

EDITORIAL

Clinical and Experimental Allergy

Extra-intestinal manifestations of gastro-intestinal allergy: effector and regulatory T cells in the balance

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It is well appreciated that the manifestations of food allergy are not confined to the oro-gastrointestinal tract but extend to include localized manifestation in other tissues, especially the respiratory tract and the skin [1, 2]. Furthermore, experimental food allergy models have revealed that gastrointestinal antigen sensitization not only enhances allergic airway exposure to the same antigen but also to unrelated aeroallergens [3]. By the same token, the effects of oral tolerance induction are systemic. Tolerance-inducing therapies including oral feeding in experimental animals and sublingual immunotherapy (SLIT) in humans act to suppress allergic manifestation in different tissues outside the gastrointestinal tract including the airways [4, 5]. Are the two phenomena related and if so by what underlying mechanisms? Recent reports, including one in this issue of *Clinical and Experimental Immunology*, have begun to clarify aspects of this connection.

Using a murine model of gastrointestinal sensitization to ovalbumin (OVA), Ozdemir et al. [6] demonstrate that CD4⁺ T cells isolated from mesenteric lymph nodes of sensitized mice triggered allergic airway inflammation upon transfer into naïve recipient mice that were subsequently challenged with aerosolized OVA. These findings indicated that CD4⁺ T cells are both necessary and sufficient for mediating allergy airway inflammation upon gastrointestinal sensitization.

Sensitization in the gut is mediated by local antigen presentation in gut-associated lymphoid tissues (GALT), such as the Peyer's Patches and the mesenteric lymph nodes, to naïve T cells. Antigen presentation by dendritic cells (DCs) of GALT up-regulates the expression by T cells of the gut homing receptor $\alpha 4\beta 7$ integrin, which interacts

with the mucosal addressin cell adhesion molecule 1 (MaDCAM-1), and the chemokine receptor CCR9, which responds to the thymus-expressed chemokine ligand expressed by epithelial cells [7]. Up-regulation of both markers is dependent on retinoic acid, which is converted from vitamin A by the action of the enzyme retinal dehydrogenase [8]. Because of their high-level expression of retinal dehydrogenase, antigen presentation by GALT-associated DCs imprints gut homing specificity on responding T cells. An analogous vitamin D-dependent mechanism orchestrates the imprinting of skin homing specificity on responding T cells [9].

Notwithstanding these tissue homing imprinting mechanisms, the capacity of gut and skin homing T cells to extend their reach to other tissues, such as the airways, suggests plasticity of tissue homing specificity. Indeed, cells that have been imprinted to home onto one tissue can be reprogrammed to home to a different tissue upon antigen presentation by DCs of the second tissue or the appropriately draining lymph nodes [10]. It should be noted however that while no lung-specific homing receptors have yet been identified, entry of antigen-specific memory T cells into the airways appears to be orchestrated by inflammatory chemokine/chemokine receptor networks [11].

The plasticity of homing mechanisms that underlies the spread of allergen-responsive T cells primed in the gut to other target organs can also be harnessed for therapeutic purposes. It is now well established that the induction of oral tolerance is associated with, and contingent upon, the *in situ* production of Foxp3⁺ regulatory T cells [12]. Reciprocally, Foxp3 deficiency, which is associated with failure of regulatory T cell differentiation and function, results in the development of severe food allergies in the context of a more global allergic dysregulatory and autoimmune lymphoproliferative disease [13, 14]. The therapeutic potential of oral tolerogenic approaches have been bolstered by recent advances in elucidating mechanisms of *in situ* conversion of naïve T cells into adaptive regulatory T cells. This conversion, which takes place

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more effectively in GALT than in any other tissues, involves antigen presentation by GALT-associated CD103⁺ DCs. Adaptive regulatory T cells optimally develop upon antigenic stimulation in the absence of co-stimulatory molecule engagement, which would shunt the responding T cells towards a T-effector phenotype, and is strictly dependent on action of TGF- β . Importantly, it is greatly augmented by retinoic acid, and reciprocally antagonized by inhibitors of retinal dehydrogenase [15–18]. These findings open up the possibility of pharmacologically enhancing oral tolerogenic therapies such as SLIT with retinoic acid analogues or concurrent vitamin A supplementation. A more intriguing possibility, so far untested, is the reprogramming of antigen-specific memory T cells into adaptive regulatory T cell by means of oral tolerogenic interventions. More studies into the basic biology of adaptive regulatory T cells would be required to assess the feasibility of such approaches.

References

- 1 James JM. Respiratory manifestations of food allergy. *Pediatrics* 2003; **111** (Part 3):1625–30.
- 2 Werfel T, Ballmer-Weber B, Eigenmann PA *et al.* Eczematous reactions to food in atopic eczema: position paper of the EAACI and GA(2)LEN. *Allergy* 2007; **62**:723–8.
- 3 Brandt EB, Scribner TA, Akei HS, Rothenberg ME. Experimental gastrointestinal allergy enhances pulmonary responses to specific and unrelated allergens. *J Allergy Clin Immunol* 2006; **118**:420–7.
- 4 Oldenhove G, de Heusch M, Urbain-Vansanten G *et al.* CD4⁺ CD25⁺ regulatory T cells control T helper cell type 1 responses to foreign antigens induced by mature dendritic cells *in vivo*. *J Exp Med* 2003; **198**:259–66.
- 5 Cox LS, Linnemann DL, Nolte H, Weldon D, Finegold I, Nelson HS. Sublingual immunotherapy: a comprehensive review. *J Allergy Clin Immunol* 2006; **117**:1021–35.
- 6 Ozdemir C, Sel S, Schöll I *et al.* CD4⁺ T cells from mice with intestinal immediate type hypersensitivity induce airway hyper-reactivity. *Clin Exp Allergy* 2007; **37** (this issue).
- 7 Mora JR, Bono MR, Manjunath N *et al.* Selective imprinting of gut-homing T cells by Peyer's patch dendritic cells. *Nature* 2003; **424**:88–93.
- 8 Iwata M, Hirakiyama A, Eshima Y, Kagechika H, Kato C, Song SY. Retinoic acid imprints gut-homing specificity on T cells. *Immunity* 2004; **21**:527–38.
- 9 Sigmundsdottir H, Pan J, Debes GF *et al.* DCs metabolize sunlight-induced vitamin D3 to 'program' T cell attraction to the epidermal chemokine CCL27. *Nat Immunol* 2007; **8**:285–93.
- 10 Mora JR, von Andrian UH. T-cell homing specificity and plasticity: new concepts and future challenges. *Trends Immunol* 2006; **27**:235–43.
- 11 Wardlaw AJ, Guillen C, Morgan A. Mechanisms of T cell migration to the lung. *Clin Exp Allergy* 2005; **35**:4–7.
- 12 Mucida D, Kutchukhidze N, Erazo A, Russo M, Lafaille JJ, Curotto de Lafaille MA. Oral tolerance in the absence of naturally occurring Tregs. *J Clin Invest* 2005; **115**:1923–33.
- 13 Chatila TA, Blaeser F, Ho N *et al.* JM2, encoding a fork head-related protein, is mutated in X-linked autoimmunity-allergic dysregulation syndrome. *J Clin Invest* 2000; **106**:R75–81.
- 14 Chatila TA. Role of regulatory T cells in human diseases. *J Allergy Clin Immunol* 2005; **116**:949–59; quiz 60.
- 15 von Boehmer H. Oral tolerance: is it all retinoic acid? *J Exp Med* 2007; **204**:1737–9.
- 16 Benson MJ, Pino-Lagos K, Roseblatt M, Noelle RJ. All-trans retinoic acid mediates enhanced T reg cell growth, differentiation, and gut homing in the face of high levels of co-stimulation. *J Exp Med* 2007; **204**:1765–74.
- 17 Sun CM, Hall JA, Blank RB *et al.* Small intestine lamina propria dendritic cells promote de novo generation of Foxp3 T reg cells via retinoic acid. *J Exp Med* 2007; **204**:1775–85.
- 18 Coombes JL, Siddiqui KR, Arancibia-Carcamo CV *et al.* Functionally specialized population of mucosal CD103⁺ DCs induces Foxp3⁺ regulatory T cells via a TGF- β - and retinoic acid-dependent mechanism. *J Exp Med* 2007; **204**:1757–64.