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REVIEW – PATHOGENESIS OF *HELICOBACTER PYLORI* INFECTION

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Abstract: *Helicobacter pylori* is a Gram-negative bacterium that colonizes the human stomach and is considered as the primary risk factor for the development of gastroduodenal pathology, such as gastric cancer and gastric MALT lymphoma. The bacteria-mediated pathogenesis is governed by an interplay between its virulence factors and genetic polymorphisms of the host, as well as environmental factors. Gastric inflammatory response has been characterized as the key element that promotes disease, however, additional new knowledge on underlying mechanisms related to the deregulation of numerous host biological processes have been shown to contribute to pathogenesis over the last 35 years. The present review summarizes some of the most important studies published between April 2020 and March 2021 offering further insight on how *H. pylori* infection can perturb host biological processes such as immune response, gene expression, genome maintenance, cell proliferation, survival and death, as well as the microbiota profile, thus inducing pathogenesis.

Keywords: Colonization, Virulence, Inflammation, Gene expression regulation, Autophagy, Genomic instability, Gastric disease, Carcinogenesis, Microbiota.

INTRODUCTION

Helicobacter pylori infection is the main cause of gastric inflammation and peptic ulcer disease and the primary risk factor for gastric cancer development, inducing chronic inflammatory response favoring continuous injury and repair of gastric mucosa. This is controlled by deregulation of biological processes, such as cell proliferation, apoptosis, inflammatory response, oxidative stress regulation and genome integrity maintenance, leading to alterations of the gastric mucosa genome, cell motility and adherence and thus contributing to carcinogenesis. Expression and activity of specific *H. pylori* virulence factors and genetic polymorphisms that dictate host inflammatory response, as well as environmental factors (e.g., diet, smoking, high salt consumption), seem to determine the clinical outcome and the potential pathogenesis of the infection.

COLONIZATION AND BACTERIAL ADHERENCE

H. pylori selectively colonizes the human gastric epithelium; however, infection seems to occur *via* the oral route, despite the absence of carcino-embryonic antigen-related cell adhesion molecules (CEACAMs) in cells of the oral epithelium[1]. Colonization of the bacterium and resulting virulence can be regulated by numerous bacterial factors, such as Autoinducer-2 (AI-2), a quorum sensing signal molecule, which can suppress the virulence potential when the population is increased, thereby inhibiting bacterial adherence, expression and translocation of CagA and activation of NF-κB signaling pathway and IL-8 expression, thus attenuating inflammatory responses[2]. *H. pylori* colonization, virulence and disruption of the epithelial barrier has been shown to be regulated, in part, by nickel-regulated small RNA (sRNA) NikS which can repress numerous virulence factors, including CagA and VacA, post-transcriptionally, via sRNA-mRNA pairing[3].

VIRULENCE FACTORS AND REGULATION OF VIRULENCE

The aforementioned bacterial and host cell interactions can shape a micro-niche where colonization and virulence properties remain under continuous and dynamic modification, thereby modulating genetic and functional features of *H. pylori* within the same host over time, capable of potentially shifting pathology[4].

The type 4 secretion system (T4SS), among other functions, can also mediate the translocation of microbial DNA, resulting in TLR9 activation, potentially in a HopQ-related manner, as type I hopQ alleles were reported to be associated with T4SS function, TLR9 activation *in vitro*, and the severity of gastric inflammation and damage *in vivo*[5]. Furthermore, HopQ was also reported to contribute to the T4SS-dependent activation of non-canonical NF-κB signaling and CagA translocation and those processes were supported by the HopQ-binding of CEACAM-1, -5 and -6[6]. OipA can also induce virulence, as supported by its impact on IL-8 expression, adherence, apoptosis and cell cycle of gastric epithelial cells, independently of its copy number[7]. CagA virulence factor, upon its intracellular translocation, has been reported to promote further deregulation of biological processes, one of them being IL-6 expression in gastric cells by recruiting protein kinase Cδ (PKCδ) *via* eukaryotic translation elongation factor 1-alpha 1 (eEF1A1) in the cytoplasm, thereby increasing STAT3 phosphorylation at serine 727 (pS727-STAT3) in the nucleus[8]. In addition, more evidence points to the obligate requirement for IL-11 signaling *via* constitutive pS727-STAT3 in Helicobacter-induced gastric carcinogenesis[9]. Src Homology 2 (SH2) domain-containing phosphatidylinositol-5'-phosphatase 2 (SHIP2) was identified as a novel CagA-binding host protein, binding more robustly to the EPIYA-C segment of Western CagA compared to the EPIYA-D segment of East Asian CagA, *via* the SH2 domain, in a tyrosine phosphorylation-dependent manner proportional to the number of EPIYA-C repeats[10]. This interaction is suggested to promote CagA delivery into gastric epithelial cells, which, in turn, potentiates CagA-SHP2 pro-oncogenic interaction and induces the hummingbird phenotype.

Gamma-glutamyltransferase (GGT) was proposed to promote gastric carcinogenesis by activating the Wnt/β-catenin signaling pathway *via* the upregulation of ten-eleven translocation-1 (TET1), a factor already reported to be overexpressed in gastric tissues of *H. pylori*-infected patients and mice and a potential poor prognosis biomarker in gastric cancer patients[11]. The bacterial chaperone and protease high temperature requirement A (HtrA), containing a protease domain and two C-terminal PDZ1 and PDZ2 domains, is known to mediate stress endurance and proteolysis of tight and adherens junctions. While both PDZ domains are dispensable for the chaperone-like activity, PDZ1 seems to be critical for HtrA oligomerization and efficient substrate cleavage, whereas growth of *H. pylori* under stress conditions seems to be regulated by PDZ1, but not PDZ2[12].

Novel reports utilizing *H. pylori* strains producing m2/m1 chimeric VacA proteins, in which segments of the m1 sequence in the parental strain were replaced by corresponding m2 sequences, exhibited decreased binding to the plasma membrane and reduced capacity in promoting vacuolation as well as membrane depolarization or death, compared to that of the parental m1 protein[13]. In addition, both VacA forms were found bound at higher levels to the basolateral surface of organoid monolayers, compared to the apical surface, and caused increased cell vacuolation when interacting with the basolateral surface.

Results from a human volunteer challenge study on the genomic and epigenomic evolution during the first weeks of *H. pylori* infection using a *cag*PAI-negative strain, suggested that the detected genetic changes contained a very high proportion of non-synonymous mutations, in affected genes with surface-related roles as well as in genes important for chemotaxis, motility, transport, outer membrane proteins, or a predicted function in peptide uptake[14]. Interestingly, genome-wide methylomes were also found to be varied in reisolates from the vaccine volunteers, mostly by activity switching of phase-variable methyltransferase genes.

Coccoid forms of *H. pylori* have always been considered as a subpopulation that is metabolically active, but slow-growing and highly tolerant to antibiotics and stress conditions, thereby presenting an important cause of resistance of chronic bacterial infections to therapy. New evidence has emerged that a type I toxin-antitoxin system (AapA1-IsoA1), expressed by *H. pylori*, can cause growth arrest associated with rapid transformation from the spiral-shaped bacteria to coccoid cells, by targeting the inner membrane and probably interfering with cell elongation and division, thereby maintaining membrane integrity and metabolism[15]. Interestingly, deletion of these *H. pylori* gene clusters only delayed the oxidative stress induction of coccoid formation, suggesting that these toxins are probably not the only triggers of coccoid transformation.

IMMUNE RESPONSE

The gastric epithelium responds to *H. pylori* infection by activating and inducing a complex expression of TLRs and pro-inflammatory cytokines, although not all pro-inflammatory cytokines exert the same effect. IFN-γ and IL-1β seem to play a reciprocal role in the induction of gastrin and antral hyperplasia, with Sonic hedgehog and IL-1β signaling requiring primary cilia on G cells to modulate gastrin expression and antral transformation *via* glioma-associated oncogene family zinc finger 2 (GLI2)[16]. *H. pylori* CagA-dependent induction of mTORC1 signaling and upregulation of its feedback inhibitor DEPTOR seem to control production of pro-inflammatory cytokines/chemokines, including TNF-α, IL-1β, IL-6, CCL-7 and CXCL-16, and antimicrobial peptide LL37, thus regulating inflammation and host defense, leading to a decrease in bacterial burden in gastric mucosa, thereby preventing excessive inflammation[17]. Flagellin mutations have been proposed to contribute to evasion of TLR5 activation induced by *H. pylori* infection, which is correlated with the severity of gastric inflammation and malignant progression[18-20]. CagY, which is a T4SS core component, was suggested to be an additional flagellin-independent agonist of TLR5, containing five TLR5 binding sites within its N-terminal domain, thereby promoting adherence, TLR5 activation and intracellular signal transduction[21]. Furthermore, in a CagA-related manner, pro-inflammatory cytokines IL-1β and TNF-α were observed to synergistically induce ETS1 expression during the infection, in an NF-κB-dependent manner, thus promoting the expression of ETS1 transcription factor in gastric epithelial cells[22]. Incidentally, ETS1 was reported to be upregulated in *H. pylori*-infected mice and humans, linking the ETS1 expression to the severity of gastritis.

H. pylori induces an inflammatory response characterized by mucosal infiltration of different cells like polymorphonuclear leukocytes, T cells, macrophages and plasma cells. Infected human and mice gastric epithelial cells seem to exhibit elevated ARRDC3 expression *via* a CagA-mediated activation of ERK and PI3K-AKT signaling pathways, thereby promoting CXCL2 chemokine production *via* lysosomal degradation of PAR1, leading to neutrophil recruitment[23]. Furthermore, chronic active gastritis is associated with an increased $CD4^+/CD8^+$ T cell ratio and accumulation of $CD4^+$ T-helper lymphocytes in the lamina propria. Notch1 signaling seems to be involved in the differentiation of Th1 cells during *H. pylori* infection, since expression levels of Notch1 receptor, its target gene transcription factor Hes-1, the Th1 master transcription factor T-bet and IFN-γ, were found increased in $CD4^+$-T cells from *H. pylori*-infected patients[24]. *H. pylori* infection can also modulate host immune interactions by hijacking dendritic cell (DC) signaling and T-cell response by induction of SOCS3 in DCs *via* an autocrine loop involving the T4SS, TNF-α release and activation of p38 MAP kinase signaling[25]. SOCS3 expression limits *H. pylori*-induced secretion of pro- and anti-inflammatory cytokines by DCs and dampens programmed death-ligand 1 (PD-L1) expression resulting in increased T-cell proliferation. In addition, *H. pylori* cholesteryl glucosides, such as cholesteryl acyl α-glu-

coside (αCAG) and cholesteryl phosphatidyl α-glucoside (αCPG) derived from host cholesterol conversion, were reported as non-canonical ligands for macrophage-inducible C-type lectin (Mincle) receptor and DC immunoactivating receptor (DCAR) C-type lectin receptors[26]. The production of αCAG and αCPG was reported to enhance *H. pylori* virulence promoting inflammation without affecting humoral immune responses. Host TLR2-dependent NLRP3 inflammasome priming, coupled with T4SS-dependent caspase-1 activation, as well as CagL, FlaA and bacterial motility involvement were demonstrated to play a pivotal role in *H. pylori*-induced IL-1β production by neutrophils[27].

The cellular and inflammatory microenvironment is a critical contributor to gastric lymphomagenesis. The potential role of elevated APRIL expression levels during *H. pylori* infection was demonstrated using an APRIL transgenic mouse model of MALT lymphoma as well as human gastric biopsy specimens, to identify APRIL-producing eosinophilic polynuclear cells located within lymphoid infiltrates and tumoral B lymphocytes found to be targets of APRIL[28]. Furthermore, utilizing RNA-Seq-based analysis, *H. pylori* infection has been shown to deregulate the expression of numerous genes including JUN, FOSL2, HSPA1B, SRC, CXCR3, TLR4, TNF-α, CXCL8, CCL2, CCL4, MHC class I and MHC class II molecules, validated at the transcriptional and protein level, thereby modulating a number of processes in B cells, including inflammation, migration, proliferation, survival and death pathways[29]. On the other hand, NLR family CARD domain containing 5 (NLRC5) in macrophages has been suggested to negatively regulate pro-inflammatory chemokine/cytokine responses as well as B cell-activating factor production, thereby acting as a protective mechanism against *H. pylori*-induced gastritis and B-MALT lymphoma development[30].

IMPACT ON HOST CELL GENOMIC INSTABILITY AND CELLULAR SENESCENCE

H. pylori infection predisposes for genomic instability *via* the induction of oxidative and replication stress and a plethora of DNA damages. The introduction of DNA damage in gastric cells requires the activation of a DNA damage response which has been reported to be modulated by the infection. *H. pylori* infection has been demonstrated to increase spermine oxidase (SMOX) expression, thereby promoting H_2O_2 production and increasing oxidative DNA damage and gastric cancer development risk. Using a Smox-deficient mouse model of *H. pylori* infection and employing proteomic analysis in mouse gastric organoids, SMOX expression was demonstrated to significantly enrich cancer pathways, including β-catenin signaling and its activation was also reported in *H. pylori*-infected human gastric organoids[31]. Furthermore, *H. pylori* has been shown to induce the promotion of replication stress and double-strand-break (DSB) introduction via innate immune recognition of the T4SS-delivered metabolite β-ADP-heptose, which activates NF-κB signaling in an ALPK1/TIFA signaling pathway-dependent manner. *H. pylori* produces β-ADP-heptose by a biosynthesis pathway involving the RfaE enzyme and translocates the heptose *via* the T4SS, both being key elements of the aforementioned mechanism[32]. In the same study, *H. pylori* were observed to reside in close proximity to replicating cells in the gastric mucosa of gastritis patients, thereby promoting replication stress and DNA damage *via* the formation of R-loops, as a result of the above-described β-ADP-heptose/ALPK1/TIFA/NF-κB signaling. The activation of phosphorylated histone H2AX (γH2AX) and checkpoint kinase 2 (CHEK2) is an important stage during DNA damage response. Using *in vitro* and *in vivo* experimental infection systems, the activation of γH2AX and CHEK2 during *H. pylori* infection was related to the upregulation of RNF43[33]. Potential loss of RNF43 function in gastric cells could impair DNA damage response, apoptosis and favor tumor resistance during DNA damage-inducing therapy. Employing RNA-Seq-based analysis in an *in vitro* experimental *H. pylori* infection system, the deregulation of numerous DNA damage repair (DDR) genes was demonstrated, leading to a potential attenuation of base excision repair and mismatch repair and a more intricate deregulation of nucleotide excision repair, homologous recombination (HR) and non-homologous end-joining (NHEJ)[34]. Furthermore, it was suggested that CagA can act as a significant compromising factor of DDR, as it can contribute to the downregulation of a notable number of critical DDR genes, including NTHL1, MUTYH, FEN1, RAD51, POLD1 and LIG1, observations that were also reported at the protein level. The CagA-related decrease in RAD51 was also reported by two other studies proposing two different underlying mechanisms. In the first, CagA is postulated to be involved in the

upregulation of the lncRNA SNHG17 which perturbs miR3909/RING1/RAD51 and NONO pathways resulting in decreased RAD51 levels[35], thereby shifting repair of DSBs from HR towards the error prone NHEJ. In the second study, *H. pylori* infection is thought to inhibit autophagy, in a CagA-related manner, subsequently resulting in an accumulation of autophagic substrate p62 which directly promotes RAD51 ubiquitination, attenuating DDR and thus promoting genomic instability and potentially carcinogenesis[36]. The infection-dependent downregulation of NEIL2 highlighted its suppressive role in inflammation and accumulation of oxidative DNA base damage[37]. Moreover, gene expression analysis of gastric biopsies underlined that NEIL2 downregulation in early gastric cancers is correlated with poor prognosis. Furthermore, an analysis of gastric tissues from *H. pylori* positive patients at successive stages of gastric pathology and cancer, showed that PMS2 and ERCC1 protein levels are substantially decreased in epithelial cell nuclei, both at early and late stages of *H. pylori*-induced gastric carcinogenesis[38]. *H. pylori* infection *via* the CagA-dependent activation of PI3K/AKT signaling pathway induces the phosphorylation of XIAP E3 ubiquitin ligase and thus promotes proteasomal degradation of Siva1 apoptosis inducing factor thus inhibiting apoptosis and DNA damage response[39].

The induction of gastric atrophy in the context of *H. pylori* infection was proposed *via* the promotion of cellular senescence regulated by the CXCR2[40]. In fact, an investigation of human and mouse gastric precancerous lesions and gastric epithelial cell lines demonstrated that CXCR2-mediated cellular senescence is critically regulated by TP53-P21 signaling and the formation of a potential positive feedback loop between CXCR2 and TP53 can enhance senescence in gastric mucosa.

H. PYLORI INFLUENCE ON AUTOPHAGY

Novel links between *H. pylori* virulence factors and autophagy have been reported recently, as already mentioned in the above chapter for CagA[36]. A potential link between autophagy, the promotion of epithelial-to-mesenchymal transition (EMT) and the emergence of gastric cancer stem cells (CSC) during *H. pylori* infection, was proposed, as both the CD44 gastric CSC marker and the LC3 autophagy marker were observed increased in *H. pylori*-infected murine stomachs[41]. In addition, *H. pylori*-infected gastric cancer cell lines treated with autophagy inhibitors revealed the critical involvement of autophagy in the development of EMT-like and CSC properties. Furthermore, it was suggested that *H. pylori* infection can regulate the elimination of damaged mitochondria, through association of pS727-STAT3 induction with LC3 mitochondrial accumulation and consequent autophagosome sequestering in the infected gastric epithelial cells, thus maintaining homeostasis or promoting inflammation and disease, depending on the mitophagy extent[42]. Since conflicting evidence between inhibitory or enhancing effects of autophagy by *H. pylori* is presented in the publications cited above, this apparent discrepancy should be resolved or explained in future studies.

EPIGENETIC REGULATION AND NON-CODING RNA RESPONSE IN HOST CELLS

H. pylori infection has been shown to induce aberrant DNA hypermethylation, an effect increasing the oncogenic potential. CagA was reported to promote cell proliferation, migration and colony formation, as well as to enhance DNA methylation of the KLF4 gene promoter, thereby inhibiting KLF4 tumor suppressive activity and suggesting a link with TET1 downregulation[43]. Caudal type homeobox 2 (CDX2) promoter methylation was shown to be increased in *H. pylori* infected non-cancerous gastric mucosa by age, while the promoter is demethylated in intestinal metaplasia, dysplasia and gastric cancer[44]. Furthermore, increased expression of neuritin 1 (NRN1), a gene suggested to be involved in the tumor developing processes through its role in hypoxia, angiogenesis, apoptosis, and proliferation, was associated with NRN1 promoter hypomethylation in advanced stage tumors and the presence of *H. pylori* infection[45]. The infection has also been shown to induce silencing via hypermethylation of the cholinergic receptor muscarinic 2 (CHRM2) and miR490-3p, leading to enhanced expression of DARPP-32, activation of PI3K/AKT and JAK2/STAT3 signaling pathways which can promote chemotherapy resistance in gastric cancer patients[46].

The contribution of lncRNAs in *H. pylori*-associated carcinogenesis remains poorly understood. Using an RNA-Seq-based analysis of *in vitro* infected gastric epithelial cells, the consistent deregulation of 298 mRNAs and 73 lncRNAs was reported and verified by qRT-PCR[47], including RELB, SLC7A11, lncRNA51663 and FLJ46906 in accordance with their increased expression levels in gastric cancer tissues. Furthermore, OipA-dependent *H. pylori*-induced gastric mucosal injury was suggested to be mediated by inhibition of cystine-glutamate transporter (xCT) activity, via the upregulation of miR30b[48]. Another report also suggested that upregulation of TET-targeting miRNAs, such as miR20A, miR26B, and miR29C, in the context of Helicobacter-triggered chronic gastritis, can induce a deleterious combination of TET repression and increased DNMT activity, leading to a synergistic effect on the induction of aberrant DNA methylation[49]. Finally, novel data suggest that in the context of *H. pylori* infection, observed overexpression of miR18a-3p and miR4286 can suppress benzodiazepine receptor-associated protein 1 (BZRAP1) expression and thus favor cancer development and progression[50].

INFLUENCE ON HUMAN CELL PROLIFERATION, SURVIVAL AND MOTILITY

A study using a mouse model of infection showed that sustained *H. pylori* colonization of gastric mucosa can induce urokinase-type plasminogen activator receptor (uPAR) expression[51], a factor known to control, through cross-talk with tyrosine kinase receptors, the shift between tumor dormancy and proliferation which usually precedes metastasis formation. Mining data from The Cancer Genome Atlas and Gene Expression Omnibus, has identified protogenin (PTRG) upregulation as a poor prognosis marker in gastric cancer and a key mechanism during *H. pylori*-mediated carcinogenesis, which involves the stabilization and recruitment of EMT transcription factor ZEB1 to the PRTG promoter, thereby activating cGMP/PKG signaling pathway and promoting proliferation, metastasis and chemoresistance[52]. Moreover, *H. pylori* infection, in a CagA-related manner, was reported to activate the NF-κB signaling pathway, resulting in the upregulation of LIN28A which, in turn, leads to let-7a suppression, a subsequent increase in the expression of its target molecule human telomerase reverse transcriptase (hTERT), thus promoting telomerase reactivation and favoring carcinogenesis[53]. Moreover, hTERT was shown to induce gastric cancer cell proliferation and LIN28A expression, forming a positive feedback regulation between hTERT and the NF-κB/LIN28A/let-7a pathway, thus maintaining the hTERT upregulation in gastric cancer. *H. pylori* infection was also proposed to induce SET domain bifurcated histone lysine methyltransferase 1 (SETDB1) expression via binding of the transcription factor 4 (TCF4) to its promoter, thereby inducing gene expression and the formation of a complex between SETDB1 and the ETS transcription family factor ERG and affecting downstream expression of cyclin D1 (CCND1) and matrix metalloproteinase 9 (MMP9)[54]. Furthermore, consistent with increased proliferation, invasion, migration and anchorage-independent growth, was the observation that *H. pylori*-infected gastric epithelial cells as well as metastatic gastric cancer tissue, exhibited increased expression and phosphorylation of E3 ubiquitin ligase seven in absentia homolog 2 (SIAH2), at serine 6 and threonine 279 residues, which was mediated by the interaction with Myotonic dystrophy kinase-related Cdc42-binding kinase beta (MRCKβ) which, in turn, was ubiquitinated resulting in its proteasomal degradation[55]. Finally, *H. pylori* infection was shown to induce, in a CagA-related manner, the transcriptional co-activator with PDZ binding motif (TAZ) expression and activity resulting in ZEB1 upregulation, EMT promotion and acquisition of invasive and cancer stem cell-like tumorigenic properties[56].

Cancer associated fibroblasts (CAFs) are activated fibroblasts that are considered to favor gastric cancer progression. *H. pylori* infection has been reported to activate human stomach fibroblasts and induce gene alterations, including vascular adhesion molecule 1 (VCAM1). Moreover, the infection, through the JAK/STAT1 signaling pathway, was shown to upregulate VCAM1 in CAFs within gastric carcinoma and its expression levels were positively associated with lymph node metastasis, TNM stage and poor prognosis[57].

Colonization by *H. pylori* was demonstrated to induce EMT in human cholangiocytes, with concomitant changes in levels of mRNA expression of EMT-encoding factors including snail, slug, vimentin, MMPs, zinc finger E-box-binding homeobox and the CSC marker CD44, as well as increased migration and invasion by the cholangiocytes[58].

INTERPLAY WITH THE MICROBIOTA AND ENVIRONMENTAL FACTORS

An increasing number of studies support the idea that infectious agents should not be considered as single entities, but as a complex dynamic interplay between the resident microbiota and the host, since microbiota can be modified by an infection, as well as shape critical elements of pathogen virulence, such as, in the case of *H. pylori*, downregulation of T4SS function[59]. In this respect, the common loss of T4SS function observed during *H. pylori* infection of mice, gerbils, non-human primates and even humans, was reported to be dampened in a mouse co-infection model, by systemic *Salmonella* sp. infection and completely abolished by dietary iron restriction[60]. Furthermore, studies on Helicobacter-infected mice with different genotypic backgrounds have highlighted that genotype differences could define the microbiota diversity of the stomach and affect the risk for the development of gastric cancer upon Helicobacter infection[61]. In addition, enterohepatic *Helicobacter* species seem to be able to trigger persistent inflammation, oxidative DNA damage and dysbiosis in IL-10$^{-/-}$ mice leading to colon cancer development[62]. Finally, 16S ribosomal RNA gene analysis in paired gastric biopsies and stool samples, has demonstrated that *H. pylori* infection can result in reduced abundance and richness in the resident microbiota, as well as a higher microbial dysbiotic index, in *H. pylori*-positive mucosa and lesions such as intestinal metaplasia or dysplasia[63]. More importantly, successful eradication of *H. pylori* infection can lead to the reversal of the aforementioned indices, thereby pointing towards restoration of the gastric microbiota to a similar status of *H. pylori*-negative individuals.

CONCLUSIONS

Despite the declining incidence of *H. pylori* infection in the Western world, the infection still remains one of the most common worldwide, with a major public health impact to society and health economics. Currently, the attention on *H. pylori* virulence mechanisms has oscillated more toward the mechanisms induced on the host side, including carcinogenesis signaling events, probably also reflecting the intensified search for host-directed therapeutic and prophylactic potential. Since infections are an important and preventable cause of cancer, implementation of available vaccination strategies as one major arm of prophylaxis could be widely supported. However, in the case of *H. pylori* infection there is no vaccine available yet, and vaccine success is probably hampered by both bacterial genetic and epigenetic evasion mechanisms as well as by the impeded host response. Moreover, well-documented evidence suggests that successful *H. pylori* eradication can arrest or reverse pre-malignant changes in the gastric mucosa, albeit hampered by increasing frequency of eradication failure due to the emergence of antibiotic resistance. Therefore, the continued investigation into the mechanisms and factors governing *H. pylori* pathogenesis are worthwhile and will hopefully lead to the development of more targeted and personalized therapeutic or preventive tools to reduce the burden of the disease.

Conflict of interest

The authors have no disclosures of interest.

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