MALT Lymphoma: Recent Advances in Aetiology and Molecular Genetics

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Mucosa-associated lymphoid tissue (MALT) lymphoma is a common low grade B-cell lymphoma arising from a background of chronic inflammatory disease at a number of mucosal sites. Those originating in the stomach are causatively linked to Helicobacter pylori infection and eradication of the bacterium with antibiotics leads to long-term complete regression of the lymphoma in ~70% of cases. Now, there is further evidence of linking Campylobacter jejuni, Borrelia burgdorferi and Chlamydia psittaci infection with immunoproliferative small intestine disease, MALT lymphoma of the skin and ocular adnexa respectively. t(11;18)/API2-MALT1, t(1;14)/IGH-BCL10, t(14;18)/IGH-MALT1 and t(3;14)/IGH-FOXP1 occur at considerably variable incidences in MALT lymphomas of different sites. The first three chromosome translocations are specifically associated with the MALT lymphoma entity and the oncogenic products of these translocations have been shown to target a common molecular pathway, i.e. the nuclear factor-kB pathway. Here, I review the recent advances in our understanding of the association of microbial pathogens with MALT lymphoma of various sites and the molecular genetics underlying the lymphoma development.

Keywords: mucosa-associated lymphoid tissue lymphoma, microbial pathogens, chromosome translocation, pathogenesis

INTRODUCTION

Extranodal marginal zone B cell lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) is the third commonest form of non-Hodgkin lymphoma and its incidence has risen steadily over the last two decades. MALT lymphoma occurs in a number of extra-nodal sites including both mucosal organs such as the gastrointestinal tract, lung, salivary gland, thyroid, ocular adnexa and liver, and non-mucosal organs for example the orbit and skin. Interestingly, these organs are normally devoid of any organised lymphoid tissue and lymphoma at these sites arises from the MALT acquired as a result of chronic inflammatory or autoimmune disorders, such as Helicobacter pylori (H. pylori) associated chronic gastritis, lymphoepithelial sialadenitis and Hashimoto thyroiditis. The microbial pathogens that underlie such chronic inflammatory diseases, also play a pivotal role in both malignant transformation and subsequent clonal expansion of the transformed clone. This is best exemplified by the causative role of H. pylori infection in development of gastric MALT lymphoma, which led to successful innovative treatment of the lymphoma with antibiotics. Several other infectious agents have now been linked with MALT lymphoma of different sites and eradication of the infectious agents leads to complete remission of the lymphoma in some cases. In addition, there are important advances in characterisation of the molecular genetics, particularly chromosomal translocations, of MALT lymphomas. Here I review the recent advances in our understanding of the association of microbial pathogens with MALT lymphoma of various sites and the molecular genetics underlying their development.

MICROBIAL PATHOGENS AND MALT LYMPHOMA

Helicobacter pylori and gastric MALT lymphoma

A link of H. pylori infection with gastric MALT lymphoma is first provided by identification of the bacteria in the vast majority of the lymphoma specimens. This association is firmly supported by subsequent epidemiological studies. Now, there is compelling evidence that gastric MALT lymphoma is caused by infection with H. pylori (Table 1). Laboratory studies show that the growth of the lymphoma B-cells can be stimulated by intratumoral H. pylori specific T-cells, involving direct B and T cell interaction via surface co-
stimulatory molecules. Clinically, eradication of *H. pylori* with antibiotics leads to long term complete regression of gastric MALT lymphoma in ∼ 75% of cases. It is believed that *H. pylori* eradication leads to the disappearance of intratumoral *H. pylori* specific T-cells, and thus removal of the growth support of neoplastic B cells, which eventually causes the lymphoma to regress. Approximately, 5-10% of gastric MALT lymphomas appear to be negative for *H. pylori* and the aetiological factor in these cases remains unclear. Some cases may be explained by undiagnosed *H. pylori* infection, and others may be associated with *H. heilmannii*. Interestingly, gastric MALT lymphomas associated with *H. heilmannii* infection have been shown to respond to antibiotic therapy. Thus, the pathogenic role of *H. heilmannii* infection in gastric MALT lymphoma development is likely similar to that of *H. pylori*.

**Table 1. Evidence of linking a specific microorganism to MALT lymphoma of different sites**

<table>
<thead>
<tr>
<th>Koch’s postulates for linking a specific microorganism to a disease (1882)*</th>
<th>Gastric MALT lymphoma</th>
<th>IPSID</th>
<th>Cutaneous MALT lymphoma</th>
<th>Ocular adnexal MALT lymphoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>The organism is found in the lesion of the disease.</td>
<td><em>H. pylori</em></td>
<td><em>C. jejuni</em></td>
<td><em>B. burgdorferi</em></td>
<td><em>C. psittaci</em></td>
</tr>
<tr>
<td>The organism can be isolated and grown <em>in vitro</em>.</td>
<td>~ every case</td>
<td>Some cases</td>
<td>Variable</td>
<td>Variable</td>
</tr>
<tr>
<td>Inoculation of the organism causes lesions in healthy susceptible animals</td>
<td>Yes</td>
<td>not yet</td>
<td>not yet</td>
<td>not yet</td>
</tr>
<tr>
<td>The organism can be recovered from the experimental animal.</td>
<td>Yes</td>
<td>unknown</td>
<td>unknown</td>
<td>unknown</td>
</tr>
</tbody>
</table>

*Although there are limitations, Koch’s postulates are still a useful benchmark in judging whether there is a cause-and-effect relationship between an infectious agent and a clinical disease. MALT: mucosa-associated lymphoid tissue, IPSID: immunoproliferative small intestine disease, *H. pylori*: *Helicobacter pylori*, *C. jejuni*: *Campylobacter jejuni*, *B. burgdorferi*: *Borrelia burgdorferi*, *C. psittaci*: *Chlamydia psittaci*|

Growing evidence indicates that the development of non-gastric MALT lymphoma is also associated with infection by microbial pathogens (Table 1). IPSID (previously known as alpha chain disease), a variant of MALT lymphoma, has been thought to be triggered by bacterial infections as the disease at early stages respond favourably to treatment with antibiotics. A recent study showed that *Campylobacter jejuni* (*C. jejuni*) was present in 5/7 cases of IPSID and eradication of the organism with antibiotics led to complete remission in an index case. A subsequent investigation showed *C. jejuni* in 12/27 (47%) cases of IPSID and 14/87 (16%) cases of other intestinal lymphomas, but not in non-intestinal lymphoma and normal/reactive intestinal biopsies. These results therefore confirm that *C. jejuni* is associated with IPSID. However, it remains to be investigated whether *C. jejuni* has a causative role in the development of IPSID.

**Borrelia burgdorferi** and cutaneous marginal B cell lymphoma

*Borrelia burgdorferi* is the etiological agent of Lyme disease, a tick borne zoonosis, which is associated with chronic skin infection. There is increasing evidence suggesting a link between *Borrelia burgdorferi* infection and development of primary cutaneous B-cell lymphoma. A number of studies demonstrate the presence of *Borrelia burgdorferi* in primary cutaneous B-cell lymphoma, with a higher prevalence in marginal zone B-cell lymphoma than other lymphoma subtypes. Furthermore, several independent studies show that *Borrelia burgdorferi* associated cutaneous marginal B cell lymphoma completely regresses following antibiotic treatment. The disappearance of the microorganism following antibiotic treatment is accompanied by a marked decline in the number of plasma cells and CD3+ T cells, strong indicators of active immune responses. These findings support a pathogenic role for *Borrelia burgdorferi* in sustaining the antigen-driven growth of cutaneous marginal zone B-cell lymphoma, similar to *H. pylori* infection in gastric MALT lymphoma.
Chlamydia psittaci infection and ocular adnexal MALT lymphoma

A recent study from Italy showed that Chlamydia psittaci was present in 87% of ocular adnexal MALT lymphomas. However, such an association was not demonstrated in cases of ocular adnexal MALT lymphomas from South Florida and Rochester areas in the USA. A recent study from our laboratory demonstrated that C. psittaci was variably associated with ocular adnexal MALT lymphoma in different geographical regions, being most frequent in Germany (47%), followed by the East Coast of the USA (35%) and the Netherlands (29%), but relatively uncommon in Italy (13%), the UK (12%) and Southern China (11%). Such geographical variations are also supported by a study showing a high prevalence (78%) of C. psittaci in ocular adnexal MALT lymphoma of patients from South Korea. The prevalence of C. psittaci was significantly higher in MALT lymphoma than in non-marginal zone lymphoma and non-lymphoproliferative disorders of the ocular adnexa, suggesting a role for C. psittaci infection in the development of ocular adnexal MALT lymphoma. This is further supported by demonstration of complete or partial regression of ocular adnexal MALT lymphoma in 13 of 27 cases (48%) following eradication of C. psittaci with antibiotics. Interestingly, among the 13 cases responded to antibiotic treatment, 6 cases were negative for C. psittaci by polymerase chain reaction (PCR). This finding suggests undiagnosed C. psittaci infection by PCR and/or presence of other bacterial species.

It remains to be investigated whether microbial pathogens play a role in the development of MALT lymphoma at other sites. Nonetheless, those derived from the salivary gland and thyroid are closely associated with autoimmune disorders, namely Sjögren’s syndrome and Hashimoto thyroiditis respectively.

Molecular genetics of MALT lymphoma

A number of chromosomal structural and numerical alterations have been described in MALT lymphoma. t(11;18) (q21;q21), t(1;14)(p22;q32), t(14;18)(q32;q21) and t(3;14) (p13;q32) have been characterised at the genetic level, and their incidences in MALT lymphoma of various sites have been extensively investigated. The functional characterisation of the oncogenes involved in t(11;18), t(1;14) and t(14;18) has also provided important insights in our understanding the molecular pathogenesis of MALT lymphoma.

Chromosomal translocations

t(11;18)(q21;q21): In most of the translocation positive cases, t(11;18) is the sole chromosomal aberration. The translocation generates a functional API2-MALT1 fusion, which invariably comprises the N-terminal region of the API2 with three intact BIR domains and the C-terminal region of the MALT1 containing an intact caspase-like domain (Fig. 1). The specific selection of these domains of the API2 and MALT1 genes to form a fusion product indicates their impor-

Fig. 1. The oncogenes involved in MALT lymphoma associated chromosomal translocation. T(11;18) generates a chimeric functional API2-MALT1 fusion product, while t(1;14), t(14;18) and t(3;14) juxtapose the BCL10, MALT1 and FOXP1 gene to the immunoglobulin locus respectively and up-regulate their expression.
tance in the oncogenic activity of the fusion product. API2 inhibits the biological activity of caspases of 3, 7 and 9 and is believed to be an apoptosis inhibitor, whereas MALT1 is involved in antigen receptor mediated nuclear factor (NF-κB) activation. Although neither wild type API2 nor wild type MALT1 alone is capable of activating NF-κB, the API2-MALT1 fusion product is capable of activating this transcriptional factor.

Extensive screening of lymphomas for t(11;18) shows that this translocation is specifically associated with MALT lymphoma and has not been found in other lymphoma subtypes including nodal and splenic marginal zone B-cell lymphoma, and the inflammatory disorders associated with MALT lymphoma including H. pylori associated gastritis, lymphoepithelial sialoadenitis and Hashimoto’s thyroiditis. The translocation occurs at variable frequencies in MALT lymphoma of different sites, being most frequent in those from the lung (40%) and stomach (25%), followed by those from the ocular adnexa (10%), but rare or absent in those from the salivary gland, thyroid and skin (Fig. 2). In gastric MALT lymphoma, we have shown that t(11;18) is more frequently associated with cases at stage II or above than those at stage I, and the translocation positive cases, including those at the stage I, do not respond to H. pylori eradication. Intriguingly, despite the strong association of t(11;18) with adverse clinical features, the translocation is only rarely found in transformed MALT lymphoma.

**t(1;14)(p22;q32) and t(1;2)(p22;p12):** These translocations bring the entire BCL10 gene under the regulatory control of the IG gene and hence deregulate its expression. BCL10 contains a CARD domain in its N-terminal region and is rich in serine and threonine in its C-terminal region (Fig. 1). Early in vitro studies showed that BCL10 can act in a weakly pro-apoptotic manner despite its role in activation of NF-κB. However, later studies of BCL10 knockout mice have shown that BCL10 does not have a pro-apoptotic activity in vivo and is essential for both the development and function of B and T-cells, specifically linking antigen receptor signalling to the NF-κB pathway.

**t(1;14) or its variant is specifically associated with MALT lymphoma and has not been found in other lymphoma subtypes. The translocation is primarily seen in MALT lymphoma from the lung (9%) and stomach (4%), being rare or absent in those from the ocular adnexa, salivary gland, thyroid and skin (Fig. 2). Most of the t(1;14) positive cases are diagnosed at advanced stages.**

In addition to chromosomal translocation, BCL10 is also targeted by gene amplification, which has been observed in pancreatic cancers and a single case of nodal diffuse large

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**Fig. 2.** Frequency of t(11;18)/API2-MALT1, t(1;14)/IGH-BCL10 or variants, and t(14;18)/IGH-MALT1 in MALT lymphomas of various sites. OA: Ocular adnexa; SG: salivary gland. Number in bracket indicates the number of cases studied.
B-cell lymphoma (DLBCL).65

t(14;18)(q32;q21) : This translocation involves the MALT1 but not the BCL2 gene in MALT lymphoma.66,67 The translocation brings the entire MALT1 gene under the regulatory control of the IGH gene and hence deregulates its expression. Like the above two chromosomal translocations, t(14;18)/IGH-MALT1 also occurs at variable frequencies in MALT lymphoma of different sites.66,68-70 By retrospective study of a large cohort of MALT lymphoma, we have shown that the translocation mainly occurs in those from the liver (17%), lung (9%) and ocular adnexa (7%), but not in those from the salivary gland, thyroid and skin (Fig. 2).71 t(14;18)/IGH-MALT1 has also been observed in rare cases of extranodal DLBCL.67,72 Furthermore, MALT1 gene amplification has been found in cell lines derived from marginal zone B cell lymphoma and Burkitt lymphoma and primary cutaneous DLBCL.67,73

t(3;14)(p13;q32) : This is a newly identified chromosomal translocation in MALT lymphoma. This translocation deregulates the expression of the FOXP1 gene,74-76 which belongs to the Forkhead box (Fox) family of winged-helix transcription factors that have diverse functions in different cell and tissue types. FOXP1 contains an N-terminal polyglutamine domain, followed by a glutamine-rich domain, a leucine zipper, a forkhead domain and an acidic domain (Fig. 1), and is involved in regulation of the Rag1 and Rag2 expression, thus essential for B-cell development.77 The initial studies have shown the presence of the translocation in MALT lymphomas of the thyroid (3/6), ocular adnexa (4/20), skin (2/20) and stomach (1/21), but not in those of the salivary gland and lung, and also in cases of extranodal DLBCL and B-cell non-Hodgkin’s lymphoma not otherwise specified.78 A recent study found the translocation in 4/53 cases of extranodal DLBCL and 1/49 nodal DLBCL but not in 122 cases of MALT lymphoma of various sites.78 FOXP1 is also targeted by gene amplification, which has been described in cases of DLBCL.75

Common molecular mechanisms targeted by different chromosomal translocations

Mounting evidence indicates that the oncogenic activities of t(1;18), t(1;14) and t(14;18) is linked by physiological roles of BCL10 and MALT1 in activating the NF-κB pathway in lymphocytes (Fig. 3).39,61,62,79 Upon antigen receptor stimulation, CARMA1 (also known as CARD11 or Bimp1) is recruited into lipid rafts and is activated by phosphorylation via PKCδ in B cells or PKCθ in T cells.80,81 The activated CARMA1 acts as a scaffolding protein and recruits BCL10 through a CARD/CARD interaction, inducing BCL10 oligomerisation.82-84 BCL10 binds to the Ig-like domain of MALT1 through a short region (amino acids 107-119) downstream of the BCL10 CARD domain, and induces MALT1 oligomerization, and hence its activation.41 Activated MALT1 binds to TRAF6 (tumour necrosis factor receptor associated factor 6) and induces its oligomerisation, resulting in the activation of TRAF6 ubiquitin ligase activity, which leads to the multi-ubiquitination of NF-κB essential modulator (NEMO, also known as IKKγ).85,86 Rather than targeting it for proteosomal degradation, ubiquitination of NEMO is thought to regulate its function or its protein-protein interactions. Although the precise mechanism is unknown, this triggers the activation of IκKa and IκKβ, which causes phosphorylation and degradation of IκB and the release of NF-κB. NF-κB then translocates to the nucleus and transactivates genes, such as cytokines and growth factors, that are important for cellular activation, proliferation, survival and induction of effector functions of lymphocytes.

As outlined above, CARMA1, BCL10 and MALT1 form a ternary complex and play a central role in the signalling cascade leading to NF-κB activation (Fig. 3).82-84 Essentially, the activation of these molecules is triggered by their self-oligomerisation. In MALT lymphoma with t(1;14) in which BCL10 is over-expressed, BCL10 is thought to form oligomers via its CARD domain, thus triggering MALT1 oligomerisation, then NF-κB activation. Similarly, in MALT lymphoma with t(14;18), the oligomerisation and activation of MALT1 is thought to be dependent on BCL10 since MALT1 does not have a structural domain that is capable of mediating self-oligomerisation.40,41,84 This is supported by the observation that MALT1 acts synergistically with BCL10 to activate NF-κB activation.84 In line with this hypothesis, both MALT1 and BCL10 were found to be highly expressed in the cytoplasm of MALT lymphoma cells with t(14;18)(q32;q21).67,71 It is likely that MALT1 interacts with and stabilises BCL10, causing its accumulation in the cytoplasm of tumour cells bearing t(14;18)(q32;q21). In MALT lymphomas with t(11;18), the fusion protein is oligomerised through a non-homotypic interaction mediated by the API2 moiety,87 and thus can activate the NF-κB pathway without the need for upstream signalling.84 This is supported by the finding that the API2-MALT1 fusion product, but not wild type API2 nor wild type MALT1 alone, is capable of activating the NF-κB pathway in vitro.40,41,84 Constitutive activation of NF-κB enhances both cell proliferation and survival, thus contributing to lymphoma development.

Interplay between MALT lymphoma associated oncogenic products and immunological stimulations

As suggested by the indolent nature of MALT lymphoma, the oncogenes specifically associated with this lymphoma entity most likely confer weak rather than strong oncogenic activities. In support of this, both Eμ-API2-MALT1 and Eμ-
BCL10 transgenic mice developed splenic marginal zone expansion, but not lymphoma.\textsuperscript{88,89} These findings indicate that these chromosomal translocations alone are insufficient for malignant transformation. The chromosomal translocations seen in MALT lymphoma are always mutually exclusive and are often the principal genetic aberration, particularly in the case of t(11;18). Although there may be potential oncogenic cooperation between these chromosomal translocations and other genetic abnormalities not yet identified, emerging evidence suggests that there is also a synergistic interplay be-

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**Fig. 3.** The chromosomal translocations involving \textit{BCL10} and \textit{MALT1} in MALT lymphoma affect a common molecular pathway.

In MALT lymphomas with t(1;14), BCL10 is over-expressed and forms oligomers via its CARD domain, leading to constitutive NF-κB activation. In MALT lymphomas with t(14;18)(q32;q21), MALT1 is over-expressed, and the oligomerisation and activation of MALT1 is thought to depend on BCL10. In MALT lymphomas with t(11;18), the resulting API2-MALT1 fusion products self-oligomerize via a non-homotypic interaction mediated by the API2 moiety, thus leading to constitutive NF-κB activation. These oncogenic products are most likely synergistic with both innate and acquired immune stimulations in their activation of the NF-κB pathway.

CARD: caspase recruitment domain; DD: death domain; Ig: Ig-like domain; Casp-L: caspase-like domain; BIR: baculovirus IAP repeat;
MALT lymphoma

As discussed above, chromosomal translocations occur at variable frequencies in MALT lymphoma of different sites, but overall are present in only a minority of cases. Although several chromosomal trisomies are frequently associated with MALT lymphoma, particularly those negative for t(11;18), the molecular genetics of translocation negative MALT lymphoma is poorly understood. We recently screened the chromosomal gains and losses in gastric MALT lymphoma with and without t(11;18) by comparative genomic hybridisation. Recurrent chromosomal gains involving whole or major parts of a chromosome were seen for chromosomes 3, 12, 18 and 22 (23%, 19%, 19% and 27% respectively). Discrete recurrent chromosomal gains were found at 9q34 (11/26 = 42%). In a parallel investigation of 19 salivary gland MALT lymphomas that are negative for known chromosomal translocations, we have found recurrent chromosomal gains at 1p32-ter (42%), 9q33-34 (84%), 11q11-13 (42%), 17 (58%) and 18q21-22 (42%). Notably, chromosomal gains at 9q34, 11q13 and 18q21 were frequently concurrent with 12/19 cases harbouring gains at least two of the three loci. Interphase fluorescent in situ hybridization with probes targeting the TRAF2 and CARD9, RELA and CCND1, and MALT1 gene loci confirmed the genomic gain at 9q34, 11q13 and 18q21 respectively.

As discussed above, positive regulators of NF-xB, such as BCL10 and MALT1, have a synergistic effect in their activation of the NF-xB pathway. At least some of these positive regulators, for example, API2-MALT1, have also been shown to act synergistically with CD40 stimulation in NF-xB activation. It can be hypothesised that gains of extra copies of MALT1, TRAF2, CARD9, RelA, CCND1 and others yet to be identified proteins, together with immunological stimulations via surface antigen receptor and co-stimulatory molecules may bear a synergistic effect in NF-xB activation and lead to a biological consequence similar to that caused by the chromosomal translocations associated with MALT lymphoma.

FUTURE INVESTIGATIONS

Despite the recent advances in the aetiology of MALT lymphoma of several sites. The aetiological factors underlying the development of extra-gastric MALT lymphoma, particularly those of the salivary glands, thyroid and lung, are largely unknown. Identification of microbial pathogens associated with the development of MALT lymphoma at these sites will improve our understanding of the pathogenesis of these lymphomas and potentially lead to innovative treatments. Such investigations may be accomplished by conventional approaches such as serological screening and PCR-based detection, as well as by more robust high throughput microarray based screening. MALT lymphoma has so far not been extensively investigated by conventional metaphase cytogenetic analysis due to the poor in vitro growth of the lymphoma cells. The spectrum of chromosomal translocations associated with this lymphoma entity remains to be determined. With the improved cell culture strategies, a number of novel chromosomal translocations including t(5;14)/IGH-ODZ2, t(9;14)/IGH-JMJD2C, t(1;14)/IGH-CNN3, t(3;14)(q21;p16), t(2;19)(p15; q13.4), t(5;17)(p11;p11), t(1;22)(q11;p11), t(1;3)(q32;p14.2) and t(x;6)(q22;q13) have been recently identified in MALT lymphomas of various sites. The incidences of these newly identified translocations in MALT lymphomas of various sites and their impact on clinico-pathological presentation remain to be investigated.

Despite the identification of the above chromosome translocations in MALT lymphoma, it is highly likely that a high proportion of MALT lymphomas are negative for chromosome translocation. Comparative genomic hybridisation investigations of translocation negative MALT lymphoma of the stomach and salivary glands show a conserved pattern of chromosomal gains. It is important to further explore whether these recurrent chromosomal gains are a common feature of translocation negative MALT lymphomas at the other sites and to identify the genes targeted by such common genomic gains.

There is now substantial evidence indicating that the oncogenic activity of t(11;18), t(1;14) and t(14;18) may not be confined to activation of the cytoplasmic signalling cascade of the NF-xB pathway. This is particularly highlighted by the finding of aberrant BCL10 nuclear expression in MALT lymphoma, particularly those with t(1;14) or t(11;18). In contrast, the protein is expressed predominantly in the cytoplasm of normal B cells including marginal zone B cells, the normal cell counterpart of MALT lymphoma, in line with the known physiological role of BCL10 in normal lymphocytes. Study of the regulation of BCL10 subcellular localisation and identification of the molecules that are responsible for BCL10 nuclear transportation will help to investigate the unknown function of BCL10.
ACKNOWLEDGEMENT

The studies described from the author’s laboratory were supported by research grants from the Leukaemia Research Fund, U.K., Association for International Cancer Research, and the Leukaemia and Lymphoma Society, U.S.A.

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