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Helicobacter pylori and Gastric Inflammation: Role of MUC1 Mucin

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Abstract

More than half of the world's population is infected with *Helicobacter pylori*, which is strongly linked to the development of chronic gastric inflammation (gastritis), peptic ulcer disease, and stomach cancer. However, for unknown reasons, the vast majority of infected individuals are asymptomatic beyond histologic inflammation. This review article will summarize current knowledge on the molecular mechanisms of *H. pylori* colonization of the gastric mucosa, with a particular focus on the biochemistry of MUC1 mucin in the host response to bacterial infection.

Keywords

Helicobacter pylori; stomach; epithelium; MUC1 mucin

1. Introduction

Helicobacter pylori is a Gram-negative, microaerophilic, flagellated bacterium that colonizes the human stomach [1]. *H. pylori* infections are acquired in childhood, particularly in developing countries and, in the absence of antibiotic therapy, persist for the lifetime of the individual [2]. Currently, greater than 50% of the world's population is infected with *H. pylori*, making it the most globally common bacterial infectious agent. In spite of its high prevalence in the human population, greater than 80% of infected individuals remain asymptomatic apart from histologic gastritis. For example, from an estimated 50–100 million individuals in the U.S. currently infected with *H. pylori*, only about 25,000 new cases of stomach cancer are diagnosed each year [3]. It is enigmatic why only a subset of infected individuals develops serious gastric disease. In this review article, we propose a novel molecular mechanism that addresses this question, namely those defects in the anti-inflammatory MUC1 mucin glycoprotein in a limited cohort of *H. pylori*-infected individuals predisposes to uncontrolled inflammation that ultimately evolves to peptic ulcer disease and/or stomach cancer.

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2. *H. pylori* infection of the gastric mucosa

The relatively high prevalence of *H. pylori* infection is due, in large part, to the inability of host immunity to clear bacterial colonization, in spite of an overt gastric inflammatory response [4]. Within the group of *H. pylori*-infected individuals who do display clinical symptoms, epidemiologic and pathologic studies have confirmed a progressive increase in disease symptomology and severity over several decades, starting with chronic inflammation, followed by the development of noncancerous and precancerous lesions, and finally gastric adenocarcinoma [5]. It has been proposed that chronic gastritis during a lifetime of bacterial infection generates a proinflammatory environment characterized by the activation of intracellular signaling pathways that promote the progression to gastric cancer [6]. Indeed, *H. pylori* infection is associated with increased gastric epithelial cell mutations, inhibition of apoptosis, and stimulation of angiogenesis and cell proliferation, all of which contribute to development of a cancer phenotype [7]. Therefore, better understanding of host proinflammatory pathways, as well as the counter-regulatory anti-inflammatory mechanisms, will provide important new information that is relevant for the treatment of *H. pylori*-infected patients who are at increased risk for developing life-threatening gastric diseases.

3. *H. pylori* adhesion to gastric mucosa

A central dogma in bacterial pathogenesis is that microbial adhesion to host cell surface receptors is a prerequisite for successful infection [8]. *H. pylori* colonization of the stomach is initiated through pathogen binding to cell surface receptors expressing the sialyl-Lewis a (sLe^a), Lewis b (Le^b), and sialyl-Lewis x (sLe^x) glycoconjugates [9]. The corresponding *H. pylori* adhesins, BabA (blood group antigen binding adhesion) and SabA(sialic acid binding adhesion), interact with these host receptors [10]. Among the epithelial glycoproteins containing these Lewis antigens are gastric mucins. At low pH, BabA binds to the soluble MUC5AC mucin glycoprotein, whereas under neutral pH conditions BabA binds both to the MUC5AC mucin and to the cell-associated MUC1 mucin [11,12].

4. Gastric mucins

Mucus is a viscous, gel-like material containing a mixture of high molecular weight, extensively glycosylated mucin proteins that are produced by most secretory epithelia [13]. Currently, 20 mucin genes have been identified and their encoded glycoproteins have been classified as secreted mucins and cell-associated mucins [13–15]. By convention, mucin genes are designated as MUC in humans and Muc in animals, followed by an Arabic numeral indicating their order of discovery. Secreted mucins accumulate in large secretory granules of specialized epithelial cells known as mucous/goblet cells. Under the appropriate extracellular stimulus, exocytosis of the secretory granules releases the packaged mucin molecules that subsequently establish intermolecular associations to form a continuous, viscoelastic layer covering the epithelial mucosa. Transmembrane mucins are membrane-embedded glycoproteins that are localized on the apical surface of epithelial cells.

Mucins expressed by the gastric mucosa include secreted mucins, e.g. MUC5AC, and membrane-tethered mucins, e.g. MUC1. The deduced amino acid sequence of the MUC1 gene indicates a multidomain structure of the encoded protein, consisting of a large molecular weight extracellular (EC) domain, a transmembrane (TM) domain, and an intracellular cytoplasmic tail (CT) domain (Fig. 1) [16,17]. Autocatalytic proteolysis of the MUC1 protein generates a heterodimeric structure that resides on the cell surface with the EC domain noncovalently associated with a small subunit containing the TM and CT domains [18,19]. The separate EC and TM/CT subunits can be detected on SDS-PAGE gels using antibodies specific for each region (Fig. 2). The EC domain contains a variable

number of 20-amino acid tandem repeats (VNTRs). The CT domain contains 72 amino acids, 7 of which are evolutionarily conserved tyrosines that are potential sites of phosphorylation (Fig. 3). Similar to cytokine and growth factor receptors, MUC1 CT tyrosine phosphorylation occurs in consensus amino acid sequence motifs for signaling kinases and adaptor proteins including phosphoinositide 3-kinase (PI3K), Shc, c-Src, and Grb-2 [20,21].

5. Phosphorylation of the MUC1 CT

Given the receptor-like structure of MUC1, it is not surprising that numerous studies have shown that its CT region is phosphorylated at multiple tyrosine residues [20–32]. Chinese hamster ovary (CHO) cells over-expressing hamster Muc1 and treated with whole bacteria, or with bacterial flagellin protein, had increased phosphorylation of the Muc1 CT [28]. In another cell culture system, we utilized the human MUC1 CT that was linked to the EC domain of CD8 and the resulting CD8/MUC1 chimeric protein was expressed into COS7 cells. Treatment of CD8/MUC1-COS7 cells with anti-CD8 antibody induced tyrosine phosphorylation of the MUC1 CT at 4 tyrosine residues, Y^{20}, Y^{29}, Y^{46}, and Y^{60} [21]. These 4 tyrosines are located within consensus amino acid sequence motifs for binding to the PI3K, Shc, c-Src, and Grb-2 signaling proteins (Fig. 3), suggesting that MUC1 CT phosphorylation activates downstream, intracellular signaling transduction.

Because previous studies demonstrated that the extracellular signal-regulated kinase (ERK) was constitutively activated by MUC1 in mammary epithelial cells [33], ERK1/2 phosphorylation was investigated in response to treatment of CHO-Muc1 cells with bacterial flagellin protein. Flagellin activated ERK1/2 in CHO-Muc1 cells, but not in Muc1 negative CHO cells [28]. Further, anti-CD8 antibody treatment of CD8/MUC1-COS7 cells stimulated a Ras → MEK1/2 → ERK1/2 cascade [34]. Collectively, these results demonstrated that extracellular stimulation of the full-length Muc1 molecule with flagellin, or the CD8/MUC1 chimera with anti-CD8 antibody, stimulated phosphorylation of the intracellular MUC1/Muc1 CT, leading to activation of an ERK1/2 signaling pathway.

6. MUC1 CT interaction with β-catenin

The MUC1 CT region binds to β-catenin at a -S-A-G-N-G-G-S-S-L- amino acid sequence (Fig. 3). This sequence fits a canonical β-catenin binding motif (-S-X-X-X-X-X-S-S-L-) that is conserved with other β-catenin binding partners, including the epithelial E-cadherin protein [25,32,35,36]. β-Catenin was originally identified in the Wnt signaling pathway, a major oncogenic pathway associated with gastric tumorigenesis [37]. Subsequently, β-catenin was demonstrated to form a multiprotein complex that anchors the cytoplasmic domain of E-cadherin to the actin cytoskeleton, thereby regulating epithelial barrier formation, the paracellular pathway, and polarity in normal cells [38]. However, the role of MUC1/β-catenin interaction in regulating the host gastric epithelial cell response *H. pylori* colonization is unknown.

7. Counter-regulatory role of gastric MUC1 mucin in *H. pylori* infection

Mucosal epithelial cells, including those of the gastric epithelium, express multiple surface receptors, in addition to MUC1, that signal the presence of invading pathogens and activate host inflammatory responses [39]. While much is known concerning the inflammatory pathways that are activated following microbial colonization, relatively few studies have characterized the counter-balancing, anti-inflammatory responses. We recently reported that expression of MUC1/Muc1 counter-regulated *H. pylori*-induced gastric inflammation [40]. Using a mouse model of *H. pylori* infection, Muc1 knockout ($Muc1^{-/-}$) mice displayed increased bacterial load and greater levels of gene transcripts encoding the proinflammatory

cytokines tumor necrosis factor-α (TNF-α) and keratinocyte chemoattractant (KC) in the stomach, compared with $Muc1^{+/+}$ mice. Knockdown of MUC1 expression using in vitro cultures of AGS human gastric epithelial cells was correlated with greater activation and nuclear translocation of nuclear factor-κB (NF-κB), decreased activity of the NF-κB inhibitor, IκBα, and augmented IL-8 production, compared with MUC1-expressing cells. By contrast, transfection of AGS cells with a MUC1 expression plasmid was associated with decreased NF-κB activation and nuclear translocation, and reduced IL-8 production, compared with cells expressing MUC1 endogenously. Cotransfection of AGS cells with MUC1 plus the IκB kinase (IKK), which phosphorylates the inhibitory IκBα protein resulting in dissociation from NF-κB and activation of NF-κB, reversed the MUC1 inhibitory effect. Finally, the MUC1 CT formed a protein complex with IKK, suggesting that MUC1 binds to IKK, thereby inhibiting formation of the catalytically active IKK complex and blocking the ability of *H. pylori* to stimulate IκBα phosphorylation, NF-κB activation, and downstream inflammatory responses.

8. Host versus bacteria initiated events in *H. pylori* pathogenesis

While it is well-known that pro- and anti-inflammatory responses during *H. pylori* infection are initiated in reaction to a variety of bacterial products, the relative roles of these host responses versus direct activity of the bacterial components in mediating pathogenesis/carcinogenesis remain controversial. A chronic inflammatory microenvironment during a lifetime of *H. pylori* infection has been suggested to promote host-dependent alterations in gastric epithelial cell phenotypes that ultimately culminate in neoplastic transformation. For example, augmented production of proinflammatory mediators in response to bacterial infection may increase gastric epithelial cell mutations in tumor suppressor genes, ultimately leading to cancer [7]. The perigenetic hypothesis proposes that *H. pylori*-induced up-regulation of inflammatory proteins, such as TNF-α, alters gastric epithelial cell adhesion and/or proliferation, thus leading to the dispersion and propagation of precancerous epithelial cells into mature tumors without the need for additional genetic mutations [41,42]. On the other hand, the *H. pylori* cytotoxin-associated gene A (CagA) protein has been proposed as a major factor determining the progression to gastric epithelial tumorigenesis. In the absence of bacterial exposure, Ohnishi *and colleagues* [43] reported that transgenic mice expressing a recombinant CagA protein in vivo developed greater gastric epithelial hyperplasia and adenocarcinomas, compared with nontransgenic mice. Further studies are required to elucidate the relative roles host versus bacterial events in *H. pylori* pathogenesis.

9. Role of *H. pylori* CagA protein in virulence

The *H. pylori* CagA virulence factor is a 120–145 kDa protein encoded by the 40 kb Cag pathogenicity island (PAI) [44]. Approximately 60% of *H. pylori* isolates in Western countries encode the Cag PAI, whereas nearly 100% of East Asian isolates are CagA positive. Individuals infected with bacterial strains carrying the Cag PAI have a stronger gastric inflammatory response, and are at a greater risk of developing gastric cancer, compared with individuals infected with strains lacking the Cag PAI [45]. The Cag PAI encodes a type IV secretion apparatus that delivers the CagA protein into gastric epithelial cells [46]. Intracellular CagA disrupts the actin cytoskeleton, modifies cell-cell adhesion, alters cell polarity, and deregulates intracellular signaling pathways [47]. Some of these effects are mediated as a result of c-Src- or Abl-dependent CagA phosphorylation at a COOH-terminal -E-P-I-Y-A- repetitive amino acid sequence, leading to activation of the SHP-2 protein tyrosine phosphatase.

CagA positive strains of *H. pylori* also have been shown to activate the epidermal growth factor receptor (EGFR) receptor protein tyrosine kinase [48]. Activation of EGFR by *H.*

pylori is associated with altered signal transduction in host epithelial cells that may contribute to bacterial pathogenesis. More specifically, among the intracellular signaling cascades that are affected by CagA is the β-catenin pathway [49–51]. In this regard, binding of β-catenin to the MUC1 CT is regulated by EGFR [26]. Because the IL-8 gene promoter is transcriptionally activated by β-catenin [52], it was hypothesized that up-regulation of MUC1 expression during *H. pylori* infection reduces CagA-dependent β-catenin nuclear localization and concomitant IL-8 production. In support of this hypothesis, we recently reported that *H. pylori*-infected $Muc1^{-/-}$ mice had increased neutrophil infiltration of the gastric mucosa, an IL-8-dependent event, compared with $Muc1^{+/+}$ mice [53]. Further, β-catenin formed protein complexes with both MUC1 and CagA in human AGS cells, and MUC1 over-expression reduced CagA/β-catenin interaction. Finally, over-expression of MUC1 decreased the levels of *H. pylori*-driven nuclear β-catenin in *H. pylori*-infected cells. These combined results suggested that *H. pylori*-dependent IL-8 production, neutrophil infiltration, and stomach inflammation may be reduced by future therapeutic strategies designed to increase MUC1 expression.

10. Attenuation of *H. pylori* gastric inflammation by MUC1 and PPARγ

In addition to MUC1, interleukin-10, transforming growth factor-β, and peroxisome proliferator-associated receptor γ (PPARγ) have been identified as anti-inflammatory mediators in the gastric mucosa [54,55]. PPARs comprise a family of ligand-activated transcription factors, PPARα, β, and γ [56]. Following engagement by endogenous (free fatty acids and eicosanoids) or synthetic (thiazolidinediones) ligands, PPARs translocate to the nucleus where they heterodimerize with retinoid X receptors and transcriptionally activate gene expression. PPARs regulate multiple cellular processes, including glucose metabolism, cell differentiation, carcinogenesis, and inflammation [57]. Because activation of PPARγ is known to suppress gastric inflammatory responses to *H. pylori* [54], and because the MUC1 promoter contains a PPARγ response element [58], we conducted a series of experiments to investigate the potential role of MUC1 in PPARγ-dependent regulation of *H. pylori*-driven gastric inflammation. Our results demonstrated that treatment of AGS cells with the PPARγ agonist, troglitazone, reduced *H. pylori*-stimulated IL-8 levels in cell culture supernatants, compared with cells treated with *H. pylori* alone [59]. Moreover, following knockdown of MUC1 expression by RNA interference, no differences in IL-8 levels were seen between cells treated with troglitazone plus *H. pylori* versus cells treated with *H. pylori* alone. Finally, PPARγ was shown to bind to the MUC1 gene promoter in AGS cells, and troglitazone treatment increased MUC1 promoter activity and augmented MUC1 protein levels compared with vehicle controls. These combined results suggested that PPARγ stimulated MUC1 expression by AGS cells, thereby attenuating *H. pylori*-induced IL-8 production and gastric inflammatory responses.

11. Summary

Chronic inflammation of the gastric mucosa is a serious public health problem worldwide. The principal association of gastritis is with stomach infection by *H. pylori*. Yet, the majority of individuals colonized by *H. pylori* fail to progress from low-grade gastric inflammation to peptic ulcer disease and adenocarcinoma. On the basis of the studies reviewed herein, a mechanistic hypothesis to explain why a subset of *H. pylori*-infected patients develops the more clinically serious stomach pathologies can now be proposed. Specifically, as summarized in Fig. 4, evidence is presented that details the multiple pathways through which MUC1 mucin counter-regulates gastric inflammatory responses. We hypothesize that a defect in the anti-inflammatory activity of MUC1 mucin results in a heightened, persistent state of *H. pylori*-driven gastritis that creates a self-perpetuating, auto-amplifying, proinflammatory environment and ultimately promoting carcinogenesis. We

hope that this review article will serve as an impetus for future studies directed at addressing this possible mechanism.

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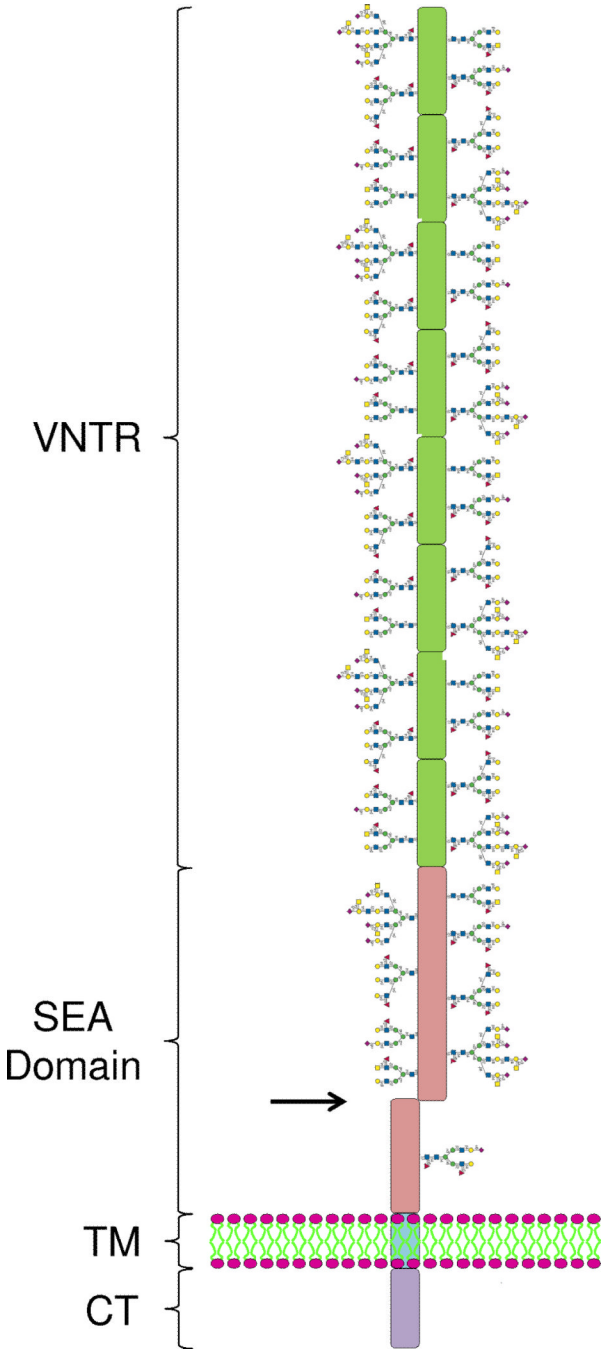

Figure 1.
Schematic structure of the MUC1 mucin glycoprotein. The extracellular region consists of a variable number of tandem repeats (VNTR) and the sea urchin sperm protein, enterokinase and agrin (SEA) domain, both of which contain numerous glycan side chains. Autocatalytic proteolysis within the SEA domain (arrow) creates the noncovalently-associated, heterodimeric structure. Distal to the SEA domain is a single-pass transmembrane (TM) region, and an intracellular cytoplasmic tail (CT) region.

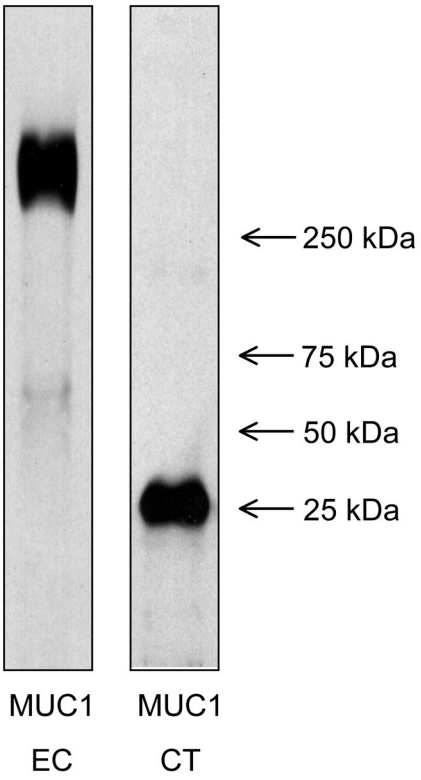

Figure 2.
Heterodimeric structure of MUC1 mucin glycoprotein. A detergent lysate of AGS human gastric epithelial cells was resolved on denaturing SDS-PAGE gels to separate the large molecular weight MUC1 extracellular (EC) region and the smaller cytoplasmic tail (CT) region. The separated proteins were probed on immunoblots with antibodies specific for the MUC1 EC and CT regions.

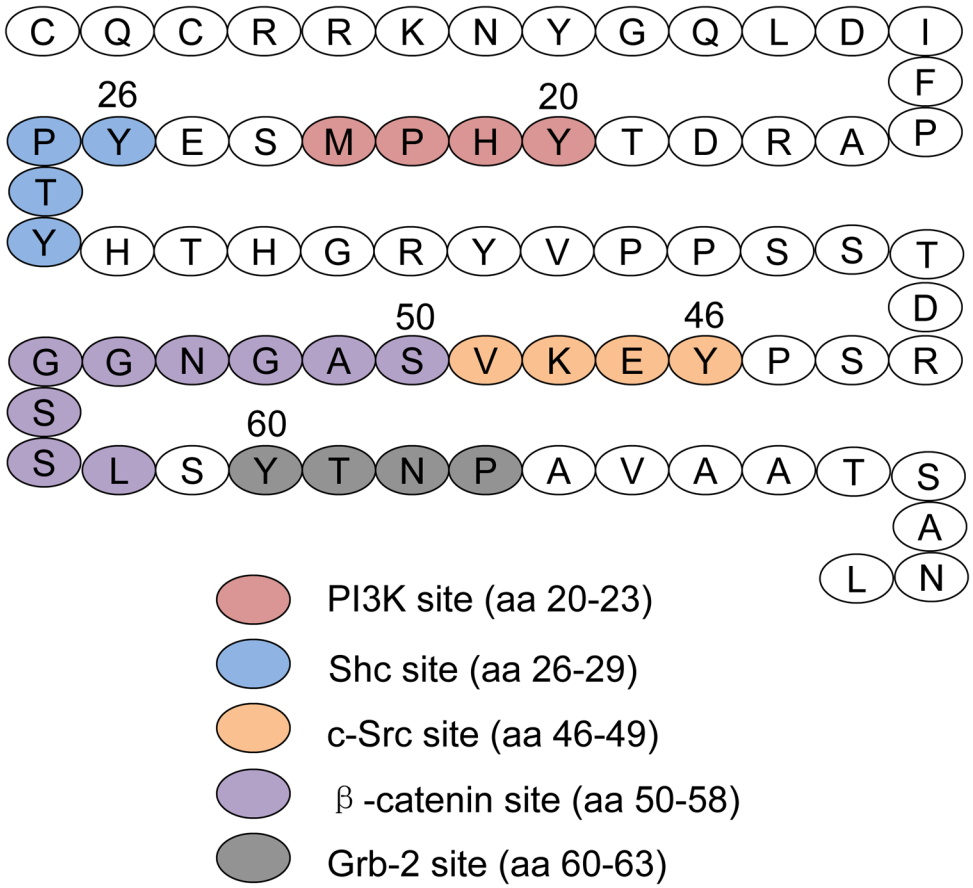

Figure 3.
Schematic structure of the MUC1 CT. The 72-amino acid (aa) CT contains binding sites for PI3K, Shc, c-Src, β-catenin, and Grb-2.

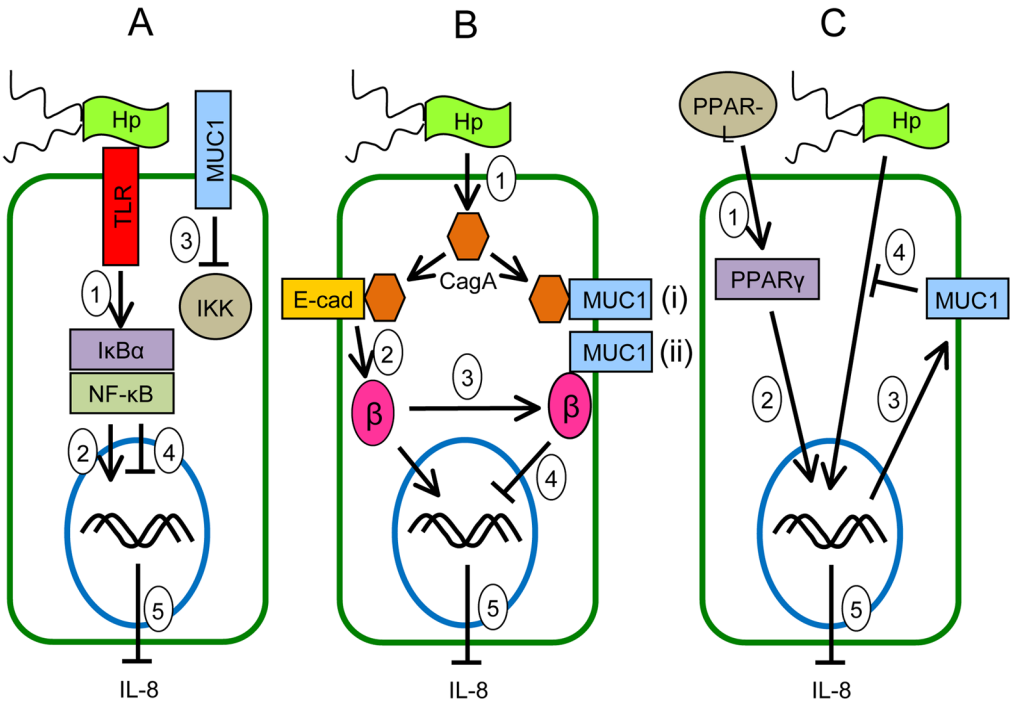

Figure 4.

Schematic illustration depicting the possible molecular mechanisms of the anti-inflammatory activities of MUC1 in gastric epithelial cells during *H. pylori* infection. (A) Inhibition of NF-κB signaling: *H. pylori* binds to cell surface receptors (e.g. Toll-like receptors, TLRs) that activate NF-κB following phosphorylation of IκBα by IKK (step 1). NF-κB enters the nucleus to activate proinflammatory (IL-8) gene expression (step 2). MUC1 blocks the ability of IKK to phosphorylate IκBα (step 3), thus inhibiting NF-κB nuclear translocation (step 4) and blocking IL-8 production (step 5). (B) Inhibition of β-catenin signaling: *H. pylori* delivers CagA into the cytosol (step 1). CagA binds to E-cadherin (step 2), thereby releasing β-catenin that translocates into the nucleus to activate proinflammatory (IL-8) gene expression. MUC1 binds to β-catenin (step 3) released by CagA, thus inhibiting its nuclear translocation (step 4) and blocking IL-8 production (step 5). (C) PPARγ-dependent inhibition: Endogenous PPAR-γ ligands (PPAR-L) activate PPARγ (step 1). PPARγ enters the nucleus (step 2) to activate MUC1 gene expression (step 3). MUC1 protein inhibits the *H. pylori*-driven NF-κB and/or β-catenin pathways (step 4), thus blocking IL-8 production (step 5).