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Review Article

Current Insights of *H. Pylori* Infection on Gastric Cancer -

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ABSTRACT

The incidence rate of stomach cancer is much higher in some regions, such as Asia, and part of Europe, than the rest of the world. The epidemiological studies showed there may be a strong correlation between *Helicobacter pylori* (*H. pylori*), a type of gastritis-causing bacteria, and the carcinogenesis of gastric cancer. Although the precise mechanism is not fully understood yet, it is generally accepted that *H. pylori* may cause gastric cancer by inflammation, mutation and stimulation of cell proliferation. This review summarizes the mechanisms of how this bacterium may stimulate cell proliferation, cause mutations, thus to trigger stomach cancer.

INTRODUCTION

Stomach cancer, also called gastric cancer, starts in the stomach, and most stomach cancers are derived from "The gland cells in the inner stomach lining". The location of stomach cancer can be classified into the following subsites: "cardia, fundus, body, antrum, pylorus, and lesser or greater curvature" [1]. Diffuse and intestinal gastric cancers are the two major histologic types [1]. Although the incidence rate of stomach cancer has dropped in most countries, the mortality rate still remains high, ranking the third among all the cancers [2].

In the United States, stomach cancer is relatively rare compared to some other countries. Data from National Cancer Institute shows that there is an estimate of 28,000 new cases of stomach cancer in 2017, representing 1.7% of all new cancer incidence; there is an estimate of 10,960 people who will die from stomach cancer in 2017, constituting 1.8% of all cancer deaths. In contrast, stomach cancer is more prevalent in other countries, especially in Asian countries. More than 70% stomach cancer cases were observed in developing countries in 2008 [3]. Consistently, the stomach cancer incidence rates for male in 2012 were 35.4 per 100,000 people in Eastern Asia and 20.3 per 100,000 people in Central and Eastern Europe, whereas they were only 5.5 per 100,000 people in North America and 6.7 per 100,000 people in Australia/ New Zealand [4]. Geographical variations in stomach cancer incidence rates are possibly due to different living habits, such as higher use of alcohol or tobacco and higher prevalence of *Helicobacter pylori* (*H. pylori*) infection in less developed countries [4]. Additionally, stomach cancer is more prevalent in men than women, which partially may be due to the disruption of the homeostasis of Androgen Receptor (AR) which is activated by the binding of androgen in men [5].

Tipα induces inflammatory response and cell proliferation

H. pylori infection has been recognized as one of the reasons causing stomach cancer, but the mechanisms of how this bacterium works in cancer progress is still not very clear. Recent research has made significant progresses and unveiled this bacterium may contribute to cancer development in multiple ways. *H. pylori* secretes a protein called tumor necrosis factor-α inducing protein (Tipα), which is a strong inducer of chemokine gene expressions [6,7]. Tipα is a homodimer protein consisting of two cysteine residues in the N-terminal domain that can form disulfide bond, and the formation of the homodimer is critical to the induction of carcinogenic activity of Tipα. Tipα is responsible for inducing the expression of a variety of chemokine genes in stomach cancer cells, among which are genes encoding for Ccl2, Ccl7, Ccl20, Cxcl1, Cxcl2, Cxcl5 and Cxcl10. The chemokine family includes CC chemokines, which have two cysteine residues next to each other, and CXC chemokines, which have another amino acid in between the two cysteine residues. The chemokines induced by Tipα are expressed in gastric epithelial cells and the gastric mucosa. The chemokine proteins are able to induce the migration of various types of immune cells, such as natural killer, dendritic cells, and neutrophils, leading to chronic inflammatory responses in gastric epithelial cells and the consequent stomach cancer. This Tipα-chemokine signaling cascade suggests that Tipα is a major player in the stomach cancer development due to *H. pylori* infection [6,7].

Apart from the chemokine genes induced by Tipα secreted from *H. pylori* that contributes to stomach cancer, Tipα also induces a lot of other genes resulting in gastric carcinogenesis [6]. The expression of interleukin 6 (IL-6), β-catenin, ATP-binding cassette, sub-family B member 4 (Abcb4), Mid-1-related chloride channel 1 (Mclc), and reticuloendotheliosis oncogene (Rel) is induced by Tipα secreted from *H. pylori*. Unlike chemokines inducing a series of inflammatory reaction, these genes are responsible for cell proliferation [6]. Furthermore, the activation of NF-κB, which is a target of Tipα, stimulates the gene expression of chemokines, IL-6, etc. to favor inflammation and cell proliferation [6]. Taken together, Tipα plays an important role in stomach cancer development via both inflammation and inducing cell proliferation.

In addition, Tipα secreted by *H. pylori* stimulates inflammatory response via not only the induction of chemokines, but the induction of Tumor Necrosis Factor-α (TNFα). TNFα activates NF-κB, which then activates prostaglandin-endoperoxide synthase 2 (COX-2). COX-2 can not only suppress cell apoptosis, but produce prostaglandin E_2, which induces an inflammatory response [6-8].

Another important aspect of Tipα in terms of carcinogenesis is the fact that Tipα may induce Epithelial-Mesenchymal-Transition (EMT) in gastric epithelial cells [9,10]. Work done by Chen G. et al. and Han Y. et al. showed that Tipα may decrease the expression of E-cadherin and Programmed-Cell-Death-Protein 4 (PDCD4), as well as increase the expression of N-cadherin, vimentin, and TWIST1. The decreased expression of E-cadherin may result in the activation of β-catenin, which could modify the expression of cyclin D1, CD44, c-Myc, etc., facilitating tumor progression [11]. The PDCD4 mainly contributes to the inhibition of transcription and translation of TWIST1 and the inhibition of invasion-related urokinase plasminogen activator receptor expression; as a result, the lower level of PDCD4 triggered by Tipα promotes tumorigenesis [10]. Moreover, the changed expression levels of these markers during EMT may cause cells to lose adhesion and polarity, to increase mobility, to become more stem-cell like, to resist to apoptosis, and to degrade extracellular matrix. All these aspects could accelerate tumor malignancy and metastasis in gastric cancer [10]. Additionally, the pathway through which Tipα induces EMT process was determined to be IL-6/STAT3 [12].

The virulence factor of *H. pylori*: CagA and VacA

Different strains of *H. pylori* bacteria may possess different virulence factors. The virulence factors may be membrane-associated, secreted or translocated into cytosol of the host cells. Among those factors, cytotoxin-associated gene A (CagA), vacuolating cytotoxin

(VacA) and outer membrane proteins (OMPs) are directly or indirectly implicated in *H. pylori* carcinogenesis [13,14]. For example, CagA protein can be directly translocated into B cells where it inhibits apoptosis and promotes cell proliferation [15]. In addition, CagA leads to silencing of the tumor suppressor genes *RUNX1*, *TFF1*, and *CDH1* by increased methylation in the promoter region. CagA can also activate the expression of the oncogenes *EGFR*, *MET*, *PI3K*, *AKT*, and *CTNNB1* (which codes for β-catenin) [16]. Furthermore, *H. pylori* infection with the presence of CagA and VacA has a synergistic effect on the development of gastric cancer with IL-1β gene polymorphisms, and the highest prevalence of severe gastric abnormalities are found in patients with both host and bacterial high-risk genotypes (cagA(+)/vacAs1(+)/IL-1β-511T) [17]. In a more recent study on stem cell-derived gastric organoids, CagA activated the c-Met receptor and resulted in a rapid induction of epithelial cell proliferation [18]. CagA could also activate the Wnt/β-catenin signaling pathway, leading to the transcription of oncogenes [10]. Moreover, CagA may induce EMT process, which partially depends on the regulation of PDCD4 [10]. The expression level of CagA may be elevated by high salt diet [19].

In addition to the carcinogenesis of CagA, VacA of *H. pylori* also plays an essential role in both induction of apoptosis in gastric epithelial cells and vacuolating cytotoxicity [20,21]. Studies by Kuck Dirk et al. demonstrated that VacA may activate the CD95 receptor and ligand system to induce apoptosis [21,22]. Moreover, VacA can form a hexameric anion-selective channel in cell membrane at an acidic pH, through which the toxin gets transmitted into cytosol, and the toxin may interfere with a substance that controls the membrane trafficking of endosomes and lysosomes. Mucosal damage and the consequent gastric tumorigenesis can be attributed to both factors of VacA of *H. pylori* infection [21].

H. pylori upregulates reactive species in host individuals

The infection of *H. pylori* may increase the formation of oxy- and nitro- radical species in gastric mucosa, such as Myeloperoxidase (MPO), inducible Nitric Oxide Synthase (iNOS), and NADPH oxidase [9]. The expression of these reactive species is derived from activated macrophages, neutrophils, or monocytes [23,24]. The long-term effect of the radical species may include inflammation, tissue damage, and carcinogenesis [23]. It is worth noting that Reactive Oxygen Species (ROS) and Nitric Oxide (NO), which is a product of iNOS, can cause DNA damage as well. During NO synthesis, DNA deamination may occur, and thus mutations of gastric epithelial cells could happen. Additionally, the release of ROS and NO may result in DNA methylation in the CpG Island in promoter, causing genetic alterations and thus carcinogenesis [9].

H. pylori downregulates host DNA repair mechanisms

Another negative impact *H. pylori* may have on the stomach tissue is that the bacteria may downregulate DNA repair mechanisms; as a result, host genome becomes increasingly unstable, allowing potential mutations in the tumor suppressor genes and oncogenes to occur [25,26]. The impacts of *H. pylori* include reduction in mismatched repair, base excision repair, and double-strand break repair [26]. The reduced stability of host genome and downregulation of DNA repair contribute to carcinogenesis through increasing the host cells' possibility of mutations and their maintenance. The reduced ability of DNA repair mechanisms render the host cells less protected from exogenous insults.

TREATMENT OPTIONS

H. pylori infection has been associated with various gastric problems, including gastric cancer. However, treatment of *H. pylori* remains a challenge, due to the rising prevalence of antimicrobial resistance, mainly to clarithromycin, efficacy of standard triple therapies has declined to unacceptably low levels in most parts of the world. Novel regimens, such as bismuth quadruple, concomitant, have been shown to improve the therapeutic outcome against antibiotic-resistant *H. pylori* strains [27].

In addition, a vaccine would overcome these drawbacks, but currently there is not any *H. pylori* vaccine licensed. In seeking alternative treatment, the use of probiotics has been proposed in order to optimize the eradication rates. Several clinical trials indicated that administration of probiotics can reduce the side effects of *H. pylori* eradication treatment by antibiotics, increasing tolerability and often increasing the overall efficacy [28].

Gastrin is responsible for the secretion of gastric acid, and hyperacidity is a contributing factor to *H. pylori* infection. Curcumin is an anticancer agent, which is naturally from the root of *Curcuma longa* and exerts the anti-*H. pylori* effect by inhibiting the acid secretion in stomach. Inhibiting the level of gastrin secretion, curcumin significantly raises gastric pH *in vivo* and prevents *H. pylori* infection [29].

Another anticancer agent is evodiamine, which is an alkaloid compound that naturally occurs in *Evodia rutaecarpa*. It may induce autophagy and apoptosis of gastric cancer cells. During the process of autophagy, auto phagosomes are formed to degrade tumor cells. On the other hand, the pro-survival gene expression of *Bcl-2* in gastric cancer cells is inhibited by evodiamine, while the pro-apoptotic gene expression of *Bax* is activated [30].

PREVENTION

To prevent stomach cancer caused by *H. pylori* infection, anti-inflammatory agents and anti-oxidants could be applied during the course of *H. pylori* treatment [31]. Nonsteroidal anti-inflammatory drugs can be promising to eradicate inflammatory response due to *H. pylori* infection and thus prevent from stomach cancer. Anti-oxidants can be applied with dietary supplementation, such as ascorbic acid and β-carotene, since they can "induce regression of precancerous lesions in patients with intestinal metaplasia and/or multifocal atrophic gastritis" [31]. A clinical trial demonstrated that the eradication of *H. pylori* indeed slowed down the stomach cancer progression [31].

Moreover, the National Cancer Institute suggests that avoiding adverse lifestyle may lower the risk of getting stomach cancer, such as smoking cessation and healthy dietary. Low intake of salt, high intake of fresh fruits and vegetables that contain vitamin C, and high intake of whole-grain cereals, carotenoids, allium compounds, and green tea may all decrease the risk of getting stomach cancer.

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