Epicutaneous but not Oral Immunotherapy Induces Antigen-Specific Gastrointestinal Tregs and Protects from Food-Induced Anaphylaxis

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Rationale: Epicutaneous immunotherapy (EPIT) is being investigated for the treatment of food allergies. We studied the mechanism of tolerance induction by EPIT in comparison to oral immunotherapy (OIT) in a mouse model of food-induced anaphylaxis.

Methods: C3H/HeJ mice were sensitized to ovalbumin (OVA) orally or through the skin and treated with EPIT or OIT using OVA-Viaskin® patches or oral OVA. Mice were orally challenged with OVA to induce anaphylaxis. Antigen-specific Treg induction was assessed by flow cytometry using a transgenic T cell transfer model.

Results: OVA-EPIT induced the appearance of antigen-specific LAP+Foxp3- cells in the mesenteric lymph nodes that were absent in OIT-treated mice. The suppressive activity of the LAP+ cells was confirmed in vitro. LAP+ cells primed in the skin-draining lymph nodes expressed the gut-homing marker CCR9 (85% LAP+ vs 7% LAP-) and the mucosal-homing marker CCR6 (55% LAP+ vs 9% LAP-). Both LAP+ and LAP- cells expressed high levels of the skin-homing marker CCR4 (84% and 88%, respectively). The induction of antigen-specific Tregs in the gut by EPIT was associated with protection from food-induced anaphylaxis. 100% of skin or oral-sensitized EPIT-treated mice were protected from anaphylaxis, whereas only skin-sensitized mice were protected by OIT.

Conclusions: EPIT induces the generation of gastrointestinal-homing antigen-specific Tregs in the skin-draining lymph nodes, which translates into an increased number of Tregs in the gastrointestinal tract. Induction of gastrointestinal Tregs is associated with an enhanced protection of mice from food-induced anaphylaxis by EPIT versus OIT.

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