



Larger homing receptor expression on Tregs suggests increased efficacy of epicutaneous compared to oral or sublingual immunotherapy for the treatment of food allergy.

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Background: Allergen specific immunotherapy is an attractive strategy to actively treat food allergy. In the 3 different routes investigated, oral (OIT), sublingual (SLIT) and epicutaneous (EPIT), regulatory T cells (Tregs) play a pivotal role. Their sites of induction may influence their homing properties and organ targeting. The aim of the study was to compare the expression of homing receptors on Tregs after EPIT, OIT or SLIT.

Method: BALB/c mice were orally sensitized to peanut and then treated by EPIT, OIT, SLIT or not treated (Sham). After 8 weeks of treatment with 100µg of peanut protein extract, the proportion of Tregs and their expression of homing receptors (CCR9, CLA, CCR4, CCR8, CCR6, CXCR3 and CCR3) was analyzed by flow cytometry in spleen and in related lymph nodes (inguinal (iLN) or mesenteric (mLN)).

Results: Whatever the method, spleen Foxp3⁺ Tregs increased with immunotherapy ($p < 0.001$ compared to Sham), more significantly with EPIT ($p < 0.01$ compared to OIT and SLIT). In spleen, whereas Tregs CCR4 expression increased with the 3 methods ($p < 0.05$ compared to sham), only EPIT-induced Tregs significantly increased expression of CCR8, a well-defined Th2 homing receptor. Analysis of skin (CLA) and gut (CCR9) homing receptors revealed a significant induction of CLA+CCR9⁺ Tregs by EPIT ($p < 0.001$ compared to Sham, OIT and SLIT) and CLA-CCR9⁺ Tregs by OIT ($p < 0.01$ compared to Sham, EPIT and SLIT) whereas SLIT-induced Tregs increased neither CLA nor CCR9 expression. In iLN, Tregs level increased only after EPIT with induction of CLA+CCR9⁻ and CLA+CCR9⁺ Tregs. In mLN, only EPIT and OIT induced higher level of Tregs with increased expression of CCR9 ($p < 0.001$ compared to Sham and SLIT).

Conclusion: EPIT induced more Tregs than OIT or SLIT. The increase in gut homing receptor CCR9 and in Th2 homing receptor CCR8 in these Tregs strongly suggests a wider range of action for EPIT over SLIT and OIT during food allergy.

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