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REVIEW: GASTRIC MALIGNANCIES – MICROBES, BIOMARKERS AND MOLECULAR MECHANISMS

J. Sousa[1,2], I. Castro[1,2,3], J. Figueiredo[1,2,3], R.M. Ferreira[1,2]

[1]Instituto de Investigação e Inovação em Saúde, Universidade do Porto (i3S), Porto, Portugal
[2]Institute of Molecular Pathology and Immunology of the University of Porto (IPATIMUP), Porto, Portugal
[3]Faculty of Medicine of the University of Porto (FMUP), Porto, Portugal

J. Sousa and I. Castro contributed equally

Corresponding Author: Rui Ferreira, Ph.D; e-mail: ruif@i3s.up.pt

Abstract – Gastric carcinoma is a very common and lethal cancer, posing a serious burden worldwide. The exact contribution of microbial risk factors for this malignancy remains to be fully understood, impairing the implementation of effective preventive strategies. In addition, insufficient knowledge of Helicobacter pylori-mediated gastric carcinogenesis mechanisms, absence of screening programs based on accurate biomarkers, and lack of efficient therapeutics contribute to persistent high mortality rates. This past year has witnessed the emergence of new findings on the role of microorganisms in the development of gastric cancer, on potential anti-*H. pylori* vaccines, and on novel diagnostic and prognostic biomarkers. Experimental and clinical data provided further insights into the molecular programs activated in gastric cancer, offering alternative targets for therapeutic interventions and patient stratification. This article provides an overview of the research highlights related to these topics published from April 2022 to March 2023.

Keywords: Gastric cancer, *Helicobacter pylori*, Microbiota, Epstein-Barr Virus, Cancer signaling, Cancer therapy.

INTRODUCTION

Gastric cancer is a major public health problem worldwide, with more than 1 million new cases and 768,000 deaths annually[1]. Gastric cancer develops as a consequence of a long and complex interplay between microorganisms, environmental factors, and host genetic susceptibility. This heterogeneous disease presents distinct histological identities reflecting different molecular subtypes, which include tumors characterized by microsatellite instability, Epstein-Barr virus (EBV) infection, genomic stability, or chromosomal instability. Of note, molecular subtypes are associated with different clinicopathological features and prognoses. Despite advances regarding gastric cancer molecular characterization, the contribution of risk factors and mechanisms underlying gastric cancer development remain largely unexplored. Herein, we provide an overview of the latest studies addressing these issues and highlight their value for improved management of cancer patients.

NEW METHODS FOR DETECTION OF HELICOBACTER PYLORI VIRULENCE FACTORS

Helicobacter pylori is the main risk factor for gastric cancer development. Therefore, its detection is essential for timely therapeutic intervention. Conventional methods, including PCR, urea breath test, and serological tests, are widely used for the identification of infection, however, they present limitations regarding sensitivity, specificity, and information on *H. pylori* virulence. Taking this into account, Habimana et al[2] developed a new method based on a modified CRISPR/Cas12a that detects *cag*A and *vac*A genes, which are important virulence markers associated with inflammation and carcinogenesis[2]. This method can be applied directly to gastric biopsies or clinical isolates, and improves sensitivity in 16-time fold, when compared to conventional methods[2]. A similar method was established by Liu et al[3] through combination of CRISPR/Cas12a with recombinase polymerase amplification directed to the *ure*B gene[3]. The method showed good performance in monitoring and localizing the infection in the gastric mucosa from different clinical settings. In addition, this fast detection system requires a low amount of biological material and uses common equipment, providing an important tool for low-income countries[3]. With the purpose of setting up a non-invasive method, Nieuwenburg et al[4] implemented an innovative fecal immunochemical test. Using fecal samples from 182 patients, the method proved to have a sensitivity of 94.2% and accuracy of 77.6%, which were higher than that reached by conventional stool antigen test[4]. An anti-*H. pylori* IgG ELISA was also tested as a non-invasive approach using serum of 1678 patients. This retrospective study demonstrated that in comparison with urea breath testing, the ELISA was more sensitive and less expensive, suggesting its potential in future screening programs across populations[5].

In fact, eradication of *H. pylori* infection is an effective strategy to reduce gastric cancer incidence, as shown by Yan et al[6] in a prospective randomized study conducted in China[6]. Upon 26.5 years of follow-up, participants receiving *H. pylori* treatment had a lower incidence of gastric cancer when compared with placebo group[6]. So far, most eradication regimens are based on the combination of antibiotics with a proton pump inhibitor. Nonetheless, antibiotic usage presents numerous challenges, namely the emergence of resistant strains and side effects on resident microbiota.

In the last year, two oral vaccines have emerged as promising approaches for *H. pylori* prevention[7,8]. Guo et al[7] produced a vaccine that delivers antigens of Urease, CagA, VacA and neutrophil activating proteins, using the probiotic *Lactococcus lactis*, as the delivery vector[7]. In contrast, Ghasemi et al[8] engineered another system using *Salmonella typhimurium* as a vector for the delivery of four *H. pylori* antigens: *H. pylori* adhesion A (*HpA*), neutrophil activating protein (Hp-NAP), and Urease A and B[8]. Both studies[7,8] showed that, in mice, vaccines were safe and provided protective immunity against *H. pylori* infection.

MICROBIAL FACTORS IN GASTRIC CANCER

A critical feature of *H. pylori* infection is the induction of inflammation in the gastric mucosa, which is modulated not only by bacterial virulence but also by the host immune response[9,10]. Chronic inflammation triggered by *H. pylori* may lead to development of gastric atrophy, intestinal metaplasia, dysplasia, and cancer in a proportion of the infected individuals. By combining several techniques, including RNA-sequencing, flow cytometry, immunohistochemistry, and Chipcytometry, Koch et al[11] investigated the specific role of CD8+ T-cells in *H. pylori*-mediated inflammation both in mice and in humans[11]. They showed that upon *H. pylori* infection, the T-cell population is dominated by CD8+, as an inverse correlation was detected between this cell type and bacterial colonization[11]. Furthermore, it was demonstrated that CD8+ T-cells constitute the tissue-resident memory cells, persisting in the gastric mucosa after *H. pylori* eradication, and expanding after a secondary contact with the bacterium[11]. Importantly, the study revealed that CD8+ T-cell infiltration was directed to the major bacterial antigen CagA, which suggests that early elimination of *cag*A-positive strains could prevent the development of premalignant lesions and reduce gastric cancer risk[11].

Gobert et al[12] used the INS-GAS mouse model of gastric carcinogenesis to show that *H. pylori* colonization, hyperplasia, gastrointestinal intraepithelial and immune cells were decreased

by treatment with hydroxylbenzylamine (2-HOBA). Accordingly, treatment with 2-HOBA, a scavenger of reactive aldehydes generated during inflammation, induced significant downregulation of inflammation markers, including IL-1B, TNFA, NOS2, CXCL1, IL-17 and IFN-γ, and decreased levels of DNA damage[12].

Approximately 9% of gastric cancers are positive for EBV, the great majority of them being also positive for *H. pylori*. In an attempt to assess EBV oncogenic effects, Noh et al[13] performed a retrospective study involving 956 patients who underwent surgery for gastric cancer resection[13]. The relationship between the status of EBV and *H. pylori* with clinicopathological features was evaluated through multivariate analysis. EBV infection alone was inversely associated with overall survival, despite presenting similar clinicopathological features to those cases with coinfection[13]. Aligned with this idea, Duque et al[14] investigated whether EBV infection could be associated with changes in the circulating levels of iron, facilitating *H. pylori*-induced carcinogenesis. The authors found that EBV infection is associated with higher levels of hepcidin, a negative regulator of iron entry into circulation. Data from TCGA further supported the association between EBV infection and the BMP-SMAD and the IL-1/IL-6 pathways, which control the hepcidin expression[14].

Other microorganisms constituting the gastric microbiome might also influence the development of gastric cancer by increasing the amount of nitrosating compounds in the stomach. Recently, the microbial composition of paired samples from the gastric epithelium and gastric fluid was shown to change along gastric carcinogenesis, concomitantly with increased levels of nitrite and a decrease in gastric acidity[15]. Corroborating the existence of a cancer-associated microbiota profile, Liu et al[16] identified an enrichment of opportunistic pathobionts, including *Fusobacterium*, *Parvimonas*, *Veillonella*, *Prevotella,* and *Peptostreptococcus species*, as well as a decrease of bacterial commensals as *Bifidobacterium*, *Bacillus,* and *Blautia species* in gastric cancer. Despite the application of a consistent bioinformatics pipeline to data from six distinct studies, this meta-analysis was biased regarding the geographic origin of patients, impairing more generalized conclusions[16].

BIOMARKERS IN GASTRIC CANCER

Gastric cancer is frequently diagnosed at advanced stages when patients present symptoms, which limits therapeutic options and results in high morbidity and mortality. Therefore, there is an urgent need to find effective gastric cancer biomarkers for early detection of the disease. In this context, circulating proteins and metabolites emerged as potential gastric cancer biomarkers[17]. Deng et al[17] performed a systematic review with meta-analysis to assess the value of circulating proteins, such as pepsinogen, transferrin, ferritin, and anti-*Helicobacter* IgG, as well as a panel of metabolites, including glucose, cholesterol and vitamins, α/ β-carotenes, or α/γ–tocopherol[17]. The analysis revealed that high levels of anti-*H. pylori* IgG, pepsinogen I (<30 μg/L), and serum pepsinogen I/II ratio (<3) were the best candidates. As an alternative approach, Otsu et al[18] screened the miRNA profile in the serum of 1206 patients, demonstrating that the combination of three miRNAs had good performance to discriminate individuals at higher risk of developing gastric cancer[18].

MOLECULAR MECHANISMS IN GASTRIC CANCER

The mechanistic basis of gastric carcinogenesis has been subject of intense investigation with the purpose of identifying novel biomarkers or therapeutic targets. Among these studies, it was found that *H. pylori* infection induces expression and secretion of Laminin γ2, an important extracellular matrix (ECM) component[19]. Laminin γ2 was found to promote survival and invasion of gastric cancer cells, increasing the activity of molecules such as AKT and Src, while repressing JNK signaling. Using mutant *H. pylori* strains, clinical isolates, and gastric cancer samples, the authors further demonstrated that this effect was dependent on a functional type IV secretion system and on CagA. They propose that cells with genetic or epigenetic alterations of E-cadherin are more susceptible to *H. pylori* effects, highlighting potential benefits of eradication treatment in carriers of E-cadherin germline variants[19,20].

The outcome of persistent *H. pylori* infection has been associated with activation of Nuclear factor kB (NF-kB), which is a well-known transcriptional factor involved in cancer development and progression. By coupling bioinformatics analysis and *in vitro* assays, *RASAL2* was identified as a candidate gene transcriptionally regulated through NF-kB in *H. pylori*-infected tissues[21]. Consistent with this, increased *RASAL2* mRNA levels were detected in human gastric tumor tissues and mouse gastric cancer models, as well as in public data sets comprising *H. pylori* infected mice[21]. The molecular mechanism underlying oncogenic functions of *RASAL2* was found to involve the AKT/β-catenin signaling axis, contributing to patient poor prognosis and chemoresistance[21]. *CDK1* was recently confirmed to be an additional target gene of NF-kB in response to *H. pylori* infection in gastric cancer cell lines, mouse models, and human tumor tissues[22]. Binding of NF-kB to the *CDK1* promoter leads to its increased expression and consequent modulation of the GSK-3β/β-catenin pathway with impact in cell growth and apoptosis[22].

Over the past decades, multiple cytokines were reported to trigger chronic gastric inflammation. High levels of IL-17A have been previously detected in serum and tumor samples of gastric cancer patients, when compared to healthy controls[23]. Recently, IL-17A inhibition was found to decrease tumor growth, oxidative stress and stemness properties of cancer cells by impairing its interaction with the IL-17RC receptor and blocking the downstream NF-kB/NOX1 pathway[24].

Along with cytokines, oxidative stress induced by the accumulation of reactive oxygen species (ROS) has emerged as a major contributor to pro-inflammatory conditions of gastric tissues and tumors. In this regard, *H. pylori* was shown to upregulate and phosphorylate the E3 ubiquitin ligase Siah2, accelerating proteasomal degradation of the 78-kDa glucose-regulated protein (GRP78) – a powerful player in antioxidant responses. As a result, ROS accumulate in gastric cancer cells conferring proliferative advantages to that cells[25].

Increased levels of the cysteine-producing enzyme cystathionine γ-lyase (CTH) were also described to accompany inflammatory response to *H. pylori*, both in humans and mice[26]. CTH enhances mitochondrial respiration and glycolysis in macrophages, supporting their metabolic activation and polarization[26].

The relevance of the various cell types present in the gastric tumor microenvironment was investigated by single-cell RNA-seq in a cohort of 31 gastric cancer patients with different cancer subtypes and stages[27]. The comprehensive analysis of more than 200,000 cells, contemplating their geographic and spatial relationship, unveiled a plasma cell program involving the epithelial-resident KLF2 in diffuse-type gastric cancer. In addition, this study has identified a novel cancer-associated fibroblast subtype characterized by high INHBA-FAP expression correlated with patient poor prognosis[27].

Overall, the use of multidisciplinary approaches identified several molecular features, including Laminin γ2, RASAL2 and CDK1, as potential prognostic biomarkers or promising targets in gastric tumors.

MOLECULAR CLASSIFICATION AND PROGNOSTIC MARKERS IN GASTRIC CANCER

Assessing the molecular subtypes of gastric cancer may provide a crucial tool to predict clinical outcome and assist clinicians in treatment decision. To improve the knowledge on mesenchymal-subtype of gastric cancer, which encompasses microsatellite stable tumors with an epithelial-to-mesenchymal transition (EMT) phenotype, a transcriptomic survey was performed on 1000 primary tumors. Based on epigenomic profiles, Ho et al[28] identified a 993-gene signature able to classify these tumors, and to predict their clinical aggressiveness or resistance to targeted therapies[28]. Notably, by analyzing DNA-regulatory elements, the authors revealed an epigenetic landscape of mesenchymal gastric cancer orchestrated by *TEAD1*[28]. This finding pinpoints the pharmacological inhibition of *TEAD1* as a potential therapeutic solution for this gastric cancer subtype[28]. Another study uncovered a similar value for *ARID1A*, one of the most frequently mutated genes in gastric cancer. In particular, it was verified that *ARID1A* inactivation is linked to distinct mutational signatures across molecular gastric cancer TCGA subtypes associated with NF-kB-driven proinflammatory microenvironment[29].

EMT signatures were investigated as prognostic biomarkers by Song et al[30]. Based on the expression level of EMT genes, patients were stratified into two groups with distinct prognosis.

Patients harboring tumors with high levels of EMT markers had poor prognosis, while those with low levels of an EMT signature had a better prognosis and could benefit from adjuvant chemo-radiotherapy[30].

The prognostic value of blood-derived markers, including carcinoembryonic antigen (CEA), carbohydrate antigen (CA) 19-9, alkaline phosphatase, neutrophils, hemoglobin, and lactate dehydrogenase, was also evaluated in 788 patients enrolled in a clinical trial[31]. High levels of CEA and CA 19-9 were associated with worse overall survival and event-free survival. The authors propose that monitoring these tumor markers could improve the prediction of patients' clinical outcome[31].

Paclitaxel is a chemotherapeutic agent with anti-mitotic effects that has been used in the treatment of gastric cancer in perioperative or postoperative settings. However, there are no prognostic biomarkers to stratify patients who would benefit from paclitaxel therapy. Sundar et al[32] applied a machine-learning model based on expression data of 476 genes from patients treated with Paclitaxel conjugated with the adjuvant tegafur-gimeracil-oteracil in phase III clinical trial. The trained algorithm was able to recognize resistant and sensitive patients through the assessment of a unique signature encompassing 19 genes. Upon validation in external cohorts, the authors proposed this gene signature as a predictive biomarker for paclitaxel benefit in gastric cancer[32].

GASTRIC CANCER TARGETED THERAPY

Interaction between programmed cell death protein 1 (PD-1) expressed in T cells and its ligand PD-L1 expressed in tumor cells has been exploited by cancer cells to evade immune surveillance. This interplay regulates T-cell activation, and thus its blockage with specific antibodies has emerged as a potential therapy for many cancer types. Oster et al[33] investigated whether *H. pylori* infection impacted the response to immune checkpoint inhibitors. In preclinical models of colon cells, *H. pylori* infection decreased the effectiveness of cancer immunotherapy[33]. This finding was further validated in a heterotopic mouse model engrafted with melanoma cells and submitted to immune checkpoint inhibitors[33]. Of note, non-infected mice transplanted with fecal microbiome of infected mice retained the ability to respond to anti-PD1 and anti-CTLA4 therapy, suggesting an *H. pylori*-specific effect independent of fecal microbiota[33]. The clinical relevance of *H. pylori*-mediated immunosuppression was also investigated in patients with non-small cell lung cancer (NSCLC). The analysis of *H. pylori*-seropositivity by ELISA revealed a decrease in the survival of NSCLC patients under anti-PD-1 therapy in two independent cohorts. The authors propose serologic detection of *H. pylori* as a powerful tool to predict the efficacy of immune therapy[33].

CONCLUSIONS

In the past year, important developments have emerged proposing novel approaches to reduce gastric cancer incidence and improve patient management. Highly sensitive methods were developed for *H. pylori* detection, which may be explored in large-scale screening programs using non-invasive tests. Moreover, the development of vaccines targeting *H. pylori* may become promising tools for gastric cancer prevention in the near future. Experimental and clinical evidence further elucidated the molecular effects of *H. pylori* and EBV infections, enabling the identification of new prognostic and patient stratification markers. Ultimately, this knowledge may be translated into tailored strategies for more effective gastric cancer prevention and treatment while creating new opportunities for research.

Conflict of Interest

The authors declare no conflict of interest.

Informed Consent

Not applicable.

Author's Contribution

RMF was responsible for the study concept and design. JS, IC, JF and RMF have drafted the article. JF and RMF critically reviewed the manuscript for important intellectual content. All authors approved the final version of the manuscript.

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ORCID ID

Rui Manuel Ferreira: 0000-0003-0961-2356
Joana Figueiredo: 0000-0002-1590-1974
Ines Castro: 0009-0006-7780-341X
Joao Sousa: 0000-0003-0895-138

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