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Gut homing receptors designate epicutaneous immunotherapy as the most appropriate route for the treatment of food allergy in a model of peanut sensitized mice

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Background: Allergen specific immunotherapy is showing promise in the treatment of food allergy. In the 3 different routes being investigated, epicutaneous (EPIT), oral (OIT) and sublingual (SLIT), regulatory T cells (Tregs) are believed to play a pivotal role. Differential expression of homing receptors determines specific migration patterns of Tregs and could modulate efficacy in vivo. This study evaluated the effect of EPIT, OIT and SLIT on Tregs expression of gut homing receptors and their long term maintenance.

Method: BALB/c mice were orally sensitized to peanut and then treated with EPIT, OIT, SLIT or not treated (Sham). The proportion of Tregs in spleen and their expression of gut homing receptors (CCR9, CCR6, and CCR3) were analyzed by flow cytometry in spleens after 8 weeks of treatment or 8 weeks after treatment termination. The in vivo suppressive activities of Tregs were evaluated by examining the decrease of peanut-specific cytokine responses and by the protection against esophageal eosinophil infiltration after oral peanut administration (Mondoulet, PLoS One 2012) in peanut-sensitized mice receiving adoptively transferred Tregs.

Results: In all treatment regimens, Foxp3+ Tregs increased at the end of immunotherapy ($p<0.001$ compared to Sham), significantly more with EPIT ($p<0.01$ compared to OIT and SLIT). EPIT-induced Tregs were both CD62L+ and CD62L- whereas OIT and SLIT mainly induced CD62L- Tregs. EPIT induced higher expression of the 3 gut homing receptors CCR9, CCR6 and CCR3 whereas OIT induced CCR9 and CCR6 and SLIT did not. Following transfer of Tregs isolated at the end of treatment, EPIT, OIT and SLIT Tregs decreased Th2 cytokine production in recipient mice, but only EPIT-Tregs protected them from eosinophil infiltration in the esophagus following intensive peanut oral administration. Eight weeks after the discontinuation of EPIT, the level and phenotype of Tregs were sustained, but not after OIT and SLIT. Moreover, transfer of Tregs isolated 8 weeks after the end of EPIT decreased Th2 cytokine production and protected mice from eosinophil infiltration in esophagus, but not after OIT or SLIT.

Conclusion: The greater increase of Tregs and their greater expression of gut homing receptors and longer sustainability suggest the potential superiority of EPIT over SLIT and OIT for the treatment of food allergy.