

## Molecular Pathogenesis of Mucosa-Associated Lymphoid Tissue Lymphoma

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### ABSTRACT

Extranodal marginal zone B-cell lymphomas of mucosa-associated lymphoid tissue (MALT) type occur in a number of anatomic sites, but share overlapping morphologic and immunophenotypic features. *Helicobacter pylori* infection has been identified as an etiologic factor in gastric MALT lymphoma, and a growing list of other infectious organisms have recently been shown to be associated with MALT lymphomas at other anatomic sites. Although cause and effect has not been established for most of these infectious agents, our understanding of the biology has significantly improved, in part through the application of standard cytogenetic analyses. The common karyotypic alterations that characterize MALT lymphomas include the trisomies 3 and 18, the translocations t(11;18)(q21;q21), t(1;14)(p22;q32), t(14;18)(q32;q21), t(3;14)(q27;q32), and the recently described t(3;14)(p14.1;q32). This apparent complexity of cytogenetic alterations that have now been implicated in the pathogenesis of extranodal MALT lymphoma serves as a paradigm for molecular cross talk in neoplastic disease. Recent data have shown that at least three of the disparate translocations affect a common signaling mechanism, and thus unify all three under a common pathogenesis, resulting in the constitutive activation of the nuclear factor kappa B (NF- $\kappa$ B) pathway. It may be that the new MALT-related translocation involving the *FOXP1* gene and other as yet undiscovered translocations may all have in common increased NF- $\kappa$ B signaling.

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### INTRODUCTION

In 1983, Isaacson and Wright<sup>1,2</sup> first described the mucosa-associated lymphoid tissue (MALT) B-cell lymphomas, which comprise approximately 8% of all non-Hodgkin's lymphomas. They observed that primary low-grade gastric B-cell lymphoma and immunoproliferative small-intestinal disease showed histologic features more in common with those of mucosa-associated lymphoid tissue than those of peripheral lymph nodes.<sup>1</sup> These authors later extended their observations to other extranodal sites, including the salivary gland, lung, and thyroid.

MALT lymphoma exemplifies the close relationship between chronic inflammation and lymphomagenesis. A strong association has been found between chronic infection with *Helicobacter pylori* and gastric MALT,

an association that satisfies Koch's postulates for an etiologic agent.<sup>3</sup> Other infectious associations, though not fulfilling these criteria, have been reported for *Borrelia burgdorferi* (skin),<sup>4</sup> *Chlamydia psittaci* (ocular adnexae),<sup>5</sup> *Campylobacter jejuni* (intestine),<sup>6,7</sup> and hepatitis C virus (splenic marginal zone lymphoma).<sup>8,9</sup> Further, other chronic inflammatory conditions or autoimmune diseases have been associated with MALT lymphoma, including Sjögren's disease in the salivary glands and bronchial-associated lymphoid hyperplasia in the lung (Table 1).<sup>10,11</sup> A role for antigen-driven clonal expansion of the tumor cells is supported by the analysis of *IGH* (immunoglobulin heavy chain) genes in lymphoma cells, which show evidence of ongoing somatic mutation.<sup>12</sup> The involvement of antigen is further supported by evidence of clonal

**Table 1.** Anatomic Site, Infectious Agents, and Translocations in MALT Lymphomas

Anatomic Site	Infectious Agent	Translocation	Frequency (%)*
Stomach	<i>Helicobacter pylori</i>	t(11;18)(q21;q21)	22
		t(1;14)(p22;q32)	3
Lung	??	t(11;18)(q21;q21)	42
	??	t(1;14)(p22;q32)	7
Intestine	<i>Campylobacter jejuni</i>	t(11;18)(q21;q21)	15
		t(1;14)(p22;q32)	10
Ocular adnexa	<i>Chlamydia psittaci</i>	t(3;14)(p14;q32)	20
		t(14;18)(q32;q21)	13
Skin	<i>Borrelia burgdorferi</i>	t(14;18)(q32;q21)	14
		t(3;14)(p14.1;q32)	10
Salivary gland	Autoimmune?	t(14;18)(q32;p21)	5
Thyroid	Autoimmune?	t(3;14)(p14.1;q32)	50

Abbreviation: MALT, mucosa-associated lymphoid tissue.  
\*Frequency data are based on references 27, 28 and 65.  
†Data supporting a definitive role for these organisms is lacking.

evolution within the tumor, suggesting pressure to increase affinity of the surface immunoglobulin for antigen.<sup>13</sup> Thus, in early stages of gastric lymphoma development, neoplastic growth may be facilitated by antigen-driven T cells specific for the *H. pylori* organism<sup>14</sup> (Fig 1) and the eradication of *H. pylori* infection with antibiotics is consistent with this postulate.<sup>15</sup> However, much less is known about the role of the host immune response in pathogenesis, as demonstrated by the fact that only a small minority of infected patients ever develop gastric lymphoma.<sup>16</sup> Differences in MALT lymphoma incidence may correlate with different inflammatory cytokines and HLA polymorphisms.<sup>17,18</sup> Chronic inflammation induced by persistent infection or autoimmune disorders may result in organized lymphoid tissue and a microenvironment that facilitates lymphomagenesis. Important determinants of risk may relate to the etiology of the inflammation (ie, characteristics of infectious microorganisms such as *H. pylori*) and/or the specific nature of the host immune response.<sup>19</sup> One or both of these may be required for the acquisition of initial genetic aberrations, which when present, allow irreversible progression to MALT lymphoma.

### CLASSIFICATION

In the mid-1990s, MALT lymphomas were reclassified as marginal zone lymphomas (MZL) with nodal, primary splenic, and extranodal subtypes.<sup>20,21</sup> Despite different anatomic sites and distinct clinical behaviors, MZLs often display overlapping morphologic and immunophenotypic features.<sup>22-25</sup> However, more recent cytogenetic and molecular genetic data have demonstrated the distinctiveness of these lymphoid neoplasms, and, according to WHO classification, each is now considered to be a unique lymphoma subtype.<sup>26</sup>

### Cytogenetic Abnormalities

Cytogenetic data accumulated in recent years have proved useful in demonstrating similar alterations in

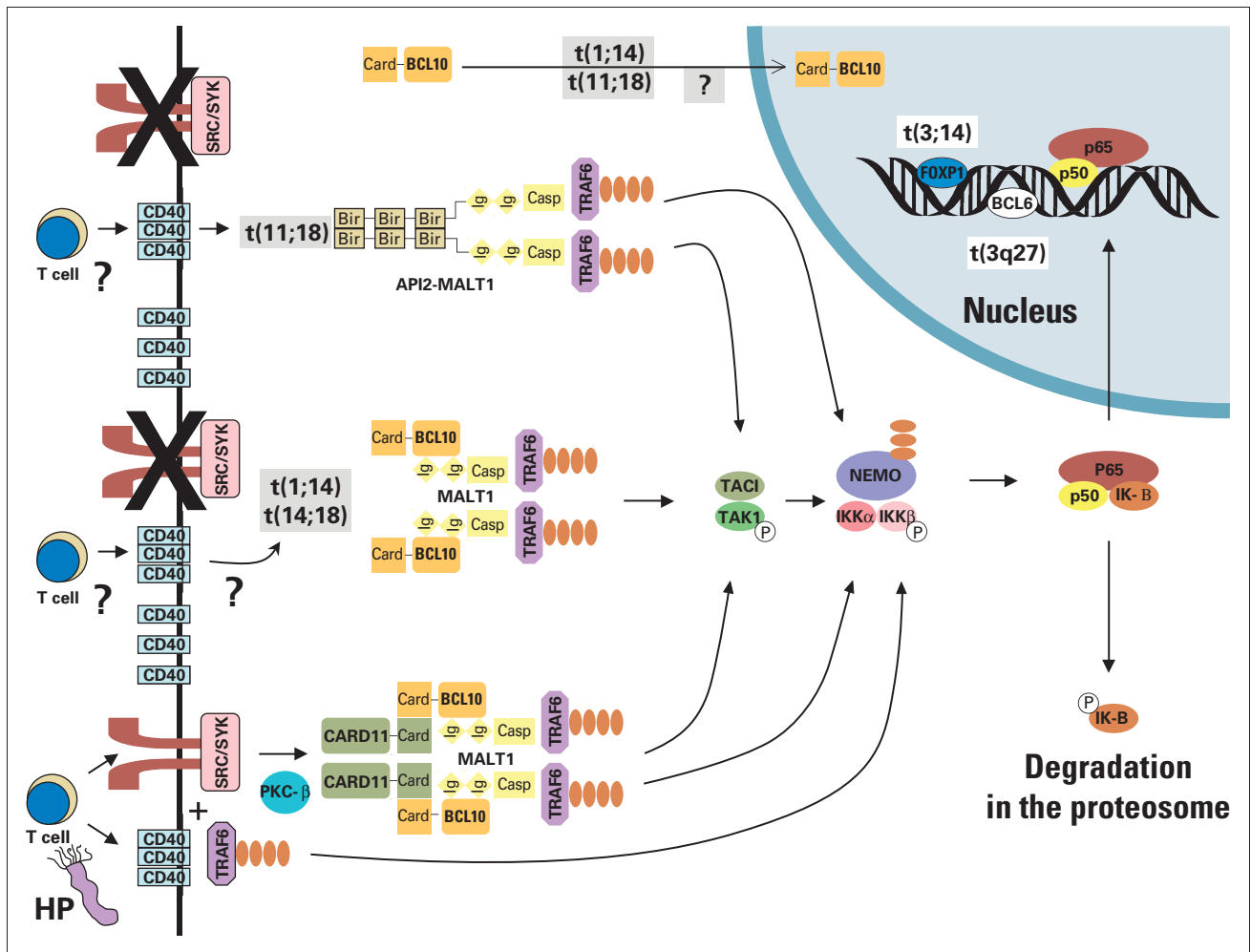
MALT lymphomas from distinct anatomic sites. These abnormalities include trisomies 3 and 18 and a number of translocations, which are mutually exclusive, as will be discussed further (Fig 1, Table 1). The frequency of these cytogenetic aberrations varies considerably at different anatomic locations (Table 1). Trisomies 3 and/or 18 are present as the sole abnormality in 22% of the cases, but in many of these cases are associated with one of the characteristic translocations, which are present in 22% to 36% of cases.<sup>27,28</sup>

### t(11;18)(q21;q21)

The t(11;18)(q21;q21), occurring in 13.5% to 35% of cases, is the most common chromosomal abnormality associated with MALT lymphomas.<sup>29</sup> It has been found in MALT lymphomas at a number of anatomic sites, including the lung, stomach, intestine, and, less commonly, the skin, orbit, and salivary gland (Table 1).<sup>27,30-37</sup> Importantly, t(11;18)(q21;q21) is restricted to MALT lymphomas and has not been detected in nodal or splenic MZLs. In most of these translocation-positive cases, t(11;18)(q21;q21) is the sole chromosomal aberration and only exceptionally has it been detected in de novo diffuse large B-cell lymphomas (DLBCL) arising at mucosal sites.<sup>32,33,38,39</sup> This translocation is not characteristic of *H. pylori* gastritis and other premalignant diseases associated with MALT lymphoma, with the exception of a single case of conjunctival lymphoid hyperplasia.<sup>36,39,40</sup>

The t(11;18) translocation is seen more frequently in cases that show dissemination to regional lymph nodes or distal sites than in those confined to the stomach, and it has been associated with cases that do not respond to *H. pylori* eradication.<sup>36,40,41</sup> In the stomach, the detection of the translocation identified 70% of cases that were unresponsive to antibiotic therapy alone, including 60% of those confined to the stomach (stage IE).<sup>36,41</sup> As noted above, this translocation is seen only rarely in transformed MALT lymphoma.<sup>39,42</sup>

The t(11;18) represents the fusion of the *API2* (apoptosis inhibitor-2) gene on chromosome 11 and the *MALT1* (MALT lymphoma-associated translocation) gene on chromosome 18.<sup>43-45</sup> *API2*, which is expressed highly in lymphoid cells, is a member of the inhibitors of apoptosis (*IAPs*) gene family. *IAP* genes contain one to three copies of a BIR (baculovirus inhibitor of apoptosis repeat) motif, a caspase recruitment domain (CARD), and a C-terminal zinc-binding really interesting new gene (RING) finger domain.<sup>46</sup> Several of the *IAP* family proteins are potent inhibitors of apoptosis, due to their ability to inhibit activated caspases via interaction with tumor necrosis factor (TNF) receptor-associated factor (TRAF) proteins. *API2* codes for a protein known as c-IAP2, which suppresses apoptosis by binding to and inhibiting the activity of caspase 3 and caspase 7 as well as by inhibiting cytochrome C activation of procaspase 9.<sup>47</sup> The *MALT1*



**Fig 1.** Major chromosomal translocations in mucosa-associated lymphoid tissue (MALT). Physiologic signaling during *H. pylori* (HP) infection in the stomach occurs through a T-cell dependent activation of the antigen receptor on B cells producing the oligomerization of the BCL10/MALT1 complex together with TNF receptor-associated factor 6 (TRAF6). This serves to activate IκB kinase-γ (IKKγ), which in turn phosphorylates IκB, targeting it for degradation and allowing nuclear factor kappa B (NF-κB) to translocate freely into the nucleus, upregulating a number of NF-κB-responsive genes. The t(1;14) and t(14;18) upregulate BCL10 and MALT1, respectively. The t(11;18) results in a fusion molecule, the API2-MALT1 protein, which is capable of bypassing normal signaling and activating IKK directly. Translocation of BCL10 protein into the nucleus occurs with either the t(1;14) or t(11;18), and appears to be important in the biology of MALT, although the precise mechanism is unknown. Lastly, the role of the two new translocations recently identified is incompletely understood, but both BCL6 and FOXP1 are transcription factors and thus are likely to act within nucleus. Whether these involve NF-κB activation is unknown. Casp, caspase; Card, caspase recruitment domain; Bir, baculovirus inhibitor of apoptosis repeat; PKC-β, protein kinase C beta; TACI, transmembrane activator and CAML interactor; TAK1, transforming growth factor beta-activated kinase; NEMO, NF-κB essential modulator.

gene comprises an N-terminal death domain, followed by two immunoglobulin-like domains and a caspase-like domain.<sup>48</sup> The fusion junctions at the transcript level have been well characterized. For the *API2* gene, the breakpoints are always downstream of the third BIR domain, but upstream of the C-terminal RING domain, with 91% occurring just proximal to the CARD domain.<sup>34,36,40,49-51</sup> For the *MALT1* gene, breakpoints are consistently upstream of the C-terminal caspase-like domain. Thus, the resulting API2-MALT1 fusion transcript always comprises the N-terminal API2 with three intact BIR domains and the C-terminal MALT1 region containing an intact caspase-like domain.<sup>31,34,43,44,49,52</sup> The specific selection of these domains of the *API2* and

*MALT1* genes to form a functional fusion product strongly suggests their importance and synergy in oncogenesis.

Breakpoints observed in the t(11;18) are clustered in the regions of intron 7 and exon 8 of the *API2* gene and introns 4, 6, 7 and 8 of the *MALT1* gene, possibly reflecting the presence of fragile sites in these chromosomal regions. High frequencies of deletions and duplications in both the *API2* and *MALT1* genomic sequences are also found, which strongly suggests that multiple double-strand DNA breaks (DSBs) must have occurred during the translocation process.<sup>53</sup> Studies have failed to show a specific sequence-mediated chromosomal recombination mechanism involved in the t(11;18).<sup>54</sup> Rather, this translocation appears to result from illegitimate nonhomologous end

joining after DSBs. Although the exact cause and nature of the DSBs in MALT lymphoma are as yet unknown, emerging data suggest that etiologic factors underlie the dramatically variable frequencies of this translocation, ranging from 0% to 1% in the thyroid and salivary gland to 30% to 50% in the stomach and lung.<sup>28,36</sup> These differences might result from different exposures to various infectious agents or to variable genetic insults introduced by premalignant disorders (ie, inflammatory conditions) associated with MALT lymphoma in different locations.

In gastric MALT lymphoma, the t(11;18) translocation has been shown to be significantly associated with infection of CagA-positive strains of *H. pylori*, which are more likely to be associated with inflammatory responses and the induction of potent chemokines (interleukin-8) that cause neutrophil activation.<sup>36</sup> This neutrophil response leads to the generation of genotoxic agents such as reactive oxygen species that are known to cause a wide range of DNA damage, particularly DSBs.<sup>36,55,56</sup> It is tempting to hypothesize that the DSBs and deletions of the *API2* and *MALT1* gene sequences may be related to genotoxic insults caused by inflammatory responses in premalignant lesions associated with MALT lymphoma, specifically in mucosal sites more exposed to exogenous environmental inflammatory stimuli such as the lung and stomach.

#### **t(1;14)(p22;q32) and t(1;2)(p22;p12)**

The t(1;14)(p22;q32)<sup>57</sup> and variant t(1;2)(p22;p12)<sup>58</sup> occur in 1% to 2% of MALT lymphomas and have been reported in the stomach, lung and skin.<sup>27,28</sup> As a result of the translocation, the entire coding region of the *BCL10* gene on chromosome 1 is relocated to chromosome 14, thereby bringing *BCL10* gene under control of the *IGH* enhancer region (or *IGLK* region in the case of variant translocations). The t(1;14) results in overexpression of nuclear BCL10 protein, a finding that can be seen using routine immunohistochemistry.<sup>59</sup> BCL10 is an intracellular protein that is essential for both the development and function of mature B and T cells, linking antigen-receptor signaling to the nuclear factor kappa B (NF- $\kappa$ B) pathway. Several lines of evidence from transgenic mice models indicate that *BCL10* is not a tumor suppressor gene, nor is it heavily implicated in apoptotic signaling.<sup>60,61</sup> Rather, it is the deregulated expression of wild-type *BCL10* resulting from translocation that is important in MALT lymphomagenesis.

The t(1;14)(p22;q32) and t(1;2)(p22;p12) have been reported exclusively in MALT lymphoma, and these cases typically display additional genomic abnormalities. Similar to cases with t(11;18), patients present with advanced stage and are unlikely to respond to *H. pylori* eradication.<sup>59</sup>

#### **t(14;18)(q32;q21)**

The t(14;18) translocation occurring in 15% to 20% of MALT lymphomas brings the *MALT1* gene under the

control of the *IGH* enhancer on chromosome 14, resulting in deregulated expression of MALT1 and downstream activation of the NF- $\kappa$ B pathway (Fig 1).<sup>37,62</sup> This translocation occurs more frequently in nongastrointestinal MALT lymphomas, particularly those involving the liver, lung, and ocular adnexa.<sup>28,63</sup> In contrast to MALT lymphomas with t(11;18)(q21;q21), those with t(14;18)(q32;q21) frequently harbor additional genetic aberrations, including trisomies 3 and/or 12 and 18.

The 18q21 breakpoints involve the *MALT1* gene that lies 5 Mb centromeric of the *BCL2* gene, which is involved in the t(14;18) characteristic of follicular lymphoma. The occurrence of the t(14;18) translocations affecting closely linked genes, strengthens the hypothesis of Roix et al<sup>64</sup> that the formation of specific translocations in human lymphomas is determined in part by spatial proximity of translocation-prone genetic loci. The overexpression of the MALT1 protein in the cytoplasm of t(14;18)-positive cells can be detected using immunohistochemistry.<sup>27</sup> BCL10 protein is also overexpressed, but in contrast to cases with the t(11;18) and t(1;14), the increased BCL10 protein is located in the cytoplasm and not the nucleus.

#### **t(3;14)(p14.1;q32)**

The recently described t(3;14)(p14.1;q32) brings the *FOXP1* gene at 3p14.1 under the control of the *IGH* gene enhancer and deregulates its expression.<sup>65</sup> *FOXP1* (forkhead box protein P1) is a member of the FOXP subfamily (FOXP1-4) of forkhead transcription factors, characterized by a common DNA binding winged-helix or forkhead domain together with N-terminal zinc finger and leucine zipper domains.<sup>66</sup> There is little information on how FOXP transcription factors mediate signaling and affect gene regulation. Recent data have shown *FOXP1* to be strongly overexpressed in a subset of DLBCLs, in which it is associated with inferior survival.<sup>67,68</sup> This novel translocation has been associated with MALT lymphomas involving uncommon sites and distinct from those involving the t(11;18). These sites include the thyroid (50%), ocular adnexa (20%), and skin (10%).<sup>65</sup> Cases with the translocation show overexpression of *FOXP1* protein. *FOXP1* protein is also overexpressed in cases of MALT lymphoma with trisomy of chromosome 3, suggesting that increased gene copy number may be another mechanism of deregulated gene expression. A case of a gastric lymphoma with a DLBCL morphology with t(3;14)(p14.1;q32) was reported recently.<sup>69</sup> This finding raises the possibility that MALT lymphomas harboring this translocation may occur in the stomach and that such lymphomas may be at risk to transform to DLBCL.

#### **BCL6 Translocations**

A recent study of a large number of well characterized MALT lymphomas from several anatomic locations has suggested that 3q27 translocations, involving the *BCL6*

gene, may be found in a small number of cases.<sup>70</sup> Ye et al in a study of 306 cases of MALT lymphoma detected translocations involving the *BCL6* gene in six cases using an interphase fluorescence in situ hybridization (FISH) technique. In three of these cases, the translocation partner was the *IGH* gene at chromosome 14q32. The presence of the translocation appeared to correlate with *BCL6* protein expression. Anatomical sites of MALT lymphomas with *BCL6* translocations included the stomach, salivary gland, lung, skin and thyroid. These preliminary data will need to be substantiated before implicating the *BCL6* oncogene in MALT lymphomagenesis.

### UNIFYING HYPOTHESIS

Under normal circumstances, signaling through the antigen receptor facilitates the interaction BCL10 and MALT1, which synergize to activate the downstream transcription factor NF- $\kappa$ B (Fig 1). The expression of both proteins is restricted primarily to lymphoid tissues, predominantly in the cytoplasm of activated germinal-center B cells.<sup>59,71</sup> In contrast to normal lymphoid tissue, MALT lymphomas show variable patterns of expression of these two proteins depending on the underlying translocation (Table 2).<sup>27</sup> In *H. pylori*-associated gastritis and during the early phases of MALT lymphoma development, antigens expressed by *H. pylori* in conjunction with specific T cell help signal through the antigen receptor of polyclonal B cells and promote the interaction of normal BCL10 and MALT1 proteins, leading to NF- $\kappa$ B signaling. This interaction is important, as BCL10 is required to promote MALT1 oligomerization and subsequent downstream signaling. In time, a subclone with one of the characteristic MALT lymphoma translocations may emerge with an obvious growth advantage. In this setting constitutive NF- $\kappa$ B results, eliminating the need for persistent infection and thus, a disease state no longer responsive to *H. pylori* eradication therapy.

BCL10 activates NF- $\kappa$ B by promoting the ubiquitination of I $\kappa$ -B kinase- $\gamma$  (IKK $\gamma$ ). The upstream activator of BCL10 is CARMA1 (CARD, membrane-associated guanylate kinase [MAGUK], protein 1).<sup>72</sup> CARMA1 interacts with the antigen-activated B-cell receptor in the lipid rafts (areas of plasma membrane rich in cholesterol, glycosphingolipids, and glycolipid-enriched membrane domains) where the TNF receptor CD40 also aggregates. CARMA1 forms

a complex with BCL10 and MALT1 that induces the oligomerization of the latter.<sup>72-74</sup> The MALT1 oligomerization and CD40 activation allow the formation of a complex with TNF receptor-associated factor 6 (TRAF6) and TRAF6 oligomerization, which induces the ubiquitin ligase activity of TRAF6 and results in polyubiquitination of IKK $\gamma$ .<sup>75,76</sup> This triggers the phosphorylation and degradation of I $\kappa$ B and the release of NF- $\kappa$ B, allowing it to translocate to the nucleus where it transactivates genes responsible for lymphocyte proliferation and survival.

In MALT lymphoma with t(1;14)(p22;q32), in which BCL10 is overexpressed, BCL10 is believed to form oligomers through its CARD domain without the need for upstream signaling, and so triggers MALT1 oligomerization and aberrant NF- $\kappa$ B activation. In MALT lymphoma with t(14;18)(q32;q21), MALT1 is overexpressed. It is likely that MALT1 interacts with and stabilizes BCL10, causing its accumulation in the cytoplasm of tumor cells bearing t(14;18)(q32;q21). The t(11;18) results in the formation of a novel fusion gene, *API2-MALT1*, and subsequent fusion protein. The fusion protein can activate NF- $\kappa$ B directly, although neither wild-type API2 nor wild-type MALT1 alone has this activity. Both the BIR domains of the API2 molecule and the caspase-like domain of MALT1 are required. It is believed that the BIR domains facilitate self-oligomerization and subsequent downstream constitutive NF- $\kappa$ B activation. MALT lymphomas with the t(11;18) like the t(1;14) ones, show strong or moderate BCL10 expression in the nucleus, a finding whose mechanism is still unknown.<sup>59</sup> Other findings suggest that the t(11;18) may be unique among the MALT-related translocations, not only increasing signaling through the NF- $\kappa$ B pathway, but also having a more direct role in the inhibition of apoptotic signaling.<sup>77,78</sup> The mechanisms underlying the pathogenesis of the newly described t(3;14)(p14.1;q32) are unknown, but may be unrelated to the NF- $\kappa$ B pathway.<sup>65</sup>

### MALT Lymphoma Progression and Transformation

The initial stage of MALT, involving continuous antigen-dependent growth of B lymphocytes, eventually progresses to a true low-grade lymphoma, involving autonomous proliferation that may, in some cases, develop DLBCL.<sup>79-81</sup> The frequent coexistence of small- and large-cell components in extranodal MALT lymphomas suggests a clonal progression of these small-cell lymphomas to a DLBCL in some cases. Immunohistochemical studies of immunoglobulin light chain restriction of both components provided the first evidence of a clonal relationship in such cases.<sup>80</sup> Subsequently, a clonal link between small- and large-cell components in gastric B-cell lymphomas was shown by sequence analysis of the rearranged *IGH* gene.<sup>79</sup> These findings support the

**Table 2.** MALT Translocations and Protein Expression

Protein → Translocation	MALT	BCL10	FOXP1
t(11;18)(q21;q21)	Weak cytoplasmic	Strong nuclear	?
t(1;14)(p22;q32)	Weak cytoplasmic	Strong nuclear	?
t(14;18)(q21;q32)	Strong cytoplasmic	Strong cytoplasmic	?
t(3;14)(p14.1;q32)	?	?	Nuclear

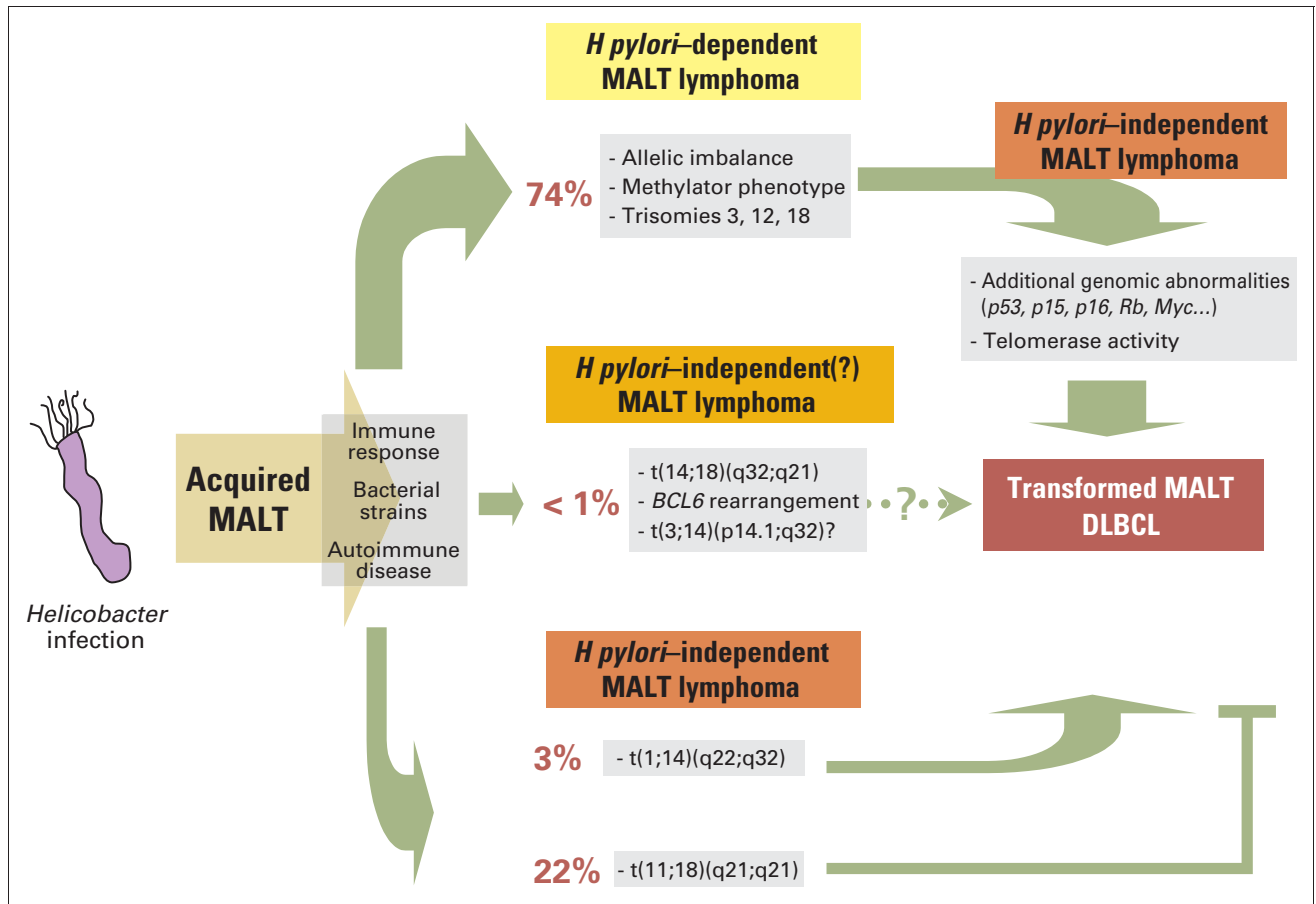
Abbreviation: MALT, mucosa-associated lymphoid tissue.

common occurrence of low- and high-grade components as well as the morphologic variants of high-grade gastric lymphomas with features suggestive of underlying low-grade MALT lymphoma (ie, DLBCL with lymphoepithelial lesions).

The exact mechanisms underlying the transition of low-grade MALT lymphoma to an aggressive lymphoma including DLBCL remain unclear. As in other neoplasms, MALT lymphoma development is marked by a series of genetic aberrations that contribute to increasing genomic instability and the establishment of autonomously replicating neoplastic cells. A number of genetic alterations has been associated with histologic transformation including *p53* allelic loss and mutation, hypermethylation of *p15* and *p16*, and *p16* deletions.<sup>82-85</sup> There is evidence to suggest that aberrant telomerase activity may be involved in some cases of MALT lymphoma showing histologic progression. High levels of telomerase activity in high-grade

gastric lymphoma and only weaker levels in low-grade MALT lymphoma have been reported.<sup>86</sup>

Barth et al<sup>87</sup> studied 52 cases of extranodal B-cell lymphomas including 18 MALT, seven composite lymphomas with both MALT and DLBCL components and 27 de novo DLBCL of the stomach using tissue microdissection, comparative genomic hybridization and FISH. The translocation t(11;18) was found as the sole aberration in two MALT lymphomas only. In contrast to this, t(11;18)-negative cases were characterized by frequent gains on chromosome 3 and DNA amplifications of chromosomal region 2p13-p15. A clonal lymphoma progression from small-cell to large-cell component was found with accumulation of gains and losses of chromosomal material in the large-cell component and in the composite cases. In an analysis of 24 gastric MALT lymphomas, Starostik et al<sup>88</sup> similarly identified the absence of t(11;18) as a marker of genomic instability and ultimate progression to DLBCL. When



**Fig 2.** Major pathways involved in the development of gastric mucosa-associated lymphoid tissue (MALT) lymphoma. *H. pylori* infection produces gastritis with a polyclonal proliferation of B cells. The most frequent pathway to the development of a MALT lymphoma affects approximately 75% of cases and results from allelic imbalances, the acquisition of a methylator phenotype, or a number of different trisomies. This pathway produces a MALT lymphoma that is still antibiotic sensitive, but may transform to an antigen-independent tumor and subsequently to a diffuse large B-cell lymphoma (DLBCL) following a number of clonal evolution events. The middle pathway depicts clones that results from a number of rare MALT-related translocations, including t(14;18), t(3;14) and possibly the newly described *BCL6* translocations. The antibiotic response and risk for transformation to DLBCL is not known. Lastly, the translocations t(1;14) and t(11;18) occur in 3% and 22% of gastric MALT lymphoma cases, respectively. These cytogenetic alterations identify a tumor that has become antibiotic resistant and at least in the case of the t(1;14), may progress to DLBCL. The t(11;18)-positive cases, on the other hand, rarely progress to an aggressive histology, but commonly spread to other mucosal sites.

the patients were grouped according to t(11;18) status, t(11;18)-negative cases showed more clonal evolution. The most frequent aberration, amplification of the 3q26.2-27 chromosomal region (which harbors the *BCL6* locus and a number of other genes), was found in 21% of patients, all of whom were exclusively t(11;18) negative. Zhou et al<sup>89</sup> reported similar findings, showing that both chromosomal gains and losses were much more frequent in t(11;18)-negative cases than positive cases.

Another group analyzed DNA methylation patterns among *H. pylori*-dependent and -independent cases (ie, those without *H. pylori* colonization or those showing resistance to eradication therapy) and compared them with t(11;18)-positive MALT lymphomas, gastric DLBCL and *H. pylori*-associated chronic gastritis.<sup>90</sup> Using methylation-specific polymerase chain reaction, the authors found an *H. pylori*-dependent group that was associated with a high level of methylation in comparison with a low level of methylation in the *H. pylori*-independent group. It is important to note that hypermethylation of multiple CpG islands is frequently found in other tumors that have arisen from chronic inflammatory conditions such as hepatocellular carcinomas with cirrhosis/hepatitis and ulcerative colitis associated with colonic carcinoma.

Together these findings support a model of increasing genomic instability from low-grade to high-grade disease, with the accumulation of additional genetic aberrations. Moreover, the number of molecular alterations that appear to underlie transformation of MALT lymphomas suggests a significant degree of molecular heterogeneity.

### MALT Lymphoma Pathways

Focusing exclusively on gastric MALT lymphomas, evidence suggests that these tumors develop along two major molecular pathways that emerge from an oncogenic inflammatory milieu, one dependent on the presence of t(11;18) and the other associated with a CpG island methylator-prone phenotype (CIMP<sup>+</sup>; Fig 2). In either setting, *H. pylori* infection leads to chronic gastritis characterized by a strong inflammatory response, increased cell turnover and damage by reactive oxygen species, which induces in a susceptible host either (1) MALT lymphoma that once established, is independent of the *H. pylori*, harbors the cytogenetically stable t(11;18), lacks a methylator phenotype, and shows fewer genomic imbalances; these tumors rarely accumulate secondary aberrations, perhaps required for transformation into DLBCL, and thus remain as typical

MALT lymphomas; or (2) MALT lymphoma that is t(11;18) negative, has other genomic imbalances such as trisomy of chromosomes 3 and 18, has translocations involving *BCL10* or *MALT1* loci, and may accumulate additional allelic imbalances, some of which are identical to those found in DLBCL, implying that it is this group of MALT lymphomas that shows transformation into secondary high-grade DLBCL.<sup>88</sup> These may have a methylator phenotype and result in tumors prone to clonal evolution (Fig 2).

### CONCLUSION

Classical cytogenetic studies and, more recently, locus-specific FISH analysis have been instrumental in furthering our understanding of MALT lymphoma biology. *BCL10*, *MALT1* and *API2-MALT1* affect the same signaling pathway, bringing these disparate translocations into a unifying pathogenesis for MALT lymphoma development and progression. The activation of NF- $\kappa$ B and nuclear localization of BCL10 protein appear critical to disease progression and antibiotic resistance in MALT lymphomas. Increased cytoplasmic expression of BCL10 resulting from the t(14;18) may confer similar clinical features, but requires further study. Importantly, the precise role of BCL10 in MALT lymphomas will be central to our understanding of the molecular mechanisms underlying these three translocations. In addition, recent cytogenetic and loss-of-heterozygosity data suggest that there are at least two kinds of MALT lymphomas: one associated with chromosomal instability [t(14;18) and t(1;14)] and the other [t(11;18)] which is not. Much less is known about the t(3;14)(p14.1;q32) involving the *FOXP1* gene and the more recently described *BCL6* translocations, which require further study.

As the list of cytogenetic alterations currently implicated in MALT lymphoma grows, there is obvious excitement as candidate loci involving other NF- $\kappa$ B pathway members become potential targets for recurrent alterations in this lymphoma. Strategies employing FISH, *IGH* break-apart probes and long-distance inverse polymerase chain reaction may become commonplace as we search for new translocation partners involving chromosome 14q32 and, as yet, undiscovered MALT-related genes.

### Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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