Ex vivo Expanded Human Regulatory T Cells Modify Neuroinflammation in a Preclinical Model of Alzheimer’s disease

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Abstract

Background: Regulatory T cells (Tregs) play a neuroprotective role by suppressing microglia and macrophage-mediated inflammation and modulating adaptive immune reactions. We previously documented that Treg immunomodulatory mechanisms are compromised in Alzheimer’s disease (AD). Ex vivo expansion of Tregs restores and amplifies their immunosuppressive functions in vitro. A key question is whether adoptive transfer of ex vivo expanded human Treg can suppress neuroinflammation and amyloid pathology in a preclinical mouse model.

Method: An immunodeficient mouse model of AD was generated by backcrossing the 5xFAD onto Rag2 knockout mice (5xFAD-Rag2KO). Human Tregs were expanded ex vivo for 24 days and administered to 5xFAD-Rag2KO. Changes in amyloid burden and microglia characteristics were evaluated using ELISA and confocal microscopy. NanoString Mouse AD multiplex gene expression analysis was applied to explore the impact of ex vivo expanded Tregs on the neuroinflammation transcriptome.

Result: Elimination of adaptive immune system in 5xFAD-Rag2KO mice was associated with upregulation of 95 inflammation genes, amplified number of reactive microglia and increased plaque size. Following peripheral administration, ex vivo expanded human Tregs crossed blood-brain barrier of 5xFAD-Rag2KO and reduced amyloid burden and reactive microglia. Interrogation of inflammation gene expression documented down-regulation of pro-inflammatory cytokines (IL1A&B, IL6, Tnfa, IFNγ), complement cascade (C1qa, C1qb, C1qc, C4a/b), toll-like receptors (Tlr3, Tlr4 and Tlr7) and microglial activations markers (CD14, Tyrobp,Trem2).

Conclusion: Ex vivo expanded human Tregs, with amplified immunomodulatory function, suppressed neuroinflammation and alleviated AD pathology in vivo. Our results provide preclinical evidences for Treg cell therapy as a potential treatment strategy in AD.