Journal of Cell and Molecular Research (2025) 17 (1), 51-59 DOI: 10.22067/jcmr.2025.92344.1106

Research Article

Downregulation of EPHA2 Receptor Tyrosine Kinase by *Helicobacter pylori* in Gastric Epithelial Cells: Implications for Gastric Cancer Progression

Sedigheh Kohgard, Saber Zahri *, Saeid Latifi Navid, Maryam Jahanvar

Department of Biology, Faculty of Science, University of Mohaghegh Ardabili, Ardabil, Iran

Received 25 February 2025 Accepted 27 August 2025

Abstract

Helicobacter pylori is a Gram-negative bacterium that persistently colonizes the gastric mucosa, leading to various gastrointestinal disorders, including gastritis, peptic ulcers, and gastric cancer. Chronic *H. pylori* infection triggers inflammatory responses and modulates host signaling pathways, particularly receptor tyrosine kinases (RTKs), which regulate essential cellular processes such as adhesion, migration, proliferation, and survival. Among these, EphA2 is a key RTK involved in epithelial cell signaling and maintaining structural integrity, while E-cadherin plays a critical role in cell-cell adhesion and tumor suppression. Disruptions in these signaling molecules can contribute to gastric epithelial dysfunction and cancer progression. This study aimed to evaluate the effects of an Iranian *H. pylori* vacA d1/-i1 strain on the expression of EPHA2 and E-cadherin in AGS gastric epithelial cells. Following co-culture with *H. pylori*, total RNA was extracted, and quantitative real-time PCR (qRT-PCR) was performed to analyze gene expression levels. Hematoxylin and eosin (H&E) staining was used to assess morphological changes, revealing structural alterations indicative of cellular stress and epithelial disruption after *H. pylori* infection. Gene expression analysis demonstrated a significant downregulation of EPHA2 in *H. pylori*-infected cells compared to controls ($p < 0.0001$), suggesting bacterial interference with EPHA2-mediated signaling pathways. In contrast, no significant change in E-cadherin expression was observed, indicating that *H. pylori* may not strongly impact cell adhesion under these conditions. The selective suppression of EPHA2, along with observed morphological changes, suggests a novel mechanism by which *H. pylori* contribute to gastric epithelial dysfunction, potentially promoting tumorigenesis. Further research is needed to elucidate the molecular pathways involved and their implications for gastric disease pathogenesis and targeted therapeutic strategies.

Keywords: *Helicobacter pylori*, EPHA2, E-cadherin, receptor tyrosine kinases, gastric epithelial cells, gastric cancer, hematoxylin and eosin staining

Introduction

Helicobacter pylori is a prevalent Gram-negative bacterium that causes lifelong infections in the human gastric mucosa, surviving despite the host's immune response. As a class I carcinogen, *H. pylori* is associated with gastric adenocarcinomas, peptic ulcers, chronic gastritis, and gastric mucosa-associated lymphoid tissue lymphoma (Abdi et al. 2017; Bakhti et al. 2016; Baj et al. 2020; Wen et al. 2021; Piscione et al. 2021). The bacterium interacts persistently with the human stomach epithelium, activating host signaling pathways, particularly receptor tyrosine kinases (RTKs). Among these, *H. pylori* preferentially activate members of the EGFR and MET receptor families, which regulate critical cellular processes such as migration, invasion, proliferation, apoptosis, and autophagy. The EPH receptor family, a major group of RTKs, includes fourteen members categorized into two classes: class A (EPHA1-EPHA8 and EPHA10) and class B (Choura and Rebaï 2011; Salokas et al. 2022). These classes are differentiated based on the binding affinities of their ligands to ephrins (EFNs) and their sequence homology. Unlike the soluble ligands of other receptor tyrosine kinases (RTKs), EPH receptors and EFN ligands are membrane-bound (Kataoka et al. 2002). This membrane anchoring enables bi-directional signaling when cells expressing either EPH or EFN come into direct contact (Kullander and Klein 2002). EPH kinase activity remains autoinhibited under resting conditions. Upon ephrin ligand binding, tyrosine residues in the juxtamembrane region are phosphorylated, releasing the autoinhibition and enabling the kinase domain to assume an active conformation, which triggers downstream signaling (Klein 2012; Wei et al. 2014). EPH-containing

* Corresponding author's e-mail address: zahri@uma.ac.ir

Licensed as Open Access CC-BY

receptors mediate various biological processes, including cell adhesion, migration, invasion, and angiogenesis. Dysregulation of their expression and/or function has been linked to various clinical diseases, including cancer (Chen, Song, and Amato 2015; Brantley-Sieders et al. 2004). EPHA2 is commonly overexpressed at both the mRNA and protein levels in various solid tumors, including primary tumor samples and cancer cell lines. Overexpression of the EPHA2 receptor has been associated with poor prognosis in gastric cancer patients, as well as with metastasis and the epithelial-to-mesenchymal transition (KUROSE et al. 2019; Nikas et al. 2022; Xiao et al. 2020).

E-cadherin (CDH1) is a transmembrane glycoprotein found in epithelial cells, essential for facilitating calcium-dependent cell-to-cell adhesion. *E-cadherin* plays an essential role in neoplastic transformation and metastasis by forming complexes and linking actin filaments with α-, β-, and γ-catenins (Sicairos, Alam, and Du 2023; Burandt et al. 2021). Reduced cell adhesion may facilitate the early neoplastic process, particularly by enabling the loss of contact inhibition of growth. Furthermore, decreased cadherin function can lead to cancer cell detachment and promote metastasis (Kaszak et al. 2020; Na et al. 2020). Gastric carcinogenesis is a complex, multistep process characterized by significant morphological changes and driven by diverse genetic and epigenetic alterations. CDH1 plays a vital role as a putative tumor suppressor gene. In gastric carcinoma (GC), *E-cadherin* expression is reduced by 17% to 92%, with this decrease being more prevalent in diffuse-type carcinomas compared to intestinal-type carcinomas (Flores et al. 2022; Gullo et al. 2021).

This study aims to investigate the expression levels of EPHA2 and *E-cadherin* receptor genes in a coculture model of *Helicobacter pylori* and the AGS gastric epithelial cell line. Specifically, the research focuses on how the interaction between *Helicobacter pylori* and AGS cells influences the regulation of these genes. EPHA2 is a receptor tyrosine kinase involved in cell signaling pathways associated with tumorigenesis. At the same time, E-cadherin is a critical cell adhesion molecule crucial for maintaining epithelial integrity and preventing cancer metastasis. Studying how gene expression changes in response to *H. pylori* infection can offer essential insights into the molecular processes that drive the development of gastric cancer and other stomach-related diseases. To our knowledge, no previous studies have specifically examined the expression of EPHA2 and E-cadherin in a coculture model of *Helicobacter pylori* and AGS gastric epithelial cells. Although considerable research has explored the role of *Helicobacter pylori* in altering E-cadherin expression and promoting gastric carcinogenesis (Leite et al. 2020; Baj et al. 2020; Lim, Kim, and Kim 2003).This study is novel in investigating the concurrent expression of EPHA2 and E-cadherin in response to *Helicobacter pylori* infection using the AGS cell line.

Materials and Methods

Bacterial Culture and Preparation of *Helicobacter pylori*

In this study, we utilized the *Helicobacter pylori* vacA d1/-i1 strain from Iran, previously characterized in our related research (Article 2013). *H. pylori* were isolated and cultivated on Brucella agar (Merck, Germany) as the primary culture medium. To prepare the medium, 41 grams of Brucella agar powder were dissolved in one liter of distilled water, heated, and sterilized by autoclaving at 121°C for 15 minutes. Once cooled to room temperature, 5-7% defibrinated human blood, sourced from the Ardabil Blood Transfusion Organization, was added. To prevent contamination, vancomycin (10 mg/ml, Gibco), trimethoprim (5 mg/ml, Gibco), and amphotericin B (4 mg/ml, Gibco) were added to the culture medium. The bacteria were then inoculated onto Brucella agar plates and incubated at 37°C with 5% CO_2 and 97% relative humidity under aerobic conditions for 48 hours to promote optimal growth. Before co-cultivation with AGS cells, the *Helicobacter pylori* suspension was harvested in Dulbecco's phosphate-buffered saline (PBS; pH 7.4) and adjusted to an optical density at 600 nm (OD_{600}) corresponding to ~1×10^8 CFU/mL. This cell density yielded a multiplicity of infection (MOI) of 50:1 (bacteria:cell) in subsequent experiments (Schneider et al. 2011).

Gram Staining of *Helicobacter pylori*

A bacterial smear was first prepared on a microscope slide to perform Gram staining (Gram Stain Kit, Merck). A drop of sterile distilled water was placed on the slide, and a small portion of the bacterial colony was suspended using a sterile loop. Once air-dried, the smear was heat-fixed to adhere the bacteria to the slide surface. The smear was stained with crystal violet 200 µL for 30-45 seconds, turning all bacteria purple. After rinsing with water, Lugol's iodine was applied at 200 µL for 30-45 seconds to form a crystal violet-iodine complex within the bacterial cells. At this stage, the bacteria

remained purple. Next, the smear was decolorized using an acetone-alcohol solution 200 µL for 10-15 seconds. Following decolorization, the slide was counterstained with fuchsin for 30-45 seconds, which rendered the Gram-negative bacteria red. After a final rinse and drying, the bacteria were observed under a microscope (Olympus CX23, Olympus Corporation, Tokyo, Japan; magnification 100× and 400×), allowing for clear differentiation between Gram-positive and Gram-negative bacteria.

Biochemical Identification Tests for *Helicobacter pylori*

Three biochemical tests were performed to confirm the identity of *Helicobacter pylori*: the catalase, oxidase, and urease tests. For the catalase test, a drop of sterile physiological saline was placed on a clean slide, followed by the addition of a bacterial colony suspended in the saline. A drop of hydrogen peroxide (H_2O_2; Sigma-Aldrich) was then added. The oxidase test was carried out by placing a small portion of the bacterial colony onto filter paper on a slide. After applying 2-3 drops of oxidase reagent (tetramethyl-p-phenylenediamine dihydrochloride; Sigma-Aldrich). For the urease test, a bacterial colony was aseptically transferred to a urea agar medium plate and incubated at 37°C (Wafy, Abdelmalek, and Mostafa 2022; Nevoa et al. 2017; Shen et al. 1997).

Cell Culture

AGS cells, obtained from the Center for Genetic Resources, were cultured in RPMI-1640 medium (Gibco) supplemented with 20% FBS (Gibco) and 1% Penicillin-Streptomycin (Gibco). Cells were incubated at 37°C in a 5% CO_2 environment. At 80% confluence, cells were washed with PBS (Gibco), detached using 0.25% Trypsin-EDTA (Gibco), and neutralized with FBS-containing medium. After centrifugation at 1,200 rpm for 10 minutes, the pellet was resuspended in fresh medium and transferred to new flasks. For experiments, equal numbers of cells were seeded into 6-well plates and allowed to proliferate to 80% confluence.

Co-cultivation of *Helicobacter pylori* with AGS Cells

A suspension of *Helicobacter pylori* was prepared, and its optical density was measured to ensure uniformity. Equal volumes of the bacterial suspension were added to each well containing AGS cells in a six-well plate. A sterile slide was placed in one well before cell seeding to allow cell adherence for subsequent staining. After adding the bacteria, the plates were incubated to promote bacterial-cell interaction. Following a few hours of co-incubation, excess bacteria were removed by washing the wells with phosphate-buffered saline (PBS). A fresh culture medium with 20% fetal bovine serum (FBS) was added, and the cells were incubated with the bacteria for 72 hours. The effects of *H. pylori* on AGS cell growth were then evaluated.

Hematoxylin and Eosine staining

Hematoxylin and Eosine (H&E) staining was performed to evaluate cellular morphology in AGS cells and their co-culture with *Helicobacter pylori*. Reagents were obtained from Sigma-Aldrich (St. Louis, MO, USA). Following the culture period, the wells were gently washed twice with 1 mL phosphate-buffered saline (PBS), and the cells were fixed with 500 µL of 10% formalin for 10 minutes at room temperature. For nuclear staining, 200 µL hematoxylin was applied to each well for 5 min, followed by rinsing three times with distilled water (1 mL each rinse). Cytoplasmic staining was then performed by adding 200 µL of eosin for 2 min, followed by two rinses with distilled water. After staining, the slides were air-dried for approximately 10 min before microscopic observation. This method provided clear differentiation of cellular structures, allowing for detailed observation of bacterial colonization and morphological changes in the co-culture.

Total RNA extraction

To extract RNA, 1.5 mL of Trizol Reagent (Thermo Fisher Scientific) was added to each well (n = 10), and the plate was agitated for 5 minutes to detach the cells. The Trizol-cell mixture was transferred to microtubes, vortexed briefly, and incubated at room temperature for 10 minutes. After adding 300 µL of chloroform, the tubes were gently inverted, chilled on ice for 5 minutes, and centrifuged (Eppendorf, Germany) at 12,000 rpm for 15 minutes at 4°C. The aqueous phase was collected, mixed with isopropanol, incubated on ice for 15 minutes, and centrifuged again. The RNA pellet was washed with 75% ethanol, air-dried, and resuspended in 50 µL of DEPC-treated water. RNA was quantified and assessed for quality using a Nanodrop spectrophotometer (Thermo Scientific) at Mohaghegh Ardabili University (Jahanvar et al. 2024).

Gene expression

Reverse transcription was performed using Oligo (dT) primers to synthesize complementary DNA (cDNA) from total RNA (n = 10). cDNA synthesis was carried out using the ReverTra Ace™ qPCR RT

kit (Toyobo, Osaka, Japan) according to the manufacturer's protocol. The synthesized cDNA was used in quantitative real-time PCR (qRT-PCR) to analyze gene expression for *EPHA2* and *E-cadherin*. Primer sequences were designed using NCBI data and Beacon Designer 8.10 software. The forward and reverse primers for E-cadherin were GAGCAGCAGAATCAGAATTAGC and GAGCAGCAGAATCAGAATTAGC, respectively, with a product length of 100 bp. For *EPHA2*, the forward and reverse primers were GAGAAGGATGGCGAGTTC and TTGCTGTTGACGAGGATG, respectively, with a product length of 134 bp. The GAPDH primers used were AGAACATCATCCCTCCTCTACTG for the forward and CCTCCGACGCCTGCTCACG for the reverse, yielding a product length of 156 bp. Amplification was conducted with a Rotor-Gene 6000 system using the SYBR Green kit (Ekta Equipment, Iran), with GAPDH as the housekeeping gene for normalization. The qRT-PCR cycling conditions were as follows: initial denaturation at 95 °C for 5 min, followed by 40 cycles of denaturation at 95 °C for 15 s, annealing at 60 °C for 30 s, and extension at 72 °C for 30 s. Fluorescence data were collected at the end of each extension step. Upon completion, melting curve analysis was conducted from 65 °C to 95 °C in 0.5 °C increments to confirm amplicon specificity. PCR product specificity was further validated by electrophoresis.

Statistical analysis

Expression analysis was conducted using the $2^{-\Delta\Delta Ct}$ method (Livak and Schmittgen 2001) to quantify relative gene expression. Data were presented as the mean ± standard error of the mean (SEM). All statistical tests were two-tailed, with significance set at a p-value of less than 0.05 ($p < 0.05$). Statistical analysis and graphical representation of the data were performed using GraphPad Prism software, version 8.2.1.

Results

Culture of *Helicobacter pylori*

Analysis of *Helicobacter pylori* culture following 48 to 72 hours of incubation on Brucella agar reveals the emergence of mucoid and transparent colonies measuring 1 to 2 mm in diameter (Figure 1. A).

Assessment of *Helicobacter pylori*

Gram staining of *Helicobacter pylori* colonies revealed both coccobacillary and spiral forms. The bacterium exhibited dimensions of approximately 3 microns in length and 0.5 microns in diameter, consistent with its typical morphology (Figure 1. B). The oxidase test, conducted with an oxidase reagent, confirmed that the cultured *Helicobacter pylori* strain tested positive for oxidase. The appearance of a dark blue color within 5-10 seconds indicated a positive result. The catalase test, conducted by adding hydrogen peroxide to the bacterial colonies, produced oxygen gas bubbles, confirming the presence of the catalase enzyme in the bacteria. Furthermore, when *Helicobacter pylori* colonies were cultivated on urea broth culture medium, an apparent color change from yellow to pink was observed over time. This shift indicates the activity of the urease enzyme, which hydrolyzes urea, further confirming the biochemical characteristics of *H. Pylori*.

AGS Cell Culture and Co-cultivation with *Helicobacter pylori* vacA d1/-i1 strains

AGS cells were cultured and maintained under standard conditions until they reached approximately 70-80% confluence (Figure 1. C). Cells exhibited typical epithelial morphology, adhering as monolayers with visible tight junctions between neighboring cells (Figure 1. D). Co-cultivation of AGS cells with *Helicobacter pylori* resulted in significant morphological changes indicative of cellular stress and response to bacterial interaction. Cells transitioned from elongated to rounded morphologies and exhibited increased clustering. Additionally, areas of decreased cell adhesion were evident, likely reflecting disruptions mediated by *H. pylori* targeting adhesion molecules (Figure 1. E). These observations highlight the pathogenic influence of *H. pylori* on gastric epithelial cell integrity, contributing to our understanding of its role in gastric disease mechanisms (Schneider et al. 2011).

Hematoxylin and Eosin (H&E) staining

Evaluation of Hematoxylin and Eosin (H&E) staining of AGS cells co-cultured with *Helicobacter pylori* revealed distinct cellular morphology. Hematoxylin stained the nuclei of AGS cells a blue-purple color, while eosin stained the cytoplasm pink. The presence of *H. pylori* within the culture was clearly observed, providing visual confirmation of

bacterial interaction with the host cells (Figure 1. F, G).

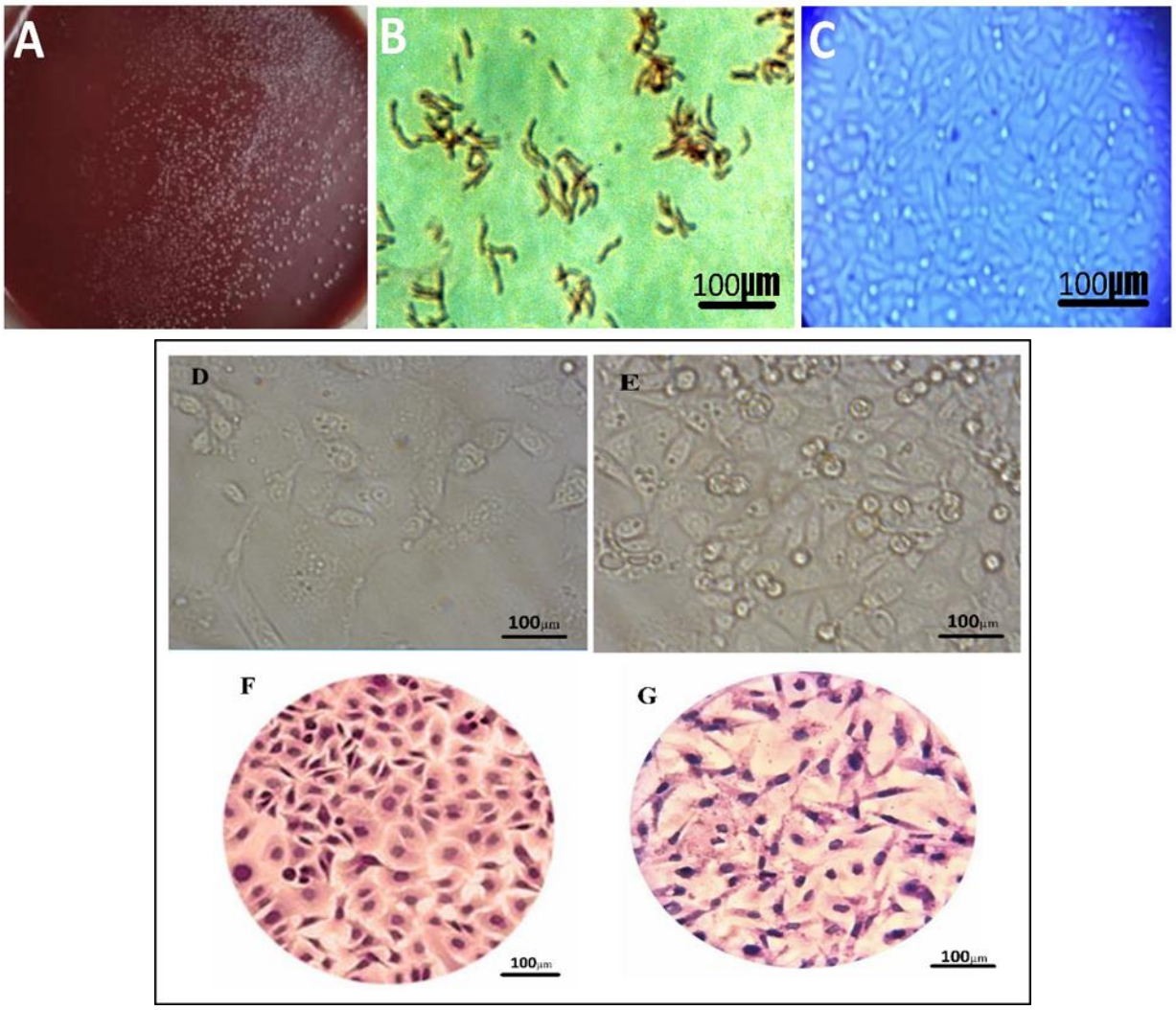

Figure 1. (A) Brucella agar culture medium displaying visible colonies of Helicobacter pylori, illustrating successful bacterial growth. (B) Gram staining of Helicobacter pylori colonies, demonstrating characteristic morphology and Gram-negative staining. (C) AGS cell monolayer arranged in six-well plates, prepared for co-cultivation studies. (D) AGS cells in culture without Helicobacter pylori, serving as a control. (E) Co-cultivation of AGS cells with Helicobacter pylori, demonstrating interaction between bacterial colonies and AGS cells. (F) Hematoxylin and eosin (H&E) staining of AGS cells alone, highlighting cellular morphology. (G) H&E staining of AGS cells co-cultured with Helicobacter pylori, illustrating morphological changes due to bacterial interaction.

PCR and Gel Electrophoresis Analysis

The PCR reaction result was subjected to electrophoresis on a 1% agarose gel. The results indicated that the genes *GAPDH*, *EPHA2*, and *E-cadherin* (*CDH1*) were exclusively amplified, measuring 100 bp, 134 bp, and 156 bp in length, respectively (Figure 2. B).

Analysis of gene expression

Quantitative real-time PCR analysis of *EPHA2* gene expression in AGS cell line (control) samples and AGS cells co-cultured with *Helicobacter* (treatment group) demonstrated a significant reduction in *EPHA2* expression in the co-culture condition, with a P-value of <0.0001. Quantitative real-time PCR analysis of CHD1 gene expression in control and treatment groups demonstrated no significant difference between the two conditions, with a P-value of > 0.05 (Figure 2. A).

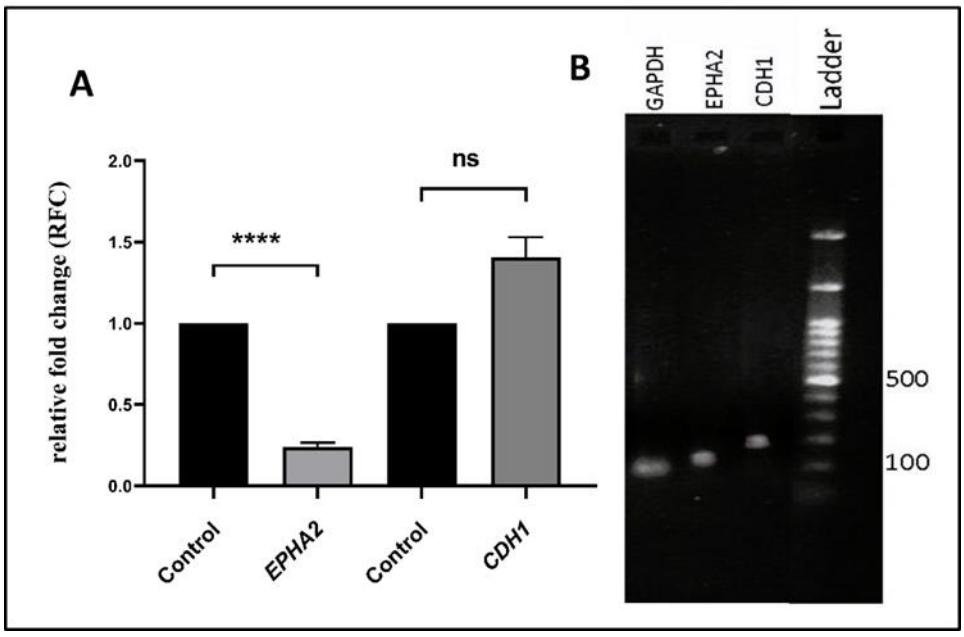

Figure 2. (A) The expression of the E-cadherin gene (CDH1) did not exhibit a significant difference between the AGS cell line (control) and the AGS co-cultured with Helicobacter pylori group (ns = not significant, $p > 0.05$). The expression of the EPHA2 gene in the AGS and Helicobacter co-culture group (treatment) exhibited a substantially reduced level compared to the control group, **** $p < 0.0001$. (B) The electrophoresis results indicate that the housekeeping gene GAPDH measures around 100 base pairs, whereas the EPHA2, 134 base pairs, and the E-cadherin gene measures 156 base pairs.

Discussion

Gastric cancer, characterized by a poor prognosis, has been the subject of extensive research, particularly concerning the role of kinases in its development (Sexton et al. 2020). Receptor tyrosine kinases (RTKs) are of significant interest due to their involvement in critical cellular processes, such as growth and survival. *Helicobacter pylori*, a key pathogen linked to gastric cancer, manipulates host signaling pathways, including those involving RTKs, to promote its survival and the pathogenesis of related diseases. While numerous signaling pathways are altered by *H. pylori* infection, RTKs play a prominent role in the bacterium's ability to induce abnormal cellular behaviors, such as unchecked proliferation and resistance to cell death, contributing to cancer development. However, the specific mechanisms through which *H. pylori* affects RTKs remain underexplored. This area of research is crucial, as a deeper understanding of *H. pylori*-induced RTK activation could lead to the development of targeted therapies aimed at disrupting these pathogenic processes, potentially improving outcomes for gastric cancer patients (Chichirau et al. 2019; Pachathundikandi, Tegtmeyer, and Backert 2013; Backert and Tegtmeyer 2017).

E-cadherin is a critical transmembrane glycoprotein that plays a central role in cell signaling, proliferation, invasion, and migration. As a key mediator of cell-cell adhesion in epithelial tissues, it is essential for maintaining tissue structure and integrity (Bhatt et al. 2013). In cancers, particularly gastric cancer, the loss or dysfunction of E-cadherin disrupts cell adhesion, leading to increased cell motility and enhanced invasive potential through the epithelial-mesenchymal transition (EMT). This disruption also alters intracellular signaling, promoting tumor progression and metastasis (Yu et al. 2019). Consequently, E-cadherin is a crucial regulator of cellular behavior, and its impairment is closely associated with cancer

progression (Yuksel, Ocalan, and Yilmaz 2021). E-cadherin promoter methylation, often observed in non-cancerous gastric epithelium associated with *Helicobacter pylori* infection, suppresses the expression of this key adhesion molecule (Matsusaka, 2014). As a member of the cell-to-cell adhesion molecule family, E-cadherin is crucial for maintaining epithelial tissue structure and cell differentiation. Its functional loss disrupts adhesive junctions, leading to altered cell adhesion and proliferation signaling pathways (Flores et al. 2022). This dysfunction contributes to abnormal cellular behavior, potentially promoting gastric disease progression. EphA2 and E-cadherin are co-localized at cell-cell contact sites in epithelial cells, with E-cadherin playing a regulatory role over EphA2 (Xie et al. 2017; Muhammad, Eladl, and Khoder 2019). This study aims to explore the effects of *Helicobacter pylori* infection on the expression of *EPHA2* and *E-cadherin* in co-cultures with the gastric epithelial cell line AGS. *H. pylori* is known to alter host signaling pathways, and understanding its impact on these two molecules could reveal key mechanisms involved in gastric disease. Extensive research over the years has focused on various gene expressions related to *H. pylori* infection, highlighting the importance of this area of study. A study from 2009 revealed that the binding of *Helicobacter pylori* to receptors on gastric epithelial cells is a key factor in initiating its pathogenicity. This interaction not only aids in the positioning of the bacteria but also activates intracellular signaling pathways, leading to cellular changes and tissue damage. *H. pylori* can also bind to laminin and collagen via its Type IV secretion system proteins, enhancing its adhesion and pathogenic potential within the gastric environment (Jiménez-Soto et al. 2009; Odenbreit et al. 2009).

This study demonstrated that *Helicobacter pylori* infection had no statistically significant effect on E-cadherin expression ($p > 0.05$), whereas EPHA2 expression was markedly reduced ($p < 0.0001$). This selective downregulation suggests that *H. pylori* specifically interfere with EPHA2-mediated signaling, potentially altering gastric epithelial dynamics. These findings, consistent with those reported by Marina Leite and colleagues (Leite et al. 2020). highlight the bacterium's capacity to disrupt epithelial integrity and contribute to gastric pathogenesis.

From a translational perspective, the suppression of EPHA2 points to a potential therapeutic target. Strategies aimed at preserving or restoring EPHA2 function may help protect epithelial homeostasis during infection and limit tissue damage. However, the study's reliance on a single gastric epithelial cell line (AGS) limits the generalizability of the results. Future work should extend to additional cell lines or primary gastric epithelial cells and investigate downstream signaling pathways, as well as other bacterial factors beyond CagA and VacA, to better define the molecular basis of EPHA2 regulation.

Acknowledgment
We would like to express our sincere appreciation to the authors whose valuable research and articles contributed to the foundation of this study. Their work has been instrumental in shaping our research efforts.

Conflict of Interests
The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

Abdi E., Latifi-Navid S., Zahri S., Yazdanbod A., and Safaralizadeh R. (2017) Helicobacter Pylori Genotypes Determine Risk of Non-Cardia Gastric Cancer and Intestinal- or Diffuse-Type GC in Ardabil: A Very High-Risk Area in Northwestern Iran. Microbial Pathogenesis 107 (June): 287–92.

Anonymous (2013) Helicobacter Pylori VacA. Article, Original. 16 (6): 330–37.

Backert S., and Tegtmeyer N. (2017) Type IV Secretion and Signal Transduction of Helicobacter Pylori CagA through Interactions with Host Cell Receptors. Toxins 9 (4): 115.

Baj J., Korona-Głowniak I., Forma A., Maani A., Sitarz E., Rahnama-Hezavah M., et al. (2020) Mechanisms of the Epithelial–Mesenchymal Transition and Tumor Microenvironment in Helicobacter Pylori-Induced Gastric Cancer. Cells 9 (4): 1055.

Bakhti S. Z., Latifi-Navid S., Mohammadi S., Zahri S., Bakhti F. S., Feizi F., et al. (2016) Relevance of Helicobacter Pylori Vac A 3′-end Region Polymorphism to Gastric Cancer. Helicobacter 21 (4): 305–16.

Bhatt T., Rizvi A., Rao Batta S. P., Kataria S., and Jamora C. (2013) Signaling and Mechanical Roles of E-Cadherin. Cell Communication & Adhesion 20 (6): 189–99.

Brantley-Sieders D., Schmidt S., Parker M., and Chen J. (2004) Eph Receptor Tyrosine Kinases in Tumor and Tumor Microenvironment. Current Pharmaceutical Design 10 (27): 3431–42.

Burandt E., Lübbersmeyer F., Gorbokon N., Büscheck F., Luebke A. M., Menz A., et al. (2021) E-Cadherin Expression in Human Tumors: A Tissue Microarray Study on 10,851 Tumors. Biomarker Research 9 (1): 44.

Chen J., Song W., and Amato K. (2015) Eph Receptor Tyrosine Kinases in Cancer Stem Cells. Cytokine & Growth Factor Reviews 26 (1): 1–6.

Chichirau B. E., Diechler S., Posselt G., and Wessler S. (2019) Tyrosine Kinases in Helicobacter Pylori Infections and Gastric Cancer. Toxins 11 (10): 591.

Choura M., and Rebaï A. (2011) Receptor Tyrosine Kinases: From Biology to Pathology. Journal of Receptors and Signal Transduction 31 (6): 387–94.

Flores A., Rêma A., Mesquita J., Taulescu M., Seixas F., Gärtner F., et al. (2022) E-Cadherin Expression in Canine Gastric Carcinomas: Association with Clinicopathological Parameters. Veterinary Sciences 9 (4): 172.

Gullo I., Oliveira C., van der Post R. S., van Dieren J. M., Davis J. L., Bougen-Zhukov N., et al. (2021) Updated Perspective and Directions on Hereditary Diffuse Gastric Cancer. In Research and Clinical Applications of Targeting Gastric Neoplasms, 217–58. Elsevier.

Huang F.-Y., Chan A. O.-O., Rashid A., Wong D. K.-H., Cho C.-H., and Yuen M.-F. (2012) Helicobacter Pylori Induces Promoter Methylation of E-cadherin via Interleukin-1β Activation of Nitric Oxide Production in Gastric Cancer Cells. Cancer 118 (20): 4969–80.

Jahanvar M., Zahri S., Abdolmaleki A., and Asadi A. (2024) Evaluation of Decellularized Sheep Kidney Scaffolds for Renal Tissue Engineering: Biocompatibility and Stem Cell Differentiation Potential. Tissue and Cell, November, 102594.

Jiménez-Soto L. F., Kutter S., Sewald X., Ertl C., Weiss E., Kapp U., et al. (2009) Helicobacter Pylori Type IV Secretion Apparatus Exploits B1 Integrin in a Novel RGD-Independent Manner. Edited by Tran Van Nhieu G. PLoS Pathogens 5 (12): e1000684.

Kaszak I., Witkowska-Piłaszewicz O., Niewiadomska Z., Dworecka-Kaszak B., Toka F. N., and Jurka P. (2020) Role of Cadherins in Cancer—A Review. International Journal of Molecular Sciences 21 (20): 7624.

Kataoka H., Tanaka M., Kanamori M., Yoshii S., Ihara M., Wang Y.-J., Song J.-P., et al. (2002) Expression Profile of EFNB1, EFNB2, Two Ligands of EPHB2 in Human Gastric Cancer. Journal of Cancer Research and Clinical Oncology 128 (7): 343–48.

Klein R. (2012) Eph/Ephrin Signalling during Development. Development 139 (22): 4105–9.

Kullander K., and Klein R. (2002) Mechanisms and Functions of Eph and Ephrin Signalling. Nature Reviews Molecular Cell Biology 3 (7): 475–86.

KUROSE H., UEDA K., KONDO R., OGASAWARA S., KUSANO H., SANADA S., NAITO Y., et al. (2019) Elevated Expression of EPHA2 Is Associated With Poor Prognosis After Radical Prostatectomy in Prostate Cancer. Anticancer Research 39 (11): 6249–57.

Leite M., Marques M. S., Melo J., Pinto M. T., Cavadas B., Aroso M., Gomez-Lazaro M., Seruca R., and Figueiredo C. (2020) Helicobacter Pylori Targets the EPHA2 Receptor Tyrosine Kinase in Gastric Cells Modulating Key Cellular Functions. Cells 9 (2): 513.

Lim J. W., Kim H., and Kim K. H. (2003) Cell Adhesion-Related Gene Expression by Helicobacter Pylori in Gastric Epithelial AGS Cells. The International Journal of Biochemistry & Cell Biology 35 (8): 1284–96.

Livak K. J., and Schmittgen T. D. (2001) Analysis of Relative Gene Expression Data Using Real-Time Quantitative PCR and the 2−ΔΔCT Method. Methods 25 (4): 402–8.

Matsusaka K. (2014) DNA Methylation in Gastric Cancer, Related to Helicobacter Pylori and Epstein-Barr Virus. World Journal of Gastroenterology 20 (14): 3916.

Muhammad J. S., Eladl M. A., and Khoder G. (2019) Helicobacter Pylori-Induced DNA Methylation as an Epigenetic Modulator of Gastric Cancer: Recent Outcomes and Future Direction. Pathogens 8 (1): 23.

Na T.-Y., Schecterson L., Mendonsa A. M., and Gumbiner B. M. (2020) The Functional Activity of E-Cadherin Controls Tumor Cell Metastasis at Multiple Steps. Proceedings of the National Academy of Sciences 117 (11): 5931–37.

Nevoa J. C., Rodrigues R. L., Menezes G. L., Lopes A. R., Nascimento H. F., Santiago S. B., et al. (2017) Molecular Technique for Detection and Identification of Helicobacter Pylori in Clinical Specimens: A Comparison with the Classical Diagnostic Method. Jornal Brasileiro de Patologia e Medicina Laboratorial.

Nikas I., Giaginis C., Petrouska K., Alexandrou P., Michail A., Sarantis P., et al. (2022) EPHA2, EPHA4, and EPHA7 Expression in Triple-Negative Breast Cancer. Diagnostics 12 (2): 366.

Odenbreit S., Swoboda K., Barwig I., Ruhl S., Borén T., Koletzko S., et al. (2009) Outer Membrane Protein Expression Profile in Helicobacter Pylori Clinical Isolates. Infection and Immunity 77 (9): 3782–90.

Pachathundikandi S. K., Tegtmeyer N., and Backert S. (2013) Signal Transduction of Helicobacter Pylori during Interaction with Host Cell Protein Receptors of Epithelial and Immune Cells. Gut Microbes 4 (6): 454–74.

Piscione M., Mazzone M., Di Marcantonio M. C., Muraro R., and Mincione G. (2021) Eradication of Helicobacter Pylori and Gastric Cancer: A Controversial Relationship. Frontiers in Microbiology 12 (February).

Salokas K., Liu X., Öhman T., Chowdhury I., Gawriyski L., Keskitalo S., et al. (2022) Physical and Functional Interactome Atlas of Human Receptor Tyrosine Kinases. EMBO Reports 23 (6).

Schneider S., Carra G., Sahin U., Hoy B., Rieder G., and Wessler S. (2011) Complex Cellular Responses of Helicobacter Pylori-Colonized Gastric Adenocarcinoma Cells. Edited by Blanke S. R. Infection and Immunity 79 (6): 2362–71.

Sexton R. E., Al Hallak M. N., Diab M., and Azmi A. S. (2020) Gastric Cancer: A Comprehensive Review of Current and Future Treatment Strategies. Cancer and Metastasis Reviews 39 (4): 1179–1203.

Shen Z., Fox J. G., Dewhirst F. E., Paster B. J., Foltz C. J., Yan L., et al. (1997) Helicobacter Rodentium Sp. Nov., a Urease-Negative Helicobacter Species Isolated from Laboratory Mice. International Journal of Systematic Bacteriology 47 (3): 627–34.

Sicairos B., Alam S., and Du Y. (2023) A Comprehensive Analysis of Different Types of Databases Reveals That CDH1 MRNA and E-Cadherin Protein Are Not Downregulated in Most Carcinoma Tissues and Carcinoma Cell Lines. BMC Cancer 23 (1): 441.

Wafy H., Abdelmalek S., and Mostafa A. E. (2022) Isolation and Identification of Helicobacter Spp. From Gastric Biopsies and Autopsies in Human and Animal Gastric Patients. Journal of Current Veterinary Research 4 (2): 159–65.

Wei Q., Liu J., Wang N., Zhang X., Jin J., Chin-Sang I., et al. (2014) Structures of an Eph Receptor Tyrosine Kinase and Its Potential Activation Mechanism. Acta Crystallographica Section D Biological Crystallography 70 (12): 3135–43.

Wen J., Lau H. C.-H., Peppelenbosch M., and Yu J. (2021) Gastric Microbiota beyond H. Pylori: An Emerging Critical Character in Gastric Carcinogenesis. Biomedicines 9 (11): 1680.

Xiao T., Xiao Y., Wang W., Tang Y. Y., Xiao Z., and Su M. (2020) Targeting EphA2 in Cancer. Journal of Hematology & Oncology 13 (1): 114.

Xie Y., Zhou J. J., Zhao Y., Zhang T., and Mei L. Z. (2017) H. Pylori Modifies Methylation of Global Genomic DNA and the Gastrin Gene Promoter in Gastric Mucosal Cells and Gastric Cancer Cells. Microbial Pathogenesis 108 (July): 129–36.

Yu W., Yang L., Li T., and Zhang Y. (2019) Cadherin Signaling in Cancer: Its Functions and Role as a Therapeutic Target. Frontiers in Oncology 9 (October).

Yuksel H., Ocalan M., and Yilmaz O. (2021) E-Cadherin: An Important Functional Molecule at Respiratory Barrier Between Defence and Dysfunction. Frontiers in Physiology 12 (October).

Open Access Statement:
This is an open access article distributed under the Creative Commons Attribution License (CC-BY), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.