestation of the disease and demyelination of neurons. Research has shown that autoreactive $CD4^+$ T cells can recognize myelin sheath proteins, such as myelin basic protein (MBP), myelin-associated glycoprotein (MAG), and myelin oligodendrocyte glycoprotein (MOG), in both MS patients and

healthy individuals. However, $CD4^+$ T cells in MS patients exhibit an activated and memory phenotype with a higher affinity for these proteins compared to naive myelin-specific CD4+ T cells from healthy controls.

The former understanding of the primary effector cell in EAE and MS was believed to be Th1, but recently Th17 lymphocytes were shown to induce other cell types to produce proinflammatory mediators such as IL-6, GM-CSF, matrix metalloproteases and CXC chemokines, including CXCL8 (a powerful neutrophil chemoattractant), suggesting that Th17 cells may contribute to inflammation in the CNS. This is supported by the fact that the infusion of Th17 cells worsens EAE progression, while the infusion of Th1 cells does not have a significant effect. Additionally, an increase in IL-17 transcripts has been observed in chronic MS lesions compared to acute lesions or healthy individuals, further supporting the role of Th17 cells in autoimmunity in the brain (Komiyama et al., 2006).

4.3.2. CD8 $^+$ T cells in MS

The role of $CD8^+$ T cells in CNS autoimmunity has recently gained attention, despite the focus of research traditionally being focused on $CD4^+$ T cells. (Goverman, Perchellet & Huseby, 2005). Although depleting $CD4^+$ T lymphocytes in MS patients has not led to improvement, alemtuzumab, which targets both $CD4^+$ and $CD8^+$ T cells, has been found to have a positive impact. Further, $CD8^+$ lymphocytes have been found in MS lesions and CSF of these patients (Friese & Fugger, 2005). The activity of $CD8^+$ T cells in the pathology of CNS autoimmunity is still not well understood, but some studies suggest that they can play either a beneficial or harmful role. Depletion of $CD8^+$T lymphocytes results in a lower mortality rate in EAE models, suggesting a regulatory role coinciding with stages of disease remission. However, specific myelin-reactive $CD8^+$ T cells have also been reported to be highly pathogenic for the disease, and infusion of MBP-reactive $CD8^+$ T cells in healthy animals induces demyelination, clearly demonstrating their role in pathogenesis (Huseby, Liggitt, Brabb, Schnabel, Ohlen & Goverman, 2001). Further research is needed to fully understand the activity of $CD8^+$ T cells in CNS autoimmunity and their potential to regulate or contribute to pathology.

4.3.3. γδ T ςελλς ιν ΜΣ

Despite limited research, there are some studies that associate γδ T cells with the pathogenesis of MS and EAE. However, their exact role in the process remains uncertain. γδ T cells have been found to accumulate in MS plaques, displaying oligoclonal expansion, which is an indication of their involvement in antigen-specific responses (Blink & Miller, 2009). Like $CD8^+$ T lymphocytes, γδ T cells appear to have a dual role in the pathology. On the one hand, they may have a regulatory effect in EAE, as studies that depleted γδ T cells resulted in a more severe disease and mice lacking γδ T cells exhibited a reduced ability to achieve remission from EAE. On the other hand, studies suggest a pathogenic role for γδ T cells in EAE, as they contribute to a proinflammatory environment and are a primary source of IL-17 and other proinflammatory cytokines in the disease (Komiyama et al., 2006; Lees, Iwakura & Russell, 2008; Ponomarev & Dittel, 2005). Therefore, more research is necessary to determine the circumstances under which γδ T cells may change their role, particularly if these cells are to be explored as a therapeutic target.

4.3.4. CD4 $^+$ Regulatory T cells in MS

In TCR transgenic mouse models specific for myelin, $CD4^+$ $FOXP3^+$ Treg cells prevent spontaneous EAE by suppressing $CD4^+$myelin-specific T cell activation in the periphery. MBP-specific T cells acquire an anti-inflammatory phenotype after encountering endogenous antigen presented on lymphoid tissues in the presence of Treg cells (Cabbage, Huseby, Sather, Brabb, Liggitt & Goverman, 2007). However, if Treg cells are absent or immunogenic stimuli are present during the interaction between MBP-specific T cells and peripheral APCs, tolerance is not generated and autoimmunity prevails. The function of Treg cells in preventing inflammation within the CNS is also controversial (McGeachy, Stephens & Anderton, 2005) Although there is a correlation between the presence of IL-10-producing $FOXP3^+$ Treg cells and recovery of the CNS and disease, Treg cells appear to be ineffective in suppressing effector T cells in the CNS until local levels of IL-6 and TNFα decrease. Currently, the mechanisms of suppression, antigen specificity and efficacy of Treg cells in suppressing Th1, Th17 and $CD8^+$ T cells in the CNS are not elucidated. The function of

$CD4^+$ Treg cells in the peripheral blood of MS patients appears to be compromised, indicating a weakened ability to restrain the activation of T cells that target myelin in the peripheral compartment. In MS tissue sections, the presence of $FOXP3^+$ Treg cells has not been detected. However, it is unclear whether their absence is a result of a migration defect or reduced survival in the CNS. (Tzartos et al., 2008).

4.3.5. Regulatory $CD8^+$ T cells in MS

The presence of regulatory $CD8^+$ T cells have been observed in both EAE and MS patients. Different subtypes of regulatory $CD8^+$ cells are involved in inhibiting effector $CD8^+$ T cells, including natural $CD8^+CD122^+$ T cells, which secrete IL-10 to inhibit effector $CD8^+$ T cells; HLA-G^+ $CD8^+$ T cells, which suppress effector T cells through the secretion of soluble factors; induced $CD8^+$ Tregs that act at the CNS level; and $CD8^+CD28^-$ T cells that can induce tolerogenic effects on dendritic cells and inhibit disease. $CD8^+$ Tregs generated by the expansion of $CD4^+$ effector T cells in the periphery can eliminate activated $CD4^+$ T cells by recognizing the non-classical MHC molecule Qa-1 on their surface. Modulating $CD8^+$ and $CD4^+$ Treg responses may have therapeutic potential for MS patients. MS patients vaccinated with myelin-specific $CD4^+$ T cell clones generate $CD8^+$ Tregs capable of eliminating effector T cells. The benefits of glatiramer acetate therapy, commonly administrated to MS patients, may also be mediated partly by the regulation of $CD8^+$ T cells (Tennakoon, Mehta, Ortega, Bhoj, Racke & Karandikar, 2006).

4.4. Ischemic stroke

Under physiological conditions, brain barriers maintain homeostasis of the CNS by protecting the parenchyma from the constantly changing bloodstream (Mapunda, Tibar, Regragui & Engelhardt, 2022). As discussed previously, these barriers divide the CNS into different compartments that have varying levels of permeability to innate and adaptive immune cells. Another condition that alters the BBB is the ischemic stroke. During this event, an imbalance between proinflammatory and anti-inflammatory immune populations contributes to BBB disruption through several mechanisms. Activated proinflammatory T cells directly damage the BBB by producing cytokines. The secretion of IFNγ, IL-17 and IL-21 by Th1 and Th17 cells in the acute phase of ischemic stroke degrades tight junctions (TJ), leading to increased permeability and reduced integrity of the BBB. γδ T cells play a pathogenic role by producing IL-17, which decreases the expression of occludin and zonula occludens-1 (ZO-1), increasing BBB permeability. Monocytes and neutrophils are also recruited due to increased expression of CCL2 and CXCL1 in endothelial cells. (Wojkowska, Szpakowski & Glabinski, 2017). IL-17 also degrades endothelial TJ by boosting ROS generation through NADPH oxidase or xanthine oxidase (Huppert et al., 2010). However, Th17 cells produce IL-26, a BBB-protective cytokine by upregulating the expression of occludin, claudins and ZO-1 in endothelial cells. During oxygen-glucose deprivation, NK cells can increase the permeability of the brain microvascular endothelium through the production of IFNγ and reactive oxygen species. $CD8^+$ T cells can also contribute to BBB permeability by inducing cytotoxicity, secreting granzyme B, FasL, TNFα, and IFNγ, and degrading claudin-5. After an ischemic event, Treg cells, which regulate the immune response, are decreased. However, Tregs and Th2 cells play a protective role in the ischemic hemisphere by preventing an excessive immune response that could cause secondary injury (Stubbe et al., 2013). The presence of Tregs after an acute ischemic stroke (AIS) controls the overactivity of resident microglia and infiltrated T cells. Through the upregulation of IL-10 and TGFβ, Tregs reduce the levels of proinflammatory factors such as TNFα, IFNγ and IL-1β. Furthermore, Tregs restrict the production of matrix metallopeptidase 9 in neutrophils through crosstalk of programmed death 1 (PD-1) and its ligand (PD-L1), leading to improved BBB integrity (Qiu et al., 2021).

The sequence of immune cell appearance and duration of persistence in the aftermath of the AIS has been characterized. Neutrophils are the first to swarm the tissue and reach their highest level of infiltration at 24 hours, followed by a peak in monocyte presence at 3-7 days. T cells begin to extravasate at 24 hours and reach their peak at 3 days, but remain persistent over time and can still be detected even one month after the stroke (Gill, Sivakumaran, Aravind, Tank, Dosh & Veltkamp, 2018). Double negative T cells (DNT) and $CD8^+$ T lymphocytes can be observed within the first 24 hours with their peak at 3 days (Liesz et al., 2009), while $CD4^+$ T cells are found at 24 hours and Tregs appear later but are more persistent over time (Chu et al., 2014; Stubbe et al., 2013). The recruitment of Treg and γδ T cells is governed by the CCL5/CCR5 and

CCL6/CCR6 axis, respectively, while NK cells are dependent on the IP10/CXCR3 and CX3CL1/CX3CR1 axis, with the latter having a shorter duration over time (Gan et al., 2014). Clinical research has revealed that differentiation of T lymphocyte groups towards proinflammatory subpopulations occurs after stroke.

Following an AIS, the number of Treg cells decreases dramatically, leading to a weak immune response. This is due to a decrease in the number of CD39+ Treg cells, which results in a decline in the production of anti-inflammatory cytokines such as TGFβ and IL-10 (Ruhnau et al., 2016). Conversely, there is a rise in proinflammatory populations, including Th17 lymphocytes and γδ T cells. An increase in $CD4^+$ $CD28^+$ T cells has also been linked to increased tissue damage in the aftermath of an AIS (Dolati et al., 2018). Additionally, the number of T-cell immunoglobulin and mucin-domain containing-3 (TIM-3), mediated by a Th1 response, increases, along with TNFα, leading to a heightened inflammatory response (Dolati et al., 2018; Huppert et al., 2010; Zhao et al., 2011).

It is important to note that these immune responses are connected to the digestive system through the gut-brain axis. After an ischemic stroke, the gut microbiome can become imbalanced, leading to either amplification or reduction of the immune response. Therefore, controlling the gut microbiome may be a potential strategy for mitigating the impact of ischemic strokes (Li et al., 2019).

5. T CELLS AS THERAPEUTIC TARGET

The modulation of T cell-mediated immune response is of particular interest in diseases such as MS, where successful first-line immunotherapies and monoclonal antibody therapies, such as Natalizumab, are used to treat patients with severe symptoms (Warnke et al., 2010). Natalizumab targets the α4β1 integrin on T cells, preventing them from binding to VCAM1 on BBB endothelial cells and entering the CNS. This is demonstrated by the marked decrease in various T cell populations in the CSF of MS patients treated with natalizumab compared to controls (Stuve et al., 2006). However, treatment with this antibody in these patients can result in various immune deficiencies, such as opportunistic infections and leukoencephalopathies (Warnke, Olsson & Hartung, 2015).

The sphingosine 1-phosphate receptors (S1PRs) S1PR1, S1PR3, S1PR4, and S1PR5 are expressed in many cell types, including lymphocytes and endothelial cells. They play a crucial role in regulating biological processes, such as lymphocyte trafficking and vascular permeability. The use of S1PR modulators, such as Fingolimod, Siponimod, Ozanimod, or Ponesimod, which are approved for the treatment of MS, helps to reduce the trafficking of immune cells to the CNS (Mapunda, Tibar, Regragui & Engelhardt, 2022). However, due to the multifactorial nature of this autoimmune disease, it is important to continue searching for new autoantigens to provide more targeted and effective treatments with minimal side effects.

The regulation of the immune response can also be of interest in diseases other than those with a clear immunological component. In the case of AIS, preclinical approaches aim to alleviate its adverse effects, such as using monoclonal antibodies like anti-VLA4, which blocks CD49d (Liesz et al., 2011) or FTY720/Fingolimod, an agonist of S1P1 receptors (Salas-Perdomo et al., 2019). These aim to prevent immune cells from infiltrating the CNS. Regulators of immune homeostasis, such as Vitamin D and Resveratrol, which regulate PPARγ function (Matsuura, Egi, Yuki, Horikawa, Satoh & Akira, 2011), as well as modulators of the intestinal microbiota (Dou, Rong, Zhao, Zhang & Lv, 2019), like sodium butyrate and valproic acid, have been shown to reduce infarct size and a decrease in cognitive impairment.

The regulation of T cell-mediated responses in AD is not well explored compared to other pathologies. While some preliminary studies have investigated the use of monoclonal antibodies against Aβ peptides and phosphorylated Tau protein (Wisniewski & Goni, 2015), and early-stage clinical trials aimed at restoring the suppressive activity of Treg cells by expanding them ex vivo (Faridar et al., 2020), a deeper understanding is needed to effectively implement these therapies. The APOE protein is an important modulator of T cell response and a powerful risk factor in AD, making it an interesting target for regulating abnormal T cell activation in this pathology.

The contribution of T cells to the development of PD has been well established, leading to the development

of numerous neuroprotective therapies that show a T cell-mediated mechanism (Table 2). Specifically, increasing the number or function of Tregs has been shown to be effective in providing neuroprotection in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) induced mouse model of PD. The recognition of the immune response's role in PD opens up new opportunities for diagnosis and treatment. Identifying individuals with HLA alleles that increase their risk for specific α-synuclein-specific T cells could lead to early diagnosis and treatment. Additionally, these clonal T cells could be used as early biomarkers of disease, identifying self-protein autoimmunity before motor symptoms develop. One promising avenue of treatment is Sargramostim, a granulocyte-macrophage colony-stimulating factor, which has been used to treat patients receiving bone marrow transplants or undergoing cancer treatment, by promoting myeloid recovery and inducing Treg responses. Results from a phase I clinical trial show that patients receiving the drug showed improvement after 6-8 weeks of treatment, with increased numbers and function of Tregs compared to patients receiving a placebo. Additional clinical research will shed light on the potential of immunomodulatory drugs for the treatment of PD (Garretti, Agalliu, Lindestam Arlehamn, Sette & Sulzer, 2019).

6. CONCLUSION

T cells ability to mediate the immune response makes them a valuable tool in treating conditions where the immune system plays a crucial role. With advances in medical research and technology, techniques have been developed to modulate T cell activity, offering new therapeutic strategies for many medical conditions. The traditional belief that the CNS is immune-isolated has been challenged by recent evidence of the presence of immune cells within the CNS in both normal and pathological conditions. T cells are demonstrated to enter the CNS through the lymphatic vasculature and the fenestrated capillaries within the CP and populate the dura mater and the CSF. Further understanding of T cells in the CNS and the molecular processes behind these changes in normal conditions can open up new avenues of research in autoimmune diseases like MS, caused by T cells targeting myelin. The presence of T cells also may play a role in AD and PD, with APOE as a key factor in AD and T cell modulation as a potential treatment strategy in PD. The BBB regulates the traffic of immune cells into the CNS, but pathological conditions like MS and stroke can disrupt it. There are various therapies that target T cells to reduce symptoms of MS such as Natalizumab, Fingolimod, and others, while regulation of T cell-mediated response is being explored in AD and Tregs in PD. T cells may also serve as early biomarkers in PD.

However, T cells are not just crucial in pathological conditions, they also play a fundamental role in aging. The aging process leads to a decline in cellular and molecular function, resulting in chronic diseases and increased risk of ARDs. Chronic inflammation, also known as "inflammaging", is a hallmark of aging linked to cognitive decline and pathology. T cells are affected by aging and the accumulation of senescent T cells leads to pro-inflammatory cytokine release. This age-related systemic inflammation is connected to impaired cognitive function. Despite this field is an active field of research, more information is needed to fully understand the impact of T cell aging on cognitive decline.

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AUTHOR CONTRIBUTIONS

I. R-F., R. S-D, E. O-S. and P.M.: writing original draft, collected bibliography, designed figure and tables, and editing. I. R-F. and P.M.: conceived the review and revised the manuscript.

CONFLICT OF INTEREST

R. S-D and P.M. are inventors on a patent (WO 2017/093353). All others authors have no conflict of interest.

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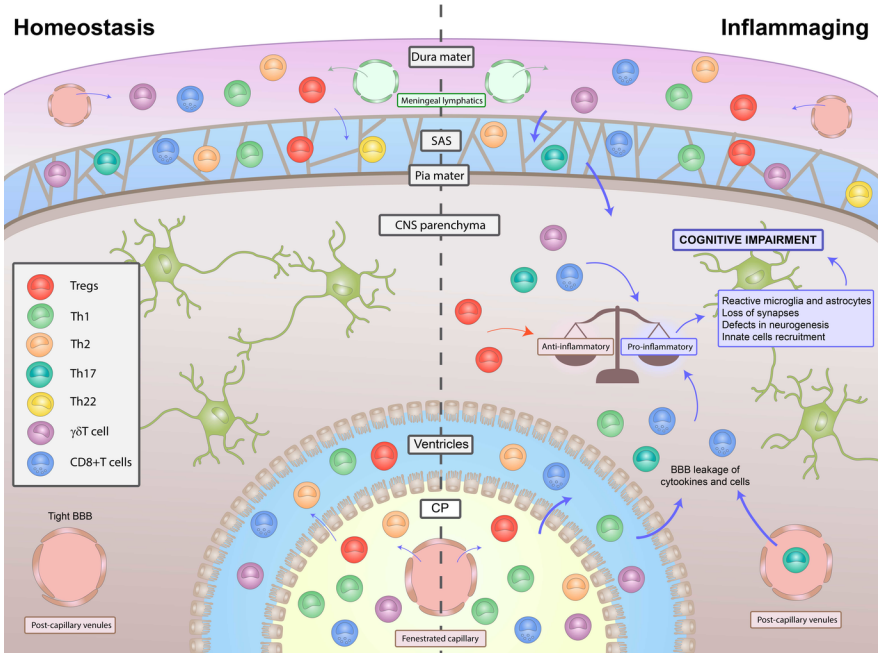
FIGURE LEGENDS

Figure 1. Schematic view of the role and location of T cell subsets in homeostasis and inflammaging in the different compartments of the brain. In homeostatic conditions (left), the vascular BBB, the blood-CSF barrier and the meningeal barrier limits the access of the T cell population to the CNS. In the context of aging (right), these barriers are compromised by the increased pro-inflammatory cytokine release, allowing the entry of mostly CD8+ T cells, T regulatory cells and other effector T cells into the parenchyma. If the contribution of the different cytokine signatures results in a pro-inflammatory microenvironment, the consequences on the resident immune cells, glia and neurons would induce cognitive impairment.



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