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Rapamycin rescues loss-of-function in blood-brain barrier-interacting regulatory T cells

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In autoimmunity, it has been established that FOXP3+ regulatory T cells (Tregs) skew towards a pro-inflammatory, non-suppressive phenotype, making them unable to control the exaggerated autoimmune response. This largely impacts the success of autologous Treg therapy which is currently under investigation for autoimmune diseases, including multiple sclerosis (MS). There is a need to ensure in vivo Treg stability before successful application of Treg therapy. Using genetic fate-mapping mice, we demonstrate Tregs which have lost FOXP3 expression (exFOXP3 T cells) accumulate in the central nervous system during experimental autoimmune encephalomyelitis. In a human in vitro model, we discovered that interaction with inflamed blood-brain barrier endothelial cells (BBB-ECs) induces a loss of suppressive function in Tregs. Transcriptome and cytokine analysis revealed that in vitro migrated Tregs have a disrupted regenerative potential, a pro-inflammatory Th1/17 signature and upregulate the mTORC1 signaling pathway. In vitro treatment of migrated human Tregs with the clinically-approved mTORC1 inhibitor rapamycin restored their suppressive capacity. Finally, flow cytometric analysis identified an enrichment of inflammatory, less suppressive CD49d+ Tregs in the cerebrospinal fluid of people with MS. In sum, interaction with BBB-ECs is sufficient to affect Treg function, and BBB transmigration triggers an additive pro-inflammatory phenotype switch. These insights will help to improve the efficacy of autologous Treg therapy of MS.

