

The Landscape of *Helicobacter pylori*-related Gastric Carcinogenesis

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ABSTRACT

The relationship between *Helicobacter pylori* (*H. pylori*) and humans remains a complex enigma. While other factors contribute to gastric cancer (GC), their impact pales in comparison to the central role of *H. pylori*. Various cofactors, such as dietary carcinogens and Epstein-Barr virus infection, can lead to GC independently of *H. pylori*. However, it is likely that the combination of mechanisms, especially those driven by *H. pylori*, represents the primary force behind GC development. Identifying individuals at high risk of developing *H. pylori*-related GC or detecting the disease in its earliest stages remains a significant challenge. To address this, we aim to refine the existing gastric carcinogenic model by incorporating molecular data, oncological concepts common to many cancers, and data from innovative experimental approaches. This updated model, applicable to both intestinal and diffuse GC, builds on Pelayo Correa's carcinogenesis pathway while expanding our understanding of *H. pylori*'s role in gastric carcinogenesis. It not only emphasizes the direct cellular effects of *H. pylori* virulence factors but also integrates underrecognized carcinogenic mechanisms, including the interactions between *H. pylori* and stem cells, providing a more comprehensive view of *H. pylori*'s contribution. By acknowledging additional molecular drivers in GC and recognizing *H. pylori*'s potential involvement in these processes, this model could offer more precise interpretations of GC development and open new avenues for clinical interventions.

Key words: *Helicobacter pylori* – gastric cancer – carcinogenesis model – molecular mechanisms – stem cells.

Abbreviations: GC: gastric cancer; HDGC: hereditary diffuse GC; *H. pylori*: *Helicobacter pylori*; HR: homologous recombination; NH: non-homologous recombination.

INTRODUCTION

The relationship between *Helicobacter pylori* (*H. pylori*) and humans remains an enigma to be deciphered. The infection of human stomachs was described 40 years ago [1]. Usually, this infection is harmless, starting in childhood and lasting for the whole life unless treated [2].

Unfortunately, some patients develop gastric cancer (GC) as a consequence of disrupting this peaceful or minimally harmful relationship. Epidemiological studies estimate that approximately 90% of GC cases are attributable to *H. pylori* infection. However, the

underlying reasons for the disparity between the high prevalence of *H. pylori* infection and the relatively lower incidence of GC, as well as the observed decrease in *H. pylori* abundance within the gastric microbiota in GC cases compared to benign conditions, remain poorly understood [3].

The ability to identify patients at higher risk of developing *H. pylori*-related GC or even during the initial steps of this process is a big challenge [4]. Correa's cascade, a seminal work published over forty years ago, stands as a beacon in our understanding of gastric carcinogenesis [5]. Its enduring relevance for clinical translation is underscored by its alignment with clinical and molecular data, which were yet to be available at its inception.

Describing steps that anticipate the fully developed GC created the basis for current prevention and early diagnosis measures. Nevertheless, among these patients harboring pre-neoplastic lesions [6], the majority will never develop GC. Utilizing severity scores to classify these pre-neoplastic lesions minimizes their unpredictability while requiring high-quality endoscopic and pathologic reports [7-11]. Conversely, in some

individuals, the GC emerges without clinically identifiable lesions [12].

By revisiting the gastric carcinogenic model and incorporating oncological concepts applied to most human cancers, molecular data, and experimental innovations, we aim to deepen our comprehension of *H. pylori*-driven GC and enhance clinical intervention possibilities [13-17]. This approach holds promise for identifying higher-risk patients, facilitating early diagnosis, and mitigating the GC burden.

The model is feasible for both intestinal and diffuse GC and, beyond supporting the carcinogenesis pathway proposed by Pelayo Correa, promotes insights that may pave the way for establishing broadly available clinical innovations.

Although additional etiological factors for GC exist beyond the "centered on the role of the *H. pylori* model", their impact on GC burden is comparatively weaker. Several co-factors such as dietary carcinogens [18], Epstein-Barr virus infection [19], bile reflux [20], and auto-immune gastritis [21, 22], among others, can lead to GC, even independently of *H. pylori* infection. However, the combination of mechanisms, primarily those attributed to *H. pylori*, will likely be the driving force behind GC [12, 23]. The proposed model remains flexible and can incorporate additional factors while maintaining scientific rigor.

HELICOBACTER PYLORI'S ROLE IN GASTRIC CANCER

Stem Cells as the Origin of the Cancer

The recognition of stem cells as the origins of human cancers is widely accepted [24-27]. The necessity of accumulating many molecular driver events to allow a cancer to develop turns mature differentiated cells incapable of generating human cancers since these cells do not survive for enough time nor resist many mutations without being eliminated from the epithelium [16, 28]. Additionally, plasticity and replicative potential are lost during the differentiation process as shown in Fig. 1.

The target cells for *H. pylori* molecular lesions are stem cells with higher replicative potential, extended life, plasticity to generate different cell types, and the ability to accumulate the necessary driver mutations without discharge [29-33].

Beyond its known capacity to survive in the superficial layer of gastric mucosa, *H. pylori* can also penetrate the gland deeply and form colonies near the stem cell niche (Fig. 2), reinforcing the hypothesis of stem cell origins of *H. pylori*-induced gastric carcinogenesis [29-31, 33]. As we delve into these interactions, numerous fascinating discoveries illuminate this complex relationship. Moreover, *H. pylori*, which is located deep in the glands, has been observed in additional clinical scenarios, including among long-term proton pump inhibitors (PPI) users (personal observation by R. G. unpublished), whose clinical importance must be explored.

The interactions between *H. pylori* and stem cells have been documented, resulting in cell proliferation [34]. Additionally, as discussed below, *H. pylori* may induce stem cell DNA damage [14].

Some strains of *H. pylori* can inject the CagA protein and potentially other metabolites into host stem cells, a pivotal

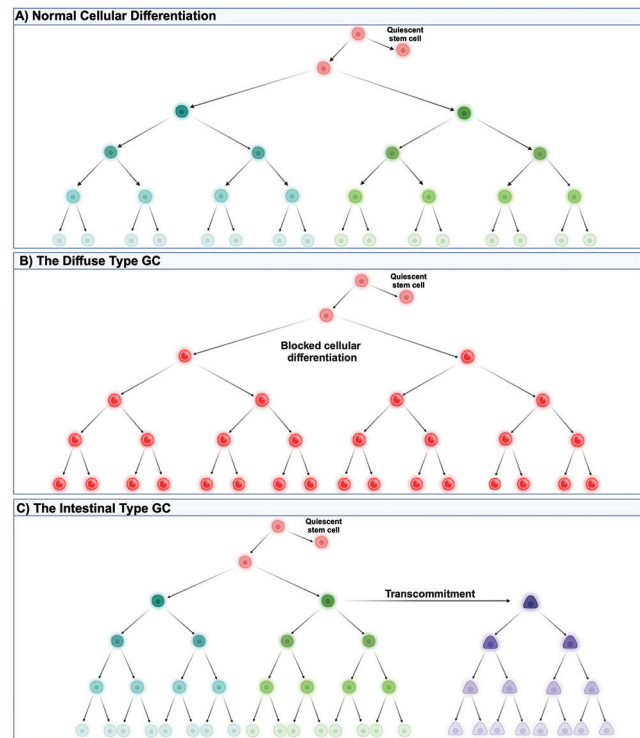


Fig. 1. Cellular Differentiation: Normal, Diffuse type GC, and Intestinal type GC scenarios. A) Normal: Red circles represent stem cells that can generate multiple types of cells (represented by different colors) due to their high plasticity. Along the proliferative process, the daughter cells gain specialization, becoming committed to generating specific types of cells, losing plasticity, longevity, and resistance to destruction. The terminally differentiated cells lack the capabilities to sustain the cancer process. B) Instead of becoming progressively differentiated the daughter cells remain with a phenotype characterized by lacking features of specialized cells. This lack of differentiation is typical of the diffuse type of GC. C) Progenitor cells that should be committed to generating specialized gastric cells instead give rise to specialized intestinal-type cells resembling intestinal metaplasia. This reproduces the mechanism proposed by Correa, as seen in the intestinal type of GC. Created with Biorender.com.

mechanism in developing GC. This process triggers the activation of oncogenic pathways, leading to proliferation and the induction of DNA double-strand breaks and genomic instability [14, 33, 35, 36]. Among the consequences of injected metabolites, the ADP-heptose activation of NF κ B pathways produces pro-inflammatory cytokines that favor proliferation and the acquisition of genomic instability [33, 37, 38].

Additionally, the injection of CagA by the TSS4 injection system blocks the Par1b phosphorylation of *BRCA1*, which will stay in the cytoplasm. Lack of *BRCA1* in the nucleus impairs the correction of double-strand breaks by homologous recombination (HR), resulting in non-homologous recombination (NH) corrections that are error-prone and may give rise to driver mutations and trigger the carcinogenic process. These miscorrected errors should activate other controller mechanisms, avoiding the persistence and propagation of such errors. However, impairment of these controller mechanisms turns the cell tolerant, resulting in unstable genomic cells that are non-discarded [14, 39].

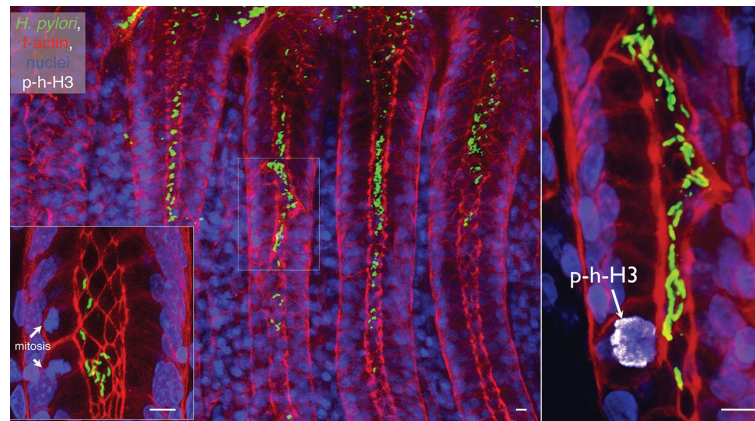


Fig. 2. *H. pylori* colonize and interact directly with the progenitor and stem cell compartments of the human gastric glands. Confocal reconstruction of human antral glands stained to visualize *H. pylori* (green), the host actin cytoskeleton (red), and nuclei (blue). *H. pylori* colonize the proliferative zone of antral glands and interact with the surface of dividing epithelial cells (white arrows) and stem cells. Cells in mitosis are marked in the high magnification insets (mitosis) or stained with anti-phospho-histone H3 antibodies (p-h-H3). Scale bars 10 μ m. C

Therefore, the interaction between *H. pylori* strains and stem cells can provoke lesions in the host DNA. Concomitantly, it impairs the precision corrections of these lesions and allows the persistence of the errors, favoring gastric carcinogenesis [35, 39].

Unlocking Replicative Plasticity

Recently, unlocking replicative plasticity, a feature of stem cells, was included as a new cancer hallmark [40]. This new understanding added other possibilities to the arsenal of cancer pathways, including blockage of differentiation and dedifferentiation.

Regarding gastric adenocarcinoma types, the diffuse tumors should result from stem cell differentiation blockage, which may happen earlier during the differentiation process, leading to the typical histologic undifferentiated phenotype of the diffuse type adenocarcinomas (Fig. 1B).

This early onset may imply the less common appearance of classical pre-neoplastic lesions, contrarily to what is described for the intestinal type GC [41]. Although not generating morphological features during this long-standing process, putative molecular markers can be explored, opening new avenues for prevention and earlier interventions [42].

Accordingly, this differentiation blockage was also demonstrated in other human cancers such as melanoma and, especially, in some acute leukemias in which progenitor cells cannot undergo terminal differentiation [43]. However, in such malignancies, the differentiation blockage can be reverted by treatment interventions [44-48]. Unveiling these molecular mechanisms may be a field for future investigations, resulting in translation to clinical practice as therapeutic alternatives in this aggressive GC.

The intestinal type GC might arise from a transcommitment mechanism when undifferentiated progenitor cells, instead of generating only specialized gastric cells, start to form cells with an intestinal phenotype (Fig. 1C) [49]. Contrary to what happens in the diffuse type GC, this perversion in the

differentiation process results in cells with peculiar phenotypes along the process, allowing their identifications as “pre-neoplastic features” [49, 50]. This cancer mechanism was elegantly described for pancreatic ductal adenocarcinomas, where stem cells that should generate acinar specialized cells, in their place, give rise to ductal cells and favor *KRAS* transformation [51-55].

In the case of gastric intestinal-type adenocarcinoma, identifying precursor cells with markers of stemness typical of intestinal stem cells instead of those from gastric stem cells strengthens this hypothesis [34]. Deciphering such molecular events might pave the way for future interventions to be applied to GC and even to high-risk pre-neoplastic lesions [49], since an endoscopic biopsy may detect the presence of such molecular alterations and allow more criterions follow-up and even molecular treatments.

The possibility of chief cells acquiring stem cell properties has also been investigated as an alternative cancer mechanism. The process of paligenosis—a cellular mechanism that initiates autophagy and subsequently redirects cell fate—is considered a potential pathway for carcinogenesis originating in chief cells [49, 56].

Gastric atrophy is defined as the loss of appropriate glands. Such a definition includes the intestinalization of native glands. Intestinal metaplasia is often associated with an increased number of glandular units, and intestinalized epithelia show an increased cell turnover. Atrophic gastritis, although bringing a false impression of absence of proliferation, is a scenario of intense proliferative stimulus that might result in a “dedifferentiation” of mature cells to repopulate the gland or, more probably, the recruitment of proliferative cells to respond to the repopulation necessity [49, 56].

Accordingly, *H. pylori* can trigger both diffuse and intestinal carcinogenesis due to injuries to stem cells directly or by inducing stem cells’ niche oncogenic molecular signalizations [13, 15, 29, 33, 57]. The diverse features among these two main histological types of GC will result from different molecular

events (including random ones) in different moments of the differentiation process affecting the stem cells.

Multiple molecular driver events will shape the carcinogenesis process [17], and even passenger molecular events (not essential to cancer establishment but much higher in number) might contribute to diverse cancer morphologies and phenotypes, such as the histologic subtypes described in the WHO classification.

The GC molecular classifications, including from TCGA, may also result from combinations of driver and passenger molecular events that followed the initial insults to gastric stem cells [16, 58].

The Molecular Driver Events

A stem cell must suffer at least three molecular driver events, including mutations and other critical genetic or epigenetic insults, to achieve a clinically relevant cancer phenotype, i.e., a condition that harms the patient. This process takes many years from the primary driver event, reinforcing the concept of stem cell origin of cancers since mature cells do not survive for enough time to allow the accumulation of the necessary set of driver mutations without being discharged [17].

The long duration of the carcinogenic process must be seen as an opportunity to discover its molecular steps, find markers for anticipating diagnosis, and identify targets for interventions. The leading causes of driver events that can trigger and sustain carcinogenesis were didactically divided into three groups of origins: replicative (R), environmental (E), and hereditary (H). Replicative ones are consequences of aleatory errors occurring at each stem cell's division and used to be the most frequent mechanism of molecular driver events among human cancers [16].

Even considering some criticism regarding the random errors during stem cell divisions, arguing that this is not uniform and may vary in some specific cell types, functional situations, and along different development stages of human lives, this concept is widely accepted, mainly because it is strongly related to epidemiologic data [24].

Furthermore, dividing the causes of driver mutations among the mentioned types helped understand the mechanisms of many human cancers and may shed light on comprehension of gastric carcinogenesis [24]. Additionally, these mechanisms are not mutually excluding and, conversely, work together to allow the occurrence of the necessary number of molecular driver events to cause a clinically relevant cancer [16].

According to the proposed sources of driver events, *H. pylori* plays a role in every described mechanism. This holistic view may help understand its carcinogenic role more dynamically and consistently clinically. Innovations inspired by this new interpretation may contribute to GC control.

H. pylori Contributes to Each Type of Molecular Driver Event

Environmental (E)

H. pylori is recognized as a type 1 carcinogen due to its direct effect on gastric cells attributed to its pathogenicity factors, including the bacteria's ability to swim within the mucus, very close to the surface of the epithelium, the capacity of adherence

and survival on the epithelial surface, the CagA, TSS4, and VacA genes, among others, and the induced inflammatory and immune response, triggering oncogenic pathways [3]. These direct effects have been considered the central and even unique mechanisms of carcinogenesis attributed to chronic infection by *H. pylori* [3]. However, the role of *H. pylori* in gastric carcinogenesis to its direct pathogenic factors is insufficient to explain many real-world clinical and epidemiological features.

Considering *H. pylori*'s direct effects in GC carcinogenesis as the sole mechanism sufficient to cause GC is at odds with global incidence data [59]. Although most *H. pylori* strains that infect the human stomach harbor virulence factors, and approximately 50% of the world's population is infected [60], the annual global incidence of GC is around 1 million cases [59]. This discrepancy highlights the need for additional mechanisms, beyond the direct pathogenic effects, to account for the molecular driver events necessary for cancer development [17, 33].

Additionally, attributing the discrepancy between the number of infected patients and the number of GC cases exclusively to host genetic features is not sustained by accumulating data from genome-wide association studies (GWAS) that fail to show substantial germline variants. The genetic pattern of GC patients is not so different from that of non-cancer patients [61, 62].

The direct effects of *H. pylori* do have a role in gastric carcinogenesis, perhaps mainly through the virulence factors that allow the injection of its carcinogenic products into stem cells. In particular, CagA causes proliferation and DNA damage and blocks both DNA repair and the elimination of cells containing unrepaired DNA and promote chronic inflammation resulting in carcinogenic risk enhancement [14, 33, 35].

Another problem with exclusively considering direct effects of *H. pylori* pathogenicity to cancer occurrence is that *H. pylori* populations diminish in numbers and new bacteria populate the gastric microbiome during neoplastic progression, raising the possibility that other microorganisms contribute to carcinogenesis in the latter stages of cancer development [63-65].

The importance of the microbiome in different human cancers is currently proposed as a new cancer hallmark ("the polymorphic microbiome"), which may also play a role in gastric carcinogenesis [40]. Accordingly, evidence of the potential role of non-*H. pylori* microorganisms in stomach carcinogenesis are widely available. Experimental models using germ-free animals demonstrated that it is harder to develop *H. pylori*-induced GC, reinforcing the importance of additional microbiota in this process [15, 57, 66].

Microbiota studies using DNA sequencing demonstrated the presence of microorganisms with high carcinogenic potential among the dominant ones in GC samples. Although different methodological approaches result in the non-uniform identification of specific agents, bacteria from the mouth and the colon are frequently reported as the putative candidates. Additionally, viruses and fungi might contribute to GC [67-69].

The current model attributes to *H. pylori* the exclusive role along the carcinogenesis cascade. Nevertheless, robust data have shown that *H. pylori*'s dominance in the stomach

microbiome is evident during the early events but falls along the carcinogenesis. At the same time, gastric atrophy increases gastric pH, establishing a new non-*Helicobacter*-dominant microbiota that also has carcinogenic potential. This other microbiome must be included in the carcinogenic models [63, 68, 70-72].

Although not the dominant microbiota during the latter stages of the carcinogenesis cascade, *H. pylori* is the cause of the gastric atrophy that makes possible the colonization of the gastric mucosa by this non-*Helicobacter* carcinogenic microbiota, exposing already injured cells to the carcinogenic effects of this new dominant microbiome [65].

Consequently, *H. pylori*, beyond its direct carcinogenic effect by causing DNA damage (the first hit), is the potential cause of this “second hit,” provoking gastric atrophy and the colonization of already damaged mucosa by a non-*Helicobacter* carcinogenic microbiota during the progress of gastric carcinogenesis.

Gastric atrophy is a field suitable for molecular insults since the proliferative environment, together with exposure to carcinogens from these new dominant microorganisms, conspire to trigger the cancer process (Fig. 3) [64, 73, 74]. Therefore, related to the environmental causes of driver molecular events, *H. pylori* induces two hits: a) a direct one due to its pathogenic factors and b) a second hit by provoking gastric atrophy and colonization of the injured and under proliferative stimulus mucosae by a potential new carcinogenic microbiota.

Replicative

Chronic infection by *H. pylori* triggers stem cells to replicate and repopulate stomach cells lost due to increased cellular turnover during many years of infection [15, 33, 57].

Additionally, experimental models have shown that the numbers of stem cells increase in infected models compared to non-infected ones and demonstrate stem cell replications near colonies of *H. pylori*, as shown in Fig. 2 [15].

The increased number of stem cell replications results in an augmentation of replicative errors and, consequently, a higher chance of molecular driver events contributing to gastric carcinogenesis (Fig. 4).

Moreover, the injection of ADP-heptose and CagA into the cells through the T4SS system induces DNA double-strand breaks, impairs the adequate correction of those DNA breaks due to disturbing HR, and favors the propagation of errors and genomic instability during stem cell replication [14, 33, 35].

Briefly, *H. pylori* induces stem cell divisions (the main source of driver mutations in human cancers), favors the occurrence of additional mutations in those dividing cells induced by *H. pylori* LPS metabolites, and impairs the corrections of DNA damages by the CagA interaction with Par1b [75]. Par1b blocks *BRCA1* phosphorylation, maintaining these proteins in the cytoplasm. The absence of *BRCA1* in the nucleus impairs the HR of DNA double-strand breaks, leading to error-prone recombination, genomic instability, and increased cancer risk [14].

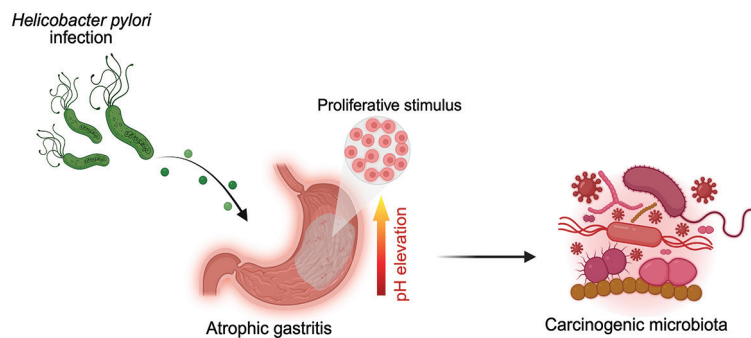


Fig. 3. Beyond its direct carcinogenic effects, *H. pylori* provokes atrophic gastritis, reducing acidity. This favors the colonization of the injured and under proliferative stimulus stomach mucosa by a new microbiota with carcinogenic potential, enhancing the cancer risk by this „double hit.” Created with Biorender.com.

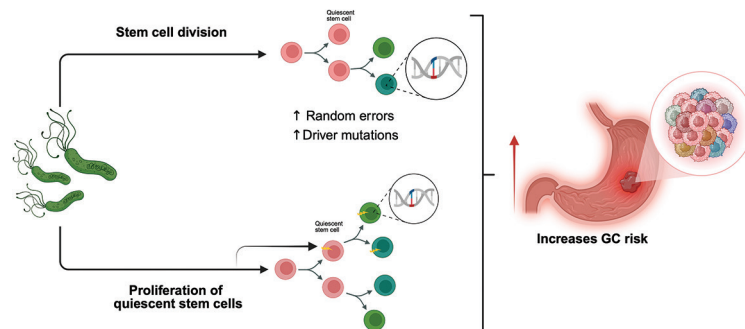


Fig. 4. Chronic infection by *H. pylori* results in more stem cell divisions and increases random errors. These random errors at each cellular replication augment the chance of driver mutations. Additionally, when exposed to *H. pylori* chronic infection, quiescent stem cells harboring driver mutations are triggered to proliferation. Created with Biorender.com.

Additionally, quiescent stem cells harboring a driver molecular event usually do not progress to carcinogenesis. Nevertheless, when exposed to chronic infection, such as chronic *H. pylori* gastric infection, these quiescent stem cells are triggered to proliferation and propagation of driver molecular events, favoring the carcinogenesis process [24].

Succinctly, *H. pylori* contributes to this major cause of molecular driver events among human cancers (and about half of those driver events in the case of stomach cancers) by triggering stem cell replication, resulting in a higher risk of GC and, additionally, increases the risk of replicative errors by inducing quiescent stem cells harboring driver events to proliferate (Fig. 4).

The replicative errors are random, and only a minority of such errors may result in driver mutations. These driver mutations' type and chronological order are also random if they happen [16]. Consequently, being infected by pathogenic strains of *H. pylori* will not universally result in cancer, and if it occurs, multiple different cancer morphologies and phenotypes can appear.

The proposed model is compatible with the heterogeneity typically found in GC, and highlighting the importance of multiple molecular mechanism interactions may provide insights into future discoveries to be translated into daily practice.

Hereditary

The most studied hereditary GC type is hereditary diffuse gastric cancer (HDGC). These cancers are caused by germinative pathogenic mutations in the *CDH1* gene, which codes for E-cadherin [76, 77]. The affected individuals are born with the mutation in one allele and usually lose the other allele due to diverse mechanisms, including epigenetic silencing induced by *H. pylori* (Fig. 5).

Losing E-cadherin per se is insufficient to ensure the aggressive phenotype commonly seen in this syndrome. As discussed, clinically relevant cancers require multiple driver events. That explains the harmless cases of patients harboring *CDH1* pathogenic mutations that develop only intra-mucosal foci of adenocarcinomas without evolving into an aggressive disease [78].

Helicobacter pylori infection can collaborate with the occurrence of additional driver events (Fig. 5) in susceptible individuals, mainly by silencing repair and tumor suppressor genes, favoring the typical aggressive phenotype of these tumors [79]. Accordingly, the current recommendations for the management of HDGC include the eradication of *H. pylori* [78].

Another mutual interaction between hereditary conditions and the *H. pylori* mechanism of carcinogenesis is the higher risk of GC among patients with a genetic condition that increases the

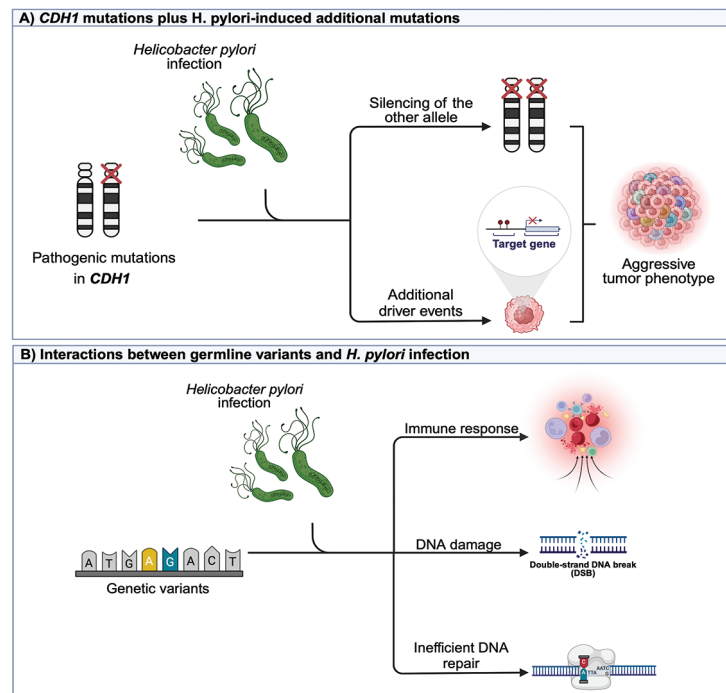


Fig. 5. *H. pylori*'s role in hereditary gastric cancer aggressiveness. A) Patients with diffuse hereditary gastric cancer syndrome are born with a pathogenic mutation in the *CDH1* gene and usually lose the other allele (including due to *H. pylori* epigenetic silencing). These events are not enough to ensure the aggressive phenotype typical of this syndrome. *H. pylori* may play an essential role by provoking additional molecular driver events leading to a more aggressive phenotype. B) Germline variants can enhance *H. pylori* inflammatory and immune response. Additionally, carriers of *BRCA1* variants hamper DSB corrections. *H. pylori* infected carriers have a significantly higher cancer risk. Created with Biorender.com.

effects of *H. pylori* pathogenicity factors, such as some variants in interleukin genes that enhance the inflammatory and immune consequences of *H. pylori* infection and cancer risk [80-82].

Furthermore, germline variants in the *BRCA1* and other genes work together with the direct effects of injected CagA in impairing the HR repair of *H. pylori*-induced DNA double-strand breaks. This interaction was strongly demonstrated in a study involving over 10,000 patients and around 38,000 controls, which showed that carrying a germline variant in *BRCA1* does not cause a significant increase in the risk of GC in non-infected patients. However, carriers of these variants that are infected by *H. pylori* have a much higher risk of developing cancer, which supports the presented model [79].

Accordingly, *H. pylori* is also related to the higher GC risk attributed to hereditary factors of driver mutations (Fig. 5) and may contribute to aggressive phenotypes in hereditary GC syndromes. Eradication of *H. pylori* is advised whenever managing these hereditary conditions [78].

Implication

The proposed review will demand substantial implications for understanding *H. pylori*-related gastric carcinogenesis, finding new risk markers, and modifying clinical practice.

However, the formal indication for *H. pylori* eradication, attention to the presence of *H. pylori* colonization deep in the gastric glands as a putative marker of the bacteria's interaction with proliferative cells should be considered [29, 33]. This finding could be studied by pathologists as a marker for risk of progression of disease.

Regarding initiating the carcinogenesis process, the stem cells' origin of GC and the long time it takes to achieve a clinically relevant cancer represent windows of opportunity to find markers of the ongoing process, propose prevention strategies, and search for putative targets for clinical interventions [24].

Gastric molecular signalizations of differentiation are specific to the stomach and regulate the differentiation process in its normal mucosa [83]. Alterations in the expressions of those genes may become biological markers of the risk of carcinogenesis accessible in endoscopic biopsies, together with histological abnormalities, or even in the absence of suspected lesions.

Medical interventions over cancer differentiation are already included in the arsenal of some malignant neoplasms, showing success in reverting the process by these new target therapies [44, 46]. Even considering the barriers to delivering therapeutic molecules in the case of GC and keeping them stable and active, the advances experimented with other diseases, such as using a single dose of iRNA for long-term control of arterial hypertension or targeting lipoprotein levels, among others, raise the expectance for innovative strategies that may avoid or treat GC at the initial stages, by using molecular approaches to fix these dysregulated gene expressions [84].

Molecular markers of transcommitment, i.e., expression of intestinal differentiation molecules, may also become a marker to be targeted. Translating this strategy in the case of intestinal type of GC will be less tricky than in the case of pancreatic stem cell transcommitment related pancreatic cancer since

stomach biopsies are widely accessible for diagnosing the molecular alterations as well as for following up on the target therapy outcome [49].

Regarding the molecular mechanisms of DNA damage directly caused by *H. pylori* to the stem cells, markers of such damage can be addressed and identified in conventional gastric biopsies, mainly in the case of associated pre-neoplastic lesions [39]. These markers may become a pivotal sign of the ongoing carcinogenic process and must come into clinical practice. This finding may also be investigated in other cancer sites, sharing the molecular features of DNA damage that are even caused by other etiologies [85].

Considering the double hit mechanism, the importance of atrophy as a status of high proliferative stimulus, together with the participation of other carcinogenic microorganisms, constitutes a sum of forces that trigger the carcinogenic process initiated by *H. pylori* infection.

Conversely, an extensive revision of the consequences of antibiotic therapies in this scenario is urgent. The current treatment is probably affecting off-target microorganisms whose effects are unknown. Moreover, *H. pylori* will not remain the unique target for antibiotics, and the specific timing for treating it should be reconsidered.

Recognizing the importance of *H. pylori*-related increases in stem cell replications in carcinogenesis leads to many potential interventions. Long-course *H. pylori* infection must be avoided, reinforcing the importance of primary prevention and early eradication. *H. pylori* may trigger carcinogenesis and induce stem cell proliferation and genomic instability that can sustain carcinogenesis even in the absence of continued infection, the "hit-and-run" mechanism [14, 86].

Therefore, a current negative test for the presence of *H. pylori* does not exclude an ongoing carcinogenesis [87, 88]. Consequently, the investigation of markers of DNA damage must drive clinical management and surveillance [85].

In the case of germline risk factors and *H. pylori* infection, the broader availability of molecular tests will make it much more common for gastroenterologists and clinicians to deal with this molecular diagnosis, since many genetic panels usually include *CDH1* and other genes that may increase the risk of GC. *H. pylori* eradication will be a formal recommendation due to the risk enhancement of having the genetic variant and *H. pylori* infection. A test and treatment strategy should be adopted as early as possible regarding the children of affected patients.

Accordingly, tremendous implications are expected, from the pathologist's evaluation of stomach biopsies to the clinician's surveillance, treatments, and follow-up approaches. A new era of molecular diagnosis applied to stomach biopsies will allow a reduction of GC burden and diagnosis of tumors in earlier stages, hopefully resulting in better outcomes.

CONCLUSIONS

The proposed model (Fig. 6) aims to update the current ones, primarily based on the direct cellular effects of the *H. pylori* virulence factors, by adding carcinogenic mechanisms usually not recognized among the potential contributions of *H. pylori* to gastric carcinogenesis.

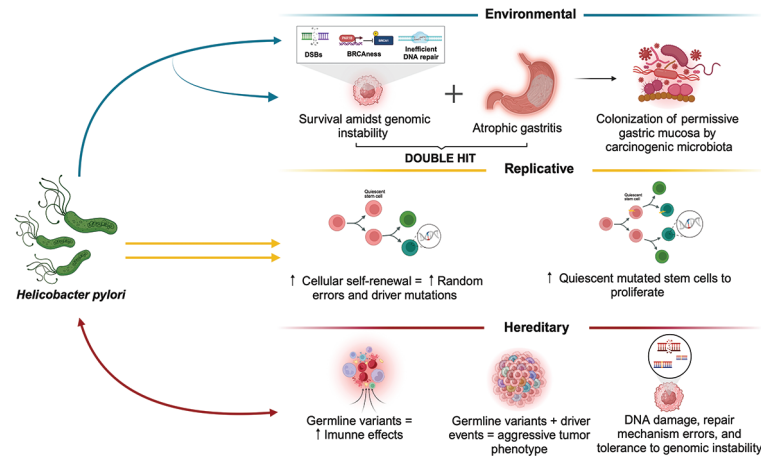


Fig. 6. *H. pylori* can contribute to every type of driver mutation source beyond its direct effects on the carcinogenic process. Being infected by *H. pylori* will not necessarily result in GC since multiple molecular driver events (including random ones) are needed. GC can also seldom occur in uninfected patients. However, *H. pylori* is the leading risk factor for GC because it can favor the accumulation of such necessary molecular driver events due to a wide range of mechanisms. Created with Biorender.com.

The model included oncologic concepts, favoring a broader interpretation of *H. pylori*'s role in gastric carcinogenesis and understanding some current gaps in the relationship between clinical findings and *H. pylori* contributions.

Considering that there are additional sources of molecular driver events in gastric carcinogenesis beyond the direct effects of *H. pylori* and, mainly, the potential contribution of *H. pylori* to these sources of cancer causes may allow a more precise interpretation of the process and pave the way for future interventions.

Conflicts of interest: None to declare.

Authors' contributions: P.A. was responsible for the study's conception and design. J.S. designed the images. R.G., M.C., M.A., and M.R. contributed to drafting the manuscript, with M.A. also providing experimental data. All authors participated in critically revising the manuscript, approved the final version for publication.

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