Infection-associated lymphomas derived from marginal-zone B-cells: a model of antigen-driven lymphoproliferation

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Abstract
Non-Hodgkin lymphomas develop from nodal and extranodal lymphoid tissues. A distinct subset of extranodal lymphomas arising from B-cells of the marginal zone (MZ) of mucosa-associated lymphoid tissue (MALT) or spleen has been individualized. Growing evidence indicates that MZ lymphomas are associated with chronic antigenic stimulation by microbial pathogens and/or autoantigens. Molecular investigations have allowed the lengthening of the list of microbial species associated with MZ lymphoproliferations, which now comprises at least five distinct members: *H. pylori, C. jejuni, B. burgdorferi, C. psittaci*, and HCV. A pathophysiological scenario involving chronic and sustained stimulation of the immune system leading to lymphoid transformation has emerged. It defines a distinct category of infection-associated lymphoid malignancies, in which the infectious agent does not directly infect nor transform lymphoid cells, as do the lymphotropic oncogenic viruses EBV, HHV8 and HTLV1, but rather indirectly increases the probability of lymphoid transformation by chronically stimulating the immune system to maintain a protracted proliferative state.
Introduction

The geographic heterogeneity in the incidence of B-cell non-hodgkin lymphomas (NHL) suggests that environmental factors such as infections might have a role in lymphomagenesis\textsuperscript{1,2}. Because of the inherent genetic instability of lymphocytes, lymphoid proliferation increases the risk of transformation, and sustained activation of the lymphoid system which can be observed during chronic infection, immunodeficiency and autoimmunity constitutes a risk factor for lymphomas\textsuperscript{3-5}. Congenital and acquired immunodeficiencies associated with HIV infection and solid organ or hematopoietic transplantation increase the risk of developing B-cell NHLs\textsuperscript{6,7}. Similarly, Sjögren syndrome and other autoimmune conditions are also associated with an increased risk of lymphomas\textsuperscript{8,9}.

Certain types of lymphomas are associated with specific microbial infections, and infection-associated lymphomas currently fall in diverse histopathological categories (Table 1)\textsuperscript{10}. Infections may contribute to lymphomagenesis by promoting favorable conditions for lymphocyte transformation, such as increased proliferation or decreased apoptosis of lymphoid cells\textsuperscript{11}. Direct lymphocyte transformation by a given microbial agent is the simplest scenario accounting for infection-associated lymphomas. Lymphotropic transforming viruses such as Epstein-Barr virus (EBV), human herpesvirus 8 (HHV8) and human T-lymphotropic virus 1 (HTLVI), directly infect a subset of lymphoid cells in which they express viral oncogenes\textsuperscript{12-14}. An alternative scenario to direct transformation of lymphocytes has more recently emerged for microbial species associated with lymphomas but which do not directly infect nor transform lymphoid cells. They have in common the ability to persist chronically in host tissues and trigger a sustained lymphoid proliferation giving a selective advantage to lymphoid clones that still remain dependent upon antigen stimulation\textsuperscript{15,16}. According to this model, the microbial pathogen is neither intrinsically transforming nor oncogenic, but can be viewed as a chronic source of antigens increasing the proliferative rate of lymphoid effectors, hence fuelling the transformation process. This model has emerged with the description of several lymphomas developing in the context of chronic antigen-dependent immune stimulation, amongst which \textit{H. pylori}-associated gastric mucosa-associated lymphoid tissue (MALT) lymphoma is the best characterized\textsuperscript{15,17,18} (Figure 1). Precise elucidation of the mechanisms underlying this “indirect” lymphomagenesis as well as completion of the inventory of the microbial species driving these antigen-dependent
lymphoproliferations may provide important clues for their early diagnosis and the rationalization of the therapeutic interventions for this subtype of lymphomas.

This group of lymphomas often involves extranodal sites – normally devoid of organized lymphoid tissue – and manifests initially as indolent low-grade proliferations, reminiscent of the normal lymphoid hyperplasia driven by a physiologic antigenic stimulation\textsuperscript{19-21}. With the progression of the disease, additional oncogenic events may occur – such as constitutive activation of signaling pathways following chromosomal translocations or inactivation of tumor suppressor genes by hypermethylation or mutations – leading the lymphoproliferation to become independent of antigenic stimulation\textsuperscript{22}.

Although these lymphomas are associated with diverse microbial species, they all appear to originate from “marginal zone” (MZ)-lymphocytes. These cells are anatomically positioned in the lymphoid organs (spleen and lymph nodes) and in the MALT to function as a first line of defense against invading pathogens\textsuperscript{23,24}. Furthermore, the low activation threshold of these cells may predispose them to neoplastic transformation\textsuperscript{16,25}.

**Different B-cell subsets participating in the antigenic response: germinal center (GC) vs. marginal zone (MZ) B-cells**

Mature B-cells are heterogeneous with respect to their microanatomical location in the lymphoid organs and functional properties (Figure 2). Follicular (FO) B-cells (\(\text{IgM}^{\text{low}}\text{IgD}^{\text{high}}\text{CD21}^{\text{inter}}\text{CD23}^{\text{high}}\)) constitute the major subset of B-cells and participate in T-cell dependent (TD) immune responses in the germinal center (GC), where they receive help from antigen-specific T-cells (i.e. cognate interactions) through CD40-CD40L engagement. The GC reaction leads to isotype class-switched memory B-cells (\(\text{IgM}^{+}\text{IgD}^{+}\text{CD27}^{+}\)) with somatic hypermutations (SHM) in their immunoglobulin gene segments. Upon antigenic rechallenge, they rapidly undergo terminal differentiation into plasma cells producing large amounts of high affinity antibodies.

The marginal zone (MZ), which surrounds B-cell follicles in the spleen and in extranodal lymphoid tissue, contains a distinct subset of B-cells, the MZ B-cells (\(\text{IgM}^{\text{high}}\text{IgD}^{\text{low}}\text{CD21}^{\text{high}}\text{CD23}^{\text{low/-}}\))\textsuperscript{26}. MZ B-cells participate in T-cell independent (TI) “innate-like” immune responses to microbial pathogens\textsuperscript{27}, and can rapidly proliferate and differentiate into
IgM or even switch to other isotype-secreting plasma cells, producing the bulk of the primary antibody response. TI responses do not generate memory B-cells, consistent with a relatively short-lived antibody production. MZ B-cells can be viewed as a bridge between the innate and adaptive immune responses to pathogens invading the host. In contrast to rodents, most human MZ B-cells are somatically mutated (IgM⁺IgD⁺CD27⁺). It is still debated if these mutated MZ B-cells in humans are in fact memory B-cells originating from TD-responses occurring in the GC and later homing to the MZ or whether they are generated through a preimmune, antigen-independent diversification pathway. There is evidence that these mutated MZ B-cells could be positively selected by autoantigens during B-cell ontogeny. Autoantigens or commensal bacterial antigens could be candidates for such selection processes occurring outside of the GC, and possibly involving CD40-CD40L cognate help by NKT cells or BAFF-mediated non cognate help by MZ-resident macrophages or dendritic cells. Both B-cell subsets cooperate during the immune response to microbial polysaccharides: MZ B-cells constitute the initial rapid response and can efficiently prime CD4 T-cells that will subsequently provide co-stimulation to GC B-cells. MZ B-cells can also participate, though less efficiently than FO B-cells, in TD antibody responses. Not surprisingly, owing to their frequent auto- and cross-reactive repertoire and to their relative hyper-reactivity to activation, these cells are found in various pathological conditions involving auto-immunity and infection. Lymphomas arising from MZ B-cells can thus be expected to retain some of their seminal features, as it is exposed below.

**Direct transformation of lymphoid cells by a microbial pathogen**

EBV is associated with a number of B-cell malignancies including Burkitt’s lymphoma (BL), Hodgkin’s disease (HD), post-transplant lymphoproliferative disorder (PTLD), as well as a subset of T and NK cell malignant proliferations and frequently arise in the course of an underlying immunodeficiency. EBV infects, immortalizes and transforms B-cells in vitro and establishes a persistent latent infection (Figure 3). Viral genes expressed during latency subvert normal proliferation and survival pathways. One of the major oncogenes, the latent membrane protein 1 (LMP1) functions as a constitutively active member of the TNF-R family, closely related to CD40, a receptor whose engagement on normal B cells leads to B-cell activation. LMP1 expression is required for proliferation and transformation and is critical for in vitro
immortalization of B-cells\textsuperscript{38,39}. LMP2A is another EBV latent protein that can mimic survival signals from the B-cell receptor and rescue B-cells lacking surface immunoglobulin\textsuperscript{40,41}. In HD, the malignant Reed-Sternberg cells are thought to derive from GC cells that have undergone extensive crippling mutations of their immunoglobulin genes, precluding the expression of a functional surface receptor. Normal GC B-cells, in this situation, would be eliminated by apoptosis, and one possible role for EBV in the pathogenesis of HD would be to provide proliferative and anti-apoptotic signals (through LMP1 and LMP2) to “crippled” GC B-cells which would enable them to escape apoptosis\textsuperscript{42}. HHV8 is closely related to EBV and is also associated with a number of B-cell lymphoproliferative disorders including multicentric Castleman’s disease and primary effusion and plasmablastic lymphomas\textsuperscript{43}. As EBV, HHV8 encodes several genes that interfere with cell signaling pathways involved in proliferation and survival, and which may play a role in cellular transformation (for review see \textsuperscript{41}). The human oncogenic retrovirus HTLV-1 infects and immortalizes CD4\textsuperscript{+} T-cells. The Tax oncoprotein interferes with numerous cell-signaling pathways and is thought to play a major role in immortalization\textsuperscript{14,44}.

In general, the relationship between viral cycle and viral oncogenesis is complex. As a retrovirus, HTLV-1 integrates in the genome of infected cells. Although HTLV-1 replication is present in infected individuals, leukemic cells in ATL harbor latent integrated virus. The genomes of EBV and HHV8 are maintained as episomes in latently infected cells and viral replication is not required for B-cell transformation of EBV-infected cells. Although HHV8 also establishes a latent infection in B-cells, there is evidence that lytic replication is implicated in the early steps of oncogenesis\textsuperscript{43}. Since antiviral drugs target replication, they are mostly ineffective against virus-associated lymphoproliferations. HTLV-1 however stands out as an exception because antiretroviral therapy with azidothymidine and high dose interferon alfa has shown to be effective, at least in previously untreated ATL\textsuperscript{14}, although these drugs may also act at different levels by modulating cellular and viral gene expression such as inhibition of NF-κB and upregulation of viral genes\textsuperscript{45}. 
Indirect transformation of lymphoid cells by a microbial pathogen

Since the identification of the role of Helicobacter pylori in the pathogenesis of gastric MALT-lymphoma, several other low-grade B-cell lymphomas have been associated with chronic infections (see below). Strikingly, most if not all of these lymphomas are derived from MZ B-cells.

The International Lymphoma Study Group now recognizes 3 distinct lymphoma entities deriving from MZ B-lymphocytes\textsuperscript{10,46}: (i) splenic MZ lymphomas, (ii) extranodal MZ lymphoma of MALT-type and (iii) nodal MZ lymphomas. Although many aspects of their histology and molecular pathogenesis are distinct, these entities share a number of common features, the most striking being their possible association with chronic antigenic stimulation by microbial and/or auto-antigens.

MALT lymphomas

Low-grade lymphomas originating from the MALT were originally described in the stomach and small-intestine\textsuperscript{47,48}. They may also develop in other mucosal sites such as the salivary and lacrymal glands, the thyroid and the bronchi. They have now all been classified in the same nosologic entity generically called “MALT lymphoma”\textsuperscript{15,49,50}. The majority of the organs in which MALT lymphomas develop are normally devoid of lymphoid tissue and in most cases, MALT acquisition is induced prior to the development of lymphoma, as a response to a persistent antigenic stimulation\textsuperscript{16}.

Neoplastic cells in MALT lymphomas exhibit features of MZ B-cells from which they are thought to derive within the MALT\textsuperscript{19,20,51-54}. In MALT-lymphomas, the MZ is expanded and surrounds residual GCs (Figure 4A). The neoplastic cells are small and resemble centrocytes, hence often called “centrocyte-like cells” (CCL) (Figure 4B). They extend in the adjacent epithelial mucosa and invade the glandular epithelium, producing pathognomonic lympho-epithelial lesions (LEL) (Figure 4B and C)\textsuperscript{18}. A prominent plasmacytic differentiation is common.

Gastric MALT lymphoma and Helicobacter pylori: a model for infection-associated MALT lymphomas
Gastric MALT-lymphoma is the most common MALT lymphoma and represents the majority of lymphomas involving the stomach\textsuperscript{15,17,18}. Gastric MALT-lymphoma develops on a background of chronic inflammation and lymphoid infiltration displaying features of classic MALT architecture, of which the gastric mucosa is physiologically devoid of\textsuperscript{47}.

Gastroduodenal \textit{Helicobacter pylori} infection is strongly associated with gastric MALT-lymphoma\textsuperscript{18} (Figure 4D). \textit{H. pylori} is a Gram-negative bacterium that colonizes the gastric mucosa and is associated with peptic ulcers and gastric adenocarcinomas\textsuperscript{55-57}. \textit{H. pylori} is present in gastric biopsy samples of the majority of patients with gastric MALT lymphoma\textsuperscript{58}. The incidence of gastric MALT-lymphoma is the highest in regions where \textit{H. pylori} infection is endemic\textsuperscript{59} and the seroprevalence of \textit{H. pylori} is higher in patients with gastric MALT-lymphomas\textsuperscript{60} than in control patients without MALT-lymphomas. Eradication of \textit{H. pylori} leads to complete regression of the lymphoma during the early stages of the disease in nearly 80% of the cases\textsuperscript{61-64}. Low-grade gastric MALT-lymphoma may evolve into aggressive large-cell gastric lymphoma, which is typically refractory to antibiotics\textsuperscript{17,65-67}. Retrospective analysis have shown that clonal B-cells were already present in the gastritis, years before the clinical emergence of the lymphoma\textsuperscript{68}.

\textit{Immunoproliferative small intestinal disease: the quest for a microbial association}

Immunoproliferative small intestinal disease (IPSID), also called alpha heavy-chain (\textit{\textalpha}HC) disease or Mediterranean lymphoma, is a MALT lymphoma arising in the small intestine. The malignant cells have a distinctive lymphoplasmacytic phenotype and secrete a monotypic, truncated immunoglobulin \textit{\textalpha}-heavy chain lacking an associated light chain, which can be detected as a paraprotein in the serum of patients\textsuperscript{69-71}. Histological features of IPSID range from early lymphoplasmacytic intestinal infiltration to overt malignant diffuse large B-cell lymphoma. IPSID shares all the histological features of MALT lymphomas, namely the presence of CCL, LEL and plasma cell differentiation\textsuperscript{47,72}. IPSID is chiefly observed in young adults originating from the Mediterranean basin, the Middle East, the Far East and Africa\textsuperscript{71}. Antimicrobial therapy with tetracycline, ampicillin or metronidazole is effective in early stage IPSID\textsuperscript{71}, a finding that led the first investigators to hypothesize, years before \textit{H. pylori} was identified and even more associated with gastric MALT lymphoma, that a microbial species might play an etiologic role in IPSID development\textsuperscript{71}. Nevertheless, despite repeated attempts using classical culture-based approaches,
the efforts made towards the identification of a microbial species associated with IPSID remained vain. Although *H. pylori* was recently proposed to be involved in IPSID, this proposition was not corroborated in a subsequent retrospective analysis of more than 20 cases\textsuperscript{73,74}. Applying an unbiased molecular approach previously used with success to identify the bacterial species associated with bacillary angiomatosis (*Bartonella henselae*)\textsuperscript{75} and Whipple’s disease (*Tropheryma whipplei*)\textsuperscript{76}, we have demonstrated the presence of *C. jejuni*-specific sequences in intestinal tissue samples of an IPSID patient with a spectacular response to antimicrobial therapy. These results were confirmed by *in situ* hybridization and immunohistochemistry (Figure 4E) on this index case and 4 out of 6 archival additional cases\textsuperscript{77}. Identification of *C. jejuni* in 5 out of 7 patients with IPSID and the dramatic response observed in the index patient after microbial eradication is a strong argument for the association of *C. jejuni* with IPSID\textsuperscript{78}. However, association is not proof for causation, although it is usually the first step in proving the microbial etiology of a disease. To definitively demonstrate that *C. jejuni* infection causes IPSID, Koch’s postulate would need to be fulfilled (i.e.: Is *C. jejuni* detectable in the host’s intestine in early stages of the disease? Can *C. jejuni* be cultivated from the diseased tissue? Can *C. jejuni* trigger the disease in an animal model? Can *C. jejuni* be isolated from the diseased animal?). However, recent advances in molecular diagnostic tools have led to the restatement of new criterias that take into account the putative uncultivability and host specificity of microbial species identified by molecular techniques\textsuperscript{79,80}. Demonstration of long-term *C. jejuni* intestinal persistence is important for incriminating this bacterial species in IPSID development. The epidemiology *C. jejuni* in developing countries, in which IPSID is exclusively observed, sharply contrasts with that reported in developed countries. Up to 15% of asymptomatic children in developing countries carry *Campylobacter* organisms in their stools, whereas in developed countries, fecal *Campylobacter* is present in less than 0.5%\textsuperscript{81}. It is not known whether *C. jejuni* can persistently colonize the small intestinal mucosa without concomitant detectable fecal shedding. Future studies need to focus on the extent of the asymptomatic and long-term intestinal carriage, its putative correlation with *lamina propria* lymphoid infiltration that might precede the emergence of lymphoma, and ultimately its causal relationship with IPSID. The absence of a functional B-cell receptor in IPSID raises the question as to how antigens might persistently stimulate these cells. In the early stages of infection, antigen-specific B-cells in the lamina propria responding to microbial antigens (and possibly
cross-reacting with auto-antigens) would be stimulated and proliferate. During persistent stimulation, mutations would accumulate, leading to the selection of a clone having lost the ability to express a complete immunoglobulin and thus rendered insensitive to a negative feedback loop\textsuperscript{71}. According to this model, the subsequent proliferation would depend on survival factors (e.g. BAFF) induced in the inflamed mucosa by persisting infection, as well as a proliferative advantage of the clone due to the loss of the negative regulation of normal IgA synthesis\textsuperscript{82}. Extra-intestinal MALT-type lymphomas may also be associated with chronic infections due to so far unidentified bacterial species. A similar approach to that used for IPSID could show promises in identifying such bacterial species.

Other bacteria-associated MALT-lymphomas

The presence of \textit{Borrelia burgdorferi} has been reported in primary cutaneous B-cell lymphoma (PCBCL) tissue\textsuperscript{83-85}. Despite contradictory reports from investigators from other geographic areas\textsuperscript{86,87}, there is significant support to the hypothesis that \textit{B. burgdorferi} infection might be associated with chronic antigen-driven lymphomagenesis in the skin, a tissue in which \textit{B. burgdorferi} is known to establish a persistent infection\textsuperscript{85,88}. Skin is the portal of entry of \textit{B. burgdorferi}, and is the most commonly affected tissue in Lyme borreliosis\textsuperscript{88}. Late in the disease, lymphocytes may infiltrate the dermis and produce the characteristic borrelial “lymphocytoma”. \textit{B. burgdorferi} is present within the early skin lesions of \textit{erythema migrans} and later in lymphocytoma and its DNA can be readily amplified from biopsies of diseased skin. PCBCL is a rare entity that commonly displays the histological features of MZ lymphoma\textsuperscript{89}. The incidence of PCBCL is higher in areas endemic for Lyme disease, and borrelial DNA has been amplified from skin biopsies\textsuperscript{85,90}. Regression of the lymphoma after antimicrobial therapy has been reported\textsuperscript{84,91,92}. Histologically, borrelial lymphocytoma can be difficult to distinguish from PCBCL, and has led to the improper term of “\textit{Borrelia}-associated pseudolymphoma”\textsuperscript{93}. Having in mind the \textit{H. pylori}-model of gastric MALT lymphomagenesis, the cutaneous manifestations of Lyme borreliosis could be viewed as a multistep progression from lymphocytoma to “pseudolymphoma” eventually leading to PCBCL\textsuperscript{90,93}. Evidence of B-cell monoclonality may help distinguish between the different stages of the disease\textsuperscript{90,93}, although it does not constitute a definitive proof of malignancy.
Recently, *Chlamydia psittaci* infection has also been associated with ocular adnexal MALT-lymphomas\(^\text{94,95}\). Adnexal MALT-lymphomas have been described in the context of chronic conjunctivitis, and particularly “inclusion conjunctivitis”, which can be associated with *Chlamydia* infection\(^\text{96,97}\). The presence of *Chlamydia psittaci* DNA in biopsy material and peripheral blood mononuclear cells from patients with ocular adnexal lymphomas\(^\text{94}\) was demonstrated by targeted PCR, and *C. psittaci* DNA was detected in 80% of ocular adnexal lymphoma samples. In some patients, antimicrobial treatment with doxycyclin was associated with a clinical response\(^\text{94}\). Together, these data argue for a putative role for *C. psittaci* in ocular adnexal MALT lymphomagenesis.

**Splenic marginal zone lymphoma (SMZL) and splenic lymphoma with villous lymphocytes (SLVL)**

SMZL is a rare low-grade B-cell lymphoma involving predominantly the spleen\(^\text{54}\). A leukemic phase with cytologically distinct lymphocytes defines the SLVL variant of SMZL\(^\text{98}\). SMZL usually presents as an indolent lymphoma, and autoimmune manifestations such as serum rheumatoid factor (RF), are frequently associated. Histologically, the marginal zone surrounding the follicular areas is expanded and neoplastic cells have cytological and phenotypical features of marginal zone lymphocytes\(^\text{98,99}\), clearly distinguishing them from the lymphocytes present in the follicular center or the mantle area.

**Hepatitis C Virus (HCV) infection and MZ-lymphomas: a correlation between lymphoid proliferation and viral load**

We have reported the association of a subset of SLVL with chronic HCV infection\(^\text{100,101}\), a finding which has now been confirmed by other investigators\(^\text{102}\). HCV is an RNA virus associated with extra-hepatic manifestations, such as essential mixed cryoglobulinemia (ECM) and B-cell lymphoproliferations\(^\text{103}\). HCV-associated SLVL is indistinguishable from classic SLVL, except for the presence of HCV viral replication\(^\text{100}\). ECM is constantly present in HCV-associated SLVL\(^\text{101}\). Antiviral treatment with interferon alfa +/- ribavirin results in a marked reduction of lymphocytosis and splenomegaly in HCV-associated SLVL, whereas it is ineffective in HCV-negative SLVL\(^\text{100,101}\). Complete virological response correlates with sustained hematological response, and virological relapse is associated with re-emergence of circulating villous...
lymphocytes and splenomegaly. Reduction in HCV viral load after restarting of the antiviral treatment correlates with hematological remissions. Overall, these data indicate a strong correlation between serum viral load and tumor burden in HCV-associated SLVL, and support the existence of a causal relationship between HCV chronic antigenic stimulation and the MZ lymphomatous process\textsuperscript{104}.

Other HCV-associated lymphomas

ECM is considered as a non-malignant B-cell lymphoproliferation characterized by the synthesis of a monoclonal IgM with RF activity against immune complexes containing HCV proteins\textsuperscript{105-107}. Several epidemiological studies have reported an association between HCV infection and B-cell lymphomas\textsuperscript{108-112}, and most cases of these HCV-associated lymphomas are low grade MZ-lymphomas\textsuperscript{53,109,112}. MALT-lymphomas of the salivary glands may be associated with HCV infection\textsuperscript{113}. Monoclonal B-cells can be detected during chronic HCV infection, especially in patients with HCV-associated ECM\textsuperscript{103}. Furthermore, the existence of a cryoglobulinemia is an independent risk factor for lymphomas in HCV-infected patients\textsuperscript{112} and may thus be considered as an early marker of HCV-associated lymphoproliferation.

MZ-lymphomas and auto-immunity

Sjögren syndrome (SS) and autoimmune Hashimoto’s thyroiditis (HT) are characterized by auto-reactive T and B lymphocyte infiltration of the salivary glands and the thyroid, respectively. Chronic inflammation and the ensuing cellular damage are associated with massive exposure of auto-antigens to the immune system. B-lymphocytes infiltrating the salivary glands in SS and the thyroid in HT progressively organize into a lymphoid infiltrate that reproduces the distinctive histological architecture of normal MALT, including the presence of numerous reactive follicles\textsuperscript{114}. The risk for developing a B-cell lymphoma is increased by a factor of 44 in patients with SS\textsuperscript{8}. Similarly, indolent lymphomas of the thyroid, most often of the MALT-type, develop on a background of autoimmunity\textsuperscript{115,116}. Thus, autoantigenic stimulation observed during SS and AT appears to recapitulate the chronic microbial antigenic stimulation observed during persisting infections, and as in chronic infections, the failure to eradicate the antigenic source in auto-immunity leads to sustained B-cell stimulation thus favoring lymphoid transformation and lymphomas.
Pathophysiological aspects of antigen-driven MZ lymphomagenesis

H. pylori and gastric MALT-lymphoma
Converging evidence support a causative role for H. pylori in gastric MALT-lymphomas\textsuperscript{117,118}: T-cells from patients with gastric MALT-lymphomas are able to sustain the \textit{in vitro} proliferation of autologous malignant B-cells in the presence of H. pylori extracts, in a CD40-CD40L dependent manner, supporting the role of H. pylori in triggering the lymphoproliferation\textsuperscript{119} (Figure 1A). Strikingly, neoplastic B-cells from gastric MALT-lymphoma are not specific for H. pylori antigens but rather for auto-antigens found in the gastric mucosa. These autoreactive B-cells are thought to receive cognate help from H. pylori-specific T-cells displaying cross-reactivity with gastric auto-antigens (Figure 1A and next section). Thus, the malignant B-cells could derive from TD GC B-cells that homed to the MZ and thus display MZ-type phenotype and function. Alternatively, they could also be true MZ B-cells participating in a TD response\textsuperscript{26,28}.

H. pylori-infected gastric mucosal cells produce pro-inflammatory cytokines (such as lymphotoxin beta) and B-cell homing factors (such as BCA-1), leading to the emergence of MALT in the gastric mucosa\textsuperscript{120}. Infection of mice with \textit{Helicobacter} species, including H. pylori and the related species H. felis and H. heilmannii, also leads to the development of chronic gastritis and gastric MALT lymphomas with similarities to the human disease\textsuperscript{117,118}. Thus H. pylori not only fulfils Koch’s postulate for gastric ulcer and carcinomas, but can also be convincingly incriminated in gastric MALT lymphomagenesis. H. pylori-associated gastric MALT-lymphomagenesis thus stands as the best defined paradigm for infection-associated indirect lymphoid transformation.

Microbial persistence: implications in lymphoproliferation and autoimmunity
Pathogens inducing chronic infection have selected countless mechanisms allowing them to persist in the host and colonize their specific niches.
Molecular mimicry, a situation in which microbial pathogens express antigenic motifs shared with the host, is also a mechanism that favors microbial persistence, given the tolerization of the immune system towards autoantigens. Several H. pylori antigens resemble autoantigens, notably the fucosylated Lewis antigens expressed on the surface of the gastric mucosa and the epitopes of
self gastric parietal cell H(+)/K(+)-ATPase\textsuperscript{57,121} (Figure 1A). Other examples of auto-reactivity elicited by antimicrobial immune responses have been described for the aforementioned microbial species associated with antigen-driven lymphomagenesis: \textit{C. jejuni} is associated with Guillain-Barré syndrome, an acute polyneuropathy induced by cross-reactive antibodies directed against \textit{C. jejuni} lipo-oligosaccharides (LOS) and nervous system gangliosides\textsuperscript{122}; \textit{B. burgdorferi} OspA protein is structurally homologous to human Lymphocyte Function Antigen-1 (LFA1) which may play a role in the autoimmune manifestations of the disease\textsuperscript{123}. \textit{Chlamydia} species also share immunoreactivity with eukaryotic heat shock proteins\textsuperscript{124}, and this has been proposed to play a role in autoimmunity associated with this bacterium. Finally, the basis for the strong association between the immune response to HCV and the detection of a RF may lie in the structural and antigenic homologies between the N-terminal region of the HCV E2 envelop protein and the human immunoglobulin variable domains, and as such can be recognized by anti-human antibodies\textsuperscript{125,126}.

All the aforementioned microbial pathogens may also evade the immune system by antigenic variation as has been documented in detail for \textit{H. pylori}\textsuperscript{57}, \textit{B. burgdorferi}\textsuperscript{127} and HCV\textsuperscript{128}. This process also contributes to chronic stimulation of the immune system by continuously modifying microbial antigenic determinants.

\textbf{Evidence for antigenic selection in MZ-lymphomas}

Indirect evidence for the role of an antigen in a B-cell proliferation can be deduced from the analysis of the V gene usage and the assessment of SHM in immunoglobulin V genes, because they constitute molecular signatures for antigen selection\textsuperscript{129-131}. All MZ-lymphomas associated with chronic infection and/or auto-immunity exhibit a biased immunoglobulin V gene usage and SHM\textsuperscript{132-134}. The recent finding that MALT-lymphomas stand out among other B-cell lymphomas as frequently expressing immunoglobulin V genes with strong homology to RF\textsuperscript{135} underscores the links between chronic antigenic stimulation, autoimmunity and development of MZ-derived lymphoproliferations. Analysis of the immunoglobulin specificity from 2 HCV-associated lymphoma tumor cells demonstrated that they bound the HCV E2 glycoprotein similarly to human anti-E2 antibodies\textsuperscript{125}. Furthermore, B-cell clones in HCV-associated EMC and lymphomas often use the VH1-69 gene segment which is also used by anti-E2 antibodies elicited by HCV\textsuperscript{133,134,136}. Many auto-antigens have been identified in both SS and AT and a common feature to both
conditions is the frequent presence of RF and some cases of salivary gland lymphomas arising in SS also use immunoglobulin segments with RF activity, further supporting the role of chronic antigen stimulation in the pathogenesis of this condition\(^{137}\).

**Ongoing mutations in proliferating lymphocytes**

Reactive oxygen species (ROS) produced during inflammation are genotoxic and favor the occurrence of oncogenic DNA damage in proliferating lymphocytes\(^{138}\). The intrinsic genetic instability of B-cells during isotype class-switching and SHM\(^{139,140}\) also increases the risk of transformation during protracted proliferation associated with inflammation. *H. pylori* chronic infection is associated with the production of ROS, chronic inflammation and DNA damage\(^{57,141,142}\). Most isolates of *C. jejuni* produce a toxin called CdtB (cytolethal distending toxin B) that causes direct DNA damage\(^{143}\). CdtB induces double-strand DNA breaks and growth arrest in T-lymphocytes and may thus participate in immune evasion mechanisms during infection with CdtB producing bacteria\(^{143}\), as well as the emergence of the DNA breaks in B-cells leading to the synthesis of a truncated immunoglobulin as seen in IPSID patients\(^{71}\). The conjunction of CdtB and SHM occurring in the MALT during *C. jejuni* chronic infection could lead to large deletions of the variable region of the \(\alpha\)HC precluding the association with a light chain and leading to the synthesis of a truncated \(\alpha\)HC\(^{139,143}\).

**Mechanisms of clonal progression of antigen-dependent B-cells.**

Inactivation of cell-cycle regulating genes such as the cyclin-dependent kinase inhibitors p15 and p16 is observed in early stages of gastric MALT-lymphomas (Figure 1B)\(^{144}\). Fas/CD95, involved in apoptosis and homeostasis of normal and auto-reactive B-cells\(^{145}\), is often mutated in non gastric MALT-lymphomas and in other MZ-lymphomas\(^{146,147}\). These alterations confer a clonal advantage to antigen-specific cells and ultimately lead to transformation. Early transformed B-cells would still rely on signals from the antigen-receptor for their proliferation and survival, as attested by their antigen dependence which is illustrated by the efficacy of antigenic eradication (Figure 1B).
Molecular pathogenesis and cytogenetic features of MZ lymphomas

Recurrent cytogenetic abnormalities are found in most MZ/MALT lymphomas. The t(11;18), which fuses the *API2* and *MALT1* genes and generates a functional API2-MALT1 fusion product, has been found in several cases of MALT-lymphomas arising in various mucosal sites. t(11;18) is usually the sole chromosomal aberration and occurs early. Other translocations, including t(1;14) and t(14;18), which fuse the *BCL10* and *MALT1* genes to the *IGH* locus, respectively (Figure 1C), have also been described, and can be associated with other cytogenetic aberrations such as chromosome 3 trisomy. More recently, the occurrence of a t(3;14) translocation has been described in 10% of MALT lymphomas, but not in nodal or splenic MZ-lymphomas. This translocation which fuses *FoxP1* to the *IgH* locus is mutually exclusive with the other MALT-lymphoma specific translocations, t(11;18), t(1;14) and t(14;18).

In SMZLs, the most common cytogenetic abnormality is the deletion of the long arm of chromosome 7 (7q21-32) which likely involves cdk6, and trisomy 3, whereas the t(11;18), t(1;14) and t(14;18) translocations are not found.

The oncogenic activity of the three chromosomal translocations t(11;18), t(1;14) and t(14;18) is linked to the physiological role of BCL10 and MALT1 in antigen receptor-mediated NF-κB activation and inhibition of apoptosis. Constitutive activation of the NF-κB pathway by these translocations bypasses the requirement for the B-cell receptor signaling and accounts for the antigen-independence of cells harboring these translocations (Figures 1 and 5). The oncogenic role of the *IgH-FoxP1* fusion transcript is unknown.

Alterations of B-cell functions by HCV

The HCV E2 glycoprotein interacts with CD81 on the surface of B-lymphocytes and is a target of the humoral response against the virus. CD81 engagement on B-cells enhances signaling through the BCR. Engagement of CD81 and virus-specific BCR by E2 could perturb B-cell function and lead to lymphoma. Mutations in the p53, *Bcl6* and *β-catenin* genes may occur in B-cell lines infected *in vitro* with HCV as well as in peripheral blood mononuclear cells from patients with chronic HCV infection. Induction of nitric oxide synthase by the viral core protein (C) and non-structural protein 3 (NS3) has been implicated in the occurrence of these mutations.
Although HCV can infect B-cells in vitro, possibly through CD81, only one case of B-cell lymphoma associated with direct infection of B-cells by HCV has been described so far. A lymphoid cell line derived from an HCV-infected patient presenting with a mantle cell lymphoma produced virus in vitro. Thus, direct infection of lymphocyte by HCV does not appear to be a prerequisite for most HCV-associated lymphomas, in agreement with what one would expect for an antigen-driven lymphoproliferation according to the “indirect” model of lymphomagenesis. Moreover, recombinant HCV E2 binding to CD81 on B-cells has been shown to induce hyper-mutations at the immunoglobulin locus. E2 is exposed on the virion surface and can interact externally with the CD81 co-receptor on B-cells. This mechanism of mutagenesis would be independent of direct infection of B-cells by HCV.

Conclusions and perspectives

Antigen-driven lymphoproliferations constitute a pathophysiological concept that took root with the description of the MALT-lymphoma entity in the early eighties and bloomed with the identification of H. pylori as the causal agent of gastric MALT-lymphoma in the early nineties. This concept assumes that the marginal zone B-lymphocyte is the cell from which these types of lymphomas derive, through a protracted proliferation induced by a persisting antigen, mostly of microbial origin. This entity now includes numerous additional examples of lymphoproliferations, which fall into the wider category of “MZ-lymphomas”. The recent deciphering of the antigenic specificity of B-cell responses from the MZ have yielded important clues in relation to MZ-lymphomagenesis associated with persistent antigenic stimulation. The spectacular responses observed after microbial eradication in a number of MZ/MALT-lymphomas associated with chronic infections is of great pathophysiological but also clinical importance, because many patients can be treated without antineoplastic chemotherapy, at least during the early stage of the disease. Unbiased approaches aimed at the identification of novel or unsuspected pathogens associated with MZ/MALT-lymphomas will undoubtedly lead to the lengthening of the list of microbial pathogens associated with lymphoproliferations. Additional work is now critically needed to provide irrefutable evidence demonstrating not only the association but also the causative role of the microbial pathogens identified with this approach.
Acknowledgements
We thank Nicole Brousse, Antoine Martin and Françoise Valensi for kindly providing pictures for Figure 4 and Bruno Varet for helpful support. We apologize to colleagues whose work could not be cited because of space limitations.

Conflict of interest statement
The authors have no conflict of interest to declare.

Figure and table legends
Figure 1: H. pylori and gastric MALT lymphomagenesis paradigm for infection-associated indirect lymphoid transformation.

(A) Persisting antigens (Ag) elicit a polyclonal B-cell response. Costimulation is provided by cytokines, and members of the tumor necrosis factor superfamily (CD40-CD40L in T-cell dependent responses and B-cell activating factor (BAFF)/B-lymphocyte stimulator (BLyS) or A Proliferation Inducing Ligand (APRIL) produced by dendritic cells in T-cell independent responses). In the case of H. pylori, T-cells specific for H. pylori epitopes provide help to B-cells that recognize cross-reactive autoantigens present in the gastric mucosa such as fucosylated sialyl-Lewis X through CD40-CD40L costimulation.

(B) Occurrence of genetic events such as p15 and p16 hypermethylation provide a selective advantage leading to the outgrowth of an antigen-responsive clone. Antigen-dependence reflects the requirement for BCR signals such as NF-κB activation (see also figure 5).

(C) Progression towards antigen-independent (therefore antimicrobial-insensitive) MALT-lymphoma is associated with the occurrence of additional genetic events. Chromosomal translocations involving MALT1 and Bcl-10 lead to a constitutive activation of NF-κB, bypassing the requirement for BCR-dependent signals (Figure 5). The t(11;18) translocation occurs early during B-cell proliferation and accelerates the transformation process in an antigen-independent fashion. The t(1;14) and t(14;18) translocations also lead to BCR-dependant NF-κB activation but occur later after an antigen-dependant phase, and can be associated with additional cytogenetical abnormalities. The t(3;14) translocation produces an IgH-FoxP1 transcript in 10% of MALT lymphomas that do not harbor other translocations involving the MALT1/Bcl-10 pathway. The
precise role of t(3;14) is not known. *P53* mutations is associated with transformation to high-grade lymphoma.

**Figure 2:** Organization of the lymphoid organs and B-cell responses.
Top: Schematic view of a Peyer’s patch (left) and lymphoid follicles in the spleen (right) surrounded by the arteriolar marginal sinus. MZ: marginal zone. GC: germinal center. DC: dendritic cell. FDC: follicular dendritic cell. The marginal zone is less conspicuous in the lymph nodes.
Bottom Left: Antigens having access to B-cell follicles are presented to B-cells by FDC. Antigen specific B-cells are activated by their BCR (signal 1) and proliferate, leading to the formation of the GC. Costimulation (signal 2) is provided by T-cell derived cytokines and CD40L-CD40 interactions. GC T-cells also express FasL and autoreactive B-cells (expressing Fas) are deleted by FasL-Fas interactions.
Bottom Right: Antigens captured in the blood by dendritic cells, or directly accessing the MZ are presented to MZ B-cells. MZ B-cells are activated by BCR signal (signal 1). Costimulation (signal 2) is provided by DC-derived cytokines and the tumor necrosis factor superfamily member BAFF/BlyS or APRIL. Activated MZ B-cells rapidly differentiate into plasma cells that secrete large amounts of IgM. In MZ B-cells, mutations in immunoglobulin genes are either acquired during ontogeny in an antigen-independent fashion (29), or during T-cell dependant responses occuring in the GC (31).

**Figure 3:** EBV infection and direct transformation of B-cells.
EBV infects naive B-cells through 2 surface receptors, CD21 and the class II MHC, HLA-DQ. During latency, the virus is maintained as an episome in the nucleus of infected cells, and viral genes are expressed, in the absence of lytic replication of the virus. EBV subverts normal B-cell differentiation, notably by the expression of LMP1, a viral latent protein expressed at the surface of infected cells. LMP1 associates with transduction molecules such as TRADD and TRAF and activate the NF-κB pathway in a CD40-like manner. LMP1 is required for the activation and immortalization of B-cells. LMP2 is a viral transmembrane protein that associates with Lyn/Syk PI3- kinases and leading to the activation of PKC and AKT respectively. LMP2 can substitute for signals emanating from the BCR. Both LMP1 and LMP2 converge to activate proliferation and
survival pathways in EBV latently infected cells. EBNA2 transactivates LMP1 and a number of cellular genes involved in activation and proliferation. Polyclonal infected B-cells proliferate and produce immortalized lymphoblastoid cell lines in vitro. In vivo, EBV infected B-cells are negatively controlled by anti-EBV cytotoxic T-lymphocytes (CTL). Failure to control EBV infected B-cells may lead to the development of post-transplant lymphoproliferative disorder (PTLD). Additional oncogenic mutations lead to clonal selection and evolution towards monoclonal tumours such as Burkitt’s lymphoma (BL), Hodgkin’s disease (HD) and diffuse large B-cell lymphomas (DLBCL) in immunocompromised patients.

**Figure 4:** Histopathologic illustration of MALT/MZ lymphomas

(A) Low power view (x50) of the lymphoid infiltration in a gastric biopsy sample tissue section stained with hematoxylin and eosin from a patient with *H. pylori*-associated gastric MALT lymphoma. The arrow shows a germinal center surrounded by an enlarged marginal zone infiltrating the gastric lamina propria.

(B) High-power view (x400) of an intestinal biopsy sample tissue section stained with hematoxylin and eosin from a patient with *C. jejuni*-associated IPSID, revealing centrocyte-like cells (CCL) infiltrating the crypt epithelium and forming lymphoepithelial lesions. (LEL).

(C) Sections of jejunum (x100) stained with primary antibodies directed against the B-cell marker CD20 (appears brown when stained with enzyme-linked secondary antibodies) and counterstained with hematoxylin show CD20-positive centrocyte-like lymphocytes pervading the lamina propria surrounding crypts (The top inset shows a higher-power view of the epithelium). CD20-positive CCLs infiltrate the crypt epithelium and produce characteristic LEL (arrow).

(D) High power view (x400) of a gastric biopsy sample tissue section stained according to the Giemsa technique from a patient with *H. pylori*-associated gastric MALT lymphoma. The gastric mucosa is heavily infected by *H. pylori* (arrow).

(E) Immunohistochemical analysis of a jejunal section (x400) from a patient with IPSID and stained with an anti-*C. jejuni* monoclonal antibody (brown) and hematoxylin. The arrows point to immunolabeled material shown at a higher magnification in the top right inset. The top left inset shows a crypt section with intraluminal immunolabeled bacteria.
(F) A blood smear (x1000) coloured according to the May-Grunwald-Giemsa technique showing a typical villous lymphocyte from a patient with HCV-associated splenic lymphoma with villous lymphocytes.

**Figure 5:** Gastric MALT lymphoma translocations lead to a bypass of the BCR-mediated NF-κB activation.

**Table 1:** World Health Organization classification lymphoma subtypes associated with infections. Abbreviations: DLBCL indicates diffuse large B-cell lymphoma; MZ, marginal zone; MALT, mucosa-associated lymphoid tissue; PTLD, post-transplant lymphoproliferative disorders; SLVL, splenic lymphoma with villous lymphocytes; IPSID, immunoproliferative small intestinal disease.
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Table 1: WORLD HEALTH ORGANIZATION CLASSIFICATION LYMPHOMA SUBTYPES ASSOCIATED WITH INFECTIONS

<table>
<thead>
<tr>
<th>MICROBIAL PATHOGEN</th>
<th>WORLD HEALTH ORGANIZATION (WHO) HISTOLOGIC SUBTYPE</th>
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<tbody>
<tr>
<td>Human T-lymphotropic virus 1 (HTLV-1)</td>
<td>Adult T-cell leukemia/lymphoma</td>
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<tr>
<td>Human immunodeficiency virus (HIV)</td>
<td>Hodgkin’s disease</td>
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<tr>
<td></td>
<td>Burkitt’s lymphoma (with or without EBV)</td>
</tr>
<tr>
<td></td>
<td>DLBCL (including primary effusion lymphoma and plasmablastic lymphoma)</td>
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<tr>
<td></td>
<td>Extranodal MZ-lymphoma, MALT type (rare)</td>
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<tr>
<td></td>
<td>T-cell lymphoma (rare)</td>
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<tr>
<td>Epstein-Barr virus (EBV)</td>
<td>Hodgkin’s disease</td>
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<tr>
<td></td>
<td>Polymorphic PTLD</td>
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<tr>
<td></td>
<td>Burkitt’s lymphoma</td>
</tr>
<tr>
<td></td>
<td>Monomorphic PTLD (DLBCL)</td>
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<tr>
<td></td>
<td>Primary effusion lymphoma (with HHV8)</td>
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<td>Human herpesvirus 8/Kaposi sarcoma associated herpesvirus (HHV8/KSHV)</td>
<td>Primary effusion lymphoma</td>
</tr>
<tr>
<td></td>
<td>Plasmablastic lymphoma (DLBCL)</td>
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<tr>
<td></td>
<td>PTLD (rare)</td>
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<tr>
<td>Hepatitis C virus (HCV)</td>
<td>SLVL (splenic MZ-lymphoma)</td>
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<td></td>
<td>Other marginal zone lymphoma</td>
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<tr>
<td></td>
<td>DLBCL</td>
</tr>
<tr>
<td>Helicobacter pylori</td>
<td>Gastric MALT-lymphoma (extranodal MZ-lymphoma, MALT type)</td>
</tr>
<tr>
<td>Campylobacter jejuni</td>
<td>IPSID (extranodal MZ-lymphoma, MALT type)</td>
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<tr>
<td>Borrelia burgdorfer</td>
<td>Primary cutaneous B-cell lymphoma (various WHO subtypes including extranodal MZ-lymphoma, MALT type)</td>
</tr>
<tr>
<td>Chlamydia psittaci</td>
<td>Ocular adnexal lymphoma (extranodal MZ-lymphoma, MALT type)</td>
</tr>
</tbody>
</table>
Figure 1

A. Proliferation of polyclonal Ag-specific B-cells

B. Ag-dependent expansion of a transformed B-cell clone

C. Ag-independent expansion of fully transformed B-cells

H. pylori antigens and/or autoantigens

BCR-dependent NF-κB activation

CD4

CD4

CD4

CD4

CD4/CD40L

CD4

CD4

Cytokines

BAFF

APRIL

p15, p16 alterations

Accelerated transformation

Chronic gastritis

Antimicrobial-sensitive MALT lymphoma

Antimicrobial-insensitive MALT lymphoma

t(1;14)

t(14;18)

bypass of BCR-dependent NF-κB activation

role?

t(3;14)
Figure 2

**GC: T-cell dependent B-cell response**

- **Follicular DC**
  - BCR
  - CD4
  - Fas/FasL
  - Cytokines: BAFF/BLyS and APRIL

**MZ: T-cell independent B-cell response**

- **Marginal zone DC**
  - BCR
  - Cytokines: BAFF/BLyS and APRIL

- **Ag-independent somatic hypermutations?**

**GC formation**
- B-cell proliferation
- Somatic hypermutation
- Isotype switch
- Memory B-cells
- Long-lived plasma cells
- Ab secretion (IgG, IgA)

**Longitudinal marginal sinus**

**Peyer’s patches and other MALTs**

**Splenic lymphoid follicles**

**Lamina propria**

**Arteriolar marginal sinus**
Figure 3
Figure 4:
Infection-associated lymphomas derived from marginal-zone B-cells: a model of antigen-driven lymphoproliferations

Felipe Suarez, Olivier Lortholary, Olivier Hermine and Marc Lecuit