Regulating the regulators: the negative fine-tuning of Regulatory B cells by SLAMF5

Radomir Lihi*[1], Perpinial Michal[1], Schottlander Nofar[1], Wiener Anna[1], Lewinsky Hadas[1], Gavish-David Keren[1], Kramer Matthias[1], Becker-Herman Shirley[1], Aharoni Rina[1], Milo Ron[2,3], Mauri Claudia[3], Shachar Idit[1].

* Main Author

1 Department of Immunology, The Weizmann Institute of Science , Rehovot, Israel

2 Department of Neurology, Barzilai Medical Center, Ashkelon 3 Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer-Sheva

3 Centre for Rheumatology Research, Department of Medicine, University College London, UK

The essential role of B-cells in Multiple sclerosis (MS) pathology and therapy has been recently recognized B cells are known to contribute to MS by secretion of antibodies, production of pro- inflammatory cytokines and by acting as antigen presenting cells. However, a distinct small subpopulation of B cells was found to negatively regulate inflammation. This subpopulation, known as Regulatory B cells (Bregs), is characterized by the secretion of the anti-inflammatory cytokine IL-10 and their ability to restrain inflammation. In MS patients, Bregs numbers are impaired. In addition, several MS treatments were shown to increase Breg levels. In EAE, the MS mouse model, Bregs were shown to be crucial for overcoming the disease.

SLAMF5 is a homophilic receptor belonging to the SLAM (Signaling Lymphocytic Activating Molecules) family. SLAMF5 is expressed mainly hematopoietic cells and facilitates cell-cell interactions and downstream signaling.

In this study, we investigated the role of the receptor SLAMF5 in the fine-tuning of Breg numbers and functionality. We followed the role of SLAMF5 in EAE; WT and SLAMF5 deficient ($SLAMF5^{-/-}$) mice were induced with MOG_{35-55}. 100% of WT mice exhibited clinical symptoms, while $SLAMF5^{-/-}$ mice manifested delayed disease onset and milder symptoms with prevalence of only 77%. $SLAMF5^{-/-}$ showed an increase of Breg levels with no change of periphery T cells levels. Blocking SLAMF5 *in-vitro*, both in humans and murine cultures, had a specific effect on Bregs survival and an increase in the expression of the transcription factor cMAF, which was shown to upregulate IL10 expression. Finally, in vivo blocking of SLAMF5 in EAE induced mice elevated Breg levels and mitigated the disease.

Taken together, our results suggest that SLAMF5 can serve as a new therapeutic target of MS by inducing the accumulation of more functional Bregs.