Oral Tolerance: A Local Affair?

Oral tolerance is the phenomenon by which oral administration of nonpathogenic antigens leads to inhibition of immune responses on subsequent challenge with immunogenic antigen.[1] Known for many years, it is often cited as the universal process that restricts inflammatory reactions to food proteins and commensal bacteria in the mucosa, thus preventing celiac disease and inflammatory bowel disease (IBD). In practice, most experimental models have used soluble antigens such as proteins or haptens and have examined extraintestinal responses after parenteral challenge. The status of mucosal immunity is often not ascertained, and it is controversial whether local IgA production is primed, tolerized, or unaffected.[2] However, old work showed that it was possible to induce T-cell-mediated mucosal immunopathology directed at food proteins if oral tolerance was prevented,[3] indicating that orally induced tolerance affects effector T cells both locally and systematically.

The work that has been done with commensal microbiota suggests that they do not induce systemic tolerance and indeed may never be seen at all in the systemic immune system, probably being sequestered within dendritic cells (DCs) or macrophages in the mesenteric lymph nodes (MLNs).[4,5] However, they are clearly recognized within the gut lymphoid tissues. Not only are DCs loaded with such organisms in Peyer's patches and MLNs, but secretory IgA specific for commensal microbiota is abundant in the normal intestine.[6,7] Furthermore, animal models of commensal-dependent IBD are normally prevented by bacteria-specific regulatory T (Treg) cells, and such cells have been identified in lamina propria and MLNs.[8,9] There thus appears to be a locally induced state of tolerance or immune deviation that drives secretory IgA production but prevents effector T-cell function in the mucosa via the generation of Treg cells.[6] The explanation for this is probably uptake of commensals by $CD103^+$ DCs in mucosal lymph nodes and MLNs. By producing retinoic acid, these DCs have unique abilities to drive the development of gut-homing B cells and $FoxP3^+$ Treg cells, as well as to switch IgA production by B cells [10–12].

Recently, it has become common to assume that oral tolerance to soluble antigens is also induced and expressed only in the gut and its lymphoid tissues. This is based partly on elegant experiments that emphasize the need for CCR7-dependent migration of mucosal $CD103^+$ DCs to the MLNs in oral tolerance.[13] This would account for unresponsiveness at the mucosal level via induction of $CCR9^+$ gut-seeking Treg cells. This work also showed that systemic recognition of and tolerance to fed antigen required cellular emigration from the MLNs.[13] However, it is not known what cells might be involved in this process, or how they could influence responsiveness in distant tissues. Furthermore, this idea is complicated by older studies that showed the rapid appearance of tolerogenic material in the serum of protein-fed animals, in the form of either native protein or exosomes.[1,14] These findings suggest that the systemic aspects of oral tolerance may be induced outside the intestine or MLNs and are consistent with evidence that T-cell recognition may occur simultaneously in MLNs and distant lymphoid organs after feeding protein.[15,16] Finally, the gut-restricted induction of tolerance does not explain the long-proposed role of the liver, a tissue whose potential involvement has been highlighted by recent studies suggesting deletion of $CD8^+$ T cells by unusual antigen-presenting cells, such as plasmacytoid DCs, in the liver.[17,18]

Altogether, the challenge is to learn more about the site and mechanisms of tolerance to food proteins and commensal microbiota, using the sophisticated tools and models now available to track antigen, DCs, and T cells during the induction and expression phases of the phenomenon. These may include multiphoton microscopy; mice with reporter genes in T cells, DCs, and epithelial cells; and novel ways of labeling antigens.

Allan M Mowat, Associate Editor

1. Strobel, S. & Mowat, A.M. Oral tolerance and allergic responses to food proteins. *Curr. Opin. Allergy Clin. Immunol.* **6**, 207–213 (2006).
2. Mowat, A.M., Faria, A.M. & Weiner, H.L. Oral tolerance: basic mechanisms and clinical implications. In *Mucosal Immunology* 3rd edn (Mestecky, J., Bienenstock, J., Lamm, M.E., Strober, W., McGhee, J.R. & Mayer, L., eds) 487–538 (Academic Press, San Diego, 2005).
3. Mowat, A.M. The regulation of immune responses to dietary protein antigens. *Immunol. Today* **8**, 93–95 (1987).
4. MacPherson, A.J. & Uhr, J. Induction of protective IgA by intestinal dendritic cells carrying commensal bacteria. *Science* **303**, 1662–1665 (2004).
5. Mazmanian, S.K., Liu, C.H., Tzianabos, A.O. & Kasper, D.L. An immunomodulatory molecule of symbiotic bacteria directs maturation of the host immune system. *Cell* **122**, 107–118 (2005).
6. Iweala, O.I. & Nagler, C.R. Immune privilege in the gut: the establishment and maintenance of non-responsiveness to dietary antigens and commensal flora. *Immunol. Rev.* **213**, 82–100 (2006).
7. Cerutti, A. & Rescigno, M. The biology of intestinal immunoglobulin A responses. *Immunity* **28**, 740–750 (2008).
8. Khoo, U.Y., Proctor, I.E. & Macpherson, A.J. CD4+ T cell down-regulation in human intestinal mucosa: evidence for intestinal tolerance to luminal bacterial antigens. *J. Immunol.* **158**, 3626–3634 (1997).
9. Gad, M., Pedersen, A.E., Kristensen, N.N. & Claesson, M.H. Demonstration of strong enterobacterial reactivity of CD4+CD25– T cells from conventional and germ-free mice which is counter-regulated by CD4+CD25+ T cells. *Eur. J. Immunol.* **34**, 695–704 (2004).
10. Mora, J.R. & von Andrian, U.H. Role of retinoic acid in the imprinting of gut-homing IgA-secreting cells. *Semin. Immunol.* **21**, 28–35 (2009).
11. Coombes, J.L. & Powrie, F. Dendritic cells in intestinal immune regulation. *Nat. Rev. Immunol.* **8**, 435–446 (2008).
12. Agace, W.W. T-cell recruitment to the intestinal mucosa. *Trends Immunol.*; e-pub ahead of print 4 October 2008.
13. Worbs, T., Bode, U., Yan, S., Hoffmann, M.W., Hintzen, G., Bernhardt, G. *et al.* Oral tolerance originates in the intestinal immune system. *J. Exp. Med.* **203**, 519–527 (2006).

14. Karlsson, M., Lundin, S., Dahlgren, U., Kahu, H., Pettersson, I. & Telemo E. "Tolerosomes" are produced by intestinal epithelial cells. *Eur. J. Immunol.* **31**, 2892–2900 (2001).
15. Sun, J., Dirden-Kramer, B., Ito, K., Ernst, P.B. & Van Houten, N. Antigen-specific T cell activation and proliferation during oral tolerance induction. *J. Immunol.* **162**, 5865–5875 (1999).
16. Smith, K.M., Davidson, J.M. & Garside, P. T-cell activation occurs simultaneously in local and peripheral lymphoid tissue following oral administration of a range of doses of immunogenic or tolerogenic antigen although tolerized T cells display a defect in cell division. *Immunology* **106**, 144–158 (2002).
17. Limmer, A. *et al*. Cross-presenting liver endothelial cells and T regulatory cells leads to CD8+ T cell tolerance. *Eur. J. Immunol.* **35**, 2970–2981 (2006).
18. Goubier, A., Dubois, B., Gheit, H., Joubert, G., Villard-Truc, F., Asselin-Paturel, C. *et al.* Plasmacytoid dendritic cells mediate oral tolerance. *Immunity* **29**, 464–475 (2008).