Immunology Letters 248 (2022) 26–30

Contents lists available at ScienceDirect

Immunology Letters

journal homepage: www.elsevier.com/locate/immlet

Invited Review

Brain-resident regulatory T cells and their role in health and disease

Adrian Liston [a,*], James Dooley [a], Lidia Yshii [b,c,*]

[a] Immunology Programme, The Babraham Institute, Babraham Research Campus, Cambridge, CB22 3AT United Kingdom
[b] KU Leuven, Department of Microbiology, Immunology and Transplantation, Leuven 3000, Belgium
[c] KU Leuven, Department of Neurosciences, Leuven 3000, Belgium

ARTICLE INFO

Keywords:
Brain
Regulatory T cells
Tregs
Neuroimmunology
Multiple sclerosis
Stroke
Alzheimer's disease

ABSTRACT

Regulatory T cells (Tregs) control inflammation and maintain immune homeostasis. The well-characterised circulatory population of $CD4^+Foxp3^+$ Tregs is effective at preventing autoimmunity and constraining the immune response, through direct and indirect restraint of conventional T cell activation. Recent advances in Treg cell biology have identified tissue-resident Tregs, with tissue-specific functions that contribute to the maintenance of tissue homeostasis and repair. A population of brain-resident Tregs, characterised as $CD69^+$, has recently been identified in the healthy brain of mice and humans, with rapid population expansion observed under a number of neuroinflammatory conditions. During neuroinflammation, brain-resident Tregs have been proposed to control astrogliosis through the production of amphiregulin, polarize microglia into neuroprotective states, and restrain inflammatory responses by releasing IL-10. While protective effects for Tregs have been demonstrated in a number of neuroinflammatory pathologies, a clear demarcation between the role of circulatory and brain-resident Tregs has been difficult to achieve. Here we review the state-of-the-art for brain-resident Treg population, and describe their potential utilization as a therapeutic target across different neuroinflammatory conditions.

1. Introduction

The maintenance of immune homeostasis is of vital importance in the prevention of autoimmunity and the restraint of excessive effector immune response and host tissue injury [1]. In organs where the loss of cells can be irreversible, such as the central nervous system (CNS), the need to prevent damaging immune responses is crucial. Among the myriad of immunoregulatory mechanisms are regulatory T cells (Tregs). Tregs are $CD4^+$ T cells characterised by the expression of the transcription factor Foxp3, critical for coordination of the regulatory transcriptional state, and the interleukin 2 (IL2) receptor α-chain (CD25), required for survival and homeostasis [2].Tregs are crucial for the development and maintenance of self-tolerance, capable of suppressing the responses of most innate and adaptive leukocyte cell types. Deletion of Treg cells in mice triggers severe inflammation and development of autoimmune diseases [3] with similar pathology occurring in patients with *FOXP3* mutation [4]. While the CNS is generally thought to be isolated from peripheral immunity, a reduction in the functionality or number of Treg is observed across common neuroinflammatory diseases [5], implicating Treg suppressive properties as inhibitory in the pathology of neuroinflammation.

1.1. Brain-resident Tregs

Most research on Tregs has focused on the population circulating through the blood and peripheral lymphoid organs. Despite this, there is growing evidence that key functions for Tregs take place in the tissues, with sizeable numbers of Tregs found across nearly all tissues assessed. These "tissue Tregs", resident in non-lymphoid tissues are thought to develop unique functions and phenotypes. Among the first examples of distinct tissue Treg populations present in non-lymphoid tissues was the discovery of visceral adipose tissue Tregs [6]. Following this, other tissue Tregs with unique phenotype with characteristics specialized for each tissue have been acknowledged, such as Tregs from skeletal muscle [7] and cardiac muscle [8], lungs [9], gut [10], skin [11], liver [12], and brain [13, 14]. While sharing Foxp3 expression and much of the core Treg transcriptome, unique markers and features have been ascribed to each of these populations (Table 1). After development and maturation in the thymus, Tregs migrate to non-lymphoid tissues. Skin Tregs, for example, accumulate during neonatal period and are is believed to be

* Corresponding authors.
E-mail addresses: adrian.liston@vib.be (A. Liston), lidia.yshii@kuleuven.be (L. Yshii).

https://doi.org/10.1016/j.imlet.2022.06.005
Received 2 March 2022; Received in revised form 3 June 2022; Accepted 9 June 2022
Available online 10 June 2022

originated from thymus. Here we aim to provide an overview of the function and phenotype of brain Tregs and assess the potential as a therapeutic target in neuroinflammatory conditions.

For decades, the CNS has been considered an immune-privileged tissue, because of its limited interactions with the systemic immune system under homeostatic conditions. Although it was classically thought that immune cells do not cross the healthy blood-brain barrier (BBB), a growing body of work identifies T cells present in the meninges, with effector cytokines influencing the development and function of the brain[15, 16]. A small resident population of T cells is also found in the parenchyma of healthy brain tissue in mice and humans [13, 17] (Fig. 1). While sparsely distributed across the brain, the total number of these parenchymal resident T cells is estimated to outnumber the concentrated population present in the meninges [17]. Within the brain-resident T cell population is a small fraction of Tregs, expressing canonical Treg markers (Table 1). These Tregs stay in the brain for a long time, establishing a resident Treg population[18], which express residency markers such as CD69. Analysis suggests the brain-resident Treg population is dynamic across the murine life-course, with first detection around the point of birth, and enrichment of the population occurring with both age and environmental stimulation [13]. Unlike the resident conventional T cell population, however, brain-resident Tregs are relatively refractory to numerical or phenotypic modulation by microbiota [13]. The kinetic of residency has been assessed through parabiotic studies, demonstrating that most entry of Tregs to the brain occurs in an activated state, with rapid conversion of a minority of infiltrating cells to the $CD69^{+}$ residential profile. While activated non-resident Tregs persist in the brain for hours to days, these resident cells can dwell for several weeks prior to apoptosis or de-differentiation and egress [13]. During this infiltrating period, brain-resident Tregs appear to be engaged with self-antigens within the brain and are primed for the expression of anti-inflammatory mediators such as amphiregulin and IL10, and neurotrophic factors, such as brain-derived neurotrophic factor (BDNF) [13–20]. The nature and identification of the self-antigens recognised by brain Tregs remain, however, unknown.Fig. 2.

1.2. Tregs in neuroinflammation

There is an extensive literature on proposed functions for Tregs in neuroinflammation. We consider here three conditions: multiple sclerosis (MS), an autoimmune neuroinflammatory disease, stroke, a neuroinflammatory injury, and Alzheimer's Disease, a neurodegenerative disease with neuroinflammatory components.

The protective capacity of Tregs in MS is supported through both patient data and mouse models. Environmental and genetic factors for susceptibility or heterogeneity can pinpoint crucial molecules. The critical role of Tregs in MS is additionally supported by the analysis of the genetic variants associated with the disease, where genome-wide association studies pinpointed associations with susceptibility of MS for the *IL2RA* and *IL7RA* loci, with both genes strongly implicated in function of Tregs [21]. Analysis of peripheral Tregs from MS patients identifies defects in their suppressive role, with lower expressions of FOXP3, CTLA4 and TGF [22, 23]. In MS therapy such as with Fingolimod, Tregs frequency are increased among circulating CD4 T cells [24, 25]. In MS mouse model experimental autoimmune encephalomyelitis (EAE), there is strong evidence that the associations identified in patients are causative: for example, the systemic depletion of Tregs led to worsening of clinical score [26]. In these models, Tregs are effective at quenching the autoreactive response of conventional T cells, reducing the strength of the autoreactive process [27–29]. Additional protective effects are also apparent, with compromised remyelination in Treg-deficient mice, and evidence that the adoptive transfer of Tregs promotes oligodendrocyte precursor cell maturation and rescues remyelination [30].

In the context of stroke, circulating Treg cell numbers and suppressive function were reduced in patients with stroke compared with controls [31, 32]. In the mouse model of stroke, it appears that the Treg response limits the extent of pathology following stroke [33]. Tregs accumulate in the brain at the chronic phase of ischemic brain injury, with an oligoclonal TCR expansion suggestive of self-antigen recognition within the brain [14]. Systemic depletion of Tregs in this model reduced white matter repair and functional recovery after stroke [33, 34], demonstrating the protective nature of this population. Brain Tregs from the stroke mouse model expresses high levels of Amphiregulin (Areg) and Osteopontin [14, 35]. Areg is proposed to suppress IL6 production from microglia and astrocytes, limiting inflammation [14], while Osteopontin enhances microglia-mediated repair. The transfer of Tregs also suppressed astrocytes activation and STAT3 phosphorylation [35]. Together, these findings suggest that brain Tregs can play a protective role during stroke, via multiple mediators.

Impairment of the suppressive function associated with Tregs has been correlated with the severity of neurodegenerative diseases, such as Alzheimer's Disease [36]. The number of circulating Tregs in Alzheimer's Disease patients declines compared to matched controls, suggesting that their dysregulation in the periphery reduces their suppressive capacity [37]. Moreover, the immunosuppressive functions of Tregs in AD patients are reduced [38]. The role of Tregs in Alzheimer's Disease is, however, controversial, with different studies suggesting either a protective role of Tregs [39], or Tregs being deleterious [40–42]. Low doses of systemic IL2 increased the number of Tregs in the peripheral blood, leading to amelioration of cognitive ability of Alzheimer's Disease mouse model [43]. Taken together, these results suggest that Tregs play a role in neuroinflammation in AD, although most studies using a methodology that does not allow for discrimination of the peripheral and brain Tregs.

1.3. Unraveling the functions of circulating versus brain-resident Tregs

Despite the formal demonstration of a neuroprotective function for Tregs during neuroinflammation, complete with attractive mechanistic pathways, the role of circulating versus brain-resident Tregs remains largely untested. Patient-based data on Tregs is almost entirely based on samples from the peripheral blood, which are then extrapolated out to the brain-resident population. A key limitation spanning most of the mouse model work is that strategies for formal testing of Treg function relies on a systemic approach, which impacts both the circulating and brain-resident populations. For example, Treg depletion systems typically rely on anti-CD25 antibody injection or diphtheria toxin injection into $Foxp3^{DTR}$ mice, where both the circulating and brain-resident populations will be removed [14–44]. Thus, while the functional

Table 1
Molecular signature of brain-resident Tregs compared to key peripheral tissue counterparts.

	Transcription factors	Chemokines & receptors	Cytokines & receptors	Characteristic markers
Visceral adipose tissue	Foxp3, Pparg, Rora, Gata3	Cxcl2, Cxcr6, Ccr1, Ccr2	IL10, IL5, IL1rl1, IL9r	PD1, CTLA4, CD80, lipid metabolism molecules (Dgat1, Gdat2, CD36)
Skeletal muscle	Foxp3, Rora	Ccr1,Ccr2	IL10, AREG, ST2	CTLA4, CD103, KLRG1, Tim3, PDGF, Neb, Nebl
Skin	Foxp3, Batf, Irf4, Gata3, Maf, Blimp1, Rora	Ccr2, Ccr6, Ccr8, Ccr10, Cxcr4, Cxcr6	IL10, ST2, AREG, Granzyme B	KLRG1, CTLA4, CD127, Jagged1, PENK
Brain	Foxp3, Blimp1	Ccr6, Ccr8	AREG, ST2, IL10	CD69, PD1, KLRG1, 5-HT7, CD103, Neuropeptide Y, Osteopontin

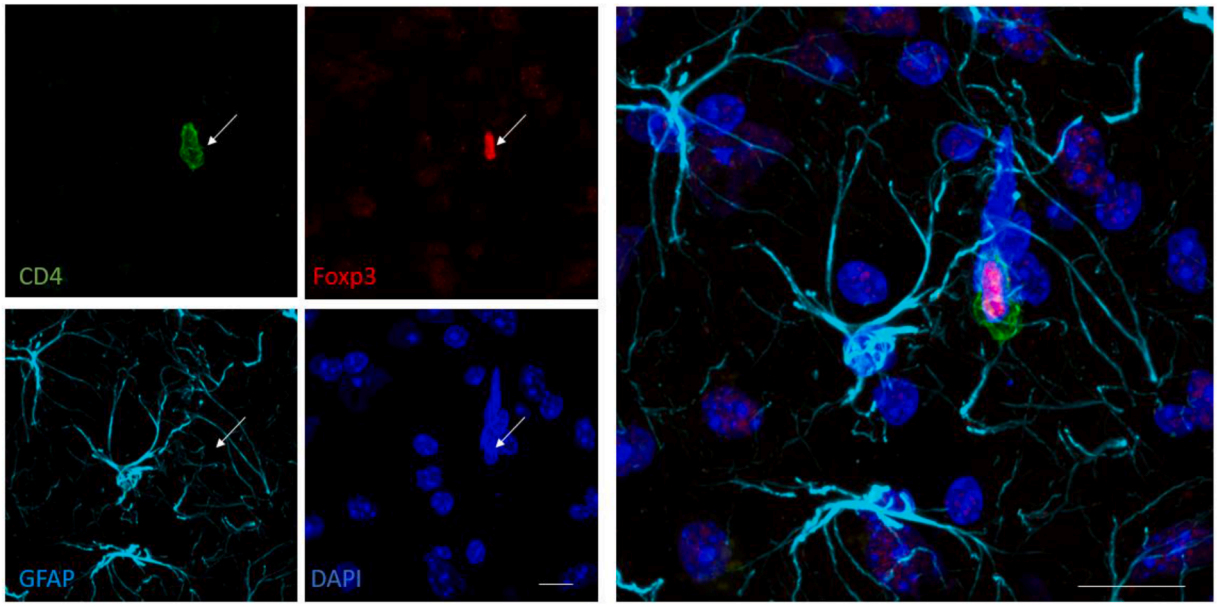

Fig. 1. Confocal imaging of brain Tregs. Healthy perfused mouse brains from wildtype mice were imaged for brain-resident Tregs by immunofluorescent confocal imaging. CD4 (green), Foxp3 (red), GFAP (astrocytes, cyan) and DAPI (blue). Single and combined channel representative image of a Treg in the parenchyma of the mid-brain. Scale bar, 50 μm. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

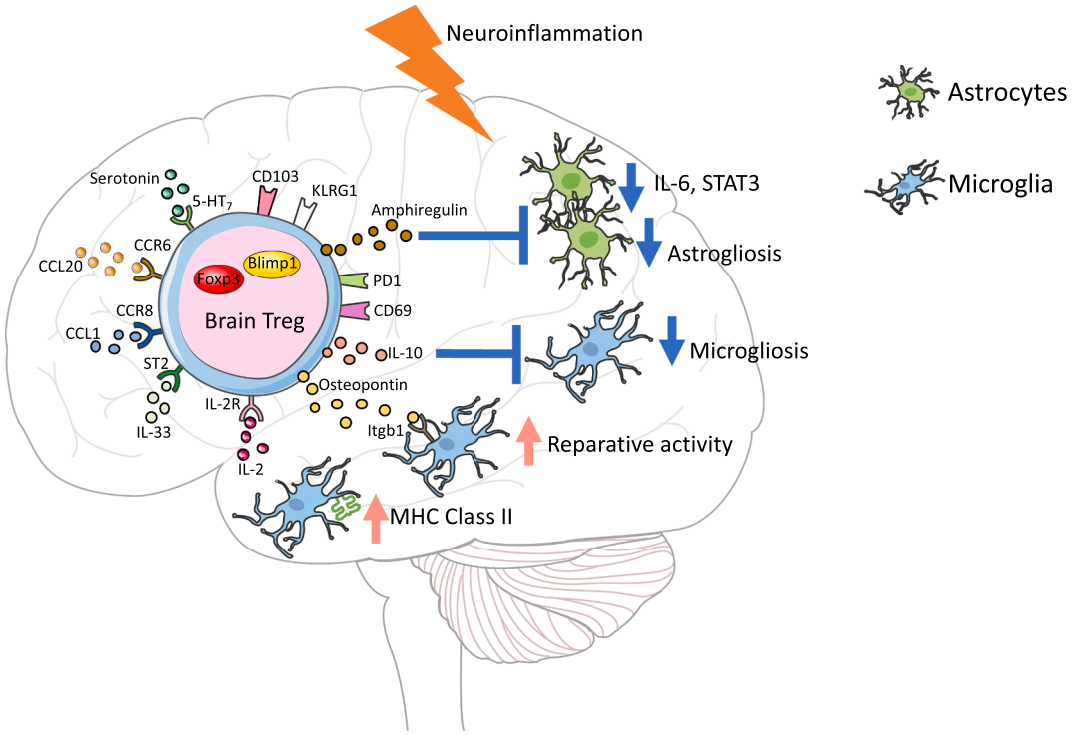

Fig. 2. Proposed functions for brain Tregs during neuroinflammation. Left, Key phenotypic markers and proposed regulatory mediators for brain-resident Tregs. Right, proposed mechanistic pathways initiated by neuroinflammation, including inhibition of astrogliosis and microgliosis, with potential mediators.

effects observed may be attributed to brain-resident Tregs, they can equally be driven by the well-characterised role of the peripheral Treg compartment in controlling systemic inflammation. With known links between systemic inflammation and the outcomes of neuroinflammation [45–48], a peripheral-based effect of Tregs is highly plausible.

One strategy for distinguishing between the peripheral and CNS-based functions of Tregs during neuroinflammation is through selective expansion of the brain-resident population. Brain-resident Tregs have been shown to be responsive to serotonin, through serotonin receptor 7, and IL33, through ST2 [14, 49], with effects on Treg proliferation. A key limitation of the population size, however, appears to be the very low levels of IL2 present in the brain [50]. IL2 is a key driver in Treg homeostasis and function [51, 52]. While abundantly expressing the interleukin 2 receptor α-chain (IL-2Rα; CD25), Tregs are poor producers of the cytokine, making them reliant on external sources [53]. Provision of exogenous IL2 is a well-validated approach to in vivo functional testing of Treg capacity, and has been used in neuroinflammatory settings such as stroke [35], EAE [54] and Alzheimer's

Disease [39]. While these approaches expand both the peripheral and brain-resident population, we recently developed a gene-delivery system allowing supplemental IL2 production to be limited to the CNS [50]. This system drives the brain-restricted expansion of Treg number, without impacting the peripheral circulating population, thereby allowing discrimination of effects mediated by the two populations. Expanded brain-resident Tregs maintained high expression of Areg and were associated with a regulatory polarization of microglia, including upregulation of Osteopontin [55]. Mice with expanded brain-resident Tregs were protected against models of MS, stroke and traumatic brain injury [50]. In neurodegenerative models, by contrast, effects are more limited, with a moderate protective effect in Amyotrophic lateral sclerosis [56] and no effect in Alzheimer's Disease [57]. Surprisingly, improvement was even observed following treatment of aged mice in normal age-related cognitive decline [58]. These results validate the brain-resident Treg population as neuroprotective across a range of neuroinflammatory pathologies.

1.4. Future perspectives

Brain-resident Tregs constitute a high potential target for neuroinflammatory pathologies. Despite the paucity of studies distinguishing between the effects of brain-resident and peripheral Tregs, there is promising data suggesting that the brain-resident population may be effective at preventing and reversing the pathological consequences of neuroinflammation. Strategies to enrich this population, either directly through cell therapy or indirectly through biologics or gene therapy, have the potential to mitigate CNS inflammation while preserving the capacity of the peripheral immune system to combat infections. AAV-based systems with safe profiles are being approved (i.e. Zongensma-Zolgensma), and gene delivery systems, such as the ones using a Tet-On system to deliver IL2 in the brain [50] have high translational potential.

Due to the frequently immunocompromised state of neuroinflammatory patients, brain-resident Tregs have a higher potential safety profile since the expansion of Tregs will be restricted to the brain not affecting the peripheral immune system, as IL2 and Treg therapies move towards clinical trials in the neuroinflammatory space.

Acknowledgements

The work was supported by the Biotechnology and Biological Sciences Research Council through Institute Strategic Program Grant funding BBS/E/B/000C0427 and BBS/E/B/000C0428, and the Biotechnology and Biological Sciences Research Council Core Capability Grant to the Babraham Institute. The authors are inventors on patents for therapeutic manipulation of brain-resident Tregs and potential financial beneficiaries of future commercialization.

References

[1] A. Liston, D.H. Gray, Homeostatic control of regulatory T cell diversity, Nat. Rev. Immunol. 14 (3) (2014) 154–165.
[2] S. Hori, T. Nomura, S. Sakaguchi, Control of regulatory T cell development by the transcription factor Foxp3, Science 299 (5609) (2003) 1057–1061.
[3] J.M. Kim, J.P. Rasmussen, A.Y. Rudensky, Regulatory T cells prevent catastrophic autoimmunity throughout the lifespan of mice, Nat. Immunol. 8 (2) (2007) 191–197.
[4] C.L. Bennett, J. Christie, F. Ramsdell, M.E. Brunkow, P.J. Ferguson, L. Whitesell, T. E. Kelly, F.T. Saulsbury, P.F. Chance, H.D. Ochs, The immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome (IPEX) is caused by mutations of FOXP3, Nat. Genet. 27 (1) (2001) 20–21.
[5] M. DuPage, J.A. Bluestone, Harnessing the plasticity of CD4(+) T cells to treat immune-mediated disease, Nat. Rev. Immunol. 16 (3) (2016) 149–163.
[6] M. Feuerer, L. Herrero, D. Cipolletta, A. Naaz, J. Wong, A. Nayer, J. Lee, A. B. Goldfine, C. Benoist, S. Shoelson, D. Mathis, Lean, but not obese, fat is enriched for a unique population of regulatory T cells that affect metabolic parameters, Nat. Med. 15 (8) (2009) 930–939.
[7] D. Burzyn, W. Kuswanto, D. Kolodin, J.L. Shadrach, M. Cerletti, Y. Jang, E. Sefik, T. G. Tan, A.J. Wagers, C. Benoist, D. Mathis, A special population of regulatory T cells potentiates muscle repair, Cell 155 (6) (2013) 1282–1295.
[8] A. Saxena, M. Dobaczewski, V. Rai, Z. Haque, W. Chen, N. Li, N.G. Frangogiannis, Regulatory T cells are recruited in the infarcted mouse myocardium and may modulate fibroblast phenotype and function, Am. J. Physiol. Heart Circ. Physiol. 307 (8) (2014) H1233–H1242.
[9] N. Arpaia, J.A. Green, B. Moltedo, A. Arvey, S. Hemmers, S. Yuan, P.M. Treuting, A. Y. Rudensky, A distinct function of regulatory T cells in tissue protection, Cell 162 (5) (2015) 1078–1089.
[10] C. Schiering, T. Krausgruber, A. Chomka, A. Frohlich, K. Adelmann, E.A. Wohlfert, J. Pott, T. Griseri, J. Bollrath, A.N. Hegazy, O.J. Harrison, B.M.J. Owens, M. Lohning, Y. Belkaid, P.G. Fallon, F. Powrie, The alarmin IL-33 promotes regulatory T-cell function in the intestine, Nature 513 (7519) (2014) 564–568.
[11] M.D. Rosenblum, I.K. Gratz, J.S. Paw, K. Lee, A. Marshak-Rothstein, A.K. Abbas, Response to self antigen imprints regulatory memory in tissues, Nature 480 (7378) (2011) 538–542.
[12] M. Delacher, C.D. Imbusch, D. Weichenhan, A. Breiling, A. Hotz-Wagenblatt, U. Trager, A.C. Hofer, D. Kagebein, Q. Wang, F. Frauhammer, J.P. Mallm, K. Bauer, C. Herrmann, P.A. Lang, B. Brors, C. Plass, M. Feuerer, Genome-wide DNA-methylation landscape defines specialization of regulatory T cells in tissues, Nat. Immunol. 18 (10) (2017) 1160–1172.
[13] E. Pasciuto, O.T. Burton, C.P. Roca, V. Lagou, W.D. Rajan, T. Theys, R. Mancuso, R. Y. Tito, L. Kouser, Z. Callaerts-Vegh, A.G. de la Fuente, T. Prezzemolo, L.G. Mascali, A. Brajic, C.E. Whyte, L. Yshii, A. Martinez-Muriana, M. Naughton, A. Young, A. Moudra, P. Lemaitre, S. Poovathingal, J. Raes, B. De Strooper, D.C. Fitzgerald, J. Dooley, A. Liston, Microglia require CD4 T cells to complete the fetal-to-adult transition, Cell 182 (3) (2020) 625–640, e24.
[14] M. Ito, K. Komai, S. Mise-Omata, M. Iizuka-Koga, Y. Noguchi, T. Kondo, R. Sakai, K. Matsuo, T. Nakayama, O. Yoshie, H. Nakatsukasa, S. Chikuma, T. Shichita, A. Yoshimura, Brain regulatory T cells suppress astrogliosis and potentiate neurological recovery, Nature 565 (7738) (2019) 246–250.
[15] N.C. Derecki, A.N. Cardani, C.H. Yang, K.M. Quinnies, A. Crihfield, K.R. Lynch, J. Kipnis, Regulation of learning and memory by meningeal immunity: a key role for IL-4, J. Exp. Med. 207 (5) (2010) 1067–1080.
[16] A.J. Filiano, Y. Xu, N.J. Tustison, R.L. Marsh, W. Baker, I. Smirnov, C.C. Overall, S. P. Gadani, S.D. Turner, Z. Weng, S.N. Peerzade, H. Chen, K.S. Lee, M.M. Scott, M. P. Beenhakker, V. Litvak, J. Kipnis, Unexpected role of interferon-gamma in regulating neuronal connectivity and social behaviour, Nature 535 (7612) (2016) 425–429.
[17] B. Korin, T.L. Ben-Shaanan, M. Schiller, T. Dubovik, H. Azulay-Debby, N. T. Boshnak, T. Koren, A. Rolls, High-dimensional, single-cell characterization of the brain's immune compartment, Nat. Neurosci. 20 (9) (2017) 1300–1309.
[18] T. Korn, J. Reddy, W. Gao, E. Bettelli, A. Awasthi, T.R. Petersen, B.T. Backstrom, R. A. Sobel, K.W. Wucherpfennig, T.B. Strom, M. Oukka, V.K. Kuchroo, Myelin-specific regulatory T cells accumulate in the CNS but fail to control autoimmune inflammation, Nat. Med. 13 (4) (2007) 423–431.
[19] M. Kerschensteiner, E. Gallmeier, L. Behrens, V.V. Leal, T. Misgeld, W.E. Klinkert, R. Kolbeck, E. Hoppe, R.L. Oropeza-Wekerle, I. Bartke, C. Stadelmann, H. Lassmann, H. Wekerle, R. Hohlfeld, Activated human T cells, B cells, and monocytes produce brain-derived neurotrophic factor in vitro and in inflammatory brain lesions: a neuroprotective role of inflammation? J. Exp. Med. 189 (5) (1999) 865–870.
[20] L. Xie, G.R. Choudhury, A. Winters, S.H. Yang, K. Jin, Cerebral regulatory T cells restrain microglia/macrophage-mediated inflammatory responses via IL-10, Eur. J. Immunol. 45 (1) (2015) 180–191.
[21] C. International Multiple Sclerosis Genetics, D.A. Hafler, A. Compston, S. Sawcer, E.S. Lander, M.J. Daly, P.L. De Jager, P.I. de Bakker, S.B. Gabriel, D.B. Mirel, A. J. Ivinson, M.A. Pericak-Vance, S.G. Gregory, J.D. Rioux, J.L. McCauley, J. L. Haines, L.F. Barcellos, B. Cree, J.R. Oksenberg, S.L. Hauser, Risk alleles for multiple sclerosis identified by a genomewide study, N. Engl. J. Med. 357 (9) (2007) 851–862.
[22] K. Venken, N. Hellings, M. Thewissen, V. Somers, K. Hensen, J.L. Rummens, R. Medaer, R. Hupperts, P. Stinissen, Compromised CD4+ CD25(high) regulatory T-cell function in patients with relapsing-remitting multiple sclerosis is correlated with a reduced frequency of FOXP3-positive cells and reduced FOXP3 expression at the single-cell level, Immunology 123 (1) (2008) 79–89.
[23] M. Dominguez-Villar, C.M. Baecher-Allan, D.A. Hafler, Identification of T helper type 1-like, Foxp3+ regulatory T cells in human autoimmune disease, Nat. Med. 17 (6) (2011) 673–675.
[24] J. Haas, A. Schwarz, M. Korporal-Kunke, S. Jarius, H. Wiendl, B.C. Kieseier, B. Wildemann, Fingolimod does not impair T-cell release from the thymus and beneficially affects Treg function in patients with multiple sclerosis, Mult. Scler. 21 (12) (2015) 1521–1532.
[25] M. Ghadiri, A. Rezk, R. Li, A. Evans, P.S. Giacomini, M.H. Barnett, J. Antel, A. Bar-Or, Pre-treatment T-cell subsets associate with fingolimod treatment responsiveness in multiple sclerosis, Sci. Rep. 10 (1) (2020) 356.
[26] A.J. Bieber, S. Kerr, M. Rodriguez, Efficient central nervous system remyelination requires T cells, Ann. Neurol 53 (5) (2003) 680–684.
[27] Y. Liu, I. Teige, B. Birnir, S. Issazadeh-Navikas, Neuron-mediated generation of regulatory T cells from encephalitogenic T cells suppresses EAE, Nat. Med. 12 (5) (2006) 518–525.
[28] T. Matsushita, M. Horikawa, Y. Iwata, T.F. Tedder, Regulatory B cells (B10 cells) and regulatory T cells have independent roles in controlling experimental autoimmune encephalomyelitis initiation and late-phase immunopathogenesis, J. Immunol. 185 (4) (2010) 2240–2252.
[29] A.P. Kohm, P.A. Carpentier, H.A. Anger, S.D. Miller, Cutting edge: CD4+CD25+ regulatory T cells suppress antigen-specific autoreactive immune responses and

central nervous system inflammation during active experimental autoimmune encephalomyelitis, J. Immunol. 169 (9) (2002) 4712–4716.
[30] Y. Dombrowski, T. O'Hagan, M. Dittmer, R. Penalva, S.R. Mayoral, P. Bankhead, S. Fleville, G. Eleftheriadis, C. Zhao, M. Naughton, R. Hassan, J. Moffat, J. Falconer, A. Boyd, P. Hamilton, I.V. Allen, A. Kissenpfennig, P.N. Moynagh, E. Evergren, B. Perbal, A.C. Williams, R.J. Ingram, J.R. Chan, R.J.M. Franklin, D. C. Fitzgerald, Regulatory T cells promote myelin regeneration in the central nervous system, Nat. Neurosci. 20 (5) (2017) 674–680.
[31] Q. Li, Y. Wang, F. Yu, Y.M. Wang, C. Zhang, C. Hu, Z. Wu, X. Xu, S. Hu, Peripheral Th17/Treg imbalance in patients with atherosclerotic cerebral infarction, Int. J. Clin. Exp. Pathol. 6 (6) (2013) 1015–1027.
[32] X. Meng, J. Yang, M. Dong, K. Zhang, E. Tu, Q. Gao, W. Chen, C. Zhang, Y. Zhang, Regulatory T cells in cardiovascular diseases, Nat. Rev. Cardiol. 13 (3) (2016) 167–179.
[33] A. Liesz, E. Suri-Payer, C. Veltkamp, H. Doerr, C. Sommer, S. Rivest, T. Giese, R. Veltkamp, Regulatory T cells are key cerebroprotective immunomodulators in acute experimental stroke, Nat. Med. 15 (2) (2009) 192–199.
[34] K.A. Zera, M.S. Buckwalter, T cells direct microglial repair of white matter after stroke, Trends Neurosci. 44 (10) (2021) 769–770.
[35] L. Shi, Z. Sun, W. Su, F. Xu, D. Xie, Q. Zhang, X. Dai, K. Iyer, T.K. Hitchens, L. M. Foley, S. Li, D.B. Stolz, K. Chen, Y. Ding, A.W. Thomson, R.K. Leak, J. Chen, X. Hu, Treg cell-derived osteopontin promotes microglia-mediated white matter repair after ischemic stroke, Immunity 54 (7) (2021) 1527–1542, e8.
[36] F. He, R. Balling, The role of regulatory T cells in neurodegenerative diseases, Wiley Interdiscip. Rev. Syst. Biol. Med. 5 (2) (2013) 153–180.
[37] F. Ciccocioppo, P. Lanuti, L. Pierdomenico, P. Simeone, G. Bologna, E. Ercolino, F. Buttari, R. Fantozzi, A. Thomas, M. Onofrj, D. Centonze, S. Miscia, M. Marchisio, The characterization of regulatory T-cell profiles in Alzheimer's disease and multiple sclerosis, Sci. Rep. 9 (1) (2019) 8788.
[38] D. Rosenkranz, S. Weyer, E. Tolosa, A. Gaenslen, D. Berg, T. Leyhe, T. Gasser, L. Stoltze, Higher frequency of regulatory T cells in the elderly and increased suppressive activity in neurodegeneration, J. Neuroimmunol. 188 (1–2) (2007) 117–127.
[39] S. Alves, G. Churlaud, M. Audrain, K. Michaelsen-Preusse, R. Fol, B. Souchet, J. Braudeau, M. Korte, D. Klatzmann, N. Cartier, Interleukin-2 improves amyloid pathology, synaptic failure and memory in Alzheimer's disease mice, Brain 140 (3) (2017) 826–842.
[40] K. Baruch, N. Rosenzweig, A. Kertser, A. Deczkowska, A.M. Sharif, A. Spinrad, A. Tsitsou-Kampeli, A. Sarel, L. Cahalon, M. Schwartz, Breaking immune tolerance by targeting Foxp3(+) regulatory T cells mitigates Alzheimer's disease pathology, Nat Commun. 6 (2015) 7967.
[41] Y. Yang, Z. He, Z. Xing, Z. Zuo, L. Yuan, Y. Wu, M. Jiang, F. Qi, Z. Yao, Influenza vaccination in early Alzheimer's disease rescues amyloidosis and ameliorates cognitive deficits in APP/PS1 mice by inhibiting regulatory T cells, J. Neuroinflammation 17 (1) (2020) 65.
[42] H. Baek, M. Ye, G.H. Kang, C. Lee, G. Lee, D.B. Choi, J. Jung, H. Kim, S. Lee, J. S. Kim, H.J. Lee, I. Shim, J.H. Lee, H. Bae, Neuroprotective effects of CD4+CD25+ Foxp3+ regulatory T cells in a 3xTg-AD Alzheimer's disease model, Oncotarget 7 (43) (2016) 69347–69357.
[43] C. Dansokho, D. Ait Ahmed, S. Aid, C. Toly-Ndour, T. Chaigneau, V. Calle, N. Cagnard, M. Holzenberger, E. Piaggio, P. Aucouturier, G. Dorothee, Regulatory T cells delay disease progression in Alzheimer-like pathology, Brain 139 (Pt 4) (2016) 1237–1251.
[44] C. Raposo, N. Graubardt, M. Cohen, C. Eitan, A. London, T. Berkutzki, M. Schwartz, CNS repair requires both effector and regulatory T cells with distinct temporal and spatial profiles, J. Neurosci. 34 (31) (2014) 10141–10155.
[45] J. Xie, L. Van Hoecke, R.E. Vandenbroucke, The impact of systemic inflammation on Alzheimer's disease pathology, Front. Immunol. 12 (2021), 796867.
[46] D. Tejera, D. Mercan, J.M. Sanchez-Caro, M. Hanan, D. Greenberg, H. Soreq, E. Latz, D. Golenbock, M.T. Heneka, Systemic inflammation impairs microglial Abeta clearance through NLRP3 inflammasome, EMBO J 38 (17) (2019), e101064.
[47] M. Kleinewietfeld, D.A. Hafler, Regulatory T cells in autoimmune neuroinflammation, Immunol. Rev. 259 (1) (2014) 231–244.
[48] D.W. Simon, M.J. McGeachy, H. Bayir, R.S. Clark, D.J. Loane, P.M. Kochanek, The far-reaching scope of neuroinflammation after traumatic brain injury, Nat. Rev. Neurol. 13 (3) (2017) 171–191.
[49] M. Klein, T. Bopp, Cyclic AMP represents a crucial component of Treg cell-mediated immune regulation, Front. Immunol. 7 (2016) 315.
[50] L. Yshii, E. Pasciuto, P. Bielefeld, L. Mascali, P. Lemaitre, M. Marino, J. Dooley, L. Kouser, S. Verschoren, V. Lagou, H. Kemps, P. Gervois, A. de Boer, O.T. Burton, J. Wahis, J. Verhaert, S.H.K. Tareen, C.P. Roca, K. Singh, C.E. Whyte, A. Kerstens, Z. Callaerts-Vegh, S. Poovathingal, T. Prezzemolo, K. Wierda, A. Dashwood, J. Xie, E. Van Wonterghem, E. Creemers, M. Aloulou, W. Gsell, O. Abiega, S. Munck, R. E. Vandenbroucke, A. Bronckaers, R. Lemmens, B. De Strooper, L. Van Den Bosch, U. Himmelreich, C.P. Fitzsimons, M.G. Holt, A. Liston, Astrocyte-targeted gene delivery of interleukin 2 specifically increases brain-resident regulatory T cell numbers and protects against pathological neuroinflammation, Nat. Immunol. (2022).
[51] J. Collison, Low-dose IL-2 therapy for autoimmune diseases, Nat. Rev. Rheumatol. 15 (1) (2019) 2.
[52] E. Pierson, S.B. Simmons, L. Castelli, J.M. Goverman, Mechanisms regulating regional localization of inflammation during CNS autoimmunity, Immunol. Rev. 248 (1) (2012) 205–215.
[53] C.E. Whyte, K. Singh, O.T. Burton, M. Aloulou, A. Moudra, C.P. Roca, F. Naranjo, F. Lombard-Vadnais, T. Hochepied, T. Halim, S. Schlenner, S. Lesage, J. Dooley, A. Liston, Context-dependent effects of IL-2 rewire immunity into distinct cellular circuits, BioRxiv (2021).
[54] K.E. Webster, S. Walters, R.E. Kohler, T. Mrkvan, O. Boyman, C.D. Surh, S.T. Grey, J. Sprent, In vivo expansion of T reg cells with IL-2-mAb complexes: induction of resistance to EAE and long-term acceptance of islet allografts without immunosuppression, J. Exp. Med. 206 (4) (2009) 751–760.
[55] L. Yshii, E. Pasciuto, P. Bielefeld, L.G. Mascali, P. Lemaitre, M. Marino, J. Dooley, L. Kouser, S. Verschoren, V. Lagou, H. Kemps, S. Tareem, C.P. Roca, S. Poovathingal, T. Prezzemolo, K. Wierda, A. Dashwood, J. Xie, E. Van Wonterghem, E. Creemers, M. Aloulou, W. Gsell, O. Abiega, S. Munck, R. Vandenbroucke, A. Bronckaers, R. Lemmens, B. De Strooper, L. Van Den Bosch, U. Himmelreich, C. Fitzsimons, M.G. Holt, A. Liston, Astrocyte-targeted gene delivery of interleukin 2 specifically increases brain-resident regulatory T cell numbers and protects against pathological neuroinflammation Nat, Immunol. (2022).
[56] E. Pasciuto, L. Yshii, K. Staats, J. Dooley, L. Van Den Bosch, M.G. Holt, A. Liston, Astrocyte-mediated IL2 gene delivery moderately increases survival in SOD1-G93A mice, BioRxiv (2022).
[57] L. Yshii, L.G. Mascali, L. Kouser, P. Lemaitre, M. Marino, J. Dooley, O. Burton, J. Haughton, Z. Callaerts-Vegh, B. De Strooper, M.G. Holt, E. Pasciuto, A. Liston, The AppNLFG mouse model of Alzheimer's disease is refractory to regulatory T cell treatment, BioRxiv (2022).
[58] P. Lemaitre, S. Tareem, E. Pasciuto, L.G. Mascali, A. Martirosyan, Z. Callaerts-Vegh, J. Dooley, M.G. Holt, L. Yshii, A. Liston, Molecular and cognitive signatures of ageing partially restored through synthetic delivery of IL2 to the brain, BioRxiv (2022).