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Review

Helicobacter pylori Infection Synergistic with IL-1β Gene Polymorphisms Potentially Contributes to the Carcinogenesis of Gastric Cancer

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Abstract

Helicobacter pylori (H. pylori) infection is the most common chronic bacterial infection in the world and the etiological agent for most gastric cancer (GC). Interleukin-1β (IL-1β) is a potent proinflammatory cytokine, and its deregulation is closely associated with the tumorigenesis of several cancers. Recent studies have revealed that the IL-1β-31 and -511T alleles are closely associated with gastric carcinogenesis due to their roles in the induction of gastric precancerous lesions and hypochlorhydria. Furthermore, *H. pylori* infection has a synergistic effect on the development of GC 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). Therefore, these recent advances demonstrate that *H. pylori* synergistic with IL-1β gene polymorphisms contribute to the gastric carcinogenesis by their involvement in precancerous gastric lesions and low gastric acid secretion.

Key words: gastric cancer, IL-1β, gene polymorphism, precancerous lesion

Introduction

Gastric cancer (GC) is one of the leading causes of cancer-related death worldwide [1, 2]. The intestinal type of GC develops through a cascade of well-defined and recognizable processes: inflammation, atrophy, intestinal metaplasia, dysplasia, and carcinogenesis [3]. The annual incidence of GC patients with atrophic gastritis, intestinal metaplasia, mild-to-moderate dysplasia, and severe dysplasia are 0.1%, 0.25%, 0.6%, and 6.0%, respectively [4]. GC is closely associated with the environment, diet and gene mutations [5-8]. *Helicobacter pylori (H. pylori)* infection is the aetiological agent for most GC [9], and its related host gene polymorphisms are associated with the susceptibility to gastric carcinogenesis [10]. Interleukin-1β (IL-1β) is a potent proinflammatory cytokine that contributes to gastric carcinogenesis mainly through its gene polymorphisms [11, 12]. However, the underlying mechanisms by which *H. pylori* promote the tumorigenesis of GC and the synergistic effects with IL-1β gene polymorphisms remain to be determined. Here, we review the recent advances concerning synergistic role of *H. pylori* with IL-1β gene polymorphisms in gastric carcinogenesis and the associated potential mechanisms.

H. pylori infection promotes carcinogenesis of GC

GC is one of many cancers associated with inflammation, which is induced by *H. pylori* infection [13, 14]. Furthermore, GC develops merely in persons with *H. pylori* infection, and is more prone to occur in

patients with histologic findings of severe gastric atrophy, corpus-predominant gastritis, or intestinal metaplasia [15, 16]. On the other hand, *H. pylori* eradication may reduce the prevalence of precancerous gastric lesions and prevent the development of gastric cancer, even in those patients without precancerous lesions and in healthy asymptomatic infected Asian individuals [17-21]. In addition, metachronous gastric carcinoma can be prevented by *H. pylori eradication* in patients who received endoscopic resection of early GC [22]. These studies demonstrate that *H. pylori* infection is closely associated with gastric carcinogenesis.

IL-1β gene polymorphisms promote carcinogenesis of GC

IL-1β gene polymorphisms are closely associated with GC

IL-1β is involved in a variety of cellular activities including inflammatory response and secretion of gastric acid [23, 24]. Deregulation of IL-1β has been found in several cancers. IL-1β gene polymorphisms including IL-1β-31 (T > C) and IL-1β-511 (C > T) have been shown to be closely related to gastric tumorigenesis [25-28]. The IL-1β-31C/T and IL-1β-511C/T genotypes (CT carriers) are found to more frequently occur in patients with GC and have been considered as risk factors for GC in Chinese population [29, 30]. CT carriers have a higher risk of sporadic, early, diffuse or noncardia GC [31]. Meanwhile, the IL-1β-511 T allele is significantly associated with an increased risk of GC [32, 33], especially in patients with IL-1β-511TT [12, 34, 35]. Interestingly, healthy volunteers from the high prevalence region have a higher frequency of the IL-1β-511T/T genotype compared to those from the low prevalence region of GC [28]. These facts clearly demonstrate that the IL-1β-31 and -511T alleles are closely correlated to GC.

Furthermore, IL-1β polymorphisms may be associated with the histological type of GC [12, 36]. Intestinal type of GC, but not the diffuse or mixed-type of GC, more frequently occur in patients with IL-1β-511T genotype [12, 37-39]. The most common histological type of GC is poorly differentiated in patients with TT genotype [12].

In addition, IL-1β gene polymorphisms have been demonstrated to be associated with GC progression. The proportion of patients with IL-1β-31TT (or IL-1β-511CC) increases with advancing stages. In particular, the prevalence of either IL-1β-31TT or IL-1β-511CC genotype is double in patients with stage IV cancer compared to those with stage I cancer [40]. Interestingly, the IL-1β-31CC genotype carrier may have a protective effect against GC progression, as GC patients who have both the IL-1β-31CC and IL-1β-511TT genotypes are associated with a better prognosis [41].

Thus, IL-1β gene polymorphisms play multiple roles in the tumorigenesis of GC; however, the underlying mechanism is largely unknown. Current available data suggest that IL-1β gene polymorphisms may promote GC by its involvement in precancerous gastric lesions and low gastric acid secretion.

IL-1β gene polymorphisms are closely associated with precancerous gastric lesions

Atrophic gastritis, intestinal metaplasia, and dysplasia are putative precancerous gastric lesions [42]. Patients with intestinal metaplasia are at an increased risk for GC [15, 43]. An intestinal metaplasia patient has 10.9 times higher probability of developing GC than a subject without intestinal metaplasia [44]. High-grade dysplasia is clinically more ominous and susceptible to coexist with or progress to adenocarcinoma [45]. Therefore, in order to elucidate the roles of IL-1β gene polymorphisms in gastric carcinogenesis, it is of vital importance to study its correlation to precancerous gastric lesions.

A previous study indicates that differences in IL-1β gene expression due to the high frequency of a single nucleotide polymorphism may have significant biological impacts in the population [46]. The IL-1β-31 polymorphism is found to be closely associated with the degree of mononuclear cell infiltration and atrophy in the antrum [47]. The highest atrophy and gastritis scores frequently occur in patients with the IL-1β-511 T/T genotype [48]. These results verify the association between IL-1β polymorphisms and both of gastric inflammation and atrophy [49]. Intriguingly, all Mozambican subjects with intestinal metaplsia are IL-1β-511 T carriers [50]. Furthermore, the prevalence of dysplasia is significantly higher in patient with IL-1β-511 TT genotype [51]. These studies demonstrated that the IL-1β T alleles are associated with premalignant gastric lesions.

IL-1β gene polymorphisms are correlated to low gastric acid levels

The rate of adenocarcinoma significantly increases in Mongolian gerbils infected with *H. pylori* after a long-term administration of a proton pump inhibitor by promoting the progression of atrophic corpus gastritis [52]. Moreover, progressive hyperplasia as well as mucocystic and incomplete intestinal metaplasia develop in aged mice with chronic achlorhydria because of lacking the gastric H/K-ATPase [53]. These data suggest that the use of acid-suppressive drugs is associated with an

increased risk of GC through inhibition of gastric acid secretion [54]. In support of this hypothesis, the prevalence of body atrophy and intestinal metaplasia increases in patients with hypochlorhydria [55], and those with a low acid output have a relatively high risk to develop GC [56].

IL-1β potentially inhibits acid secretion by downregulating H+/K+ATPase expression and repressing gastrin expression [57, 58], which subsequently suppresses expression of Sonic Hedgehog, ultimately leading to gastric atrophy [24].

IL-1β-511 TT and C noncarriers have higher levels of IL-1β than CT and C carriers, respectively [59]. Similarly, when compared to cells transfected with a plasmid expressing IL-1β-31C, up to a 3-fold increase of IL-1β expression occurs in gastric carcinoma cells transfected with IL-1β-31T expression plasmid [60]. IL-1β gene polymorphisms may enhance the production of IL-1β variants, leading to repression of gastric acid secretion, which is associated with the grade of gastric atrophy in patients with *H. pylori* infection [11, 24, 61].

Recently, a study discloses that the IL-1β-511 T allele stimulates the expression of IL-1β but does not decrease gastric acid output, suggesting that there are alternative mechanisms by which IL-1β polymorphisms enhance GC development [62]. Similarly, as previously mentioned, patients with *H. pylori* infection and IL-1β polymorphisms with increased production of IL-1β are susceptible to GC through the CpG island methylation [34]. Meanwhile, IL-1β has been found to increase the invasion of carcinoma cells through activation of NF-kappa B, hence enhancing the expression of matrix metalloproteinase-9 [63]. Moreover, IL-1β has been reported to stimulate IL-8 expression through mitogen-activated protein kinase and reactive oxygen species signaling, both of which are directly correlated with the vascularization of GC [64].

H. pylori infection is associated with IL-1β expression

H. pylori infection induces IL-1β and suppresses acid secretion, while the expression of IL-1β decreases after *H. pylori* eradication, followed by an increase in gastric acidity [65, 66]. It is discovered that mucosal levels of IL-1β increases prior to the development of GC in an experimental mouse model with *H. pylori* infection [67]. In addition, gastric concentrations of IL-1β in children with *H. pylori* infection are significantly higher than those without *H. pylori* infection [68]. Furthermore, higher mucosal IL-1β levels are observed in *H. pylori*-infected GC patients with IL-1β-31TT compared to those with IL-1β-31CT and IL-1β-31CC [69]. On the other hand, population with IL-1β-31 CT and TT genotypes in Asia and Latin America are more susceptible to infection by *H. pylori*, compared to those with IL-1β-31 CC [70]. Overall, these studies indicate that *H. pylori* infection has an interactive relationship with IL-1β, especially in patients with IL-1β-31TT.

H. pylori has a synergistic role with IL-1β polymorphisms in gastric carcinogenesis

H. pylori infection has a synergistic effect with IL-1β gene polymorphisms on the development of GC [29]. IL-1β-511 T allele is more frequently observed in *H. pylori*-positive patients than in *H. pylori*-negative patients with noncardia GC [71]. Interestingly, though *H. pylori* infection alone has only a modest effect on GC development, the risk for GC is significantly increased when combined with the IL-1β-511T/T genotype [28]. Similarly, patients with the IL-1β-511TT genotype with active infection of *H. pylori* have higher risk for developing GC [27, 34]. In particular, patients with both bacterial and host high-risk genotypes (vacuolating cytotoxin gene A s1 region (vacAs1)/IL-1β-511*T carrier, vacAm1/IL-1β-511*T carrier, and cytotoxin-associated gene A (cagA)-positive/IL-1β-511*T carrier) present the highest risk [72].

Children with IL-1β-511TT/-31CC have an increased risk of developing relatively severe gastric mucosal histological changes in South China, where *H. pylori* infection is prevalent [73]. Likewise, an increased prevalence of intestinal metaplasia and atrophic gastritis is found in patients with IL-1β-511T/-31C [74, 75]. In addition, *H. pylori*-related atrophic gastritis has been shown to be the more malignant phenotype compared to *H. pylori*-negative atrophic gastritis in patients with IL-1β-31CC/-511TT genotypes [76]. A modestly higher prevalence of intestinal metaplasia is observed in patients with *H. pylori* infection, especially in those infected with vacA m1 strain [77]. Furthermore, patients with both host and bacterial high-risk genotypes (cagA(+)/vacAs1(+)/IL-1β-511T) have the highest prevalence of severe gastric abnormalities (severe lymphocytic and granulocytic infiltration, atrophic gastritis and intestinal metaplasia) [75].

Mechanistically, *H. pylori* infection induces the expression of IL-1β, which in turn promotes gastric carcinogenesis by affecting both inflammatory and epithelial cells [78]. In addition, hypochlorhydria and atrophic gastritis can be induced by IL-1β polymorphisms, which depends on *H. pylori* infection [48]. These results demonstrate that *H. pylori* infection synergistic with IL-1β polymorphisms results in gastric precancerous lesions and hypochlorhydria, which contribute to the gastric carcinogenesis.

Challenges and a look to the future

The positive correlation of IL-1β gene polymorphisms to GC and its precursors has been observed in numerous studies. However, this conclusion still awaits confirmation by further investigation. It has been reported that IL-1β polymorphisms have no effect on the degree of gastric neutrophil and mononuclear cell infiltration, or gastric atrophy [79]. In addition, no evidence of an association of haplotypes of IL-1β with an increased risk of developing either chronic gastritis or intestinal metaplasia has been observed [80, 81]. Furthermore, in atrophic body gastritis patients, IL-1β-511 polymorphisms are not associated with the development of gastric neoplastic lesions after long-term follow up [82]. In some populations, no significant correlation is found between IL-1β gene polymorphisms and GC [83-87], and IL-1β has no predictive value for the development of GC [81]. Similarly, no association has been found between IL-1β polymorphisms and diffuse or intestinal GC [88]. Finally, IL-1β-511C/T and the T carrier have been reported to have a decreased risk for gastric carcinoma in Japanese individuals [89]. These inconsistent findings may result from a range of factors such as heterogeneity of cancer subtypes, limited sample size, gene-environment interactions [90], and ethnic differences [83].

Thus, multi-centered, large sample scale, multi-racial, perspective, randomized, and controlled studies are needed to verify the association of IL-1β gene polymorphisms with GC. Meanwhile, the underlying mechanisms of the synergistic effect of *H. pylori* infection and IL-1β gene polymorphisms in gastric carcinogenesis are still elusive. Furthermore, it remains to be determined if there are any other related gene polymorphisms, in coordination with IL-1β, that play a synergistic role in the development of GC.

Conclusion

H. pylori infection synergistic with IL-1β gene polymorphisms may promote gastric carcinogenesis by their involvement in precancerous gastric lesions and hypochlorhydria. Further investigation is needed to verify these findings in different populations and subtypes of GC, and to disclose alternative underlying mechanisms.

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Competing Interests

The authors have declared that no competing interest exists.

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