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REVIEW ARTICLE

Gastric carcinogenesis

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Abstract
Introduction In most patients, gastric cancer is diagnosed in advanced stage. Curative treatment options are limited and the mortality is high. The process of gastric carcinogenesis is triggered by *Helicobacter pylori*-driven gastritis and is further characterized by its complexity of interaction with other risk factors. Health care systems are challenged for the improvement of prevention, early diagnosis, and effective treatments.
Methods An extensive literature research has been performed to elucidate the interplay between etiological factors involved in gastric carcinogenesis.
Results H. pylori is the most important carcinogen for gastric adenocarcinoma. Evidence is provided by experiments including animal studies as well as clinical observational and interventional studies in humans. Eradication has the potential to prevent gastric cancer and offers the greatest benefit if performed before premalignant changes of the gastric mucosa have occurred. Bacterial virulence factors are essential players in modulating the immune response involved in the initiation of the carcinogenesis in the stomach. Host genetic factors contribute to the regulation of the inflammatory response and in the aggravation of mucosal damage. The harmful role of environmental factors is restricted to salt intake and smoking of tobacco. The ingestion of fruit and vegetables has some protective effect.
Conclusion Infection with *H. pylori* is the major risk factor for gastric cancer development, and thus, eradication of the *Helicobacter* offers a promising best option for prevention of the disease. Bacterial virulence, host genetic factors, and environmental influences are interacting in the multifactorial process of gastric carcinogenesis.

Keywords Gastric cancer · *Helicobacter pylori* · Intestinal metaplasia · CagA · Interleukin-1 beta

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Introduction and background

The incidence of gastric cancer shows an impressive fall in certain areas in the world and still on a global scale represents the second most common cause of cancer-related death with about 700,000 patients dying each year [1]. In more than two thirds of patients, gastric cancer is advanced at initial presentation, and only palliative therapy can be offered at this stage. The clinical history of tumor-related symptoms is usually of recent date with alarm symptoms, weight loss, decreasing appetite, anemia, nausea, and vomiting. About 40% of patients never report dyspeptic symptoms within their recent or remote medical history [2]. The 1-year and 5-year survival rates are low with only 42% and 24%, respectively [3].

Therefore, the challenge is to combat gastric cancer with adequate and cost-effective screening programs that allow an early diagnosis. General population screening facilitates the detection of early gastric cancer but is implemented in large scales only in Japan and Korea [4, 5]. It is questionable if these programs are transferable to other regions in the world and particularly to areas where the incidence of gastric cancer is considerably lower. A retrospective calculation from Singapore estimated the cost-effectiveness of mass screening on the basis of a 24-year period. According to this estimation, endoscopic screening for stomach cancer is cost-effective in moderate

to high-risk populations but not in low-incidence regions as in most parts of Europe or North America [6]. There is high demand for cheaper and non-invasive tools of gastric cancer screening with the primary aim to detect premalignant lesions.

A further approach to fight gastric cancer is the assessment of changes in gene systems (genomics) and in protein expression (proteomics). With the help of these and other new technologies, new information can be gained about biological behavior and prognosis of the tumor concerning the response to current therapy modalities as well as for the development of new therapies.

Gastric cancer of the sporadic type has three major contributing factors. The current concept recognizes the trigger of *Helicobacter pylori* infection, specific host susceptibility, including familiary factors, and environmental influences. Completely distinct is the development of hereditary gastric cancer with familial association where a single gene mutation is responsible.

Hereditary gastric cancer

Hereditary genetic alterations are rare and reported in the literature to be associated with 5% of all gastric cancer cases with the majority of these being of the diffuse type according to Barber et al. [7]. The causative germ line mutation has been identified to be *CDH1*, the *e-cadherin* gene. Endoscopic surveillance has not been successful in sufficiently protected subjects with the *CDH1* gene mutation, and therefore the option of prophylactic gastrectomy has been offered as the best available therapeutic management. In families with *CDH1* gene mutation, gastric cancer has been identified in 76.5% to 100% of the resected specimens after prophylactic gastrectomy [8–10].

Mutation of the *e-cadherin* gene represents an initial step in the process of downstream gene activation leading towards further enhancement of proliferation and cancer formation. A malfunction of the e-cadherin/β-catenin complex frees β-catenin from the cell membrane and provides a higher cytoplasmatic pool, activating the Wnt-dependent signaling pathways that play a major role in gastric carcinogenesis [11]. By this and the β-catenin-related activation of T cell factor-dependent transcription, a cascade is orchestrated including several target genes like cyclins and matrix metalloproteinases that are relevant for the initiation of invasive gastric cancer [12]. The mutation of the *CDH 1* is of the recessive type with one allele being altered and the other subsequently being inactivated directly in the gastric tissue either by hypermethylation, somatic mutation, and loss of heterozygosity, intragenic deletion, or specific polymporphisms. However, alterations of the *CDH 1* gene are reported not only for hereditary gastric cancer. Hypermethylation of the *CDH 1* promoter can be detected in 40–80% of all primary gastric cancer [13].

Sporadic gastric cancer

Sporadic cancer accounts for 95% of all cases. It has a complex pathogenesis, in which several factors are involved including a familial risk and environmental factors. The key player is the *H. pylori* infection.

H. pylori

H. pylori—the epidemiological evidence

Infection with *H. pylori* is the major risk factor for the development of gastric cancer, and medical intervention represents the best option for prevention of the disease [14]. In 1994, the WHO classified *H. pylori* as class I carcinogen based mainly on epidemiological evidence for its role in the pathogenesis of gastric adenocarcinoma and has been reinforced in the more recent WHO contribution by the IARC in 2010 [15]. The prevalence of *H. pylori* infection varies among populations with rates up to 80% and is still high (40–50%) in people over 50 years of age in many Western countries.

First substantial evidence was obtained from animal studies on Mongolian gerbils, where *H. pylori* is a complete carcinogen that is capable of inducing gastric adenocarcinomas without the influence of any cocarcinogens [16, 17]. There were also hints for the multifactorial etiology of gastric cancer, when supplementation of the animals with nitrosamines lead to higher rates of cancer incidence and a more rapid carcinogenesis [18, 19].

Numerous studies attempted to assess the attributable risk of *H. pylori* infection for gastric carcinogenesis in the human system. In 2003, the *Helicobacter* and Cancer Collaborative Group combined data from all available case–control studies nested with prospective cohorts to assess more reliably the relative risk for gastric cancer. In this study, 1,228 patients were included and a clear association of *H. pylori* infection to non-cardia gastric cancer (OR 3.0; 95% CI 2.3–3.8) was reported. This association was even stronger when blood samples for *H. pylori* serology were obtained 10 years or longer before cancer diagnosis (OR 5.9; 95% CI 3.4–10.3) [20]. A possible explanation is the loss of *H. pylori* colonization in the presence of atrophic gastritis and IM, so that gastric cancer patients have a loss of anti-*H. pylori* antibodies at the time of disease manifestation.

Another meta-analysis from Asia analyzed 19 studies with approximately 2,500 gastric cancer patients and almost 4,000 matched controls resulting in an OR of 1.92 (95% CI

1.32–2.78) for the development of non-cardia gastric cancer in *H. pylori* positive patients [21] which was in concordance with a previous similar analysis [22].

For a more meticulous assessment of the *H. pylori*-attributable risk for gastric carcinogenesis, bacterial virulence factors had been taken into consideration for risk analysis. Several studies have shown that the risk of gastric cancer is influenced by the presence of the CagA, and moreover, antibodies to CagA persist longer in the serum. Ekström reported an increase of the *H. pylori*-attributable OR for non-cardia cancer from 2.2 to 21.0 if the CagA status was co-evaluated by immunoblot analysis [23]. In this analysis, 71% to 91% of gastric cancer in the studied population was attributable to *H. pylori* infection. A meta-analysis by Huang and colleagues revealed a further 1.64-fold increase of gastric cancer risk for CagA-positive strains compared to CagA-negative ones (16 studies, n=5,054) [24]. Again, the lower risk is due to the loss of antibodies in advanced stage gastric cancer. In fact, in patients with early gastric cancer, the prevalence of *H. pylori* antibodies is much higher compared to individuals with advanced gastric cancer resulting in a different attributable risk [21]. Further relevance is given by the time of serum sampling. The associated OR for gastric cancer development in case of *H. pylori* infection is significantly higher if serum samples are taken within 90 days after tumor gastrectomy [25].

While most studies claim that *H. pylori* infection is only related to distal gastric cancer, we could recently demonstrate a high prevalence also in patients with proximally located adenocarcinomas. Approximately 80% of patients with proximal gastric cancer revealed positive evidence for an actual or past infection with *H. pylori* if correct allocation of the primary tumor is performed and adenocarcinomas of the distal esophagus are strictly excluded [26]. Finally, the risk for gastric carcinogenesis by *H. pylori* infection is equal in intestinal and diffuse type gastric cancer [26, 27].

H. pylori and bacterial virulence factors

Several bacterial virulence factors define the malignant potential of each *H. pylori* strain. The best investigated factor is the cag pathogenicity island (PAI) type IV secretion system that can induce a more severe inflammatory response and can increase the risk for gastric carcinogenesis [28–30]. This type IV secretion system is a prerequisite for translocation of pathogenetic virulence factors (e.g., CagA) of *H. pylori* into the epithelial cell [31, 32]. CagA is rapidly phosphorylated by host Src-kinases and has subsequently the potential to change intracellular signal transduction and to disrupt epithelial cell junctions [33, 34]. The injected CagA leads to activation of the Ras-mitogen-activated protein kinase (MAPK) pathway, involving the Ras-dependent kinases ERK-1 and ERK-2, with further transactivation of host-related pathways [35–37]. CagA-dependent activation of the Ras-Erk cascade increases also IL-8 release and consequent NF-κB activation responsible for invasion of neutrophil granulocytes into the gastric mucosa [38]. NF-κB-related carcinogenesis is enhanced by *H. pylori*-associated release of tumor necrosis factor-α-inducing protein (Tip-α) inducing high expression of TNF-α with further involvement of IL-8 and COX-2-dependent pathways [39, 40]. Interaction of CagA with the e-cadherin/β-catenin system can lead to a direct transactivation of *CDX1* and by this to metaplastic changes in the mucosa [41]. CagA is further thought to contribute to epithelial–mesenchymal transition, a hallmark of epithelial-derived carcinogenesis [42, 43].

Although the EPIC study has shown that the increased risk for gastric cancer in case of a positive CagA status is independent from environmental factors like diet, smoking habits, or body mass, recent data suggested that CagA expression can be increased under a high-salt diet leading also to increased IL8 secretion [44, 45]. Furthermore, it has been shown that genetic diversity of the *Helicobacter* plays an important role in *H. pylori*-driven carcinogenesis. Once injected in the host cell, CagA is phosphorylated at certain glutamate-isoleucine-tyrosine-alanine (EPIYA) motifs. Due to variations in the surrounding amino acid sequence, four distinct EPIYA-motifs are described (EPIYA-A, -B, -C, -D) [46, 47]. Prevalence of these motifs varies by region. They further influence the CagA-induced immune response as well as the related cancer risk. The odds ratio (OR) for gastric cancer development is 7.37 (95% CI 1.98–27.48) in case of one EPIYA-C segment and 32.5 (95% CI 8.41–125.58) in case of two or more segments [48].

A similar diversity has been identified for the vacuolating cytotoxin A (VacA) showing variations in its gene structure which can be divided into a signaling (s), a middle (m), and an intermediate (i) region [49]. After first identification of s1/m1 strains showing a higher attributable risk for gastric cancer development, more recently also, i1 strains have been demonstrated to be associated with not only dysplastic but also malignant invasive tissue formation [48, 50].

VacA has an inhibitory effect on GSK3β- (glycogen synthase kinase 3-β)-regulated signaling pathways by phosphorylation through an Akt/PI3K- (phosphatidylinositol-3-kinase) mediated pathway, which leads to a β-catenin release and furthermore modulation of apoptosis- and cell cycle-regulation [51, 52].

The outer-membrane protein BabA is expressed by 40–95% of the *H. pylori* strains, in dependency of the geographic region [53]. Patients infected with a BabA positive strain show a higher density of bacterial colonization in the stomach and have an enhanced inflammation due

to increased IL-8 levels [54]. *H. pylori* strains expressing all three genes (CagA, VacA, BabA) are associated with the highest risk for developing gastric cancer [55].

For a comprehensive review on further virulence factors of *H. pylori* and their interaction with intracellular signaling and host immune response mechanisms, see the article from Wroblewksi et al. [49].

Inflammatory response in the gastric mucosa

The inflammatory response to infection with *H. pylori* of the gastric mucosa is complex. A key role in the immune response to *H. pylori* and in the complex pathogenesis of *H. pylori*-related diseases is taken by regulatory T cells (Treg), mostly $CD4^{+}CD25^{+high}$ Treg [56].

Treg are associated with increasing bacterial colonization [57], chronic inflammatory changes [58, 59], and the expression of immuno-suppressive cytokines like IL-10, IL-17, and TGF-β [60, 61]. Eradication therapy of *H. pylori* infection leads to a significant reduction of Treg cells and corresponding cytokine levels in gastroduodenal mucosa [59]. In case of gastric cancer, numbers of Treg cells are increased both in the gastric mucosa and the peripheral blood [62–64]. Notably, the ratio of Th1/Th2-derived cytokines is the highest in asymptomatic gastritis showing a steady decrease in gastric atrophy, intestinal metaplasia and intraepithelial neoplasia towards gastric adenocarcinoma. This is associated with a concomitant increase of the Treg cell compartment in the peripheral blood and the persistence of CagA positive strains favoring a Treg cell-mediated chronic inflammation [64].

A retrospective immunohistochemical study found increased numbers of FOXP3-expressing $CD4^{+}CD25^{+}CD117^{low}$ Treg cells associated with vascular, lymphatic, and perineural invasion of gastric tumor cells. Higher numbers of Treg cells were correlated with advanced tumor stage and correlated negatively with overall survival of these patients [65].

Host factors

Gene polymorphisms of immune response genes

Genetic alterations of factors that modulate and mediate the inflammatory response to *H. pylori* infection have been suggested to play a major role in the development of gastric cancer. Among these are cytokine genes (e.g., *TNF-α*, *IL-10*, *IL-8*, *IFN-γ*) involved in the adaptive immune system [66–68] and pattern recognition factors (*TLR-4*, *NOD-1, NOD-2*) initiating the innate immune system [69, 70]. Furthermore, variation of genes encoding for proteases [71], xenobiotic metabolism enzymes [72], cell cycle regulators [73, 74], mucins [75], HLA-molecules [76], and DNA-repair enzymes [74, 77] have been reported to bear an increased risk for gastric cancer (Fig. 1).

IL-1β is the most powerful proinflammatory cytokine produced in response to *H. pylori* infection, known to act also as a strong acid inhibitor on a molecular basis [78]. About a decade ago, it has been postulated that carriers of specific single nucleotide gene polymorphisms (SNPs) in the *IL-1β* gene or the gene of the IL-1-receptor antagonist (*IL-1RN*) have an up to fourfold increased risk for developing gastric cancer [79]. Numerous studies in various ethical groups have been published since and revealed conflicting results.

In a meta-analysis by Kamangar and colleagues, including 35 studies with about 5,500 patients and more than 7,800 controls, a decreasing association of these polymorphisms with gastric cancer risk was shown for the accumulative data until 2006 [80]. The OR for developing gastric cancer in case of present *IL-1β* gene-mutation varies from 0.82 to 1.99 depending on the geographic region of occurrence, the histological subtype of gastric cancer, and the genetic locus that is altered [80]. More recent meta-analyses report an increased risk for gastric cancer in case of SNPs of the locus *IL-1β-511 T* and of the *IL-1RN* for Caucasians if an adequate stratification of the included study populations is performed concerning ethnicity [81–83]. We could not confirm this conclusion [84].

Furthermore, a functional relevance with respect to altered gene expression of defined cytokine haplotypes

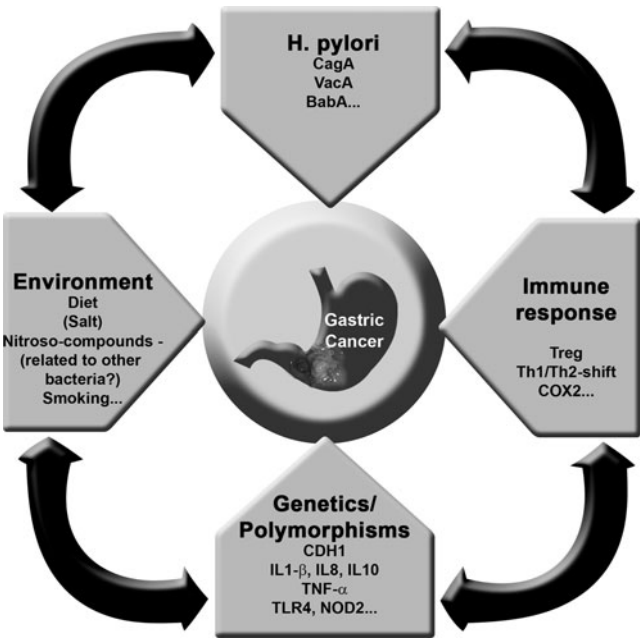

Fig. 1 Risk factors involved in gastric carcinogenesis. Gastric cancer is a multifactorial disease. Host genetic factors are mainly involved in modulation of the patient's immune response to *H. pylori* infection. The increased mucosal proliferation induced by exogen carcinogenic agents represents a further factor. There is a complex interplay between the main risk factors

was demonstrated for *IL-10* [85], *TNF-α* [86], and *IL-8* [87]. The majority of these studies identified significant associations between specific haplotypes and an increased risk for developing gastric cancer. In most cases (except *IL-10*), these cytokine polymorphisms result in a higher secretion of the corresponding cytokine leading to a stronger Th1-dominant immune response (Fig. 2).

A comprehensive review on host polymorphisms of immune-modulatory genes has recently been published by Wex et al. [88].

Interleukin-1β and gastric physiology—interplay with H. pylori

The functional relevance of polymorphisms in the *IL-1β* gene are based on several pleiotropic effects mediated by this cytokine. IL-1β, mostly secreted by macrophages and to a lesser extent by epithelial and dentritic cells, induces the expression of other cytokines such as IL-12, TNF-α, IL-2, and interferons that subsequently shift the immune balance towards a mixed or Th1-predominant inflammation as it is seen in *H. pylori*-mediated gastritis [89–91]. The subsequent infiltration of granulocytes and lymphocytic cells leads to a chronic inflammatory condition that will last as long as the bacterium is colonizing the gastric mucosa. The degree of colonization and gastritis is dependent on various factors, like the presence and activity of regulatory T cells or the initial (naive) parietal cell mass reflecting the acid secretory capacity [60, 91–93]. An additional impact of IL-1β is given by its cytoprotective, anti-ulcerative effects and capability to delay gastric emptying by modulating gastric motility [78]. Furthermore, IL-1β regulates gastrin and histamine levels in the stomach and is capable to inhibit acid secretion from parietal cells [78, 94, 95]. Gastrin itself is important for an intact mucosal homeostasis in the stomach. A complex role in gastric carcinogenesis has been revealed, including the gastrin-induced mediation of proliferation, angiogenesis, and tissue invasion (Fig. 3) [96].

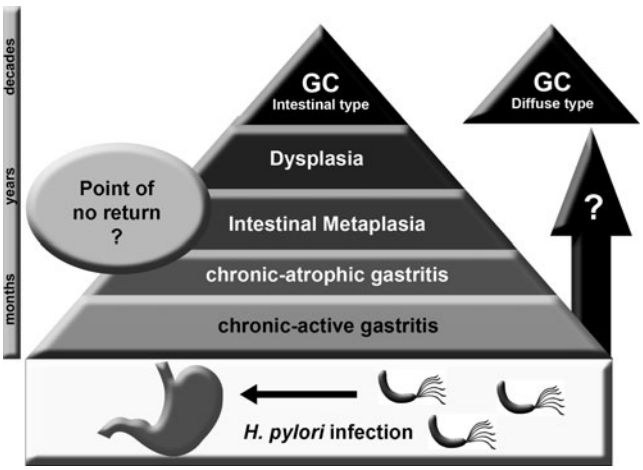

Fig. 2 Schematic image of the Correa-Model. Model of sequential mucosal alterations in the development of intestinal type gastric cancer on the basis of *H. pylori*-driven chronic active gastritis. In contrast to the adenoma-carcinoma sequence for colorectal cancer, order of appearance can be different and certain steps can be missed. A specific sequence leading to diffuse type gastric cancer is not described yet

Figueiredo et al. [97] were the first who explored the relationship between the *IL-1* polymorphisms and bacterial virulence factors. They analyzed different CagA and VacA genotypes of the *H. pylori* strains isolated from patients with gastric cancer or non-atrophic gastritis in context to the presence of the "IL-1 proinflammatory genotype" and identified combinations with either low or high risk, resulting in 6 to 87-fold differences in the OR for gastric cancer.

When *H. pylori* infection is predominantly located in the antrum, the proinflammatory effects of IL-1β contribute to the development focal gastritis at this location. In this case, the acid secretion is mostly unchanged or can even be increased, resulting in "hyperchlorhydria", a condition that predisposes individuals to develop duodenal and gastric ulcer. If *H. pylori* colonization is predominantly located in the corpus of the stomach, the anti-secretory effect of IL-1β leads to a vicious cycle by induction of hypochlorhydria which in turn facilitates the further spreading of *H. pylori* in the corpus and fundus mucosa. The resulting corpus-predominant inflammation goes hand in hand with mucosal atrophy and intestinal metaplasia.

Hwang et al. [98] showed the linkage between the "proinflammatory" genotype and elevated IL-1β levels in human gastric mucosa. In a Japanese study, Furuta and colleagues identified higher atrophic and gastritis scores in *H. pylori*-infected patients with the proinflammatory *IL-1β-511 T/T* genotype and demonstrated an elevation of the gastric juice pH as well as decreased pepsinogen I/II ratios [99]. Additionally, they showed that in the *H. pylori*-negative group, the *IL-1β* genotype did not have any effect on physiological or histological parameters of gastric mucosa [99]. Similar results were reported from Thailand, where the *IL-1β-511 TT* carriers had significantly higher IL-1β levels in their antrum than corresponding controls, also influenced by bacterial factors (e.g., CagA type) [100]. In contrast, data from Korea showed higher mucosal IL-1β levels in patients with "wildtype haplotype" compared to those with "proinflammatory haplotype" [101].

Environmental factors

Alimentary factors and the interaction with H. pylori

Animal studies have proven that ingestion of salt causes gastritis by destroying the mucosal barrier leading to inflammation and damage with diffuse erosions and

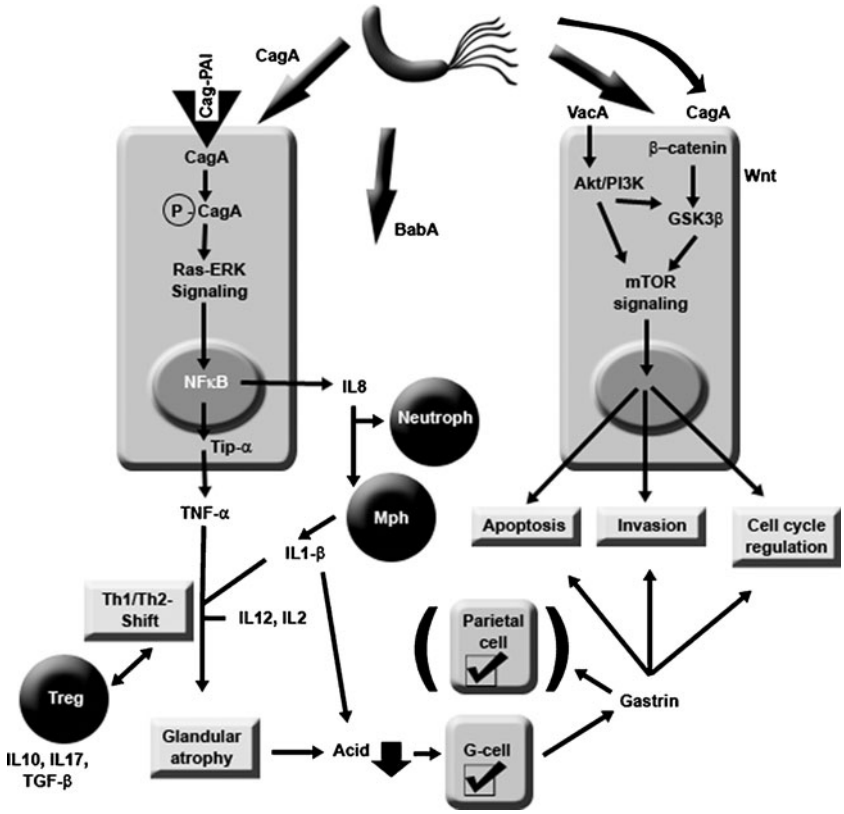

Fig. 3 Overview on basic mechanisms of the mucosal response to *H. pylori*. Certain bacterial virulence factors of *H. pylori* can modulate intracellular signaling in the gastric epithelial cell. The resulting paracrine and endocrine mediators lead to a shift in the inflammatory response and may have a synergistic effect on the alteration of cell cycle regulation and the induction of proliferation and invasive tissue formation

epithelial degeneration [102–104]. The hypothesis tells that this leads to an increase of regeneration processes with the promotion of food-driven carcinogenesis. In 1997, the World Cancer Research Fund and the American Institute for Cancer Research analyzed 16 case–control studies, stating an association between salt or salted food and the risk of gastric cancer [105]. More recent case–control studies confirmed this association [106–109]. However, most studies including the presence of *H. pylori* infection in the analysis demonstrated that a significant effect was only achieved in patients in which the gastric mucosa was already "pre-damaged" by *H. pylori* induced chronic-active inflammation [108, 110]. One prospective study examined the prevalence of gastric cancer in 2,476 men and women and evaluated the salt intake by a 70-item food frequency questionnaire. In this population, 93 cases of gastric cancer were identified, and the strongest effect of a high-salt diet was seen in patients with both *H. pylori* infection and atrophic changes of the mucosa [110].

H. pylori infection reduces the bioavailability of vitamin C, leading subsequently to decreased concentrations in the plasma and gastric juice [111, 112], whereas the luminal concentration of reactive oxygen species is increased [113]. In a randomised controlled trial carried out in Colombia, patients at high risk for gastric cancer were treated after *H. pylori* eradication with a combination of vitamin C and beta-carotene or placebo. In the group with vitamin C supplementation, regression of premalignant lesions was observed [114]. The EPIC (European Prospective Investigation into Cancer and Nutrition) study, a large European prospective study including more than 500,000 participants in ten countries analyzed the association of plasma vitamin C with the risk for gastric cancer development, while taking into account factors like body mass index, total energy intake, smoking, and *H. pylori* status. This study did not confirm an association of vitamin C levels with gastric cancer development [115].

Chronic alcohol abuse is a major health care problem worldwide. More than 40 epidemiological, mostly retrospective studies have been carried out, and they did not confirm an association between chronic alcohol consumption and gastric cancer. Even intake of large amounts of alcohol (more than 200 g per day) was not significantly associated with increased risk for gastric adenocarcinomas, neither was the type of alcohol nor the concentration (percentage of ethanol) [116, 117]. In two prospective studies and four case–control studies, no significant correlation between alcohol consumption and cancer of the gastric cardia was reported [118].

A systematic review analyzed the relation between cigarette smoking and gastric cancer including 42 cohort, case–cohort, and case–control studies. The study provided solid evidence that smoking was significantly associated with an elevated relative risk (RR) for both gastric cardia

(RR=1.87; 95% CI 1.31–2.67) and non-cardia cancers (RR=1.60; 95% CI 1.41–1.80). This conforms with a previous meta-analysis [119] and the results of the EPIC-study which estimated that 17.6% (95% CI 10.5–29.5%) of gastric cancer are related to smoking [120]. In conclusion, smoking seems to be the most important lifestyle risk factor for gastric cancer.

Gonzalez and colleagues recently published a review on the interaction of various environmental, especially alimentary carcinogenic agents with *H. pylori* infection [121]. Concerning smoking of tobacco, the OR for smoking and the development of gastric cancer varied between 1.04 and 9.2 in the studies analyzed, whereas the OR for *H. pylori* infection alone was higher than the OR for smoking in all but one study (OR 1.77–6.93). The OR for the combined presence of both risk factors was highest in all studies (2.3–19.0), although no trial revealed an additive effect, and the statistical analysis for risk factor interaction was negative [121]. The increased risk for gastric carcinogenesis in persons with a high intake of meat (total meat, processed meat, and red meat, OR 1.93–5.32) was demonstrated only in *H. pylori* positive subjects without the statistical term for interaction being positive [122].

Only for high-salt intake, a further direct influence on the risk for gastric cancer development by infection with *H. pylori* could be documented (p for interaction 0.047) [121].

The results for a negative association of high intake of fruits and vegetables with gastric carcinogenesis show especially for the plasma levels of vitamin C, vitamin E, and retinol, a protective effect only for the *H. pylori* positive group, although this interaction could again not be statistically confirmed [115, 123, 124].

Prevention of gastric cancer—clinical evidence

Eradication of *H. pylori* for gastric cancer prevention

It has been demonstrated by a recent meta-analysis that eradication of *H. pylori* has the potential to prevent gastric cancer [125]. In total, data of 6,695 patients were included showing that *H. pylori* eradication reduces gastric cancer risk (relative risk 0.65 [95% CI 0.43–0.98]). Overall, 56 of 3,307 (1.7%) untreated (control) participants developed gastric cancer compared with 37 of 3,388 (1.1%) treated patients.

Most data on the preventive effect of *H. pylori* eradication were generated in high incidence regions in Asia. A retrospective multicenter study from Japan analyzed the gastric cancer incidence in patients after *H. pylori* eradication for a 5-year follow-up in 23 centers including more than 3,000 patients [126]. Out of these, gastric cancer developed in 1% of patients who had been successfully eradicated and in 4% of patients with persistent infection (OR 0.36; 95% CI 0.22–0.62). In an observational study by Uemura et al. [127], gastric cancer developed only in patients infected with *H.* pylori, but not in uninfected. Patients (1,526) with dyspeptic symptoms and an endoscopy-based diagnosis were followed up for 7.8 years. Thirty-six of the *H. pylori*-positive patients (2.9%) developed gastric cancer, but in no case (0%) gastric malignancy was detected among the *H. pylori*-negative patients [127].

In a prospective interventional study from Japan, patients with *H. pylori*-induced peptic ulcer disease have been followed up (n=1,342) for a median of 3.4 years [128]. Eradication therapy was not successful in 15% gastric cancer occurred in 0.8% of the successfully eradicated patients in contrast to 2.3% of patients with eradication failure [128].

The only prospective, randomized, placebo-controlled, population-based primary prevention study has been performed in China [129]. In total, 1,630 healthy individuals were recruited for randomization on either *H. pylori* eradication or placebo treatment. Within a follow-up period of 7.5 years, there have been 18 new cases of gastric cancer, 7 in the eradication group and 11 in the placebo group. Subgroup analysis revealed that all of the six patients with newly diagnosed gastric cancer presented with preneoplastic mucosal alterations (gastric atrophy, IM) at baseline, whereas no case of gastric cancer was diagnosed in without baseline mucosal changes (p=0.02) [129]. This gives the rational to search for the "point of no return" in the cascade of mucosal changes, when eradication of *H. pylori* will have no longer a protective effect to halt further progression of IM and atrophic gastritis towards gastric cancer (Fig. 2) [130].

The point of no return

A prospective observational study from Japan including 1,787 patients for a 9-year follow-up period described the clinical and histopathological characteristics of patients who still develop gastric cancer after eradication [131]. All of these patients presented with severe atrophic gastritis at baseline [131]. The risk for gastric carcinogenesis has been reported to be even increased with a significant correlation to the degree of baseline atrophy [132]. In a prospective study from Japan, 4,655 healthy, asymptomatic individuals have been followed up endoscopically for 7.7 years presenting a Hazard Ratio (HR) for gastric cancer of 7.13 in case of *H. pylori* infection without glandular atrophy, 14.85 if both conditions had been detected and 61.85 if *H. pylori* infection could not be detected any more due to the atrophic changes of the gastric mucosa [133]. It is noteworthy, that infection with *H. pylori* remains the major risk factor for the development of chronic atrophic gastritis [134].

Compared to chronic atrophic gastritis, there is less evidence for the influence of intestinal metaplasia on gastric cancer risk. However, in multiple logistic regression analysis, degree and distribution of IM have also been demonstrated to be independent risk factors for gastric cancer development [135]. A recent nationwide cohort study from the Netherlands, including more than 90,000 participants demonstrated a stepwise increase of gastric cancer incidence within 5 years follow-up and was 0.1% in patients with chronic atrophic gastritis, 0.25% in patients with IM, 0.6% in case of mild or moderate dysplasia, and 6% in case of severe dysplasia at baseline assessment, the latter resulting in a HR of 40.14 (95% CI 32.2–50.1) [136].

H. pylori eradication and reversibility of preneoplastic changes (atrophy, IM)

The degree of IM decreased after eradication therapy in patients endoscopically treated for early gastric cancer in a 3-year follow-up [137]. These results have been confirmed for healthy volunteers in China without any history of malignant disease [138]. Many studies have since been published with several limitations and flaws.

The data about the actual regression of IM or glandular atrophy is controversial. Several authors report an improvement only of inflammation within 1 year after eradication but no effect on the degree of metaplasia or atrophy [139, 140]. Rokkas and colleagues presented a meta-analysis on the long-term effect of eradication therapy on gastric histology [141]. The risk for atrophic gastritis was reduced by 45% in total (OR 0.554 [95% CI 0.372–0.825) and by almost 80% for alterations in the gastric corpus (OR 0.209 [95% CI 0.081–0.538]). An influence on IM could not be confirmed. This was also the case in a recent meta-analysis presented by Wang et al. [142]. The pooled data of the 12 studies analyzed showed that eradication of *H. pylori* led to significant improvement of atrophy in the gastric corpus, but not in the antrum, and to no improvement in IM. However, in this analysis, the degree of mucosal changes is not mentioned, which is crucial since only extensive atrophic alterations impact on gastric function.

It was suggested that the decisive factor whether or not there is an effect of *H. pylori* eradication is the time of follow-up. It has been shown that an improvement of mucosal inflammation can be documented within the first 6 to 12 months after eradication, whereas a follow-up period of more than 1 year is necessary to demonstrate an effect on IM and atrophic changes [143, 144]. Also, the side of biopsy sampling may be an important influencing factor [144]. Other risk factors for progression of IM/atrophy are age, male gender, abuse of alcohol, and drinking water from a well [145].

However, the issue of the necessary time of follow-up is not solved yet, since even after longer control periods, there might be no change or even progression in the degree of IM or atrophic gastritis, which refers one to the unsolved question of the “point of no return” [146].

The chance for prevention

The point of time at which *H. pylori* eradication still has an effect on gastric cancer prevention remains the burning question in this debate. Fukase and colleagues reported recently that even after endoscopic resection of early gastric cancer, recurrence of metachronous gastric cancer is significantly reduced by *H. pylori* eradication [147]. On the other hand, Wu et al. presented a cohort study with 80,255 patients included and came to the conclusion that the earlier *H. pylori* gets eradicated after peptic ulcer disease, the smaller is the risk for gastric cancer. Compared to the general population, patients that received early *H. pylori* eradication have no significant gastric cancer risk. Furthermore, independent protective factors for gastric cancer were identified in the frequent use of nonsteroidal anti-inflammatory drugs and aspirin [148, 149].

In the recently published updated Japanese guidelines for the management of *H. pylori* and related disease, it was finally stated that eradication is useful for the prevention of gastric cancer [150]. However, in case of present mucosal alterations at baseline assessment, a close and effective endoscopic follow-up and surveillance is mandatory, even after successful *H. pylori* eradication [151–153].

One important challenge of the near future is the development of efficient diagnostic tools for the identification of individuals at high risk for gastric cancer development to enable a cost-effective surveillance strategy even in low-incidence areas. The most promising tool is the non-invasive identification of subjects with chronic atrophic gastritis by blood analysis for pepsinogen 1 and 2 as well as the pepsinogen 1/2 ratio [154, 155].

Chemoprevention

The main focus in the issue of chemoprevention of gastric cancer has been on the effect of inhibition of cyclo-oxygenase-2 (COX-2) in the gastric mucosa. Expression of this enzyme is induced in case of gastric cancer development and shows an association to invasive growth, lymph vessel invasion, and nodal involvement, especially for intestinal type tumors [156–158]. Since changes in COX-2 expression can already be detected in early dyplastic lesions, induced by *H. pylori*-driven inflammation, they are considered to be an early event in gastric carcinogenesis and thus a target for prevention [159]. Several case–control and cohort studies have been carried

out on this issue. The largest assessment was performed in the USA by Thun and colleagues who observed more than 650,000 individuals taking aspirin for different reasons for about 10 years [160]. A protective effect against gastric cancer, with an almost 50% reduction of gastric cancer incidence was observed in participants who took aspirin more often than 16 times a month (OR 0.53 [95% CI 0.34–0.81]). Non-aspirin NSAID use was analyzed from the population-based North Jutland prescription database and the Danish Cancer Registry, following more than 170,000 individuals for over 9 years showing a clear trend for gastric cancer risk reduction with reaching statistical significance (OR 0.70 [95% CI 0.4–1.1]) [161]. Several case–control studies confirm these data and an association between duration of aspirin or NSAID intake and gastric cancer risk reduction rose [162]. Even a positive effect on IM regression has been reported for patients on selective COX-2 inhibitors [163]. However, these data have not been transferred into clinical practice due to the reason of cost-effectiveness and drug-induced morbidity, e.g., NSAID-induced gastric ulcer bleeding, which has to be considered as a severe side-effect causing high morbidity and mortality.

Conclusion and a glimpse to the future

H. pylori eradication has proven to be effective in the prevention of gastric cancer and to be even more effective if provided before the development of atrophic changes and IM. A prophylactic vaccine as primary prevention is likely to represent the best strategy to protect from *H. pylori* and its consequences including gastric cancer. From the socio-economic point of view, the use of a prophylactic vaccine is cost-effective, and the vaccine development is more than desirable, especially considering decreasing eradication rates using antibiotic regimens [164, 165]. Animal studies as well as data from first trials on healthy human volunteers revealed promising results that deserve a committed follow-up [166, 167].

Conflicts of interest None.

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