We conclude that V1-69/Vk3-20 and V3-7/Vk3-15 MALT lymphoma–derived Igs are ligand-selected, monospecific high-affinity antibodies.

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Response

Gastric MALT lymphoma–derived tumor immunoglobulins are polyreactive and respond to a variety of self and foreign antigens

Multiple attempts have been made in the past 2 decades to delineate the antigen specificity of tumor immunoglobulins expressed by mucosa-associated lymphoid tissue (MALT) lymphoma. These studies have produced rather discrepant results, which may be attributable to the different approaches to tumor-derived antibody generation and their screening. The tumor Ig specificity further
appears to depend on the anatomical location from which the lymphomas originate.

Hussel et al first addressed the issue of Ig specificity using anti-idiotypic antibodies derived from 3 cases of gastric MALT lymphoma; these authors detected polyreactivity in one case and described reactivity toward follicular dendritic cells and mucosal post capillary venules in the others.1 Greiner et al also did not identify a specific antigen, but concluded that the target ligand is a common antigen of IgA+ and IgM+ mucosal B cells.2 Lenze et al screened 7 single-chain fragment variable antibodies derived from gastric and nongastric MALT lymphomas and failed to identify binding partners for the majority of their Igs.3 Finally, Bende et al reported that many MALT lymphomas express B-cell receptors with strong CDR3 homology to rheumatoid factors (RFs).4 Specifically, these authors found that 8 of 45 gastric (18%), 13 of 32 salivary gland (41%) and none of the 19 (0%) pulmonary MALT lymphomas expressed RFs, and confirmed this finding experimentally for 7 of 10 independent antibodies. The majority of these antibodies were derived from parotid gland lymphomas, whereas only 2 of the 10 were from gastric lymphomas; one of these was paired with a nonmatching light chain. In this issue of Blood, the authors extend their previous findings by showing that a subset of this panel, again comprising predominantly parotid gland lymphoma–derived antibodies, fail to bind to other antigens, suggesting monoreactivity with IgG.

In contrast, we have recently shown that gastric MALT lymphoma antibodies derived from 7 patients as well as 5 Helicobacter-infected mice showed features of polyreactivity, that is, they bound to a panel of unrelated foreign and auto-antigens including Helicobacter extract, gastric extract, ssDNA, and lipopolysaccharide.5 Our antibodies also bound to IgG, albeit with lower affinity compared with the other antigens tested. We concluded from our results that IgG is only one of several target antigens. In an independent study, we showed recently that explanted tumor cells indeed respond to a variety of cognate antigens ex vivo, as treatment with Helicobacter and gastric extract, but also with ssDNA- and IgG-induced tumor cell proliferation.6

Whereas MALT lymphoma generally develops as a result of chronic antigenic stimulation in a variety of mucosal sites, the etiology is clearly organ-specific. Helicobacter pylori is known to induce MALT lymphomas of the stomach; parotid gland lymphomas have been linked to Sjögren syndrome. Patients with Sjögren syndrome can in fact be diagnosed based on serum and salivary fluid concentrations of RF.7 The IgG reactivity of parotid gland lymphomas as described by Bende et al4 is therefore not entirely surprising. To date, no link has been made between Helicobacter infection and RF production. We believe that the anatomical location and etiology must be taken into account when investigating the role of antigenic stimulation in MALT lymphomagenesis.

References
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