Microbiome Control in the Prevention and Early Management of Cancer

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Abstract Data accumulated during the past 15–20 years have established that chronic infections may contribute to the development of tumors in humans. Although the impact of certain viruses on human carcinogenesis has been known for some time, the involvement of bacteria in such process was not demonstrated until *Helicobacter pylori* was confirmed as an etiological agent for stomach cancer. Later, other bacterial species (i.e., *Borrelia*, *Campylobacter*, *Chlamydia*) have been associated with different human malignancies. The availability of antibiotics to these pathogens boosted eradication as the main prevention and therapeutic strategy to manage bacterially-promoted cancers. However, more recently, the not surprising emergence of antibiotic-resistant cases, along with recent information on the remarkable qualitative and quantitative changes that take place in the normal tissue/organ-specific microbiota at different stages of the carcinogenic process, have suggested the possibility of modifying or restoring the microbiota for cancer prevention strategies and, either alone or in combination with conventional anticancer agents, for therapeutic approaches. This chapter focuses on *Helicobacter* species (*H. pylori* in particular) as biological tumor-inducing agents, the proposed mechanisms underlying the oncogenic processes which they contribute to initiate, such as gastric cancer, colorectal adenocarcinoma, lung cancer, gastric MALT lymphoma, gastric diffuse large-B-cell lymphoma (DLBCL), and biliary tract cancer. Eradication versus microbiota manipulation alternatives are discussed in this context.

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1 Introduction

The International Agency for Research on Cancer (IARC), the specialized cancer agency of the World Health Organization, revealed global cancer statistics based on 28 types of cancer in 184 countries worldwide. World cancer burden rose to 14.1 million new cases and 8.2 million cancer deaths in 2012, compared with 12.7 and 7.6 million, respectively, in 2008. The prevention and early management of cancer development remains one of the most important goals in global health. Solid tumors (e.g., colorectal adenocarcinoma, lung and gastric cancers) and some lymphomas exhibit significant interest in public health due to their prevalence and death rates (Ferlay et al. 2013, 2015). Prevalence estimates for 2012 indicated that 32.6 million people (over the age of 15 years) were alive five years after being diagnosed a cancer. Globally, the most frequently diagnosed tumors were lung (1.8 million), breast (1.7 million), and colorectal (1.4 million) cancers. Regarding cancer-related deaths, the most common causes were lung (1.6 million), liver (0.8 million), and stomach (0.7 million) tumors (Ferlay et al. 2013, 2015). Data analysis also demonstrated that, in 2012, more than half of all cancers (56.8 %) and cancer deaths (64.9 %) were reported in developing countries (Ferlay et al. 2013, 2015).

On the other hand, the emergence of treatment resistant infectious agents has become another source of public health, as well as scientific, concern. In fact, the eradication of bacterial infections is far to be achieved. The epidemiology of resistance shows that it is now a worldwide problem. It affects not only Africa and developing countries, but also industrialized areas, Europe (with the highest rate in the Mediterranean countries), North America (mostly higher in the United States than in Canada), East Asia, and South America (with the worst resistance patterns). Therefore, such a long-term exposure to these pathogens may lead to dramatic consequences. There is growing evidence showing bacteria as biological causes of cancers as well as virus and parasites (Chang and Parsonnet 2010; Schwabe and Jobin 2013).

In this chapter, we present some *Helicobacter* species (*H. pylori* in particular) as biological tumor-inducing agents as well as the mechanisms proposed to understand their contribution to the oncogenic processes. It is clear that a good understanding of these events besides the microbiome control may shed some light on new strategies to reduce cancer evolution. Due to the growth and aging of the global population, the prevalence is expected to increase to 19.3 million new cancer cases by 2025. By that time in less developed regions of the world, the estimations of the proportions of all cancers (>56 % in 2012) and cancer deaths (>64 % in 2012) will also increase further (Ferlay et al. 2013, 2015). Although the proportion of tumors initiated as a consequence of bacterial infections is relatively small, the fact that the initial etiologic agents are known offers the possibility of designing targeted strategies that may contribute to reduce the overall incidence of cancer in the human population. In this regard, a critical question that remains unsolved to date relates to the nature of the disease management approaches: eradication of the infectious

pathogens by the use of antibiotics or manipulation of the microbiota of the affected tissue or organ to maintain, or regain, its normal characteristics, and restore microbiota-host symbiotic interactions that guard general homeostasis.

Recent culture-independent technological advances (i.e., next-generation sequencing) have moved the field of microbiota analysis far beyond the limitations of traditional culture-based identification methods (Engstrand and Lindberg 2013; Arora et al. 2015; Schulz et al. 2015), thus facilitating the quantitative and qualitative characterization of the normal human microbiota as well as our understanding of the dynamic changes in tissue/organ-specific bacterial populations that accompany the onset and progression of cancer and other disease. The possibility of manipulating the human microbiota for cancer prevention purposes and, either alone or in combination with conventional anticancer agents, to design therapeutic strategies is becoming a tangible option, which could make the use of antibiotics to eradicate the infectious bacteria, with all its possible negative consequences, an obsolete approach.

2 *Helicobacter* spp. and Tumorigenesis

The genus *Helicobacter* includes around 33 validity proposed members. Species within the *Helicobacter* genus are non-spore-forming gram-negative bacteria. Their cellular morphology may be curved, spiral, or fusiform, being typically 0.2–1.2 μm in diameter and 1.5–10 μm long. The percent G + C content of their chromosomal DNA ranges from 30 to 48. Some *Helicobacter* species (e.g., *H. pylori*, *H. acinonychis*, *H. bizzozeronii*, *H. felis*, *H. mustelae*, *H. salomonis*) are associated with gastric mucosa, whereas others (e.g., *H. bilis*, *H. canis*, *H. hepaticus*, *H. rodentium*) associate with the intestinal mucosa (Enterohepatic). *H. pylori* has emerged as one of the most important members of the genus, and is known to colonize the human stomach in about 50 % of the population of the world. It is responsible of more than 90 % of duodenal ulcers and up to 80 % of gastric ulcers.

Helicobacter pylori is a spiral-shaped gram-negative bacterium, 2.5–5.0 μm long and 0.5–1.0 μm wide, with 4–6 polar-sheathed flagella (Goodwin and Armstrong 1990). After colonizing the human stomach, it can generate a long-term infection of the gastric mucosa leading in adults and children to chronic gastritis, peptic ulcer disease, and cancers (gastric and lymphoma). The number of Americans suffering from peptic ulcer disease during their lifetime is estimated to be around 25 million. During the past decade (2006), the annual ulcer-related new cases and hospitalizations were approximately 500,000–850,000 and 1 million, respectively. The risk of developing gastric cancer and mucosal-associated-lymphoid-type (MALT) lymphoma is increased two to sixfold in infected patients compared to uninfected subjects. *H. pylori* and other *Helicobacter* species have therefore been related to an increased risk of cancers such as mucosa-associated lymphoid tissue (MALT) lymphoma, gastric adenocarcinoma, colorectal adenocarcinoma, and biliary tract cancer.

2.1 Gastric Cancer

Gastric cancer can be divided into cardia and noncardia gastric adenocarcinoma (NCGA). Although, the global incidence of NCGA has declined, its death rate in patients is extremely high. Currently, gastric cancer is the fifth most common cancer in the world after lung, breast, colon, rectum, and prostate. However, according to Globocan 2012, it is the third leading cause of death in both sexes (723,000 deaths) from cancer (Bray et al. 2013). More than 70 % of this cancer occurs in developing countries. Interestingly, for 60 % of total cases was reported in three East Asia countries (China, Japan, and Korea). Several studies demonstrated the relation between long-term infection with *H. pylori* and the development of gastric cancer. In 1994, the IARC definitively listed *H. pylori* as a human oncogenic agent. In this section, we have summarized some mechanisms and factors involved in *Helicobacter*-induced gastric cancer.

2.1.1 Chronic Inflammation, Host Genetic Polymorphisms and Impairment of DNA Repair System

In human stomach, chronic infection by *H. pylori* ultimately leads to chronic inflammation. After the infection several processes, such as persistent cell necrosis and regeneration, alterations in cell differentiation, dramatically change the gastric mucosa. Inflammation is a mechanism induced by the host to eliminate the invading *H. pylori*. The epithelial cells then release the reactive oxygen and nitrogen oxide species (ROS and RNOS) to combat pathogens, interleukin-8 (IL-8), Gro-a, and chemokines that attract and activate lymphocytes, neutrophils, and macrophages (Ernst et al. 1997). Accompanying this recruitment is the induction of a Th1-predominant cellular immune response and subsequently the secretion of some pro-inflammatory cytokines (IL-1 beta, TNF-alpha, and gamma interferon—IFN-γ—) (Kraft et al. 2001). Recently, oipA (Outer inflammatory protein), also called HopH, that plays a role in the gastric mucosa colonization (Islami and Kamangar 2008) and is involved in the bacterial adherence to gastric epithelia, was demonstrated to be a pro-inflammatory outer membrane protein. It is present in about 97.5 % of patients with gastric or duodenal ulcer. It strongly correlates with mucosal IL-8 production by gastric epithelial cell lines. In contrast, IL-8 levels are substantially reduced when oipA expression is inhibited (oipA knockout mutants). The oipA status is also highly linked to *cag*PAI (cagA), *vacA*, and *babA2* genotypes (Kiviat et al. 1985; Kraft et al. 2001). By phosphorylating multiple signaling cascades interacting with *cag*PAI (CagA)-related pathways, oipA therefore induces inflammation and actin dynamics (Klein and Silverman 2008; Kondo et al. 2009). And such chronic inflammatory process may lead to tumorigenesis.

Host genetic polymorphisms are also involved in gastric cancer development. This process also links chronic inflammation to the oncogenic phenomenon. Several gene polymorphisms associated with increased risk for gastric cancer have

been described. For example, the pro-inflammatory cytokines (TNF-alpha, IL-8, and IL-17), the anti-inflammatory cytokine (IL-10), the hypochlorhydria factor IL-1 that reduces gastric acid secretion (El Omar et al. 2000; Lu et al. 2005; Wang et al. 2007). Globally, the free radicals and secondary products derived from ROS and RNOS may damage DNA, proteins, and cell membranes and indirectly induce cell repair (Coussens and Werb 2002). Inflammation process stimulates regenerative cell division that may lead to point mutations, deletions, or translocations since there is an impairment of the DNA repair system. The damaged and aberrant DNA is then transmitted to next generations by subsequent cell divisions and may result in oncogenesis. For example, the initial oxidative damage by ROS increases the levels of 8-Hydroxyguanine (8HdG) that causes G–T and A–C substitutions in the DNA (Cheng et al. 1992). Another oxidative damage marker, cyclooxygenase-2, displays a gene expression upregulation. In *H. pylori*-infected patients, those levels of the mutagenic metabolite 8HdG and cyclooxygenase-2 confirmed to be high, returned to baseline once eradicated *H. pylori* (Burkitt et al. 2009). An additional hypothesis suggests that *H. pylori* may cause tumor by activating mechanisms mediated by the proto-oncogenes c-*fos* and c-*jun*, both mitogenic signal transduction pathways (Meyer-ter-Vehn et al. 2000).

2.1.2 Hormones. Human Gastrin Hormone

There is growing evidence linking hormones to cancers. Some studies have postulated that chronic infection with *H. pylori* may also cause carcinogenesis through hypergastrinemia, a mechanism particularly related to Gastrin. This hormone is one of the most important peptide hormones in the human stomach. It is produced by neuroendocrine G cells in the antrum of the stomach. Gastrin and its precursors are involved in gastrointestinal tumors including gastric cancer. *H. pylori* harbors, at the tip of the T4SS pilus, a ligand (CagL) that activates the gastrin promoter by interacting with αvβ5-integrin and integrin $\alpha_5\beta_1$ receptor of the gastric epithelial cells via integrin linked kinase (ILK) signaling complex and via Arg-Gly-Asp (RGD) motif, respectively (Abramson et al. 2005). Therefore, besides the previously known function of CagL as an activator of epidermal growth factor receptor (EGFR), Raf cascade and MAP kinase (EGFR/Raf/MAP/Erk signaling pathway), it has been also shown to increase gastrin expression. Gastrin then binds to cholecystokinin 2 receptors and activates directly acid secretion or indirectly by previously stimulating histamine release that further binds to histamine 2 receptors (Aly et al. 2004; Anderson et al. 2008). The subsequent hypergastrinemia induced by *H. pylori* may trigger gastric precancerous conditions. *H. pylori* infection together with gastrin hormone can promote the secretion of heparin-binding epidermal growth factor (HB-EGF) and other growth factors as inducers of cell cycling and proliferation (Varro et al. 2002; Dickson et al. 2006). Finally, some findings also show that CagL, the mentioned activator of gastrin promotor, is essential for injection of the oncoprotein CagA into gastric epithelial cells. This issue will be discussed further.

2.1.3 Oncogenic Determinants

In this section, we describe the contribution of *H. pylori* oncoproteins to cell transformation. In particular, we will focus on CagA and VacA.

CagPAI and CagA: *Cag*PAI is a 40 kb region of chromosomal DNA, harboring approximately 31 genes. It encodes a functional type IV secretion system (T4SS) that forms a pilus to deliver the oncoprotein CagA into the cytosol of gastric epithelial cells through a rigid needle structure (Covacci and Rappuoli 2000; Rohde et al. 2003; Backert and Selbach 2008). *CagA* is a polymorphic gene with different numbers of repeated sequences in its C-terminal region. Each of these repeated regions contains Glu-Pro-Ile-Tyr-Ala (EPIYA) motifs with a tyrosine phosphorylation site (Hatakeyama 2004). Four distinct EPIYA segments (EPIYA-A, EPIYA-B, EPIYA-C, and EPIYA-D), each of which contains a single EPIYA motif, have been identified in the EPIYA-repeat region (Fig. 1). The EPIYA-repeat region of CagA from Western *H. pylori* isolates is A–B–C-type CagA and the EPIYA-C segment is frequently one to three times repeated in tandem (Fig. 1). Whereas CagA from East Asian *H. pylori* isolates is A–B–D-type and the EPIYA-D segment is unique to East Asian CagA (Higashi et al. 2002; Hatakeyama 2009) (Fig. 1). In the host target cells, this effector oncoprotein is phosphorylated by Src and Abl kinases (Miehlke et al. 2000) at EPIYA motif located in the 3′ region of CagA. Phosphorylated CagA then deregulates SHP2 phosphatase activity through the interaction with this eukaryotic protein (Higashi et al. 2002; Backert and Selbach 2005).

SHP-2 specifically binds to the tyrosine-phosphorylated EPIYA-C (light union) or EPIYA-D (strong binding) segment. Therefore, East Asian CagA (A–B–D-type) exhibits stronger SHP-2 binding than does Western CagA (A–B–C-type). A consequence of this process is the possible production of precancerous lesions and gastric cancer (Higashi et al. 2002; Hatakeyama 2009). Similarly, in Western CagA species, those with a greater number of EPIYA-C segments display higher interaction with SHP-2. These findings may explain the higher incidence of gastric cancer in East Asia and the geographic variability in the incidence of this tumor in Western countries. For example, the incidence of this cancer is higher in Colombia (with 57 % of the isolates exhibiting two EPIYA-C segments) than in USA (with only 4 % of the isolates showing two EPIYA-C segments) (Yamaoka 2010; Yamaoka and Graham 2014). CagA-deregulated SHP2 activates Erk MAP kinase signaling (in both Ras-dependent and Ras-independent pathways) promoting proliferation, and also inhibits focal adhesion kinase (FAK) activity related to cell-extracellular matrix interaction (Higashi et al. 2004; Tsutsumi et al. 2006). Phosphorylated CagA also induces the activation of pro-inflammatory cytokines, cell proliferation, motility, elongation (Wessler and Backert 2008) as well as the dysregulation of β-catenin signaling (Franco et al. 2005; Murata-Kamiya et al. 2007), an increase of cell motility and oncogenic transformation (Suzuki et al. 2005; Franco et al. 2008). Recent studies indicated that *cag*PAI activates gastric interleukin-8 (IL-8) production, a potent neutrophil-inducing chemokine (Brandt et al. 2005) and that

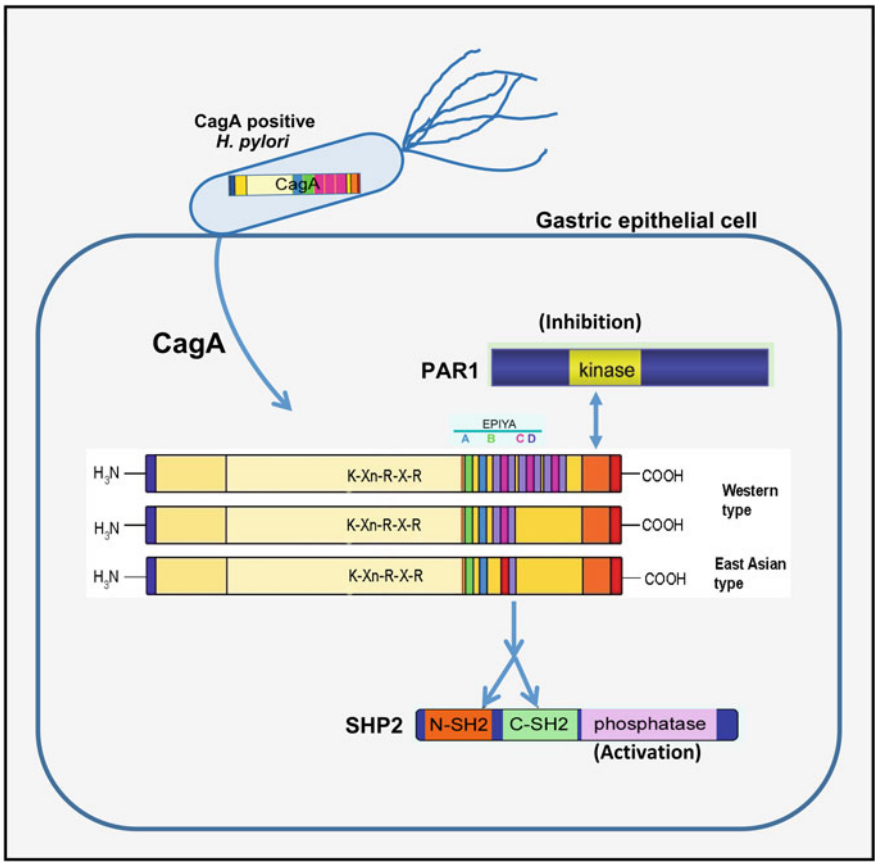

Fig. 1 Schematic representation of the structure of the most common *Helicobacter pylori* CagA variants of the western and East Asian types. Two important CagA protein-protein interactions are shown. Upon entry into gastric epithelial cells, CagA interacts and activates the SHP2 phosphatase, in a tyrosine phosphorylation-dependent manner. In addition, CagA interacts with PAR1 and inhibits its serine/threonine kinase activity. These interactions result in profound morphological alterations and polarity changes in the host cells, thus contributing to their neoplastic transformation. This figure was designed by combining portions of (1) a figure from Morales-Guerrero et al. (2013) (© 2012 Morales-Guerrero SE, Mucito-Varela E, Aguilar-Gutierrez GR, López-Vidal Y, Castillo-Rojas G) that was originally published under CC BY 3.0 license (available from: http://dx.doi.org/10.5772/53136), and (2) of a figure from an article (Yamahashi and Hatakeyama, 2013, available online from: http://wwww.tandfonline.com/ doi:10.4161/cam.21936) published by Taylor & Francis in the Jan–Feb 2013 issue of *Cell Adhesion and Migration*, licensed to VN (no. 3742711162415, on Nov 5, 2015)

CagL plays an important role in the injection of CagA into gastric epithelial cells (Tegtmeyer et al. 2010).

Vacuolating Cytotoxin Gene (*vacA*): The gene encoding VacA is present in all *H. pylori* strains. Upon the secretion of the cytotoxin VacA from the bacteria, this large polypeptide (140-kDa) is trimmed at both ends and latter delivered as an

active form to host cells. VacA exerts multiple cellular activities: alteration in the endosomal maturation leading to epithelial cell vacuolation, induction of membrane-channel formation, release of cytochrome c from mitochondria and activation of a pro-inflammatory response through the interaction with cell membrane receptors (Amieva and El Omar 2008). VacA toxins exhibit distinct capability of inducing vacuolation in epithelial cells (Atherton et al. 1995; Blaser and Atherton 2004) and its cytotoxic activity varies among strains (Amieva and El Omar 2008; Wroblewski et al. 2010). VacA has been associated with an increased risk of developing gastric epithelial injury and gastric cancer (Atherton et al. 1995; Basso et al. 2008; Lopez-Vidal et al. 2008; Yamaoka 2010).

2.1.4 Antigens. Blood Group Antigen-Binding Adhesion (*BabA*)

The adhesin BabA belongs to a family of highly conserved OMPs (Outer-Membrane Proteins) and binds to ABO histo-blood group antigens and corresponding Le^b antigens (also called MUC5AC) expressed on gastric human epithelial cells (Ilver et al. 1998). There are three *bab* alleles (*babB*, *babA1*, *babA2*). BabA2 is the only one required for Le^b binding activity (Abadi et al. 2013). *BabA2* prevalence in gastric cancer patients was found to be 95 % in some regions of the Middle East (Toller et al. 2011). There is a co-expression between *babA2* and *cagA*, and *vacA* (Zambon et al. 2003). They exert their activity synergistically fostering the inflammation. The bacterial adhesion via *babA* has been suggested to participate in the DNA double-strand breaks (DSB) induced upon *H. pylori* infection (Toller et al. 2011). DSB phenomenon may finally provoke genetic instability and the frequent chromosomal alterations found in gastric cancer.

2.1.5 Toxic Bacterial Metabolites—Nitrosamines

Bacterial cells could also produce toxic metabolites that may damage host cell DNA initiating oncogenic process. Nitrosamines are one of the most powerful mutagens. They methylate oxygen and nitrogen atoms of the DNA. *H. pylori* promotes the local production of radicals, like *N*-nitroso compounds, that play an important role in the initiation of gastric cancer. There is a higher susceptibility of the infected gastric mucosa cells to these DNA-damaging agents because the effect induced by nitrosamines is synergistic to that caused by the infection. The excess of ammonia, a product of *H. pylori* urease, in gastric cells may be involved in this process. In fact, by stimulating neutrophils and phospholipases, ammonia may induce indirect mucosal injury. Furthermore, by degrading phospholipids and producing ulcerogenic precursor factors, it may damage the gastric mucosa. A posited mechanism of action is that the interaction between *H. pylori*-induced free radicals and the gastric mucosa cell membranes subsequently might generate several products of lipid peroxidation that finally destroy the integrity of the gastric epithelium (Figura 1997; Arabski et al. 2006). Another mechanism that may allow also the development of

gastric cancer is related with the finding that *N*-nitroso compounds are higher during chronic atrophic gastritis. Interestingly with gastric cancer, *H. pylori* sometimes caused hypochlorhydria. Therefore, such conditions prompt the overgrowth of diverse bacteria that deliver nitrosamines (Carboni et al. 1988).

2.2 Colorectal Adenocarcinoma

Colorectal cancer was the third most common cancer in the world in 2012. That year there were approximately 1.4 million new cases diagnosed. The adenocarcinoma subtype represents nearly 95 % of the colorectal cancers. Other possible subtypes are mucinous carcinomas and adenosquamous carcinomas. The highest incidence of colorectal cancer was in Oceania and Europe and the lowest incidence in Africa and Asia. More than 50 % of colorectal cancer cases were detected in industrialized countries. In the United States, from data available in 2010, 131,607 people (67,700 men and 63,907 women) were diagnosed with colorectal cancer and 52,045 persons (27,073 men and 24,972 women) died. It is the third most common cancer diagnosed in the United States and globally (both sexes combined), it is the second leading cause of cancer-related deaths. Overall, the lifetime risk of developing colorectal cancer is around 5 % (1 in 20). For past year (2014), the estimations of new cases were 96,830 for colon cancer and 40,000 for rectal cancer. On the other hand, 50,310 deaths were expected (American Cancer Society 2014). Several studies have demonstrated the presence of *H. pylori* in colorectal adenomas and colorectal cancer tissues (Kapetanakis et al. 2013; Kountouras et al. 2013, 2014). There is an increased risk of colorectal cancer due to *H. pylori* infection (Zhao et al. 2008; Kapetanakis et al. 2013). Herein, we suggest some mechanisms and factors involved in the described association between *H. pylori* infection and colorectal neoplasia.

2.2.1 Inflammation, Proliferation, Stem Cells Recruitment

Recent data indicate that *H. pylori* colonizing colonic malignant tissue may increase cell proliferation and impair apoptotic cell death mainly in tumor specimens. This process may also lead to colon cancer progression (Kountouras et al. 2003). In colorectal adenomas and colorectal cancer tissues, the presence of *H. pylori* was accompanied with immunohistochemical expression of proliferation marker Ki-67, anti-apoptotic Bcl-2, CD45 (assessing T and B lymphocytes locally) and stem cells marker CD44 (indicator of cancer stem cells—CSCs—, and/or bone marrow-derived stem cells—BMDSCs—) (Kountouras et al. 2013, 2014).

2.2.2 Gastrin Hormone and Its Receptor CCK-2

CCK2 (cholecystokinin-2), encoded by the CCKBR gene, is a G protein-coupled receptor for gastrin and cholecystokinin (CCK), regulatory peptides of the brain and gastrointestinal tract. Both gastrin and its receptor, cholecystokinin-2 (CCK-2) receptor, exhibited high levels in many premalignant colonic lesions. These proteins seem to be important in colorectal tumorigenesis, and tumor growth (Chao et al. 2010). Four carboxy-terminal amino acids of gastrin are essential for activation of the CCK2 receptor (Hollestelle et al. 2008). *H. pylori* induced gastrin release that may act as a promoter of cell proliferation and differentiation. These cell processes are mainly promoted by inducing COX-2 overexpression and PI3-kinase-mediated tyrosine phosphorylation of E-cadherin and β-catenin) in the colon and different gastrointestinal tract sites (Kountouras et al. 2000). Subsequently and as aforementioned, the bone-marrow-derived stem cell recruitment observed during *H. pylori* infection also plays a role during colon cancer progression (Kountouras et al. 2006).

2.3 Other Cancers

2.3.1 Lung Cancer

A hypothesis gaining widespread acceptance suggests that *H. pylori* infection increases the risk of lung cancer. Several authors have postulated that *H. pylori* may induce lung carcinogenesis by mechanisms and factors similar to those described for gastric cancer. In lung cancer patients, the levels of serum gastrin are higher compared to controls. Furthermore, such levels correlate with tumor stage (Zhou et al. 1992). Gastrin has been shown to be co-expressed with COX-2 (Subramaniam et al. 2008). Therefore, both may stimulate tumor growth and angiogenesis (Gocyk et al. 2000). As previously mentioned, CagA is initially phosphorylated by Src. The activation of FAK and Src leads to the injection of CagA. A substrate of Src kinase is p130cas. Once activated by Src, p130cas can recruit a Crk (v-crk sarcoma virus CT10 oncogene homolog)/DOCK180 (dedicator of cytokinesis) complex (Gu et al. 2001). The Crk/p130cas complex plays a critical role in *H. pylori*-infected gastric epithelial cells, promoting bacteria-induced migration and invasive growth of gastric epithelial cells (Schneider et al. 2008). In cancer cells including lung tumors, p130cas is involved in carcinogenesis (tumor cell growth and migration, cell cycle progression) (Huang et al. 2012). It also mediates cell survival and delays the death of cancer cells (Wei et al. 2002). P130cas is implicated in tumor prognosis, and in lung cancer samples its overexpression is also correlated with poor overall survival (Huang et al. 2012). All these data suggest that p130cas may be involved in *H. pylori*-mediated carcinogenesis in the lung. The surface enzyme of *H. pylori* called Urease has shown to be involved in bacterial infection and survival. Furthermore, urease is being highly expressed in gastric cancer specimens

(Wu et al. 2007) likely promoting cell proliferation and gastric mucosal hyper-proliferation. The detection of *H. pylori* urease proteins in lung (Herndon et al. 2013) support the hypothesis that *H. pylori* urease may induce proliferation and carcinogenesis of the pulmonary mucosa.

2.3.2 Gastric MALT Lymphoma

As aforementioned, chronic infection with *H. pylori* may also generate an environment allowing lympho-proliferation and gastric MALT lymphoma. The most common site (approximately 50 % of all cases) for MALT lymphoma to develop is in the stomach (Gastric MALT lymphoma). Gastric MALT lymphoma represents 5 % of all primary gastric cancers (tumors starting in the stomach) and therefore remains an unusual type of stomach cancer. MALT lymphoma may start in a context of chronic inflammation, especially in an *H. pylori* infection background (Swerdlow et al. 2008). In more than 80 % of cases, a robust association between chronic *H. pylori* infection and MALT gastric lymphoma has been observed. It is well demonstrated in this tumor pathogenesis that the aforementioned bacterial infection plays a key role (Stolte et al. 2002; Psyrri et al. 2008; Swerdlow et al. 2008). Chronic *H. pylori* infection induces the antigenic stimulus, leading to the clonal proliferation of lymphoid cells arising to the MALT lymphoma. Some particular strains of *H. pylori* are important in this process, those expressing CagA protein since they carry the major histocompatibility complex (MHC) class II T cell epitope. After an infection with this specific strain, CD4+T cells activation occurs and it has been postulated that such conditions may therefore allow tumor development (Arnold et al. 2011). On the other hand, in most of patients (75–80 %) with early stage MALT lymphoma, the eradication of *H. pylori* was followed by a complete regression of such low-grade disease (Stolte et al. 2002; Yoon et al. 2004; Jezersek et al. 2006; Nakamura et al. 2008). This approach was particularly successful in patients exhibiting infection only in gastric mucosa or submucosa. However, elsewhere location of infection (muscularis propria or serosa, nodal disease) correlated with the decrease of complete response rates (Levy et al. 2002; Stolte el al. 2002; Nakamura et al. 2003, 2008; Yoon et al. 2004; Chen et al. 2005; Jezersek et al. 2006; Fischbach 2010).

2.3.3 Burkitt Lymphoma (BL)

Burkitt lymphoma (BL) is an aggressive mature B cell neoplasm. This form of non-Hodgkin's lymphoma is highly prevalent in children and young adults. The WHO classification describes three types of BL. All three variants exhibit chromosomal rearrangement of c-MYC oncogene. This biological phenomenon leads to some modifications of cell cycle regulation, cellular metabolism, adhesion, differentiation, and apoptosis driving to cancer development (Pagano et al. 2009). Studies performed in the past decade suggested the role of *H. pylori* in BL. In fact,

it has been reported the complete remission of BL after the administration of *H. pylori* eradication therapy (Baumgaertner et al. 2009).

2.3.4 Gastric Diffuse Large-B-Cell Lymphoma (DLBCL)

Gastric Diffuse Large-B-Cell Lymphoma (DLBCL) is another form of extra-nodal non-Hodgkin's lymphoma detected in gastric tissue. The mechanisms related to *H. pylori* infection in primary DLBCL and leading to tumor development are similar to those described above (for Gastric MALT lymphoma).

3 Disease Management Strategies

Evidence for the tumor-promoting effects of the bacterial microbiota has been obtained from studies in both animals and humans (Cho and Blaser 2012; Schwabe and Jobin 2013). Tumor incidence in germ-free rodents exposed to a variety of carcinogenic insults was generally lower than that observed in normal animals under the same conditions. In addition, fewer tumors developed in antibiotic-treated animals than in untreated controls. Similarly, eradication of bacterial pathogens with antibiotic treatment caused a reduction in cancer progression, or even regression, in the treated patients (Schwabe and Jobin 2013; Bultman 2014). Although the preponderant evidence supports the tumor-promoting effects of the bacterial microbiota, the correlation is not perfect. Nevertheless, *H. pylori* has become the best example of the capacity of an infectious bacteria to drive the carcinogenic process in gastric tumors (McColl 2010; Polk and Peek 2010; Wroblewski and Peek 2013) and, consequently, the prime model for the evaluation of diverse strategies to manage the infection and, particularly, to provide anticancer benefits.

An important consideration to make relates to the fact that, in addition to being associated with increased cancer risk and demonstrated greater stomach cancer incidence, the presence of *H. pylori* (particularly of CagA-positive strains) in the gastric environment correlates with parallel changes in the nature and number of other phylotypes present not only in the stomach itself, but also in the lower esophagus as well as in the upper intestinal tract (Khurana 2012; Engstrand and Lindberg 2013; Sheh and Fox 2013, Arora et al. 2015; Nardone and Compare 2015; Schulz et al. 2015). These observations support the notion that the alteration of the normal microbiota may contribute to carcinogenic progression by having additional effects on host factors and, thus, further changing the environment. However, it is not clear whether *H. pylori* causes these microbiota alterations, or whether these changes come first and enhance the pro-carcinogenic activity of *H. pylori*. It seems still possible that the microbiota changes by themselves may be the initiating event in the carcinogenic process, as complete tumor regression has not been achieved with antibiotics to *H. pylori* alone.

Regardless of whether *H. pylori* colonization of the gastric epithelium or the observed microbiota alterations came first, bacterial eradication with effective antibiotics seems to be the most intuitive and immediate course of action to prevent cancer development or to treat already established stomach tumors. However, there are several limitations to the eradication approach. For instance, eradication does not have uniform beneficial effects at all stages of stomach cancer development (Arora et al. 2015). Although significant gastric cancer risk reductions were observed when eradication treatments were performed on normal individuals or in patients with non-atrophic gastritis (NAG) or on those with atrophic gastritis without intestinal metaplasia (IM), there was no benefit for cases with IM or for those with dysplastic changes (Arora et al. 2015). Furthermore, not only *H. pylori* eradication efforts have not been as widely beneficial as expected, but it has increased the incidence of inflammatory bowel disease (IBD) and, most importantly, of esophageal cancer. In fact, these data are so significant that a protective beneficial role against esophageal adenocarcinoma has been attributed to *H. pylori* (Blaser 2008; Sheh and Fox 2013; Abadi 2014). According to this notion, *H. pylori* would have dual protective and pathogenic roles (Blaser 2008; Atherton and Blaser 2009; Dorer et al. 2009; Sheh and Fox 2013). Finally, there is always the risk that inappropriate use of antibiotics may result in the selection of *H. pylori* antibiotic-resistant isolates, as it was the case for other diseases caused by bacterial pathogens. For all these reasons, eradication must be carried out, if at all, in a well-balanced fashion (Blaser 2008).

A second disease management alternative is based on the notion that protocols designed to minimize the negative effects of *H. pylori* colonization on the stomach mucosa is more appropriate than eradication approaches. The goal is to manipulate the microbiota to maintain that of normal individuals in such a way that protection against *H. pylori* and/or against the negative effects of *H. pylori* eradication may be provided (Arora et al. 2015; Schulz et al. 2015). Protocols for microbiota restoration that are being developed with prophylactic purposes include the use of dietary prebiotics (i.e., fiber sources or polyphenols) and, most frequently, of probiotics (Cho and Blaser 2012; Bultman 2014; Patel et al. 2014), including fecal transplantation approaches (Bowman et al. 2015). An important aspect regarding the use of probiotics relates to the use of either single probiotic strain or several strains in combination, as results to date do not seem to fully support one way or the other (Schulz et al. 2015). The goal of ongoing research efforts is to get to the point of having "designer probiotics" for the personalized treatment, prophylactic or therapeutic, of individual patients suffering from diverse diseases, including cancer. In the case of therapeutic protocols, a pre-therapeutic characterization of probiotic strains before use in combination seems to be essential (Patel et al. 2014; Schulz et al. 2015).

In the context of *H. pylori*-associated cancers, an important limitation of the microbiota manipulation strategy derives from the fact that it has not yet been conclusively demonstrated whether the pro-carcinogenic events result from the direct action of *H. pylori*, to the alterations of the stomach microbiota, or to both. Consequently, there are important considerations to take into account when deciding how to modify the stomach microbiota. Four suggestions may be useful in

this regard: (1) Identification (and replacement with) bacterial strains present in the stomach prior to *H. pylori* infection; this is something that can be accomplished by individuals getting a personalized microbiome "identity card" that should be updated regularly; (2) Usage of probiotics to induce a general gastric normalization process, not only in the stomach but also in the lower esophagus and the upper intestine; (3) Minimization of the action of host factors known to contribute to *H. pylori* pathogenesis; and (4) Inclusion of bacterial strains that may compete with *H. pylori* and thereby decrease its cancer malignancy promoting action. For example, as it seems consistently clear that the promotion of stomach cancer is primarily due to CagA-positive *H. pylori* cells, one could consider the possibility of including CagA-negative strains in microbiota replacement protocols. The competition of CagA(−) with CagA(+) cells might minimize their disease-promoting effects and contribute to establish an overall level of *H. pylori* in the stomach that will be compatible with a more balanced microbiota and will not increase the risk of esophageal cancer.

4 Perspectives and Conclusions

The field of microbiome research is currently advancing at a great pace. Nevertheless, we still need a deeper understanding of the underlying cellular and molecular mechanisms of bacterial-induced carcinogenesis and the role of host-derived contributing factors to reach the point of being able to applying microbiome manipulation strategies at the clinical level. From the perspective of cancer detection, the advantage of *H. pylori* related cases is that infection with *H. pylori*, and indeed with other Helicobacter species, causes the appearance of gastritis symptoms early in the process. The early detection of *H. pylori* may allow to establish an "active surveillance" strategy to time disease stage-specific microbiome remodeling interventions. Personalized microbiome modulation is a likely possibility in the not so distant future for the management of cancer and other human disease states.

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