*Commentary*

# Origin and Homing of Intestinal IgA Antibody-secreting Cells

Michael E. Lamm[1] and Julia M. Phillips-Quagliata[2]

[1]*Department of Pathology, Case Western Reserve University, Cleveland, OH 44106*
[2]*New York University School of Medicine, New York, NY 10016*

The fact that IgA comprises the body's major isotype of antibody on a biosynthetic basis is not widely appreciated because IgG, not IgA, is the predominant isotype in serum. Nevertheless, the bulk of the body's Ig-producing cells reside in the various mucosal and exocrine sites, especially along the intestinal tract, and most of them make IgA antibodies against environmental antigens, including the local microbial flora. These antibodies can then function in multiple ways as a first line of immune defense at boundaries with the external environment (1).

It has long been recognized that a major source of the precursors of the IgA plasma cells in the intestine is the organized lymphoid tissue of the Peyer's patches (2). Here B cells in the germinal centers are thought to switch from IgM to IgA under the influence of T cells and cytokines, in particular TGF-β (3, 4). They then migrate from the Peyer's patches to the draining mesenteric lymph nodes, where they continue to divide and differentiate. Finally they exit the lymph nodes and pass via the thoracic duct lymph into the blood, which carries them to the lamina propria of the gut. Here they complete their differentiation into the mature IgA-secreting plasma cells so characteristic of this location (5, 6). During this process such Th2 cytokines as IL-5, IL-6, and IL-10 are thought to be important in inducing the switched B cells to make IgA for secretion (3, 4). With regard to this IgA cell cycle, two points are worth emphasizing. One, the precursors of the plasma cells become committed to producing IgA well before they reach the intestinal lamina propria, and two, trafficking to lamina propria is independent of specific antigen even though the presence of antigen in the lamina propria can enhance the proliferation of the newly arrived B cells.

From a mechanistic viewpoint, what accounts for the attraction of circulating IgA B cells to the mucosa of the gut? The paradigm has been that the regional specificity of lymphocyte trafficking is governed by the net effect of sets of interacting local vascular endothelial receptors and their respective counterreceptors on circulating lymphocytes (7). These interactions are thought to account for the series of steps that begins with transient binding of the lymphocytes to endothelium and ends with their diapedesis across the vascular wall. For trafficking to the gut, the MAdCAM-1 addressin on local venules and the $\alpha 4\beta 7$ integrin on the lymphocyte are thought to be the key receptor–counterreceptor pair. In addition to interactions between moieties on lymphocytes and vascular endothelial cells, it was proposed some years ago that a factor derived from mucosal and/or exocrine epithelium might selectively attract the circulating precursors of mucosal IgA plasma cells, and evidence for the existence of such a chemotactic factor with specificity for B cells committed to IgA was presented (8). In marked contrast, however, to the wealth of molecular information that has been published on lymphocyte and endothelial receptors and their interactions, essentially no progress was forthcoming in identifying a chemotactic factor for IgA-committed B cells or its receptor on homing lymphocytes. This situation has just changed.

In this issue, Bowman et al. (9) provide compelling evidence for such an IgA B cell chemotactic factor, namely the chemokine thymus-expressed chemokine (TECK) (CCL25). The research reported builds on work published last year in which TECK was shown to be produced in peripheral tissues mainly in the epithelium of the small intestine (10). Bowman et al. (9) have gone on to demonstrate convincingly that TECK can attract IgA-committed B cells from spleen, Peyer's patches, and mesenteric lymph nodes in a highly selective manner. Moreover, splenic IgA- but not IgG-producing B cells also express high levels of mRNA for the TECK receptor, CCR9. Based on these data the authors propose that TECK and its receptor are key participants in the mechanism of selective recruitment of circulating IgA B cells to the gut lamina propria.

In earlier work, Bowman et al. (11) also showed that, although very early in B cell development in the bone marrow prepro-B cells were highly responsive and pro-B cells were somewhat responsive to TECK, by the immature, $IgM^+$ B cell stage they had lost their responsiveness to TECK. The implication is that reacquisition of TECK responsiveness by IgA-committed B cells is somehow associated with this commitment. It could be, however, that the timing of acquisition of TECK responsiveness and its

Address correspondence to Michael E. Lamm, Dept. of Pathology, Case Western Reserve University, BRB 924, 10900 Euclid Ave., Cleveland, OH 44106-4943. Phone: 216-368-1265; Fax: 216-368-1300; E-mail: mel6@po.cwru.edu


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association with commitment to IgA is B-1 versus B-2 cell-lineage dependent. In this regard, Fagarasan et al. (12) have recently provided evidence that switching to IgA production by a substantial population of $B220^+IgM^+$ B cells actually takes place in the gut lamina propria rather than in the Peyer's patches. Their studies indicate that stimulation of $B220^+IgM^+$ B cells isolated from lamina propria with a combination of LPS, IL-5, and TGF-β is sufficient to induce the switch to IgA and that T cells and CD40–CD40 ligand interaction are not required. Moreover, factors produced by lamina propria stromal cells have markedly enhancing effects on IgA-switching in lamina propria B cells induced by LPS, IL-5, and TGF-β and support plasma cell differentiation.

At the interface between the work of these two groups is the timing of entry of B cells into the lamina propria. In the work of Bowman et al. (9) responsiveness to TECK, which presumably promotes entry into the lamina propria, is seen only in IgA-committed B cells in organized lymphoid tissues, whereas from the work of Fagarasan et al. (12), the lamina propria of mice that lack activation-induced cytidine deaminase, whose $IgM^+$ B cells are incapable of switching to IgA, contains many $IgM^+$ B cells and plasma cells. Presumably, these $IgM^+$ B cells can respond to TECK.

The results in the two studies may, perhaps, be reconciled by considering that those of Bowman et al. (9) focus mainly on conventional B-2 cell populations derived from the bone marrow in adult mice. These undergo antigenic stimulation and switching to IgA in the germinal centers of organized lymphoid tissues including Peyer's patches. The studies of Fagarasan et al. (12), on the other hand, focus on lamina propria $IgM^+$ B cells many of which could be B-1 cells previously reported to give rise to a high proportion of IgA plasma cells in lamina propria (13). B-1 cells are $IgM^{hi}/IgD^{lo}$, Mac-$1^+$, $B220^{lo}$, FcεR-negative and are selected for overutilization of $V_H$ and $V_L$ genes that are associated with specificity for certain "self" as well as microbial antigens (14). In fetal mice, B-1 cell precursors develop in the liver and omentum (15, 16), and in adult mice they form a self-renewing population in the peritoneal and pleural cavities (14). By contrast, conventional B-2 cells are $IgM^{lo}/IgD^{hi}$, Mac-$1^-$, $B220^{int\ to\ hi}$ and are continuously produced in adult mice from stem cells in the bone marrow. An important behavioral difference between B-1 and B-2 cells is that the former do not enter lymphoid follicles in lymph nodes or spleen. Reconciliation between the two sets of findings under discussion (9, 12) would be partially achieved if it could be demonstrated that $IgM^+$ B-1 cells in the peritoneal cavity and/or peripheral blood, unlike the $IgM^+$ pre-

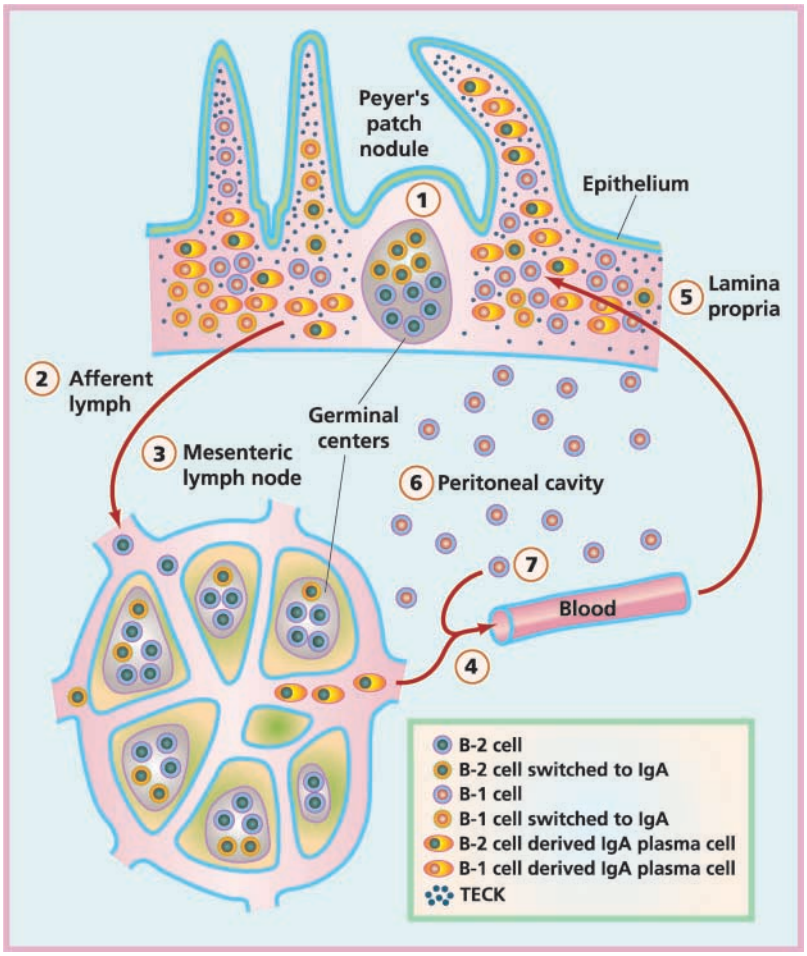


**Figure 1.** An updated scheme for the IgA cell cycle. (1) Switching of B-2 $IgM^+$ cells to IgA occurs in the germinal centers of Peyer's patches in the small intestine. (2) B-2 cells from the Peyer's patch leave in lymph and go to the draining mesenteric lymph node. (3) Further proliferation and maturation take place in the mesenteric lymph node. (4) IgA-committed plasmablasts derived from B-2 cells leave the mesenteric lymph node in the efferent lymph and travel via the thoracic duct to the blood, which transports them to the small intestine. (5) At this site, TECK produced locally by epithelial cells attracts the IgA plasmablasts into the lamina propria. (6) In contrast, B-1 cells sojourn in the peritoneal cavity. (7) $IgM^+$ B-1 cells leave the peritoneal cavity and enter the bloodstream. It is not known for certain how they do this. One possibility, consistent with the behavior of particles injected into the peritoneal cavity, is that they traverse the diaphragm in lymphatics and enter the mediastinal lymph nodes via their afferent lymphatics. They then pass through the marginal, cortical, and medullary sinuses without entering the follicles and exit via the efferent lymphatics which take them to the thoracic duct and thence to the blood. There they join the IgA plasmablasts derived from B-2 cells. Like them, they exit from the blood into lamina propria (at 5), presumably in response to TECK, but unlike them, they are still $IgM^+$. They switch to IgA in the lamina propria.

sumably B-2 cells in the spleen studied by Bowman et al. (9), are responsive to TECK. Perhaps the set of stimuli that keeps B-1 cells ticking over in the peritoneal cavity also promotes or maintains upregulation of CCR9. Once TECK-responsive $IgM^+$ B-1 cells reach the blood, their attraction to lamina propria would inevitably expose them to stromal influences, especially LPS and TGF-β, that promote switching to IgA. Further reconciliation would require demonstration that $IgM^+$ and $IgG^+$ B-2 cells in Peyer's patches are TECK unresponsive. If they are unresponsive, then it may be that the same stimulus set that promotes switching to IgA, namely CD40 ligand and TGF-β, upregulates CCR9 while the stimulus sets consisting of CD40 ligand and IL-4 or IFN-γ, which promote switching to IgG1 or IgG2a, respectively, do not. Fig. 1 presents a scheme for the development of B-1 and B-2 IgA plasma cells in the intestinal lamina propria.

It is likely that CCR9 expression is upregulated by other stimulus-receptor sets besides those that promote switching to IgA, not only because TECK is expressed on bone marrow prepro-B cells (11), but also because subsets of T cells also evidence trafficking to the gut (17). Both CD4 and CD8 gut-seeking T cells express the α4β7 integrin and the CCR9 chemokine receptor, and are attracted by TECK (10). This consideration strengthens the conclusion that although isotype-switching and differentiation toward secretion of IgA by the B-2 cell precursors of gut plasma cells develops spatially and temporally along with their ability to traffic to the lamina propria, this is apparently not true of the B-1 cell precursors. It may only be in the Peyer's patch that the two functions are controlled by the same stimuli.

What are some of the implications of the paper by Bowman et al. (9) and related papers for our understanding of regional immunity, for future research, and for dealing with disease? For one, the data strongly suggest that local mechanisms for attracting lymphocytes to mucosal tissues involve more than vascular endothelial receptors and specifically implicate chemokines. In this regard it will be important to demonstrate in intact animals that TECK and its receptor are indeed critical for homing to the intestinal lamina propria. Second, the data provide further evidence that homing by lymphocytes can be highly localized, even within the so-called "common mucosal immune system" and even within the gastrointestinal tract. Thus, the interaction between the CCR9 receptor and the TECK chemokine applies much more to the small than to the large intestine, and does not appear to apply at all to other mucosae, such as in the respiratory tract. Even within the small intestine TECK appears to be expressed more in jejunum and ileum than in duodenum (10). Therefore, fruitful studies will undoubtedly be directed toward understanding the particular receptor-counterreceptor pairs that promote homing to other mucosal sites, most importantly, in the context of infectious disease, in the upper respiratory tract. Through such knowledge it should be possible in the case of selected diseases to develop specific inhibitors capable of reducing the traffic of the offending subset(s) of lymphocytes to the site where disease is manifest. The implications for inflammatory bowel disease and perhaps asthma, for example, are evident. On the other hand, to enhance the effectiveness of vaccines that are designed to induce protective immunity against infections at particular mucosal sites, it might be possible to take advantage of agents that upregulate the receptors responsible for selective migration of immunocytes to the site. Finally, if the differentiation pathway described by Fagarasan et al. (12), in which IgM-producing cells switch to IgA production in situ in the intestinal mucosa, is in fact a B-1 cell pathway of significance in humans, by exploiting knowledge of the mechanisms underlying recruitment of the IgM precursor cells, it should be possible to develop vaccination regimens to enhance production of local IgA antibodies able to counter infections caused by the kinds of bacteria to which B-1 cell responses are directed.

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## References

1. Lamm, M.E. 1997. Interaction of antigens and antibodies at mucosal surfaces. *Annu. Rev. Microbiol.* 51:311–340.
2. Craig, S.W., and J.J. Cebra. 1971. Peyer's patches: an enriched source of precursors for IgA-producing immunocytes in the rabbit. *J. Exp. Med.* 134:188–200.
3. McIntyre, T.M., and W. Strober. 1999. Gut-associated lymphoid tissue: regulation of IgA B-cell development. *In* Mucosal Immunology. P.L. Ogra, J. Mestecky, M.E. Lamm, W. Strober, J. Bienenstock, and J.R. McGhee, editors. Academic Press, San Diego, CA. 319–356.
4. Husband, A.J., K.W. Beagley, and J.R. McGhee. 1999. Mucosal cytokines. *In* Mucosal Immunology. P.L. Ogra, J. Mestecky, M.E. Lamm, W. Strober, J. Bienenstock, and J.R. McGhee, editors. Academic Press, San Diego, CA. 541–557.
5. Phillips-Quagliata, J.M., and M.E. Lamm. 1994. Lymphocyte homing to mucosal effector sites. *In* Handbook of Mucosal Immunology. P.L. Ogra, J. Mestecky, M.E. Lamm, W. Strober, J.R. McGhee, and J. Bienenstock, editors. Academic Press, San Diego, CA. 225–239.
6. Phillips-Quagliata, J.M. 2002. Adhesion molecules and circulation and differentiation of lymphocytes in gut-associated lymphoid tissue and mammary glands. *In* Food Allergy and Intolerance. 2nd edition. S.J. Challacombe, and J. Brostoff, editors. Harcourt Health Sciences, London, UK. In press.
7. Butcher, E.C., M. Williams, K. Youngman, L. Rott, and M. Briskin. 1999. Lymphocyte trafficking and regional immunity. *Adv. Immunol.* 72:209–253.
8. Czinn, S.J., and M.E. Lamm. 1986. Selective chemotaxis of subsets of B lymphocytes from gut associated lymphoid tissue: implications for the generation of mucosal plasma cells. *J. Immunol.* 136:3607–3611.
9. Bowman, E.P., N.A. Kuklin, K.R. Youngman, N.H. Lazarus, E.J. Kunkel, J. Pan, H.B. Greenberg, and E.C. Butcher. 2002. The intestinal chemokine thymus-expressed chemokine (CCL25) attracts IgA antibody-secreting cells. *J. Exp. Med.* 195:269–275.
10. Kunkel, E.J., J.J. Campbell, G. Haraldsen, J. Pan, J. Boisvert,

A.I. Roberts, E.C. Ebert, M.A. Vierra, S.B. Goodman, M.C. Genovese, et al. 2000. Lymphocyte CC chemokine receptor 9 and epithelial thymus-expressed chemokine (TECK) expression distinguish the small intestinal immune compartment: Epithelial expression of tissue-specific chemokines as an organizing principle in regional immunity. *J. Exp. Med.* 192:761–767.

11. Bowman, E.P., J.J. Campbell, D. Soler, Z. Dong, N. Manlongat, D. Picarella, R.R. Hardy, and E.C. Butcher. 2000. Developmental switches in chemokine response profiles during B cell differentiation and maturation. *J. Exp. Med.* 191: 1303–1317.
12. Fagarasan, S., K. Kinoshita, M. Muramatsu, K. Ikuta, and T. Honjo. 2001. *In situ* class switching and differentiation to IgA-producing cells in the gut lamina propria. *Nature.* 413: 639–643.
13. Kroese, F.G.M., J.J. Cebra, M.J.F. van der Cammen, A.B. Kantor, and N.A. Bos. 1995. Contribution of B-1 cells to intestinal IgA production in the mouse. *Methods.* 8:37–43.
14. Herzenberg, L.A. 2000. B-1 cells: the lineage question revisited. *Immunol. Rev.* 175:9–22.
15. Solvason, N., A. Lehuen, and J.F. Kearney. 1991. An embryonic source of Ly 1 but not conventional B cells. *Int. Immunol.* 3:543–550.
16. Solvason, N., and J.F. Kearney. 1992. The human fetal omentum: a site of B cell generation. *J. Exp. Med.* 175:397–404.
17. Guy-Grand, D., C. Griscelli, and P. Vassalli. 1978. The mouse gut T lymphocyte, a novel type of T cell. Nature, origin, and traffic in mice in normal and graft-versus-host conditions. *J. Exp. Med.* 148:1661–1677.