The interaction of *Helicobacter pylori* with cancer immunomodulatory stromal cells: new insight into gastric cancer pathogenesis

ABSTRACT

Gastric cancer is the fourth most common cause of cancer-linked deaths in the world. Gastric tumor cells have biological characteristics such as rapid proliferation, high invasiveness, and drug resistance, which result in recurrence and poor survival. *Helicobacter pylori* (*H. pylori*) has been proposed as a first-class carcinogen for gastric cancer according to the 1994 world health organization (WHO) classification. One of the important mechanisms by which *H. pylori* affects the gastric environment and promotes carcinogenesis is triggering inflammation. *H. pylori* induces an inflammatory response and a plethora of different signal transduction processes, leading to gastric mucosal disturbance, chronic gastritis, and a multi-step complex pathway that initiates carcinogenesis. It seems undeniable that the interaction between various cell types, including immune cells, gastric epithelium, glands, and stem cells, is vital for the progression and development of carcinogenesis concerning *H. pylori*. The interactions of *H. pylori* with surrounding cells play a key role in cancer progression. In this review, we discuss the interplay between *H. pylori* and tumor-supportive cells, including mesenchymal stem cells (MSCs), cancer-associated fibroblasts (CAFs), tumor-associated macrophages (TAMs), and myeloid derived-suppressor cells (MDSCs) in gastric cancer. It is hoped that clarifying the specific mechanisms for 'cross-talk' between H. pylori and these cells will provide promising strategies for developing new treatments.

Keywords: Cancer-associated fibroblasts, Helicobacter pylori, Tumor-associated Macrophages, Cancer, Myeloid-derived suppressor cells, Mesenchymal stem cells

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1. Introduction

Gastric cancer is the fourth most common cause of cancer-associated deaths all over the world. Ninety percent of all stomach tumors are determined to be malignant. Although the prevalence of gastric cancer has been declining over the past several years, it is still a significant healthcare issue. Despite technical advancements in treatments, including targeted therapy, adjuvant chemotherapy, radiotherapy, and advanced surgical methods, patients still experience cancer metastasis and recurrence. Gastric tumor cells have some biological characteristics, such as rapid proliferation, high invasiveness, and anti-apoptotic properties, which typically result in recurrence and poor survival. Additionally, in some cases, therapeutic resection is not possible due to the invasive nature of gastric cancer. The prognosis of advanced and metastatic gastric cancer with both extensive lymph node invasion and metastasis is poor, whereas early detection of gastric cancer is correlated with good survival [1, 2].

As Rudolf Virchow described many years ago, the tumor microenvironment is believed to play a pivotal role in the development of tumors [3]. Inflammation in the tumor microenvironment impacts many malignancy features, including the expansion and survival of tumor cells, metastasis, and angiogenesis [4-6]. The relationship between cancer and inflammation can result from two pathways: an intrinsic pathway, determined by genetic changes, such as oncogenes, that lead to neoplasia and inflammation; and an extrinsic pathway, induced by inflammatory leukocytes in the context of chronic infections and persistent inflammatory conditions, such as *Helicobacter pylori* (*H. pylori*) infection as well as inflammatory bowel disease (IBD), which increase cancer risk. In gastric cancer, the chronic inflammation induced by *H. pylori* infection plus the inflammatory milieu of the tumor microenvironment result in cancer progression [2]. Therefore, there is a need to clarify the interaction between *H. pylori* and these predominant tumor stromal cells.

1.1. Helicobacter pylori and the gastric microbiome

There are several risk factors for gastric cancer, including *H. pylori* infection, genetic host, and environmental variables. The extent to which *H. pylori* infection is identified as a risk factor for gastric adenocarcinoma can vary greatly across various populations with relatively similar rates *H. pylori* infection [7, 8]. The interaction between *H. pylori* strains and the various gastric microbiota complexes is one of the probable causes of thse differences [9]. Most *H. pylori* strains can modify the gastric environment and hence affect the habitat of resident bacteria to raise the risk of gastric carcinogenicity [8, 10]. The stomach features a distinct microbiota of five main phylae, including *Proteobacteria*, *Firmicutes*, *Actinobacteria*, *Bacteroidetes*, and *Fusobacteria*. Most findings demonstrate that *H. pylori*-positive and -negative microbiota are mainly dominated

by the same phyla, albeit with different relative percentages [11, 12]. The predominant phyla in the pediatric population were also *Proteobacteria*, *Firmicutes*, *Bacteroides*, and *Actinobacteria*. However, the relative proportions differed between *H. pylori*-positive and negative children [13]. In another study, *H. pylori*-positive individuals showed significant concentrations of *Proteobacteria*, *Spirochetes,* and Acidobacteria, but *Actinoculitis*, *Bacteroidetes* and *Firmicutis* were identified only to a limited extent [12]. Therefore, the involvement of *H. pylori* in gastric disorders might be mediated by the gastric microbiota composed of only 3 species of commensal gastric and intestinal microbiota (*Clostridium*, *Bacteroides*, and *Lactobacillus*) in combination with *H. pylori* infection which was sufficient to stimulate gastric neoplasia in germ-free mice. It can be concluded that these genera are increased in the stomachs of patients with premalignant and malignant lesions [8, 14].

Previous research has shown that the microbiota may either contribute to deleterious effects by producing carcinogenic nitrosamines under hypochlorhydria conditions or show beneficial influences by improving the healing of gastric ulcers, reducing the secretion of pro-inflammatory cytokines, or inactivating *H. pylori* colonization [8]. An examination of patients at diverse histologic stages of gastric carcinogenesis revealed an inverse relationship between *H. pylori* abundance and microbial diversity in non-cancer gastric biopsies, but gastric cancer was associated with a lower diversity compared to other samples with similar *H. pylori* abundance, whereas antibiotic therapy reversed the difference [15]. Children with *H. pylori* infection are more likely to have helminth infections and have been shown to have a lower chance of survival for gastric adenocarcinoma [16].

A recent study examined gastric biopsy specimens before, and one year after *H. pylori* eradication. It was demonstrated that *Roseburia* and *Sphingomonas* were decreased in individuals with chronic inflammation one year after *H. pylori* eradication. The occurrence and persistence of gastric atrophy and intestinal metaplasia one year after *H. pylori* eradication were associated with a cluster of oral bacteria that included *Peptostreptococcus*, *Parvimonas*, *Streptococcus*, *Granulicatella,* and *Rothia*. This study supports the assumption that the presence of *H. pylori* provides different microbiome niches that contribute to the development of gastric cancer [17].

Bacteriology research has indicated that the number of bacteria in patients with gastric cancer is higher than those who suffer from other gastric diseases and are more colonized by different species [18]. *H. pylori* infection results from prolonged gastric inflammation and destruction of

stomach hydrochloric acid-producing glands, eventually leading to the precancerous modification of atrophic gastritis and intestinal metaplasia [18]. Bacterial overgrowth in the stomach may be caused by hypochlorhydria associated with atrophic gastritis, which may play a role in the development of gastric cancer [18].

The gastric mucosa consists of a thick layer of mucus that serves as a protective barrier for gastric microbiota colonization and diversity. Helicobacter dominates the gastric mucosa in *H. pylori*-positive individuals with chronic gastritis, resulting in a decreased microbial diversity. Pre-neoplastic lesions are progressed due to *H. pylori* and gastric bacterial colonization that is also influenced by risk factors. This can be caused by the interplay between the innate immune response and gastric bacteria. Reduction of *H. pylori* in the gastric mucosa is noted in later stages of carcinogenesis. Microbial diversity is decreased in gastric cancer, and bacteria types of the oral or intestinal are enriched [18]. *H. pylori*-experienced dendritical cells maintain a semi-mature state and lead to the development of regulatory T cells (Treg) instead of Th1 or Th17 cells from naïve Th cells during chronic *H. pylori* infection. Tregs generated are trafficked to other lymphoid tissues to employ an immunoregulatory function [18].

The *H. pylori*-inducing immunoregulating effect enhances host tolerance to microbiome disturbance and can lead to a higher microbiota diversity. In addition, chronic *H. pylori* infection modifies the stomach acidic environment, allowing more microorganisms to bypass the gastric acid barrier and colonize the distal intestine. The gut microbiota can also induce regulatory T cells, which involve a complex interaction between *H. pylori* and the colon microbiota [18]. There has been much research on the complex interaction between *H. pylori* and the gastric microbiome and the role of the immune system in their interaction. However, these findings are still far from being conclusive.

1.2. Helicobacter pylori, CagA virulence factor, Inflammation, and gastric cancer

H. pylori is a Gram-negative, helix-shaped, flagellated, and microaerophilic bacteria that can form a biofilm and is capable of being converted from a spiral into a coccoid shape. Due to having several virulence factors, this microorganism is a highly invasive bacterium with the highest prevalence among chronic infections, such that up to eighty percent of infected people are asymptomatic [19].

Vacuolating cytotoxin (VacA), cytotoxin-associated gene A (CagA), neutrophil-activating protein A (NAP), outer inflammatory protein A (OipA), duodenal ulcer promoting gene A (DupA), heat shock proteins (Hsp10, Hsp60), urease, and sialic acid-binding adhesin (SabA) are some of the virulence factors of *H. pylori* [20-22]. Infection with *H. pylori* initiates a cascade of events, which consequently leads to a high incidence of cancer development, progression, recurrence, metastasis, invasiveness, and increased chemoresistance [23].

The CagA oncoprotein and type 4 secretion system (T4SS), among many virulence factors of *H. pylori*, plays a crucial role in carcinogenesis. However, *H. pylori* is an effective activator of nuclear factor-κB (NF-κB) in gastric epithelial cells. The injection of CagA into a target cell by T4SS-formed pilus induces ERK1/2-dependent NF-κB and transforms this cell into a “hummingbird phenotype” cell with high expression of mesenchymal markers such as Snail, ZEB-1, and vimentin [24, 25].

It has been shown that after CagA is injected into gastric epithelial cells, it is phosphorylated by Src family kinases. Following phosphorylation, CagA interacts with SHP-2, leading to the stimulation of the ERK/MAPK pathway in a Ras-independent manner, which consequently dephosphorylates and inactivates focal adhesion kinase (FAK). CagA can also directly interact with STAT3, thus supporting increased hyperactivation transcriptional activity [26]. CagA+ *H. pylori* also initiate the Wnt/β-catenin pathway in the cancer cell to induce expression of cancer stem cell markers, including CD44, Lgr5 Oct4, Nanog, and c-myc [27]. Yes-Associated-Protein (YAP) is another oncogene that is upregulated with CagA injection in target cells. The overexpression of YAP decreases epithelial markers, including E-cadherin, and induces epithelial-to-mesenchymal transition (EMT) and migratory properties in transfected cells [28]. These markers are the characteristics of EMT induction in tumor cells [25].

As discussed, *H. pylori* induces an inflammatory response and a plethora of different signal transduction processes, leading to a constant gastric mucosal disturbance, chronic gastritis, and a multi-step complex pathway and process that initiates carcinogenesis. These pathways impact cellular processes such as apoptosis, proliferation, epithelial transformation, and mobility [29]. Stimulation of NF-κB by CagA infection initiates the expression of a wide variety of genes, including those encoding various cytokines (e.g., TNF-α, IL-1, IL-6, IL-8, vascular endothelial growth factor (VEGF)), enzymes (e.g., cyclooxygenase-2 (COX-2), and inducible nitric oxide synthase (iNOS)), cell-cycle regulators, the matrix metalloproteinases (e.g., MMP-2, MMP-7, MMP-9), and adhesion molecules (E-cadherin, N-Cadherin, and vascular cell adhesion molecule 1 (VCAM1)) [2].

It is recognized that the interaction of different cell types, including immune cells, gastric epithelium, glands, and stem cells, is vital for the progression and development of *H. pylori*-associated carcinogenesis. One of the important mechanisms by which *H. pylori* affects the gastric environment and promotes carcinogenesis by triggering inflammation [30]. *H. pylori*-induced inflammation attracts several mediators and activates cell signaling effectors such as chemokines, cytokines, and growth factors that have been identified as initiating the process of carcinogenesis. Furthermore, the alteration in the extracellular matrix (ECM), as well as the increased activation of anti-apoptotic proteins and a decrease in the expression of tumor suppressor genes, have been implicated in the pathogenesis of *H. pylori*-induced gastric cancer [30].

2. The interplay between H. pylori and Immune-suppressive cells

It is believed that the tumor microenvironment determines the behavior of cancer through alterations in genetic and epigenetic modalities, or *via* changes in the composition of tumor stroma [31]. To briefly review this process, the tumor microenvironment consists of tumor cells and stroma. Stroma is composed of surrounding non-cancerous cells, including endothelial and epithelial cells, immune and blood cells, fibroblasts, and extracellular matrix (ECM). Among stromal cells, fibroblasts, macrophages, mesenchymal stem cells, and immature myeloid cells are vital players and the predominant cells within the tumor microenvironment. Their interactions with surrounding cells play a key role in cancer progression. In this review, our goal was to discuss the interplay between *H. pylori* and tumor-supportive cells, including mesenchymal stem cells (MSCs), cancer-associated fibroblasts (CAFs), tumor-associated macrophages (TAMs), and myeloid derived-suppressor cells (MDSCs) in gastric cancer.

2.1. Tumor-associated Macrophages (TAMs)

Macrophages are the most plentiful immune cells in the tumor microenvironment, and are involved in the induction of inflammation in cancer. TAMs fall into two subtypes: M1 and M2. M1 macrophages, which are referred to as classical macrophages, are mainly induced by IFNγ, TNFα, and LPS, while M2 macrophages are stimulated by IL-4 [32].

M1 macrophages have cytotoxic and pro-inflammatory functions. However, M2 macrophages are conditioned by the tumor microenvironment and have no cytotoxic functions. Growth factors, cytokines, and chemokines, such as TGF-β, M-CSF, PGE2, IL-6, IL-10, CCL2, and CCL5, potentially modulate the polarization of monocytes mainly into M2 macrophages. Following this process, M2-polarized macrophages promote tissue remodeling and angiogenesis and secrete

several cytokines and growth factors. Through the secretion of a set of cytokines and growth factors, M2-polarized macrophages promote tumor growth and progression [33].

The involvement of macrophages in carcinogenesis, metastasis, and tumor invasion is generally attributed to TAMs, a major source of TNF-α in the tumor microenvironment, which release various growth factors, cytokines, and inflammatory mediators. Investigations have uncovered a relationship between the expression of *H. pylori*-induced TNF-α and concurrent upregulation of IL-1β and IL-6 (see Figure.1.A). Moreover, the overexpression of CXCR4 is related to TNF-α upregulation. Importantly, *H. pylori* infection leads to the overproduction of TNF-α from macrophages, resulting in upregulation of CXCR4, which has been proposed as the most common overexpressed chemokine receptor in various cancers, including gastric cancer [34].

IL-1β is considered one of the primary cytokines secreted by TAMs, and its overexpression has been linked to a elevated risk of *H. Pylori*-associated gastric cancer [35]. Mesenchymal-epithelial transition (MET) factor is a proto-oncogene tyrosine kinase that has been shown to be induced in *H. pylori*-infected human gastric adenocarcinoma (AGS) cells. Further investigation has proposed that this protein can be phosphorylated and transferred to the surrounding cells through exosomes. The delivery of MET to TAMs activates these cells *via* the AKT/MAPK signaling pathway. Upon TAM activation, the production and secretion of IL-1β are induced, consequently resulting in inflammation in the gastric microenvironment and tumorigenesis [36].

NLRP3 is a component of the inflammasome. Its activation also induces IL-1β secretion in macrophages and promotes cyclin-D1 transcription in gastric epithelial cells to stimulate epithelial cell proliferation and tumorigenesis. Additionally, miR-22 has been proven to target NLRP3 and inhibit its expression. Importantly, *H. pylori* infection inhibits the expression of miR-22 and subsequently augments NLRP3 expression, which initiates unrestrained proliferation of epithelial cells and IL-1β secretion from macrophages to provide an inflammatory environment for the emergence of gastric cancer [37].

Induction of immune tolerance is one of the pivotal functions of TAMs in tumor development and progression. The ligand expression of cytotoxic T-lymphocyte antigen 4 (CTLA-4) and programmed cell death protein 1 (PD-1) inhibitory receptors on TAMs contribute to this process. The expression of these ligands on TAMs, and their ligation on T cells, B-cells, and natural killer (NK) T cells, inhibit their functions [38]. Shen et al. have shown that *H. pylori* infection can induce PD-1 and its ligand, PD-L1, in the tumor microenvironment [39]. In fact, the induction of these two molecules inhibits the CD8+ T cell’s fight against gastric cancer cells [39, 40].

TAMs promote tumor development by secretion of anti-inflammatory mediators such as IL-4, IL-10, and IL-13. Moreover, TAMs also produce IL-6, IL-10, IL-17, IL-23, TGF-β, and indoleamine 2,3-dioxygenase (IDO) to inhibit the response of cytotoxic T lymphocytes (CTL's), which enhances the invasion and metastatic spreading of tumor cells. Since TAMs are the major source of TGF-β, it has been concluded that the induction of TH17 and Treg cells is associated with the function of TAMs [41].

H. pylori infection has also been shown to affect macrophage-dependent specific T cell responses through the regulation of non-coding RNAs. Codolo et al. have suggested that *H. pylori,* by induction of let-7i-5p, miR-146b-5p, and miR-185-5p in macrophages, inhibits and targets class II major histocompatibility complex transactivator (CIITA). It is well-accepted that CIITA is a "master control factor" for the expression of MHC class II genes in macrophages. This process mediates the inhibition of the *H. pylori*-induced T cell response and promotes a pro-neoplastic environment for gastric cancer development [42].

It is also important to note that RUNX family transcription Factor 3 (runx3), which is a tumor-suppressive gene, undergoes methylation of its promoter regions and has been described in gastric cancer. Specifically, it has been shown that *H. pylori* infection mediates the production of NO in macrophages through the induction of the iNOS enzyme, which leads to methylation of the runx3 gene in MKN45 cells so as to promote their proliferation. Therefore, iNOS inhibitors have been suggested as a therapeutic intervention in the suppression of tumors [43]. However, in another study, it was suggested that a spermine-dependent decrease in NO production in macrophages results in the persistence of *H. pylori*, which poses a greater risk for gastric cancer [44].

Lastly, the expression of the urokinase plasminogen activator receptor (uPAR) has been documented in gastric cancer-resident macrophages and neutrophils. It is thought that uPAR expression on cells aids in cell migration and promotes cancer cells to metastasize *via* their interaction with ECM or other cell-surface proteins, such as integrins. Alpízar-Alpízar et al. have shown that the level of uPAR expression is upregulated in *H. pylori*-induced gastric cancer, which significantly impacts the prognosis of the disease [45].

2.2. Cancer-associated Fibroblasts

In addition to tumor cells and innate, or adaptive, immune cells, the tumor microenvironment is comprised of a large number of cancer-associated fibroblasts (CAFs). These cells are differentiated from tumor-resident fibroblasts, mesenchymal stem cells, and epithelial and

endothelial cells. CAFs, as a key element of the tumor microenvironment, interact with other stromal and tumor cells which has a pivotal role in cancer development [46, 47]. It has been suggested that at the time of initiation of tumorigenesis, it is the nature of the tumor cells that determine their development, invasiveness, aggressiveness, and capacity to metastasize. Nevertheless, recent investigations have indicated that CAFs mediate tumor cell proliferation, invasion, and metastasis by releasing specific growth factors and chemokines, as well as causing the degradation of ECM proteins [48]. The 'cross-talk' between tumor cells and fibroblasts leads to CAF development and, subsequently, cancer development. Tumor cells, *via* the secretion of IL-6 and TGF-β, accelerate fibroblast transformation to CAFs and induce CAF-phenotype markers, including vimentin, alpha-smooth muscle actin (α-SMA), fibroblast specific protein (FSP)-1, and fibronectin activation protein (FAP) in these cells. In turn, these 'developed', or modified CAFs release chemokines (e.g., CXCL14) and cytokines (e.g., IL-6) to induce strong inflammatory responses in the tumor microenvironment [49, 50].

Following activation, CAFs produce matrix metalloproteinases (MMPs) to degrade ECM, which leads to EMT and metastasis. Additionally, vascular endothelial growth factor (VEGF) and fibroblast growth factors (FGF) are secreted from CAFs to facilitate angiogenesis. By secretion of chemokines, CAFs attract innate and acquired immune cells to the tumor microenvironment and promote inflammation. Moreover, CAFs upregulate transporter proteins for detoxification and induction of drug resistance and, in so doing, construct and secure the tumor microenvironment [49, 51].

It has been shown that CagA+ *H. pylori* infection results in overexpression of CAF phenotype markers, including FSP and FAP and induces MSC conversion into CAF (see Figure.1.B) [52]. Moreover, long-term fibroblast co-culture with CagA+VacA+*H. pylori* induces α-SMA, vimentin, TGF-βR, and N-cadherin marker and suppresses E-cadherin in these cells, suggesting a stimulatory effect of *H. pylori* on CAF differentiation [53, 54]. Further investigation has indicated that this conversion is mediated by the triggering of TGF-βR signaling in gastric fibroblasts [55]. The co-culture of activated fibroblast cells with *H. pylori*-infected RGM-1 (normal rat gastric epithelial cells) downregulates E-cadherin and upregulates β1-integrin and COX-2 in RGM-1 cells, supporting the induction of EMT in these cells [53].

IL-6 and PGE2 coordinate interaction and 'cross-talk' between CAFs and tumor cells. The presence of these two factors mediates tumor formation and progression and CAF development. PGE2 promotes angiogenesis and inhibits apoptosis in the tumor microenvironment. It has been shown that miR-149 targets and inhibits IL-6 expression and subsequently CAF activation. *H.*

pylori infection induces the expression of COX2 and PGE2 production. Importantly, an enhanced level of PGE2 mediates hypermethylation of miR-149 promoter, resulting in IL-6 overexpression and CAF development [56].

H. pylori induces the expression of toll-like receptor (TLR)2, TLR4, STAT3, and the NF-κB/RelA subunit, resulting in an inflammatory microenvironment generation. These alterations in fibroblasts are accompanied by remarkably enhanced secretion of HGF, CXCL12, and CXCL8 from *H. pylori*-infected fibroblasts, and subsequently, an increased activation of the CAF phenotype of these cells [57]. Vascular adhesion molecule (VCAM)-1, or CD106, is an adhesion molecule whose interaction with integrin αvβ1/5 on gastric cancer cells facilitates tumor invasion. It has been demonstrated by Shen et al. that *H. pylori* increase JAK/STAT1 signaling in CAFs, which ultimately induce upregulation of VCAM1 and tumor invasiveness [58].

In the context of apoptosis, it is known that the hepatoma-derived growth factor (HDGF) is a growth factor involved in anti-apoptosis, tumor cell proliferation, lymph node metastasis, and VEGF expression. Its overexpression is associated with human gastric cancer with a poor prognosis. HDGF confers the CAF-like phenotype to the myofibroblast, including increased expression of α-SMA, FAP, FSP-1, and S100A4. Liu et al. have demonstrated that *H. pylori* induces the expression of HDGF in human gastric cancer cells. The increased expression of this protein in human BM-derived MSCs endows a CAF-like phenotype to these cells. Of note, the use of anti-HDGF antibodies inhibits the recruitment of MSCs and the expression of these markers [59].

Lastly, in addition to mediating fibroblast conversion into CAFs, Krzysiek-Maczka et al. have indicated that *H. pylori* infection provides a condition for CAF maintenance. In this regard, it has been observed that VacA+ *H. pylori* induces HIF-1α, collagen I, and HSP70 and inhibits pro-apoptotic Bax expression, suggesting an enhanced protective role of *H. pylori* to maintain fibroblast integrity [60].

2.3. Mesenchymal Stem Cells (MSCs)

MSCs are present in the bone marrow and various other tissues, and are considered an assorted class of multipotent and self-renewing progenitor cells. They exhibit a range of unique characteristics, such as localizing at sites of injury, the ability to suppress immune responses, and cooperation in the renewal and repair of damaged tissues [61]. MSCs are increasingly recognized as major tumor growth facilitators in the context of cancer. Since MSCs are fundamental elements of the cancer stroma in clinical and in experimental settings, they demonstrate a substantial

propensity to develop tumors, which is related to their abilities to heal wounded tissues. Several studies have also shown that human MSCs accelerate tumor development and/or metastasis in a wide variety of tissue-derived neoplasms [61].

MSCs secrete a set of molecules, such as cytokines, chemokines, and growth factors, which act in a paracrine manner on surrounding cancer cells, thereby regulating tumor development and progression. Cytokines and growth factors produced by MSCs, including IL-6, IL-8, and EGF, have been shown to enhance tumor cell invasiveness in the context of cancers [62, 63]. Similarly, MSC-derived chemokines, such as Gro-α (CXCL1), MIP2α (CXCL2), and SDF-1 (CXCL12), have been found to mediate tumor cell proliferation [64, 65]. MSCs also exert immune regulatory function on both innate and adaptive immune responses. In this regard, it has been shown that MSCs directly inhibit the proliferation of CD4+ and CD8+ T cells, suggesting a significant effect of MSCs on immune surveillance [66]. Moreover, MSCs decrease the percentage of IFNγ-producing T cells in the tumor microenvironment [67]. It should also be mentioned that MSCs express immune receptors. In fact, it has been shown that MSCs highly express the toll-like receptors TLR3 and TLR4. Activation of these two receptors in MSCs induces expression of the Notch ligand, Delta-like 1, resulting in the induction of Treg cells [68]. Additionally, this process is facilitated by the secretion of TGF-β from MSCs [69].

MSCs are inherently capable of being transformed into other cells. On the one hand, they can be converted into endothelial cells. Upon conversion, these cells produce keratinocyte growth factor (KGF), VEGF-A, EGF, IGF-1, and galectin-1 to promote the development of newly-formed blood vessels and angiogenesis. On the other hand, MSCs have the ability to transform into tumor stromal cells such as CAFs [61]. As mentioned earlier, the injection of CagA into a target cell by T4SS-formed pilus induces ERK1/2-dependent NF-κB activation, and transforms this cell into a “hummingbird phenotype” cell with increased expression of mesenchymal markers such as Snail, ZEB-1, and vimentin [24, 25]. During the MSC conversion into CAF, these cells acquire CAF-phenotype markers, including α-SMA, vimentin, FSP1, and FAP [70]. The functions of CAFs in cancer have been discussed in the section entitled “Cancer-associated Fibroblasts”.

H. pylori-induced inflammation in the stomach of infected mice has been shown to be associated with the release of signaling molecules and activation of pathways such as TGFβ signaling *via* SMAD3 and Hedgehog signaling, during chronic *H. pylori* infection, which leads to the rapid infiltration of MSCs to the inflamed stomach (see Figure.1.C). The importance of CXCR4 and CXCL12 interaction for the recruitment of MSCs to stomach tissue has also been reported [71]. Moreover, an in vitro study has shown that co-cultured epithelial cells with *H. pylori* lead to TNF-

α and CCL2 production. The secretion of these two factors and their ligation by SCs initiates NF-κB signaling, which gives rise to accelerated recruitment of MSCs for gastric cancer development [72].

Once MSCs migrate towards the chronic *H. pylori*-infected gastric tissue to exert their innate function for wound-healing-like activities, they are trapped in the microenvironment that contains *H. pylori* bacterium and tumor cells. Following the attraction to the inflamed gastric microenvironment, MSCs interact with gastric tumor cells and *H. pylori* bacteria. The interaction of MSCs initially leads to upregulation of the Bcl2 gene and MMP2 and MMP9 in these cells, which results in an increase in tumor invasiveness. In fact, the active phenotype of MSCs in the tumor microenvironment promotes tumor development [73].

MSCs also exert a modulatory function on the adaptive immune system. It has been demonstrated that MSCs can secrete IL-10 and TGF-β, while decreasing the secretion of IFN-γ. This process results in the induction of Foxp3+ CD4+ CD25+ Treg cells. Lin et al. have demonstrated that the transplantation of MSCs in *H. pylori*-adapted 44-week old mice remarkably induced local and systemic IL-10-secreting T cells and triggered Treg functions [74]. The effect of *H. pylori* infection on immune responses has also been shown to be age-dependent. In this regard, Altobelli et al. showed that VacA *H. pylori* infection in neonatal mice skewed T cells to Foxp3+ Treg cells. In contrast, infection in adult mice leads to the polarization of T cells toward RoRγt+ TH17 cells. These data indicate that neonatal infection results in immune tolerance to *H. pylori,* in which VacA protein acts as an immunomodulator in this case [75].

Tumor research focuses on the function of MSCs in the development of tumors via inducing immune suppression, angiogenesis, and extracellular matrix deformation [76]. Research findings reveal the involvement of MSC in tumor support, whereas some studies have demonstrated MSC's anti-tumor roles in malignancies such as glioma, melanoma, and HCC [77-79]. Regarding gastric cancer, there are conflicting results that show MSC can prevent the progression of gastric cancer through the apoptosis of cancer cells. A compelling explanation for this difference is the process of reprogramming tumor cells that transforms MSCs, which often has a different effect on the progression of tumors, into pro-tumorigenic trained MSCs [80, 81]. Another explanation for these inconsistent outcomes relates to the differences between tumor models, MSC heterogeneity, time and injected dose of MSCs, which affect the MSC-cancer interaction process [76, 82].

2.4. Myeloid-derived Suppressor Cells (MDSCs)

MDSCs are immature and heterogeneous groups of myeloid-derived cells. Altered hematopoiesis resulting from cancer, or infection-induced chronic inflammation, provides a pathological situation that leads to the expansion and development of MDSCs [83, 84]. Given the immunosuppressive properties of MDSCs, rather than immunostimulation, they are detected from other myeloid lineage-derived cells, including monocytes, neutrophils, macrophages, and dendritic cells [83, 85]. Like other myeloid-derived cells, MDSCs communicate with a range of immune cells such as lymphocytes, dendritic cells, natural killer (NK) cells, and macrophages to influence their function [86, 87]. In addition to the spleen, lymph nodes, and bloodstream, MDSCs can infiltrate into the tumor microenvironment [88, 89]. The secreted cytokines, as well as growth and inflammatory factors, including macrophage-colony stimulating factor (M-CSF), granulocyte macrophage-colony stimulating factor (GM-CSF), VEGF, prostaglandin E2 (PGE2), IL-1β, IL-6, and IL-13, are responsible for the induction of MDSCs from bone marrow [90-92]. CCAAT/enhancer-binding protein (C/EBP)-β, Janus kinase (JAK)2, signal transducer and activator of transcription (STAT)1, STAT3, STAT5, NF-κB, and hypoxia-inducible factor 1-α (HIF-1α), are the primary transcription factors that induce MDSCs [83, 93, 94]. The induction of the PI3K-AKT signaling pathway is a vital step for the induction of MDSCs [94].

In a study by Hayakawa et al., it was shown that apoptosis signal-regulating kinase 1 (ASK1) counteracts *H. pylori*-induced MDSC infiltration. ASK1, and its downstream Jun/MAPKs, are considered regulators of epithelial maintenance and host immune responses in *H. pylori* infection. Importantly, activation of this pathway suppresses macrophage apoptosis and IL-1β secretion, and loss of ASK1 enhances STAT1 and NF-κB activation, as well as MDSC recruitment in the *H. pylori*-infected stomach. In fact, following *H. pylori* infection, ASK1 is activated to suppress inflammation induced by infiltrated MDSCs. Hence, ASK1 is an anti-inflammatory mechanism against *H. pylori,* such that ASK1 knockdown leads to MDSC-induced hyperinflammatory responses. Collectively, it has been concluded that ASK1 is activated following CagA injection to enable anti-inflammation mechanisms in the stomach, suggesting a protective function in stomach cells against inflammation and gastric cancer [95].

The primary immune inhibitory function of MDSCs is the suppression of the function of lymphocytes, especially cytotoxic T cells (CTLs or $CD8^+$ T cells). Other immune cells, such as DCs, NKs, and macrophages, are also inhibited by MDSCs in the tumor microenvironment [86, 96]. There are multiple mechanisms involved in the immunosuppressive role of MDSCs in cancer. Nitric oxide (NO), produced by arginase-1 (ARG1) enzyme from L-arginine, and reactive oxygen

species (ROS) are necessary for immunosuppression by MDSCs [97]. NO and ROS downregulate and dissociate the ζ-chain in the CD3 component of T cell receptors (TCRs) [97, 98]. MDSCs also produce IL-10 and TGF-β to promote the generation of $Foxp3^{+}/CD25^{+}$ T reg cells [99]. Moreover, secretion of ADAM17 (a disintegrin and metalloproteinase 17) from MDSCs disrupts T cell infiltration into lymph nodes [99].

The interaction of *H. pylori* with MDSCs has illustrated in Figure.1.D. GLI1, a zinc-finger protein, functions as a DNA-binding protein and a transcriptional activator. Schlafen 4 (SLFN4) is a myeloid differentiation factor that is considered to be a GLI1 target gene, and its expression is associated with spasmolytic polypeptide-expressing metaplasia (SPEM). It has been suggested that SLFN4+ myeloid cell recruitment from the bone marrow to peripheral organs implies preneoplastic alterations in the gastric microenvironment. It has been demonstrated that the expression of SLFN4 in patients with intestinal metaplasia in the stomach can be attributed to *H. pylori* infection. It has also been proposed that SLFN4 expression relies on sonic hedgehog (SHH) ligand, and that SHH ligand expression accelerates the infiltration of SLFN4+ MDSCs into the gastric microenvironment [100].

Mesali et al. demonstrated that *H. pylori* infection is associated with an increased population of MDSCs in the biopsies of the antrum of the stomach of patients with peptic ulcer and gastric cancer. However, the mechanism of this infiltration and recruitment to the gastric tissues has not been elucidated [101]. Zhuang et al. showed that CagA+ *H. pylori* infection induces DCs and epithelial cells to express IL-23 and IL-22R, respectively. IL-23 induces Th22 cells to produce IL-22, which leads to activation of IL-22R-expressing epithelial cells for CXCL2 secretion. Accordingly, secretion of CXCL2 activates MDSCs to infiltrate the gastric mucosa. Therefore, the *H. pylori*-induced IL-23/IL-22R/CXCL2 axis plays a pivotal role in creating a pro-inflammatory microenvironment to promote gastric cancer [102].

3. Therapeutic Approaches

About 70% of cases of gastric cancer may be due to *H. pylori infection*, but only about 1-4% of *H. pylori*-infected individuals actually develop gastric cancer. Therefore, antibiotic therapy has been suggested as a first-line treatment, which might prove useful for preventing gastric cancer. Nevertheless, there are conflicting clinical reports relating to whether antibiotic therapy decreases the risk of gastric cancer [103].

A study by Chiang et al. investigated the benefits of mass screening and eradication of *H. pylori* infection in an area with highly endemic *H. pylori* infection and high rates of gastric cancer. This

study showed that a significant reduction in *H. pylori* infection was associated with a reduction in premature malignant gastric lesions and gastric cancer without an increased likelihood of adverse outcomes [104]. Therefore, more evidence from ongoing research is required to determine whether mass screening and *H. pylori* eradication would reduce the occurrence of gastric cancer.

As discussed in this review, the induction of inflammation is the primary means by which *H. pylori* triggers dysplasia and carcinogenesis in the gastric microenvironment. The *H. pylori*-induced inflammation is primarily mediated by the CagA factor *via* induction of NF-κB. Therefore, suppression of the function of CagA, or blocking NF-κB activation, may represent a therapeutic approach for inhibiting inflammation and, consequently, development of gastric cancer.

The antioxidant, antimicrobial, and anti-tumor potential of natural extracts have been widely investigated as medicinal compounds for a variety of diseases. Silibinin, a major constituent of flavonolignans complex mixture (Silymarin), has been shown to possess anti-*H. pylori* activity, together with suppression of NO synthesis and the production of cytokines such as TNF-α, IL-6, and IL-10 in *H. pylori*-infected macrophages. Moreover, silibinin has been shown to exhibit significant cytotoxic properties against adenocarcinoma cells, with a higher selectivity index than cisplatin. The use of silibinin may provide a vital therapeutic alternative for the prevention and treatment of *H. pylori* infection and, subsequently, gastric cancer [105].

In silico studies have identified several anti-inflammatory compounds that could potentially be used to alleviate inflammation and tumor progression induced by *H. pylori*. In this regard, naphthopyranones, extracted from *Paepalanthus sp*, might be valuable alternatives either in the prevention or in the treatment of *H. pylori* infection and the diseases associated with this infection, especially gastric cancer [106].

Artesunate is derived from artemisinin, which is an effective anti-malarial drug. Additionally, studies have shown that artesunate has inhibitory effects on cancer cell growth, invasion, and migration. It limit the growth of gastric cell lines in a concentration-dependent manner [107]. Artesunate employs a number of methods to limit the growth of cancer cells by promoting cell oncosis through an impact on calcium concentration, VEGF, and calpain-2 expression [108]. Apoptosis can also be caused in cancer cells by Bax and caspase-3 upregulation and inappropriate CDC25A and Bcl-2 regulation [109]. Moreover, by blocking the NF-κB signaling pathway, artesunate dampens tumor growth in the gastric carcinoma mice model. Artesunate also prevents the proliferation and adherence of *H. pylori* to gastric cancer cells and reduces ROS production [110].

Finally, it should be mentioned that the use of nanoparticles as carriers for medicinal substances is increasing. Using nanocarriers containing new medicinal compounds, whether derived from natural sources or synthetically prepared, that exhibit cytotoxicity toward *H. pylori* is attracting much attention, since it is possible to treat the offending agent without affecting other mammalian cells, especially regenerative stem cells. For example, it has been shown that zinc oxide nanoparticles (ZnONPs) induce apoptosis in *H. pylori* bacteria. In addition to the ZnONPs triggering apoptosis of *H. pylori* bacteria, it was also demonstrated that they were not toxic to human MSCs and could be used as an effective 'pseudo-nano-antibiotic' to decrease the risk of gastric cancer [111].

4. Conclusions

Gastric cancer has become more prevalent throughout the world, particularly in east-Asian countries. Since inflammation has been concluded to be the most important factor in cancer development, it has been speculated that the development of gastric cancer is also triggered by inflammation. *H. pylori* have been recognized as a microorganism that is highly effective at inducing inflammation in the stomach. Recent studies have described a synergistic interaction between the tumor microenvironment stroma and *H. pylori* infection. A better understanding of how *H. pylori* and these cells interact should introduce new insights and perspectives on the treatment of gastric cancer, as well as novel biomarkers that may be used for early detection. As mentioned, tumor stromal cells, including TAMs, CAFs, MSCs, and MDSCs, play a critical role in gastric cancer development. The interaction of these types of cells with *H. pylori* has been shown to induce inflammation in the stomach.

TAMs, as the primary immune cell present in the gastric tumor microenvironment, are the cells most affected by *H. pylori*. *H. pylori* trigger the induction of NF-κB in these cells, leading to increased secretion of TNF-α and IL-1β. Increased secretion of TNF-α and IL-1β exacerbates the inflammatory milieu in the stomach. Moreover, the 'cross-talk' between TAMs and *H. pylori* decreases the expression of CIITA and increases PD-1, which leads to inhibition of CD8+ T cells and anti-tumor responses. MDSCs are another type of cell with immunomodulating properties in the gastric cancer microenvironment. The interaction of *H. pylori* with MDSCs initiates SHH signaling, mediates the CXCL2/IL-23/IL-22R axis, and enhances infiltration of MDSCs into the tumor microenvironment.

H. pylori inject virulence factor, CagA, into stromal cells and modulate them, mainly through induction of NF-κB. Moreover, the co-culture of *H. pylori* and fibroblasts or MSCs triggers a set of

signaling pathways, which leads to the expression of CAF-like phenotype markers, and ultimately, to the development of CAF. Additional mechanisms for enhanced inflammation in the tumor microenvironment involve *H. pylori*-induced secretion of mediators, for example, IL-6, MMPs, CXCL14, and PGE2. Furthermore, *H. pylori* stimulates the expression of VCAM1, HIF-1α, and anti-apoptotic proteins in CAFs to maintain the integrity of activated fibroblasts and increase tumor invasiveness. The interplay between *H. pylori* and MSCs leads to the secretion of CXCL12, which leads to further MSC recruitment to the tumor microenvironment. The MSCs that have infiltrated the tumor microenvironment induce immune regulation through the induction of Treg cells. Finally, MSCs incubated with *H. pylori* express MMPs, which trigger tumor invasiveness.

Since *H. pylori* infection induces vigorous immune responses in stomach tissues, it has been suggested that the resulting inflammation promotes tumor development in gastric tissue. Most studies examining the effect of *H. pylori* on the aforementioned cells have been conducted in vitro. Therefore, it is suggested that future investigations should be extended to in vivo situations (***e.g.***, using experimental animal models), as well as clinical studies. Another remaining challenge is to address the exact mechanisms underlying the 'cross-talk' between *H. pylori* and tumor stroma, which may help to better clarify the role of *H. pylori* in gastric cancer. It is also hoped that biomedical/pharmaceutical strategies to target H. pylori specifically will provide promising therapeutic approaches for gastric cancer prevention that may potentially arise secondary to infection with *H. pylori*.

References

[1] M. Apicella, S. Corso, S. Giordano, Targeted therapies for gastric cancer: failures and hopes from clinical trials, Oncotarget 8(34) (2017) 57654-57669.

[2] H.W. Chung, J.-B. Lim, Role of the tumor microenvironment in the pathogenesis of gastric carcinoma, World J Gastroenterol 20(7) (2014) 1667-1680.

[3] S.P. Hussain, C.C. Harris, Inflammation and cancer: an ancient link with novel potentials, Int J Cancer 121(11) (2007) 2373-80.

[4] A.G. Shabgah, M.T. Qasim, S.M. Mostafavi, A.O. Zekiy, F. Ezzatifar, M. Ahmadi, S.M. Haftcheshmeh, J.G. Navashenaq, CXC chemokine ligand 16: a Swiss army knife chemokine in cancer, Expert Reviews in Molecular Medicine 23 (2021).

[5] A.G. Shabgah, Z.H. Al-Qaim, A. Markov, A.V. Yumashev, F. Ezzatifar, M. Ahmadi, S.M. Gheibihayat, J.G. Navashenaq, Chemokine CXCL14; a double-edged sword in cancer development, International Immunopharmacology 97 (2021) 107681.

[6] A. Gowhari Shabgah, A. Amir, Z.R. Gardanova, A. Olegovna Zekiy, L. Thangavelu, M. Ebrahimi Nik, M. Ahmadi, J. Gholizadeh Navashenaq, Interleukin-25: New perspective and state-of-the-art in cancer prognosis and treatment approaches, Cancer Medicine (2021).

[7] P. Correa, M.B. Piazuelo, Gastric cancer: the Colombian enigma, Revista Colombiana de Gastroenterologia 25(4) (2010) 334-337.

[8] G. Ozbey, E. Sproston, A. Hanafiah, Helicobacter pylori infection and gastric microbiota, Euroasian journal of hepato-gastroenterology 10(1) (2020) 36.

[9] I. Yang, S. Woltemate, M.B. Piazuelo, L.E. Bravo, M.C. Yepez, J. Romero-Gallo, A.G. Delgado, K.T. Wilson, R.M. Peek, P. Correa, Different gastric microbiota compositions in two human populations with high and low gastric cancer risk in Colombia, Scientific reports 6(1) (2016) 1-10.

[10] D.R. Mitchell, M.H. Derakhshan, A.A. Wirz, C. Orange, S.A. Ballantyne, J.J. Going, K.E. McColl, The gastric acid pocket is attenuated in H. pylori infected subjects, Gut 66(9) (2017) 1555-1562.

[11] H.J. Jo, J. Kim, N. Kim, J.H. Park, R.H. Nam, Y.J. Seok, Y.R. Kim, J.S. Kim, J.M. Kim, J.M. Kim, Analysis of gastric microbiota by pyrosequencing: minor role of bacteria other than Helicobacter pylori in the gastric carcinogenesis, Helicobacter 21(5) (2016) 364-374.

[12] J. Yang, X. Zhou, X. Liu, Z. Ling, F. Ji, Role of the gastric microbiome in gastric cancer: from carcinogenesis to treatment, Frontiers in Microbiology 12 (2021).

[13] L. Llorca, G. Pérez-Pérez, P. Urruzuno, M.J. Martinez, T. Iizumi, Z. Gao, J. Sohn, J. Chung, L. Cox, A. Simón-Soro, Characterization of the gastric microbiota in a pediatric population according to Helicobacter pylori status, The Pediatric infectious disease journal 36(2) (2017) 173-178.

[14] J.M. Noto, R.M. Peek Jr, The gastric microbiome, its interaction with Helicobacter pylori, and its potential role in the progression to stomach cancer, PLoS pathogens 13(10) (2017) e1006573.

[15] T.H. Li, Y. Qin, P.C. Sham, K. Lau, K.-M. Chu, W.K. Leung, Alterations in gastric microbiota after H. pylori eradication and in different histological stages of gastric carcinogenesis, Scientific reports 7(1) (2017) 1-8.

[16] M.T. Whary, S. Muthupalani, Z. Ge, Y. Feng, J. Lofgren, H.N. Shi, N.S. Taylor, P. Correa, J. Versalovic, T.C. Wang, Helminth co-infection in Helicobacter pylori infected INS-GAS mice attenuates gastric premalignant lesions of epithelial dysplasia and glandular atrophy and preserves colonization resistance of the stomach to lower bowel microbiota, Microbes and infection 16(4) (2014) 345-355.

[17] J.J. Sung, O.O. Coker, E. Chu, C.H. Szeto, S.T.Y. Luk, H.C.H. Lau, J. Yu, Gastric microbes associated with gastric inflammation, atrophy and intestinal metaplasia 1 year after Helicobacter pylori eradication, Gut 69(9) (2020) 1572-1580.

[18] C.-C. Chen, J.-M. Liou, Y.-C. Lee, T.-C. Hong, E.M. El-Omar, M.-S. Wu, The interplay between Helicobacter pylori and gastrointestinal microbiota, Gut microbes 13(1) (2021) 1-22.

[19] W.K. Leung, Helicobacter pylori and gastric neoplasia, Contrib Microbiol 13 (2006) 66-80.

[20] M. Rajilic-Stojanovic, C. Figueiredo, A. Smet, R. Hansen, J. Kupcinskas, T. Rokkas, L. Andersen, J.C. Machado, G. Ianiro, A. Gasbarrini, M. Leja, J.P. Gisbert, G.L. Hold, Systematic review: gastric microbiota in health and disease, Aliment Pharmacol Ther 51(6) (2020) 582-602.

[21] A. Pormohammad, R. Ghotaslou, H.E. Leylabadlo, M.J. Nasiri, H. Dabiri, A. Hashemi, Risk of gastric cancer in association with Helicobacter pylori different virulence factors: A systematic review and meta-analysis, Microb Pathog 118 (2018) 214-219.

[22] Y. Yamaoka, D.Y. Graham, Helicobacter pylori virulence and cancer pathogenesis, Future Oncol 10(8) (2014) 1487-500.

[23] B.J. Dicken, D.L. Bigam, C. Cass, J.R. Mackey, A.A. Joy, S.M. Hamilton, Gastric adenocarcinoma: review and considerations for future directions, Ann Surg 241(1) (2005) 27-39.

[24] M.H. Lee, J.Y. Yang, Y. Cho, H.J. Woo, H.J. Kwon, D.H. Kim, M. Park, C. Moon, M.J. Yeon, H.W. Kim, W.D. Seo, S.H. Kim, J.B. Kim, Inhibitory Effects of Menadione on Helicobacter pylori Growth and Helicobacter pylori-Induced Inflammation via NF-κB Inhibition, Int J Mol Sci 20(5) (2019).

[25] I.S. Sougleri, K.S. Papadakos, M.P. Zadik, M. Mavri-Vavagianni, A.F. Mentis, D.N. Sgouras, Helicobacter pylori CagA protein induces factors involved in the epithelial to mesenchymal transition (EMT) in infected gastric epithelial cells in an EPIYA- phosphorylation-dependent manner, Febs j 283(2) (2016) 206-20.

[26] G. Coulombe, N. Rivard, New and Unexpected Biological Functions for the Src-Homology 2 Domain-Containing Phosphatase SHP-2 in the Gastrointestinal Tract, Cell Mol Gastroenterol Hepatol 2(1) (2015) 11-21.

[27] X. Yong, B. Tang, Y.F. Xiao, R. Xie, Y. Qin, G. Luo, C.J. Hu, H. Dong, S.M. Yang, Helicobacter pylori upregulates Nanog and Oct4 via Wnt/β-catenin signaling pathway to promote cancer stem cell-like properties in human gastric cancer, Cancer Lett 374(2) (2016) 292-303.

[28] N. Li, Y. Feng, Y. Hu, C. He, C. Xie, Y. Ouyang, S.C. Artim, D. Huang, Y. Zhu, Z. Luo, Z. Ge, N. Lu, Helicobacter pylori CagA promotes epithelial mesenchymal transition in gastric carcinogenesis via triggering oncogenic YAP pathway, Journal of Experimental & Clinical Cancer Research 37(1) (2018) 280.

[29] G. Posselt, S. Backert, S. Wessler, The functional interplay of Helicobacter pylori factors with gastric epithelial cells induces a multi-step process in pathogenesis, Cell Commun Signal 11 (2013) 77.

[30] H.J. Ahn, D.S. Lee, Helicobacter pylori in gastric carcinogenesis, World J Gastrointest Oncol 7(12) (2015) 455-465.

[31] I.P. Witz, Tumor-microenvironment interactions: dangerous liaisons, Adv Cancer Res 100 (2008) 203-29.

[32] R. Ostuni, F. Kratochvill, P.J. Murray, G. Natoli, Macrophages and cancer: from mechanisms to therapeutic implications, Trends Immunol 36(4) (2015) 229-39.

[33] A. Mantovani, S. Sozzani, M. Locati, P. Allavena, A. Sica, Macrophage polarization: tumor-associated macrophages as a paradigm for polarized M2 mononuclear phagocytes, Trends Immunol 23(11) (2002) 549-55.

[34] C. Zhao, X. Lu, X. Bu, N. Zhang, W. Wang, Involvement of tumor necrosis factor-alpha in the upregulation of CXCR4 expression in gastric cancer induced by Helicobacter pylori, BMC Cancer 10 (2010) 419-419.

[35] M.S. Krakowiak, J.M. Noto, M.B. Piazuelo, D.M. Hardbower, J. Romero-Gallo, A. Delgado, R. Chaturvedi, P. Correa, K.T. Wilson, R.M. Peek, Jr., Matrix metalloproteinase 7 restrains Helicobacter pylori-induced gastric inflammation and premalignant lesions in the stomach by altering macrophage polarization, Oncogene 34(14) (2015) 1865-1871.

[36] Y. Che, B. Geng, Y. Xu, X. Miao, L. Chen, X. Mu, J. Pan, C. Zhang, T. Zhao, C. Wang, X. Li, H. Wen, Z. Liu, Q. You, Helicobacter pylori-induced exosomal MET educates tumour-associated macrophages to promote gastric cancer progression, J Cell Mol Med 22(11) (2018) 5708-5719.

[37] S. Li, X. Liang, L. Ma, L. Shen, T. Li, L. Zheng, A. Sun, W. Shang, C. Chen, W. Zhao, J. Jia, MiR-22 sustains NLRP3 expression and attenuates H. pylori-induced gastric carcinogenesis, Oncogene 37(7) (2018) 884-896.

[38] V. Gambardella, J. Castillo, N. Tarazona, F. Gimeno-Valiente, C. Martínez-Ciarpaglini, M. Cabeza-Segura, S. Roselló, D. Roda, M. Huerta, A. Cervantes, T. Fleitas, The role of tumor-associated macrophages in gastric cancer development and their potential as a therapeutic target, Cancer Treatment Reviews 86 (2020) 102015.

[39] B. Shen, A. Qian, W. Lao, W. Li, X. Chen, B. Zhang, H. Wang, F. Yuan, Y. Sun, Relationship between Helicobacter pylori and expression of programmed death-1 and its ligand in gastric intraepithelial neoplasia and early-stage gastric cancer, Cancer Manag Res 11 (2019) 3909-3919.

[40] Y. Kono, H. Saito, W. Miyauchi, S. Shimizu, Y. Murakami, Y. Shishido, K. Miyatani, T. Matsunaga, Y. Fukumoto, Y. Nakayama, C. Sakurai, K. Hatsuzawa, Y. Fujiwara, Increased PD-1-positive macrophages in the tissue of gastric cancer are closely associated with poor prognosis in gastric cancer patients, BMC Cancer 20(1) (2020) 175.

[41] E. Bettelli, Y. Carrier, W. Gao, T. Korn, T.B. Strom, M. Oukka, H.L. Weiner, V.K. Kuchroo, Reciprocal developmental pathways for the generation of pathogenic effector TH17 and regulatory T cells, Nature 441(7090) (2006) 235-8.

[42] G. Codolo, M. Toffoletto, F. Chemello, S. Coletta, G. Soler Teixidor, G. Battaggia, G. Munari, M. Fassan, S. Cagnin, M. de Bernard, Helicobacter pylori Dampens HLA-II Expression on Macrophages via the Up-Regulation of miRNAs Targeting CIITA, Front Immunol 10 (2020) 2923-2923.

[43] Y. Katayama, M. Takahashi, H. Kuwayama, Helicobacter pylori causes runx3 gene methylation and its loss of expression in gastric epithelial cells, which is mediated by nitric oxide produced by macrophages, Biochem Biophys Res Commun 388(3) (2009) 496-500.

[44] F.I. Bussière, R. Chaturvedi, Y. Cheng, A.P. Gobert, M. Asim, D.R. Blumberg, H. Xu, P.Y. Kim, A. Hacker, R.A. Casero, Jr., K.T. Wilson, Spermine causes loss of innate immune response to Helicobacter pylori by inhibition of inducible nitric-oxide synthase translation, J Biol Chem 280(4) (2005) 2409-12.

[45] W. Alpízar-Alpízar, B.S. Nielsen, R. Sierra, M. Illemann, J.A. Ramírez, A. Arias, S. Durán, A. Skarstein, K. Ovrebo, L.R. Lund, O.D. Laerum, Urokinase plasminogen activator receptor is expressed in invasive cells in gastric carcinomas from high- and low-risk countries, Int J Cancer 126(2) (2010) 405-15.

[46] D.F. Quail, J.A. Joyce, Microenvironmental regulation of tumor progression and metastasis, Nature medicine 19(11) (2013) 1423-37.

[47] A.G. Shabgah, H. Mohammadi, P. Goleij, M. Hedayati-Moghadam, A. Salmaninejad, J.G. Navashenaq, The role of Non-coding Genome in Cancer-associated Fibroblasts; state-of-the-art and perspectives in cancer targeted therapy, Curr Drug Targets (2021).

[48] Y. Yamamura, N. Asai, A. Enomoto, T. Kato, S. Mii, Y. Kondo, K. Ushida, K. Niimi, N. Tsunoda, M. Nagino, S. Ichihara, K. Furukawa, K. Maeda, T. Murohara, M. Takahashi, Akt-Girdin signaling in cancer-associated fibroblasts contributes to tumor progression, Cancer research 75(5) (2015) 813-23.

[49] K. Shiga, M. Hara, T. Nagasaki, T. Sato, H. Takahashi, H. Takeyama, Cancer-Associated Fibroblasts: Their Characteristics and Their Roles in Tumor Growth, Cancers (Basel) 7(4) (2015) 2443-2458.

[50] M. Augsten, C. Hägglöf, E. Olsson, C. Stolz, P. Tsagozis, T. Levchenko, M.J. Frederick, Å. Borg, P. Micke, L. Egevad, CXCL14 is an autocrine growth factor for fibroblasts and acts as a multi-modal stimulator of prostate tumor growth, Proceedings of the National Academy of Sciences 106(9) (2009) 3414-3419.

[51] T. Liu, L. Zhou, D. Li, T. Andl, Y. Zhang, Cancer-Associated Fibroblasts Build and Secure the Tumor Microenvironment, Front Cell Dev Biol 7 (2019) 60-60.

[52] Q. Zhang, M. Wang, F. Huang, T. Yang, J. Cai, X. Zhang, W. Zhu, H. Qian, W. Xu, H. pylori infection-induced MSC differentiation into CAFs promotes epithelial-mesenchymal transition in gastric epithelial cells, Int J Mol Med 32(6) (2013) 1465-73.

[53] G. Krzysiek-Maczka, A. Targosz, U. Szczyrk, M. Strzałka, Z. Sliwowski, T. Brzozowski, J. Czyz, A. Ptak-Belowska, Role of Helicobacter pylori infection in cancer-associated fibroblast-induced epithelial-mesenchymal transition in vitro, Helicobacter 23(6) (2018) e12538.

[54] G. Krzysiek-Maczka, T. Wrobel, A. Targosz, U. Szczyrk, M. Strzalka, A. Ptak-Belowska, J. Czyz, T. Brzozowski, Helicobacter pylori-activated gastric fibroblasts induce epithelial-mesenchymal transition of gastric epithelial cells in vitro in a TGF-β-dependent manner, Helicobacter 24(5) (2019) e12653.

[55] G. Krzysiek-Maczka, A. Targosz, U. Szczyrk, T. Wrobel, M. Strzalka, T. Brzozowski, J. Czyz, A. Ptak-Belowska, Long-Term Helicobacter pylori Infection Switches Gastric Epithelium

Reprogramming Towards Cancer Stem Cell-Related Differentiation Program in Hp-Activated Gastric Fibroblast-TGFβ Dependent Manner, Microorganisms 8(10) (2020) 1519.

[56] P. Li, J.-X. Shan, X.-H. Chen, D. Zhang, L.-P. Su, X.-Y. Huang, B.-Q. Yu, Q.-M. Zhi, C.-L. Li, Y.-Q. Wang, S. Tomei, Q. Cai, J. Ji, J.-F. Li, L. Chouchane, Y.-Y. Yu, F.-Z. Sun, Z.-H. Xu, B.-Y. Liu, Z.-G. Zhu, Epigenetic silencing of microRNA-149 in cancer-associated fibroblasts mediates prostaglandin E2/interleukin-6 signaling in the tumor microenvironment, Cell Res 25(5) (2015) 588-603.

[57] G. Krzysiek-Maczka, A. Targosz, U. Szczyrk, M. Strzalka, T. Brzozowski, A. Ptak-Belowska, Involvement of epithelial-mesenchymal transition-inducing transcription factors in the mechanism of Helicobacter pylori-induced fibroblasts activation, J Physiol Pharmacol 70(5) (2019).

[58] J. Shen, J. Zhai, Q. You, G. Zhang, M. He, X. Yao, L. Shen, Cancer-associated fibroblasts-derived VCAM1 induced by H. pylori infection facilitates tumor invasion in gastric cancer, Oncogene 39(14) (2020) 2961-2974.

[59] C.J. Liu, Y.K. Wang, F.C. Kuo, W.H. Hsu, F.J. Yu, S. Hsieh, M.H. Tai, D.C. Wu, C.H. Kuo, Helicobacter pylori Infection-Induced Hepatoma-Derived Growth Factor Regulates the Differentiation of Human Mesenchymal Stem Cells to Myofibroblast-Like Cells, Cancers (Basel) 10(12) (2018).

[60] G. Krzysiek-Maczka, A. Targosz, A. Ptak-Belowska, E. Korbut, U. Szczyrk, M. Strzalka, T. Brzozowski, Molecular alterations in fibroblasts exposed to Helicobacter pylori: a missing link in bacterial inflammation progressing into gastric carcinogenesis?, J Physiol Pharmacol 64(1) (2013) 77-87.

[61] B.G. Cuiffo, A.E. Karnoub, Mesenchymal stem cells in tumor development: emerging roles and concepts, Cell Adh Migr 6(3) (2012) 220-230.

[62] S. Liu, C. Ginestier, S.J. Ou, S.G. Clouthier, S.H. Patel, F. Monville, H. Korkaya, A. Heath, J. Dutcher, C.G. Kleer, Y. Jung, G. Dontu, R. Taichman, M.S. Wicha, Breast cancer stem cells are regulated by mesenchymal stem cells through cytokine networks, Cancer research 71(2) (2011) 614-24.

[63] X.L. Yan, C.J. Fu, L. Chen, J.H. Qin, Q. Zeng, H.F. Yuan, X. Nan, H.X. Chen, J.N. Zhou, Y.L. Lin, X.M. Zhang, C.Z. Yu, W. Yue, X.T. Pei, Mesenchymal stem cells from primary breast cancer

tissue promote cancer proliferation and enhance mammosphere formation partially via EGF/EGFR/Akt pathway, Breast Cancer Res Treat 132(1) (2012) 153-64.

[64] J.L. Halpern, A. Kilbarger, C.C. Lynch, Mesenchymal stem cells promote mammary cancer cell migration in vitro via the CXCR2 receptor, Cancer Lett 308(1) (2011) 91-9.

[65] L.V. Rhodes, J.W. Antoon, S.E. Muir, S. Elliott, B.S. Beckman, M.E. Burow, Effects of human mesenchymal stem cells on ER-positive human breast carcinoma cells mediated through ER-SDF-1/CXCR4 crosstalk, Mol Cancer 9 (2010) 295.

[66] S. Glennie, I. Soeiro, P.J. Dyson, E.W. Lam, F. Dazzi, Bone marrow mesenchymal stem cells induce division arrest anergy of activated T cells, Blood 105(7) (2005) 2821-7.

[67] M. Krampera, S. Glennie, J. Dyson, D. Scott, R. Laylor, E. Simpson, F. Dazzi, Bone marrow mesenchymal stem cells inhibit the response of naive and memory antigen-specific T cells to their cognate peptide, Blood 101(9) (2003) 3722-9.

[68] I. Rashedi, A. Gómez-Aristizábal, X.-H. Wang, S. Viswanathan, A. Keating, TLR3 or TLR4 Activation Enhances Mesenchymal Stromal Cell-Mediated Treg Induction via Notch Signaling, STEM CELLS 35(1) (2017) 265-275.

[69] S.A. Patel, J.R. Meyer, S.J. Greco, K.E. Corcoran, M. Bryan, P. Rameshwar, Mesenchymal stem cells protect breast cancer cells through regulatory T cells: role of mesenchymal stem cell-derived TGF-beta, J Immunol 184(10) (2010) 5885-94.

[70] Q. Zhang, S. Chai, W. Wang, C. Wan, F. Zhang, Y. Li, F. Wang, Macrophages activate mesenchymal stem cells to acquire cancer-associated fibroblast-like features resulting in gastric epithelial cell lesions and malignant transformation in vitro, Oncology letters 17(1) (2019) 747-756.

[71] J.M. Donnelly, A.C. Engevik, M. Engevik, M.A. Schumacher, C. Xiao, L. Yang, R.T. Worrell, Y. Zavros, Gastritis promotes an activated bone marrow-derived mesenchymal stem cell with a phenotype reminiscent of a cancer-promoting cell, Dig Dis Sci 59(3) (2014) 569-582.

[72] J. Ferrand, P. Lehours, A. Schmid-Alliana, F. Mégraud, C. Varon, Helicobacter pylori infection of gastrointestinal epithelial cells in vitro induces mesenchymal stem cell migration through an NF-κB-dependent pathway, PLoS One 6(12) (2011) e29007.

[73] S.L. Moradi, G. Eslami, H. Goudarzi, Z. Hajishafieeha, M. Soleimani, A. Mohammadzadeh, A. Ardeshirylajimi, Role of Helicobacter pylori on cancer of human adipose-derived mesenchymal stem cells and metastasis of tumor cells-an in vitro study, Tumour Biol 37(3) (2016) 3371-8.

[74] R. Lin, H. Ma, Z. Ding, W. Shi, W. Qian, J. Song, X. Hou, Bone marrow-derived mesenchymal stem cells favor the immunosuppressive T cells skewing in a Helicobacter pylori model of gastric cancer, Stem Cells Dev 22(21) (2013) 2836-48.

[75] A. Altobelli, M. Bauer, K. Velez, T.L. Cover, A. Müller, Helicobacter pylori VacA Targets Myeloid Cells in the Gastric Lamina Propria To Promote Peripherally Induced Regulatory T-Cell Differentiation and Persistent Infection, mBio 10(2) (2019) e00261-19.

[76] Y. Li, X. Zhong, Y. Zhang, X. Lu, Mesenchymal Stem Cells in Gastric Cancer: Vicious but Hopeful, Frontiers in oncology 11 (2021) 1677.

[77] Z. Wu, W. Liu, Z. Wang, B. Zeng, G. Peng, H. Niu, L. Chen, C. Liu, Q. Hu, Y. Zhang, Mesenchymal stem cells derived from iPSCs expressing interleukin-24 inhibit the growth of melanoma in the tumor-bearing mouse model, Cancer cell international 20(1) (2020) 1-10.

[78] L. Lu, G. Chen, J. Yang, Z. Ma, Y. Yang, Y. Hu, Y. Lu, Z. Cao, Y. Wang, X. Wang, Bone marrow mesenchymal stem cells suppress growth and promote the apoptosis of glioma U251 cells through downregulation of the PI3K/AKT signaling pathway, Biomedicine & Pharmacotherapy 112 (2019) 108625.

[79] R. Serhal, N. Saliba, G. Hilal, M. Moussa, G.S. Hassan, O. El Atat, N. Alaaeddine, Effect of adipose-derived mesenchymal stem cells on hepatocellular carcinoma: In vitro inhibition of carcinogenesis, World J Gastroenterol 25(5) (2019) 567.

[80] J. Zhao, Z. Zhang, Q. Cui, L. Zhao, Y. Hu, S. Zhao, Human adipose-derived mesenchymal stem cells inhibit proliferation and induce apoptosis of human gastric cancer HGC-27 cells, 3 Biotech 10(3) (2020) 1-9.

[81] M.-Y. Meng, L. Li, W.-J. Wang, F.-F. Liu, J. Song, S.-L. Yang, J. Tan, H. Gao, Y.-Y. Zhao, W.-W. Tang, Assessment of tumor promoting effects of amniotic and umbilical cord mesenchymal stem cells in vitro and in vivo, Journal of cancer research and clinical oncology 145(5) (2019) 1133-1146.

[82] F. Rahmatizadeh, S.G.-G. Aziz, K. Khodadadi, M.L. Ataei, E. Ebrahimie, J.S. Rad, M. Pashaiasl, Bidirectional and opposite effects of naïve mesenchymal stem cells on tumor growth and progression, Advanced pharmaceutical bulletin 9(4) (2019) 539.

[83] A.G. Shabgah, A. Salmaninejad, L. Thangavelu, M. Alexander, A.V. Yumashev, P. Goleij, M. Hedayati-Moghadam, H. Mohammadi, M. Ahmadi, J.G. Navashenaq, The role of non-coding genome in the behavior of infiltrated myeloid-derived suppressor cells in tumor microenvironment; a perspective and state-of-the-art in cancer targeted therapy, Prog. Biophys. Mol. Biol. (2020).

[84] J.G. Navashenaq, P. Zamani, A.R. Nikpoor, J. Tavakkol-Afshari, M.R. Jaafari, Doxil chemotherapy plus liposomal P5 immunotherapy decreased myeloid-derived suppressor cells in murine model of breast cancer, Nanomedicine: Nanotechnology, Biology and Medicine 24 (2020) 102150.

[85] D.I. Gabrilovich, S. Ostrand-Rosenberg, V. Bronte, Coordinated regulation of myeloid cells by tumours, Nat Rev Immunol 12(4) (2012) 253-68.

[86] A. Mantovani, The growing diversity and spectrum of action of myeloid-derived suppressor cells, Eur J Immunol 40(12) (2010) 3317-20.

[87] E. Taghizadeh, F. Taheri, P.G. Renani, Ž. Reiner, J.G. Navashenaq, A. Sahebkar, Macrophage: A Key Therapeutic Target in Atherosclerosis?, Curr Pharm Des 25(29) (2019) 3165-3174.

[88] P. Allavena, A. Mantovani, Immunology in the clinic review series; focus on cancer: tumour-associated macrophages: undisputed stars of the inflammatory tumour microenvironment, Clin Exp Immunol 167(2) (2012) 195-205.

[89] J.G. Navashenaq, P. Zamani, A.R. Nikpoor, J. Tavakkol-Afshari, M.R. Jaafari, Doxil chemotherapy plus liposomal P5 immunotherapy decreased myeloid-derived suppressor cells in murine model of breast cancer, Nanomedicine 24 (2020) 102150.

[90] S. Tomić, B. Joksimović, M. Bekić, M. Vasiljević, M. Milanović, M. Čolić, D. Vučević, Prostaglanin-E2 Potentiates the Suppressive Functions of Human Mononuclear Myeloid-Derived Suppressor Cells and Increases Their Capacity to Expand IL-10-Producing Regulatory T Cell Subsets, Front Immunol 10 (2019) 475.

[91] M. Elkabets, V.S. Ribeiro, C.A. Dinarello, S. Ostrand-Rosenberg, J.P. Di Santo, R.N. Apte, C.A. Vosshenrich, IL-1β regulates a novel myeloid-derived suppressor cell subset that impairs NK cell development and function, Eur J Immunol 40(12) (2010) 3347-57.

[92] R.P. Tobin, K.R. Jordan, P. Kapoor, E. Spongberg, D. Davis, V.M. Vorwald, K.L. Couts, D. Gao, D.E. Smith, J.S.W. Borgers, S. Robinson, C. Amato, R. Gonzalez, K.D. Lewis, W.A. Robinson, V.F. Borges, M.D. McCarter, IL-6 and IL-8 Are Linked With Myeloid-Derived Suppressor Cell Accumulation and Correlate With Poor Clinical Outcomes in Melanoma Patients, Frontiers in oncology 9 (2019) 1223.

[93] I. Marigo, E. Bosio, S. Solito, C. Mesa, A. Fernandez, L. Dolcetti, S. Ugel, N. Sonda, S. Bicciato, E. Falisi, F. Calabrese, G. Basso, P. Zanovello, E. Cozzi, S. Mandruzzato, V. Bronte, Tumor-induced tolerance and immune suppression depend on the C/EBPbeta transcription factor, Immunity 32(6) (2010) 790-802.

[94] T. Condamine, D.I. Gabrilovich, Molecular mechanisms regulating myeloid-derived suppressor cell differentiation and function, Trends Immunol 32(1) (2011) 19-25.

[95] Y. Hayakawa, Y. Hirata, M. Hata, M. Tsuboi, Y. Oya, K. Kurokawa, S. Abe, J. Arai, N. Suzuki, H. Nakagawa, H. Fujiwara, K. Tateishi, S. Maeda, K. Koike, Dysregulated Immune Responses by ASK1 Deficiency Alter Epithelial Progenitor Cell Fate and Accelerate Metaplasia Development during H. pylori Infection, Microorganisms 8(12) (2020).

[96] S. Kusmartsev, Y. Nefedova, D. Yoder, D.I. Gabrilovich, Antigen-specific inhibition of CD8+ T cell response by immature myeloid cells in cancer is mediated by reactive oxygen species, J Immunol 172(2) (2004) 989-99.

[97] A.V. Ezernitchi, I. Vaknin, L. Cohen-Daniel, O. Levy, E. Manaster, A. Halabi, E. Pikarsky, L. Shapira, M. Baniyash, TCR zeta down-regulation under chronic inflammation is mediated by myeloid suppressor cells differentially distributed between various lymphatic organs, J Immunol 177(7) (2006) 4763-72.

[98] S. Nagaraj, A.G. Schrum, H.I. Cho, E. Celis, D.I. Gabrilovich, Mechanism of T cell tolerance induced by myeloid-derived suppressor cells, J Immunol 184(6) (2010) 3106-16.

[99] B. Huang, P.Y. Pan, Q. Li, A.I. Sato, D.E. Levy, J. Bromberg, C.M. Divino, S.H. Chen, Gr-1+CD115+ immature myeloid suppressor cells mediate the development of tumor-induced T regulatory cells and T-cell anergy in tumor-bearing host, Cancer research 66(2) (2006) 1123-31.

[100] L. Ding, M.M. Hayes, A. Photenhauer, K.A. Eaton, Q. Li, R. Ocadiz-Ruiz, J.L. Merchant, Schlafen 4-expressing myeloid-derived suppressor cells are induced during murine gastric metaplasia, J Clin Invest 126(8) (2016) 2867-2880.

[101] H. Mesali, A. Ajami, H. Hussein-Nattaj, A. Rafiei, Z. Rajabian, H. Asgarian-Omran, V. Hosseini, T. Taghvaei, M. Tehrani, Regulatory T Cells and Myeloid-Derived Suppressor Cells in Patients with Peptic Ulcer and Gastric Cancer, Iran J Immunol 13(3) (2016) 167-77.

[102] Y. Zhuang, P. Cheng, X.F. Liu, L.S. Peng, B.S. Li, T.T. Wang, N. Chen, W.H. Li, Y. Shi, W. Chen, K.C. Pang, M. Zeng, X.H. Mao, S.M. Yang, H. Guo, G. Guo, T. Liu, Q.F. Zuo, H.J. Yang, L.Y. Yang, F.Y. Mao, Y.P. Lv, Q.M. Zou, A pro-inflammatory role for Th22 cells in Helicobacter pylori-associated gastritis, Gut 64(9) (2015) 1368-78.

[103] K. Fall, W. Ye, O. Nyrén, Antibiotic treatment and risk of gastric cancer, Gut 55(6) (2006) 793-796.

[104] T.-H. Chiang, W.-J. Chang, S.L.-S. Chen, A.M.-F. Yen, J.C.-Y. Fann, S.Y.-H. Chiu, Y.-R. Chen, S.-L. Chuang, C.-F. Shieh, C.-Y. Liu, Mass eradication of Helicobacter pylori to reduce gastric cancer incidence and mortality: a long-term cohort study on Matsu Islands, Gut 70(2) (2021) 243-250.

[105] M.L.F. Bittencourt, R.P. Rodrigues, R.R. Kitagawa, R.C.R. Gonçalves, The gastroprotective potential of silibinin against Helicobacter pylori infection and gastric tumor cells, Life Sci 256 (2020) 117977.

[106] J.S. Ardisson, R.C.R. Gonçalves, R.P. Rodrigues, R.R. Kitagawa, Antitumour, Immunomodulatory activity and in silico studies of naphthopyranones targeting iNOS, a relevant target for the treatment of Helicobacter pylori infection, Biomed Pharmacother 107 (2018) 1160-1165.

[107] X. Yang, Y. Zheng, L. Liu, J. Huang, F. Wang, J. Zhang, Progress on the study of the anticancer effects of artesunate, Oncology Letters 22(5) (2021) 1-12.

[108] X. Zhou, W.-J. Sun, W.-M. Wang, K. Chen, J.-H. Zheng, M.-D. Lu, P.-H. Li, Z.-Q. Zheng, Artesunate inhibits the growth of gastric cancer cells through the mechanism of promoting oncosis both in vitro and in vivo, Anti-Cancer Drugs 24(9) (2013) 920-927.

[109] L. Wang, L. Liu, J. Wang, Y. Chen, Inhibitory effect of artesunate on growth and apoptosis of gastric cancer cells, Archives of medical research 48(7) (2017) 623-630.

[110] T. Su, F. Li, J. Guan, L. Liu, P. Huang, Y. Wang, X. Qi, Z. Liu, L. Lu, D. Wang, Artemisinin and its derivatives prevent Helicobacter pylori-induced gastric carcinogenesis via inhibition of NF-κB signaling, Phytomedicine 63 (2019) 152968.

[111] M. Saravanan, V. Gopinath, M.K. Chaurasia, A. Syed, F. Ameen, N. Purushothaman, Green synthesis of anisotropic zinc oxide nanoparticles with antibacterial and cytofriendly properties, Microb Pathog 115 (2018) 57-63.

5. **Figures' Legends:**

Figure. 1. The cross-talk between H. pylori with immunosuppressive cells in gastric cancer. **A)** The interaction between *H. pylori* and TAMs in the tumor microenvironment. **B)** The crosstalk between MDSCs and *H. pylori* in the tumor microenvironment. **C)** The interplay of *H. pylori* and CAFs in the tumor microenvironment. **D)** The interaction of *H. pylori* and MSCs in the tumor microenvironment.