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Emerging T cell immunoregulatory mechanisms in multiple sclerosis and Alzheimer's disease

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Multiple sclerosis (MS) and Alzheimer's disease (AD) are neuroinflammatory and neurodegenerative diseases with considerable socioeconomic impacts but without definitive treatments. AD and MS have multifactorial pathogenesis resulting in complex cognitive and neurologic symptoms and growing evidence also indicates key functions of specific immune cells. Whereas relevant processes dependent on T cells have been elucidated in both AD and MS, mechanisms that can control such immune responses still remain elusive. Here, a brief overview of select recent findings clarifying immunomodulatory mechanisms specifically induced by tolerogenic dendritic cells to limit the activation and functions of neurodegenerative T cells is presented. These insights could become a foundation for new cutting-edge research as well as therapeutic strategies.

KEYWORDS

multiple sclerosis, Alzheimer's disease, tolerance, Tcells, dendritic cells

The roles of T cells in multiple sclerosis and Alzheimer's disease

Multiple sclerosis (MS) is a complex autoimmune disease characterized by inflammation of the central nervous system (CNS) following the attack of immune cells that destroy components of the myelin sheath surrounding the neuronal axons of the nerves, leading to demyelination and neurologic dysfunction. In most cases, MS is characterized by a relapsing–remitting disease course, although some patients with MS suffer from the primary-progressive form characterized by its steady progression. Many MS patients eventually develop a secondary-progressive MS characterized by a steady progression of symptoms (Dendrou et al., 2015; Baecher-Allan et al., 2018). Both genetic and environmental factors including past viral infections can contribute to the development of MS but the exact mechanisms resulting in MS pathogenesis in individual patients are unknown. Nevertheless, the processes directly leading to development of MS depend on an aberrant response of the immune system directed against specific antigens derived from components of the CNS (Hafler et al., 2007; Patsopoulos et al., 2011; Beecham et al., 2013; Lill et al., 2013). This autoimmune process can be initiated when specialized antigen presenting cells (APCs), including conventional dendritic cells (cDCs), activate autoreactive $CD4^+$ T lymphocytes (cells). Such neural antigen-specific (encephalitogenic) $CD4^+$ T cells can enter the CNS and be re-activated by the functions of microglia and possibly other of myeloid cells resulting in a recruitment of cytotoxic $CD8^+$ T cells and establishing an inflammatory lesion (Kawakami et al., 2005; Raddassi et al., 2011; Jones and Hawiger, 2017; Absinta et al., 2021; Schnell et al., 2021; Lanz et al., 2022). Further,

$CD4^+$ T cells orchestrate functions of autoreactive B cells that, along with natural killer (NK) cells and macrophages, crucially contribute to MS immunopathology (Dendrou et al., 2015; Baecher-Allan et al., 2018).

The pathogenesis of another notorious neurologic disorder, Alzheimer's disease (AD), remains elusive. AD is a devastating, progressive neurodegenerative disease affecting millions of people, including a large percentage of the population over 85 years old. Microscopic hallmarks of the disease are characterized by early deposition of amyloid-β (Aβ) plaques followed by formation of neurofibrillary tangles composed of hyperphosphorylated tau protein. Although deposition of Aβ is a necessary factor in AD pathogenesis, its accumulation appears as insufficient for neurodegeneration and cognitive decline. In contrast, pathological tau accumulation is closely linked with neurodegeneration and cognitive decline (DeMarshall et al., 2016; Chen et al., 2023). In contrast to MS and other autoimmune disease in which the key roles of T cells have been well established, T cells have been only recently implicated in pathogenesis of in AD. Previous results have suggested that T cells promote tissue pathology and cognitive defects in AD but these immune cells may also have beneficial functions such as clearing the amyloid plaques (Mietelska-Porowska and Wojda, 2017; Chen et al., 2023). The specific T cell antigens and the relevant functions of major T cell types including $CD4^+$ T helper(Th)1, Th17, Th2, and $CD8^+$ cytotoxic T cells, whose specific functions have been delineated in case of MS, remain less clear in AD. For example, Th1 cells were found to either exacerbate neuroinflammation or, conversely, had beneficial effects helping to clear amyloid plaques (Mietelska-Porowska and Wojda, 2017). Such contradictory results have been attributed to specific disease models used for research as well as various stages of a disease process at which corresponding roles of T cell were investigated. In contrast, most recent results obtained from a highly relevant AD tauopathy model have clearly implicated the role of pathogenic T cells and their specific effector cytokines in pthogensis of AD (Chen et al., 2023). These authors discovered relevant T cell adaptive immune responses, further supported by findings that T cells are present in the brain parenchyma from AD patients and that enrichment of T cells highly correlates with the severity of brain atrophy. Crucially, the inhibition of interferon-gamma, a major Th1 cytokine, significantly ameliorated brain atrophy. Further, a unique TCR clonal expansion of pathogenic T cells observed in this study is consistent with the underlying pathologies that may be shared with a similarly observed expansion of autoimmune T cells during MS (Cao et al., 2015; Hayashi et al., 2021; Chen et al., 2023). Further consistent with finding AD-associated neurodegenerative T cells in the CNS, such relevant T cells were also recently detected in peripheral blood from AD patients by the transcriptomic analysis that utilized a newly established Seqtometry platform based on direct profiling of gene expression (Kousnetsov et al., 2024). These results are also in agreement with the known paths of T cell circulation between CNS and the peripheral immune system (Kawakami et al., 2005; Raddassi et al., 2011; Jones and Hawiger, 2017; Absinta et al., 2021; Schnell et al., 2021; Lanz et al., 2022). Overall, the regulation of T cell functions appears as a critical objective for achieving successful immunotherapies in case of both AD and MS.

The indispensable roles of pT_{REGS} and conventional dendritic cells in immunoregulation

The T cell-driven neuroinflammation is susceptible to a control by $Foxp3^+$ regulatory $CD4^+$ T cells (T_{REGS}) (Jones and Hawiger, 2017). Accordingly, T_{REGS} have been established to play a pivotal role in protection and recovery from MS and its animal models by suppressing relevant autoreactive T cells (O'Connor and Anderton, 2008; Lowther and Hafler, 2012; Kleinewietfeld and Hafler, 2014). The functions of T_{REGS} in AD are still being elucidated and a depletion of T_{REGS} resulted in either blocking or promoting the AD disease process (Mietelska-Porowska and Wojda, 2017). A key recent study uncovered that increased numbers of T_{REGS} indeed correlated with the decreased disease severity, further establishing the beneficial roles of T_{REGS} in the AD process (Chen et al., 2023). In MS models, early pioneering studies showed that T cell receptor (TCR)-transgenic mice specific for myelin basic protein (MBP), a major neural antigen, succumbed to experimental autoimmune encephalitis (EAE), a mouse model of MS, when such animals were crossed onto a genetic background that precluded a development of T_{REGS} while allowing a development of autoreactive T cells (Lafaille et al., 1994). Consistently, a depletion of T_{REGS} *in vivo* by anti-CD25 antibody also exacerbated EAE (Kohm et al., 2006). Based on these early insights, therapies focused on functions of T_{REGS} have been proposed as an approach to block neuroinflammation (O'Connor and Anderton, 2008; Spence et al., 2015; Cheng et al., 2017).

Foxp3-expressing T_{REGS} are a heterogenous group of T cells that includes thymically derived (t)T_{REGS} developing in the thymus. Whereas functions of such tT_{REGS} are indispensable for the maintenance of immune homeostasis, they are not sufficient to prevent an initiation of specific autoimmune process such as in EAE. Instead, mechanisms blocking antigen-specific autoimmunity rely on other Foxp3-expressing T_{REGS} that are induced *de novo* outside the thymus from T cells in response to corresponding self-antigens (Iberg et al., 2017; Jones and Hawiger, 2017). By focusing on relevant antigens, such peripherally induced (p)T_{REGS} can efficiently limit harmful effector autoimmune responses (Kretschmer et al., 2005; Iberg et al., 2017). Therefore, a *de novo* induction of antigen-specific peripheral pT_{REGS} critically complements the functions of tT_{REGS}, and has a major role in shaping the immune homeostasis. Experimental results in animal disease models confirmed that induction and functions of pT_{REGS} were required for blocking neurologic symptoms in EAE despite the normal presence of thymically-derived tT_{REGS} (Jones et al., 2015, 2016; Jones and Hawiger, 2017). Similar findings were also extended to some other autoimmune disease models (Iberg and Hawiger, 2020a; Bourque and Hawiger, 2022a).

Given their importance, the induction of pT_{REGS} from naive T cells must be carefully regulated. A key role in this processes is performed by specialized cDCs that can present antigens in the tolerogenic context that depends on a specific molecular crosstalk between cDCs and T cells to skew the actively induced T cell differentiation toward pT_{REGS} instead of priming effector responses (Iberg and Hawiger, 2020a). Overall, the versatility of T cell differentiation depends on comprehensive characteristics of cDCs which represent a heterogenous group of cells including two major types 1 and 2 (cDC1 and cDC2) that differ in their specific development, phenotypes, and immune functions (Durai and Murphy, 2016; Murphy et al., 2016). Whereas all

cDCs excel at presentation of antigens to T cells, the CCR7^{+} migratory cDCs can deliver various peripherally-acquired antigens to lymph nodes (LNs) (Bourque and Hawiger, 2022a). Such cDCs also express immunoregulatory molecules including PD-L1, PD-L2, and CD200, and can promote relevant T cell tolerance in the case of multiple antigens (Leventhal et al., 2016; Maier et al., 2020). However, migratory cDCs also have key roles in the initiation of effector responses (Scheinecker et al., 2002; GeurtsvanKessel et al., 2008; Kim et al., 2010; Bajana et al., 2012; Krishnaswamy et al., 2018; Jenkins et al., 2021). In contrast, other types of cDCs present in lymphoid organs such as LNs and spleen, specialize in promoting induction of pT_{REGS} with anti-autoimmune roles (Iberg and Hawiger, 2020a; Bourque and Hawiger, 2022a). These pT_{REGS}-inducing cDC1s are characterized by high expression of immunomodulatory molecules B and T lymphocyte associated/attenuator (BTLA) and T-cell immunoglobulin mucin-3 (TIM-3) (Kim et al., 2020; Bourque and Hawiger, 2022a; Tang et al., 2022). The constitutive expression of these pro-tolerogenic immunomodulators, as part of the pre-determined developmental program, provides BTLA^{hi} cDC1s with inherent capabilities to facilitate induction of pT_{REGS} from T cells activated in response to various antigens presented by these cDC1s (Bourque and Hawiger, 2019, 2022a; Iberg and Hawiger, 2020a). Specifically, through interactions with herpesvirus entry mediator (HVEM) expressed in naive T cells, BTLA increase expression of CD5 in T cells (Jones et al., 2016; Bourque and Hawiger, 2019). This BTLA-HVEM-CD5 immunomodulatory axis facilitates the pT_{REGS} conversion from naive T cells by decreasing the sensitivity of T cells to various pro-inflammatory cytokines through limiting functions of mammalian target of rapamycin (mTOR) (Chen et al., 2003; Henderson et al., 2015; Jones et al., 2016; Bourque and Hawiger, 2019). Therefore, tolerogenic functions of BTLA^{hi} cDC1s also crucially rely on other mechanisms notably including the production and activation of transforming growth factor beta (TGF-β), well established as critically required for the *de novo* expression of *Foxp3* in developing pT_{REGS} (Chen et al., 2003; Bourque and Hawiger, 2018). Additional mechanisms such as those dependent on indoleamine 2,3-dioxygenase (IDO) and aryl hydrocarbon receptor (AHR) also can play important roles in these tolerogenic processes (Bourque and Hawiger, 2018). In the absence of specific tolerogenic functions of BTLA^{hi} cDC1s, the *de novo* induction of pT_{REGS} controlling specific autoimmune responses is compromised, as observed using either *Btla* genetic deletion or a treatment with anti-BTLA blocking antibodies in mouse models *in vivo* (Jones et al., 2016; Iberg et al., 2017, 2022). Nevertheless, while IDO may complement tolerogenic functions of BTLA^{hi} cDC1s, recent results have also shown IDO activation in some mature cDC1s with high CCR7 expression, and not corresponding to BTLA^{hi} cDC1s, that may promote the tolerogenic functionality in autoimmune models including non-obese diabetes (NOD) and EAE (Price et al., 2015; Tabansky et al., 2018; Gargaro et al., 2022).

The understanding of the tolerogenic roles of cDCs comes mostly from studies that focused on these functions among the cDCs present in the peripheral immune system, outside the CNS. However, because T cells trafficking to the CNS also recirculate to the peripheral immune system where they can be maintained and activated (Kawakami et al., 2005; Raddassi et al., 2011; Jones and Hawiger, 2017; Absinta et al., 2021; Schnell et al., 2021; Lanz et al., 2022), the tolerogenic mechanisms initiated in the periphery extend to the control of the pathogenic immune processes in the CNS (Jones et al., 2015; Jones and Hawiger, 2017). Therefore, not only are the molecular mechanisms underlying the tolerogenic roles of cDCs of acute research interest, but they could also become potential therapeutic targets.

Tolerogenic mechanisms under pro-inflammatory conditions

The *in vivo* targeted delivery of self-antigens to BTLA^{hi} cDC1 utilizing recombinant antibodies and other reagents binding to specific surface receptors on these cells represents a key pro-tolerogenic strategy (Iberg and Hawiger, 2019, 2020b; Bourque and Hawiger, 2021, 2022b). However, the full realization of such therapeutic potentials, especially for translationally relevant settings, still remains limited by the complexities of molecular mechanisms within the cDCs. Recent results have revealed that even under steady conditions (in the absence of specific, disease-associated pro-inflammatory signals), some cDCs induce CD4^{+} T cells with an increased potential for autoimmune differentiation (Opejin et al., 2020; Bourque and Hawiger, 2022a). In EAE models such "pre-effectors" can readily convert into encephalitogenic effector T cells resulting in a development of autoimmune disease. Therefore, a careful consideration is required when selecting specific targets and routes for antigen delivery to cDCs with intended pro-tolerogenic effects (Bourque and Hawiger, 2022a,b).

Recent findings also uncovered that tolerogenic BTLA^{hi} cDC1s are highly susceptible to pro-inflammatory conditions that result in ablation of these cells through an acute cell death mediated by TNF-α (Iberg et al., 2022; Bourque and Hawiger, 2023a). TNF-α is released by cDCs, T cells, and other types of immune cells upon their initial immune activation (Bourque and Hawiger, 2023b). TNF-α has been shown in numerous mouse models to be crucially involved in a propagation of the maturation (activation) of cDCs (Bardou et al., 2021; Cabeza-Cabrerizo et al., 2021). Consistently, TNF-α is involved in the pathogenesis of several autoimmune and pro-inflammatory disease in humans including AD and MS and also others such as Crohn's disease and arthritis (Chang et al., 2017; Jang et al., 2021). Significantly, the levels of TNF-α are increased in blood of patients with AD, and clinical and animal studies have demonstrated a link between excess TNF-α levels in the brain and AD development (Chang et al., 2017). At the same time, anti-TNF-α treatments have been only partially successful, and their lack of effectiveness, particularly in case of MS, can likely be attributed to complex signaling pathways that are initiated by TNF-α sensed by two different receptors, tumor necrosis factor receptor 1 (TNFR1) and TNFR2 (Bourque and Hawiger, 2023b). The expression patterns and functions of these receptors differ depending on the cell type. Both receptors can respond to TNF-α bound to a membrane but only TNFR1 can proficiently respond to TNF-α in its soluble form (Wajant and Siegmund, 2019). TNFR1 is expressed by nearly all cell types, whereas TNFR2 expression is restricted to regulatory T cells, myeloid cells, glial cells, certain endothelial cells, and is also induced by certain T and B cell subsets, epithelial cells, and fibroblasts (Wajant and Siegmund, 2019). Both receptors activate proinflammatory pathways such as the NF-κB (Wajant and Siegmund, 2019). TNFR1 induces necroptotic and apoptotic cell death through complex processes dependent on receptor-interacting serine/threonine-protein kinase 3 (RIPK3) and caspase 8, respectively (Wajant and Siegmund, 2019). These diverse mechanisms mediated by TNF-α underscore the pleiotropic outcomes of the sensing

of this cytokine by cDCs that interact with different types of effector and regulatory T cells. Recent results have elucidated that, among all cDCs, the highest expression of TNFR1 characterizes tolerogenic BTLA^{hi} cDC1s (Iberg et al., 2022). Therefore, under pro-inflammatory conditions the BTLA^{hi} cDC1s die rapidly in response to the released TNF-α whose copious amounts are also produced in the autocrine/paracrine fashion by these cells (Iberg et al., 2022). Although the ablation of BTLA^{hi} cDC1s is only transient, with the populations of cDCs returning to their homeostatic numbers within a week, the acute absence of these tolerogenic cDCs shifts a balance away from the induction of pT$_{REGS}$ (Iberg et al., 2022; Bourque and Hawiger, 2023b). Such conditions blocking pro-tolerogenic mechanisms can be instead more conducive to differentiation and function of potentially pathogenic effector T cells (Bourque and Hawiger, 2023b). Therefore, designs of new therapies focused on either induction or restoration/enhancement of tolerogenic mechanisms must also account for a loss of cDCs with tolerogenic functions occurring under conditions that underly various pro-inflammatory diseases.

Conclusions and future directions

It is becoming increasingly clear that specific immunoregulatory mechanisms can limit the disease process in MS, and possibly also in AD. Whereas it is still not possible to fully utilize such processes for translationally relevant clinical applications, recent insights into the tolerogenic mechanisms of dendritic cells as well as the impact of key pro-inflammatory mediators on these functions, could pave the way for designing effective strategies that could better counter pathologies underlying MS and AD. Further, new tools may facilitate a detection of neurodegenerative T cells in AD and MS patients for early diagnostic as well as monitoring therapeutic outcomes. Overall, the future advances will lead to designing targeted and antigen-specific immunotherapies to fully utilize the potential of regulatory T cell mechanisms.

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Conflict of interest

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