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Review article

Role of Interleukin-8 in *Helicobacter pylori* induced gastric cancer: Targeting Il-8 can have a potential antitumor effect.

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Introduction:

Helicobacter pylori is a spiral-shaped Gram negative bacteria that is specialized in colonizing the human gastric mucosa, where it causes a variety of clinical outcomes ranging from asymptomatic carriage to gastritis, peptic ulcers, and cancer.[1] Since *H. pylori* is a noninvasive bacterium, it has been assumed that trans-epithelial signal transmission must be involved in initiating the inflammatory response in *H. pylori*-associated gastritis.[2] Of the many cytokines that can be induced by a bacterial infection followed by the pathologic changes seen in inflammation; chemokines are possible candidates to act as a signal following the contact of bacteria with the epithelium.[3,4] An important cytokine that plays a central role in the pathogenesis of *H. pylori*-induced diseases is Interleukin 8. It is a potent chemoattractant for neutrophils and lymphocytes. It also has effects on cell proliferation, migration, and tumor angiogenesis.[5]

Genetic factors like cytokine gene polymorphism is also responsible for the pathogenesis and severity of gastroduodenal disease. The IL-8 gene has a well-established promoter polymorphism at position -251 (*IL-8*-251 Thymine/Adenine). The A allele is associated with increased production of IL-8 in *H. pylori*-infected gastric mucosa. It was also found to increase the risk of severe inflammation and precancerous gastric abnormalities in white and Asian populations.[6,7]

IL-8 polymorphisms may increase the risk of gastric cancer. Taguchi et al reported the association of the IL-8-251 A/Tpolymorphism with higher expression of IL-8 protein, severe neutrophil infiltration and higher risk of atrophic gastritis and gastric cancer.[6]

Role of IL-8 in developing H.pylori induced gastric cancer:

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 some growth factors that promote angiogenesis as a part of cancer progression. 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. In contrast, inhibition of IL-8 decreases angiogenesis in gastric cancer.[8]

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. It binds with high specificity to CXCR1 and with less specificity to CXCR2 expressed on stromal, endothelial and tumor cells. 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.[9] IL-8 has also been linked with cell adhesion and migration in gastric cancer. IL-8 activates NF-κB 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.[10]

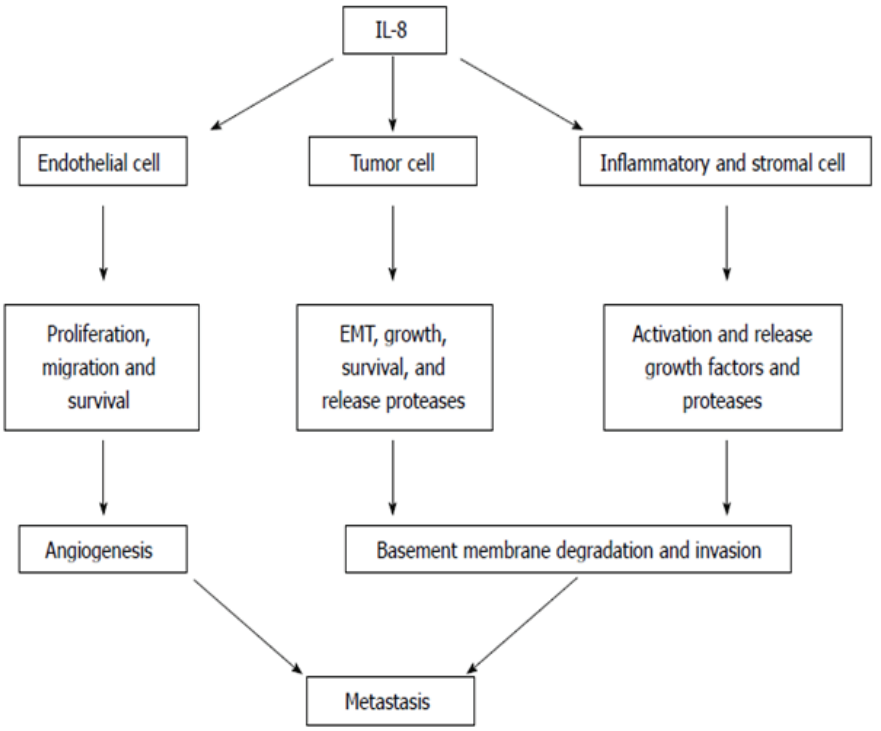

Figure 1: Roles for interleukin-8 in tumor progression and metastasis.[11]

(EMT: Epithelial-mesenchymal transition; IL-8: Interleukin-8.)

Although it is well known that *H. pylori* enhances IL-8 expression in gastric cancer cells, the molecular mechanism of the underlying fact is not fully understood. Genomic structure analysis of IL-8 showed many potential targets for both transcriptional and post-transcriptional regulation. Within its 3'-flanking region, the IL-8 gene contains a repetitive ATTTA motif, which destabilize various cytokine mRNAs. Within the 5'-flanking region, the gene contains multiple cis elements including a CCAAT box, steroid-responsive factors, interferon regulatory factor-1, hepatocyte nuclear factor-1, binding sites for activator protein-1 (AP-1), CCAAT/enhancer binding protein and NF-κB. These stimulations can induce *IL-8* gene transcription.[13,14]

Mutation and deletion analyses demonstrated that, these promoter elements are regulated in cell type-specific manners. A cascade of intracellular signals mediates 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).[14] ROS plays pivotal role in the pathogenesis of *H. pylori*-associated gastric diseases that include gastric cancer.[15]

Signals involved in H. pylori-induced IL-8 in Gastric Cancer

After exposure to *H. pylori* a whole genome analysis of the epithelial response revealed *IL-8* as the most markedly upregulated gene. IL-8 play a significant role in the epithelial cell response to *H. pylori* infection and in the pathological processes leading to gastroduodenal disease.

IL-8 induction in gastric epithelial cells are correlated with a functional *cagA* gene.[16] In *vitro* examinations of *H. pylori* infection of gastric epithelial cells showed that, the proteins encoded by the *cagPAI* are required for IL-8 secretion and the regulation of IL-8 induction by the NF-κB pathway.[17,18]

ROS induce apoptotic cell death of *H.pylori*-infected gastric epithelial cells and produced by NADPH oxidase (NOX1). NOX1 produce superoxide anion and hydrogen peroxide. 13ROS also activates MAPKs, such as extracellular signal-related kinases (ERKs), c-Jun NH2-terminal kinases (JNKs) and p38 MAPK, and enhances transcription of NF- κB.Increased expression of NOX1 mRNA provokes the generation of superoxide anion, which is indicative of oxidative stress. Interestingly, IL-8 contributes to the generation of copious quantities of ROS, and induction of IL-1β, IL-6, IL-8, IL-12, tumor necrosis factor-alpha, and interferon-gamma.[19]

IL-8 activates the CD11b/CD18 dimer that can make a complex with neutrophils. This complex activates ICAM-1 on the vascular endothelial cell membrane. Infiltration of this tetramer (CD11b/CD18/ neutrophil/ICAM-1) in gastric epithelial cells facilitates the copious release of ROS through neutrophil NADPH oxidase. Ultimately an oxidative burst occurs. The ROS released from gastric epithelial cells mediate the chemoattractant function of neutrophils and monocytes in *H. pylori*-infected gastric tissues.[20,21,12]

H. pylori can activate the transcription factor AP-1 like cagPAI. The AP-1 complex activated during *H. pylori* infection is composed of c-jun and c-fos heterodimers. AP-1 is activated by MAPK. It can induce potential pro-inflammatory response, often in concert with NF-κB.[22]

H. pylori can activate MAPKs when they come in contact with gastric epithelial cells. MAPK cascades are well characterized pathways that cause signal transduction from the cell surface to the nucleus. This family includes following subgroups: ERKs, JNKs and p38 MAPK. Some bacterial factors including vacA and cagA can also activate MAPK. JNK activation during H. pylori infection also requires a functional T4SS.[22]

Peptidoglycan of *H. pylori is* delivered to the host cell via the T4SS, where cytosolic nucleotide binding and oligomerization domain 1 (NOD1) recognize it.[15]

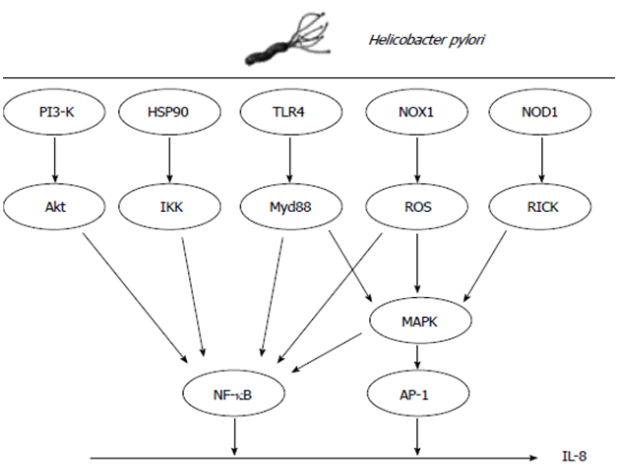

Figure 2: Scheme of signaling of Helicobacter pylori-induced interleukin-8 in gastric cancer cells.[11]

[PI3-K: Phosphoinositide 3-kinase; HSP: Heat shock protein; TLR: Toll-like receptor; NOX: NADPH oxidase; NOD: Nucleotide binding and oligomerization domain; IKK: IκB kinase; ROS: Reactive oxygen species; RICK: Receptor- interacting protein serine-threonine kinase; MAPK: Mitogen-activated protein kinase; NF-κB: Nuclear factor kappa B; AP-1: Activator protein-1.]

NOD1 with the receptor-interacting protein serine-threonine kinase 2 can trigger a pro-inflammatory response upon stimulation with purified agonist. This response is characterized by NF-κB activation and IL-8 production. In addition to activation of the classical NF-κB pathway, NOD1 is required for activation of MAPK in response to bacterial infection. This NOD1-dependent p38 MAPK activation enhances IL-8 production.[23,24] Understanding the signals involved in IL-8 expression by *H. pylori* may be beneficial to develop new therapeutics in gastric cancer.[13]

IL-8 as a Therapeutic Target in Gastric Cancer:

Increased IL-8 expression in gastric cancer suggests that IL-8 might be a potential therapeutic targetto prevent progression of cancer. Prevention of *H. pylori*-induced IL-8 expression and regulation of the IL-8 downstream signals can be achieved by many proposed inhibitors. IL-8 induction by *H. pylori* can be inhibited by polyphenols derived from natural products that include resveratrol, apigenin and anthocyanins. Resveratrol suppresses the secretion of IL-8 from *H. pylori*-infected gastric epithelial cells. It reduces ROS, inhibits MAPK, AP-1 and NF-κB. [25]

Resveratrol may inhibit the expression of IL-8 by modulation of regulatory enzymes like MAPK. Anti-oxidant anthocyanins from black soybean may inhibit IL-8 production. Anthocyanins contain abundant of Cyanidin- 3-glucoside, which is an effective anti-oxidant. It inactivates NF-κB by inhibiting phosphorylation of IκB.[15] Apigenin also inhibits NF-κB by increasing the IκBα.[26]

Phenyl-thiophenyl propenone RK-I-123 is a small molecule that suppresses the activation of NF-κB and AP-1,reduces the level of ROS and expression of IL-8 in *H. pylori*-infected gastric epithelial cells.[27]

7-Carboxymethyloxy-3',4',5-trimethoxy flavone (DA-6034) is a synthetic derivative of eupatilin that may reduce the level of IL-8 induction by *H. pylori*.[28]

Rebamipide [2-[4-chlorobenzoylamino]-3-[2[1H] quinolinon -4-yl]; OPC-12759], is a mucosal protective anti-ulcer agent; is a propionic acid derivative. It was reported to inhibit IL-8 in gastric cancer by the regulation of phospholipase D (PLD) expression.[29] Gefitinib (Iressa™, ZD1839)is an orally active quinazoline-derived agent that inhibits EGF receptor (EGFR)-tyrosine kinase thus downregulate epidermal growth factor (EGF) signals and IL-8 production in gastric cancer cells.[30]

Surprisingly some scientists observe that IL-8 production induced by *H. pylori*-activated Toll-like receptor 4 (TLR4) may be inhibited by application of probiotic, such as lactobacilli. *Lactobacillus bulgaricus* (LBG) is used in the production of yogurt, which is one of the best-studied probiotic microbes. Activation of NF-κB and IL-8 expression in *H. pylori*-infected gastric epithelial cells is also inhibited by conjugated linoleic acids (CLA) produced by Lactobacillus acidophilus (LBA).[31]

IL-8 gene expression is regulated by several microRNAs (miR); which are central regulators of several physiological processes. So, disruption of miR is associated with human diseases. Some studies suggested that miR-146a negatively regulated *H. pylori* induced IL-8 *via* reduced NF-κB activity. [32]

In a nutshell, the above mentioned discussion on the basis of a large number of published articles suggest that, IL-8 can be a potential target in *H. pylori* induced gastric cancer and have large spectrum of antitumor effect. Anti-IL-8 anticancer therapy are yet to enter in clinical trials; so, further clinical experiment based studies can open a window in the treatment of *H. pylori* induced gastric carcinoma.

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