23 HELIOS+ FOXP3+ NATURALLY OCCURRING REGULATORY T CELLS ARE PERIPHERALLY EXPANDED IN ACTIVE SYSTEMIC LUPUS ERYTHEMATOSUS

Tobias Alexander,[1,2] Lars Templin,[1,2] Siegfried Kohler,[3] Christian Groß,[4] Arne Sattler,[5] Andreas Meisel,[3] Gerd-Rüdiger Burmester,[1] Andreas Radbruch,[2] Andreas Thiel,[5] Falk Hiepe[1,2] *[1]Department of Rheumatology and Clinical Immunology, Charité – University Medicine Berlin, Germany; [2]German Rheumatism Research Center (DRFZ), Berlin, Germany; [3]Department of Neurology, Charité – University Medicine Berlin, Germany; [4]Department of Traumatology and Reconstructive Surgery, Charité – University Medicine Berlin; [5]Berlin-Brandenburg Center for Regenerative Therapies (BCRT), Charité – University Medicine, Berlin, Germany*

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Background Naturally occurring FoxP3+ regulatory T cells (Tregs) are pivotal in induction and maintenance of tolerance to self and foreign antigens. Even though intensively studied, their role in systemic lupus erythematosus (SLE) is still controversially discussed. The authors here investigated Treg expression of Helios, a member of the Ikaros transcription factor family that was recently introduced as a potential marker of thymic-derived natural T regulator (Treg) cells.

Methods Multicolor flow cytometry was performed to analyse coexpression levels of Helios, CD25, CD127, CD45RA, CD31 and Ki-67 in FoxP3+ Tregs from peripheral blood of 20 patients with SLE, 20 age- and sex matched healthy controls (HC), 10 patients with diffuse systemic sclerosis (dSSc) and 10 patients after thymectomy for myasthenia gravis. In addition, ex vivo STAT5 phosphorylation, T cell receptor Vβ chain usage and cytokine secretion was investigated in Treg subsets by flow cytometry.

Results The authors found that levels of FoxP3+ Helios+ T cells, but not their FoxP3+ Helios- or FoxP3- Helios+ counterparts were significantly increased in SLE compared to HC and dSSc patients (median 11.0% vs 5.0% vs 5.8%), and these levels correlated with disease activity using the SLEDAI score (R^2=0.73). Phenotypically, this T cell subset in SLE resembled expanded memory regulatory T cells with decreased

coexpression levels of CD31 and CD45RA almost to those found in thymectomised patients, low coexpression levels of CD127 and increased proliferation rates. Upon stimulation, effector cytokine secreting cells among FoxP3+ T cells were exclusively confined to the Helios- subset. Phospho-flow cytometry revealed significant higher ex vivo STAT5 phosphorylation levels in SLE Tregs compared to HC suggesting recent stimulation with γ-chain cytokines. In contrast to HC, expanded FoxP3+ Helios+ Tregs in SLE showed a restricted TCR Vbeta family usage.

Conclusion Our data demonstrate that increased levels of FoxP3+ Helios+ naturally occurring regulatory T cells found in peripheral blood of SLE result from peripheral expansion via a STAT5-driven pathway rather than through increased thymic output. The skewed TCR repertoire found in such expanded Tregs, however, suggests that this process is not only cytokine-dependent but presumably also driven by high-affinity TCR engagement with available autoantigens. Even though expanded in vivo, lupus Tregs may not compensate for autoreactive effector T cell responses in active disease. However, they may serve as a source for Treg-based interventions in future therapeutic approaches. So far, FoxP3+ Helios+ Tregs may be utilisable as a biomarker for disease activity in SLE.