Journal of Carcinogenesis and Mutagenesis Research
JCMR, 2(1): 15-19
www.scitcentral.com
ISSN: 2643-0541
Mini Review: Open Access

The Crosstalk of *Helicobacter pylori* Infection and Obesity in Gastric Carcinogenesis

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Received April 27, 2020; Revised May 06, 2020; Accepted May 08, 2020

ABSTRACT

Gastric cancer (GC) is currently the third leading cause of cancer-related death worldwide. The precise etiology for GC is still obscure. *Helicobacter pylori (H. pylori)* infection is well-established to be a cause for GC. Obesity is another risk factor. Here, we briefly reviewed the research progression on the crosstalk of *H. pylori* infection and obesity in induction of gastric cancer and discussed the potential molecular mechanism.

Keywords: *Helicobacter pylori*, Obesity, Inflammation, Metabolic abnormality, Gastric cancer

INTRODUCTION

GC is closely associated with *H. pylori*-induced chronic gastritis[1,2]. Epidemiological studies show that persistent *H. pylori* infection accounts for approximate 75% of confound risk factors for GC [3]. Obesity contributes to tumor development including GC, possibly due to its induction of low systemic inflammation and metabolic abnormality [4,5]. Eradication of *H. pylori* reduces GC risk by approximately 3-fold. It is interesting that *H. pylori* infection is reported to be associated with obesity, insulin resistance and metabolic syndrome, which suggests the cooperation of *H. pylori* and obesity in GC induction [6-8].

H. *pylori* Infection and GC

H. pylori infects nearly half the world's population, the infection rate can be even higher than 90% in some developing countries. The bacterium colonizes in the stomach and is usually a persistent infection for the whole lifetime. It causes chronic gastritis and peptic ulcer and is closely associated with the development of GC [1,2].

The clinical consequence of *H. pylori* infection is determined by the bacterial products and their interaction with host factors. The pathogenicity of *H. pylori* is primarily mediated by CagA (cytotoxin-associated gene A) and VacA (vacuolating cytotoxin gene) proteins, both of which can trigger severe gastric lesions, causing DNA damage and somatic mutations [9]. These bacterial products can also strongly induce host immune responses by releasing excessive amounts of pro-inflammatory cytokines, including interleukin-8 (IL-8) and IL-1[10-14], which in turn recruit and activate dendritic cells (DCs) and CD4 T cells including Th1, Th2, Th17 and Treg cells [15,16]. A mixed response of Th1 and Th17 cells plays a critical role in *H. pylori*-induced inflammatory gastric diseases and cancer [17,18]. *H. pylori* elicits Th1 response to produce interferon-γ and tumor necrosis factor-α (TNFα) causing chronic gastritis andulcers [19]. Th17-derived IL-17A favors angiogenesis and tumor growth through inducing IL-6 that activates STAT3 signaling to promote tumor survival and angiogenesis [20,21]. In contrast, accumulation of Treg and Th2 cells in the infected foci perform anti-inflammatory impacts and allow persistence of the infection and disease progression.

Obesity, Metabolic Deregulation and GC

Obesity is an important public health problem worldwide, which affects more than 300 million people in China. Obesity can lead to a state of chronic low-grade inflammation at multiple sites throughout the body and is

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Citation: Liu J, Huang J, Li X, Wong AST & Zeng JZ. (2021) There is No Credible Scientific Evidence that Glyphosate Causes Cancer, including Non-Hodgkin Lymphoma in Humans. J Carcinog Mutagen Res, 2(1): 11-14.

mechanistically linked to the metabolic abnormalities with increased incidence of gastric cancer [4,22]. The exact mechanisms responsible for increased incidence of gastric cancer in individuals with obesity are not completely clear. Metabolic endogenous hormones including insulin-like growth factors (IGF-1), ghrelin, and leptin, as well as the incremental pro-inflammatory cytokines such as IL-6 and TNFα may all play a role [4].

Obesity often leads to insulin resistance which reduces IGF binding protein (IGFBP) expression and increases free IGF-1 [23]. IGF-1 plays a vital role in mediating the effects of the growth hormone, which may promote cell growth [24,25]. Leptin is a peptide hormone produced and secreted by the white adipose tissues. Obesity induces abundant leptin production which might be involved in the development of some cancers [26,27]. Ghrelin is a hormone produced by the fundic glands of the stomach and play important roles in gastric cancer [28,29]. Obesity influence ghrelin level and signaling which involved in GC progression [30]. On the other hand, obesity is associated with a chronic systemic inflammation with a mount macrophage accumulated in adipose tissue. Adipose inflammation increases some pro-inflammatory cytokines such as TNFα, IL-6 and monocyte chemo attractant protein 1 (MCP-1) [31-33], most of these cytokines are considered oncogenic [34,35].

The Synergistic Impact of *H. pylori* Infection and Obesity on GC Development

There is growing evidence for a potential association between *H. pylori* infection and obesity. Epidemic studies showed a higher *H. pylori* prevalence in obese patients give a clue that obesity influence *H. pylori* infection [36-38]. *H. pylori* infection can remotely trigger obesity-associated adipose inflammation and insulin resistance [39,40], while obesity accelerates *H. felis*-induced gastric carcinogenesis by enhancing immature myeloid cell trafficking and Th17 response in mice [40].

H. pylori infection can induce changes in gastric mucosal leptin and ghrelin levels, which influence body weight changes and obesity [41,42]. In return, obesity linked to metabolic deregulation including hyperinsulinemia, hyperlipidemia and hyperglycemia influences leptin and ghrelin signaling [43]. In addition to abundant leptin induced by obesity, increased leptin expression in gastric tissues has also been found in patients with H. pylori infection and gastric cancer [44]. Leptin may promote cell proliferation by activating JAK/STAT signaling pathway to participate in gastric carcinogenesis [45]. *H. pylori* induced damage to gastric epithelium may alter the hormonal milieu of the stomach, leading to a decreased production of ghrelin [42]. Reduced ghrelin in circulation may enhance activity of TNFα, IL-6 and other major inflammatory cytokines, which have oncogenic function [28,46].

H. pylori infection and obesity can synergistically cause systemic inflammation. A set of inflammatory cytokines and chemokines including IL-6, resistin, PAI-1, leptin, CCL7, CXCL1, IL-17A, and granulocyte-macrophage colony stimulating factor(GM-CSF) produced by the local (gastric) and distant (adipose) sites of inflammation were detected to be elevated in the serum of *H. felis*-infected obese mice, which are collectively implicated in metabolic disorders [40]. It is worth noting that our recent study in clinical GC specimens suggests that dysregulated lipid metabolism (a manifestation of obesity) may synergize with H. pylori to promote GC development [47]. In this study, we found that high plasma triglycerides and *H. pylori* had synergy effect on IL-17A expression. Furthermore, RORγt, a key transcription factor for Th17 differentiation, is shown to be associated with H. pylori-related metabolic disorders and GC progression [47]. In agreement with our finding, *H. pylori* infection and its related gastroduodenal morbidity with metabolic syndrome was also reported in a large cross-sectional study [48]. Furthermore, both obesity surgery and *H. pylori* eradication inhibit carcinogenesis [49].

CONCLUSION & PERSPECTIVE

In summary, *H. pylori* and obesity communicate mutually to influence metabolic processing, inflammation and carcinogenesis. *H. pylori* infection increases Th17 cells in gastric mucosa causing local inflammation. It is interesting that *H. pylori*-related Th17 cells in the stomach could exert a remote control of adipose inflammation. Enhanced circulating cytokines and immune cells released from both inflamed gastric and adipose tissues result in systemic inflammation, which collectively cause insulin resistance and metabolic disorders. Adipose-derived adipokines and cytokines like leptin and IL-6 return to H. pylori-infected sites for supporting Th17 expansion and function, thus forming a positive feedback loop for Th17 activation. In this regard, obesity may exacerbate *H. pylori*-induced gastric lesions and inflammation. Obesity, hyperinsulinemia, and H. pylori synergistically contribute to GC development (**Figure 1**).

Although the association and crosstalk of *H. pylori* and obesity have been widely reported, the key factors and mechanism for their regulation in GC progression is still unclear. Inflammatory cytokines and the hormonal milieu of the stomach are believed to involve in the synergic regulation of *H. pylori* and obesity in induction of GC. More in-depth research on the precise underlying molecular mechanism by which *H. pylori* infection and obesity impact synergistically on GC development and progression warrant a further investigation.

Financial Support and Sponsorship

This work was supported by grants from 10th Singapore-China Joint Research Program (S2014GR0448), Natural

Science Foundation of Fujian Province (2019I0002), Natural Science Foundation of China (81673467), Leading Talents in Scientific and Technological Innovation, Double Hundred Talents Program of Fujian Province, and by Open Research Fund of State Key Laboratory of Cellular Stress Biology, Xiamen University.

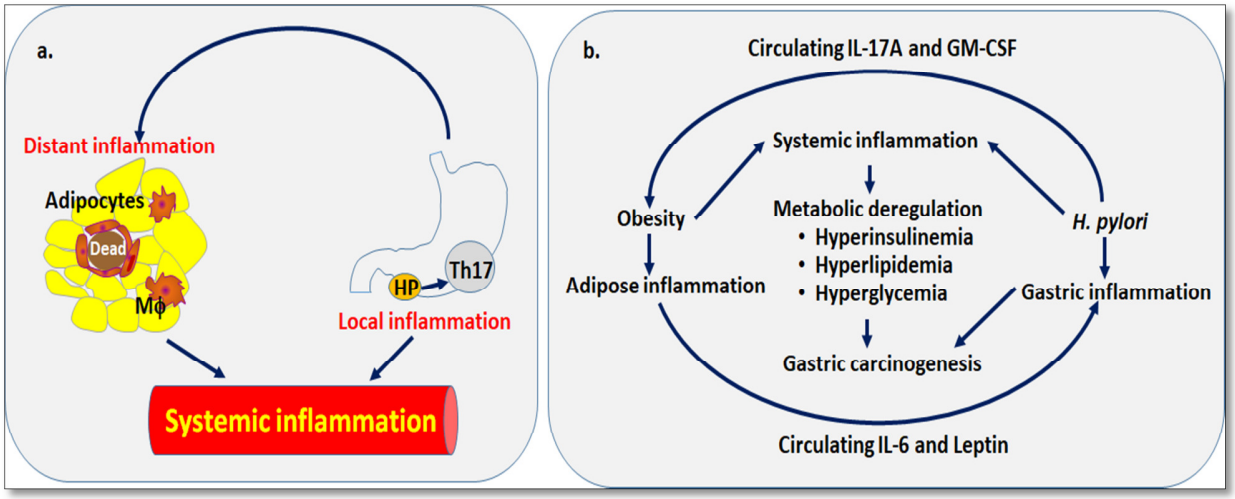

Figure 1. The synergistic effect of H. pylori infection and obesity in gastric carcinogenesis. **a.** *H. pylori* infection causes local (gastric) and distant (obese adipose) tissues' inflammation, both of which contribute to systemic inflammation. **b.** The potential mechanistic linkage of *H. pylori* and obesity in GC. Mφ: macrophage; HP: H. pylori; GM-CSF: Granulocyte-macrophage Colony Stimulating Factor.

Conflicts of Interests

There is no conflict of interests.

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