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A common migratory highway between human spleen and mucosa-associated lymphoid tissues; data from nature's own experiments

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Elegant animal models of lymphocyte traffic have uncovered routes of lymphocyte movement between and within tissues. Routes of human lymphocyte migration cannot always be extrapolated from animal studies and investigating this *in vivo* is particularly challenging. In this commentary, we consider the migratory properties of low-grade B-cell lymphomas of mucosa-associated lymphoid tissue (MALT) and describe a migratory route between the human mucosa and splenic marginal zone.

The dual origin of intestinal immunoglobulin (Ig)A plasma cells in mice has been apparent for the last 20 years.[1] The two parallel systems, considered to be independent in terms of organogenesis, anatomy and function, continue to preoccupy mucosal immunologists moving toward a better understanding of the relative contributions of innate and adaptive immunity in the protection of the intestinal mucosa. Whereas the production of the T-cell independent, polyspecific component of mucosal Ig originates from the B1 lineage in mice, the production of high-affinity, specific antibodies is attributed to B2 cells. The paper from Rosada[2] and co-authors in this issue defines the migratory pathway of precursors of B1a-derived intestinal plasma cells, identifying the spleen as a previously unknown port in their travel.

Some similarities between the human and murine intestinal IgA plasma cell response exist; specific and polyspecific human intestinal IgA have been identified.[3] In contrast, fundamental differences between human and murine B-cell systems involved in IgA responses are much easier to identify. For example, CD5 is inducible on activation of human B cells, and it is therefore not a useful lineage marker, and there is no evidence of a self-renewing B-cell subset in the human peritoneum that might contribute to the intestinal IgA plasma cell population.[4] Part of the difficulty in understanding the microanatomy of the human IgA response and migratory routes of human mucosal plasma cell precursors is the lack of scope for experimentation. However, nature has designed its own experiments in humans. Low-grade B-cell lymphomas, maintain the characteristics of the normal lineages that they derive from and can be considered to be models of human B-cell traffic and behaviour. They can be traced because they have a unique clonal signature acquired during Ig gene rearrangement that can be detected at protein and genetic level. Low-grade B-cell lymphomas are therefore valuable tools for understanding human B-cell physiology *in vivo*.

The vast majority of the mucosal low-grade B-cell lymphomas arise from mucosa-associated lymphoid tissue (MALT) and are referred as MALT lymphomas. They are believed to be of marginal zone B-cell origin because of their preferential microanatomic location around the mantle zone of reactive follicles in the marginal zone, phenotypic resemblance to the B cells in Peyer's patches and splenic marginal zones, and their gene expression profiles.[5,6] The marginal zone is one of the largest B-cell components of Peyer's patches that extends from the mantle zone up to the follicle-associated epithelium (FAE), where marginal zone B cells infiltrate the epithelium and form a lymphoepithelium. MALT lymphomas can infiltrate the epithelium, germinal centers and also differentiate into plasma cells.

MALT lymphomas arise at mucosal sites from a background of chronic inflammation that resembles GALT in Peyer's patches. The most common MALT lymphomas are those that arise in the stomach from organized lymphoid tissue acquired in response to *Helicobacter pylori* infection of the gastric mucosa. The tumors are so closely dependent on the response to *H. pylori* that they regress in many cases after *H. pylori* eradication.[7] Before the potential of this conservative strategy of patient

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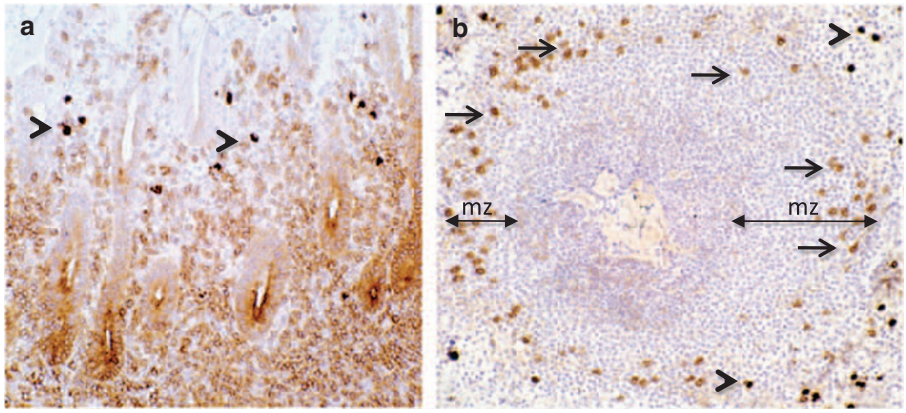

Figure 1 (**a**) Frozen section of human MALT lymphoma stained using an anti-idiotypic antibody that recognizes this tumor and no other tumors or normal cells. At the mucosal tumor site, tumor cells are distributed diffusely in the lamina propria and infiltrate between the epithelial cells forming a lymphoepithelium. Note secreted tumor-derived immunoglobulin (IgM) in the crypt epithelium, being transported into the lumen. (**b**) Frozen section of spleen from the same patient stained with the same antibody illustrates the localization of tumor cells to the splenic marginal zone (mz; black arrows). The mz is indicated with two ended arrows. Dark precipitate due to the activity of endogenous peroxidase on the substrate is indicated with arrowheads.

management was appreciated, most patients with gastric MALT lymphoma would undergo therapeutic gastrectomy that, for practical reasons during surgery, was frequently associated with splenectomy. When spleens were examined for the presence of tumor, it became apparent that the marginal zones in the spleens of patients with gastric lymphoma were frequently enlarged and were populated by normal, polyclonal, reactive marginal zone B cells.[8] It is more logical to assume that this general enlargement is associated with chronic infection and that the enlarged marginal zone is associated with the response to *H. pylori* infection than the gastric tumor, potentially linking the marginal zone B cells with chronic stimulation by bacterial antigens. This is consistent with studies suggesting that the marginal zone B cells are associated with B-cell memory and B-cell responses to T-independent antigens.[9]

When sensitive methods for detection of monoclonal B-cell proliferations were developed, it was possible to identify sparse tumor cells within the polyclonal infiltrate in many cases.[10] In fact, the tumor cells could be visualized directly in the small number of cases, in which anti-idiotypic antibodies specific for individual tumors but not for reactive cells were available (**Figure 1**).[11] This implies that human marginal zone B cell and associated plasma cells travel along a highway between the spleen and the mucosae. There is some evidence that shared microanatomic distribution is mediated by homing receptors and their endothelial ligands. MAdCAM-1 is expressed by the sinus lining cells of the splenic marginal zone and could recruit from a pool of circulating mucosal lymphoid cells, although the expression of α4β7 integrin by MALT lymphomas varies.[10]

Gastric MALT lymphomas are not the only infection-associated lymphomas that are associated with an exogenous bacterial infection. The first MALT lymphomas to be "cured" by antibiotic treatment were early-stage immunoproliferative small intestinal disease that manifests as a plasma cell infiltrate through the small bowel lamina propria that secretes truncated α-chain with no light chain. Immunoproliferative small intestinal disease also shares the other hallmarks of marginal zone lymphomas of MALT.[12] It has been associated with infection with *H. jejuni*, but a causal relationship remains to be established. It is possible to speculate that the human MALT marginal zone/splenic marginal zone axis houses an innate component of the human mucosal plasma cell response. Mucosal marginal zone B cells whether polyclonal or monoclonal can be clonally expanded by bacterial infection, consistent with support through innate receptors. In common with the murine B1 lineage cells, they are linked to autoantibody production. The antibodies produced by MALT lymphomas are usually autoreactive, including rheumatoid factors.[13] Splenic marginal zone cells have been associated with T-cell-independent B-cell responses, and also with B-cell memory.[9] It is possible that marginal zone B cells that intersect with the germinal center and that can generate plasma cells are components of the innate arm of the human mucosal B-cell response.

Neither marginal zone B cells nor MALT lymphomas express CD5, but CD5 expression may be a red herring in the search for innate humoral immunity in the human gut. Interestingly, most MALT lymphomas appear to be associated with germinal center structures and differentiate into plasma cells. The links between the human splenic and mucosal marginal zones are clearly visible. The highway between the murine spleen and the gut proposed by Rosada and colleagues in this issue is not likely to exist in humans in a precise parallel way. However, there certainly is a B-cell highway between the human spleen and the gut that may be co-incidental or may even be linked to the murine system in terms of function through parallel evolution.

DISCLOSURE

The authors declared no conflict of interest.

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