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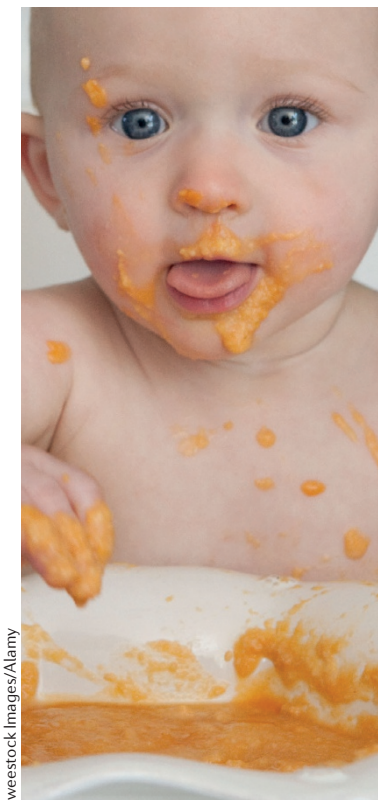
MUCOSAL IMMUNOLOGY

Weaning off food allergy

> food- and microbe-induced T_{Reg} cell populations work together to prevent food allergies

Regulatory T (T_{Reg}) cells are induced in the small intestine by exposure to solid food during weaning and protect against otherwise strong immune responses to ingested antigens, according to new research in *Science*. The results suggest that exposing children to a variety of food types from an early age might be an important factor in preventing the development of severe food allergies.

Antigen-free mice are derived by breeding germ-free mice fed an elemental liquid diet (filtered to deplete macromolecules), such that the offspring have never been exposed to microbial or food antigens. Surh and colleagues show that these antigen-free mice have smaller lymphocyte numbers in the small intestinal lamina propria (siLP), but not in the colonic lamina propria (cLP), compared with specific pathogen-free (SPF) mice, which could be accounted for by the depletion of memory $CD4^+$ T cells in the siLP. These results suggest that $CD4^+$ T cells are activated by food antigens in the small intestine but by the microbiota in the colon.



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$CD4^+$ T_{Reg} cells are abundant in the intestine and are known to be involved in oral tolerance. The total number of siLP T_{Reg} cells was five-fold lower in antigen-free mice than in germ-free or SPF mice; by contrast, antigen-free mice had a similar number of cLP T_{Reg} cells to germ-free mice, which was two-fold lower than in SPF mice. In SPF mice, 50–70% of the T_{Reg} cells in siLP and cLP are peripherally derived (pT_{Reg} cells; identified by low levels of expression of neuropilin 1); these pT_{Reg} cells are rare in the cLP of germ-free mice but present in the siLP, whereas they are depleted from both siLP and cLP of antigen-free mice. Therefore, dietary antigens induce most of the pT_{Reg} cells in the siLP.

The number of pT_{Reg} cells in the siLP was low in all mice before weaning but increased shortly after weaning onto a normal chow diet. Weaning neonatal germ-free mice onto an antigen-free diet prevented the development of siLP pT_{Reg} cells. Furthermore, when adult germ-free mice were switched to an antigen-free diet, the number of pT_{Reg} cells in siLP was decreased by 40%. Thus, siLP pT_{Reg} cells develop and are maintained in response to dietary antigens.

Antigen-free mice mounted a greater T cell response in the gut-associated lymphoid tissues than germ-free or SPF mice after adoptive transfer of ovalbumin (OVA)-specific T cells followed by oral OVA. Furthermore, the expanded OVA-specific T cell population in antigen-free mice expressed lower levels of forkhead box P3 (FOXP3) than in germ-free or SPF mice and had a greater tendency to differentiate to a T helper 1 (T_H1) cell phenotype. The results show that siLP pT_{Reg} cells are required to prevent a default pro-inflammatory T cell response to new dietary antigens. In support of this, neonatal SPF mice weaned onto an amino acid diet (to prevent the development of siLP pT_{Reg} cells) had increased susceptibility to OVA-induced intestinal allergy than control mice weaned onto a chow diet.

In summary, weaning onto solid food induces siLP pT_{Reg} cells, which are required to suppress the immune response to dietary antigens. Given the already established role of the microbiota in promoting oral tolerance, the authors suggest that food- and microbe-induced T_{Reg} cell populations work together to prevent food allergies throughout the digestive tract.

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ORIGINAL ARTICLE Kim, K. S. *et al.* Dietary antigens limit mucosal immunity by inducing regulatory T cells in the small intestine. *Science* http://dx.doi.org/10.1126/science.aac5560 (2016)