First Evidence for the Treatment of Colitis by Epicutaneous Immunotherapy in a murine model

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Background: Crohn's disease patients have a defect in inducing T-regulatory cells (Treg) via the gut. When Tregs are generated externally in response to food antigen and infused into patients, they suppress inflammation in Crohn's via bystander suppression. We hypothesized that Tregs could be induced by applying antigen to intact skin using an epicutaneous delivery device, Viaskin®, and after their migration to the gut could abrogate colitis via bystander suppression.

Method: C57BL/6 mice were exposed epicutaneously for 48 hours once a week to Viaskin patches containing ovalbumin (Viaskin-OVA). To determine if exposure blocked T-effector responses, mice were immunized with OVA, and cytokine production by draining lymph nodes (LN) was assessed by ELISA. Treg development in the MLN, spleen and intestines were determined. Then, to determine if Tregs from skin draining LNs could migrate to the gut to suppress colitis, Tregs from skin draining LNs or MLNs were co-transferred with CD45RBHI T cells in to RAG-/- mice. Mice were assessed for weight loss, colonic cytokine production and histology. Finally, to determine if epicutaneous tolerance induction could directly abrogate colitis, RAG-/- mice with colitis induced by the transfer of CD45RBHI T cells were epicutaneously exposed to Viaskin-OVA and then gavage fed OVA to activate Tregs and induce homing to the gut. Weight loss, colonic inflammatory cytokine production and histology were assessed.

Results: Epicutaneous exposure to OVA induced tolerance with suppression of OVA-specific IFN-γ from draining LNs. OVA exposure induced proliferation of OVA-specific Tregs in the spleen, MLN, and intestines. Tregs isolated from skin draining LNs were able to suppress the development of colitis as well as those isolated from MLNs. In the transfer model of colitis, 3 epicutaneous OVA exposures followed by 1 oral OVA feeding prevented weight loss ($p<0.05$), decreased colonic IFN-γ and IL-17 production ($p<0.05$), and abrogated histological colitis ($p<0.05$).

Conclusion: Epicutaneous exposure to OVA induces Tregs, which migrate to the gut and abrogate colitis via bystander suppression. Epicutaneous tolerance induction has potential as a treatment for Crohn's disease and warrants further study.