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EPIT-induced bystander effect mainly conferred by naïve Tregs via soluble factors and cell-cell contact in a murine model

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Background: Only epicutaneous immunotherapy (EPIT), as compared to oral or sublingual immunotherapy, induces naive Tregs in a model of food allergen sensitized mice (Dioszeghy et al., 2015) and prevents the induction of anaphylaxis to further allergens via regulatory T cells (Tregs) (Mondoulet et al., 2015). This study is an in-depth investigation of the role of naive Tregs in this bystander effect.

Method: Following milk sensitization, mice were treated with milk EPIT or Sham. CD4+CD25+ T cells (Tregs) were isolated with an additional CD62L+ surface marker defining naive Tregs. Naive and effector Tregs were adoptively transferred into recipient mice, which were then subjected to peanut sensitization and IV challenge with peanut. In a second experiment, TGF-β, CTLA-4 and OX40 were inhibited by the injection of blocking antibodies 24 hrs before their adoptive transfer into milk-sensitized mice or 24 hrs before an IV challenge in peanut-sensitized mice. Outcome markers included a drop in rectal temperature, hypersensitivity reactions and serum mouse mast cell protease-1 (mMCP1) measurements after IV challenge with peanut.

Results: In recipient mice sensitized to peanut and previously infused with naive Tregs induced by milk EPIT, there was no induction of peanut s-IgE but s-IgG2a was significantly increased and animals were fully protected against anaphylaxis after IV injection of peanut ($p<0.001$). However, in mice receiving effector Tregs and then sensitized to peanut, peanut s-IgE increased and s-IgG2a was unchanged, and mice were not protected against anaphylaxis after IV injection of peanut (ns). Noticeably, this protection was lost by blocking TGF-β, CTLA-4 orOX40 before the adoptive transfer ($p<0.05$, $p<0.01$ and $p<0.01$ respectively) and before the IV challenge ($p<0.05$, $p<0.01$ and $p<0.01$ respectively).

Conclusion: Naive Tregs induced by EPIT might play a central role in the bystander effect, via soluble and cell-cell contact interaction.