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VISIONS AND REFLECTIONS

Helicobacter pylori infection and gastric cancer biology: tempering a double-edged sword

Alexios-Fotios A. Mentis[1,2] · Marina Boziki[3] · Nikolaos Grigoriadis[3] · Athanasios G. Papavassiliou[4]

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Abstract

Helicobacter pylori (*H. pylori*) infection affects an estimated 4.4 billion people globally. Moreover, *H. pylori* presents the most significant risk factor for gastric cancer and low-grade mucosa-associated lymphoid tissue (MALT) lymphoma, and it is the first example of bacterial infection linked to carcinogenesis. Here, we contend that *H. pylori* research, which focuses on a cancer-causing pathogen resident in a relatively accessible organ, the stomach, could constitute an exemplar for microbial-related carcinogenesis in less tractable organs, such as the pancreas and lung. In this context, molecular biological approaches that could reap rewards are reviewed, including: (1) gastric cancer dynamics, particularly the role of stem cells and the heterogeneity of neoplastic cells, which are currently being investigated at the single-cell sequencing level; (2) mechanobiology, and the role of three-dimensional organoids and matrix metalloproteases; and (3) the connection between *H. pylori* and host pathophysiology and the gut microbiome. In the context of *H. pylori*'s contribution to gastric cancer, several important conundrums remain to be fully elucidated. From among them, this article discusses (1) why *H. pylori* infection, which causes both gastric and duodenal inflammation, is only linked to gastric cancer; (2) whether a "precision oncomicrobiology" approach could enable a fine-tuning of the expression of only cancer-implicated *H. pylori* genes while maintaining beneficial *H. pylori*-mediated factors in extra-gastric tissues; and (3) the feasibility of using antibiotics targeting the microbial DNA damage system, which shares commonalities with mechanisms for human cell replication, as chemopreventives. Additional therapeutic perspectives are also discussed.

Keywords *Helicobacter pylori* · Gastric cancer · CagA protein · DNA damage · Stem cells · Mechanobiology

Introduction

As one of the most "successful" pathogens in terms of causing infection to humans, *Helicobacter pylori* (*H. pylori*) affects an estimated 50–60% of the world's population or an estimated 4.4 billion people globally in 2015 [1, 2]. It is a common cause of treatable conditions, such as dyspepsia and peptic ulcer disease. Since the turn of the century, the prevalence of *H. pylori* infection has declined in industrialized countries and plateaued in developing and newly industrialized countries. In the 1980s, Warren and Marshall made the landmark discovery (with earlier indirect indications from Lykoudis) [3] that *H. pylori* causes gastric ulcers, which led to a "paradigm shift" challenging axiomatic beliefs that microbial populations cannot survive in the gastric pH-intensive environment. More recent discoveries of urease- and pH-sensing BabA adhesin have provided clues to the underlying mechanisms for *H. pylori*'s ability to withstand the gastric environment [4].

Helicobacter pylori infection is also a critical risk factor for gastric cancer, contributing to approximately 75% of all gastric cancer cases, as well as to low-grade mucosa-associated lymphoid tissue (MALT) lymphoma, a subcategory of primary gastric lymphoma, which accounts for approximately 30–40% of extranodal lymphomas in total [5]. Gastric cancer has remained a significant commonly

✉ Athanasios G. Papavassiliou
papavas@med.uoa.gr

1 Department of Medical Microbiology, Public Health Laboratories, Hellenic Pasteur Institute, Athens, Greece

2 Department of Microbiology, University Hospital of Larissa, University of Thessaly, Larissa, Greece

3 Department of Neurology, AHEPA University Hospital, Aristotle University of Thessaloniki, Thessaloniki, Greece

4 Department of Biological Chemistry, Medical School, National and Kapodistrian University of Athens, 75 Mikras Asias Street, 11527 Athens, Greece

diagnosed form of gastrointestinal malignancy [6]. Although morbidity and mortality from gastric cancer have decreased in the past few decades, gastric cancer remains the third leading cause of cancer for both men and women worldwide [2], constituting a global health problem. Thus, considerable efforts are focused on *H. pylori* eradication in vulnerable patients, with the goal of eliminating gastric symptoms and preventing the development of gastric cancer. This strategy has shown signs of success: for instance, the decrease in *H. pylori* infections in Japan is believed to have contributed to a decline in gastric cancer cases [2]. However, the cause of an increase in gastric cancer in young population in the USA (notably, young Hispanic men), where overall the incidence of *H. pylori* infection is also waning, is unexplained [7]. Thus, unknown factors likely unrelated to *H. pylori* infection may be contributing to a rise in gastric cancer in specific populations, further complicating the perplexing etiology of the disease.

Intensive research is focusing on the elucidation of the molecular mechanisms for *H. pylori* infection and its contribution to gastric cancer to advance diagnostics, preventions, and therapies, with the gastric cancer arena hallmarked by recent cutting-edge findings [8, 9]. Moreover, *H. pylori* research can serve as an exemplar for studying a cancer-causing pathogen that is resident in the relatively accessible stomach, which may provide insights into the mechanisms for microbial-related carcinogenesis in less tractable organs, such as the pancreas and lung.

Herein, we discuss recent trends in the understanding of *H. pylori* and its connection to gastric cancer, namely: (1) how gastric cancer evolution dynamics can be affected by the interplay between the number of stem cells in a tissue and DNA mutational burden, and how *H. pylori* may impact this dynamic; (2) the mechanobiology of gastric cancer, from matrix metalloproteases to the potential of three-dimensional (3-D) organoids; (3) the association of *H. pylori* with the microbiome and the host; and (4) the therapeutic perspectives potentially gleaned from these current trends.

Gastric cancer dynamics

Cancer dynamics and evolution in gastric tumors

Gastric neoplasms are characterized by a high degree of heterogeneity, which makes it challenging to identify which therapeutic agents should be brought to clinical trials [10]. Gastric adenocarcinoma, which comprises diffuse, intestinal, and well-differentiated subtypes is responsible for approximately 90% of gastric cancer cases [10]. Moreover, gastric cancer comprises four molecular subtypes, each of which involves distinct sets of molecular players and pathways. These subtypes are: (1) Epstein–Barr virus (EBV)-positive tumors that possess PIK3CA mutations and PD-L1/2 amplifications (interestingly, patients with EBV-positive gastric tumors have higher survival rates [11]); (2) genomically stable tumors with mutations in genes encoding E-cadherin and RHO-family GTPase-activating proteins; (3) tumors with microsatellite instability and high mutation rates that impact oncogenic proteins 3; and (4) tumors with chromosomal instability giving rise to aneuploidies (as detected by intestinal histology), mutations in TP53, and focal amplifications of Ras proteins [10, 12]. We have also previously highlighted the need to consider the BRCA1- and BRCA2-defective subgroups of gastric cancer [13].

Elucidating the molecular characteristics of a patient's tumor in the context of cancer dynamics and evolution could provide diagnostic information to inform therapeutic actions. Molecular profiling techniques such as single-cell exome and transcriptome analysis and spatiotemporal gene expression analysis could reveal the extent to which a gastric cancer tumor is synchronous or metachronous, which could be relevant to treatment [14]. Moreover, determining whether the phenotype subtype of a gastric cancer tumor is epithelial or mesenchymal could inform the clinician how to target the most relevant molecular pathways. The epithelial subtype is associated with higher mutation and survival rates and a better response to chemotherapy, but with lower sensitivity to inhibition of the IGF1/IGF1R pathway than the mesenchymal phenotype subtype [15].

Determining the critical stage at which differentiated cells become proliferative in gastric metaplasia, as assessed through human stomach biopsies, could similarly be informative for diagnostics [16]. This staging could be accomplished by analyzing human stomach biopsies to (1) identify the stages at which differentiated cell structure degradation occurs as a result of decreasing mTORC1 activity and massive up-regulation of lysosomes and autophagosome; (2) detecting metaplasia- or progenitor-associated gene induction; and (3) identifying points of cell cycle re-entry through reactivation of mTORC1 (a process called "paligenosis") [16].

A recent study applied phylogenetic techniques coupled with sequencing approaches to determine factors that contribute to the localization of intraepithelial neoplasia in another glandular epithelial tissue, the pancreas [17]. The authors concluded that pancreatic intraepithelial neoplasia is not necessarily spatially localized, but can spread through the entire ductal system. This observation helps to explain why pancreatic cancer is such a highly recurrent disease, especially when incomplete removal of pancreatic tissue (i.e., a subtotal pancreatectomy) is applied [17]. Analysis of additional patient samples is needed to determine the characteristics of precursor lesions presenting the highest risk of transformation [17], information that could potentially

be useful in the diagnosis and treatment of gastric cancer as well.

Heterogeneity of cancer predisposition in gastric tissue

The cancer risk of a particular tissue has been suggested to depend on the number of stem cell divisions that occur in the lifetime of that tissue [18]. Vogelstein and colleagues have proposed a model whereby the key factors in cancer etiology are mutations occurring during normal DNA replication, along with heredity and environmental and lifestyle factors [19]. In the model, the number of cell divisions that a tissue undergoes during its lifetime determines the extent to which mutations accumulate during DNA replication. The authors suggest that this phenomenon explains the extreme variation in cancer incidence that occurs in different tissues. It would be intriguing to explore whether this model explains the stomach's and duodenum's differing susceptibility to adenocarcinoma, despite both regions being exposed to *H. pylori* infection. The model proposed by Vogelstein suggests that the different number of stem cell divisions that each tissue undergoes determines the mutation and therefore cancer risk, which could be assessed by quantifying cell divisions in each tissue using the leucine-rich repeat-containing G-protein-coupled receptor 5 (Lgr5) biomarker (as discussed below).

Alternatively, physiological factors that vary along the length of the stomach and pylorus such as differences in oxygen concentration, pH, mucus, and nutrient availability could play a role in determining regional cancer susceptibility. In this case, therapeutic targets could be identified by determining which molecular pathways are over- and underactivated or expressed by assaying differences in the pH between the duodenum and stomach, similar to the studies of the hypoxia–HIF1 axis for breast cancer [20]. *H. pylori* genes involved in pH regulation and nickel transport have been shown to be highly expressed in gastric infection [21]. Moreover, the expression of the *H. pylori* type IV systems secretion plasticity zone cluster has been shown to be influenced by adherence and pH and its composition impacted by differential gastric IL-8 secretion [22]. These pieces of evidence align with a model proposed by Sáenz and Mills that suggests the gastric epithelium responds to injury imposed by gastric acid secretions by cellular plasticity and reprogramming: The resulting cycles of differentiation and de-differentiation then leads to an accumulation of cancer-predisposing mutations [23]. On the other hand, the pyloric environment is more alkaline, which may lead to a diminished risk of cancer because of a reduced need for tissue regeneration and the associated DNA replication stress [24, 25].

Stem cells and their biomarkers in gastric cancer

Stem cells drive the daily renewal of epithelial tissue such as the gut epithelium. As shown in Fig. 1, gastric cancer is believed to arise from genetic mutations and chromosomal aberrations that occur in epithelial cells as a result of environmental and lifestyle factors. *H. pylori* infection is one such contributing factor. In the past two decades, the role of stem cells in driving tumorigenesis has attracted increasing attention as a result of improvements in stem cell markers and Cre-mediated cell lineage-tracing techniques, which have facilitated the identification of cells of origin for various types of cancers [26, 27].

The Lgr5 receptor, whose biological ligands are R-spondin proteins, has garnered particular interest because of its role as a marker of homeostatic stem cells and reserve cells in multiple tissues [28]. Lgr5 may represent a promising pathological marker for gastric cancer to identify precancerous lesions or distinguish between synchronous and metachronous cancer, a topic of recent importance [14]. The stomach lining contains $Lgr5^+$ stem cells that mark a population of reserve stem cells termed "chief cells" that reside at the base of the corpus glands of the gastric epithelium [29]. Ablation of $Lgr5^+$ cells in the mouse corpus glands has been shown to disrupt epithelial homeostasis, suggesting that chief cells play a pivotal role in maintaining the homeostatic stem cell pool in this tissue, and that they represent the cell of origin for gastric tumorigenesis [29]. Understanding how *H. pylori* interacts with the chief cells could reveal previously unidentified mechanisms for gastric carcinogenesis.

Another study has suggested that gastric cancer stem cells originate from bone marrow-derived cells that migrate to the gastric epithelia [30]. Recent advances in single-cell-sequencing technology could enable lineage-tracing studies to elucidate the extent to which gastric stem cells originate from chief cells and bone marrow-derived cells.

Mechanobiology

Three-dimensional (3-D) organoid cultures for analyzing *H. pylori* interactions with gastric tissue during tumorigenesis

A major critique of in vitro cancer studies has been the two-dimensional character of cell lines they have usually employed [31]. Recently, developments in 3-D organoid cultures have enabled a more comprehensive mechanobiological (i.e., 3-D) perspective into studies of organ development and carcinogenesis. Such studies have illuminated the role of $Lgr5^+$ cells in 3-D organoids derived from gastric epithelia [32], gall-bladder [28], and intestine [33].

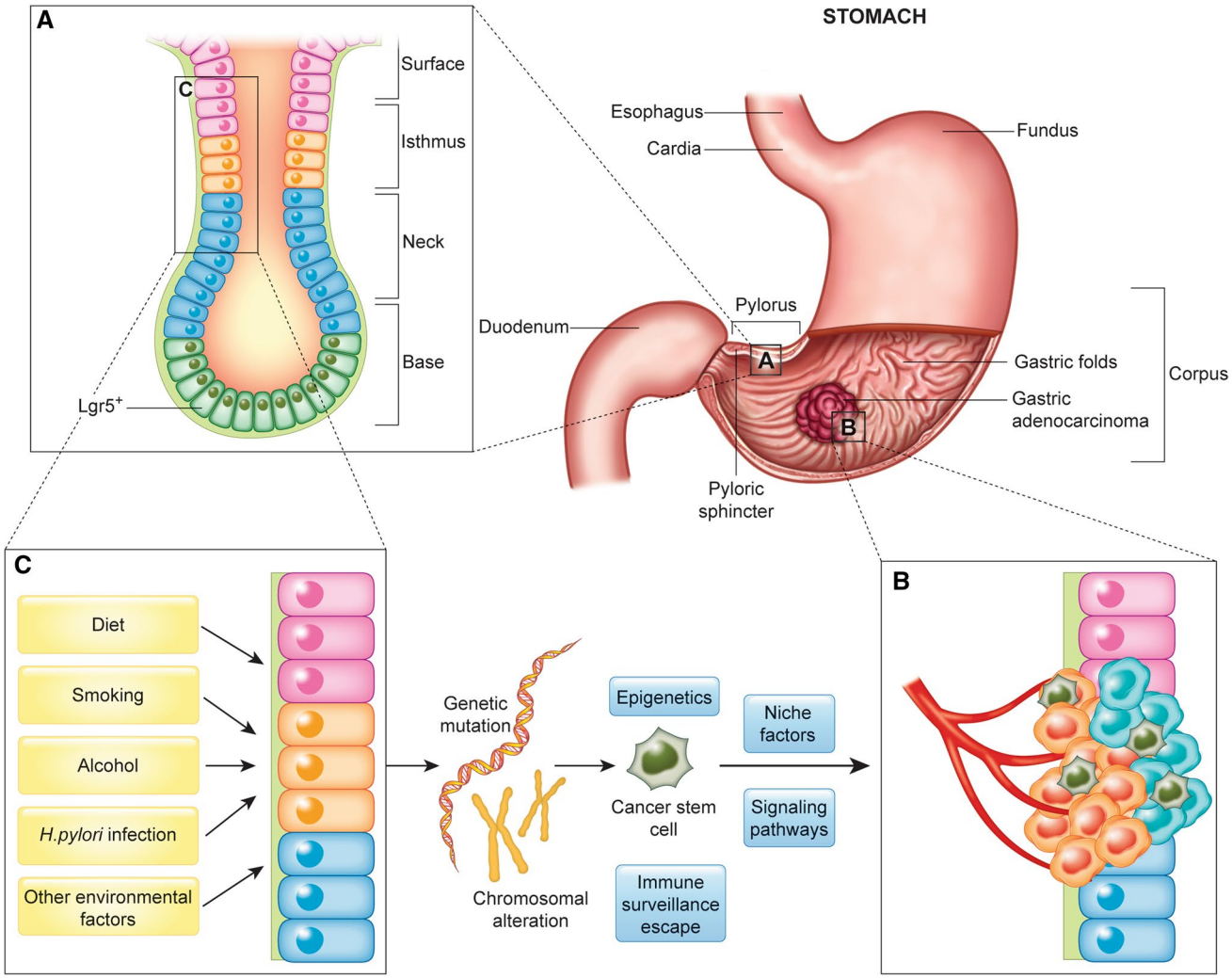

Fig. 1 The development of gastric cancer as induced by *H. pylori* and other factors. Diagram of stomach (top right) with boxes indicating the epithelial layer of the stomach lining (**a**, expanded view in the top left) and a gastric adenocarcinoma (**b**, expanded view in the bottom right). Epithelial cells of the stomach lining (inset A and top left) are transformed to gastric cancer stem cells that form tumors (inset **b** and bottom right). Multiple factors (yellow boxes in **c**, bottom left), including *H. pylori* infection, can induce the chromosomal damage and genetic mutations that give rise to cancer stem cells (bottom middle). The cancer stem cells' unique properties (blue boxes, bottom middle) mediate cell proliferation, immune surveillance escape, and vascularization, all of which promote tumorigenesis (adapted and modified from Ref. [89], © 2017, with permission from Springer Nature)

Such a system has recently been used to study the mechanisms by which *H. pylori* contributes to gastric cancer and the importance of *H. pylori* long-range interactions with gastric tissues. Sigal et al. [34] used lineage tracing in a mouse model of *H. pylori* infection to show that *H. pylori* induces R-spondin in myofibroblasts underlying the antral glands, thereby promoting proliferation of an $Axin2^+$ $Lgr5^+$-progenitor cell residing at their base. They then reconstituted these interactions in epithelial organoid cultures containing primary myofibroblasts [34]. This model system and others will provide further insights into the mechanisms by which *H. pylori* activates long-range induction of gene expression in myofibroblasts, as reviewed by Waskito et al. [35]. More recently, researchers have developed organoids containing gastric primary cells that can be viable for more than 1 year and that express $Lgr5^+$, $MUC5AC^+$, and combined cytokeratin- and E-cadherin-positive cells. The prolonged *H. pylori* infection of the organoids led to the creation of cellular vacuoles and cytokine overproduction [36].

Organoid cultures have been further employed to study the interaction of primary tumor epithelia with tumor-infiltrating lymphocytes [37]. This system might offer mechanistic clues, at the molecular level, for the lower efficacy of immunotherapy observed so far in gastric cancer [38], with the exception of the microsatellite-unstable gastric cancer

that appears to be particularly vulnerable to this therapy [12].

Matrix metalloproteases and mechanobiology

Matrix metalloproteases are molecules that function in the extracellular matrix, and thus have implications for pathological processes attributed to tissue disruption such as the "leaky vessels" phenomenon [39], the "leaky gut" in the context of sepsis [40, 41], increased blood–brain barrier permeability upon CNS autoimmune inflammation [42, 43], and local invasion as well as distant metastasis of tumors [44, 45]. Recently, researchers have identified additional roles for matrix metalloproteases in intrinsic cell functions that regulate cell differentiation and survival. For example, the presence of MMP-9 was found to mediate HER2 oncogene transcription in gastric cancer cell lines, thereby promoting tumor malignancy [46]. The newly acknowledged nuclear localization of matrix metalloproteases implies that they play a role in activating apoptotic cell death pathways [47]. On the other hand, Zhao et al. [48] showed by CRISPR/Cas9 gene editing—a technique with high potential to transform medical research (reviewed, among others, in [49])—that translocation of *H. pylori's* CagA into the host is mediated by specific carcinoembryonic antigen-related cell adhesion proteins, but not integrins, the receptors that mediate cell–ECM adhesion.

As reviewed by Ladoux and Mege [50], studies of the mechanobiology of gastric tissue could provide a rationale for the observations that gastric cancer prevalence varies among different regions of the stomach, with cancers arising in the corpus potentially caused by mechanisms distinct from the other regions [51]. Extracellular matrix adhesion molecules may contribute to the regional propensities for cancer within the stomach; thus, it will be worth investigating the extent to which adhesion molecules differ at the tissue and stomach sub-regional level (e.g., the antrum, cardia, or non-cardia areas).

Comparative studies of extracellular matrix adhesion molecules could provide a further mechanistic rationale for the elastic properties of the gastric epithelium. For example, certain matrix metalloproteases, notably the gelatinases (MMP-2 and MMP-9; the latter investigated as a drug target in gastric cancer) have three fibronectin repeats in their catalytic domain [52], which have long been associated with collagen specificity [53]. How the action of these MMPs differ in *H. pylori*-mediated gastric neoplastic mechanisms compared to other homologs lacking the fibronectin module, such as MMP-10 [54] and MMP-3 [55], is yet to be resolved.

In the context of reproducibility in science, the subject of recent calls to action [56], measurements obtained from several methods assessing cell mechanics have been found to differ by up to 1000-fold, highlighting the need for more consistently reproducible results in this field [57]. However, a recent study reporting the heterogeneous elasticity of curved epithelial sheets that enclose pressured lumens may complicate such efforts [58]. Such epithelial tissues, which include the stomach, were found to comprise "superelastic materials" resistant to extreme levels of strain. Although the overall tissue layer maintains a uniform tension, the superelastic tissues themselves are highly heterogeneous at the cellular level, which could confound efforts to measure the mechanical properties of such tissues.

H. pylori and its interaction with stomach microbiome and the host tissue

H. pylori in the microbiome and biofilm studies

The mechanisms by which *H. pylori* colonizes humans and mediates histologic, physiological, immune, and microbiologic features of the gut have attracted considerable interest. A recent study [59] has shown that a stable colonization of *H. pylori* in mice over a 6-month period resulted in an increased expression of immune response genes that was conserved across the mice for a sustained duration in the stomach, as well as transiently in the lungs. The infection led to the emergence of different structures of microbial populations within the stomach and intestines. Collectively, these data indicated that *H. pylori* influences host immune responses and the microbiota of not only the stomach, but also of distal organs [59].

Helicobacter pylori has been shown to influence the composition of the gastric microbiome, and it is correlated with the presence of species from the *Campylobacter*, *Sulfospirillum*, and *Deinococcus* genus [21]. Interestingly, the presence of *H. pylori* and *Campylobacter concisus* has been shown to be mutually exclusive, with *H. pylori* mediating protective effects in inflammatory bowel disease [6]. On the other hand, among the gastric microbiomes observed, *H. pylori* seems to play a predominant role, reducing the microbial diversity in the region [60, 61].

The success of *H. pylori*'s survival in the stomach depends on the organism's chemotactic motility, ability to produce urease, and its resistance to a constantly changing environment (reviewed in [62]). While the importance of biofilms in *H. pylori* colonization is yet to be determined, they may enable its survival under changing conditions. Biofilms are defined as bacterial communities that are associated with surfaces and embedded within an extracellular matrix containing extracellular polymeric substances. They contribute to an infection becoming chronic or recurrent, promote inflammation, and can make bacterial colonies resistant to antibiotics and the immune system [62].

Given that inflammation plays a pivotal role in gastric carcinogenesis and that *H. pylori* has beneficial effects on extra-gastric tissues, it may be therapeutically effective to fine-tune the presence of *H. pylori* in its active state in tissues where it is beneficial and target its inflammatory role in tissue where it is harmful. This strategy could align with studies that have shown the anti-inflammatory action of probiotics and other alimentary factors such as Mastiha gum against *H. pylori* [63]. Honey and yogurt consumption have also been shown to be associated with reductions in *H. pylori* and anti-CagA IgG seroprevalence, presumably because of honey's antimicrobial actions and yogurt's pro- and pre-biotic activities [64]. It would be intriguing to decipher if these effects can be attributed to biofilm activity, considering that quorum-sensing ability of biofilms can control microbial population density.

H. pylori and host tissue response

One of the crucial components of *H. pylori* is the CagA protein. CagA is part of the cag pathogenicity island, which encodes a secretion system that translocates CagA into the target cell after *H. pylori* attaches to a eukaryotic host cell. After translocation, CagA localizes to the inner surface of the cell membrane where it is phosphorylated on a tyrosine residue by Src family kinases (i.e., *Fyn* and *Lyn*). The CagA gene promotes the epithelial–mesenchymal transition, which is mediated by the effects of CagA's EPIYA polymorphism on phosphorylation [55]. Notably, Weinberg and colleagues [65, 66] have shown that the epithelial–mesenchymal transition is linked to carcinogenesis through generation of stem cell-like cells (also reviewed in [67]).

These findings have been corroborated in the clinical arena: a recent meta-analysis concluded that individuals with a $CagA^+$ H. $pylori^+$ status have an elevated risk of gastric cancer, compared to those with $CagA^-$ *H. pylori*$^+$ status [68], suggesting that the CagA protein plays a role in gastric cancer in adults. The CagA protein also activates NF-κB by interacting with the tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, epsilon (YWHAE, a member of 14-3-3 family protein) [69]. Interestingly, expression of CagA in *Drosophila* intestinal stem cells has been shown to promote dysregulation of the gut microbiota, resulting in cellular proliferation in the insect's gut epithelium [70].

Another way in which *H. pylori* interacts with the host is by injecting CagA into eukaryotic cells using its type IV secretory apparatus [71]. Type IV competence pili are a conserved mechanism for horizontal gene transfer that mediates DNA internalization by binding to DNA at their tip and then retracting [72]. The type IV secretion systems of Gram-negative bacteria mediate a range of biological functions, including exchanging genetic material with other bacteria and inserting oncogenic DNA and effector proteins into eukaryotic host cells [73].

Intriguingly, *H. pylori* and the plant pathogen *Agrobacterium tumefaciens* share some similarities, such as the ability to integrate their DNA into eukaryotic host cells by the type IV system. *A. tumefaciens* infection causes cancer-like malformations in plants called crown galls [74]. In the case of *H. pylori*, this DNA integration is followed by its recognition by the Toll-like receptor 9 [75]. It would be interesting to determine whether in the context of *H. pylori* infection of human cells, the type IV secretion system mediates sharing of DNA through such a CagA protein-mediated mechanism. Moreover, it would be interesting to determine if any of the integrated genes play a functional role in gastric cancer [76].

Although the importance of horizontal gene transfer in eukaryotes remains controversial, genomic studies have begun to reveal numerous cases of bacterium-to-eukaryotic gene transfers that may have influenced adaptive evolution in eukaryotes [74]. Donor bacterial species and recipient eukaryotic hosts appear to be more numerous than previously believed [74]. Future interdisciplinary studies comparing *H. pylori* infection to that of *A. tumefaciens* and other bacteria capable of integrating DNA into eukaryotic hosts may unravel the intriguing mechanism shared by human cancers and other cell-proliferative phenomena such as plant crown galls.

In the evolution *H. pylori*'s diverse effects on human health, the CagA protein is Janus-faced: on one hand, it promotes gastric cancer and peptic ulcers, and on the other it protects against gastro-esophageal reflux and Barrett's esophagus, a precancerous condition in the esophagus (for a review of other genes with such contradictory effects see [67]). Both the harmful and beneficial effects are theorized to trace back to the Copper Age [77]: indeed, the *H. pylori* is considered a microbial marker of human migration [78]. A better understanding of the mechanisms by which CagA exerts a protective effect in one tissue and a virulent effect in another could suggest strategies to enable the exquisite control of CagA expression. Such control could benefit patients by enabling therapeutics that balance both its beneficial and harmful activities, encapsulating the "double-edged sword" relationship of *H. pylori* with human health and disease. On the other hand, little is known about the extent to which CagA benefits the survival of the bacterium, even though it may come at the cost of the host's survival. In this vein, Klymiuk et al. [60] have suggested that CagA expression influences *H. pylori* proliferation within the stomach. Hence, in light of CagA's importance for *H. pylori* pathogenicity, elucidating the survival advantages that CagA gene offers to *H. pylori* strains may be informative.

Recent studies have shown that in addition to CagA-mediated pathogenic mechanisms, *H. pylori* also recruits the host's cellular machinery to circumvent the host's defense

and effectively colonize the gastric mucosa. For example, although *H. pylori* lipopolysaccharides (LPS) bear similarities to those of most bacteria, the structural and chemical properties of *H. pylori* LPS appears to be tolerogenic, as it allows its recognition by the host via the TLR2 receptor system, in contrast to the more common TLR4 system recruited by most bacteria [79]. This property may reduce the immunogenicity of *H. pylori*, since the TLR2 pathway mediates a relatively weak host innate immune response and acquired T cell-mediated immunity in the gastric mucosa. Moreover, under specific circumstances, *H. pylori* LPS antagonistically interferes with TLR4-mediated signaling, thus further ameliorating the host's innate response toward the bacterium [80].

Therapeutic perspectives: from bench to bedside

Since an *H. pylori*-positive status seems protective against diseases such as asthma and gastro-esophageal reflux, clinicians may eventually use genomic or transcriptomic information from *H. pylori* clinical isolates to inform clinical actions [81]. For example, therapeutic strategies could be designed to eliminate the expression of cancer-implicated *H. pylori* genes while maintaining expression of those found to be beneficial to extra-gastric tissues, an approach we propose calling "precision oncomicrobiology", in alignment with precision medicine approaches [82]. Genotypic differences also need to be considered, given that *H. pylori* strains have been shown to exhibit significant genetic variation stemming from mutations and recombination events [35].

Given advances in technologies for assessing cellular DNA damage, we contend that DNA damage should be monitored in patients with *H. pylori* infection, in parallel with determining their inflammatory status [83, 84]. At least theoretically, it may be possible to simultaneously prevent gastric cancer and eradicate *H. pylori* by targeting similar molecular, cellular, or genomic mechanisms. The topoisomerase enzyme is a potential example. On the one hand, bacterial topoisomerase is targeted by quinolones, which are used for *H. pylori* eradication in regions with high levels of clarithromycin resistance such as Europe [85] as well as in resource-poorer settings [86]. On the other hand, eukaryotic topoisomerase inhibitors are well-established anti-cancer drugs that may contribute to lower genomic instability [87].

The extended collection of gastric cancer organoids that is becoming available provides an opportunity to screen large numbers of compounds for anti-cancer effects, as well as to glean initial clues for what drugs could most effectively be repurposed for applications in gastric cancer. Promising compounds may include cyclin-dependent kinase 4 and 6 inhibitors used in breast cancer treatment, cancer cell stemness inhibitors such as napabucasin, and ATR (ataxia–telangiectasia and Rad3-related) inhibitors [88].

Conclusions

Since its first description by Warren and Marshall, *H. pylori* has inspired intensive investigations to better understand its interactions with the human host at the cellular and molecular level and in the context of its pathogenicity. Its ability to promote gastric cancer is especially intriguing and warrants further investigation to understand the underlying mechanisms and why some tissues are more susceptible to *H. pylori*-mediated carcinogenesis than others. Answering these questions may not only inform strategies for gastric cancer treatment and prevention, but thinking of *H. pylori* as a more generalizable "role model" for microbially induced carcinogenesis may lead to breakthroughs in the study of other forms of cancer in which microbes may play unrecognized, but critical roles.

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