

Differential Expression of Spermine Oxidase and Proinflammatory Cytokines in Gastric Cancer Patients With and Without *Helicobacter pylori* Infection: A Pilot Study in a Polish Cohort

Lavinia Davidescu¹, Olivia Andreea Marcu^{1*}, Stela Iurciuc¹

¹ Department of Pediatrics I, George Emil Palade University of Medicine, Pharmacy, Science and Technology of Târgu Mureș, Gheorghe Marinescu Street No 38, 540136 Târgu Mureș, Romania.

Abstract

Infectious agents are implicated in the development of various cancers, with *Helicobacter pylori* (*H. pylori*) frequently detected in gastric cancer patients. This study aimed to evaluate the expression of the SMOX gene in a cohort of Polish gastric cancer patients. SMOX is proposed to facilitate *H. pylori*-mediated carcinogenesis through mechanisms involving inflammation, DNA damage, and activation of β -catenin signaling. Additionally, we analyzed mRNA expression of selected pro-inflammatory cytokines (IL-2, IFN- γ , TNF- α) and the antimicrobial peptide cathelicidin (CAMP). Gastric tissue samples were obtained during total gastrectomy from three locations: the primary tumor, tissue 3 cm away from the tumor, and tissue from the opposite gastric wall. RNA was extracted, and quantitative PCR (qPCR) was performed to assess gene expression levels. SMOX expression was significantly elevated in gastric cancer tissues from patients with a history of *H. pylori* infection. To our knowledge, this represents the first study evaluating SMOX expression in patient-derived gastric tissue rather than in cell lines. Expression of pro-inflammatory cytokines (IL-2, IFN- γ , TNF- α) was also increased, suggesting their involvement in shaping the tumor-associated inflammatory microenvironment. In contrast, CAMP expression was reduced across all examined tissue types. The data support a role for SMOX in gastric carcinogenesis, potentially linked to *H. pylori* infection and inflammatory signaling. Further studies are warranted to clarify the contribution of inflammatory mediators and other factors, which may inform future cancer immunotherapy strategies.

Keywords: *Helicobacter pylori*, SMOX, CAMP, gastric cancer, pro-inflammatory cytokines

Corresponding author: Olivia Andreea Marcu

E-mail: marcuandreea@outlook.com

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Introduction

Chronic inflammation is recognized as a key contributor to tumor initiation and progression by promoting

mutations, genomic instability, and epigenetic alterations. It can stimulate angiogenesis, enhance the proliferation and survival of precancerous cells, and facilitate metastasis [1, 2]. Infectious agents are implicated in up to 20% of all cancers [3, 4], with viral, bacterial, and even

parasitic infections capable of altering cell growth, disrupting host immunity, and inducing cellular changes during prolonged infection [3].

Helicobacter pylori (*H. pylori*) is a well-established bacterial risk factor for gastric cancer, with high seroprevalence observed in affected patients and a positive correlation with tumor size and stage [5]. *H. pylori* infection is estimated to increase the risk of gastric cancer approximately six-fold and has been classified as a class I carcinogen by the International Agency for Research on Cancer (IARC) [4, 6].

The SMOX gene, located on chromosome 20p13 [7], encodes spermine oxidase (SMOX), an enzyme involved in polyamine metabolism that converts spermine to spermidine while generating hydrogen peroxide, a reactive oxygen species (ROS). ROS contribute to oxidative stress, epithelial cell apoptosis, and DNA damage [8–10], all of which are associated with cancer development and metastasis [11, 12]. SMOX is also implicated in *H. pylori*-induced carcinogenesis through mechanisms involving inflammation, DNA damage, and β -catenin signaling activation [8–10].

Inflammatory cytokines play a pivotal role in the tumor microenvironment of *H. pylori*-associated gastric cancer. Meta-analyses report elevated levels of IL-1, IL-4, IL-6, IL-10, IL-11, IL-12, and TNF- α , with IL-6 and TNF- α considered particularly important [13]. However, most studies are from non-European populations, and data on Polish patients are limited. In the present study, we focused on IL-2 and TNF- α , both at the mRNA level. TNF- α is crucial in host defense against infection, yet its overexpression can induce chronic inflammation, facilitating tumor development [14]. Cancer cells may also resist TNF- α cytotoxicity, promoting tumor survival and proliferation [15, 16]. IL-2 is a pleiotropic cytokine that can activate immune responses against cancer, but elevated IL-2 levels have also been associated with tumor progression, including in gastric cancer [13,17–19].

Interferon gamma (IFN- γ) is integral to both innate and adaptive immunity, contributing to antibacterial and antiviral defense [20, 21]. IFN- γ exerts anti-cancer effects by inhibiting proliferation and angiogenesis [20, 22]; however, chronic exposure may paradoxically enhance tumor growth, including in gastric cancer [22–24].

Antimicrobial peptides, such as LL-37—encoded by the CAMP gene—play additional roles in host defense. LL-37 exhibits antimicrobial activity, promotes epithelial migration, wound healing, and angiogenesis [25–27]. Interestingly, LL-37 has both anticancer properties and, in some contexts, its overexpression has been linked to tumor progression [26, 28–30].

The present study aimed to evaluate the expression of SMOX, IL-2, IFN- γ , TNF- α , and CAMP in gastric tissue from patients with gastric cancer, comparing primary

tumor sites and macroscopically normal tissue, and to examine associations with *H. pylori* infection. Notably, this research focuses on a Polish patient cohort, addressing a gap in current literature that is predominantly based on Asian populations, where gastric cancer incidence is highest.

Materials and Methods

Study material

This study included 32 patients with histologically confirmed gastric cancer who underwent total gastrectomy. During the surgical procedure, three types of gastric tissue specimens were collected: from the primary tumor, from tissue located 3 cm from the tumor margin, and from the stomach wall opposite the lesion. Each specimen weighed between 150 and 200 mg. Histopathological reports were obtained for all cases. Peripheral blood samples (two tubes, 4 mL each) were also drawn from each participant prior to surgery using sterile, anticoagulant-free tubes for serum preparation.

The study group comprised 12 females and 20 males, with a mean age of 67.78 years (95% CI: 63.02–72.54). Most patients (46.9%) had stage III disease, followed by stage II (28.1%) and stage I (25%). Comprehensive demographic and clinical details of this cohort were published earlier [5].

Methods

Tissue specimens were used to evaluate the expression of *SMOX* and selected cytokine genes, while serum samples were analyzed for the presence of anti-*H. pylori* antibodies.

RNA isolation and quantitative PCR

Total RNA was extracted from gastric tissues using the mirVana mRNA Isolation Kit (Invitrogen, Thermo Fisher Scientific, Waltham, MA, USA) following the manufacturer's instructions. The RNA samples were stored at -80°C until further processing. Reverse transcription was performed with TaqManTM Advanced MicroRNA Assays (Thermo Fisher Scientific). Each reaction included 20 μL of RT Master Mix and 10 μL of RNA sample, incubated in an Eppendorf Mastercycler Gradient thermocycler under the following conditions: 25°C for 10 min, 37°C for 120 min, 65°C for 5 min, followed by indefinite storage at 4°C .

After reverse transcription, complementary DNA (cDNA) was diluted 1:10 in $0.1\times$ TE buffer. Quantitative PCR (qPCR) was carried out using the TaqManTM Fast Advanced Master Mix (Thermo Fisher Scientific). Each 20 μL reaction contained 15 μL of the master mix and 5 μL of diluted cDNA. Amplification was conducted in an Eppendorf thermal cycler with the following program: 95

°C for 20 s, followed by 40 cycles at 95 °C for 3 s and 60 °C for 30 s.

Expression levels of *SMOX*, *IL-2*, *IFN-γ*, *TNF-α*, and *CAMP* were determined using the KAPA SYBR FAST Universal qPCR Kit (Roche, Kapa Biosystems, Johannesburg, South Africa). Gene-specific primers and probes (**Table 1**) were designed using NCBI BLAST and Primer-BLAST tools and synthesized by the Sequencing and DNA Synthesis Laboratory, IBB PAN (Lodz, Poland). Relative gene expression was calculated using the comparative cycle threshold ($\Delta\Delta CT$) method [31], with *GAPDH* as an internal control. cDNA synthesized from commercially available RNA derived from normal gastric

tissue (Human Stomach Total RNA, Invitrogen, Thermo Fisher Scientific) served as the calibrator.

Detection of Anti-*H. pylori* Antibodies

Serum levels of anti-CagA antibodies were determined using ELISA kits (EIA Helicobacter MONO IgM, IgG, IgA; TestLine Clinical Diagnostics, Brno-Královo Pole, Czech Republic). Microtiter plates were coated with *H. pylori* strains rich in CagA (120 kDa) and VacA (87 kDa) proteins. The assay was performed according to the manufacturer's protocol. Absorbance was measured at 450 nm using an ELx800 plate reader (BioTek Instruments, Winooski, VT, USA), and results were interpreted relative to the negative control wells.

Table 1. Sequences of primers (F and R) and probes for the studied genes

GENE	PRIMERS (F and R), PROBE
<i>GAPDH</i>	GAPDH-F-TGGTATCGTGGAAGGACTCATGA GAPDH-R- CCAGTAGAGGCAGGGATGATGT 5'-Cy5.5-TCCACAGTCTTCTGGGTGGCA-BHQ-3-3'
<i>SMOX</i>	SMOX-F: 5'ACTTGGACACGCCACCTTT3' SMOX-R: 5'CGCCATTCTTGGAAATAGAGG3'
<i>CAMP</i>	CAMP-F- TAACCTCTACCGCCTCCTGG CAMP-R- CTTCACCAGCCCGTCCTTC 5'-6-FAM-TGAAGCTCACAGGCTTTGGCGT-BHQ-1-3'
<i>IL-2</i>	IL2-F-CCAACTCACCAGGATGCTCA IL2-R-ATATTGCTGATTAAGTCCCTGGGT 5'-Texas Red-TCTGTGGCCTTCTTGGGCATGT-BHQ-2-3'
<i>TNF-α</i>	TNFα-F- CCTCAGCCTCTTCTCCTTCTCT TNFα-R-AGAAGATGATCTGACTGCCTGGG 5'-Cy5-CACTCCAAAGTGCAGCAGGCAGA-BHQ-3-3'
<i>IFN-γ</i>	IFNγ-F CAATAGCAACAAAAAGAAACGAGATG IFNγ-R-CTGACTCCTTTTCGCTTCCC 5'-HEX-CGACAGTTCAGCCATCACTTGGA-BHQ-1-3'

F – forward, R – reverse, 6-FAM - 6-carboxyfluorescein, Texas Red - sulfonyl chloride, Cy5 – cyanine dye, HEX - hexachlorofluorescein.

Statistical analysis

All statistical procedures were carried out using Statistica software version 13.1 (StatSoft Inc., StatSoft Polska Sp. z o.o., Cracow, Poland; <http://www.statsoft.com>). A *p*-value < 0.05 was considered statistically significant. Gene expression results were expressed as mean relative quantification (RQ) values with 95% confidence intervals (CI). Differences in gene expression levels among the three sampling sites (A, B, and C) were evaluated using the nonparametric Wilcoxon test. Associations between gene expression levels and clinical parameters were examined using Spearman's rank correlation coefficient.

Ethical approval

The study protocol was reviewed and approved by the Bioethics Committee of the Medical University of Lodz, Poland (approval numbers RNN/206/19/KE and RNN/209/19/KE). All procedures were performed in accordance with the ethical standards of the institutional and national research committees and with the 1964 Declaration of Helsinki and its later amendments. Written

informed consent was obtained from all participants before enrollment.

Results

Gene expression levels

The relative expression of the *SMOX* gene showed a marked increase in tumor tissue (sample A; RQ = 2.87), corresponding to nearly a threefold elevation compared to the calibrator. Expression levels were lower in tissue collected 3 cm from the tumor (sample B; RQ = 1.20) and in the opposite stomach wall (sample C; RQ = 0.84).

For *TNF-α*, expression was highest in tumor tissue (sample A; RQ = 14.94), nearly 15 times greater than the calibrator. Expression levels were reduced in adjacent tissue (sample B; RQ = 7.44) and further decreased in distant tissue (sample C; RQ = 4.17).

IFN-γ expression followed a similar pattern, with tumor tissue showing the strongest upregulation (sample A; RQ = 10.07), followed by lower expression in samples B (RQ = 4.62) and C (RQ = 1.07).

For *IL-2*, the mean expression in tumor tissue (sample A; $RQ = 1.84$) was approximately twice that of the calibrator, slightly lower in sample B ($RQ = 1.65$), and markedly reduced in sample C ($RQ = 0.48$).

Conversely, *CAMP* expression was consistently downregulated across all tissue types. The lowest expression was found in sample B ($RQ = 0.31$), followed by sample C ($RQ = 0.34$) and sample A ($RQ = 0.41$), corresponding to roughly 2.5-fold lower levels than the calibrator.

Significant differences in expression levels among the three sampling sites (A, B, and C) were observed for *SMOX*, *TNF- α* , *IFN- γ* , and *IL-2* ($p < 0.05$, Wilcoxon test). In the case of *CAMP*, statistically significant differences were detected between samples A and B, and between A and C ($p < 0.05$, Wilcoxon test).

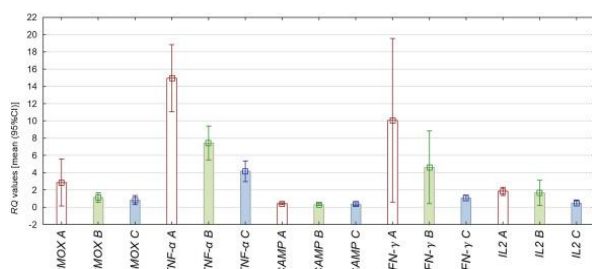


Figure 1. Box and whisker plots representing mean relative quantification (RQ) values of the studied genes in different tissue samples

Correlation between gene expression and tumor stage

As shown in **Figure 2**, analysis of gene expression across tumor stages revealed distinct trends for each gene. The *SMOX* transcript reached its highest levels in stage III tumor tissue (sample A), approximately four times greater than the calibrator, while the lowest levels occurred in stage I tissue opposite the tumor (sample C). Expression of *TNF- α* followed a similar pattern, peaking in stage III tumors and declining markedly in stage II samples from the opposite gastric wall. *IFN- γ* expression was also strongest in stage III tumors and weakest in stage III sample C. For *IL-2*, the highest levels were noted in tissue adjacent to stage III tumors (sample B), whereas the lowest were seen in stage II sample C. In contrast, *CAMP* expression was consistently downregulated in all samples, with relatively higher expression in stage II tumor tissue and the lowest values in stage II sample B and stage III sample A.

Correlation testing indicated a negative association between *SMOX* expression and tumor stage, most pronounced and statistically significant in sample B ($R = -0.366$, $p = 0.039$). A comparable trend was observed for *TNF- α* , showing inverse correlations across all sites,

reaching significance for tumor tissue (sample A; $R = -0.471$, $p = 0.013$).

Expression of *IL-2* showed a mild, non-significant positive trend in tumor samples and negative trends in surrounding and opposite tissues. *IFN- γ* demonstrated variable associations, increasing with tumor stage in samples A and C (significant only for C; $R = 0.410$, $p = 0.034$), but declining in adjacent tissue (sample B). *CAMP* expression displayed no significant correlations with tumor stage, although weak positive relationships were observed in tumor and opposite wall tissues.

Overall, the data suggest that *SMOX* and *TNF- α* expression tends to decline with advancing tumor stage, while *IFN- γ* may increase in more advanced disease, and *CAMP* remains consistently suppressed across all samples.

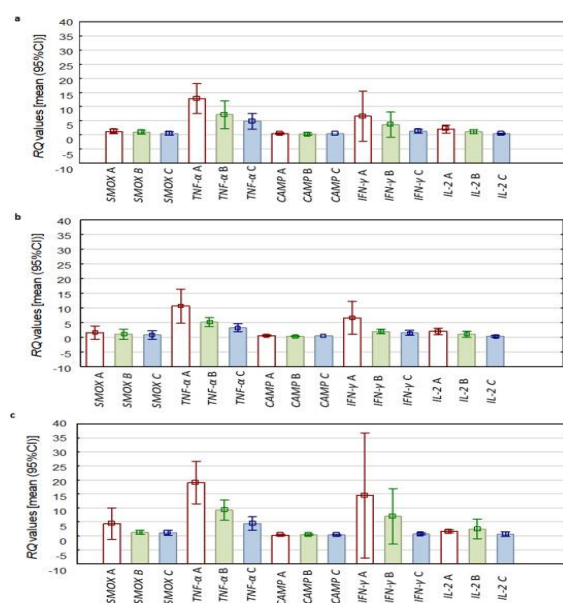


Figure 2. Box and whisker plots representing mean relative quantification (RQ) values of the studied genes regarding tumor stage and tissue type. a – Stage I; b – Stage II; c – Stage III

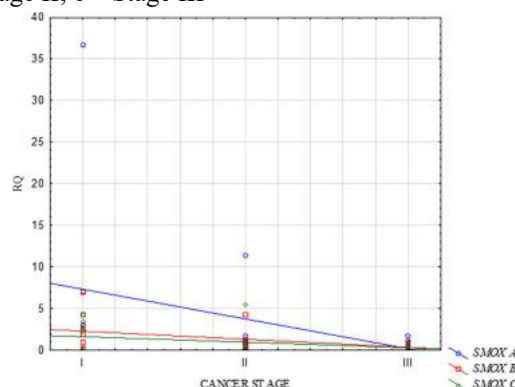


Figure 3. Correlation between *SMOX* expression level and cancer stage (I, II, III) in all examined tissue groups (A, B, C) (Spearman's rank correlation)

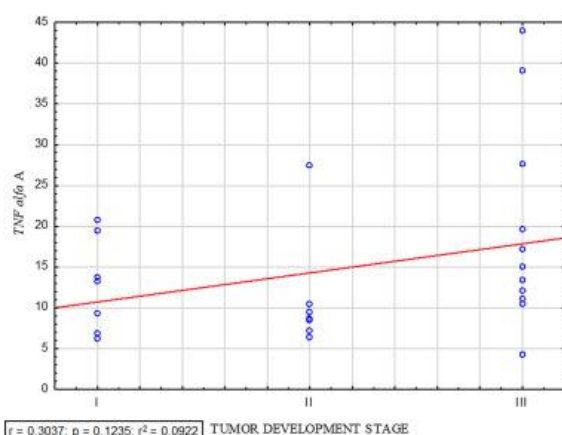


Figure 4. Correlation between *TNF-α* expression in primary tumor tissue (sample A) and tumor development stage (Spearman rank correlation)

Gene expression in relation to *H. pylori* infection history

Serological analysis revealed that 21 out of 32 patients (65.5%) were positive for anti-*H. pylori* IgG antibodies. The prevalence of infection increased with cancer stage, detected in 25% of stage I, 77.8% of stage II, and 80% of stage III patients.

As illustrated in **Figure 5**, *SMOX* expression in tumor tissue was nearly twice as high in *H. pylori*-positive individuals (mean RQ = 3.8) compared with uninfected patients (mean RQ = 1.52), although this difference was not statistically significant ($R = -0.005$, $p = 0.981$; Wilcoxon test). Expression of *SMOX* showed a negative association with *H. pylori* seropositivity across all tissue types, reaching statistical significance only in tissue collected 3 cm from the tumor ($R = -0.453$, $p = 0.009$).

For *TNF-α*, gene expression was consistently elevated across all tissue samples, regardless of *H. pylori* infection status. The strongest expression was observed in tumor tissue, and no statistically significant associations were identified ($p > 0.05$).

IFN-γ expression was also highest in tumor samples from *H. pylori*-positive patients—over twice the level observed in negative cases. Correlation analysis revealed weak, non-significant positive relationships in tumor and adjacent tissues and a slight negative correlation in tissue opposite the tumor.

Similarly, *IL-2* expression was higher in all tissue types of *H. pylori*-infected patients compared to uninfected ones, although none of these differences reached statistical significance.

By contrast, *CAMP* gene expression remained reduced in all tissues but showed a positive association with *H. pylori* infection, with the only significant correlation observed in tissue collected near the tumor ($R = 0.595$, $p = 0.015$).

In summary, *H. pylori*-positive patients tended to exhibit elevated *SMOX*, *IFN-γ*, and *IL-2* expression, suggesting a link between bacterial infection and pro-inflammatory gene activation, while *CAMP* expression remained suppressed but correlated positively with infection status.

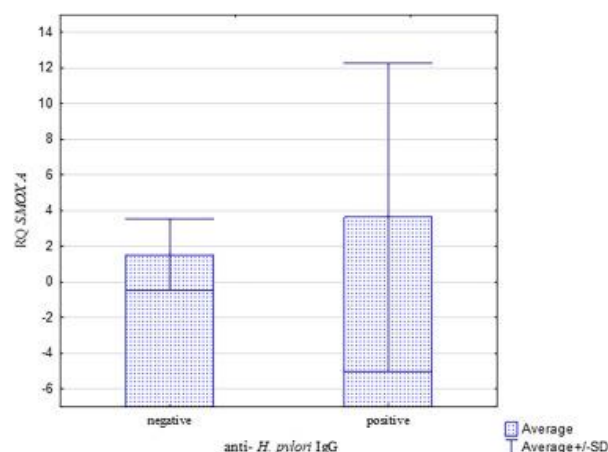


Figure 5. *SMOX* expression in the tumor tissue (sample A) regarding the presence of anti-*H. pylori* IgG antibodies in patients

Table 2. Gene expression levels in relation to the history of *H. pylori* infection in patients

Gene	RQ values [mean (95 % CI)]					
	<i>H. pylori</i> infection					
	Positive			Negative		
	A	B	C	A	B	C
<i>SMOX</i>	3.620 (−0.68–7.92)	1.022 (0.44–1.60)	0.940 (0.19–1.69)	1.521 (0.09–2.93)	1.299 (−0.02–2.62)	0.684 (−0.14–1.51)
<i>TNF-α</i>	14.829 (9.03–20.63)	8.145 (5.53–10.76)	4.293 (2.63–5.96)	15.124 (9.99–20.26)	6.247 (2.92–9.57)	3.947 (1.83–6.07)
<i>IFN-γ</i>	6.906 (2.89–10.92)	3.063 (1.30–4.82)	1.048 (0.58–1.51)	15.451 (−12.22–43.12)	7.262 (−5.04–19.56)	1.109 (0.56–1.65)
<i>IL-2</i>	1.820 (1.18–2.46)	2.064 (−0.33–4.46)	0.583 (0.01–1.16)	1.878 (0.95–2.81)	0.949 (0.39–1.51)	0.311 (0.17–0.46)
<i>CAMP</i>	0.416 (0.17–0.66)	0.374 (0.23–0.51)	0.344 (0.17–0.52)	0.406 (0.25–0.56)	0.132 (0.07–0.19)	ND (ND)

Abbreviations: RQ – relative quantification; ND – not defined.

Discussion

This study investigated the molecular mechanisms linking *Helicobacter pylori* infection to gastric cancer, focusing

on the expression of the SMOX gene, which encodes the enzyme spermine oxidase. Our findings demonstrated a marked upregulation of SMOX in primary gastric tumor tissue compared to adjacent and distant gastric samples, suggesting a potential contribution of this enzyme to carcinogenesis through the generation of reactive oxygen species (ROS). Notably, this study appears to be the first to assess SMOX expression directly in human gastric tissue rather than cell lines.

The observed association between *H. pylori* infection, increased SMOX expression, and gastric cancer supports previous evidence implicating *H. pylori*-induced oxidative stress in tumorigenesis. Earlier research has shown that *H. pylori* CagA protein activates SMOX, leading to ROS-mediated DNA damage, apoptosis resistance, and enhanced susceptibility to malignant transformation. Moreover, elevated SMOX levels have been reported across the stages of *H. pylori*-related disease, from gastritis to intestinal metaplasia. Consistent with these observations, our study revealed the highest SMOX expression in tumors from *H. pylori*-positive patients, while the lowest levels were noted in tissue from the stomach wall opposite the tumor in uninfected individuals. Although the expression difference approached sixfold, it did not reach statistical significance, likely due to limited sample size.

To better understand the inflammatory environment associated with gastric cancer, we also analyzed TNF- α , IFN- γ , IL-2, and CAMP expression. TNF- α expression was significantly elevated across all tissue types, peaking in primary tumors (a nearly 15-fold increase compared with control levels) and declining with distance from the lesion. The strong expression gradient underscores the key role of TNF- α -driven inflammation in gastric tumor development. Interestingly, TNF- α expression exhibited a significant negative correlation with tumor stage, implying that its effects may be most pronounced during the early phases of carcinogenesis. This aligns with previous studies describing TNF- α as a cytokine with both anti-tumor and pro-tumor functions—capable of promoting chronic inflammation, angiogenesis, and poor outcomes in gastric cancer. Despite its recognized link with *H. pylori*-associated gastritis, we did not find a significant correlation between TNF- α expression and *H. pylori* seropositivity, possibly due to the small number of cases analyzed.

Regarding the CAMP gene, which encodes the antimicrobial peptide cathelicidin, our data revealed a general reduction in its expression across all tissue types, with significant differences between tumor and non-tumor sites. A positive correlation between *H. pylori* infection and CAMP expression was detected, reaching statistical significance in the tissue adjacent to the tumor. These findings mirror reports indicating that cathelicidin

expression decreases during the progression from chronic gastritis to adenocarcinoma, suggesting that impaired innate immunity may contribute to sustained inflammation and tumor promotion.

The proinflammatory cytokine IFN- γ also displayed high expression in tumors and surrounding tissues, reinforcing its involvement in the tumor-associated immune response. While typically considered an antitumor cytokine, IFN- γ can exert protumor effects by promoting immune evasion through downregulation of MHC molecules and activation of immunosuppressive pathways such as IDO and checkpoint inhibitors. Our results align with previous evidence showing elevated IFN- γ in gastric cancer and *H. pylori* infection. Although not statistically significant, the strong trend toward higher IFN- γ expression in *H. pylori*-positive patients supports its role as a mediator linking infection-induced inflammation and gastric carcinogenesis.

In conclusion, this study provides evidence that SMOX, along with inflammatory mediators such as TNF- α and IFN- γ , may contribute to the development of gastric cancer, particularly in the context of *H. pylori* infection. The downregulation of CAMP further suggests that disruption of antimicrobial defense mechanisms may exacerbate chronic inflammation and promote tumor progression. However, the observed trends warrant confirmation in larger cohorts to validate these molecular associations and to further clarify their potential as therapeutic or diagnostic targets in gastric cancer.

Previous studies from Iran and Mexico have reported elevated IL-2 levels in both serum and gastric tissue of patients with gastric cancer. Our findings are consistent with these observations, showing increased IL-2 gene expression in the tumor and peritumoral tissue, with a marked decrease in the gastric wall opposite the lesion. The significant expression differences between tissue types, together with the positive correlation between IL-2 expression and tumor stage, suggest that IL-2 contributes to gastric carcinogenesis, possibly by promoting local immune activation and chronic inflammation. Although the relationship between IL-2 expression and *H. pylori* seropositivity was not statistically significant, the observed positive trend supports the hypothesis that *H. pylori* infection may trigger IL-2-mediated immune responses. Notably, earlier studies in Polish pediatric patients demonstrated an association between *H. pylori* infection and increased IL-2 concentrations in gastric biopsies, while a 2023 meta-analysis found no significant impact of *H. pylori* infection on serum IL-2 levels. This discrepancy may reflect population-specific or disease-stage-dependent differences in cytokine expression patterns.

Cytokines play central roles in mediating inflammation and orchestrating the immune response that underlies

tumor initiation and progression. Their dual function—as mediators of both antitumor immunity and chronic pro-tumor inflammation—makes them potential targets for therapeutic intervention. Indeed, biological agents modulating cytokine activity have already shown promise in various inflammatory and neoplastic diseases. However, before cytokine-targeted therapies can be applied to gastric cancer or precancerous conditions such as chronic atrophic gastritis, a more detailed understanding of the cytokine networks driving gastric tumorigenesis is needed. The regional variability in cytokine expression and its correlation with gastric cancer incidence further highlight the importance of population-specific investigations.

Limitations

The principal limitation of this study lies in its relatively small sample size, which may restrict the statistical strength and generalizability of the results. Furthermore, the collection of biological samples took place between 2018 and 2020—a period profoundly affected by the COVID-19 pandemic, which limited access to oncological care and hindered the recruitment of new patients. These logistical constraints reduced the availability of adequate biological material for analysis. Therefore, while our findings provide valuable preliminary insights, they should be interpreted with caution, and validated in future studies involving larger, multi-center cohorts.

Conclusions

This study revealed elevated SMOX expression in gastric cancer tissues, particularly in patients with *H. pylori* infection, supporting a potential role for SMOX in gastric carcinogenesis through the generation of reactive oxygen species. Although a direct causal association between *H. pylori* infection and SMOX expression could not be conclusively demonstrated, our findings emphasize the contribution of oxidative stress and inflammatory signaling to tumor development. Moreover, increased levels of TNF- α , IFN- γ , and IL-2 expression indicate that pro-inflammatory cytokines play essential roles in shaping the tumor's immune microenvironment.

A deeper understanding of the molecular and immunological mechanisms linking *H. pylori* infection, inflammation, and gastric cancer could guide the identification of novel biomarkers and therapeutic targets. Continued research in this area is essential to clarify the interplay between host immune responses and carcinogenic pathways, and to advance the development of effective immunotherapeutic strategies for gastric cancer.

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Conflict of interest: None.

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Ethics statement: None.

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