DOI: 10.1002/eji.202470200

European Journal of Immunology Clinical-Basic-Translational

736 – P3.01.18

IL-34 empowers regulatory T cells with novel non-canonical function to safeguard brain barrier integrity in neuroinflammation.

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Purpose: In the pursuit of strategies to address brain damage, brain-associated regulatory T cells (Tregs) have garnered increasing attention in recent years. Beyond their established role in immunoregulation, Tregs have emerged as significant contributors in the response to brain trauma and the restoration of damaged brain tissue in neuroinflammatory diseases. Here, we report a previously undescribed, non-canonical function of Tregs in preserving the integrity of both the blood-brain barrier (BBB) and the blood-cerebrospinal fluid (CSF) barrier (BCSFB).
Methods: Using fluorescently labeled dextrans, BBB and BCSFB integrity was assessed in *in vivo* and *in vitro* settings. Furthermore, using flow cytometry, investigations into disturbances in IL-34 expression in Tregs were conducted on samples from people with multiple sclerosis (MS), Alzheimer's disease (AD), and mild cognitive impairment (MCI). In addition, the therapeutic potential of IL-34 in the experimental autoimmune encephalomyelitis (EAE) and amyloid-β precursor protein (APP) mouse model was explored.
Results: Our results have established that Tregs are crucial for the maintenance of BBB and BCSFB integrity *in vivo*. Additionally, we have identified the cytokine IL-34 as a pivotal factor in this newfound role of Tregs. Mechanistically, IL-34 influences the expression and localization of the tight junction protein ZO-1 in BBB endothelial cells and choroid plexus epithelial cells, reinforcing the integrity of the brain barriers.
Considering the established phenomenon of compromised brain barriers and the involvement of immunological elements in neurological conditions, we observed reduced IL-34 expression in Tregs derived from MS, AD, and MCI patients. Furthermore, our study unveils the potential of IL-34 therapy in restoring the integrity of brain barriers in MS and AD animal models.
Conclusion: These discoveries illuminate the intricate interplay between Tregs, IL-34, and the maintenance of brain barrier integrity, opening up novel avenues for therapeutic interventions aimed at alleviating brain barrier dysfunction in the context of neuroinflammatory disorders.

Contributed support: Research Foundation-Flanders (FWO), Hasselt University, Ghent Univeristy, China Scholarship Council (CSC), Stichting voor Alzheimer onderzoek (SAO), Charcot Foundation, Stichting MS Research, VLAIO.

