Chapter

Revisiting the Full Spectrum of *Helicobacter pylori*-Related Gastric Lymphoma

Sung-Hsin Kuo, Kun-Huei Yeh, Chung-Wu Lin, Li-Tzong Chen, Ming-Shiang Wu and Ann-Lii Cheng

Abstract

Early stage gastric diffuse large B-cell lymphomas (DLBCLs) with histological features of mucosa-associated lymphoid tissue (MALT) origin (DLBCL[MALT]) are also closely related to *Helicobacter pylori* (*Hp*) infection, apart from the classical gastric MALT lymphoma, and are cured by *Hp* eradication therapy (HPE). Whether some gastric "pure" DLBCLs (without histological features of MALT) are also *Hp*-related is clinically very important, since this subtype of gastric lymphoma is relatively common in the population and is still universally treated with intensive systemic chemotherapy. A large proportion of early stage gastric "pure" DLBCL can achieve long-term complete remission after HPE. However, the precise mechanisms of *Hp*-dependent (with complete regression of tumors after HPE) lymphomagenesis of gastric "pure" DLBCL, DLBCL(MALT), and MALT lymphoma remain uncertain. In the classical conception, gastric MALT lymphoma is indirectly caused by *Hp* through T-cell stimulation, with the aid of costimulatory molecules. To explore the direct interactions between *Hp* and lymphoma B-cells of *Hp*-dependent gastric MALT lymphoma, DLBCL(MALT), and "pure" DLBCLs, we assessed the participation of *Hp*-encoded cytotoxin-associated gene A (CagA) in the lymphomagenesis of these tumors. We discovered that CagA oncogenic protein and its regulated signaling molecules including phospho-Src homology-2 domain-containing phosphatase (p-SHP-2) and phospho-extracellular signal-regulated kinase (p-ERK) correlated significantly with *Hp*-dependence of gastric MALT lymphoma. This finding supports previous observations that the CagA protein of *Hp* can be translocated into B-cell lymphoma cells, thereby leading to survival signals. Furthermore, we demonstrated that *Hp*-positive and CagA-expressing gastric "pure" DLBCLs behave in a less biologically aggressive manner, and have better clinical outcomes; this is a distinguishing entity, and its cell origin may include germinal center B cells. In addition, we found that the expression of CagA, p-SHP-2, and p-ERK correlated significantly with the *Hp*-dependence of gastric DLBCL(MALT) and "pure" DLBCL. These findings indicate that the spectrum of *Hp*-related gastric lymphomas including MALT lymphoma, DLBCL(MALT), and "pure" DLBCL, is much wider than was previously thought. Further explorations of the spectrum, lymphomagenesis, and therapeutics of *Hp*-related gastric lymphoma are warranted.

Keywords: *Helicobacter pylori*, MALT, DLBCL, Stomach, CagA

1. Introduction

Gastric lymphoma, the most common non-Hodgkin lymphoma, has become an interesting research topic because of its unique clinicopathological features, wide spectrum of histological subtypes, and specific treatment strategies [1–4]. Histologically, gastric lymphomas are the most common B-cell neoplasms; mucosa-associated lymphoid tissue (MALT) lymphoma (renamed as marginal zone B-cell lymphoma with MALT type) and diffuse large B-cell lymphoma (DLBCL) with and without histological evidence of MALT origin are the most common subtypes according to the World Health Organization (WHO), in addition to rare mantle cell lymphoma, follicular lymphoma, and Burkitt lymphoma [3–6]. MALT lymphoma, which histologically consists primarily of diffuse small- and medium-sized lymphocytes, resembling centrocytes (centrocyte-like cells, CCLs) and lymphoepithelial lesions (LELs), was first described by Isaacson and Wright et al. in 1983 [1, 2, 7, 8]. At the same time, Marshall and Warren described the direct link between *Helicobacter pylori* (*Hp*) (a gram-negative, spiral rod-shaped bacterium) infection, and gastritis and peptic ulcer disease [9]. After one decade, Wotherspoon and Isaacson et al. found that 31% of patients with *Hp*-positive gastritis had lymphoid follicles, and 92% of patients with gastric MALT lymphoma had *Hp* infections, indicating a close association between *Hp* infection and the development of MALT and MALT lymphoma of the stomach [10]. Subsequently, they demonstrated that approximately 60% of patients with gastric MALT lymphoma achieved complete remission (CR) after being treated with antibiotics that eradicate *Hp* infection [11]. Subsequently, most investigators started administrating first-line *Hp* eradication therapy (HPE) by combining proton pump inhibitors (PPIs), amoxicillin, clarithromycin, bismuth, metronidazole, or tetracycline in the treatment of localized *Hp*-positive gastric MALT lymphoma [12–14]. By reviewing 32 clinical studies of first-line HPE for gastric MALT lymphoma patients (most prospective studies), Zullo et al. demonstrated that 1091 (77.5%) of 1408 patients achieved CR after successful first-line HPE; among these patients, patients with stage I disease had a higher CR rate than those with stage II disease (78.4% vs. 55.6%, P = 0.0003) [15]. Although some patients with gastric MALT lymphoma may take more than 12 months to achieve CR after completing HPE, most patients achieved CR within 12 months after completing HPE [15–17]. Therefore, eradication of *Hp* infection by antibiotics in addition to a PPI has been well conceded as the first-line treatment for early-stage *Hp*-positive gastric MALT lymphoma.

In contrast to gastric MALT lymphoma, high-grade transformed MALT lymphoma, relabeled as DLBCL with histological evidence of MALT origin DLBCL(MALT), is conventionally considered as *Hp*-independent (the lack of CR of lymphoma after HPE) according to the WHO [4–6]; as per WHO, patients with DLBCL(MALT) should be treated with systemic chemotherapy [18–20]. However, in the past decade, our group and other investigators have found that early-stage gastric DLBCL(MALT) is as responsive to first-line antibiotics as its low-grade counterpart, MALT lymphoma [21–25]. These observations have led to a drastic change in the standard therapy for patients with gastric DLBCL(MALT); many of these patents are now spared from experiencing the severe toxicity of intensive systemic chemotherapy.

Gastric "pure" DLBCL (DLBCL without histological evidence of MALT origin) is generally assumed as originating de novo instead of originating from high-grade transformed MALT lymphoma, and is thus regarded as having a rare association with *Hp* infection [3–6]. Considering that gastric "pure" DLBCLs comprise approximately half of gastric lymphomas, and this subgroup of patients are conventionally treated with systemic chemotherapy [4, 6, 8], it is worthwhile to explore whether some *Hp*-positive gastric "pure" DLBCL remain *Hp*-dependent. Our explorative study showed that antibiotics alone resulted in CR in 69% of patients with early

stage gastric "pure" DLBCL, and these *Hp*-dependent (the presence of CR of lymphoma after HPE) patients remained in CR after a 4-year rigorous endoscopic follow-up, whereas patients without CR after antibiotic treatment were still responsive to subsequent salvage chemotherapy [26]. Two other studies also demonstrated that some patients with *Hp*-positive early stage gastric "pure" DLBCL achieved CR through antibiotic eradication of *Hp*, and most *Hp*-dependent patients remained lymphoma-free after long-term follow up [27, 28]. In addition, among patients with gastric "pure" DLBCL receiving systemic chemotherapy, the *Hp*-positive group had less aggressive behaviors and better clinical outcomes than the *Hp*-negative group [29–31]. These findings suggest that for patients with *Hp*-positive localized gastric "pure" DLBCL, the administration of first-line antibiotic treatment, followed by careful monitoring of tumor response before and after antibiotic treatment using meticulous endoscopic examination, may allow certain patients to avoid the adverse effects of chemotherapy. Importantly, the explanation as to why some "pure" DLBCLs are still *Hp*-dependent can allow us to explore the precise molecular mechanisms of *Hp*-dependent lymphomagenesis of gastric DLBCL.

Regarding the lymphomagenesis of gastric MALT lymphoma, the classical concept is that *Hp* can only stimulate T cells, and then *Hp*-specific T cells transform the marginal-zone B cells into lymphoma [32–35]. Direct interaction between *Hp* and B cells was not considered to exist. However, several studies have observed that *Hp*-encoding cytotoxin-associated gene A (CagA) can be translocated into B cells, thereby activating survival signals of B-lymphoma cells, including tyrosine phosphorylation-dependent and -independent signaling [35–37]. Our group further observed that the CagA molecule and its triggering signaling molecules such as phospho–Src homology-2 domain-containing phosphatase (p-SHP-2), phospho–extracellular signal-regulated kinase (p-ERK), phospho-*p38* mitogen-activated protein kinases (p-p38 MAPK), B-cell lymphoma (Bcl)-2, and Bcl-xL are expressed in tumor cells of gastric MALT lymphoma patients [38–40]. Furthermore, CagA and its controlled signaling molecules significantly correlated with the *Hp*-dependence of these tumors [40]. In addition, our group showed that CagA, p-SHP-2, and p-ERK were closely associated with the *Hp*-dependence of gastric DLBCL(MALT) and "pure" DLBCL [41]. These observations pose a strong challenge to the classical concept of indirect *Hp*-specific T-cell stimulation, and suggest the possibility that a direct interaction between *Hp* and B cells exists in a wide spectrum of gastric lymphoma including MALT lymphoma, DLBCL(MALT), and "pure" DLBCL.

In this chapter, we will describe the association between *Hp* infection and MALT lymphoma, the novel use of first-line HPE in curing gastric DLBCL with and without histological evidence of MALT, and a wide spectrum of *Hp*-related gastric lymphomas; in addition, we present the possible molecular mechanisms and cellular origins of *Hp*-related gastric lymphoma.

2. The close link between *Hp* infection and gastric MALT lymphoma

Hp, a gram-negative and spiral rod-shaped bacterium that has evolved to grow in the environment of the stomach, infects approximately 50% of the population worldwide [42, 43]. Epidemiologic studies have shown that the prevalence of *Hp* infection documented by the histological detection of bacteria or positive serology was significantly higher in gastric MALT lymphoma patients than in healthy populations [44, 45]. Asenjo et al. reviewed studies exploring the association between *Hp* prevalence and gastric MALT lymphoma patients, and revealed that the incidence of *Hp* was approximately 79% in 1844 patients with gastric MALT lymphoma, and the differential prevalence may result from the number of assessments of *Hp*

infection. For example, a higher positive rate of *Hp* infection is observed with the use of more than two methods than with the use of a single method [46]. Moreover, the *Hp* infection rate was 74% for patients whose tumors were limited to the mucosa or submucosa, whereas the *Hp* infection rate was 44% for patients whose tumors invaded the muscularis or beyond [46].

3. Gastric MALT lymphoma is cured by first-line antibiotics eradicating *Hp* infection

Zullo et al. reviewed 1408 patients with gastric MALT lymphoma from 32 studies including 23 prospective and nine retrospective studies, to explore the treatment efficacies of first-line HPE and predictive markers of *Hp*-dependence [15]. In their studies, the determination of CR was mainly based on the tumors that regressed to achieve less than grade 2 (chronic active gastritis with florid lymphoid follicle formation) of Wotherspoon's scoring system [11]. Zullo et al. reported that tumors limited to the mucosa or submucosa were significantly closely associated with a higher CR rate (mucosa/submucosa vs. muscularis propria involvement and beyond: 82.2% vs. 54.5%; P = 0.0001) [15]. In addition, patients with tumors located at the distal lesions of the stomach (antrum and/or angulus) had a higher CR rate than those with tumors located at proximal lesions (gastric body and/or fundus) (91.8% vs. 75.7%; P = 0.0037) [15]. In a long-term follow-up of 994 patients, 72 patients (7.24%) experienced relapse of MALT lymphoma; among these, 12 patients had *Hp* infections [15].

In a retrospective multicenter study from Japan, Nakamura et al. showed that among 420 patients with successful HPE, 284 (67.6%) patients achieved pathological CR (pCR, absence of CLLs and without aggregation of small lymphocytes), and 39 (9%) patients had probable minimal residual disease (pMRD; presence of atypical lymphoid aggregates or nodules in at least two following assessments) according the Groupe d'Etude des Lymphomes de l'Adult (GELA) criteria, with an overall CR rate of 77% (323 patients) [47]. The histological scoring system proposed by GELA is currently recommended to assess whether tumors of gastric MALT lymphoma can achieve CR in a series of examinations after HPE using combined endoscopic findings and histological manifestations, in which CR was defined as the total vanishing of the gross tumor and a negative histological finding (pCR or pMRD) [48, 49]. Nakamura also showed that the median time to CR for these *Hp*-dependent tumors was four months (range from 1 to 94 months), and proximal or multiple locations, and non-superficial manifestations (such as hyperemia patches) were significantly associated with *Hp*-independence [47]. Tsai et al. and Kuo et al. also showed that ulcerative lesions, proximal locations of tumors, and tumors invading the muscularis propria or serosa correlated significantly with the *Hp*-independence of gastric MALT lymphoma [25, 39]. In another large cohort study of a Korean population, Gong et al. reported that *Hp* infection was detected in 317 (91.9%) of 345 patients with gastric MALT lymphoma using histology, a urea breath test, a rapid urease test, or a serologic test [50]. Gong showed that among *Hp*-positive patients, HPE resulted in a CR rate of 84.5% (n = 268), with a median time of 9.8 months (range 7.1 to 15.6 months) to CR, whereas 29 patients (10.7%) with CR developed relapses of MALT lymphoma [50].

Regarding the duration for achieving CR of tumors after completion of HPE, most studies showed that intervals are varied, ranging from quick (one to six months) to moderate (more than six months to 12 months) [15, 16, 39, 47, 51, 52]. In a prospective study, Hong et al. revealed that 85 (94.4%) of 90 patients with gastric MALT lymphoma achieved CR after HPE, with a median time to CR of three months (range, 1 to 24 months); 79 (92.9%) patients achieved CR at six months,

and another six (7.1%) patients achieved CR at 12 months [53]. Zullo et al. also showed that the median interval to CR was five months for patients with gastric MALT lymphoma after treating HPE, whereas few patients needed at least two years to achieve CR [15]. Fischbach et al. analyzed 108 gastric MALT lymphoma patients who underwent gross normalization but had histologically minimal residuals at 12 months after HPE, and found that 35 patients (32.4%) achieved subsequent CR after more than 24 months of follow-up post-HPE [54]. Terai et al. reported that among 74 patients with gastric MALT lymphoma, 56 (75.7%) patients had CR and 12 had gross tumor regression with histological residual tumor (hRD) at 12 months after successful HPE, while 11 patients with hRD achieved CR (ranging from 14 to 40 months after HPE) at a subsequent follow-up [55]. Tsai et al. further showed among patients with *Hp*-positive gastric MALT lymphoma who entered into a prospective study of the Taiwan Cooperative Oncology Group (TCOG) 3206 trial, the median time to CR was 4.0 months (range, 1 to 16 months) after HPE; among these patients, six (23%) patients achieved CR within 6 to 12 months, and four (15.4%) patients required 12 to 24 months to attain CR [25]. These results suggest that longer observation and refraining from the immediate administration of second-line therapy (including chemotherapy or radiotherapy) are recommended for gastric MALT lymphoma patients who had improved symptoms, partial remission (PR), or stable status of tumors even at 12 months or longer after HPE. In other words, a "watch and wait" treatment strategy may be advisable for patients with gastric MALT lymphoma who achieved probable minimal residual disease or tumor PR (according to GELA criteria) after successful HPE.

4. High-grade transformation does not confer *Hp*-independence of gastric lymphoma

It was previously believed that the transformation of MALT lymphoma into high-grade MALT lymphoma, is associated with the acquisition of *Hp*-independence (lack of CR of tumors after HPE); high-grade MALT lymphoma is thus considered as a *Hp*-independent tumor that is non-responsive to antibiotics (**Figure 1**) [18–20, 56]. Clinicians who administer first-line HPE to treat patients with high-grade gastric MALT lymphoma do so as they may regard MALT lymphoma as similar to low-grade MALT lymphoma that is highly responsive to HPE. Thus, to avoid such a confusion, Harris et al. in a 1999 WHO classification advised that high-grade MALT lymphoma should be renamed as DLBCL with histologic evidence of MALT (DLBCL[MALT]), and not as transformed high-grade MALT lymphoma [57]. In 2008, the WHO lymphoma classification advocated that histological manifestations of gastric lymphoma that display large-cell B-cell transformation in the MALT lymphoma background should be classified as DLBCLs rather than as high-grade transformed MALT lymphomas [5]. In this milieu, the presence of large B cells comprising LELs does not alter the pathological diagnosis of DLBCL [5, 6]. Regardless of this, the existence of complementary MALT lymphoma components in DLBCL should be appraised consistently [4, 5, 58].

However, two independent prospective studies and one retrospective study have revealed that a certain proportion of early-stage *Hp*-positive gastric DLBCL(MALT) patients were still responsive to first-line HPE, and thus achieved CR and subsequent long-term remission [21–24]. In the first prospective study, Chen et al. (Taiwan study group) demonstrated that 10 (62.5%) of 15 patients with early-stage gastric DLBCL(MALT) achieved CR after receiving first-line HPE, and remained lymphoma-free during a long-term follow-up [21]. In another prospective study assessing the association between clinicopathological features and tumor response

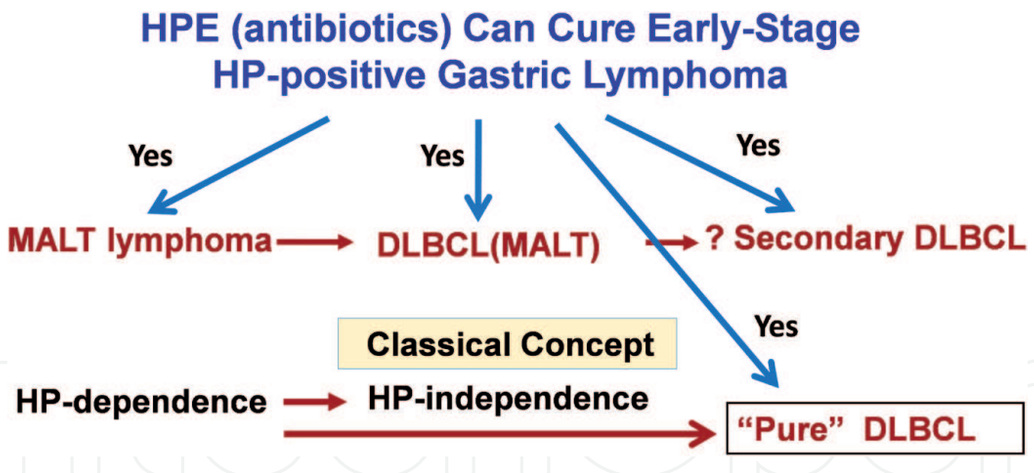

Figure 1.
Gastric diffuse large B-cell lymphoma as well as gastric mucosa-associated lymphoid tissue (MALT) lymphoma are Helicobacter pylori*-dependent, and are cured by first-line Hp eradication therapy (HPE). In contrast to the classic concept that gastric diffuse large B-cell lymphomas (DLBCLs) with and without histological evidence of MALT lymphoma are not responsive to HPE, several evidences demonstrated that* Hp*-related gastric lymphoma does not involve loss of* Hp*-dependence and is responsive to HPE, indicating that the spectrum of* Hp*-related gastric lymphoma is much wider than was originally thought.*

to HPE in gastric MALT lymphoma and DLBCL(MALT), Nakamura et al. reported that five (50%) of 10 gastric DLBCL(MLAT) patients had CR, whereas 4/6 with mucosa and submucosa involvement and 1/4 patients with tumor involvement in the muscularis propria were *Hp*-dependent [22]. Of these, five *Hp*-dependent patients were still free of lymphoma after a median follow-up of five years [22]. Mongnar et al. retrospectively analyzed eight patients with gastric DLBCL(MALT) who initially received HPE, of whom seven patients had CR [23]. Among these *Hp*-dependent patients, four patients did not receive further treatment, whereas one patient developed recurrence at six months after completing HPE, and another two patients underwent surgery later (one patient received chemotherapy because of residual MALT lymphoma in the surgical specimen) [23].

In 2005, Chen et al. reported the clinical outcome of a prospective study using first-line HPE for treating 24 patients with gastric DLBCL(MALT) and 36 patients with gastric MALT lymphoma, and demonstrated that 24 (80%) of 30 patients with MALT lymphoma and 14 (63.6%) of 22 patients with DLBCL(MALT) achieved CR after successful HPE [24]. The median time to CR after the completion of HPE for *Hp*-dependent patients was six months for DLBCL(MALT), and 10 months for MALT lymphoma [24]. Interestingly, after a median long-term follow-up (MALT lymphoma, 70 months; DLBCL[MALT], 56 months) for these *Hp*-dependent patients, the tumor did not recur in the DLBCL(MALT) case, but recurred in three cases of MALT lymphoma [24]. Regarding the depth of tumor infiltration associated with tumors responsive to HPE, the CR rate was 80% (8/10) for tumors limited to the mucosa or submucosa, and 29.4% (5/17) for tumors invading the muscularis propria or beyond (P = 0.018) [24].

In 2008, Cavanna et al. [59] reviewed the anecdotal cases series reporting the CR after antibiotic treatment for gastric DLBCL(MALT) and the results of HPE for patients with gastric DLBCL(MALT) obtained from Chen et al. [21, 24], Nakamura et al. [22], Morgan et al. [23], Hiyama et al. [60], and Alpen et al. [61]. Cavanna et al. showed that 42 (68.9%) of 61 cases of gastric DLBCL(MALT) responded completely to antibiotics eradicating *Hp*; most patients in this study presented with stage IE (30 cases), with tumor invasion to the mucosa or submucosa (21 of 33 cases were evaluable) [59]. However, age, sex, and tumor location (proximal or distal components) did not predict the response of tumors to HPE [59]. Although depth of invasion and stage of gastric DLBCL(MALT) were closely associated with

Hp-independence, there were a few cases of stage IIE1 (perigastric lymph node involvement) tumors that were dependent on *Hp* and achieved CR after HPE [59]. Zullo et al. analyzed the pooled data obtained from 1271 patients with gastric MALT lymphoma or DLBCL(MALT) through 34 studies exploring the treatment efficacy of first-line HPE, and revealed that a *Hp* eradication rate of 91% can be achieved using dual therapy for 14 days or triple therapy for seven to 14 days [62]. In their analyses, the CR rate was 78.5% for MALT lymphoma patients (n = 1215), and 62% for DLBCL(MALT) patients (n = 52) [62]. In the report of therapeutic efficacies of first-line HPE in gastric DLBCL(MALT) patients by Kuo et al. [26], the CR rate was 56.3% (18/32) with a median interval to CR of 5.0 months; the CR rate was significantly associated with the tumor extent (mucosa/submucosa vs. beyond: 80% [8/10] vs. 29.4% [5/17], P = 0.018) [26].

It should be noted that if patients with gastric DLBCL(MALT) do not respond well to antibiotic treatment, the tumor may rapidly progress and cause potential morbidities in these patients. However, for *Hp*-independent gastric DLBCL(MALT) patients, subsequent systemic chemotherapy could result in CR and let patients remain disease-free during long-term follow-up [21–25, 63]; this implies that a delay in the administration of systemic chemotherapy to 6–8 weeks after HPE with antibiotics is unlikely to influence the response of these tumors to conventional immunochemotherapy. These findings may support the contention that

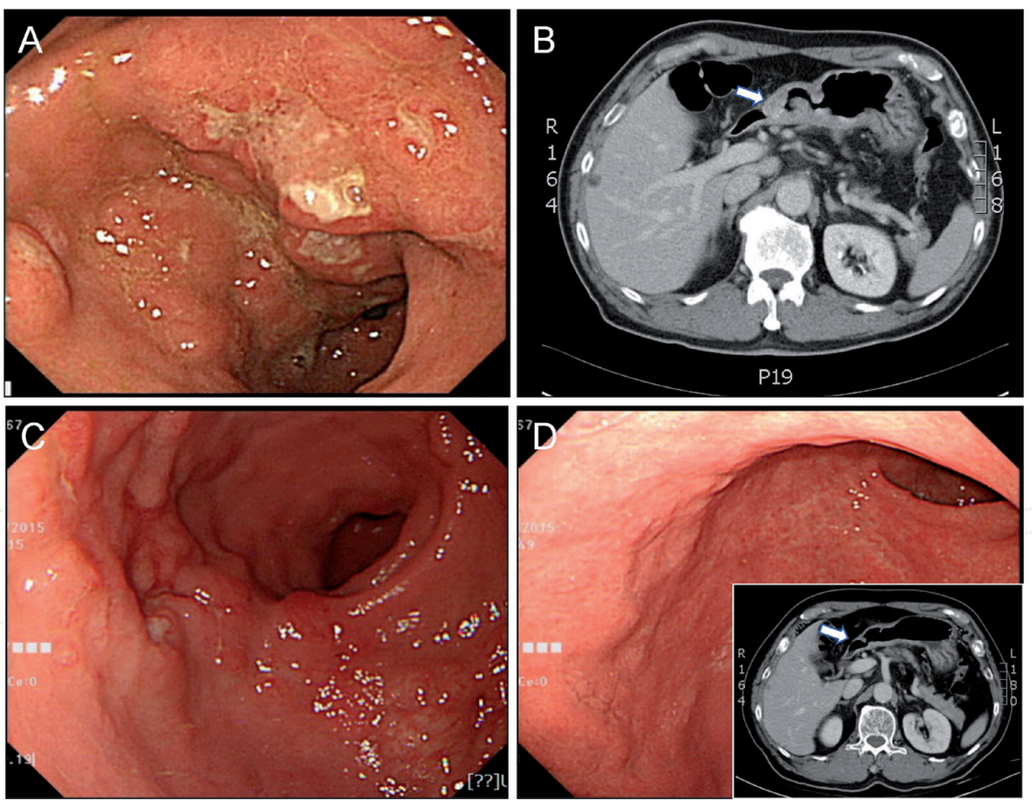

Figure 2.
Changes of endoscopic features in an example of stage IE Helicobacter pylori *(*Hp*)-dependent localized gastric diffuse large B-cell lymphoma (DLBCL) with mucosa-associated lymphoid tissue (MALT) (DLBCL[MALT]) before and after completion of Hp eradication therapy (HPE) (A) Endoscopy shows several ulcerative mass lesions with nodular and irregular margins at the antrum of a 74-year-old man before HPE (Histopathology disclosed DLBCL[MALT], DLBCL-predominant). (B) Computed tomography (CT) shows moderate wall thickening (white arrow) in the gastric antrum but no enlargement of perigastric lymph nodes in the same case A. (C) One month after the completion of HPE, endoscopy shows two partially regressed ulcerative masses at the gastric angle in the same case A (D) Four months after completion of HPE, complete remission was achieved in the same case A. Right bottom, CT shows no gastric wall thickening (white arrow).* Hp, Helicobacter pylori*; HPE, Hp eradication therapy; DLBCL, diffuse large B-cell lymphoma; MALT, mucosa-associated lymphoid tissue; CT, computed tomography; CR, complete remission.*

Authors (Ref.)	Study Group	Patients number (Men/ Women)	Age, years (median; range)	Histological subtype	Stage	First-line HPE regimen (for 2 weeks)	CR rate	Median time to CR (ms)	Follow-up period for *Hp*-dependent patients	Salvage treatment regimen for *Hp*-independent patients
Nakamura et al. [22]	Japan (2001)	10	NA	DLBCL(MALT)	IE	Proton pump inhibitor plus Clarithromycin 600 mg D Amoxicillin 2000 mg D Metronidazole 750 mg D	5/10 (50%)	NA	NA	NA
Morgner et al. [23]	Germany (2001)	4/4	26–85	DLBCL(MALT)	IE: 6 IIE1: 2	Dural regimen (2 weeks): Omeprazole 40 mg tid Amoxicillin 750 mg tid Triple regimen (1 week): Omeprazole 20 mg twice D Clarithromycin 250 mg twice D Metronidazole 400 mg twice D	7/8 (87.5%)	1 to 4 ms	6 to 66 ms	CHOP
Hiyama et al. [60]	Japan (2001)	4	NA	DLBCL(MALT)	IE	Proton pump inhibitor plus antibiotics for 1 to 2 weeks	2/4 (50%)	6 ms	18 ms	CHOP
Alpen et al. [61]	Germany (2001)	2	73–76	DLBCL(MALT)	IE	Omeprazole 40 mg D Clarithromycin 500 mg D Metronidazole 800 mg D	1/2 (50%)	1.3 ms	5.7 ms	CHOP
Chen et al. [21, 25] Kuo et al. [26]	Taiwan (2001, 2005, 2012)	12/22	55 (35–83)	DLBCL(MALT)	IE: 30 IIE1: 4	Amoxicillin 500 mg 4 times D Clarithromycin 500 mg twice D Omeprazole 20 mg twice D	18/32 (56.3%)	5.0 ms (95% CI, 2.8–7.5)	11.7 years (95% CI, 7.8–14.4)	CHOP, CEpiOP, R-CHOP, or R-CEpiOP
Tari et al. [27]	Japan (2009)	7/8	63–91 (mean: 72.9)	Pure DLBCL	IE	Rabeprazole 20 mg D Amoxicillin 750 mg twice D Metronidazole 250 mg twice D	4/15 (26.7%)	3 ms	7–100 ms (no recurrence)	R-CHOP followed by RT

Authors (Ref.)	Study Group	Patients number (Men/ Women)	Age, years (median; range)	Histological subtype	Stage	First-line HPE regimen (for 2 weeks)	CR rate	Median time to CR (ms)	Follow-up period for *Hp*-dependent patients	Salvage treatment regimen for *Hp*-independent patients
Kuo et al. [26]	Taiwan (2012)	6/10	63 (34–88)	Pure DLBCL	IE: 9 IIE1: 7	Amoxicillin 500 mg 4 times D Clarithromycin 500 mg twice D Omeprazole 20 mg twice D	11/16 (68.8%)	2.1 ms (95% CI, 0.7–6.3)	3.5 years (95% CI, 0.7 ~ 6.3)	R-CHOP or R-CEpiOP
Ferreri et al. [28]	Italy (2002)	16	NA	Pure: 11 DLBCL (MALT): 5	IE*	Clarithromycin 500 mg twice D Tinidazole or Metronidazole 500 mg twice D Omeprazole 20 mg twice D	8/16 (50%)	NA	14–114 ms (9/10 patients remain-free)	PR-rituximab SD or PD -chemo-RT
Tsai et al. [25]	Taiwan (2020)	6/4	71.5 (48–85)	DLBCL(MALT)	IE: 8 IIE1: 2	Amoxicillin 500 mg 4 times D Clarithromycin 500 mg twice D Omeprazole 20 mg twice D	8/10 (80%)	4.0 ms (range 1–10)	59 ms (95% CI, 23–95)	R-COP

Abbreviations: HPE, H. pylori *eradication therapy; DLBCL, diffuse large B-cell lymphoma; DLBCL(MALT),DLBCL with histological evidence of MALT lymphoma; "pure" DLBCL, DLBCL without histological evidence of MALT lymphoma; CR, complete remission in patients with successful HPE.* Hp*-dependent (CR after HPE);* Hp*-independent (non-CR after HPE); D, daily; ms, months; NA, non-analysis; R, rituximab; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisolone; RT, radiotherapy; CEpiOP, cyclophosphamide, epirubicin, vincristine, and prednisolone; PR, partial remission; SD, stable disease; PD, progressive disease. COP, cyclophosphamide, vincristine, and prednisolone.*IE: Perigastric lymph nodes of diameter < 1.5 cm.*

Table 1.
A summary of the efficacies of first-line Helicobacter pylori *eradication therapy for treating patients with early-stage* Helicobacter pylori*-positive gastric DLBCL(MALT) or "pure" DLBCL.*

first-line HPE should be administered to additional populations of stage IIE1 gastric DLBCL(MALT) patients. This concept is further supported by a prospective clinical trial (T3206) designed by the TCOG in evaluating the treatment efficacy of first-line HPE consisting of omeprazole, amoxicillin, and clarithromycin for 14 days in patients with *Hp*-positive stage IE or stage IIE1 MALT lymphoma, and DLBCL(MALT) of the stomach [25]. This trial revealed that 8 (80%) of 10 patients with DLBCL(MALT) and 26 (76.5%) of 36 patients with MALT lymphoma achieved CR (**Figure 2**); the CR rate was not different between stage IE (75%) and stage IIE1 (66.7%) [25]. After a median follow-up of 59 months, all eight *Hp*-dependent DLBCL(MALT) patients remained lymphoma-free, whereas three (7.7%) of the 26 *Hp*-dependent MALT lymphoma patients relapsed after a median follow-up of 82 months [25]. Notably, tumor invasions to the perigastric lymph nodes are not exclusive to *Hp*-dependent cases, suggesting that pivotal mechanisms exist in these tumors; this is because lymphoma cells of the perigastric lymph nodes communicate indirectly with the *Hp* bacteria.

Taken together, these findings show that the tumor remission rates after HPE are identical between MALT lymphoma and DLBCL(MALT) of the stomach (**Table 1**), which overthrows the classical concept that the transformation of MALT lymphoma into high-grade DLBCL(MALT) is associated with the acquisition of *Hp*-independence and thus DLBCL(MALT) is unlikely to respond to HPE. These clinical discoveries are in line with previous molecular studies showing the difference in clonalities between MALT lymphoma components and DLBCL components of the same stomach [64–66]. Kuo et al. compared the patterns of *IgH* rearrangement between DLBCL and MALT lymphoma components of the same gastric DLBCL(MALT) patients receiving HPE, and revealed that different clonal origins of the two co-existing components contributed to the differential response to HPE [67]. In the long-term follow-up of gastric MALT lymphoma without remission, Liu et al. showed that the frequency of development of DLBCL from MALT lymphoma was less than 2%, suggesting rare high-grade transformation in gastric MALT lymphoma [68]. These results indicate that some DLBCL components may evolve independently from their co-existing MALT lymphoma counterparts in gastric DLBCL(MALT). Overall, with reference to clinical impact, first-line HPE resulting in a durable CR rate of approximately 60% has revolutionized the treatment of gastric DLBCL(MALT), and has helped 60% of DLBCL(MALT) patients to avoid the risks of systemic chemotherapy (**Table 1**). With reference to molecular impact, the high-grade transformation of gastric MALT lymphoma does not confer *Hp*-independence to the tumor cells (**Figure 1**); this finding will eventually lead to the revision of the current lymphoma classification, such as the Revised European American Lymphoma Classification (REAL)/WHO. In the REAL/WHO, high-grade gastric MALT lymphoma is classified as DLBCL with histological evidence of MALT (DLBCL[MALT]), and is recommended to be treated as common DLBCL [3, 5, 57].

5. A proportion of gastric "pure" DLBCL patients can be cured by first-line HPE

Although the origin of gastric "pure" DLBCL is usually considered as de novo and not from high-grade transformed MALT lymphoma, there are several evidences demonstrating the epidemiological link between *Hp* infection and gastric "pure" DLBCL [44, 69–71]. In a case–control study in a Japanese population, Ishikura et al. disclosed a close association between *Hp* infection and risk of development of gastric lymphoma, in which the odds ratios for MALT lymphoma and DLBCL were 1.96 (95% confidence interval [CI], 1.00–3.86), and 1.92 (95% CI, 0.74–4.95), respectively [72].

Because the differentiation between "pure" DLBCL and DLBCL(MALT) is not clearly defined as per histopathological manifestations [57, 58], exploration of the therapeutic efficacy of first-line HPE in gastric "pure" DLBCL has rarely been studied as these patients should be treated with aggressive chemotherapy according to recommendations from the WHO advisory committee [5, 57]. However, a proportion of gastric "pure" DLBCL patients are elderly and have a relatively large number of comorbidities; such patients cannot tolerate the adverse effects of systemic chemotherapy. For these elderly gastric "pure" DLBCL patients with comorbidities, several anecdotal case reports showed that the administration of first-line HPE can cause complete regression of tumors [73–75], suggesting that a certain proportion of gastric "pure" DLBCLs are *Hp*-related, and the growth of these lymphoma cells is *Hp*-dependent.

Since 2001, our group and other investigators have shown that early stage gastric DLBCL(MALT) is *Hp*-dependent and is cured by first-line HPE [21–24]. Consequently, HPE has become the first-line treatment for patients with localized gastric DLBCL(MALT) at our institution. Kuo et al. further designed a pilot study to investigate the therapeutic efficacies of first-line HPE in stage IE/IIE1 gastric "pure" DLBCL patients who are monitored by the following approaches: (1) intensive endoscopic regular follow-up, and (2) immediate administration of systemic rituximab-based chemotherapy (immunochemotherapy) if tumors are stable or progressive [26]. This pilot study revealed that first-line HPE resulted in CR in 11 (68.8%) of 16 *Hp*-positive gastric "pure" DLBCL patients, with a median interval to CR of 2.1 months (**Figure 3**) [26]. Although there were a limited number of gastric "pure" DLBCL patients, the CR rate showed a trend of being higher in tumors involving the mucosa/submucosa than in tumors spread into the muscularis propria or beyond (100% [5/5] vs. 54.5% [6/11], P = 0.119) [26]. After a median follow-up of 3.9 years (95% CI, 3.7 to 4.1), 10 *Hp*-dependent patients were alive and free of lymphoma, but one patient died of lung cancer [26]. Considering that the tumors may rapidly progress and cause morbidity or mortality if tumors are unresponsive to antibiotic treatment, *Hp*-independent gastric "pure" DLBCL patients were immediately treated with immunochemotherapy, and the 5-year overall survival (OS) rate was compatible with patients receiving first-line conventional immunochemotherapy (88.9% vs. 78.3%, P = 0.551) [26].

In another retrospective study conducted in a Japanese population, Tari et al. revealed that among 15 patients with stage IE gastric "pure" DLBCL, four (26.7%) patients achieved CR after successful HPE with a HPE regimen consisting of rabeprazole, amoxicillin, and metronidazole [27]. In their studies, all four patients with CR presented with superficial endoscopic findings and remained lymphoma-free for 7–100 months, whereas 11 *Hp*-independent patients responded completely to rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP) for three courses, followed by radiotherapy [27]. Endoscopic ultrasound staging also showed the CR rate for tumors limited to the mucosa and the shallow portion of the submucosa was 80% (4/5 cases), whereas that for tumors extending to the deep portion of the submucosa or beyond, it was 0% (0/10 cases) [27]. The HG-L1 trial was a multicenter phase II study which explored first-line HPE consisting of clarithromycin, tinidazole or metronidazole, and omeprazole in 16 patients with stage I *Hp*-positive gastric DLBCL ("pure" DLBCL, n = 11; DLBCL(MALT), n = 5) [28]. Reporting on this trial, Ferrei et al. revealed that eight (50%) patients achieved CR and three patients achieved PR at two months after HPE, and the remaining two patients with PR achieved CR after receiving single rituximab treatment [28]. In addition, the remaining patients with stable or progressive diseases were all converted to CR after receiving salvaged management with R-CHOP [28]. This prospective trial demonstrated that the therapeutic efficacies of HPE in Western populations with gastric DLBCL are the same as those in Asian populations.

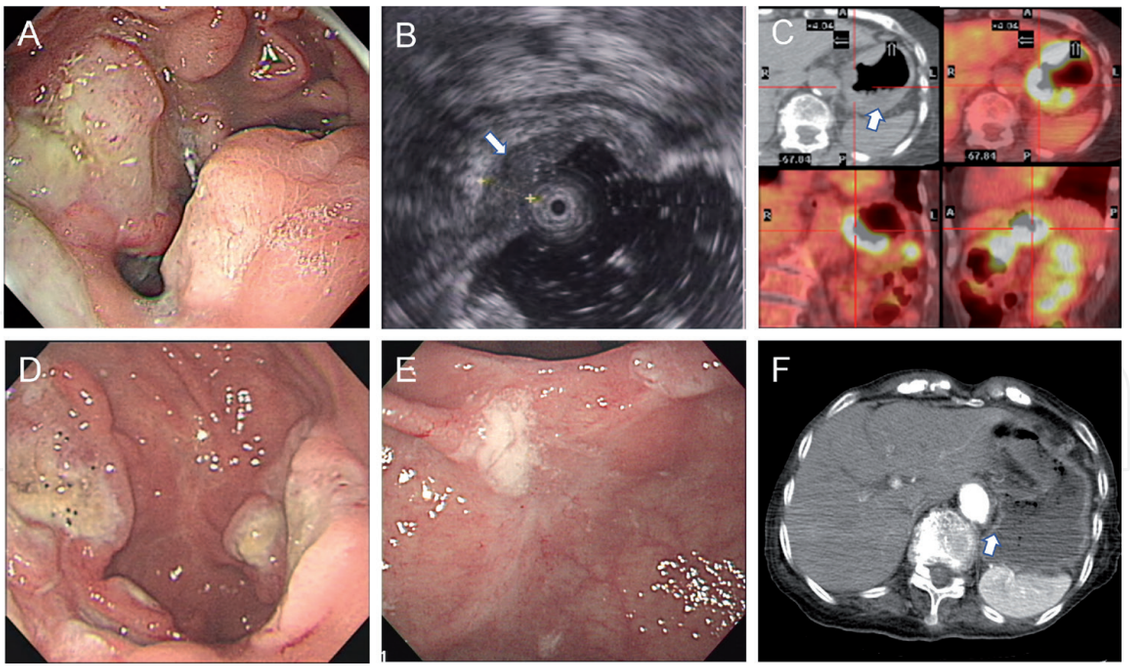

Figure 3.
Changes of endoscopic features and images in an example of Helicobacter pylori *(*Hp*)-dependent stage IIE1 gastric "pure" diffuse large B-cell lymphoma (DLBCL) before and after completion of Hp eradication therapy (HPE) (A) Endoscopy shows multiple ulcerative tumors at the anterior and posterior walls of the greater curvature of the gastric body in an 89-year-old woman before HPE (Histopathology disclosed "pure" DLBCL without histological evidence of mucosa-associated lymphoid tissue). (B) Endoscopic ultrasound examination shows increased thickness of 2nd/3rd layers (submucosal involvement) with maximal thickness (0.7 cm) (white arrow) and multiple perigastric lymphadenopathies in the body of the stomach. (C) Positron emission tomography and computed tomography (CT) reveal intense hot areas (white arrow) at the upper to middle gastric wall of the stomach (standard uptake value max early/delay = 21.5/37.6) (demonstrated at axial, coronal, and sagittal views). (D) One month after completion of HPE, endoscopy shows regressed ulcerative masses at the gastric body in the same case A. (E) Eight months after completion of HPE, complete remission was achieved except for ulcerative scarring (Histopathology disclosed chronic gastritis without intestinal metaplasia) in the same case A. (F) At the same time, CT shows no gastric wall thickening (white arrow) in the gastric body in the same case A.* Hp, Helicobacter pylori*; HPE, Hp eradication therapy; DLBCL, diffuse large B-cell lymphoma; MALT, mucosa-associated lymphoid tissue; CT, computer tomography; SUV, standard uptake value; CR, complete remission.*

Taken together, these findings indicate that approximately 50% of gastric "pure" DLBCL patients whose tumors are still *Hp*-dependent, are highly responsive to first-line HPE (**Table 1**). Importantly, HPE treatment may result in a quick response of tumors to CR and to long-lasting CR in these *Hp*-dependent gastric "pure" DLBCL patients. Even if the tumors invade the deep layer or the perigastric lymph nodes, some patients with gastric "pure" DLBCL are still cured by first-line HPE (**Figure 3**). Furthermore, gastric "pure" DLBCL patients who do not respond to first-line HPE are successfully salvaged with rituximab-based chemotherapy. Therefore, the use of first-line HPE as an exclusive treatment to avoid potential adverse effects of chemotherapy or radiotherapy for localized *Hp*-positive for gastric "pure" DLBCL patients is suggested, because this subgroup of patients is frequently older than 70 years.

6. *Hp*-positive gastric DLBCL may be part of *Hp*-related gastric malignancies

In addition to gastric DLBCL(MALT), gastric "pure" DLBCL is epidemiologically linked with *Hp* infection, and most gastric "pure" DLBCLs are diagnosed with limited-stage disease [42–44, 76]. Conventionally, patients with gastric "pure" DLBCLs are treated with immunochemotherapy, whereas immunochemotherapy

with or without subsequent radiotherapy is considered as the standard therapy for patients with localized disease [77, 78]. Considering that first-line surgical resection cannot improve the survival outcome for gastric "pure" DLBCL patients, a surgical approach is recommended for patients with severe bleeding or perforation [79–81]. Studies in Taiwanese, Japanese, and Western populations clearly demonstrated that certain patients with localized *Hp*-positive gastric "pure" DLBCL are highly responsive to first-line antibiotics eradicating *Hp*, and these patients have persistent CR for a long time after HPE [26–28]. These discoveries imply that gastric "pure" DLBCLs can be biologically classified into two types, *Hp*-related lymphoma, and *Hp*-unrelated lymphoma, each with different cellular origins, paths of tumorigenesis, and clinicopathological manifestations (**Figure 1**).

Hsu et al. retrospectively analyzed the clinicopathological features and clinical outcomes of patients with gastric DLBCL who received systemic chemotherapy, including DLBCL(MALT) (n = 17) and "pure" DLBCL (n = 26), and showed that patients with DLBCL had higher levels of serum lactate dehydrogenase (LDH 50% vs. 12%, P = 0.01) and a lower chemotherapy response rate (57.7% vs. 88.2%, P = 0.03) than those with DLBCL(MALT) [82]. Multivariate analysis identified that the presence of MALT lymphoma components, stage I and IIE1, and response to chemotherapy were independent and good prognostic factors [82]. This finding provides evidence that *Hp* infection may be associated with a better chemotherapy response and good prognosis; this is because gastric DLBCL(MALT) is generally transformed from its MALT lymphoma components in which gastric MALT lymphoma is always linked with *Hp* infection, although *Hp* examinations were not assessed in the study by Hsu et al. [82].

This hypothesis is further supported by a report from Kuo et al. who assessed the correlation between clinicopathological features and clinical outcomes, and *Hp* infection in patients (n = 95) with primary gastric "pure" DLBCLs who received conventional chemotherapy (anthracycline-based-regimens, such as CHOP or CEpirubicinOP) or immunochemotherapy (rituximab/anthracycline or rituximab-COP) as first-line therapy [29]. Kuo et al. found that the presence of *Hp* infection confirmed by histological examination, urease test, or bacterial culture, was associated with a lower International Prognostic Index score (0–1; *Hp*(+) [n = 46] vs. *Hp* (−) [n = 49]) = 65% vs. 43%, P = 0.029), a lower clinical stage (I-IIE1, 70% vs. 39%, P = 0.003), and a better CR rate (76% vs. 64%, P = 0.004) [29]. In addition, patients with *Hp* infection had a significantly better 5-year event-free survival (EFS) (71.7% vs. 31.8%, P < 0.001) and OS (76.1% vs. 39.8%, P < 0.001) than those without *Hp* infection [29]. Even among stage I-IIE1 patients, the *Hp*-positive group had a better trend for CR (88% vs. 68%, P = 0.097) and a better 5-year EFS (80.6% vs. 46.8%, P = 0.003) and OS (90.6% vs. 68.0%, P = 0.023) than the *Hp*-negative group [29]. Using multivariate analysis, Kuo et al. identified the absence of *Hp* infection as an independent predictor of worse EFS (hazard ratio [HR] = 2.509; P = 0.007) and OS (HR = 2.666; P = 0.009) [29].

The findings of Kuo et al. were endorsed by the Cheng et al. who conducted a retrospective analysis of 129 patients with primary gastric "pure" DLBCLs, in which the presence of *Hp* infection was based on a positive test for histological examination and urease breath tests [30]. In their study, the presence of *Hp* infection was significantly associated with limited stage (Stage I-II: *Hp*(+) vs. *Hp* (−), 78.6% vs. 60.3%, P = 0.027) and lower IPI score (0–1: *Hp*(+) vs. *Hp* (−), 92.2% vs. 78.2%, P = 0.022); all *Hp*-positive patients received HPE using PPI, bismuth compounds, and antibiotics, including clarithromycin, amoxicillin, tetracycline, or metronidazole, for eradicating *Hp* [30]. In addition, patients with *Hp* infections had a significantly better 5-year progression-free survival (PFS) rate (89.3% vs. 74.1%, P = 0.040) and 5-year OS (89.7% vs. 71.8%, P = 0.033) than those without *Hp* infection [30]. However,

58.9% of *Hp*-positive patients and 78.6% of *Hp*-negative patients underwent surgery as the initial treatment. Furthermore, multivariate analyses showed that in addition to ECOG performance status 0–1, the presence of *Hp* infection was a better independent predictor for PFS (HR = 0.379; P = 0.045) and OS (HR = 0.292; P = 0.021) [30].

Traditionally, MALT lymphoma is believed to be of marginal zone B-cell origin [3, 8]. Unlike MALT lymphoma, DLBCL is generally thought to originate de novo from germinal center B cells (GCB) or activated B cells [83, 84]. Previous studies showed that patients with GCB-subtype DLCBLs had better EFS and OS than those without GCB-subtype DLBCLs [85, 86]. However, in the reports of clinical outcomes of first-line chemotherapy for gastric "pure' DLBCL, Kuo et al. showed that the EFS and OS were not significantly different between GCB subtype and *non-GCB* subtype tumors according to Han's subclassification [29, 87]. Further analysis showed that the GCB subgroup lost its prognostic value in *Hp*-positive gastric DLBCL patients, but showed better survival in *Hp*-negative gastric DLBCL [29]. These results suggest that *Hp*-negative gastric DLBCL may originate de novo, and its biological significance and histologic subclassification may be more similar to that of nodal DLBCL. Similar to Kuo et al. [29], Chang et al. reported that the non-GCB subtype was not associated with the poor PFS and OS in gastric DLBCLs patients [30]. In addition, Kuo et al. showed that a proportion of *Hp*-dependent gastric DLBCLs, including DLBCL(MALT) and "pure" DLBCL, are classified as the GCB-subtype based on Han's subclassification (preliminary data) [88]. Ferreri et al. also showed that among patients with gastric "pure" DLBCL who received first-line HPE, the CR rate was comparable between GCB and non-GCB subgroups [89]. These results indicate that *Hp* may transform not only marginal zone B cells, but also GCB cells into high-grade large lymphoma cells in *Hp*-related gastric lymphoma. However,

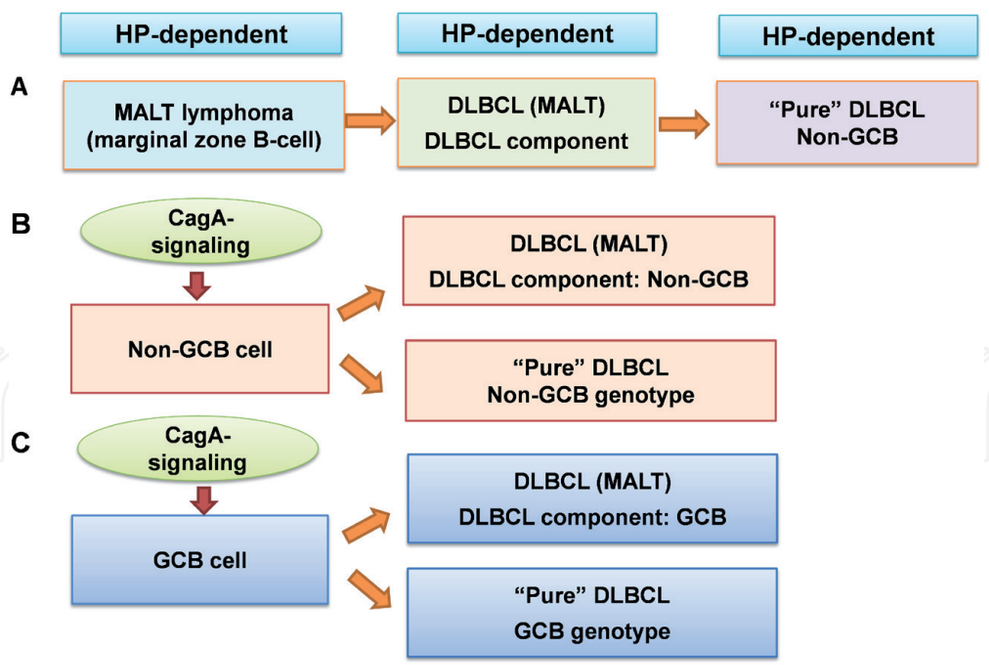

Figure 4.
Schema illustrating a hypothesis of heterogeneous cell origin of Helicobacter pylori *(*Hp*)-dependent gastric diffuse large B-cell lymphoma (DLBCL). (A) Large lymphoma B cells of* Hp*-dependent gastric DLBCL of non-GCB origin may be differentiated from* Hp*-dependent MALT lymphoma components, in which lymphoma cells often lack t(11;18)(q21;q21) [134, 135, 137]. (B) Large lymphoma B cells of* Hp*-dependent gastric DLBCL in which the non-GCBs may originate de novo. The* Hp *CagA and its CagA signaling molecules may directly affect non-GCB cells, which also contribute to the development of* Hp*-dependent large B-cell lymphoma components of gastric DLBCL. (C) Large lymphoma B cells of* Hp*-dependent gastric DLBCL in which the GCBs may originate de novo. The* Hp *CagA and its CagA signaling molecules may directly affect GCB cells, which also contribute to the development of* Hp*-dependent large B-cell lymphoma components of gastric DLBCL.*

further explorations of the cellular origins of these *Hp*-related gastric DLBCLs are warranted. Although the immunophenotypic phenomenon of the GCB subtype cannot explain the better prognosis of *Hp*-related gastric DLBCLs, the higher level of mi-R200 in *Hp*-positive tumors functionally hampering zinc-finger E-box-binding homeobox 1 (ZEB1) may thus contribute to the less aggressive behaviors of these tumors [31], since ZEB1 overexpression was reported to significantly correlate with lymph node metastases of DLCBL, and T-cell leukemia progression [90, 91].

These findings reveal that *Hp*-related gastric "pure" DLBCLs share similar clinicopathological features with gastric MALT lymphoma, such as less aggressive behavior, more limited stages, and better prognosis; this suggests an overlapping etiology between these two gastric lymphoma groups. However, the molecular mechanisms of *Hp* infection contributing to the less aggressive nature and better prognosis of gastric "pure" DLBCL remains unclear. The possible mechanisms are as follows: (1) *Hp* CagA may directly participate in the lymphomagenesis of certain portions of gastric "pure" DLBCL, (2) *Hp* may trigger antigen presentation and regulate the triggering immune communications responsible for gastric MALT lymphoma, which may also lead to *Hp*-related gastric "pure" DLBCL, and (3) *Hp* may transform not only the marginal zone B cells, but also GCB-DLBCL cells, and the mechanisms may include a direct CagA interaction with B cells (**Figure 4**). The following is a brief summary of the possible mechanisms of *Hp*-related gastric lymphoma including MALT lymphoma, DLBCL(MALT), and "pure" DLBCL.

7. *Hp*-specific CagA oncoprotein may play an important role in the molecular mechanism of *Hp*-dependent gastric lymphoma

Previous studies have demonstrated that one of the factors promoting the proliferation of *Hp*-related gastric MALT lymphoma is dependent on the communication between tumor-infiltrating T cells and tumor B cells [32–35]. In addition, CD40-mediated signaling, T helper-2-type cytokines, chemokines such as interleukin-22, the costimulatory molecule CD86, and regulatory T cells (Foxp3+) have been reported to help and promote the proliferation of MALT lymphoma cells [32–35, 92–94]. Through the eradication of *Hp*, malignant B cells are no longer subjected to antigen stimulation, *Hp*-related T-cell interaction, and immune-related regulations; this leads to their gradual regression and death [93, 94]. These findings may explain why MALT lymphomas are more likely to remain localized, and most of them are cured by HPE (**Figure 5**).

Previous studies have shown that the *Hp* strain associated with inflammatory and virulent processes carries the pathogenicity island (*cag*PAI) which includes the *cagA* gene which encodes the CagA protein [95–97]. The CagA protein contains three distinct domains (Domain I to III) at the N-terminal region, and a 5-amino acid-repetitive tandem motif (EPIYA, glutamic acid-proline-isoleucine-tyrosine-alanine) at the C-terminal region [98–100]. The EPIYA motif is characterized by the presence of a tyrosine phosphorylation site; the CagA is phosphorylated at this site by the Src-family kinase (SKFs) and c-Abl [100–102]. The *Hp* CagA-positive strain has been reported to be epidemiologically linked with the development of lymphoid follicles and neoplasms of the stomach [45, 103–105]. For example, Eck et al. reported that the positive rate of serum CagA immunoglobulin G antibodies was higher in *Hp*-positive gastric MALT lymphoma patients than in *Hp*-positive patients with chronic active gastritis (95.5% vs. 67.0%) [45]. In addition to epidemiological studies, other studies have found that CagA promotes the proliferation of B-lymphocytes through CagA-phosphorylation-dependent and -independent signaling pathways [36, 106, 107]. Ohnishi et al. reported that in CagA-transgenic

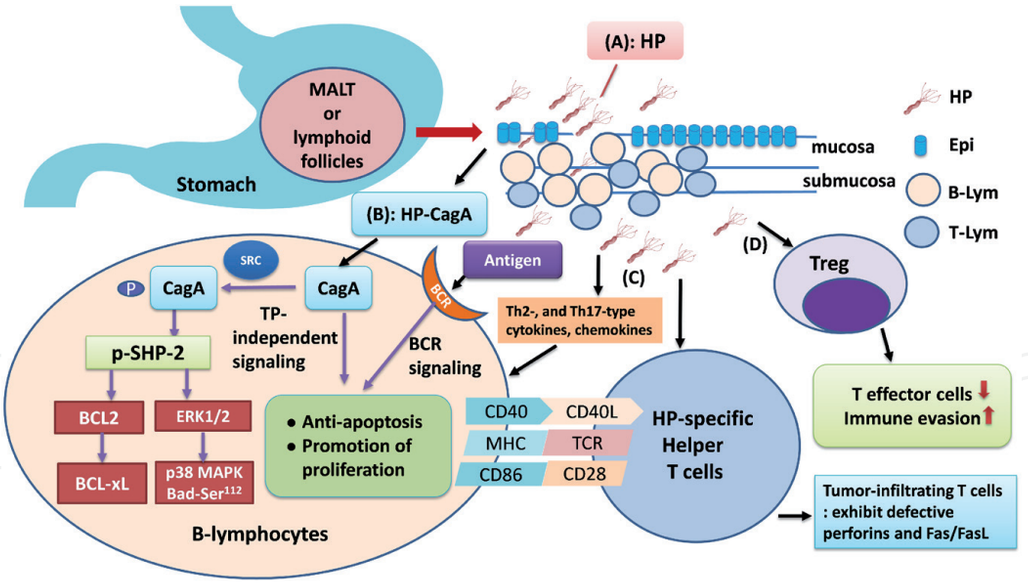

Figure 5.
Schema illustrating the direct and indirect lymphomagenesis of Helicobacter pylori *(*Hp*)-dependent gastric lymphomas, including mucosa-associated lymphoid tissue (MALT) lymphoma, diffuse large B-cell lymphoma (DLBCL) (MALT), and "pure" DLBCL. (A) After a long-term* Hp *infection,* Hp *can cause inflammation and destroy gastric epithelial cells, and stimulate immune B-lymphocytes to migrate into these lesions and progressively develop MALT or lymphoid follicle; and this phenomenon may allow the* Hp *to directly contact B-lymphocyte. Simultaneously, the* Hp *could stimulate the production of* Hp*-specific intratumoral T-helper cells. (B) When* Hp *directly communicates with B-lymphocyte, cytotoxin-associated gene A (CagA), an* Hp*-specific oncoprotein, can translocate into the subcellular area of B-lymphocyte and can undergo tyrosine phosphorylation (TP); phosphorylated CagA can interact with the cytoplasmic Src homology region 2 domain-containing phosphatase-2 and further trigger the activation of extracellular signal-regulated kinase, p38 mitogen activated protein kinase, and the production of anti-apoptosis proteins, Bcl-2, Bcl-xL, and Bad. CagA can also promote tumor growth and differentiation by activating TP-independent signaling. (C)* Hp *infection also indirectly produces antigens, which can communicate with B-cell receptors (BCRs) and elicit the BCR-related survival signal. Simultaneously,* Hp *can indirectly foster growth and differentiation of lymphoma B-cells with exhaustive help from* Hp*-stimulating helper T-cells, T helper (Th)2- or Th17-type cytokines-mediated signaling, the interaction with chemokines and their receptors, the co-communication of CD40/CD40 ligand, and stimulatory molecules such as CD86/CD28. (D)* Hp *infection can engender responses of $CD4^+CD25^+$ regulatory T-cells (Tregs) in the gastric microenvironment, and these Tregs could suppress immune-mediated pathogenesis and further cause immune evasion of these lymphoma B-cells. In addition,* Hp*-producing cytotoxic T-cells exhibit defective functionality of perforin and Fas/Fas-Ligand interaction and, thus, have less roles of cytotoxicity and apoptosis for lymphoma B-cells.* Hp, Helicobacter pylori*; Lym, lymphocyte; DLBCL, diffuse large B-cell lymphoma; MALT, mucosa-associated lymphoid tissue; CagA, cytotoxin-associated gene; TP, tyrosine phosphorylation; SHP-2, Src homology region 2 domain-containing phosphatase-2; ERK, extracellular signal-regulated kinase; MAPK, mitogen activated protein kinase; BCR, B-cell receptor; Th, T helper; Tregs: $CD4^+CD25^+$ regulatory T-cells.*

mice, CagA caused the occurrence of myeloid leukemia and malignant B-cell neoplasms (histologically similar to DLBCL) through SHP-2 phosphorylation-dependent signaling [37]. Other investigators showed that the deregulation of SHP-2 was associated with the proto-oncogenic functions associated with the creation of lymphoid and hematopoietic progenitor cells [108, 109].

Lin et al. revealed that CagA that is injected into B cells via type IV secretion systems (T4SS) can activate ERK, p38 MAPK, Bcl-2, and Bcl-xL molecules through SHP-2 phosphorylation-dependent signaling [38]. Kuo et al. found that in tumor samples of 64 gastric MALT lymphoma patients who received first-line HPE, the expression of CagA was significantly associated with *Hp*-dependence (*Hp*-dependence vs. *Hp*-independence: 68.4% [26/38] vs. 19.2% [5/26], $P < 0.001$) [39]. Among *Hp*-dependent patients, those with tumors expressing CagA responded more rapidly to HPE when compared to patients with tumors without CagA expression (median time to CR after completing HPE, 3.0 vs. 6.5 months, $P = 0.025$) [39]. In addition, in gastric MALT lymphoma patients with known tumor invasion depth, CagA expression was closely associated with less depth of tumor invasion (tumors

limited to mucosa/submucosa vs. tumor involved muscularis propria or beyond: 58.5% vs. 22.2%, P = 0.010) [39]. Furthermore, Kuo et al. found that CagA expression significantly correlated with p-SHP-2, p-ERK, p-38 MAPK, Bcl-2, and Bcl-xL expression, and the expression of the aforementioned molecules correlated with the *Hp* dependence of these tumors [40]. When compared with CagA expression alone, the co-expression of CagA, p-SHP-2, and p-ERK provided an augmented positive predictive value (93.3% vs. 81.8%) and better specificity (95.5% vs. 81.8%) for *Hp* dependence in gastric MALT lymphoma patients [40]. Based on the prospective T3206 trial, Tsai et al. reported that CagA expression correlated significantly with *Hp* dependence in gastric MALT lymphoma and DLBCL(MALT) (85.3% [29/34] vs. 33.3% [4/12], P = 0.001) [25]. Furthermore, downregulation or absence of CagA expression was documented in the residual tumor cells of *Hp*-dependent cases after HPE [25]. Ben Younes et al. also showed that CagA correlated with p-PAKT expression in the tumor cells of *Hp*-positive gastric MALT lymphoma and DLBCL patients, although this study did not show an association between CagA and *Hp* dependence [110]. In addition to CagA expression in tumor cells, Sumida et al. found that among patients with t(11;18)(q21;q21)-negative gastric MALT lymphoma, the serum titer of the CagA antibody was significantly higher in patients with *Hp*-dependent tumors than in those with *Hp*-independent tumors [111]. Taken together, these findings imply that the *Hp* CagA oncogenic protein may participate directly in the molecular mechanisms of *Hp*-dependent gastric MALT lymphoma (**Figure 5**).

In addition to gastric MALT lymphoma, the *Hp* CagA strain may be associated with the development of *Hp*-related gastric DLBCL [112, 113]. Peng first showed that the rate of detection of the CagA gene in gastric biopsy samples was significantly higher in gastric DLBCL(MALT) patients (76.7% [23/30]) than in gastric MALT lymphoma patients (37.8% [14/37]) or in patients with gastritis (30.3% [17/56]) [112]. Delchier et al. also revealed that the *Hp*-seropositive rate was greater in gastric DLBCL patients (100% [16/16]) than in those with gastric MALT lymphoma (78% [29/37]), whereas the CagA-seropositive rate was also higher in DLBCL patients than in MALT lymphoma patients (75% [12/16] vs. 44.8% [13/29], P < 0.05) [113]. Considering that a certain proportion of gastric DLBCLs, including DLBCL(MALT) and "pure" DLBCL, as well as gastric MALT lymphoma are responsive to antibiotics eradicating *Hp*, the clues from *Hp*-specific intratumor T cells and the interacting co-stimulatory molecules, and *Hp* CagA-triggering signaling in MALT lymphoma may also participate in the lymphomagenesis of gastric DLBCL [32–35, 92–94]. Regarding the interaction between *Hp*-specific T cells and co-stimulator molecule CD86 expressed in lymphoma B cells [94], Kuo et al. first showed that CD86 expression in tumor cells was significantly associated with *Hp* dependence in gastric DLBCL(MALT) (68.8% vs. 0%, P = 0.001) [114]. This finding is in line with the findings that *Hp*-dependent gastric MALT lymphoma exhibited a higher expression of CD86 than *Hp*-independent gastric MALT lymphoma [115]. Furthermore, Kuo et al. showed that among gastric "pure" DLBCL patients receiving first-line HPE, CD86 expression was more frequently found in *Hp*-dependent tumors than in *Hp*-independent tumors (61.5% [8/13] vs. 25% [2/8], P = 0.023) [41]. Lin et al. also revealed that in cocultures of *Hp* and B-lymphoma cells, *Hp* CagA upregulated CD86 expression in B cells [38], indicating that a proportion of gastric DLBCLs are still dependent on the triggering of T cells by *Hp* CagA for promoting proliferation (**Figure 5**).

When exploring the possible role of CagA in the lymphomagenesis of gastric DLBCLs, Kuo et al. revealed that CagA expression significantly correlated with p-SHP-2 expression and limited stages (I-IIE1, 82% vs. 47%, P = 0.017) in *Hp*-positive gastric "pure" DLBCL patients receiving systemic chemotherapy [29]. Kuo et al. also showed that CagA expression was associated with significantly better CR (CagA[+]

vs. CagA[−]: 89% vs. 59%, P = 0.030), 5-year EFS (CagA[+] vs. CagA[−]: 85.2% vs. 46.3%, P = 0.002), and OS (CagA[+] vs. CagA[−]: 88.9% vs. 52.9%, P = 0.003) [29]. These findings suggest that *Hp* CagA and its regulated signaling participate in the lymphomagenesis of *Hp*-related gastric "pure" DLBCL. Furthermore, Kuo et al. showed a close association between CagA expression and *Hp* dependence of patients with gastric DLBCL (including DLBCL(MALT) and "pure' DLBCL) who received first-line HPE (*Hp*-dependence vs. *Hp*-independence: 74.3% [26/ 35] vs. 25.0% [7/28], P < 0.001) [41]. Furthermore, CagA expression significantly correlated with the expression of p-SHP-2 and p-ERK, and the expression of these molecules was significantly associated with *Hp* dependence of gastric DLBCL [41]. Among *Hp*-dependent gastric DLBCL patients, the median time to CR after completing HPE was quicker in tumors with CagA expression than in tumors without CagA expression (4.0 months vs. 5.0 months, P = 0.050) [41]. Kuo et al. also observed that CagA and CagA signaling molecules were diminished or absent in a series of biopsy samples after HPE [41]. These results indicate that CagA and its regulated signaling molecules may be involved in the pathogenesis of *Hp*-dependent gastric DLBCL (**Figure 5**).

Epidemiological studies have reported that the incidence of gastric MALT lymphoma in East Asia (including Taiwan, Korea, and Japan) is higher than that in Western countries (Netherlands, Italy, and USA) [70, 72, 116–119]. In addition to the distinct prevalence of gastric lymphoma, the rate of CagA-positivity in *Hp* strains was higher in East Asian populations (at nearly 90%), when compared with that in Western populations (at approximately 60%) [120–125]. In contrast to CagA from Western *Hp* isolates containing EPIYA-A, EPIYA-B, and EPIYA-C segments, the EPIYA motifs in East Asian *Hp* strains (including those from Taiwan), mainly consist of EPIYA-A, EPIYA-B, and EPIYA-D segments [36, 97, 100, 126–128]. CagA activates ERK/MAPK signaling in gastric epithelial cells or lymphoma B-cells mainly by interacting with SHP-2; the CagA-SHP-2 complex is characterized by an interaction between the tyrosine-phosphorylated EPIYA-C or EPIYA-D segment of CagA with the SH2 domain of SHP-2 [97, 128, 129]. In addition, the *Hp* CagA strains bearing the EPIYA-D motif had a greater affinity for binding SHP-2, a capacity for phosphorylating tyrosine, and conferred a risk for developing gastric cancer [97, 126, 129, 130]. Chuang et al. assessed the intensity of tyrosine-phosphorylated CagA (p-CagA) in *Hp* strains isolated from Taiwanese patients with a distinct disease status, including gastric cancer, gastric ulcer, duodenal ulcer, and gastritis; the authors reported that the p-CagA intensity was higher in patients with gastric cancer or gastritis accompanied by intestinal metaplasia than in patients with gastritis but without intestinal metaplasia [131], indicating that a higher tyrosine phosphorylation activity of CagA may be associated with a risk of developing precancerous lesions and subsequent gastric cancer [131]. In *Hp* strains isolated from *Hp*-dependent cases of gastric lymphoma including five DLBCLs and six MALT lymphomas, Kuo et al. showed that all cases were CagA-positive strains [41]. In their studies, the positive CagA *Hp* strains were significantly associated with a rapid time to CR after completing HPE in *Hp*-dependent gastric lymphoma patients, including MALT lymphoma and DLBCLs [39, 41]. In addition, CagA expression correlated significantly with p-SHP-2 expression and the expression of tyrosine phosphorylation-dependent molecules such as ERK and p38 MAPK, in the lymphoma cells [39–41]. These findings further support the findings of a systematic review of HPE for treating gastric MALT lymphoma from Zullo et al. the authors investigated the reason for the significantly higher CR rate of tumors in Asian populations (84.1%) than that of tumors in Western populations (73.8%) (P < 0.0001) [62]. Although the association between tumors expressing CagA and the *Hp* dependence of gastric lymphoma may explain why most CagA-positive gastric MALT lymphomas (even for gastric DLBCLs) remain localized and show a quick response to HPE, approximately 30–50% of *Hp*-dependent gastric

lymphoma patients lack CagA expression in their tumors [39, 41]; this suggests that other underlying molecular mechanisms responsible for antibiotic responsiveness may exist, and need to be explored.

8. Discussion

We and other investigators have demonstrated that a large proportion of localized (stage IE to IIE1) gastric DLBCLs, including DLBCL(MALT) and "pure" DLBCL remain *Hp*-dependent and can possibly be treated by first-line HPE [21–28], indicating that DLBCL transformation is not associated with the loss of *Hp* dependence. We first discovered that most patients with *Hp*-dependent gastric DLBCL(MALT), in whom with DLBCL and MALT lymphoma showed the same clonality using laser capture microdissection and *IgH* CDR3 rearrangement analyses [67]. Starostik et al. compared the genetic aberrations of t(11;18)(q21;q21)-negative MALT lymphoma and DLBCL of the stomach [132]. They demonstrated that both lymphomas share allelic imbalances, such as 3q26.2–27 amplification [132]. Furthermore, Barth et al. found a high pathogenetic similarity between MALT lymphoma and small-cell components of DLBCL(MALT) and between DLBCL and large-cell components of DLBCL(MALT) of the stomach, through expression profile analysis [133]. These findings suggest that some of the large-cell components in patients with gastric DLBCL may be transformed from *Hp*–related MALT lymphoma [133]. Whether *Hp*-related gastric "pure" DLBCLs share biological, immunological, and molecular features of *Hp*-related gastric MALT lymphoma and DLBCL(MALT) is worth investigating in the future.

Although first-line antibiotic HPE has saved approximately 60% of early stage gastric DLBCL patients from the risks of systemic chemotherapy, approximately 40% of early stage and most patients with advanced, gastric DLBCL still receive immunochemotherapy as the primary treatment. To avoid delaying the administration of immunochemotherapy for these *Hp*-independent patients, the identification of molecular markers predicting antibiotic unresponsiveness has become an emergent issue. Previously, we discovered that canonical and noncanonical NF-κB signalings contribute to *Hp*-independent tumor growth of gastric lymphoma, including MALT lymphoma, DLBCL(MALT), and "pure" DLBCL of the stomach, and their respective determinant molecular markers, nuclear BCL10, nuclear NF-κB(p65), and B-cell-activating factor of TNF family (BAFF), closely correlated with *Hp* independence of these tumors [41, 134–136]. The incorporation of *Hp*-independent molecular markers with clinicopathological features into further personalized treatment for *Hp*-positive early stage gastric DLBCL patients is warranted. Our ongoing prospective trial (ClinicalTrials.gov, NCT02388581) is the first study to evaluate the efficacy of first-line antibiotic HPE, as determined by the CR rate and time to tumor progression, in patients with *Hp*-positive localized (stage IE and IIE1) gastric "pure" DLBCL. This trial will also validate the accuracy (sensitivity and specificity) of molecular markers, including CagA, BCL10, NF-κB(p65), and BAFF, in predicting antibiotic responsiveness. This ongoing phase II study hopes to answer the question of "whether not just MALT lymphoma," "pure" DLBCL of the stomach is still responsive to antibiotic treatment".

However, genetic abnormalities found so far in gastric MALT lymphoma, such as t(11;18)(q21;q21), are far from providing a complete understanding of the molecular mechanisms of *Hp*-related gastric DLBCL [93, 137]. *Hp* infection perturbs or changes the epigenetic status, including the methylation profiles, DNA methyltransferase, cytokines, and the inflammatory responses, and causes aberrant hypermethylation [138–140]; these *Hp*-regulated epigenetic and genetic changes are worth exploring as to their relationship with lymphomagenesis of *Hp*-related gastric lymphoma.

Although we and other investigators have demonstrated that CagA-signaling and tumor-infiltrating T-cells co-participate in the molecular mechanisms of *Hp*-related gastric lymphoma [94], *Hp* in the gastric microenvironment may alter immune responses [141–144]. In a murine model of *H. felis*-induced gastric MALT lymphoma, Craig et al. showed that the development of MALT lymphoma requires B-cell receptor signaling through the poly-reactivation of tumor immunoglobulin with certain antigens and tumor-infiltrating T-cells [145]. Most of the tumor-infiltrating CD4+ cells in gastric MALT lymphoma were shown to be $Foxp3^+CD4^+CD25^+$ regulatory T-cells (Tregs), and these Tregs were recruited by tumor cells through the chemokines, CCL17 and CCL22, secreted by $Foxp3^+$Tregs [145]. In addition, the systemic depletion of $Foxp3^+$Tregs *in vivo* efficiently resulted in the regression of MALT lymphoma [145]. Two recent *in vivo* studies examined the possible mechanisms of Tregs involvement in the immunomodulation of gastric MALT lymphoma and showed that the presence of $Foxp3^+$ expression was significantly higher in patients who achieved CR after HPE than in those without CR, suggesting that Tregs-mediated signaling contributes to *Hp*-dependent lymphomagenesis of gastric MALT lymphoma [146, 147]. Whether *Hp*-regulated chemokines, IL-22, CCL17, and CCL12, and Tregs and *Hp*-altering immune responses also contribute to the *Hp*-dependent lymphomagenesis of gastric DLBCL remains uncertain, and these clues from MALT lymphoma would push us to comprehensively explore the mechanisms by which *Hp*-related immune responses participate in the lymphomagenesis of *Hp*-related gastric DLBCL.

9. Conclusions

During the past two decades, we have discovered that the spectrum of *Hp*-related gastric lymphoma is much wider than was previously thought. In addition to the classical MALT lymphoma, we demonstrated that DLBCL with (DLBCL[MALT]) and without ("pure" DLBCL) histological evidence of MALT lymphoma are all closely related to *Hp*. Most importantly, they can all be cured by HPE, a clinical practice that saves thousands of lives and allows patients to avoid systemic immunochemotherapy-related adverse effects. Furthermore, we have identified the existence of *Hp* CagA in the entire spectrum of gastric lymphomas, including MALT lymphoma, DLBCL(MALT), and "pure" DLBCL; it is also important to note that CagA-regulated signaling molecules such as p-SHP-2 and p-ERK were also expressed in tumor cells of *Hp*-dependent gastric MALT lymphoma as well as of gastric DLBCLs. In addition, *Hp*-positive gastric "pure" DLBCLs, especially those exhibiting CagA expression, are not the same as *Hp*-unrelated gastric "pure" DLBCL in terms of clinicopathological manifestations and biological behavior. These findings indicate that CagA may lead to direct lymphomagenesis in these *Hp*-related gastric lymphomas via the regulation of pivotal tyrosine phosphorylation-related signal transduction. This is a big paradigm shift, since until very recently, the classical belief has been that MALT lymphoma is caused indirectly by the interaction of *Hp* with T cells. Since many DLBCLs are of GCB origin, the canonical concept that all *Hp*-related lymphomas are of a marginal-zone B cell origin, needs to be reappraised. However, we and other investigators have reported that a certain proportion of *Hp*-dependent gastric DLBCLs may be of GCB origin. These clues indicate that the spectrum of *Hp*-related gastric lymphomas should be revised to include not only MALT lymphoma, but also DLBCL(MALT) and "pure" DLBCL. Further investigations of the spectrum, lymphomagenesis, therapeutics, and cellular origins of *Hp*-related gastric lymphoma are warranted.

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Author details

Sung-Hsin Kuo[1,4,5], Kun-Huei Yeh[1,4,5], Chung-Wu Lin[3], Li-Tzong Chen[7,8,9,10], Ming-Shiang Wu[2] and Ann-Lii Cheng[1,2,5,6*]

1 Department of Oncology, National Taiwan University Hospital and National Taiwan University College of Medicine, Taipei, Taiwan

2 Department of Internal Medicine, National Taiwan University Hospital and National Taiwan University College of Medicine, Taipei, Taiwan

3 Department of Pathology, National Taiwan University Hospital and National Taiwan University College of Medicine, Taipei, Taiwan

4 Cancer Research Center, National Taiwan University College of Medicine, Taipei, Taiwan

5 Graduate Institute of Oncology, National Taiwan University College of Medicine, Taipei, Taiwan

6 Department of Medical Oncology, National Taiwan University Cancer Center, National Taiwan University College of Medicine, Taipei, Taiwan

7 National Institute of Cancer Research, National Health Research Institutes, Tainan, Taiwan

8 Department of Internal Medicine, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan

9 Department of Internal Medicine, National Cheng-Kung University Hospital, Tainan, Taiwan

10 Institute of Molecular Medicine, National Cheng Kung University, Tainan, Taiwan

*Address all correspondence to: alcheng@ntu.edu.tw

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