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OPINION REVIEW

How does *Helicobacter pylori* cause gastric cancer through connexins: An opinion review

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Abstract

Helicobacter pylori (*H. pylori*) is a Gram-negative bacterium with a number of virulence factors, such as cytotoxin-associated gene A, vacuolating cytotoxin A, its pathogenicity island, and lipopolysaccharide, which cause gastrointestinal diseases. Connexins function in gap junctional homeostasis, and their downregulation is closely related to gastric carcinogenesis. Investigations into *H. pylori* infection and the fine-tuning of connexins in cells or tissues have been reported in previous studies. Therefore, in this review, the potential mechanisms of *H. pylori*-induced gastric cancer through connexins are summarized in detail.

Key words: *Helicobacter pylori*; Connexin; Gap junctional intercellular communications; Gap junction proteins; Gastric cancer; Transcription factors; DNA methylation; Proliferation; Apoptosis

Core tip: *Helicobacter pylori* (*H. pylori*) is an independent pathogenic factor for gastric cancer (GC), which is related to some virulence factors of *H. pylori*. It has long been proven that various connexins (Cxs) can regulate the development of GC. Thus, we discuss in detail how *H. pylori* regulates Cxs to cause gastric cancer.

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INTRODUCTION

Helicobacter pylori (*H. pylori*) is a Gram-negative and microaerophilic bacterium that colonizes the stomach in nearly 50% of the world's population[1]. *H. pylori* synthesizes many different virulence factors that dysregulate host intracellular signaling mechanisms and contribute to neoplastic transformation[2]. *H. pylori* disrupts the balance between cell proliferation and apoptosis, which is an important driving force for the occurrence and development of gastric cancer (GC) by virulence factors[3]. Of all virulence factors, cytotoxin-associated gene A (CagA), vacuolating cytotoxin A (VacA), and lipopolysaccharide (LPS) are the most important[2,4].

The CagA gene is located downstream of the 40 kb virulence gene cluster, called the Cag pathogenicity island (cagPAI). These genes encode a type IV secretory system, forming a syringe structure that injects CagA protein and peptidoglycan into gastric epithelial cells[5,6]. CagA is an important oncoprotein that plays a critical role in gastric carcinogenesis[7]; one of the mechanisms is that it can induce hypermethylation of tumor suppressor genes[8,9]. CagA is delivered into host gastric epithelial cells, and it may trigger some signal transduction events, such as proliferation and inflammation, leading to a potential risk of GC[10,11]. In addition, intact cagPAI strains may increase the probability of GC[12].

VacA is one of the major virulence factors produced by *H. pylori*, and it is a 140 kDa precursor that produces an 88 kDa toxin after proteolysis[13,14]. The vacA alleles in different *H. pylori* strains can be divided into several families according to their sequence heterogeneity in specific areas that are associated with the biological form of VacA. There are three most extensively studied regions of heterogeneity: The signal or "s" region, the intermediate or "i" region, and the middle or "m" region[15-17]. Previous studies indicated that *H. pylori* strains with s1, i1, and m1 vacA alleles had a higher risk of GC or precancerous lesions than those with s2, i2, and m2 vacA alleles[15,18-24]. VacA-induced gastric epithelial cell death is expected to lead to increased cell proliferation, which may be associated with an increased cancer risk. VacA may disrupt the epithelial cell monolayers[25] and thereby promote the entry of carcinogens into gastric epithelial cells[26].

LPS is an important component of the cell wall of Gram-negative bacteria, for example, *Escherichia coli*[27], *Shigella flexneri*[28], and *Yersinia enterocolitica*[29], among others. Similar to other Gram-negative bacteria, *H. pylori* LPS is composed of three structural domains—lipid A, core oligosaccharide, and O polysaccharides[30,31]. Recently, studies have reported that LPS has close relationships with the development of GC *via* TLR4-dependent pathways[32-36].

Connexins (Cxs), also called gap junction proteins, are the main component of gap junctional intercellular communications that may directly enhance cell cooperation both electrically and metabolically. This intercellular communication plays a crucial role in development and homeostasis[37,38]. Cxs have complex functions in physiological and pathological processes[39,40], and they may influence the proliferation, apoptosis, migration, and invasion of different cells[41-48]. Their regulation is correlated with tumor development, and the evolution of Cxs may inhibit the progression of various cancers[39,40]. Cxs are expressed in a tissue-specific manner. Gastric tissue mainly produces Cx26, Cx32, Cx37, Cx40, Cx43, and Cx45[49-57]. Previous studies have shown that, compared to tissues or cells of the normal gastric mucosa, the expression of Cxs dramatically decreases in GC[58-61]. Therefore, the variations in Cxs can serve as important biomarkers that imply the development of different cancers. Apart from changes in the function and expression of Cxs in cancers, the aberrant cytoplasmic location of Cxs is also linked with various cancers[62-67]. The expression of Cxs in the gastrointestinal tract and liver is presented in Table 1[68-91].

LITERATURE SEARCH

A scientific literature search was conducted using the PubMed, Web of Science, and Google Scholar databases with the keywords "*Helicobacter pylori*", "Connexin", "Gap junctional intercellular communications", "gap junction proteins", "gastric cancer", "transcription factors", "DNA methylation", "proliferation", "apoptosis", and combinations of the aforementioned.

HOW TO REGULATE CONNEXINS

Based on previous studies about the relation between *H. pylori* and Cxs, this relation may involve many mechanisms and signaling pathways that are complex and

Table 1 Connexin expression in the gastrointestinal tract and liver

Tissue	Cell type	Cx members	Ref.
Liver			
	Hepatocytes	Cx32/Cx26	[161]
	Kupffer cells	Cx43/Cx26	[162-164]
	Stellate cells	Cx43/Cx26	[163-165]
	Sinusoidal endothelial cells	Cx43/Cx32/Cx26	[163,164,166,167]
	Portal vein endothelial cells	Cx43/Cx40/Cx37	[168-170]
	Hepatic artery endothelial cells	Cx43/Cx40/37	[168-170]
	Cholangiocytes	Cx43/Cx32	[171,172]
Stomach		Cx45/Cx43/Cx40/Cx37/Cx32/Cx26	[49-57,146]
	Foveolar cells	Cx32	[173]
Small intestine			
	Musculus externa cells	Cx43/Cx40	[51]
	Myenteric plexus cells	Cx45/Cx43/Cx40/Cx36	[51,174,175]
	Epithelial cells	Cx43/Cx37/Cx32	[51,176,177]
	Interstitial cells of Cajal	Cx43	[51,178]
Colon			
	Musculus externa cells	Cx43/Cx40/Cx26	[51,179]
	Myenteric plexus cells	Cx45/Cx43/Cx40/Cx36	[51,175]
	Epithelial cells	Cx43/Cx37/Cx32/Cx26	[177,180-183]
	Muscularis mucosal cells	Cx43	[51]
	Interstitial cells of Cajal	Cx43	[178]

profound. *H. pylori* can regulate the expression of key molecules that have an effect on the expression and function of Cxs by its virulence factors. In other words, Cx expression can be regulated in many processes, such as transcription, RNA processing, RNA nucleocytoplasmic transport and localization, mRNA translation, mRNA degradation, and protein activity[68]. Hence, in this review, we mainly discuss possible regulation between *H. pylori* and Cxs during the progression of GC.

CX32

Cx32, also named gap junction beta-1 protein, was primarily found in the peripheral nervous system[69,70], liver[71,72], gastric tissue[55,73], intestinal system[74], and other biological systems. It is clear that DNA hypermethylation may downregulate the level of the corresponding mRNA and protein[8,75]. A previous study reported that the expression levels of Cx32 and Cx43 mRNA decreased gradually during *H. pylori*-associated gastric carcinogenesis, and this result is associated with the hypermethylation of the promoters of these genes[76]. *H. pylori* infection may upregulate some transcription factors, such as GATA-3[77] and PBX-1[58]. These transcription factors can serve as the determinants in the Cx32 promoter targeting site and thereby inhibit Cx32 expression. However, the authors did not explain which of the virulence factors upregulate these transcription factors. Histone acetylation leads to the opening of chromatin structure, which increases the availability of gene promoters and is generally associated with enhanced transcription of DNA. Histone deacetylases (HDACs) lead to the termination of transcriptional processes *via* counteracting the function of histone acetylation[78]. Several pathogens, including *H. pylori*, manipulate host cell antibacterial responses and evade the immune system by affecting histone acetylation and histone deacetylation status[79]. It has been reported that *H. pylori* infection can decrease histone acetylation levels[80]. Vinken *et al*[81,82] have shown that HDAC inhibitors may elevate Cx32 protein levels in rat hepatocytes; however, the expression levels of Cx26 were downregulated and those of Cx43 were uncertain. Hence, histone acetylation can regulate the expression of Cxs. The p38 mitogen-activated protein kinase (MAPK) signaling pathway can be activated by a variety of extracellular signals. Extracellular signal-regulated kinase (ERK), p38 MAPK, Jun N-terminal kinase (JNK), and ERK5 are members of four subfamilies of MAPK[83,84]. CagA can activate the p38 MAPK signaling pathway[85]. Yamamoto *et al*[86] reported that p38 MAPK was activated during partial hepatectomy, thereby inhibiting

Cx32 expression. The first step for *H. pylori* to invade the gastric mucosa is to escape the host defense mechanism, and then the bacteria adhere to the epithelial surface through cell surface-specific receptors, releasing a large number of pathogenic factors and causing a mucosal inflammation response[87-91]. *H. pylori* infection can regulate the expression level of interleukins. *H. pylori* CagPAI can promote IL-1β production, involving the NOD-like receptor (NLR) family, pyrin domain containing 3 (NLRP3), and its complex, known as the NLRP3 inflammasome[92-94]. A previous study reported that in primary cultured rat hepatocytes, IL-1β causes the disappearance of Cx32, which is related to claudin-2 induction and cell membrane localization[95]. According to previous studies, Cx32 can inhibit proliferation, metastasis, and invasion[73,96-98] and has an antiapoptotic effect in different cancer cells[42,43,99]. Cx32 may regulate the metastasis and proliferation of hepatocellular carcinoma cells through the p53 and Akt pathways[97], also *via* cell cycle arrest and cell cycle regulatory proteins[73]. In other words, downregulated Cx32 may promote cell proliferation, metastasis, and apoptosis. Breaking the balance of these pathological events can promote tumor development. In addition to the changes in Cx32 expression, alterations in Cx32 location are also related to GC development[67]. However, studies about the changes in *H. pylori* and Cx32 localization are scarce.

CX43

Cx43, also called gap junction alpha-1 protein (GJA1), is expressed in many tissues and organs; it is ubiquitous in gastric tissues[39,50,61]. Cx43-dependent intercellular communication could spread cell death signals between neighboring cells through gap junctions[44,100,101], using some candidate messengers such as Ca^{2+}, cAMP, cGMP, and ATP[100,102]. *H. pylori* promoted the expression of GATA3, which can also directly bind to the promoter region of the Cx43 gene, inducing its expression inhibition, and the expression of Cx43 decreased with the progression of gastric mucosal lesions to precancerous lesions[60]. CagPAI-induced IL-1β secretion may inhibit Cx43 expression *via* ERK1/2 and p38 MAPK[93,94,103]. *H. pylori* infection triggers an inflammatory response and promotes the activity of some interleukins, such as IL-1β[92-94], IL-17[104], and IL-22[105,106]. Yu *et al*[103] pointed out that IL-1β can inhibit the level of Cx43 *via* ERK1/2 and p38 MAP kinase in human endometrial stromal cells[103]. Qin *et al*[107] announced that IL-17 can inhibit the expression of CX43 through the AKT signaling pathway, inhibiting the occurrence and development of fungal keratitis. In psoriasis, IL-22 activates the JNK pathway, which will repress the transcriptional activity of the Cx43 gene promoter[108,109]. The inflammation-cancer chain is an important theory in carcinogenesis. Interleukins are important signaling markers of the inflammatory response. The epidermal growth factor family (EGF, EGFR, and HB-EGF) plays a key role in the progression, invasion, and metastasis of GC. The EGF family proteins can be regarded as important biomarkers for GC[110,111], and *H. pylori* infection can promote molecular expression[112,113]. Among the members of the EGF family, Yoshioka *et al*[114] reported that HB-EGF secretion from cardiomyocytes can decrease Cx43 in overexpressing cells and in immediately adjacent cells. We predict that HB-EGF may be seen as a negative regulator of Cx43 in gastric tissue. Moreover, a clinical study showed that HB-EGF enhances resistance to certain cancer drugs during the period of GC treatment[115]. In contrast, Cx43 could enhance chemotherapy sensitivity in human GC[116]. However, the effect of EGF and EGFR on Cx43 expression may be opposite to that of HB-EGF[117-119]. *H. pylori* infection leads to increased reactive oxygen species as well as NADPH oxidase and Jak2/Stat3 activation[120]. The activity of the JAK2/STAT3 signaling pathway has a positive effect on the proliferation and metastasis of carcinoma cells[121,122]. Cell proliferation is a mechanism that contributes to tumorigenesis. Previous studies indicated that Cx43 downregulation promotes carcinogenesis development[60,76,123]. Tang *et al*[124] indicated that JAK2/STAT3 signaling may inhibit Cx43 expression by blocking EGFR activation. Generally, protein phosphorylation may enhance the activity of proteins. Retinoic acid (RA) is an important intermediate metabolite of vitamin A. Among the different RA structures are all-trans RA, 9-cis RA, and 13-cis RA. The absence of RA in normal human development leads to defects in the immune system, embryonic development, vision, brain function, and other systems. In *H. pylori*-infected gastric mucosa, the expression of the gastric RA biosynthetic gene is seriously damaged, which may lead to decreased RA signaling pathways, thus leading to disease progression[125]. However, RA can enhance gap junction intercellular communication by increasing the expression of Cx43[126-128]. A previous study indicated that all-trans RA (ATRA) may inhibit gastric carcinoma tumor growth by targeting GC stem cells[129]; therefore, we predict that it may be mainly due to the effect of ATRA. The LPS-TLR4 signaling

pathway has an important role in LPS-mediated disease. LPS can induce an inflammatory response and upregulate inflammatory mediators, such as inducible nitric oxide synthase, IL-6, and TNF-α, among others, *via* activation of the TLR4/NF-κB signaling pathway[130,131]. Subsequently, the activation of Cx43 may regress by inhibiting caveolin-3[132]. VacA does not affect the mRNA expression of Cx43 and may enhance resistance to the degradation of autophagy, leading to cytoplasmic accumulation of Cx43. VacA can enhance ubiquitinated Cx43 movement to the lysosome for degradation *via* endosomal or autophagic mechanisms, eventually inducing apoptotic cell death *via* glutathione (GSH) and the Rac1/ERK signaling pathway[133]. As a result, the cell membrane is destroyed, which may promote cell proliferation in response to damage repair[134]. However, *H. pylori* disturbs the balance of the proliferation and apoptosis of cells, driving GC development[3].

CX26

Cx26, also known as gap junction beta-2 protein, plays a role in tumor suppression through the regulation of the cell cycle[135]. It is true that *H. pylori* promotes the DNA promoter methylation of some biomolecules[136-138]. Some studies showed that *H. pylori* may be one of the driving forces to induce the promoter methylation of E-cadherin, mainly induced by CagA[138,139]. Such methylation can downregulate E-cadherin expression, which promotes the localization of Cx26 from the cell membrane to the cytoplasm, thereby inhibiting gap junction communication between endometrial cancer cells[140]. A loss of intercellular Cx26 expression or an increase in Cx26 expression in the cytoplasm has an important role in carcinogenesis and tumor progression[62,64-66]. This finding can be interpreted as the downregulation of Cx26 that inhibits the proliferation and migration of cells and promotes apoptosis[45]. All of these regulations may be drivers of GC development.

CX37

Cx37, also known as GJA4, like other Cxs proteins, forms connections between cells known as gap junctions. Cx37 can inhibit cell growth both *in vitro* and *in vivo* and inhibits angiogenesis[141,142]. Cx37 may induce cell death and cell cycle arrest and slow down the cell cycle[143,144]. All of those processes may produce a potential inhibitor of the proliferation of cancer cells[144,145]. A clinical study reported that *H. pylori* infection may have a closely related polymorphism of Cx37 (Cx37 C1019T) in GC by altering the frequency of the allele[146]. Further, the Cx37 C1019T polymorphism may promote tumor cell proliferation[145]. Moreover, many diseases are also associated with the Cx37 gene C1019T polymorphism, such as polycystic ovarian syndrome (PCOS)[147] and cardiovascular diseases[148-151], among others.

CONCLUSION AND PERSPECTIVE

H. pylori is a risk factor for GC. *H. pylori* eradication therapy may prevent GC occurrence[152]. In the development of *H. pylori*-induced GC, there are a series of pathological and physiological changes, such as chronic gastritis, atrophic gastritis, intestinal metaplasia, dysplasia, and gastric MALT lymphoma, among others[153-155]. In this long process, there are many interactions of biological signaling pathways. Cxs are important biomarkers that reflect the status of GC. Currently, only a few members of Cxs have been reported to have an association with GC, such as Cx26, Cx32, Cx37, and Cx43. *H. pylori* may regulate those Cxs involved in different signaling pathways, such as DNA promoter methylation[8,75,76], the p38 MAP signaling pathway[85,86], histone acetylation[79-82,156], and the JAK2/STAT3 signaling pathway[120,157]. Further, changes in the expression of Cxs may regulate the proliferation, metastasis, invasion, and apoptosis of cells. For all this, further and deeper studies of the relationship between *H. pylori*-associated GC and Cxs are necessary. The dysregulation of Cxs could cause drug resistance in cancer[116,158-160]. Moreover, improving the expression of intercellular Cxs may be a future therapeutic target for GC.

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