Review

Helicobacter pylori Strains and Gastric MALT Lymphoma

Pauline Floch, Francis Méraud and Philippe Lehours *

INSERM, Univ. Bordeaux, UMR1053 Bordeaux Research In Translational Oncology, BaRITOn, F-33000 Bordeaux, France; pauline.floch@u-bordeaux.fr (P.F.); francis.megraud@chu-bordeaux.fr (F.M.)
* Correspondence: philippe.lehours@u-bordeaux.fr; Tel.: +33-557-571-286; Fax: +33-556-514-182

Academic Editors: Jean E. Crabtree and Silja Wessler
Received: 24 January 2017; Accepted: 3 April 2017; Published: 8 April 2017

Abstract: This article summarizes the main findings concerning Helicobacter pylori associated with gastric MALT lymphoma (GML). Considered together, GML strains based on their virulence factor profile appear to be less virulent than those associated with peptic ulcers or gastric adenocarcinoma. A particular Lewis antigen profile has been identified in GML strains and could represent an alternative adaptive mechanism to escape the host immune response thereby allowing continuous antigenic stimulation of infiltrating lymphocytes.

Keywords: Helicobacter pylori; pathogenesis; virulence marker; cag pathogenicity island; MALT lymphoma

1. Introduction

Gastric MALT lymphoma (GML) is the most common marginal zone lymphoma of the digestive tract. The involvement of Helicobacter pylori in this lymphoma is now well established and is based on epidemiological, pathological, clinical, and bacteriological evidence [1]. H. pylori eradication therapy is now considered the first therapeutic approach for low grade GML [2,3]. Further studies have indeed revealed a regression of GML lesions after antibiotic eradication of the bacteria [4,5]. H. pylori eradication allows lymphoma regression in 60% to 90% of patients [6]. If a reinfection occurs, GML reappears and evolves more rapidly because neoplastic cells are already sensitized to H. pylori antigens [7].

H. pylori infection was the first bacterial infection to be considered as a type I carcinogen (maximum level) for its implication in gastric adenocarcinoma. Since its discovery, extensive research has been devoted to the identification of virulence factors or genetic markers, but H. pylori strains associated with GML have been little studied.

We will endeavor in this review to answer one main question: are there H. pylori strains which are more capable of inducing GML than others?

2. GML and Cytotoxin-Associated Gene A (CagA)

H. pylori is perfectly suited to the human stomach with an armamentarium allowing it to withstand stomach acid, move in the gastric mucosa and evade the immune response of the host [8]. The main virulence factors studied in H. pylori are those involved in inflammation and cell damage, in particular those encoded in the cag pathogenicity island (cagPAI) as well as other pro-inflammatory proteins [9]. The cagA gene, encoded by the cagPAI, is undoubtedly the most studied virulence factor. Inside the host cells, CagA can be phosphorylated and exert cellular effects dependent on tyrosine phosphorylation, but it can also exert cellular effects independent of CagA phosphorylation, namely IL-8 secretion [10–12]. CagA positive strains are considered to be more virulent and are associated with peptic ulcers and gastric adenocarcinoma [13,14] while their association with GML is contradictory.
The results of various studies based essentially on serological data (detection of CagA antibodies) have not been consistent. Some have shown an association between CagA positive strains and the occurrence of GML [15–22] and, more importantly, the prevalence of CagA positive strains in diffuse large B-cell lymphoma (DLBCL) [17,21] (Table 1).

Table 1. Specificities of gastric MALT lymphoma strains.

| Virulence Factors          | Association with Gastric MALT lymphoma                                                                 | References |
|----------------------------|--------------------------------------------------------------------------------------------------------|------------|
| CagA                       | Controversial implication. *cag* PAI present in only 50% of GML isolated strains. Association with high grade lymphoma questionable. | [17,21,28,40] |
| VacA                       | vacAm2 allele predominant in GML strains (genotype associated with the lowest biological activity)     | [39,40]    |
| BabA                       | No association with GML.                                                                               | [40]       |
| SabA                       |                                                                                                        | [40]       |
| Other adhesins             |                                                                                                        | [40]       |
| Lipopolysaccharide (LPS) antigens | *cag* PAI negative GML strains expressed Le^v^ antigens, previously associated with autoimmune manifestations. | [55,59]    |
| Genetic markers            |                                                                                                        | [40]       |
| Gene group comprised of iceA1 allele, sabA and hopZ | Association with the risk of GML development (low sensitivity marker) | [40]       |
| ORF JHP950                 | ORF encoding a protein with no specific function, association with iceA1 and sabA virulence genes. The first and only genetic marker of GML strains. | [64]       |
| DNA array                  | GML strains share common genetic background.                                                            | [65]       |
| Genome sequencing          | Further studies are needed to understand biological significance of genetic variabilities               | [65,66,68] |

Indeed, CagA is able to translocate into human B lymphocytes in vitro via the type 4 secretion system encoded by the *cag* PAI [23,24]. Once in the cytoplasm, the protein binds to SHP-2, which stimulates B lymphocyte proliferation and inhibits apoptosis via the regulation of intracellular pathways, including the activation of endoplasmic reticulum kinases 1 and 2 (ERK 1 and ERK 2) and p38 MAP kinase (MAPK) and an increase in the expression of Bcl-2 and Bcl-XL [24,25]. The correlation between CagA expression and the expression of SHP-2, ERK, MAPK, Bcl-2 and Bcl-XLT has been confirmed in humans [26]. In transgenic mice ubiquitously expressing CagA, leukocytosis is induced as well as myeloid leukemias and B lymphomas via the deregulation of SHP-2, which is in favor for its role in the pathophysiology of GML. This activity would be dependent on CagA phosphorylation [27]. CagA also acts by inhibiting the accumulation of p53, an important regulator of apoptosis and tumor suppressor, and thus allows B-cells to evade apoptosis leading to the accumulation of genetic mutations [23]. In contrast to CagA activity in the deregulation of SHP-2, this inhibitory effect of CagA would be independent of its phosphorylation [23]. CagA also has an inhibitory activity on B lymphocyte proliferation via the suppression of the JAK-STAT signaling pathway which would allow the bacterium to avoid a specific immune response [23].

Concerning the expression level, Kuo et al., [28] detected the CagA protein in malignant B cells in half of the GML patients studied. They observed that patients developing GML and infected by a CagA positive strain responded significantly faster to eradication than those infected by a CagA negative strain [28].

It is now established that *H. pylori* strains expressing the CagA protein are not associated with low grade GML, but rather with gastric DLBCL [17,21,29,30]. Serological and strain analyses showed
that the prevalence of CagA was significantly higher in gastric DLBCL (approximately 75%) than in GML (37.8% to 44.8%) [17,21]. CagA and CagA signaling molecule expression in tumor cells could be markers of *H. pylori* dependence on gastric DLBCL [30]. The results of the study conducted by Lehours et al., based on a large collection of well-characterized MALT strains, are consistent with the absence of CagA association with GML. The absence of CagA in about half of the GML strains studied indeed suggests the existence of other mechanisms in lymphomagenesis. These strains are probably less pro-inflammatory than strains associated with peptic ulcer or gastric adenocarcinoma. This was confirmed in vitro during co-culture experiments with a gastric epithelial cell line, namely AGS. GML strains and, in particular, the cagPAI negative ones did not have a particular pro-inflammatory potential in this experimental system and would probably produce no other major pro-inflammatory factor than those encoded by the cagPAI [10].

3. GML and Vacuolating Cytotoxin A (VacA)

The vacuolating cytotoxin VacA was named for its ability to induce the formation of vacuoles in some cell lines in vitro. The protein of 140 kDa is encoded by the vacA gene. All *H. pylori* strains have a copy of this gene, but only 50% possess the vacuolating ability in vitro. This is explained by its polymorphism, the variable level of gene transcription [31] and the level of the protein’s secretion [32]. Three major regions of diversity (s, i and m) in the vacA sequence gene have been described: the signal s sequence is characterized by four different families (s1a s1b, s1c, s2), the m central region by three families (m1, m2a, m2b) and the intermediate region i by three families (i1, i2, i3). Each gene has a combination of these different sequences which leads to numerous alleles and determines the activity of the toxin [33].

Epidemiological studies have shown a correlation between these alleles and the risk of developing a gastroduodenal disease. The risk of gastric adenocarcinoma or peptic ulcer development is increased in people infected with strains carrying s1, m1 or i1 alleles compared to those infected with s2, m2 or i2 strains [33–35]. It has also been shown that VacA induces epithelial cell apoptosis both in vitro and in vivo [36,37]. VacA penetrates inside the mitochondria, leading to a release of cytochrome C and thereby activating pro-apoptotic signaling pathways [38].

The combination of vacA alleles with GML was also studied. Indeed, the vacAm2 allele, corresponding to the less biologically active strains (the less vacuolating in vitro, the less pro-apoptotic and less biologically active in vivo), predominates in GML strains [39,40] (Table 1). The vacA s1m1 genotype (corresponding to a high level of cytotoxin production) was correlated to the presence of cagA and cagE, suggesting that these virulence genes are closely associated (as already described in *H. pylori* strains leading to the other diseases), however, the evolution toward GML remain to be elucidated.

Finally, VacA was shown to exhibit in vivo anti-lymphoproliferative properties, especially on T cells. This should be interpreted with care, in line with GML pathogenesis. VacA inhibits the activation and proliferation of B and T lymphocytes [41–43] and could therefore interfere with the antigen presentation of B-cells [44].

4. Other Virulence Factors

The bacterial adherence capacity is essential for good colonization and persistence of the infection. *H. pylori* multiplies in the gastric mucus and the surface of epithelial cells is reached by a small proportion of bacteria. The expression of adhesins allowed them to adhere [45]. *H. pylori* must be able to adhere to gastric epithelial cells to avoid being eliminated by the gastric peristalsis and mucus renewal [46]. Several adhesins have been described, with the most studied being BabA (Blood group antigen binding adhesin) and SabA (Sialic acid-binding adhesin). These proteins bind to Lewis antigens, which are similar to those of blood groups and are present on the surface of gastric epithelial cells [47]. There are two alleles for the babA gene: babA1 and babA2. *H. pylori* strain sequences could contain one, two or multiple copies of the babA gene [48]. The babA2 strains are associated with ulcers and
adenocarcinoma [49,50]. Recognition of SabA by neutrophils allows their activation, and thus a release of radical oxygen and nitrogen species, inducing epithelial lesions [51]. The major adhesins, BabA and SabA, and the different outer membrane proteins modulate their expression depending on the environmental context [52]. Thus, the BabA protein hence could be modulated by phase variation and antigenic variation in vivo, to facilitate adherence to the epithelium and to permit chronic infection [53].

Lehours et al. studied the presence of *H. pylori* virulence factors (cagA, cagE, vacA alleles, hopQ, iceA and babA) and functional status of both sabA and hopZ genes, in 43 GML strains compared with 39 strains isolated from gastritis [40]. None of these genes were associated with GML when considered individually. However, the gene group comprised of iceA1 allele, sabA and hopZ were identified in strains with a ten times higher risk of developing GML than strains associated with gastritis. The low prevalence of these strains among GML strains, however, made it a low sensitivity marker (Table 1).

5. GML and Lipopolysaccharide (LPS) Antigens

The O chain of *H. pylori* LPS has a similar composition to the Lewis X type antigens (Le\(^{x}\)) or the Lewis Y (Le\(^{y}\)) blood group, also found in gastric epithelial cells [54]. This bacterial mimicry results in an escape from the immune response; *H. pylori* is no longer recognized as a non-self which promotes colonization and contributes to chronic infection [55,56]. Moreover, this mimicry is involved in a phenomenon of autoimmunity leading to gastric atrophy [57]. The nature of the Lewis antigen expressed by the *H. pylori* LPS determines the interaction with dendritic cells via a C-type lectin called DC-SIGN, present on the surface of dendritic cells [58], that could influence the pro-inflammatory response. Lewis negative strains escape the association with DCs and induce a Th1 response, while strains expressing Le\(^{x}\) and or Le\(^{y}\) bind to DC-SIGN, resulting in the production of a IL-10-Treg associated response and the obstruction of a Th1 response.

LPS antigens expressed by GML strains were studied by our group [59]. cagPAI negative GML strains strongly expressed Le\(^{y}\) antigens. These Le\(^{y}\) antigens were associated in the past with autoimmune manifestations, suggesting a component of this type in the pathogenesis of GML. The association between Lewis antigen expression and disease status is not modified by vacA genotypes.

In conclusion, a particular Lewis antigen profile has been identified in cagPAI negative MALT strains, which could represent an adaptive mechanism to the host response and participate in MALT lymphomagenesis (Table 1).

The chronicity of *H. pylori* infection is believed to be essential in the context of gastric MALT lymphoma. LPS is an important effector of the TLR4 among various Gram-negative bacteria. However, *H. pylori* LPS evades TLR4 recognition, which therefore plays an important part in this "camouflage" strategy [8]. According to Suarez et al., an antigenic source of autoimmunity is provided by the chronic microbial antigenic stimulation observed during persisting *H. pylori* infection. This phenomenon leads to sustained B-cell stimulation, thus favoring lymphoid transformation and lymphoma development [60].

6. GML Strains and Genomic Data

Subtractive hybridization, a technique based on multiple steps of DNA-DNA hybridization, PCR, cloning and sequencing, was used to identify specific genetic markers of GML strains. This technique allows the identification of genes or sequences present in a strain of interest (called the tester strain) in comparison to a control strain (called the driver). It was originally used to identify the cagPAI [61].

One marker, ORF JHP950 (according to the strain J99 annotation), was identified in GML strains. It belongs to the so-called *H. pylori* plasticity zone [62,63]. This area was not initially considered as a pathogenicity island sensus stricto, but rather as a large genomic island. However, JHP950 is located close to ORF JHP947, which has been associated with strains isolated from patients with gastric adenocarcinoma [63]. A significant association of JHP950 with iceA1 and sabA virulence genes was also found in GML isolates [64] (Table 1). JHP950 ORF encodes a protein with no specific function, which therefore poses a problem to integrate its role in the pathogenesis of GML.
Only complementary approaches such as reverse genetics or even proteomics would help to answer this question. Nevertheless, ORF JHP950 is the first and only genetic marker to date that may be used to screen high-risk GML strains.

In a study performed by Thiberge et al., 43 DNAs extracted from GML strains were hybridized to high-density membranes containing a selection of 248 non-ubiquitous genes (the flexible part of the *H. pylori* genome known at that time) and 50 ubiquitous genes (the stable part) [65] (Table 1). A homogeneous subpopulation of strains exclusively composed of cagPAI negative GML strains was identified by hierarchical cluster analyses of the DNA hybridization values. These cagPAI negative strains therefore appeared more closely together than others, suggesting again that the GML strains share common genetic background.

This study motivated the same group to sequence and fully annotate the genome of one of these cagPAI negative strains. This strain, named B38, represented the smallest published genome (1,576,758 base pairs containing 1528 CDSs) compared to the six previously released *H. pylori* genomes at that time (i.e. J99, 26695, HPAG1, P12, G27 and Shi470) [65]. It contains the vacA s2m2 allele and lacks the genes encoding the major virulence factors (absence of cagPAI, babB, babC, sabB, and homB). A small prophage was identified in this strain. The presence of prophages was further confirmed in approximately 20% of *H. pylori* strains; there was with no association with GML, but with phylogeographic groups of *H. pylori* [66,67].

More recently, three *H. pylori* strains isolated from patients with GML were sequenced by Wang et al. [68]. Nine genes shared by these three strains and absent in five *H. pylori* strains isolated from gastritis and ulcer were identified by whole-genome comparison. Many gene substitutions, deletions and insertions were also revealed in these three strains. Further investigations are needed to understand the implication of these genetic variabilities in gastric lymphomagenesis (Table 1). Knowledge of the genome sequences of GML strains could open new perspectives to explore the contribution of virulence determinants in the physiopathology of *H. pylori* infection.

7. Conclusions

No specific virulence factor has been identified yet in GML-associated strains to explain gastric lymphomagenesis. The situation is very different from gastric adenocarcinoma’s associated strains, where the molecular effects induced by the cagPAI are now well characterized and linked to gastric carcinogenesis. Compared to strains associated with peptic ulcer or gastric adenocarcinoma, GML strains based on their virulence factor profile appear to be less pro-inflammatory. They can indeed be considered amongst the lowest producers of VacA cytotoxin, which could be a strategy to modulate T cell functions in vivo. Based on their genetic content and LPS profile, cagPAI negative GML strains seem to be closely related, even if no major new virulence factor has been identified in this group of strains. Some genetics variabilities in GML-associated strains have been identified, but further investigations are needed to understand their potential implication in GML development. In vivo models of GML are under development and could bring new data on the nature of stimulating and recognized antigens involved in GML pathogenesis in the near future. Are there *H. pylori* strains that are more capable of inducing GML than others? The answer is probably “no.” The information gained over the past 15 years on GML-associated strains suggests that the key point in gastric lymphomagenesis should be investigated elsewhere, probably in predisposing host factors.

Acknowledgments: The authors thank Lindsay Mégrand for English revision of the manuscript.

Author Contributions: Pauline Floch and Philippe Lehours wrote the manuscript. Francis Mégrand gave his expert opinion.

Conflicts of Interest: The authors declare no conflict of interest.
References

1. Pereira, M.-I.; Medeiros, J.A. Role of Helicobacter pylori in gastric mucosa-associated lymphoid tissue lymphomas. World J. Gastroenterol. 2014, 20, 684–698. [CrossRef] [PubMed]

2. Zucca, E.; Copie-Bergman, C.; Ricardi, U.; Thieblemont, C.; Raderer, M.; Ladetto, M. Gastric marginal zone lymphoma of MALT type: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann. Oncol. 2013, 24, vi144–vi148. [CrossRef] [PubMed]

3. Malfertheiner, P.; Megraud, F.; O’Morain, C.A.; Atherton, J.; Axon, A.T.; Bazzoli, F.; Gensini, G.F.; Gisbert, J.P.; Graham, D.Y.; Rokkas, T.; et al. Management of Helicobacter pylori infection—The Maastricht IV/ Florence Consensus Report. Gut 2012, 61, 646–664. [CrossRef] [PubMed]

4. Wotherspoon, A.C.; Dogliani, C.; Díss, T.C.; Pan, L.; Moschini, A.; de Boni, M.; Isaacson, P.G. Regression of primary low-grade B-cell gastric lymphoma of mucosa-associated lymphoid tissue type after eradication of Helicobacter pylori. Lancet 1993, 342, 575–577. [CrossRef]

5. Weber, D.M.; Dimopoulos, M.A.; Anandu, D.P.; Pugh, W.C.; Steinbach, G. Regression of gastric lymphoma of mucosa-associated lymphoid tissue with antibiotic therapy for Helicobacter pylori. Gastroenterology 1994, 107, 1835–1838. [CrossRef]

6. Montalban, C.; Boixeda, D.; Bellas, C. Helicobacter pylori eradication in gastric mucosa-associated lymphoid tissue lymphomas. Ann. Intern. Med. 1996, 124, 275. [CrossRef] [PubMed]

7. Cammarota, G.; Montalto, M.; Tursi, A.; Vecchio, F.M.; Gasbarrini, G. Helicobacter pylori re-infection and rapid relapse of low-grade B-cell gastric lymphoma. Lancet 1995, 345, 192. [CrossRef]

8. Salama, N.R.; Hartung, M.L.; Muller, A. Life in the human stomach: Persistence strategies of the bacterial pathogen Helicobacter pylori. Nat. Rev. Microbiol. 2013, 11, 385–399. [CrossRef] [PubMed]

9. Backert, S.; Ziska, E.; Brinkmann, V.; Zimny-Arndt, U.; Naumann, M.; Meyer, T.F. Translocation of the Helicobacter pylori CagA protein in gastric epithelial cells by a type IV secretion apparatus. Cell. Microbiol. 2000, 2, 155–164. [CrossRef] [PubMed]

10. Ferreira-Chagas, B.; Lasne, G.; Dupouy, S.; Gallyo, A.; Morgner, A.; Menard, A.; Fauconnier, A.; Jungblut, P.R.; Naumann, M.; Wotherspoon, A.C. In vitro proinflammatory properties of Helicobacter pylori strains causing low-grade gastric MALT lymphoma. Helicobacter 2007, 12, 616–617. [CrossRef] [PubMed]

11. Brandt, S.; Kwok, T.; Hartig, R.; König, W.; Backert, S. NF-κB activation and potentiation of proinflammatory responses by the Helicobacter pylori CagA protein. Proc. Natl. Acad. Sci. USA 2005, 102, 9300–9305. [CrossRef] [PubMed]

12. Ferreira, R.M.; Pinto-Ribeiro, I.; Wen, X.; Marcos-Pinto, R.; Dinis-Ribeiro, M.; Carneiro, F.; Figueiredo, C. Helicobacter pylori cagA Promoter Region Sequences Influence CagA Expression and Interleukin 8 Secretion. J. Infect. Dis. 2016, 213, 669–673. [CrossRef] [PubMed]

13. Blaser, M.J.; Perez-Perez, G.I.; Kleanous, H.; Ricardi, U.; Thieblemont, C.; Raderer, M.; Ladetto, M. Gastric marginal zone lymphoma of MALT type: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann. Oncol. 2013, 24, vi144–vi148. [CrossRef] [PubMed]

14. Parsonnet, J.; Friedman, G.D.; Orentreich, N.; Vogelman, H. Risk for gastric cancer in people with CagA positive or CagA negative Helicobacter pylori infection. Gut 1997, 40, 297–301. [CrossRef] [PubMed]

15. Eck, M.; Schmausser, B.; Haas, R.; Greiner, A.; Czub, S.; Müller-Hermelink, H.K. MALT-type lymphoma of the stomach is associated with Helicobacter pylori strains expressing the CagA protein. Gastroenterology 1997, 112, 1482–1486. [CrossRef]

16. Schmausser, B.; Eck, M.; Greiner, A.; Kraus, M.; Müller-Hermelink, H.K. Mucosal humoral immune response to CagA shows a high prevalence in patients with gastric MALT-type lymphoma. Virchows Arch. 2000, 436, 115–118. [CrossRef] [PubMed]

17. Delchier, J.C.; Lamarque, D.; Levy, M.; Tkobu, E.M.; Copie Bergman, C.; Deforges, L.; Chaumette, M.T.; Haïoun, C. Helicobacter pylori and gastric lymphoma: High seroprevalence of CagA in diffuse large B-cell lymphoma but not in low-grade lymphoma of mucosa-associated lymphoid tissue type. Am. J. Gastroenterol. 2001, 96, 2324–2328. [CrossRef] [PubMed]

18. Ye, H.T.; Liu, H.X.; Attygalle, A.; Wotherspoon, A.C.; Nicholson, A.G.; Charlotte, F.; Leblond, V.; Speight, P.; Goodlad, J.; Lavergne Slove, A.; et al. Variable frequencies of t(11;18)(q21;q21) in MALT lymphomas of different sites: Significant association with CagA strains of Helicobacter pylori in gastric MALT lymphoma. Blood 2003, 102, 1012–1018. [CrossRef] [PubMed]
19. De Jong, D.; van der Hulst, R.W.M.; Pals, G.; van Dijk, W.C.; van der Ende, A.; Tytgat, G.N.J.; Taal, B.G.; Boot, H. Gastric non-Hodgkin lymphomas of mucosa-associated lymphoid tissue are not associated with more aggressive Helicobacter pylori strains as identified by CagA. Am. J. Clin. Pathol. 1996, 106, 670–675. [CrossRef] [PubMed]

20. Yang, H.T.; Wu, S.V.; Pichuantes, S.; Song, M.; Wang, J.; Zhou, D.Y.; Xu, Z.M.; Quan, S.; Polito, A.; Walsh, J.H. High prevalence of cagA-positive strains in Helicobacter pylori-infected, healthy, young Chinese adults. J. Gastroenterol. Hepatol. 1999, 14, 476–480. [CrossRef] [PubMed]

21. Peng, H.; Ranaldi, R.; Diss, T.C.; Isaacson, P.G.; Bearzi, I.; Pan, L. High frequency of CagA+ Helicobacter pylori infection in high-grade gastric MALT B-cell lymphomas. J. Pathol. 1998, 185, 409–412. [CrossRef]

22. Yang, H.-B.; Sheu, B.-S.; Wang, J.-T.; Lin, S.-T.; Wu, J.-J. Serological responses of FldA and small-molecular-weight proteins of Helicobacter pylori: Correlation with the presence of the gastric MALT tissue. Helicobacter 2004, 9, 81–86. [CrossRef] [PubMed]

23. Umehara, S.; Higashi, H.; Ohnishi, N.; Asaka, M.; Hatakeyama, M. Effects of Helicobacter pylori CagA protein on the growth and survival of B lymphocytes, the origin of MALT lymphoma. Oncogene 2003, 22, 8337–9342. [CrossRef] [PubMed]

24. Lin, W.-C.; Tsai, H.-F.; Kuo, S.-H.; Wu, M.-S.; Lin, C.-W.; Hsu, P.-I.; Cheng, A.-L.; Hsu, P.-N. Translocation of Helicobacter pylori CagA into Human B lymphocytes, the origin of mucosa-associated lymphoid tissue lymphoma. Cancer Res. 2010, 70, 5740–5748. [CrossRef] [PubMed]

25. Zhu, Y.; Wang, C.; Huang, J.; Ge, Z.; Dong, Q.; Zhong, X.; Su, Y.; Zheng, S. The Helicobacter pylori virulence factor CagA promotes Erk1/2-mediated Bad phosphorylation in lymphocytes: A mechanism of CagA-inhibited lymphocyte apoptosis. Cell. Microbiol. 2007, 9, 952–961. [CrossRef] [PubMed]

26. Kuo, S.-H.; Yeh, K.-H.; Chen, L.-T.; Lin, C.-W.; Hsu, P.-N.; Wu, M.-S.; Liou, J.-M.; Tsai, H.-J.; Tzeng, Y.-S.; Cheng, A.-L. Helicobacter pylori CagA translocation is closely associated with the expression of CagA-signaling molecules in low-grade gastric mucosa-associated lymphoid tissue lymphoma. Am. J. Surg. Pathol. 2015, 39, 761–766. [CrossRef] [PubMed]

27. Ohnishi, N.; Yuasa, H.; Tanaka, S.; Sawada, H.; Miura, M.; Matsui, A.; Higashi, H.; Musashi, M.; Iwabuchi, K.; Suzuki, M.; et al. Transgenic expression of Helicobacter pylori CagA induces gastrointestinal and hematopoietic neoplasms in mouse. Proc. Natl. Acad. Sci. USA 2008, 105, 1003–1008. [CrossRef] [PubMed]

28. Kuo, S.-H.; Chen, L.-T.; Lin, C.-W.; Wu, M.-S.; Hsu, P.-N.; Tsai, H.-J.; Chu, C.-Y.; Tzeng, Y.-S.; Wang, H.-P.; Yeh, K.-H.; et al. Detection of the Helicobacter pylori CagA protein in gastric mucosa-associated lymphoid tissue lymphoma cells: Clinical and biological significance. Blood Cancer J. 2013, 3, e125. [CrossRef] [PubMed]

29. Taupin, A.; Occhialini, A.; RuskoneFourmestraux, A.; Delchier, J.C.; Rambaud, J.C.; Megraud, F. Serum antibody responses to Helicobacter pylori and the cagA marker in patients with mucosa-associated lymphoid tissue lymphoma. Clin. Diagn. Lab. Immunol. 1999, 6, 633–638. [CrossRef]

30. Kuo, S.-H.; Chen, L.-T.; Lin, C.-W.; Yeh, K.-H.; Shun, C.-T.; Tzeng, Y.-S.; Liou, J.-M.; Wu, M.-S.; Hsu, P.-N.; Cheng, A.-L. Expressions of the CagA protein and CagA-signaling molecules predict Helicobacter pylori dependence of early-stage gastric DLBCL. Blood 2017, 129, 188–198. [CrossRef] [PubMed]

31. Forsyth, M.H.; Atherton, J.C.; Blaser, M.J.; Cover, T.L. Heterogeneity in levels of vacuolating cytotoxin gene (vacA) transcription among Helicobacter pylori strains. Infect. Immun. 1998, 66, 3088–3094. [PubMed]

32. Cover, T.L.; Vaughn, S.G.; Cao, P.; Blaser, M.J. Potentiation of Helicobacter pylori Vacuolating Toxin Activity by Nicotine and Other Weak Bases. J. Infect. Dis. 1992, 166, 1073–1078. [CrossRef] [PubMed]

33. Atherton, J.C.; Cao, P.; Peek, R.M.; Tummuru, M.K.R.; Blaser, M.J.; Cover, T.L. Mosaicism in vacuolating cytotoxin alleles of Helicobacter pylori—Association of specific vacA types with cytotoxin production and peptic ulceration. J. Biol. Chem. 1995, 270, 17771–17777. [PubMed]

34. Rhead, J.L.; Letley, D.P.; Mohammadi, M.; Hussein, N.; Mohagheghi, M.A.; Eshagh Hosseini, M.; Atherton, J.C. A new Helicobacter pylori vacuolating cytotoxin determinant, the intermediate region, is associated with gastric cancer. Gastroenterology 2007, 133, 926–936. [CrossRef] [PubMed]

35. Cover, T.L. Helicobacter pylori Diversity and Gastric Cancer Risk. MBio 2016, 7. [CrossRef] [PubMed]

36. Galmiche, A.; Rassow, J.; Doye, A.; Cagnol, S.; Chambard, J.C.; Contamin, S.; de Thillot, V.; Just, I.; Ricci, V.; Solcia, E.; et al. The N-terminal 34 kDa fragment of Helicobacter pylori vacuolating cytotoxin targets mitochondria and induces cytochrome c release. EMBO J. 2000, 19, 6361–6370. [CrossRef] [PubMed]
37. Kuck, D.; Kolmerer, B.; Iking-Konert, C.; Krammer, P.H.; Stremmel, W.; Rudi, J. Vacuolating cytotoxin of *Helicobacter pylori* induces apoptosis in the human gastric epithelial cell line AGS. *Infect. Immun.* 2001, 69, 5080–5087. [CrossRef] [PubMed]

38. Yamasaki, E.; Wada, A.; Kumatori, A.; Nakagawa, I.; Funao, J.; Nakayama, M.; Hisatsune, J.; Kimura, M.; Moss, J.; Hirayama, T. *Helicobacter pylori* vacuolating cytotoxin induces activation of the proapoptotic proteins Bax and Bak, leading to cytochrome c release and cell death, independent of vacuolation. *J. Biol. Chem.* 2006, 281, 11250–11259. [CrossRef] [PubMed]

39. Koehler, C.I.; Mues, M.B.; Dienes, H.P.; Kriegsmann, J.; Schirmacher, P.; Menard, A. The Role of *Helicobacter pylori* outer membrane protein expression during experimental infection of rhesus macaques. *Proc. Natl. Acad. Sci. USA* 2006, 103, 5636–5641. [CrossRef] [PubMed]

40. Lehours, P.; Menard, A.; Dupouy, S.; Bergey, B.; Richy, F.; Zerbib, F.; Ruskone-Fourmestraux, A.; Delchier, J.C.; Megraud, F. Evaluation of the association of nine *Helicobacter pylori* virulence factors with strains involved in low-grade gastric mucosa-associated lymphoid tissue lymphoma. *Infect. Immun.* 2004, 72, 880–888. [CrossRef] [PubMed]

41. Boncristiano, M.; Paccani, S.R.; Barone, S.; Ulivieri, C.; Patrucci, L.; Ilver, D.; Amedei, A.; D'Elios, M.M.; Gebert, B.; Fischer, W.; Weiss, E.; Hoffmann, R.; Haas, R. *Helicobacter pylori* vacuolating cytotoxin inhibits T lymphocyte activation. *Science* 2003, 301, 1099–1102. [CrossRef] [PubMed]

42. Torres, V.J.; VanCompernolle, S.E.; Sundrud, M.S.; Unutmaz, D.; Cover, T.L. *Helicobacter pylori* vacuolating cytotoxin inhibits activation-induced proliferation of human T and B lymphocyte subsets. *J. Immunol.* 2007, 179, 5433–5440. [CrossRef] [PubMed]

43. Papini, E.; Satin, B.; deBernard, M.; Molinari, M.; Arico, B.; Galli, C.; Telford, J.R.; Baldari, C.T. The *Helicobacter pylori* vacuolating toxin inhibits T cell activation by two independent mechanisms. *J. Exp. Med.* 2003, 198, 1887–1897. [CrossRef] [PubMed]

44. Gebert, B.; Fischer, W.; Weiss, E.; Hoffmann, R.; Haas, R. *Helicobacter pylori* vacuolating cytotoxin inhibits T lymphocyte activation. *Science* 2003, 301, 1099–1102. [CrossRef] [PubMed]

45. Ilver, D.; Arnqvist, A.; Ögren, J.; Frick, I.-M.; Kersulyte, D.; Incecik, E.T.; Berg, D.E.; Covacci, A.; Engstrand, L.; Yamaoka, Y. Roles of *Helicobacter pylori* BabA in gastroduodenal pathogenesis. *World J. Gastroenterol.* 2008, 14, 4265–4272. [CrossRef] [PubMed]

46. Oleastro, M.; Menard, A. The Role of *Helicobacter pylori* Outer Membrane Proteins in Adherence and Pathogenesis. *Biology* 2013, 2, 1110–1134. [CrossRef] [PubMed]

47. Ilver, D.; Arnqvist, A.; Ögren, J.; Frick, I.-M.; Kersulyte, D.; Incecik, E.T.; Berg, D.E.; Covacci, A.; Engstrand, L.; Boren, T. *Helicobacter pylori* adhesin binding fucosylated histo-blood group antigen antigens revealed by retagging. *Science* 1998, 279, 279–284. [CrossRef] [PubMed]

48. Yamaoka, Y. Roles of *Helicobacter pylori* BabA in gastroduodenal pathogenesis. *World J. Gastroenterol.* 2008, 14, 4265–4272. [CrossRef] [PubMed]

49. Prinz, C.; Schoniger, M.; Rad, R.; Becker, I.; Keiditsch, E.; Wagenpfeil, S.; Classen, M.; Rosch, T.; Schepp, W.; Gerhard, M. Key importance of the *Helicobacter pylori* adherence factor blood group antigen binding adhesin during chronic gastric inflammation. *Cancer Res.* 2001, 61, 1903–1909. [PubMed]

50. Yoshikawa, T.; Naito, Y. The role of neutrophils and inflammation in gastric mucosal injury. *Free Radic. Res.* 2000, 33, 785–794. [CrossRef] [PubMed]

51. Solnick, J.V.; Hansen, L.M.; Salama, N.R.; Boonjakuakul, J.K.; Syvanen, M. Modification of *Helicobacter pylori* outer membrane protein expression during experimental infection of rhesus macaques. *Proc. Natl. Acad. Sci. USA* 2004, 101, 2106–2111. [CrossRef] [PubMed]

52. Vandenbroucke-Grauls, C.M.; Appelmelk, B.J. *Helicobacter pylori* LPS: Molecular mimicry with the host and role in autoimmunity. *Ital. J. Gastroenterol. Hepatol.* 1998, 30 (Suppl. 3), S259–S260. [PubMed]

53. Appelmelk, B.J.; Vandenbroucke-Grauls, C.M.; E. H. *pylori* and Lewis antigens. *Gut* 2000, 47, 10–11. [CrossRef] [PubMed]
56. Moran, A.P.; Appelmelk, B.J.; Aspinall, G.O. Molecular mimicry of host structures by lipopolysaccharides of Campylobacter and Helicobacter spp: Implications in pathogenesis. J. Endotox Res. 1996, 3, 521–531. [CrossRef]

57. Appelmelk, B.J.; Martin, S.L.; Monteiro, M.A.; Clayton, C.A.; McColm, A.A.; Zheng, P.; Verboom, T.; Maaskant, J.J.; Van den Eijnden, D.H.; Hokke, C.H.; et al. Phase variation in Helicobacter pylori lipopolysaccharide due to changes in the lengths of poly(C) tracts in α3-fucosyltransferase genes. Infect. Immun. 1999, 67, 5361–5366. [PubMed]

58. Bergman, M.P.; Engering, A.; Smits, H.H.; van Vliet, S.J.; van Bodegraven, A.A.; Wirth, H.P.; Kapsenberg, M.L.; Vandenburgoucke-Grauls, C.M.; van Kooyk, Y.; Appelmelk, B.J. Helicobacter pylori modulates the T helper cell 1/T helper cell 2 balance through phase-variable interaction between lipopolysaccharide and DC-SIGN. J. Exp. Med. 2004, 200, 979–990. [CrossRef] [PubMed]

59. Lehours, P.; Zheng, Z.; Skoglund, A.; Megraud, F.; Engstrand, L. Is there a link between the lipopolysaccharide of Helicobacter pylori gastric MALT lymphoma associated strains and lymphoma pathogenesis? PLoS ONE 2009, 4, e7297. [CrossRef] [PubMed]

60. Suarez, F.; Lortholary, O.; Hermine, O.; Lecuit, M. Infection-associated lymphomas derived from marginal zone B cells: A model of antigen-driven lymphoproliferation. Blood 2006, 107, 3034–3044. [CrossRef] [PubMed]

61. Censini, S.; Lange, C.; Xiang, Z.; Crabtree, J.E.; Ghiara, P.; Borodovsky, M.; Rappuoli, R.; Covacci, A. cag, a pathogenicity island of Helicobacter pylori, encodes type I-specific and disease-associated virulence factors. Proc. Natl. Acad. Sci. USA 1996, 93, 14648–14653. [CrossRef] [PubMed]

62. Alm, R.A.; Ling, L.S.L.; Moor, D.T.; King, B.L.; Brown, E.D.; Doig, P.C.; Smith, D.R.; Noonan, B.; Guild, B.C.; delonge, B.L.; et al. Genomic-sequence comparison of two unrelated isolates of the human gastric pathogen Helicobacter pylori. Nature 1999, 397, 176–180. [CrossRef] [PubMed]

63. Occhialini, A.; Marais, A.; Alm, R.; Garcia, F.; Sierra, R.; Méraud, F. Distribution of open reading frames of plasticity region of strain J99 in Helicobacter pylori strains isolated from gastric carcinoma and gastritis patients in Costa Rica. Infect. Immun. 2000, 68, 6240–6249. [CrossRef] [PubMed]

64. Lehours, P.; Dupouy, S.; Bergey, B.; Ruskone-Foumestraux, A.; Delchier, J.C.; Rad, R.; Richy, F.; Tankovic, J.; Zerbib, F.; Megraud, F.; et al. Identification of a genetic marker of Helicobacter pylori strains involved in gastric extranodal marginal zone B cell lymphoma of the MALT-type. Gut 2004, 53, 931–937. [CrossRef] [PubMed]

65. Thiberge, J.M.; Boursaux-Eude, C.; Lehours, P.; Dillies, M.A.; Creno, S.; Coppee, J.Y.; Rouy, Z.; Lajus, A.; Ma, L.; Burucoa, C.; et al. From array-based hybridization of Helicobacter pylori isolates to the complete genome sequence of an isolate associated with MALT lymphoma. BMC Genom. 2010, 11, 368. [CrossRef] [PubMed]

66. Lehours, P.; Vale, F.F.; Bjursell, M.K.; Melefors, O.; Advani, R.; Glavas, S.; Guegueniat, J.; Gontier, E.; Lacomme, S.; Alves Matos, A.; et al. Genome sequencing reveals a phage in Helicobacter pylori. MBio 2011, 2. [CrossRef] [PubMed]

67. Vale, F.F.; Vadivelu, J.; Oleastro, M.; Breurec, S.; Engstrand, L.; Perets, T.T.; Méraud, F.; Lehours, P. Dormant phages of Helicobacter pylori reveal distinct populations in Europe. Sci. Rep. 2015, 5, 14333. [CrossRef] [PubMed]

68. Wang, H.-C.; Cheng, F.-C.; Wu, M.-S.; Shu, H.-Y.; Sun, H.S.; Wang, Y.-C.; Su, I.-J.; Wu, C.-J. Genome Sequences of Three Helicobacter pylori Strains from Patients with Gastric Mucosa-Associated Lymphoid Tissue Lymphoma. Genome Announc. 2015, 3, e00229. [PubMed]