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Role of resident memory T cells in neuroinflammatory and neurodegenerative diseases in the central nervous system

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The immune system has been attracting increasing attention in the field of chronic neurological disorders in the central nervous system (CNS). Autoreactive T cells targeting CNS antigens play a crucial role in the development of various autoimmune diseases, such as multiple sclerosis (MS) and neuromyelitis optica spectrum disorder (NMOSD). Moreover, T cells are now recognized as a pivotal contributor to the pathology of neurodegenerative disorders, including Alzheimer's disease (AD), Parkinson's disease (PD), and multiple system atrophy. Among the diverse array of T cell subsets, resident memory T (Trm) cells are suspected to exert a substantial influence on the progression of these debilitating diseases. Trm cells are distinguished by their restricted localization within tissues and their unique transcriptomic signature. This perspective aims to elucidate the current understanding of Trm cells in CNS disorders and to explore future directions in this rapidly evolving field.

Resident memory T cells in autoimmune and neurodegenerative diseases of the central nervous system: The interplay between various immune cell subsets contributes to the pathogenesis of MS, including $CD4^+$ T helper cells, $CD8^+$ T cells, B cells, and monocytes. Myelin-reactive T cells are increased in the peripheral blood of patients with MS, which subsequently migrate into the CNS and attack myelin sheaths. The disease activity is strikingly reduced by the treatment with natalizumab, a monoclonal antibody against alpha 4 integrin, indicating that the migration of immune cells into the CNS is an important step in disease attacks.

Furthermore, progression independent of relapse activity is one of the major focuses in MS, which is a critical determinant of overall disability accumulation. The pathology suspected to be underlying this type of chronic progression includes: (1) accumulation of compartmentalized immune cells such as Trm cells, (2) chronic activation of microglia and/or astrocytes, and (3) formation of tertiary lymphoid structure in the meninges. All of these mechanisms are supported by various lines of evidence, including pathological findings, correlations between these factors and disease progression, and the exacerbating effects of these factors on neuroinflammation as demonstrated in animal models. Among these mechanisms, Trm cells and functionally altered microglia appear to bridge neuroinflammatory and neurodegenerative pathologies, as they are observed in the CNS of both conditions.

We recently showed that Trm-like $CD8^+$ cells are increased in the cerebrospinal fluid (CSF) from patients with chronic inflammatory diseases such as MS compared to control subjects (Kimura et al., 2024). In this study, Trm-like cells were determined as $CD69^+CD103^+CD45RA^-$ cells, which were almost absent in the peripheral blood, suggesting their compartmentalization in local tissues. These cells were highly enriched in the CSF, potentially reflecting the condition of the CNS parenchyma. It is now suggested that parenchymal interstitial fluid drains into the CSF, highlighting the close relationship between the CNS parenchyma and the CSF, although it remains unclear if the cellular components follow the same pathways. Consistently, the transcriptional profile of T cells in the CSF is known to resemble that of T cells in the brain parenchyma in a mouse model of MS, which is also suggested in patients with MS.

Notably, Trm-like $CD8^+$ cells were similarly increased in the CSF from patients with neurodegenerative diseases such as AD and PD (Kimura et al., 2024), indicating the involvement of these cells in both autoimmune and neurodegenerative conditions. $CD8^+$ Trm cells infiltrate the substantia nigra of patients with PD at the earliest stages of the disease, preceding the formation of a-synuclein aggregation and dopaminergic neuronal death (Galiano-Landeira et al., 2020). The infiltration of $CD8^+$ Trm cells is correlated with the progression of neuronal death and synucleinopathy, collectively suggesting that such T cells may trigger or enhance the pathology of PD. Our observation is consistent with these pathological changes.

In contrast to $CD8^+$ T cells, Trm-like $CD4^+$ T cells were not increased in these diseases, possibly because CD69 and CD103 are not ideal markers for identifying $CD4^+$ Trm cells, though we could not detect a difference even by using another marker, CD49a. This is of interest considering that $CD8^+$ T cells outnumber $CD4^+$ T helper cells in the brain lesions of MS. Consistently, nearly all $CD103^+$ T cells are $CD8^+$ T cells in the brain lesions of NMOSD (Nakajima et al., 2024).

We found that the Trm cell-type transcriptome was observed only in the Trm-like $CD8^+$ cells in the CSF from patients with MS, and not clear in those cells in the CSF from healthy subjects, by reanalysis of a public scRNAseq dataset (Kimura et al., 2024). The phenotype of Trm-like $CD8^+$ cells in the CSF may differ though they are expressing some Trm markers, which are CD69 and CD103 in this analysis. Even in the same disease, NMOSD, Trm cells change their function along different disease stages. For example, Trm cells express high levels of granzyme B and perforin-1 in the initial and early-active stages of NMOSD compared to the later stages (Nakajima et al., 2024). Similarly, $CD8^+$ T cells can ameliorate the amyloid pathology in a mouse model of AD (Su et al., 2023), though they can exacerbate tau-related pathology in another AD model (Chen et al., 2023). These findings highlight the complex and potentially contradictory roles of T cells in different pathological aspects even in the same disease. This complexity should be carefully considered when targeting Trm cells as a new treatment strategy.

Interaction of resident memory T cells and microglia: Accumulating evidence suggests that Trm cells significantly contribute to the chronic progression of MS through interactions with microglia, the resident immune cells in the CNS. Genome-wide association studies have shown that the risk variants for MS are closely correlated with microglia when analyzed among the cell types in the CNS, underscoring their pivotal role in the pathology. Microglia can quickly respond to environmental inflammatory changes, then exacerbating and sustaining chronic inflammation in the tissue. Some intracranial lesions of MS have hypointense paramagnetic rim by susceptibility-weighted magnetic resonance imaging, which tends to gradually expand over the years and closely correlate with disease progression (Absinta et al., 2021). The paramagnetic rim reflects accumulating microglia laden with phagocytosed iron (Absinta et al., 2021). The chronic expansion of the lesion and the resultant neurological worsening are attributed to inflammatory interaction between microglia and T cells (Absinta et al., 2021). Another paper demonstrated that microglia are highly activated in the normal-appearing white matter of MS patients compared to healthy controls (Sucksdorff et al., 2019). Notably, their activation levels positively correlated with disease progression over subsequent years. Microglial activation gradually increases, but can be abrogated by blocking infiltration of T cells with natalizumab, an anti-alpha 4 integrin antibody, further suggesting the importance of the interaction of microglia with T cells (Sucksdorff et al., 2019). T cell-microglia interaction is now suspected to be a key contributor to progression independent of relapse activity. $CD8^+$ T cells are more abundant in the lesions of chronic MS cases compared to $CD4^+$ T cells and characterized by the expression of CD69, CD103, CD44, CD49a, and PD-1 and the absence of S1P1, suggesting Trm phenotype (Fransen et al., 2020). These cells accumulate in the perivascular space and also infiltrate the brain parenchyma, where they can interact with microglia.

The interaction between T cells and microglia appears to be similarly critical in AD. T cells found in the AD brain express Trm markers and harbor a Trm-type transcriptome. T cells infiltrate the CNS by sensing microglial CXCL16, resulting in pro-inflammatory microglial phenotype and exacerbation of tau pathology of AD (Chen et al., 2023). As described above, $CD8^+$ T cells can ameliorate the amyloid pathology of AD, which is also mediated via T cell-microglia interactions (Su et al., 2023). It remains unclear whether the difference in microglial phenotype is the key factor behind these opposing effects of T cells.

Microglia can have multifaceted roles in both MS and AD. Activation of NFκB-NLRP3-inflammasome pathway in microglia results in increased severity of experimental autoimmune encephalomyelitis, a mouse model of MS (Voet et al., 2018). When microglia are stimulated with

interleukin-3 secreted by astrocytes and infiltrating T cells, they, in turn, secrete chemotactic cues and recruit additional peripheral T cells and monocytes (Kiss et al., 2023). Conversely, microglia can ameliorate the severity of experimental autoimmune encephalomyelitis through their SYK signaling (Ennerfelt et al., 2022) or by shaping the functional regulatory T cell pool (Haimon et al., 2022). Phagocytosis and clearance of myelin debris by microglia are required for efficient remyelination after attacks. Similarly, microglia can either exacerbate or ameliorate AD pathology. The hallmarks of AD are worsened by activation of microglial NLRP3-inflammasome pathway, and cGAS-STING pathway. Interestingly, the microglial SYK pathway can ameliorate AD pathology, mirroring its effects in experimental autoimmune encephalomyelitis, indicating a shared disease process mediated by microglia (**Figure 1**).

Future perspective: Trm cells are increased in the CSF in both chronic inflammatory and neurodegenerative diseases compared to control subjects, suggesting their contribution to the underlying pathology. Given that the phenotype of Trm cells in the CNS can vary depending on diseases and disease stages even in the same disease, more precise characterization of these cells is warranted. As we mentioned above, $CD8^+$ T cells exacerbate a tau-based mouse model and ameliorate an amyloid-based mouse model, which further indicates the importance of clarifying their roles in distinct pathologies within the same disease. Understanding the dynamics of Trm cells within the CNS microenvironment is essential for elucidating the mechanisms underlying neuroinflammation and neurodegeneration. Additionally, Trm cells affect the disease through their interactions with surrounding cells including microglia, which also have multifaceted roles even in the same disease. T cells also directly target neural stem cells by secreting inflammatory cytokines such as interferon-γ, resulting in age-related decline in brain function (Dulken et al., 2019). It would be crucial to study whether there is a specific correlation between distinct Trm cell states and the states of surrounding cells such as microglia and neurons, especially when we aim to find a new therapeutic target.

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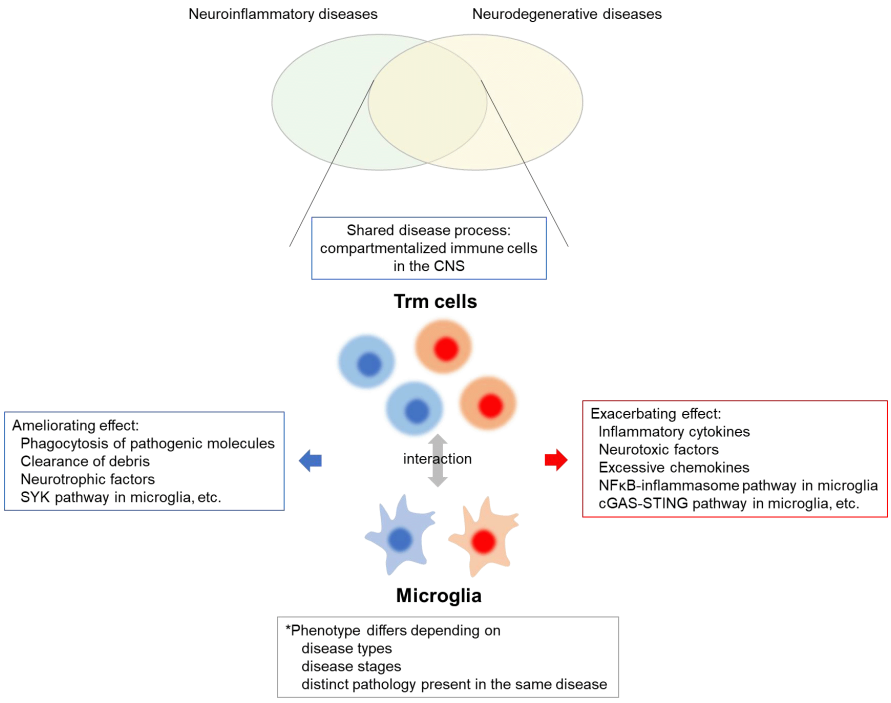

Figure 1 | **Interaction of Trm cells and microglia is involved in the pathology of both neuroinflammatory and neurodegenerative diseases.**
Created with Microsoft PowerPoint. cGAS-STING: cyclic GMP-AMP synthase-stimulator of interferon genes; CNS: Central nervous system; NFκB: nuclear factor kappa B; Trm: resident memory T.

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