CD4+ T-Cell Subtypes and their Implications in Alzheimer's Disease

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ABSTRACT

Chronic inflammation has a predisposing condition towards Alzheimer's Disease (AD), yet the mechanisms leading to neurodegeneration are largely unknown. Two systematic literature reviews analyzed the relationship between differentiated CD4+ T-Cells and neurodegeneration. The first review comprised 8 primary research articles, analyzing Th1 and Th2 cells; the other included 8 primary research articles analyzing Th17 and Treg cells. Both investigators used the PubMed database, developing a list of search criteria and restricting their results to a period of 2014 - present, including only human subjects, and excluding reviews.

There is a direct relationship between Th1 and Th2 cells, with Th2 anti-inflammatory responses working to counterbalance the pro-inflammatory effects of Th1. Th1 cells release cytokines that activate microglia and contribute to neuroinflammation while Th2 cells promote an anti-inflammatory response. In AD, an imbalance favoring Th1 responses leads to sustained neuroinflammation and neuronal damage, while decreased Th2 activity leads to inadequate neuroprotection. Tregs and Th17 cells also have a direct relationship, with Treg expression suppressing Th17-mediated pro-inflammatory responses. Th17 cells preferentially migrate into the brain, catalyzing neuroinflammation. Systemic, possibly responsive, Treg expansion enhances immediate neuroprotection against AD, yet dysregulation then influences chronic microglia activation as seen in Alzheimer's, down-regulating antigen-specific T cells throughout disease development. Over time this dysregulation leads to cognitive decline and contributes to the loss of CD4+ T cell diversity. The relationships and polarization of CD4+ T-cell subsets may account for how chronic inflammation may lead to neurodegeneration as seen in AD and other Central Nervous System disorders.

INTRODUCTION

Alzheimer's disease (AD) is the most common form of dementia. Early-onset AD occurs before age 65, and is either the common form of AD known as sporadic AD or the rare genetic form known as familial AD. More commonly, progressive cognitive decline due to neurodegeneration occurs after age 65, and is known as late-onset AD. The most common markers of late-onset AD are amyloid-beta (Aβ) plaques, and neurofibrillary tangles (Nelson et al. 2009). However, both inflammation in the body and in brain tissue are also associated with neurodegeneration and AD pathology. In the central nervous system (CNA), these mechanisms include chronic microglial activation and overproduction of pro-inflammatory cytokines such as IL-6 and TNF∝ which correspond to CD4+ T cells and often influence microglial activation. These CD4+ T-Cells differentiate into 7 different subforms, and the homeostasis between these subforms is crucial in inflammation and AD. each with their own function and contribution to dementia and Alzheimer's pathology (Liu et al. 2022, Dai et al. 2021).. These differentiated subforms can be both neurotoxic or neuroprotective, and influence one another's phenotypic expression. This analysis reviews the relationship between Th1 and Th2 cells, in addition to that between Th17 and induced Treg cells to evaluate their influence in neurodegeneration; particularly AD.

METHODS

For this analysis, two separate literature reviews were conducted. Both reviews were conducted on the NIH Pubmed Online database, and all articles had to be free full access. The first review searched the terms ("Alzheimer's disease" OR "dementia") AND ("neuroinflammation" OR "neurodegeneration") AND ("T helper cells" OR "Th1/Th2 balance") AND ("cytokines" OR "inflammation markers"). It was further constrained to include only human subjects, and these limitations resulted in 8 articles that had 519 human subjects. The other review used the terms (Th17 OR Treg) AND (Neuro*) AND (Inflammation) AND (Alzheimer's), and limited the review to those including human samples and published during or after 2014. These constraints resulted in 8 articles which had 266 human subjects in total. Models that didn't include human samples in their T-cell expansion process were excluded because no single model currently includes a single Alzheimer's-linked variant that completely develops the same pathology of AD as seen in human subjects (Ashe & Zahs, 2010).

Th1 & Th2 RESULTS

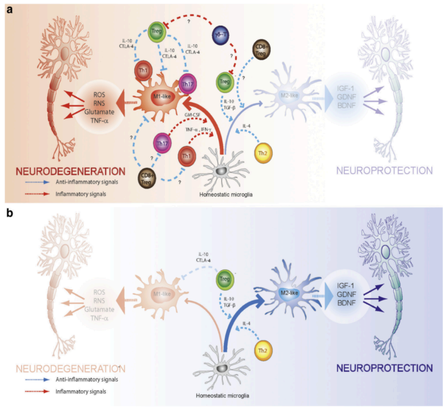

Figure 1: T-cell-mediated regulation of neuroinflammation in neurodegenerative disorders. https://pubmed.ncbi.nlm.nih.gov/25441979/

The reviewed studies indicate that Alzheimer's disease (AD) is associated with a Th1-skewed immune response, contributing to chronic neuroinflammation and cognitive decline. Elevated levels of interferon-gamma (IFN-γ) and tumor necrosis factor-alpha (TNF-α) were consistently observed in AD patients, leading to increased microglial activation and neuronal damage, while reduced levels of interleukin-4 (IL-4) and interleukin-10 (IL-10) weakened anti-inflammatory and neuroprotective mechanisms (Lewis et al., 2023; Zhang & Niu, 2022). The imbalance between Th1 and Th2 cytokines correlated with disease severity, with higher pro-inflammatory cytokine expression linked to accelerated cognitive decline and amyloid-beta accumulation. Immunomodulatory interventions showed potential in restoring immune balance, as Aloe polymannose supplementation and PR-957 treatment successfully increased IL-4 and IL-10 expression while reducing inflammatory IFN-γ and TNF-α activity leading to improved neuroinflammatory profiles (Lewis et al., 2023; Li et al., 2023). These findings suggest that targeting Th1/Th2 balance may be a promising approach for mitigating AD-related inflammation and neurodegeneration, though further longitudinal studies are necessary to confirm the long-term effectiveness of these interventions.

Th17 & Treg RESULTS

Along with the relationship between Th1/Th2 cells, there's also a relationship between Th2/Treg cells. It's been found that in Th2 polarized responses, the development of a regulatory immune response is enhanced (Lambracht-Washington & Rosenberg 2015). Tregs then crossing into the brain could create favorable conditions for an overshooting of the immune response, particularly as their immunomodulatory mechanisms are compromised in AD patients (Di Benedetto et al. 2019, Faridar et al. 2022). Also, Tregs may have contrasting effects on neurodegeneration by obstructing recruitment of immunoregulatory cells to the central nervous system (Faridar et al. 2022). The proposed mechanism of this is likely due to an increase in the regulatory immune response results in a downregulation of effector T cells, yet due to the fact that Treg function is impaired in AD, there is activation of systemic cytotoxic immune cells and an upregulation of pro-inflammatory mediators. (Lambracht-Washington & Rosenberg 2015, Faridar et al. 2022). In contrast to this, Treg expansion in a model of AD resulted in a suppression of Th17-driven pro-inflammatory responses, yet it's important to note that these were non-senescent T-Cells due to TNFR2 and TNFR1 agonists, possibly explaining the difference between these two results (Pegoretti et al. 2023). This indicates that there may be a difference in the function of these Tregs, which could explain the variability of these results Th17 cells are implicated in the selective infiltration of the blood brain barrier, and many transition to pathogenic Th17 cells, something which can occur independently of Th1 cells (Mickael et al. 2022). This may explain the significant shift seen in AD from Th1 to non-Th1 pathways during aging (Hu et al. 2019).

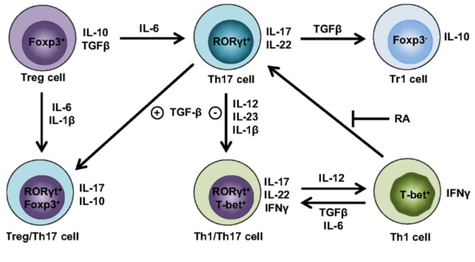

Figure 2: Cytokine regulation of Th17 & Treg balance https://pmc.ncbi.nlm.nih.gov/articles/PMC4681807/

DISCUSSIONS

Alzheimer's disease (AD) has long been associated with amyloid-beta plaques and tau tangles, but more recent research highlights chronic neuroinflammation as a key driver of disease progression. The findings of this research study indicate that a persistent Th1-dominant immune response plays a significant role in maintaining this inflammatory state, as increased levels of interferon-gamma (IFN-γ) and tumor necrosis factor-alpha (TNF-α) promote microglial activation, blood-brain barrier dysfunction, and sustained neurotoxicity (Lewis et al., 2023; Li et al., 2023; Zhang & Niu, 2022). The reduction in interleukin-4 (IL-4) and interleukin-10 (IL-10) limits the immune system's ability to resolve inflammation, allowing prolonged immune activation to contribute to synaptic damage and cognitive decline (González & Pacheco, 2014). While the precise mechanisms linking Th1/Th2 imbalance to neurodegeneration remain under unclear, these findings suggest that shifting the immune response toward Th2-mediated anti-inflammatory pathways may offer neuroprotection. However, challenges such as variability in cytokine measurements, small sample sizes, and the lack of large-scale longitudinal studies limit the ability to draw definitive conclusions about immune-targeted interventions for AD. Future research should prioritize standardized immune profiling across different disease stages to better define the role of Th1/Th2 regulation in AD progression.

In part due to the Th1 polarization seen in AD, there is an increase in T effector cells such as Th17 cells which target astrocytes to promote neuroinflammation. These Th17 cells also preferentially migrate into the brain through the blood-brain barrier, and the polarization of the Th1/Th2 cells influence the recruitment and differentiation of Tregs (St-Amour et al. 2019, Lambracht-Washington & Rosenberg 2015). Treg expansion lead to a suppression of Th17-driven astrocytic inflammation, yet the effects of Tregs on neurodegeneration are also contradictory (Pegoretti et al. 2023, Mickael et al. 2022). Tregs regulate immune homeostasis, yet block further recruitment of immunoregulatory cells to the central nervous system (Faridar et al. 2022). Then, as they become dysfunctional as seen in AD, the central nervous system can no longer recruit functional Tregs to maintain immune homeostasis in the brain, resulting in an 'overshooting' of the immune response (Di Benedetto et al. 2019 St-Amour et al. 2019). Due to the complex nature of these interrelated mechanisms, future research should focus on the variability of Treg response, and how they can become senescent over time which results in the polarized immune response that is seen in chronic neuroinflammatory conditions.

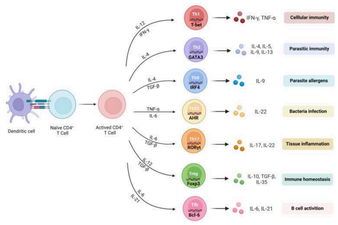

Figure 3: Subsets and Functions of CD4+ T Cells https://www.ncbi.nlm.nih.gov/pmc/articles/PMC11083511/figure/cells-13-00749-f001/

FUTURE WORK

Currently, we are a Phase II Hatchery Project team. At the moment, we are creating budgets and identifying antibodies to stain for Treg and Th17 cells in brain tissue to identify localization and interaction of peripheral Treg and Th17 cells in healthy controls, demented AD patients, and non-demented AD patients.

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