TWO COMPONENTS CONTRIBUTING TO REDUCED TREG SURFACE CD25 IN SLE PATIENTS AND THEIR UNAFFECTED RELATIVES

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Background: FOXP3+ regulatory T-cells (Tregs) in Systemic Lupus Erythematosus (SLE) are in a functionally deficient state with a characteristic reduction or absence of surface CD25 (the IL-2 receptor alpha chain). Genetic variation in the CD25-encoding IL2RA locus is associated with other autoimmune disorders.

Methods: We have studied Treg and Treg subset CD25 by flow cytometry and typed 24 SNPs in the IL2RA locus in 47 SLE patients, 108 SLE-unaffected first-degree relatives of SLE patients, and 61 unrelated control subjects.

Results: In both SLE patients and unaffected relatives, surface CD25 was found strongly reduced not only in activated, but already in circulating CD4+FOXP3+CD45RO-CD31+ recent thymic emigrant (RTE) Tregs. In contrast, unaffected relatives clearly differed from SLE patients in properties of activated CD4+FOXP3highCD45RO+ Tregs, which showed a CD25 upregulation versus non-activated CD45RO- Tregs in these relatives similar to control subjects, while not in SLE patients. The distinction of these two components contributing to the previously described SLE-characteristic Treg CD25 reduction was corroborated by our finding that the two components were influenced by polymorphisms in different regions of the IL2RA locus. Furthermore, we found that only RTE Treg CD25, as well as the genetic variants influencing it, were significantly related to numbers and relative frequencies of circulating activated Tregs, whereas CD25 upregulation upon Treg activation was not.

Conclusions: Our results point to (a) an intrathymic effect present in an extended population carrying SLE susceptibility factors that is responsible for reduced surface CD25 in early Tregs and a subsequently decreased activation capacity. This effect might be compensated in unaffected relatives by (b) CD25 upregulation upon Treg activation, which seemed functionally independent and was selectively deficient in SLE patients. This second component appears of particular interest for therapeutic targeting.