Common Threads of Mucosa-Associated Lymphoid Tissue Lymphoma Pathogenesis: From Infection to Translocation

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In this issue of the Journal, Ferreri et al. (1) add to the growing list of infectious agents that have been associated with extranodal marginal zone B-cell lymphomas of mucosa-associated lymphoid tissue (MALT lymphomas) with their finding that Chlamydia psittaci infection is associated with ocular adnexal lymphomas. Helicobacter pylori infection was first identified as a risk factor for gastric MALT lymphoma, which is invariably preceded by H. pylori-associated follicular gastritis (2). Subsequently, Isaacson et al. (2) showed that MALT lymphomas are antigen-driven clonal B-cell lymphomas and that eradication of H. pylori with antibiotic therapy could lead to lymphoma regression, at least in its early stages, prior to additional genetic events (3). More recently, Borrelia burgdorferi and Campylobacter jejuni have been linked to MALT-type lymphomas involving the skin and small intestine, respectively (4, 5). A related phenomenon may be the occurrence of essential mixed cryoglobulinemia associated with chronic hepatitis virus C infection (6). In all of these conditions, it is has postulated that the interaction of bacterial or viral antigens with host T-cells and antigen-presenting cells leads to a complex cascade resulting in clonal B-cell or plasma cell expansion. Although all immune responses are in effect clonal, MALT lymphomas are the result of immune responses gone awry (7), in which persistence of the antigen leads eventually to an autonomous clonal proliferation. Somewhat surprisingly, it has been shown (7) that B-cell proliferation in gastric MALT lymphoma is directed at auto-antigens, and not at H. pylori.

The pathogenesis of malignant lymphoma is a multi-step process that recapitulates many aspects of the normal immune response and of normal lymphocyte development. The patterns of spread of lymphomas reflect the homing patterns of normal lymphocytes, both microscopically, within lymph nodes, and macroscopically, at a clinical level. Thus, the site of presentation provides insight into the cellular origin of the neoplastic process. MALT lymphomas are primarily extranodal in distribution, retaining the phenotypic and functional properties of the mucosa-associated lymphoid system.

The neoplastic cells of B-cell and T-cell lymphomas express the differentiation antigens characteristic of normal lymphocyte subsets, and the genetic changes in most B-cell lymphomas recapitulate the alterations in the immunoglobulin genes that take place during normal B-cell development. The presence of somatic mutations characterizes the neoplastic cells as being at either a germinal-center or a post-germinal center stage of differentiation. Moreover, the molecular pathogenesis of B-cell lymphomas is often related to perturbation of a normal physiological event. For example, most B-cell lymphomas are characterized by translocations of the immunoglobulin genes or other genes critical to B-cell development, such as BCL6. These alterations appear to occur as mistakes in the normal recombination or somatic mutation processes (8,9).

Thus, MALT lymphomas are post-germinal-center–derived B-cell lymphomas that arise in and home to mucosa-associated sites that have acquired lymphoid tissue as a consequence of a chronic inflammatory process (10). Although MALT lymphomas arising in different organ systems share many pathologic and clinical similarities, there are also important differences. For example, the t(11;18)(q21;q21) translocation, involving the API2 gene (which encodes an inhibitor of apoptosis, c-IAP2) and the MALT1 gene, which was first identified in gastric MALT lymphomas (11), is common in MALT lymphomas that arise in the stomach or the lung but rare in those that arise in other extranodal locations, such as salivary gland, skin, or ocular adnexal tissues. Recently, Streubel et al. (12) identified a different translocation involving the MALT1 gene, in which the immunoglobulin heavy chain gene, rather than API2, is the partner. The t(14;18)(q32;q21) translocation was absent in gastric and pulmonary MALT lymphomas but was identified in cases of MALT lymphomas presenting in the conjunctiva and the lacrimal gland, as well as in some other unusual sites, such as liver and skin (12). It will be important to examine the ocular adnexal lymphomas associated with C. psittaci to determine whether they share an association with this translocation or another one.

Ferreri et al. (1) looked in a very limited way at clinical responses to antibiotic therapy for Chlamydia and observed an evaluable response in two of four patients. If gastric MALT lymphoma is an applicable model system to understand the sequence of events from infection to clonal B-cell proliferation and ultimately autonomous growth (13), then cytogenetic or molecular genetic studies of ocular adnexal lymphomas may show a correlation between absence of a response to antibiotic therapy and presence of a translocation. In parallel with the gastric MALT lymphoma story, the risk for lymphomatous complications appears to be both species- and strain-specific (13,14). Thus, DNA sequences of Chlamydia trachomatis or

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pneumoniae were not identified in any of the ocular adnexal lymphomas studied by Ferreri et al.

A successful immune response requires a delicate balance among antigen drive, lymphocyte proliferation, and lymphocyte apoptosis. In MALT lymphomas, unchecked proliferation of autoreactive B-cells can lead to both autoimmune disease, e.g., Sjogren’s syndrome or Hashimoto’s disease, and lymphoma (2). In a parallel fashion, defective immunoregulation of responding T cells following chronic EBV infection may result in a cytokine storm, leading to a hemophagocytic syndrome and, rarely, to T-cell lymphomas (15). Autoimmune lymphoproliferative syndrome (ALPS) is rare congenital disorder that is characterized by defects in lymphocyte apoptosis, usually secondary to germline mutations in the Fas gene (16). ALPS patients exhibit chronic lymphoproliferation, autoimmune disease, and an increased risk of B-cell derived lymphoma. Interestingly, somatic mutations in Fas also have been identified in MALT lymphoma (17), and the most common translocation of MALT lymphomas involves MALT1 and the API2 gene (10). In the above examples of lymphoma pathogenesis, defensive immunoregulation characterized by either excess lymphocyte activation and proliferation or defective apoptosis leads ultimately to clonal expansion and lymphoma.

An unanswered question is how chronic antigenic stimulation in the presence of H. pylori or C. psittaci infection leads not only to chronic B-cell proliferation but also to the specific translocations that characterize most MALT lymphomas. Intriguingly, although the details of the translocations differ among the various target organ systems, most of the molecular changes observed in MALT lymphomas involve a final common pathway. For example, the t(1;14)(p22;q32) translocation, which involves the BCL10 and immunoglobulin H genes, is a rare but recurrent translocation in MALT lymphoma (18). Nevertheless, MALT lymphomas with the more common t(11;18) translocation manifest increased nuclear staining of BCL10 and overexpression of MALT1 (19).

How these independent genetic changes are related has been a mystery. However, Lucas et al. (20) recently showed that BCL10 and MALT1 cooperate in a final common cascade of events leading to increased activity of the NF-kB signaling pathway. It is not surprising that the critical NF-kB pathway should be involved in MALT lymphomas, given that this family of transcription factors is activated by both antigenic stimulation and inflammatory cytokines. The milieu of infection and chronic inflammation provide a common background for the development of MALT lymphomas, but the specific events leading to chromosomal translocation and or mutation remain undiscovered. Recently, Ye et al. (14) postulated that the oxidative stress associated with inflammation might precipitate chromosomal damage. The results of Ferreri et al. (1) support the current model of MALT lymphoma pathogenesis and indicate that a multiplicity of infectious agents may ultimately be implicated as contributory factors. Interestingly, Chlamydia species share many features with H. pylori, because they too are associated with chronic persistent infection; induce a polyclonal lymphoid infiltrate in extranodal mucosa-associated sites (21); and have been implicated as cofactors in the development of both carcinoma and lymphoma (22,23). These common threads may prove to be part of the fabric of MALT lymphoma pathogenesis.

**References**


