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The importance of *Helicobacter pylori* in the development of gastric MALT lymphoma — induction of proliferation and immune suppression

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Marginal zone B-cell lymphomas are indolent, slow-growing lymphomas derived from mature B cells. They represent about 8% of all lymphomas and about 50% of all primary gastric lymphomas. Based on numerous epidemiological and microbiological studies, *Helicobacter pylori* is believed to be responsible for the progression of gastric MALT lymphomas (GML). Lymphoid tissue is physiologically absent from the stomach. However, GML can arise from chronic *H. pylori* infection and immune cell infiltration. This review article describes the mechanisms favouring the development of *H. pylori*-induced GML, and suggests potential targets for a more effective remission of lymphomas localized within the stomach.

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Introduction

Helicobacter pylori is a spiral and gram-negative bacterium capable of colonizing the gastric mucosa. This process occurs most often during early childhood and lasts throughout life in the absence of any adequate eradication therapy [1]. Not all people colonized with this bacteria exhibit disease symptoms, but importantly this condition predisposes towards their development [2]. It is estimated that over 90% of chronic gastritis is a result of prolonged *H. pylori* infection. Other causes include non-steroidal anti-inflammatory drugs, alcohol consumption, gastroesophageal reflux disease and autoimmune mucosa atrophy. Patients with gastritis suffer from gastrointestinal disorders which include dyspepsia, bloating, discomfort and feeling of fullness in the upper abdomen. Symptoms may be aggravated by unhealthy diets, alcohol consumption and emotional stress or fatigue [3]. The acute phase of *H. pylori* infection is associated with an intense inflammation of the gastric mucosa, characterized by infiltration of immune system cells; especially neutrophils. Increased production of proinflammatory cytokines involved in gastric tissue degradation, (including IL-1β, IL-6, IL-8, IL-12, TNF-α, CCL2-5, CCL20 and CXCL1-3), is the consequence [4]. Inflammatory mediators cause the following: epithelial lesion formation, changes in proliferation and apoptosis processes along with modulating host gene expression [2]. The acute phase is followed by a decreased antimicrobial response of the host organism and chronic *H. pylori* infection. Some people may develop gastric and duodenal ulcers, gastric cancer or mucosal associated lymphoid tissue (MALT) lymphoma [1].

Characteristics of the MALT lymphoma

MALT lymphomas can affect the majority of human body organs including lungs, thyroid gland, breast, urinary bladder and skin [5]. MALT lymphomas are most commonly found in the digestive system, particularly the stomach, which are defined as gastric MALT lymphomas (GML) [6]. GML is an indolent extranodal marginal zone B cell lymphoma (MZL). The growth of primary gastrointestinal tract lymphomas, including gastric lymphoma, is generally slow and limited to the gastrointestinal wall; it may remain asymptomatic for many years. The morbidity rates of GML increases with age. GML are diagnosed mainly in patients aged 60 years or over, and GML rates are almost the same for men and

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women [7]. MZL are non-Hodgkin lymphomas which evolve from mature B cells [8]. Lymphoid tissue is physiologically absent from the stomach. However, due to chronic *H. pylori* infection and an infiltration of immune cells, gastric MALT lymphomas can arise [9]. MALT lymphoma cells share the same cytological and immunophenotypical features: i.e. $CD20^+$, $CD21^+$, $CD35^+$, IgM^+ and IgD^- [10]. MALT lymphomas are classified as rare diseases. The annual estimated incidence of GML is approximately 1–1.5 per 100 000. In comparison, gastric cancer is 5 to 10 times more common (United States National Cancer Institute Surveillance Epidemiology and End Results data) [11].

The primary GML diagnosis should be based on clinical symptoms and on immunohistochemical and pathohistological examination of gastric biopsy tissue [11, 12]. Before undertaking such examinations, it is important to interview the patient, focusing on clinical symptoms that typically include: dyspepsia, epigastric pain, nausea, vomiting, weight loss and any alarming symptoms, such as melena and hematemesis. Some patients however can remain asymptomatic. The gold standard of the GML diagnostic process is an endoscopic examination with multiple biopsies of gastric tissue [7, 8]. Macroscopic changes defined by gastroscopy are nonspecific including thickening of mucosal folds and irregular masses with superficial erosions and superficial ulcers. Due an equivocal endoscopic picture, multiple biopsies are obligatory for pathohistological examination. Sometimes immunophenotyping and molecular examinations may be necessary [8, 12].

To evaluate the staging of both Hodgkin and non-Hodgkin lymphomas the Ann Arbor system is commonly used. However, due to its limitations for assessing primary gastrointestinal lymphomas, the Lugano and Radaszkiewicz classifications have been proposed [11]. In order to more precisely evaluate the staging of primary gastrointestinal lymphomas, the European Gastro-Intestinal Lymphoma Study Group created The Paris System; a special modification of the TNM (tumor-node-metastasis) staging system, used for classifying non-hematologic solid malignancies [13]. There are several genetic aberrations characteristic to lymphoma cells: translocations, point mutations, gene deletions and amplifications. Detecting their presence is crucial in the diagnostic process and affects the treatment of choice [11]. The genetic aberrations at translocations t(1;14) (p22;q32) and t(11;18)(q21;q21) are responsible for the response to apoptosis signals being ineffective and increased transcriptional activity of NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells). Other detected translocations, t(14;18)(q32;q21) and t(3;14) (p14;q32), are rare and their significance has not yet been defined precisely [12]. The most frequent chromosomal aberration is the t(11;18) translocation which is detected in approximately 20% of patients with MALT lymphoma, particularly those with MALT lymphomas located in the stomach, colon and lung [5].

Expression of *H. pylori* virulence factors and GML development

Based on numerous epidemiological and microbiological studies *H. pylori* is believed to be responsible for GML progression [5, 6]. In a study on 110 patients with GML, *H. pylori* infection was detected in 101 (92%) cases [14]. It is believed that *H. pylori* strains producing multiple virulence factors are associated with exacerbating gastritis. Correlations between the expression of virulence factors, especially CagA oncoprotein and VacA toxin, are relatively well documented in peptic ulcers and gastric cancer. Nevertheless, their involvement in the development of gastric MALT lymphomas remains controversial [6].

The *cag*PAI pathogenic island is a 40 kb DNA fragment containing 27 to 31 genes; eighteen of which encode information for proteins forming the IV secretory system (T4SS), which facilitates CagA oncoprotein and peptidoglycan fragment translocation [2]. CagA is a 120–145 kDa protein produced by 60–70% of *H. pylori* strains. It rearranges the host actin cytoskeleton, disrupts tight junctions and causes morphological changes of eukaryotic cells leading to the so-called hummingbird phenotype [4]. Moreover, CagA inhibits the apoptosis regulator and tumor suppressor — p53, and thus allows B cells to avoid programmed death as well as in mediating the accumulation of genetic mutations [15].

There are two pathways by which CagA deregulates intracellular signalling pathways in eukaryotic cells; i.e. phosphorylation-dependent and -independent. The first is based on tyrosine phosphorylation within the EPIYA (Glu-Pro-Ile-Tyr-Ala) motifs of the CagA protein. Modified protein induces tyrosine phosphatase 2 (SHP-2) and this activates extracellular signal-regulated kinases 1/2 (Erk1/2). The unphosphorylated CagA protein induces Erk1/2 kinase through an alternative Ras-Raf signalling pathway [2, 16]. Both processes contribute to activating the NF-κB transcription factor and increased IL-8 expression [17]. Moreover, peptydoglycan fragments delivered through T4SS to host cells also activate NF-κB and increase IL-8 secretion by inducing Nod1 proteins (nucleotide-binding oligomerization domain 1) [18]. IL-8 is not the only chemoattractant for leucocytes but also plays an important role as a mitogenic and angiogenic factor in neoplasm progression [19]. Erk1/2 stimulation and p53 expression blockade facilitates apoptosis inhibition which results in genetically dysfunctional cells being produced. This may disrupt homeostasis between programmed cell death and proliferative processes together with *H. pylori*-mediated gastric MALT lymphomas development [16]. Ohnishi et al. engineered transgenic mice that endogenously produce CagA proteins. After 72 weeks from transfection, gastric

epithelial hyperplasia was observed and in some individuals polyps and adenocarcinomas were detected. Such changes have been shown to be due to hyperactivity of SHP-2 phosphatase and Erk1/2 kinase [20].

Many epidemiological studies have attempted to elucidate any correlation between CagA production by *H. pylori* and the presence of gastric MALT lymphomas. When studying CagA seroprevalence in *H. pylori* infected patients, Eck et al. obtained positive outcomes in 95.5% (64/67) GML patients and 67% (33/49) in controls with chronic gastritis [21]. Sumida et al. demonstrated an identical prevalence of anti-CagA antibodies, i.e. 95.5% (42/44). Furthermore, it was found that patients in GML remission (86.4%; 38/44) had significantly higher levels of anti-*H. pylori* and anti-CagA antibodies than in the group without the therapeutic effect; respectively 105.2 ± 166.4 vs 24.3 ± 14.9 U/mL and 43.7 ± 25.1 vs 16.5 ± 13.2 U/mL [22]. A study by Delchier et al. divided patients into two groups, based on disease progression, i.e. to low-grade GML (LGML) and diffuse large B-cell lymphoma (DLBCL). In the first group, antibodies against CagA were detected in 44.8% (13/29) of patients, while a higher seroprevalence was found in the DLBCL group of 75% (12/16) [23]. Similar observations were made by Peng et al., who identified *cagA* through isolating DNA from patients' biopsies where gene prevalence was demonstrated in 30.3% (17/56) of patients with gastritis, 37.8% (14/37) with LGML and 76.7% (23/30) with DLBCL [24]. These results suggest that the gastric MALT lymphoma progression may be dependent on the expression of *cagA* by *H. pylori* strains, which is indirectly confirmed by GML treatment effects in Hp^+ $CagA^+$ patients. Disease remission after eradicating *H. pylori* was found to be faster in patients with $CagA^+$ *H. pylori* infection (average 3 months) than in patients infected with $CagA^-$ bacterial strains (6.5 months) [25].

The second most important virulence factor produced by *H. pylori* is VacA. All strains of this bacterium have a *vacA* gene but *in vitro* only half of them synthesize this toxin [6]. Three variable regions are present in the *vacA* sequence, i.e. the signal sequence s (s1a, s1b, s1c, s2), the middle region m (m1, m2a, m2b) and the intermediate region i (i1, i2, i3). The s1/m1/i1 variants have higher biological activity and a stronger toxic effect [26]. VacA is a highly immunogenic 95 kDa protein causing a number of pathological changes in the targeted host cells. Among these, is its ability to form anion-selective pores in cell membranes, interfere with cytoskeleton-dependent cell function and induce apoptosis via the mitochondrial cytochrome c release [2, 4]. In addition, VacA has *in vivo* antiproliferative activity against lymphocytes and the ability of modulating immune system processes [6]. Koehler et al. isolated DNA from biopsy samples of *H. pylori* infected patients with gastritis, gastric cancer and GML. It was estimated that in gastric cancer patients the dominant *H. pylori* genotype was *vacA*s1m1 (s1 alleles were detected in 93%, 26/28, and m1 in 61%, 17/28) whilst in the GML group the *vacA*s1m2 variant was dominant (alleles were found in 83%, 20/24, and 83% in 20/24) [27]. The middle region affects the toxin's ability to interact with targeted cells [26]. Thus the *vacA*m2 variant reduces antiproliferative activity [6]. For this reason, it is proposed that the presence of less active VacA toxin forms, produced by *H. pylori* strains, may contribute towards gastric MALT lymphomas developing.

Immune response modulation by *H. pylori*

Chronic inflammation of the gastric mucosa caused by *H. pylori* infection is probably the key factor responsible for GML development. The inflamed gastric mucosa furthers increased antigen presentation and recruitment of B cells [28]. Infiltration of these immune cells is accompanied by activated proliferative processes and the formation of B cell clusters and germinal centers (GC) [12, 16]. Moreover, abnormal NF-κB pathway activation initiates the transformation of gastric lymphoid tissue [12]. The transcription factor NF-κB controls B and T cells maturation and survival, exerting an anti-apoptotic effect on these cells [29]. Through CagA and peptidoglycan fragment translocation, *H. pylori* increases NF-κB activity which results in the host immune response being modulated, hyperproliferation of lymphocytes and the potential induction of GML [2, 17, 18]. Thereby, chronic or recurrent activation of the immune system by *H. pylori* can lead to lymphoid tissue growth. As supported by coexisting environmental factors and genetic predispositions this process can lead to hyperproliferation of lymphoid tissue and oncogenesis [2, 8]. Despite the possibility of B cells to undergo autostimulation-dependent activation by *H. pylori* antigens, lymphogenesis may also be mediated by T-cell stimulation [6, 12].

The main part of the host lymphocytes induced by *H. pylori* are the Th_1 and Th_{17} populations. The first of these secrete proinflammatory cytokines IFN-γ and TNF-α, which in turn activate antimicrobial activity in macrophages. Th_{17} cells also affect progression of the inflammation process through secretion of inflammatory mediators such as IL-17A, IL-17F, IL-21 and IL-22 [4]. This process is characteristic of the initial stages of *H. pylori* infection. The next step is based on the host immune response being suppressed by over-activation of $CD4^+$ $CD25^+$ (Treg cells) [9, 30, 31]. Treg cells recruitment occurs through secretion of CCL17 and CCL22 chemokines produced by B cells [32]. Treg cells promote tolerogenic signals and secrete anti-inflammatory cytokines, such as IL-10 and TGF-β [9, 30]. IL-10 increases the B cells ability to proliferate, survive and differentiate. On the other hand, these mediators also have antiproliferative and suppressive effects on other fractions of immune cells, i.e. they reduce secretion of proinflammatory IFN-γ and TNF-α by Th_1 cells and of IL-17 by Th_{17} cells. Such ac-

tivities promote carcinogenesis via inhibiting secretion of antitumor mediators [33]. TGF-β is a cytokine that inhibits excessive proliferation and repressor genes encoding for cytotoxic mediators, including perforin, granzymes A and B and IFN-γ [34]. The suppressive environment mediated by high TGF-β concentrations affords protection against tumours developing. This happens until carcinogenic cells become resistant to the stimuli initiated by this mediator, for example by the increased activity of mammalian target of rapamycin (mTOR), which makes carcinogenic cells insensitive to TGF-β-mediated antiproliferative activity [35]. In such situations, elevated TGF-β level is beneficial for lymphoma development because it disrupts cytotoxic and proapoptotic activity to tumor-altered cells [33]. In an *in vivo* mouse model, Craig et al. demonstrated the ability of *Helicobacter* spp. to promote MALT lymphoma development by Treg cells activation. In *H. felis* infected BALB/c mice, depletion of $CD4^+$ or $CD25^+$ by monoclonal antibodies resulted in tumor regression. After 18 months post-infection, 2–15 tumors were found in each individual mouse stomach. A different situation was observed in mice lacking $CD4^+$ T cells because none had developed lymphoma. In mice without $CD25^+$ T cells studies show similar results, excepting one individual with a single tumor [32]. Such results suggest that Treg cells can actively affect oncogenesis development via promoting a suppressive environment that reduces antitumor immune system activity.

In addition to the ability for recruiting Treg cells by *H. pylori*, this microorganism may suppress the excessive proinflammatory response by promoting high B7/H1 levels. These molecules are homologous to immunoglobulins and exert an inhibitory effect on programmed death-1 (PD-1) receptors on the T cells' surface. Experiments on tumor cell lines have shown that B7/H1 facilitates carcinogenic resistance to apoptosis mediated by Fas-induced cell-death. What's more, *H. pylori* increases B7/H1 expression which is also responsible for the transformation of virgin T cells into Treg cells [37]. A study by Lina et al. showed that *H. pylori* increases B7/H1 concentrations which was dependent on CagA and peptidoglycan fragment translocation into host cells. The *in vivo* effect of two *H. pylori* strains on B7/H1 expression during C57BL/6 mice infection was verified, i.e. PMSS1 — producing the T4SS system, and SS1 — having no functional T4SS. Enhancement of increased B7/H1 concentrations was observed only for the *H. pylori* PPSS1 strain, which in turn resulted in elevated bacterial growth in the mouse and higher amounts of Treg cells and raised serum IL-10 [38].

Gastric MALT lymphoma treatment

MALT lymphomas are distinguished by an indolent clinical course. Most are diagnosed at an early stage. Therapeutical choices depend on whether *H. pylori* infection and the presence of (t11;18) translocation are confirmed; the latter being reported as an adverse prognostic factor in terms of lymphoma regression after *H. pylori* eradication [8]. Chronic *H. pylori* infection can lead to lymphoid proliferation and GML development. For this reason, *H. pylori* infection should be confirmed in each patient diagnosed with GML. The diagnosis should be based on invasive and noninvasive tests including measuring IgG, IgM, IgA antibodies, monoclonal stool antigens detection, the ^{13}C-urea breath test, microbes culture and histochemical testing [39]. *H. pylori* eradication therapy should rely on highly effective antibiotics with due consideration given to possible resistance in bacterial strains [5]. Approximately 20% of *H. pylori* strains are proved to be clarithromycin resistant. As a consequence, it is strongly recommended to attempt an eradication by quadruple therapy using a bismuth salt, tetracycline, metronidazole and PPI instead of triple therapy using PPI, clarithromycin and amoxicillin [40]. *H. pylori* antibiotic therapy can lead to complete GML remission in 77.5–94% of patients [16]. Gastric lymphoma regression in response to *H. pylori* eradication can on average take from 5 to 12 months and sometimes even 45 months. After achieving remission, systematic clinical and endoscopic monitoring is mandatory including pathohistological examinations and tests for *H. pylori* infection [7]. The estimated survival rate of patients with complete lymphoma remission can reach to almost 100% after 10 years. Patients with partial remission have a 10-year survival rate of 80% [7, 41]. *H. pylori* reinfection determines MALT lymphoma recurrence. In such cases, disease progression is more dynamic as a consequence of gastric tissue sensitivity to *H. pylori* antigens [42]. In cases when pharmacological treatment fails, radiotherapy should be attempted. In patients with aggressive primary GML, i.e. large B-cell lymphoma (DLBCL), systemic polychemotherapy is recommended for first-line treatment despite the coexisting *H. pylori* infection. Patients therapy whenever advanced-stage disease occurs and in those with confirmed lymphoma recurrence is based on chlorambucil, fludarabine and rituximab treatment [5, 7, 9, 41].

Implications for medical practice and teaching

Confirming *H. pylori* status in people with diagnosed GML is a routine procedure [39]. It is suggested that besides detecting such bacteria, an important diagnostic element may also be in determining the *H. pylori* virulence profile. Such practice is important not only for epidemiological reasons (e.g. higher isolation frequency of VacAs1m2 strains), but also in planning an effective therapy. It was found that GML remission caused by $CagA^+$ *H. pylori* strains is twice as fast as that of $CagA^-$ strains [25]. Henceforth, the presence of the *cagA* gene may in future be treated as a microbial genetic marker which defines the duration of patient convalescence.

Moreover when toxins production by *H. pylori* becomes known then appropriate compounds can be incorporated that inhibit pathological metabolic changes in those eukaryotic cells exposed to bacterial toxins. Oncoprotein CagA induces rearrangement of the host actin cytoskeleton, disrupts tight junctions, elicits morphological changes and causes malignant transformation [4]. Inhibition of CagA kinases in *H. pylori* infected cells leads to a complete loss of CagA phosphorylation and decreases cell death. Pharmacological inhibition of tyrosine kinases, which mediate CagA phosphorylation, may thus become an attractive treatment option for patients with late stage GML or in those where *H. pylori* eradication proves unsuccessful [43]. Key molecules responsible for cell-cycle regulation, proliferation and apoptosis that are present in the process of MALT lymphoma oncogenesis may become specific therapy targets not only in patients with this kind of lymphoma, but also in patients with other lymphoproliferative disorders [11].

Increased levels of Treg cell recruitment and infiltration within tumor-altered stomach tissue is observed [32]. Thus in the course of GML, the inflammation intensity correlates often inversely with the density of *H. pylori* found in the stomach. On this basis, it can be falsely concluded that the absence of a strong inflammatory reaction in the gastric mucosa may suggest a low-grade disease. Finding a high bacterial titre with low-grade mucosal inflammation may, however, indicate the development of the GML process [44]. For this reason, attention should be paid to an increased oncological vigilance in physicians diagnosing patients whenever gastric lymphomas are suspected.

Elevated Treg cells level in the gastric mucosa is a key factor in reducing proliferation and cytotoxic activity of other T cells subpopulations, therapeutic failure and a poor prognosis [9, 30, 45, 46]. Studies on Treg cell activity during an ongoing *H. pylori* infection may help to find new and effective therapies focused on oncogenesis control. The course of tumor immunotherapy has shown that Treg-targeting compounds may be good candidates for treatment based on immune system modulation. Reducing Treg activity promotes the shift of the tumor microenvironment from being strongly suppressive to the physiologically active [45, 46]. Among potential methods that can achieve this effect are: IL-10 receptor blockade [47], selectin blockade [48], inhibition of chemokines responsible for Treg cells recruitment (CCL17, CCL22, CCL20 or CXCL13), blocking chemokine receptors specifically expressed by Treg effector cells (e.g. CCR4), inhibition of CTLR-4 co-inhibitory molecules expressed constitutively on the surface of Treg cells, or exogenous IL-2 administration (capable of reducing suppressive activity of Treg cells) [46]. In addition to this Treg cell-blocking therapy, it may also prove effective to administer low doses of cyclophosphamide. Such therapy selectively reduces the amount of rapidly proliferating Treg cells within tumor tissue and strengthens the anti-tumor response [49].

Conclusions

Numerous studies report a strong association between *H. pylori* gastric mucosa colonization and GML development. *H. pylori* infection mediates Treg cell recruitment, which in turn promotes tolerogenic signals and the secretion of anti-inflammatory cytokines IL-10 and TGF-β. In recent years, an increasing number of reports suggest a key role of Treg cells in perturbing cytotoxic and proapoptotic activity and probably an effect on GML development. Therefore, decrease of the activity or over-recruitment of these immune cells appears to be an important target in anti-tumor therapies based on enhancing the sensitivity of neoplastic cells. The complexity of GML pathogenesis requires extensive knowledge of oncology, microbiology and immunology to ensure delivery of effective treatment to the patient. In the light of the presented conclusions, close collaboration between gastroenterologists, oncologists and microbiologists is thus proposed as a standard procedure in the battle against GML.

Conflict of interest: none declared

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