Abstract

*Helicobacter pylori* (*H. pylori*) is a major etiological factor in the development of gastric cancer. Large-scale epidemiological studies have confirmed the strong association between *H. pylori* infection and both cancer development and progression. Interleukin-8 (IL-8) is overexpressed in gastric mucosa exposed to *H. pylori*. The expression of IL-8 directly correlates with a poor prognosis in gastric cancer. IL-8 is multifunctional. In addition to its potent chemotactic activity, it can induce proliferation and migration of cancer cells. In this review, we focus on recent insights into the mechanisms of IL-8 signaling associated with gastric cancer. The relationship between IL-8 and *H. pylori* is discussed. We also summarize the current therapeutics against IL-8 in gastric cancer.

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Key words: *Helicobacter pylori*; Interleukin-8; Signals; Gastric cancer; Therapeutics

Core tip: There is a close association between gastric cancer and *Helicobacter pylori* (*H. pylori*) infection. *H. pylori* upregulates interleukin-8 (IL-8) gene expression in gastric epithelial cells and the levels of IL-8 may be indicative of poor prognosis. We propose that IL-8 overexpression induced by *H. pylori* plays a major role in gastric cancer development and progression, and that targeting IL-8 may be a promising strategy for gastric cancer treatment.

INTRODUCTION

Gastric cancer has affected humans for millennia. The risk of gastric cancer appears to evolve over a lifetime as a possible result of changes in diet and lifestyle. In 1984, Marshall and Warren were first to describe the association between peptic ulcer disease and *Helicobacter pylori* (*H. pylori*). *H. pylori* was subsequently causally linked with the development of gastric cancer.

Despite the improved prognosis of gastric cancer resulting from the early diagnosis and development of adjuvant therapy, overall 5-year survival rates for patients with gastric cancer remain disappointing, with a mortality rate of 20% in Western countries and up to 60% in Asian countries. Although current combinatory chemotherapeutic regimes result in a median overall survival of up to...
11 mo, toxicity is increased\textsuperscript{[1,4]}. To overcome the adverse effects, novel chemotherapeutic concepts have focused on the development of targeted therapies for gastric cancer. An understanding of the detailed mechanisms of invasion and metastasis in gastric cancer would be helpful in improving the treatment outcome.

\textit{H. pylori} infection is usually asymptomatic in most hosts, as virtually all carriers develop superficial chronic active gastritis, whereas only about 10% suffer gastric or duodenal ulceration and 0.5%-2.0% develop gastric adenocarcinoma or B cell lymphoma of mucosa-associated lymphoid tissue\textsuperscript{[5]}. \textit{H. pylori} colonize the gastric mucosa of 35%-70% of people worldwide and infection with \textit{H. pylori} is the main etiologic factor for development of chronic active gastritis and peptic ulcers\textsuperscript{[6,7]}. Epidemiologic data indicate that gastric cancer occurs more frequently in populations with higher rates of \textit{H. pylori} infection, and the World Health Organization has classified this bacterium as a class 1 carcinogen for gastric cancer\textsuperscript{[8]}. Animal models have also demonstrated the importance of \textit{H. pylori} in gastric carcinogenesis\textsuperscript{[9]}. \textit{H. pylori} infection is important in the process of tissue remodeling, angiogenesis, tumor invasion and metastasis\textsuperscript{[10]}, and induces a number of genes in host cells that are potential determinants of inflammation, angiogenesis, and metastasis including interleukin-8 (IL-8), cyclooxygenase-2\textsuperscript{[11]}, monocyte chemoattractant protein-1\textsuperscript{[12]}, vascular endothelial growth factor\textsuperscript{[13]}, and matrix metalloproteinase (MMP)-9\textsuperscript{[14]}. However, it remains unclear how \textit{H. pylori} infection activates specific transcription factors and induces gene expression.

IL-8 seems to have significant potential as a prognostic and predictive cancer biomarker. IL-8 was originally identified as a chemoattractant for neutrophils that release angiogenic growth factors, stimulating angiogenesis as a part of cancer progression. As shown in Figure 1, IL-8 increases the proliferation, migration and survival of endothelial cells, potentiates the epithelial-mesenchymal transition and survival of cancer cells, and activates macrophage and immune responses at the tumor site\textsuperscript{[15]}. IL-8 enhances the production and secretion of MMP-2 and MMP-9\textsuperscript{[16,17]}, suggesting that it can modulate invasiveness and/or extracellular matrix remodeling in normal physiological conditions and in cancer progression.

An understanding of the basic principles and underlying signals by which \textit{H. pylori} regulates IL-8 may lead to the development of new therapeutic strategies in gastric cancer. With this in mind, we present a brief review.

\textbf{A ROLE FOR IL-8 IN GASTRIC CANCER}

A significant correlation between high expression levels of IL-8 in gastric mucosa and risk of gastric cancer has been reported\textsuperscript{[18]}. Macrì et al\textsuperscript{[19]} reported that the serum levels of IL-8 act as markers of gastric cancer. Increased expression of IL-8 mRNA in tissue extracts from gastric cancer patients has been associated with some clinicopathological aspects of the disease, including poor prognosis\textsuperscript{[20]}. In IL-8 transgenic mice, where expression of human IL-8 is controlled by its own regulatory elements, expression of IL-8 increased tumorigenesis, suggesting that IL-8 might have a crucial role in gastrointestinal cancers\textsuperscript{[21]}. These observations indicate that high levels of IL-8 may be associated with poor prognosis as judged by stage and histology, and that IL-8 may be indicative of more aggressive gastric cancers.

The roles for IL-8 in the angiogenesis of gastric cancer have drawn much interest. Since invasion and angiogenesis are all involved in the metastatic process, IL-8 expression in gastric cancer can influence their metastatic capabilities. Upregulation of IL-8 in human gastric carcinomas correlates closely with their angiogenesis\textsuperscript{[22]}. Kita-dai et al\textsuperscript{[23]} reported that the expression of IL-8 directly

\textbf{Figure 1 Roles for interleukin-8 in tumor progression and metastasis. EMT: Epithelial-mesenchymal transition; IL-8: Interleukin-8.
correlated with the vascularity of human gastric carcinomas and that IL-8-transfected cells produced rapidly growing, highly vascular neoplasms, compared to control cells. In contrast, inhibition of IL-8 decreases angiogenesis in gastric cancer. Wang et al. reported that CHI, a protein that interacts with the carboxy terminus of Hsc70, also interacted with nuclear factor-kappa B (NF-kB), terminating NF-kB activity and inhibiting IL-8-induced angiogenesis. IL-8 stimulates vascular endothelial growth factor (VEGF) expression in endothelial cells via CXCR-2 and thereby promotes the activation of VEGF receptors in an autocrine fashion. IL-8 has a direct role in angiogenesis by enhancing endothelial cell proliferation and survival in CXCR1- and CXCR2-expressing endothelial cells. IL-8 stimulates both endothelial proliferation and capillary tube formation in vitro, and both of these effects can be blocked by monoclonal anti-bodies to IL-8. H. pylori-derived heat shock protein 60 (HpHSP60) enhances angiogenesis by a CXCR2-mediated signaling pathway. Use of an angiogenic array showed that HpHSP60 markedly induced IL-8 and that inhibition of CXCR2, the receptor for IL-8, significantly abolished HpHSP60-induced tube formation. IL-8 has also been linked with cell adhesion and migration in gastric cancer. IL-8 activates NF-kB and Akt signals, and induces adhesion molecules including intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 and CD44 expression in gastric cancer cells. Inhibition of IL-8 with small interfering RNA reportedly decreased the adhesion, migration and invasion functions in cancer cells.

IL-8 polymorphisms may increase the risk of gastric cancer. Taguchi et al. reported the association of the IL-8-251 A/T polymorphism with higher expression of IL-8 protein, severe neutrophil infiltration and increased risk of atrophic gastritis and gastric cancer. IL-8-251 T/A and IL-8-251 A/A polymorphisms may be associated with angiogenesis in gastric carcinogenesis in H. pylori-infected Koreans. In the study, there were significant correlations between MMP-9, angiopeptin-1 concentrations and disease progression in IL-8-251 A/A and IL-8-251 A/T genotypes. Felipe et al. reported that patients with the heterozygous IL-8-251 A/T genotype, high fat intake and smokers or ex-smokers presented an increased risk of gastric cancer in a Brazilian population. However, the association of IL-8 polymorphisms and gastric cancer is controversial. The IL-8 polymorphism was not consistently associated with gastric cancer risk in a Polish population. Furthermore, a meta-analysis of epidemiological studies revealed an overall lack of association between IL-8-251 gene polymorphisms and risk of gastric cancer; any association is likely to be variable depending on histological type, tumor location, H. pylori infection, and ethnicity/country.

The downstream signals of IL-8 produced by H. pylori have been intensively studied. All biological effects of IL-8 are mediated by two receptors designated CXCR1 and CXCR2. IL-8 binds with high specificity to CXCR1 and with less specificity to CXCR2 expressed on stromal, endothelial and tumor cells. CXCR1, a cell-surface G-protein-coupled receptor, has been associated with tumorigenesis, development and progression of some tumors. Hu et al. documented that CXCR1 overexpression is associated with late-stage gastric cancer. They reported that knockdown of CXCR1 could inhibit cell proliferation in vitro and in vivo. Lin et al. reported that enforced expression of the cysteine-rich 61 (Cyr61) gene or treatment with recombinant Cyr61 protein enhanced expression of CXCR1 and CXCR2 in gastric cancer cells. The upregulated functionality of CXCR1 and CXCR2 could facilitate their chemotactic migration toward IL-8 and contribute to transendothelial migration, as well as intravasation. The interaction between IL-8 and epidermal growth factor receptor (EGFR) promotes cell proliferation through transactivation of the receptor by activation of a disintegrin and metalloproteinase. IL-8 could induce EGFR phosphorylation, while anti-IL-8 and anti-IL-8 receptor antibodies suppressed EGFR phosphorylation, indicating that H. pylori-stimulated IL-8 accelerates the processing of EGFR ligands, and that cleaved EGFR ligands bind and stimulate EGFR in paracrine and autocrine manners to induce cell proliferation.

**SIGNS SIGNALS INVOLVED IN H. PYLORI-INDUCED IL-8 IN GASTRIC CANCER**

A whole genome analysis of the epithelial response to H. pylori exposure revealed IL-8 as the most markedly up-regulated gene. IL-8 appears to play a paramount role in the epithelial cell response to H. pylori infection and in the pathological processes leading to gastric disease. IL-8, a CXC chemokine specific for neutrophil granulocyte chemotaxis, has been correlated with the histological severity of gastritis. The majority of gastric cancers are end products of an inflammatory process. A chronic H. pylori infection is characterized by an inflammation of the gastric mucosa and is accepted as the major cause of chronic gastritis.

IL-8 induction in gastric epithelial cells has been clearly correlated with a functional cagA gene. In H. pylori strains that express cagA, cytokine expression has been linked with an elevated inflammatory response. H. pylori strains are classified as cagA-positive or cagA-negative according to the presence or absence of cagA, respectively. CagA protein is a major virulence factor of H. pylori that has attracted clinical interest as a marker of H. pylori-associated disease, having been shown to confer increased gastric cancer risk. The cagA gene is located at one end of the cag pathogenicity island (cag-PAI). The island contains two segments: an upstream cag region and a downstream cag I region. PAI comprises a gene cluster of 40 kb that encodes a type IV secretion system (T4SS) that functions to translocate cagA from epithelium-adherent bacteria into gastric epithelial...
cells. Once inside the cells, cagA is phosphorylated by host cellular kinases, Src, and Akt, on a repeating glutamic acid proline-isoleucine-tyrosine-alanine tyrosine phosphorylation motif located at the carboxyl terminus of the protein. In vitro examinations of H. pylori infection of gastric epithelial cells reveals the requirement of proteins encoded by the cagPAI with the exception of cagA, for IL-8 secretion, and the regulation of IL-8 induction by the NF-κB pathway. However, H. pylori-induced pro-inflammatory responses remain controversial. Ando et al observed upregulated IL-8 expression in gastric epithelial cells infected with H. pylori containing an inactivated cagA gene, while Peng et al reported upregulation of IL-8 expression in gastric epithelial cells in response to treatment with extracts of cagA-positive and cagA-negative strains. Bacterial cagA expression may not be essential for the upregulation of IL-8 expression in H. pylori-infected gastric epithelial cells.

Although it is well known that H. pylori upregulates IL-8 expression in gastric cancer cells, the underlying molecular mechanism is not fully understood. Analyses of the genomic structure of IL-8 have revealed many potential targets for regulation at both the transcriptional and post-transcriptional levels. Within its 5′-flanking region, the IL-8 gene contains a repetitive ATTTA motif, which is responsible for destabilization of various cytokine mRNAs. Within the 5′-flanking region, the gene contains multiple cis elements including a CCAAT box, steroid-responsive element, hepatocyte nuclear factor-1 element, two interferon-regulatory factor elements and steroid-responsive element, hepatocyte nuclear factor-1 cis element, two interferon regulatory factor-1 elements and steroid-responsive element, hepatocyte nuclear factor-1 element, two interferon regulatory factor elements and steroid-responsive element, hepatocyte nuclear factor-1 element, two interferon regulatory factor elements and steroid-responsive element, hepatocyte nuclear factor-1 element, two interferon regulatory factor elements and steroid-responsive element, hepatocyte nuclear factor-1 element, two interferon regulatory factor elements and steroid-responsive element, hepatocyte nuclear factor-1 element, two interferon regulatory factor elements and steroid-responsive element, hepatocyte nuclear factor-1 element, two interferon regulatory factor elements and steroid-responsive element, hepatocyte nuclear factor-1 element, two interferon regulatory factor elements and steroid-responsive element, hepatocyte nuclear factor-1 element, two interferon regulatory factor elements and steroid-responsive element, hepatocyte nuclear factor-1 element, two interferon regulatory factor elements and steroid-responsive element, hepatocyte nuclear factor-1 element, two interferon regulatory factor elements and steroid-responsive element, hepatocyte nuclear factor-1 element, two interferon regulatory factor elements and steroid-responsive element, hepatocyte nuclear factor-1 element, two interferon regulatory factor elements and steroid-responsive element, hepatocyte nuclear factor-1 element, two interferon regulatory factor elements and steroid-responsive element. A myriad of intracellular signals have been suggested to mediate the effects of H. pylori including production of reactive oxygen species (ROS), and activation of transcription factor NF-κB, AP-1 and mitogen-activated protein kinase (MAPK).

ROS are involved in the pathogenesis of H. pylori-associated gastric diseases that include gastric cancer. Park et al reported that ROS are produced by NADPH oxidase (NOX1) and induce apoptotic cell death of H. pylori-infected gastric epithelial cells. NOX1 induced by H. pylori in gastric disease functions in the constitutive production of superoxide anion and hydrogen peroxide. Increased expression of NOX1 mRNA moderately increases the generation of superoxide anion, which leads to a reduction in aconitate activity, making NOX1 a good marker of oxidative stress. ROS induced by H. pylori stimulates MAPKs, such as extracellular signal-related kinases (ERKs), c-Jun NH2-terminal kinases (JNKs) and p38 MAPK, and upregulate transcription of NF-κB. Interestingly, IL-8 contributes to the generation of copious quantities of ROS, and can elic the induction of IL-1β, IL-6, IL-8, IL-12, tumor necrosis factor-alpha, and interferon-gamma. IL-8 activates the CD11b/CD18 dimer, which forms a complex with neutrophils. The complex activates ICAM-1 on the vascular endothelial cell membrane. The resulting tetramer (CD11b/CD18/neutrophil/ICAM-1) infiltrates gastric epithelial cells and facilitates the copious release of ROS through neutrophil NADPH oxidase, resulting in an oxidative burst. The ROS released from gastric epithelial cells may mediate the chemotactic action of neutrophils and monocytes in H. pylori-infected gastric tissues.

Co-culture of H. pylori with cells can induce IL-8 through the activation of the oxidant-sensitive transcriptional factor NF-κB. ROS are important in this process in H. pylori-infected cancer cells. NF-κB exists in a latent form in the cytoplasm, bound to the inhibitory protein, IκB. IκB kinase (IKK) directly phosphorylates IκB molecules, leading to the ubiquitin-mediated proteolysis of IκB. The NF-κB dimer that is released from IκB translocates to the nucleus where it activates target genes by binding to the promoter/enhancer region. In addition to ROS, several mechanisms for NF-κB activation by H. pylori have been proposed. H. pylori induces the phosphorylation of heat shock protein 90 (Hsp90) in gastric epithelial cells. Hsp90 associates stoichiometrically with the IKK complex, which contributes to the stabilization, activation and shutting of IKKs to the plasma membrane, because Hsp90 regulates the stability and function of a unique complement of signaling molecules. Given that Hsp90 is associated with IKK-α and IKK-β in H. pylori-infected gastric epithelial cells, the Hsp90-IKK complex may be a target for the pharmacological inhibition of the H. pylori-mediated activation of NF-κB signaling. Takeshima et al reported that NF-κB activation by H. pylori requires Akt-mediated phosphorylation of p65. Phosphorylated Akt is detected in epithelial cells of H. pylori positive gastric tissues. The application of phosphoinositols-3-kinase inhibitor, dominant-negative Akt and small interfering RNA for Akt suppresses H. pylori-induced p65 phosphorylation as well as IL-8 expression, suggesting that Akt signals are involved in H. pylori-induced NF-κB activation.

H. pylori also activates the transcription factor AP-1 in a cagPAI-dependent manner. The AP-1 complex activated during H. pylori infection is composed primarily of c-jun and c-fos heterodimers. AP-1 is activated by MAPK and is capable of inducing a strong pro-inflammatory response, often in concert with NF-κB. H. pylori rapidly activate MAPKs upon contact with gastric epithelial cells. MAPK cascades are well characterized pathways that transduce signals from the cell surface to the nucleus. The family includes distinct subgroups: ERKs, JNKs and p38 MAPK. A number of bacterial factors have been implicated in MAPK activation including vacA and cagA. The signaling events leading to rapid MAPK phosphorylation during H. pylori infection are not well understood, although T4SS is required for ERK phosphorylation of p38 MAPK and JNK. CagA is capable of activating ERK, though ERK can also be
activated by cagA-independent mechanisms\textsuperscript{[74]}, suggesting that cagA has an additive role in transcription factor activation. JNK activation during \textit{H. pylori} infection also requires a functional T4SS\textsuperscript{[73].} \textit{H. pylori} peptidoglycan is delivered to the host cell \textit{via} the T4SS, where it is recognized by cytosolic nucleotide binding and oligomerization domain 1 (NOD1)\textsuperscript{[73].} Upon stimulation with purified agonist, NOD1 associates with the receptor-interacting protein serine-threonine kinase 2, triggering a pro-inflammatory response that is characterized by NF-κB activation and IL-8 production\textsuperscript{[74].} In addition to activation of the classical NF-κB pathway, NOD1 is reported to be required for MAPK activation in response to bacterial pathogens. This NOD1-dependent p38 MAPK activation induces IL-8 production\textsuperscript{[77].} Allison \textit{et al.}\textsuperscript{[77]} observed that NOD1 was necessary for MAPK activation in the early stages of infection and that NOD1 was essential for the activation of both NF-κB and AP-1, as well as the release of IL-8 in response to \textit{H. pylori}. These observations support previous findings that cagA induces IL-8 induction \textit{via} the Ras→Raf→Mek→ERK→NF-κB signaling pathway\textsuperscript{[78]} and that cagA can activate the Ras→ERK pathway\textsuperscript{[79]}. Understanding the signals involved in IL-8 expression by \textit{H. pylori} may be beneficial to develop new therapeutics in gastric cancer (Figure 2).

### IL-8 AS A THERAPEUTIC TARGET IN GASTRIC CANCER

Gastric cancer features increased IL-8 expression, suggesting that IL-8 might be a promising therapeutic targeting to prevent cancer progression. Many inhibitors that prevent \textit{H. pylori}-induced IL-8 expression and regulate the IL-8 downstream signals have been proposed (Table 1).

Polyphenols derived from natural products that include resveratrol, apigenin and anthocyanins inhibit IL-8 induced by \textit{H. pylori}. Resveratrol suppresses the secretion of IL-8 from \textit{H. pylori}-infected gastric epithelial cells. IL-8 secretion is usually regulated by the transcription factor NF-κB and \textit{H. pylori} can induce IL-8 expression by activating a NF-κB pathway in gastric epithelial cells\textsuperscript{[80,81].} Since resveratrol inhibits NF-κB\textsuperscript{[82]}, its suppressive effect on IL-8 secretion may correlate with its NF-κB inhibitory activity. Inhibition of IL-8 expression by resveratrol may also be due to modulation of regulatory enzymes like MAPK\textsuperscript{[83].} Anti-oxidant anthocyanins from black soybean may inhibit IL-8 production\textsuperscript{[84].} Cyanidin-3-glucoside, which is abundant in anthocyanins, is reportedly an effective anti-oxidant that inactivates NF-κB by inhibiting phosphorylation of IκB\textsuperscript{[85,86].} Anthocyanins have anti-oxidant effects and the ability to downregulate enzymes like MAPK\textsuperscript{[87].} Anti-oxidant and anti-inflammatory activity, and thus inhibits NF-κB activation and decreases IL-8 expression\textsuperscript{[88].} Apigenin’s anti-inflammatory activity has been characterized \textit{in vitro} and \textit{in vivo}\textsuperscript{[89,90].}

Phenyl-thiophenyl propenone RK-I-123 is a small molecule that reportedly reduces the level of ROS and suppresses the activation of NF-κB and AP-1, and the expression of IL-8 in \textit{H. pylori}-infected gastric epithelial cells\textsuperscript{[91].} RK-I-123 was synthesized as a novel propenone compound in an attempt to develop a dual inhibitor of COX-2 and 5-LOX\textsuperscript{[91].} 7-Carboxymethyloxy-3′,4′,5-tri-methoxy flavone, abbreviated as DA-6034, is a synthetic derivative of eupatilin that also inhibits IL-8 induced by \textit{H. pylori}\textsuperscript{[92].} DA-6034 promotes the dissociation of the...
Table 1  Inhibitors targeting interleukin-8 in cancer progression

| Inhibitors         | Mechanisms                                    | Ref.     |
|--------------------|-----------------------------------------------|----------|
| Resveratrol        | Reduces ROS, inhibits MAPK, AP-1 and NF-κB    | [82,83]  |
| Anthocyanin        | Reduces ROS, inhibits MAPK, AP-1 and NF-κB    | [84-86]  |
| Apigenin           | Increases the IκBκ and thus inhibits NF-κB     | [88,89]  |
| RK-I-123           | Reduces ROS and inhibits AP-1 and NF-κB       | [91]     |
| DA-6034            | Dissociates IκKκ/HSp90 complex and inhibits NF-κB | [92,93]  |
| Rebamipide         | Prevents PLD expression via NF-κB             | [94,95]  |
| Gefitinib [Iressa™] | Inhibits EGFκ                                    | [98,99]  |
| L. bulgaricus      | Inhibits TLR4                                    | [101]    |
| L. acidophilus     | Dissociates IκKκ/HSp90 complex and inhibits NF-κB | [65,103] |
| NFR peptide       | Disrupts interaction of NFR and NF-κB         | [105]    |
| miR-146            | Negatively regulates IL-8                      | [110,111]|
| miR-155            | Inhibits MyD88 via NF-κB                      | [112,115]|
| G3IP               | Synthetic derivative of IL-8                  | [117]    |
| SCH-57213          | CXCR2 inhibitor                               | [118]    |

NRF: Nuclear factor-κB; IκKκ: Inhibitor of κκ B alpha; TLR4: Toll-like receptor 4.

IKK-Hsp90 complex and suppresses NF-κB signaling, leading to the inhibition of IL-8 expression in H. pylori-infected cells. DA-6034 also inhibits EFRK in such cells.[93]

Rebamipide [2-[4-chlorobenzoylamino]-3-[2[1H]quinolinon-4-yl] propionic acid; OPC-12759], a mucosal-protective anti- ulcer agent, was reported to inhibit IL-8 in gastric cancer by the regulation of phospholipase D (PLD) expression. Gastric cancer cells infected with H. pylori display significant induction of PLD1 expression via activation of NF-κB[94]. The level of PLD1 protein and IκBκκ phosphorylation is aberrantly upregulated in H. pylori-infected human gastric tissues. Rebamipide is a gastroprotective agent used in the treatment of gastritis and gastric ulcers.[95] It protects against gastric mucosa inflammation induced by H. pylori by inhibiting neutrophil function[96]. Moreover, rebamipide inhibits the growth of gastric cancer cells.[97] PLD and IL-8 might be novel targets of rebamipide in H. pylori-associated gastric cancer.

Gefitinib (Iressa™, ZD1839) reportedly inhibits epidermal growth factor (EGF) signals and IL-8 production in gastric cancer cells.[98] Gefitinib is an orally active, quinazoline-derived agent that inhibits EGF receptor (EGFR)-tyrosine kinase.[99] Previous studies have shown that EGFR-mediated signals contribute to the expression of IL-8 and that IL-8 may be involved, at least in part, in EGF/EGFR-induced cancer progression.[100] Kishida et al.[100] employed SN38 (an active metabolite of CPT-11) for activation of EGFR-tyrosine kinase. SN38 activates the EGF/EGFR autocrine loop and induces IL-8 in gastric cancer cells. SN38 induces binding activities in both NF-κB and AP-1, critical transcription factors for the expression of IL-8, and this reaction is inhibited by gefitinib.

Interestingly, Zhou et al.[101] suggested that the probiotic application of lactobacilli may inhibit IL-8 production induced by H. pylori-activated Toll-like receptor 4 (TLR4). Lactobacillus bulgaricus (LBG), a bacterium used in the production of yogurt, is one of the best-studied probiotic microbes. Probiotics are living microorganisms with no or low pathogenicity, which exert beneficial effects on the host. H. pylori induces mucosal inflammation including IL-8 production via TLR4 signaling.[102] Conjugated linoleic acids (CLA) produced by Lactobacillus acidophilus (LBA) also decreases the activation of NF-κB and IL-8 expression in H. pylori-infected gastric epithelial cells.[103] Kim et al.[104] demonstrated that CLA-containing conditioned medium produced by LBA has anti-inflammatory effects on H. pylori infection. In their study, conditioned medium produced by LBA significantly inhibited the activation of the core inflammatory gene signal NF-κB in gastric epithelial cells by dissociation of the complex between Hsp90 and the IκBκ kinase-subunit. CLA-containing conditioned medium also inhibited the expression of IL-8.[105] There is increasing evidence[106] that Lactobacillus has therapeutic effects on H. pylori-related diseases, including enhanced eradication of H. pylori, amelioration of resistance to antibiotics, downregulated side effects of antibiotic-based therapy, decreased recurrence of H. pylori infection, and inhibition of H. pylori-induced apoptosis.

Bartel et al.[107] suggested that a peptide capable of disrupting the interaction between NF-κB and NF-κB repressing factor (NRF) inhibits H. pylori-induced IL-8 expression. In IL-8 gene expression, exclusively, NRF had two functions. It repressed the basal transcription of IL-8 gene in unstimulated cells[108], but, following cell stimulation, it was required for the transcriptional activation of the IL-8 gene. A synthetic peptide corresponding to amino acid 223-238 of NRF interfered with the binding of endogenous NF-κB to NRF interaction, which significantly decreased endogenous IL-8 gene transcription in response to H. pylori infection.

Several microRNAs (miR) are reported to regulate IL-8 gene expression[109]. miRNAs are central regulators of various physiologic processes and their disruption is associated with human diseases.[108] Recently, Liu et al.[109] reported that miR-146a negatively regulated H. pylori-induced IL-8 via reduced NF-κB activity. miR-146a reportedly suppresses NF-κB activity through the reduction of metastatic potential in cancer cells.[110] The authors also reported that miR-146a is the negative regulator of NF-κB activity through the downregulation of IRAK1 and TRAF6 in cancer cells. Perry et al.[111] found that miR-146a was able to negatively regulate the release of IL-1β-induced IL-8, independent of IRAK1 and TRAF6 signals. miR-155 was also suggested to regulate IL-8 in H. pylori-infected gastric epithelial cells. Overexpression of miR-155 reportedly reduced the H. pylori-induced IL-8 expression[112]. miR-155 has been indicated to play a key role in the regulation of normal immune or inflammation.
response\textsuperscript{113,114}. Among a number of targets of miR-155, MyD88 is suggested for IL-8 regulation\textsuperscript{115}. miR-155 may downregulate the protein MyD88 through inhibition of translation. Most TLRs activate MyD88 leading to the nuclear translocation of transcription factors, such as NF-kB and AP-1, and thus transcriptionally regulate IL-8\textsuperscript{116}. The function of miRNAs during \textit{H. pylori} infection is complex and miR-155 may cooperate with other \textit{H. pylori}-induced miRNAs including miR-146a in response to \textit{H. pylori}. There may be crosstalk between miR-146a and miR-155 in the signal pathways leading to the downregulation of \textit{H. pylori}-induced IL-8 in gastric cancer.

Small molecule inhibitors targeting IL-8 receptors (CXCR1 and CXCR2) have been developed to suppress prostate and colon cancers\textsuperscript{17,117,118}. Inhibition of these receptors reduces cell migration and invasion, while increasing apoptosis in cancer cells\textsuperscript{119}. Liu et al\textsuperscript{120} synthesized a derivative of the human cytokine IL-8, G31P, with high-affinity for human CXCR1 and CXCR2. G31P treatment significantly reduced prostate cancer cell viability, adhesion and migration capacity. Additionally, G31P inhibited tumor tissue vascularization, which was associated with the decreased expression of vascular endothelial growth factor and NF-kB in orthotopic xenograft tissues. Another small molecule inhibitor targeting CXCR2 is SCH-527123\textsuperscript{118}. SCH-527123 is able to suppress CXCR2-mediated signal transduction as shown through decreased phosphorylation of the NF-kB, MAPK and Akt pathways in colon cancer cells. The anti-tumor activity of SCH-527123 resulted from inhibition of cancer cell growth, motility, and angiogenesis. In addition to having a direct anti-angiogenic and anti-tumor effect, targeting IL-8 or CXCR2 may also increase chemosensitivity to chemotherapeutics. Wilson \textit{et al}\textsuperscript{120} also showed that IL-8/CXCR2 signaling confers resistance to chemotherapeutics (oxaliplatin) through NF-kB activity, which is an important determinant of cancer cell sensitivity to chemotherapeutics.

**CONCLUSION**

There is a close association between \textit{H. pylori} infection and gastric cancer. IL-8 is overexpressed in gastric epithelial cells exposed to \textit{H. pylori}. IL-8 is significantly upregulated in both the tumor and its microenvironment, and acts as a key regulator of proliferation, angiogenesis and metastasis. IL-8 expression also contributes to the resistance of gastric cancer to chemotherapeutics. Although anti-IL-8 therapeutic agents are yet to enter preclinical and clinical trials, a large body of published evidence suggests that targeting IL-8 in gastric cancer could have broad-spectrum anti-tumor effects. Many advances have been made since the discovery that IL-8 regulates cell signaling in cancer development and progression independently of chemotaxis during the inflammatory process. Thus, we propose that IL-8 induced by \textit{H. pylori} plays a major role in gastric cancer and that targeting IL-8 may be a promising strategy for the treatment of cancer.

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