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REVIEW

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KEY WORDS: *Helicobacter pylori; immune response; virulence factors; peptic ulcer; stomach cancer*

List of Abbreviations
AP-1 = activator protein 1
BabA = blood group antigen-binding A
cag = cytotoxin associated genes
cag-PAI = cag pathogenicity island (a foreign DNA region in Hp)
cAMP = cyclic adenosine monophosphate
CARD4 = Caspase-activating domain 4
CpG = (DNA molecules that contain a) cytosine "C" followed by a guanine "G" dinucleotide ("p" refers to the phosphodiester backbone of DNA)
CREB-1 = cAMP response element-binding protein 1
FOXP3 = forkhead box P3 protein
GECs = gastric epithelial cells
Hops = helicobacter outer membrane proteins
Hp = Helicobacter pylori
HSP = heat shock protein
IFN-γ = interferon gamma
IL = interleukin
LPS = lipopolysaccharide
MALT = mucosa-associated lymphoid tissue
NF-κB = nuclear factor kappa-light-chain-enhancer of activated B cells
Nod = nucleotide-binding oligomerization domain
OipA = outmembrane inflammatory protein A
PAMPs = pathogen-associated molecular patterns
SabA&B = sialic acid-binding adhesin A&B
Th1 = T helper cell type 1
TLR = Toll-like receptor
TNF = tumor necrosis factor
Treg = regulatory T cell
VacA = vacuolating toxin A

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Pathogenesis of Helicobacter Pylori Infection: Colonization, Virulence Factors of the Bacterium and Immune and Non-immune Host Response

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ABSTRACT

Helicobacter pylori (Hp), a gram-negative, spiral-shaped bacterium is one of the most widely spread pathogens in humans, as it concerns half of the world population. Mechanisms that allow Hp to cause a life-long infection involve modulation of the immune response and host cellular processes which include activation of the innate immune response, resistance to phagocytosis, modulation of dendritic cell activity and regulatory T cells, and production of proinflammatory cytokines. This is accomplished via virulence factors such as colonization factors (a variety of adhesins), factors that allow it to evade host defence (flagella and motility, urease system, induction of hypochlorhydria) and factors that are responsible for tissue injury (heat shock proteins A and B, vacuolating cytotoxin A, neutrophil activating protein of Hp, and cytotoxin-associated gene A). The interaction between bacterial effectors, environmental factors (genetic susceptibility to infection) and factors that modulate the host's response, such as polymorphisms in genes encoding cytokines or cytokine receptors, have been shown to influence the clinical outcome of Hp infection either towards peptic ulcer and/or cancer. Future studies, directed toward understanding interactions between Hp and immune cells in vivo, may lead to the development of novel therapeutic approaches for eradication of Hp.

INTRODUCTION

Helicobacter pylori (Hp) is a gram-negative, spiral-shaped pathogenic bacterium that colonizes the gastric epithelium and causes chronic gastritis, peptic ulcer and/or gastric malignancies including mucosa-associated lymphoid tissue (MALT) lymphomas, while most infected people remain asymptomatic.[1] These diseases are determined by the relationship between virulence factors of bacteria, host factors such as genetic predisposition and immune response.[1,2] Regarding genetic predisposition, polymorphism in the promoter region of interleukin (IL)-1 and IL-8 receptor have been associated with an increased incidence of atrophic gastritis and gastric cancer.[3,4] Prevalence among adults is 70–90% in many developing countries and 25-50% in industrialized countries.[5]

After entering the stomach, Hp evades host defence, immunity and gastric mucosa, via virulence colonization and other factors (Table 1), including urease activity, motility mediated by the flagella, adhesins, membrane engraftment of cholesterol, vacuolating toxin A (VacA)-induced T-cell suppression, and metal acquisition proteins[6-8].

After disruption of epithelial cell junctions, the bacteria can pass through the gastric wall facing direct immune response from neutrophils, lymphocytes, mast cells and dendritic cells.[9-12] The innate immune response is mainly represented by Toll-like receptors (TLR) and nucleotide-binding oligomerization domain (Nod)-like receptors, that recognize their specific ligands, activate transcription factors such as nuclear factor kappa-light-chain-enhancer of activated B cells (NF-ϰB), activator protein 1 (AP-1), cyclic adenosine monophosphate (cAMP) response element-binding protein 1 (CREB-1), and induce production of inflammatory cytokines such as IL -8, IL-12, IL-6, IL-1β, IL-18, tumor-necrosis factor-α (TNF-α) and IL-10.[13-16] Interleukin-1β and TNF-α, which are produced locally in the gastric mucosa, are potent inhibitors of gastric acid secretion.[17]

TABLE 1. Helicobacter pylori (Hp) related virulence factors and relation to disease

Factors	Role	Disease	Ref
CagA	entry to GECs via type IV secretion system phosphorylation & binding to SHP-2 gastric cytokine production (IL-8) glycan biosynthesis in GECs	↑ risk for developing peptic ulcer or gastric cancer in Western populations 50 to 70% (+) of Hp strains	18,19
VacA	depolarization of the membrane induction of apoptosis inhibition of T-lymphocyte activation disruption of endosomal & lysosomal activity	50% (+) of Hp strains ↑ risk of peptic ulcer or gastric cancer in Western countries, Latin America, Middle East.	20-22
LPS	structural homology with Lewis blood group antigens X & Y stimulation of release of cytokines (lymphotoxin a, CCL19 and CCL21)		23,24
BabA (HopS)	adhesion to GECs	↑ risk of peptic ulcer and gastric adenocarcinoma	25-27
SabA & B (HopP)	adhesion to GECs activation of neutrophils	↑ risk of gastric cancer, intestinal metaplasia, corpus atrophy	26,28
HspA & B	adhesion to GECs	↑ risk of MALT lymphoma	29
AlpA & B	Adhesion to GECs and cytokine production		26,29
OipA (HopH)	Adhesion to GECs ↑ IL-8 expression	↑ risk of duodenal ulcers and gastric cancer	26,30,31
IceA	encodes a restriction endonuclease	↑ risk of peptic ulcer	32,33
DupA	↑ IL-8 production	↑ risk of duodenal ulcers ↓ risk for cancer	34,35
NapA	neutrophil recruitment & production of ROS upregulation of IL-12, IL-23, TNF-a, IFN-γ		36-38

Alp = alkaline phosphatase; Bab = blood group antigen-binding; Cag = cytotoxin-associated antigen; CCL = cytosine-cytosine ligand (protein); Dup = duodenal ulcer perforation; GECs = gastric epithelial cells, Hop = Helicobacter outer membrane porins; Hp = Helicobacter pylori; HSPs = heat shock proteins; Ice = IL-1beta-converting enzyme; IFN = interferon; IL = interleukin; LPS = lipopolysaccharide; MALT = mucosa associated lymphoid tissue; Nap = neutrophil-activating protein; Oip = outmembrane inflammatory protein; Ref = references; ROS = reactive oxygen species; SabA = sialic acid-binding adhesin A; SHP = Src homology 2 domain-containing tyrosine phosphatise; TNF = tumor necrosis factor; Vac = vacuolating toxin.

HELICOBACTER PYLORI RELATED VIRULENCE AND COLONIZATION FACTORS

FLAGELLA AND MOTILITY

Helicobacter pylori has been shown to require flagella for infection of the stomach. Flagella allow the bacterium to swim across the viscous gastric mucus and reach the more neutral pH below the mucus.[7]

UREASE SYSTEM

Helicobacter pylori synthesizes urease constitutively. As urease hydrolyses urea to form ammonia and carbon dioxide, and ammonia can absorb acid to form ammonium, it is natural to suspect that this dedication to make urease has a relation to survival and growth in the acidic environment of human stomach. There are data showing that the organisms do buffer their periplasm that lies between their inner and outer membrane, in acidic pH, using their intrabacterial urease activity.[8]

ADHESINS

Adhesins, such as blood group antigen-binding A (BabA), sialic acid-binding adhesin A&B (SabA&B) and outmembrane inflammatory protein A (OipA), which are helicobacter outer membrane proteins (Hops), enhance adhesion with gastric epithelial cells (GECs) by recognizing specific carbohydrate structures, such as the Lewis b blood group antigen and glycolipids having sialyl dimeric Lewis X, while other virulence factors facilitate Hp colonization and proliferation (Table 1).

IMMUNE AND NON IMMUNE RESPONSE OF HOST CELLULAR PROCESSES

ANTIBACTERIAL PROPERTIES OF THE HUMAN STOMACH

The gastric epithelial layer constitutes a physical barrier that prevents entry of bacteria into the gastric mucosa. One of the most important antibacterial properties of the human stomach is its acidic pH, while multiple factors produced by the gastric mucosa such as antibacterial peptides are obstacles for Hp colonization and proliferation.[39-41] In particular the antibacterial peptides produced by the gastric mucosa, β-defensins and lactoferrin, inhibit bacterial growth by restricting the availability of extracellular iron.[39-41]

ACUTE INFECTION

Gastric biopsies performed 2 weeks after infection showed infiltration of lymphocytes and monocytes, along with significantly increased expression of IL-1β, IL-8, and IL-6 in the gastric antrum.[9] Four weeks after infection, the numbers of gastric CD4+ and CD8+ T cells seem to increase compared to pre-infection levels, indicating the development of an early adaptive immune response.[10] Either innate immune responses to Hp or early adaptive immune responses could account for the gastric mucosal inflammatory responses and symptoms that accompany acute infection (Fig. 1).

CHRONIC INFECTION

Gastric mucosal biopsies from humans who are persistently infected with Hp revealed an increased concentration of various types of leukocytes such as lymphocytes (both T cells and B cells), macrophages, neutrophils, mast cells and dendritic cells, compared to biopsies from uninfected humans, causing an inflammatory response called "chronic superficial gastritis".[11,12] Moreover, CD4+ T cells are typically more abundant than CD8+ T cells[42,43], while T regulatory cells expressing forkhead box P3 protein (FOXP3) are usually present in higher numbers playing an important role in regulating the inflammatory response.[42] Various cell types, including B cells and CD4+ cells, sometimes organize into lymphoid follicles. The chronic gastric mucosal inflammatory response to Hp probably reflects the combined effects of a cellular immune response and an ongoing stimulation of an innate immune response associated with strong IL-12 production leading to a T helper cell type 1 (Th1)-polarized response.[44,45] Levels of numerous cytokines, including IFN-γ, TNF, IL-1β, IL-6, IL-7, IL-8, IL-10, and IL-18, are increased in the stomachs of Hp infected humans compared to uninfected humans.[14-16] Helicobacter pylori infection always results in a strong immune response of the host against the infecting strain, but this response seldom (if ever) results in clearance of the infection.

ACTIVATION OF THE INNATE IMMUNE RESPONSE

Toll-like receptors recognize conserved microbial components, termed "pathogen-associated molecular patterns" (PAMPs), and play an important role in initiating innate immune responses to bacterial pathogens including Hp. Among the TLRs that recognize gram-negative bacteria, some of the most extensively characterized include TLR2 (which recognizes lipoproteins), TLR4 [gram-negative lipopolysaccharide (LPS)], TLR5 (flagellin), and TLR9 (bacterial CpG DNA motifs).[23,24] Gastric epithelial cells (GECs) in the antrum and the corpus of the human stomach are reported to express TLR4, TLR5, and TLR9.[46] Although TLR4 is involved in the induction of an immune response against Hp[47], TLR2 and TLR5, rather than TLR4, seem to be the predominant receptors for Hp antigen-induced NF-kB activation and chemokine expression in the GECs.[48-51] However, compared to other gram-negative bacterial antigens, TLRs seem to play only a minor role in the induction of the innate immune response against Hp.[52,53] After activation of TLRs, dendritic cells, in turn, activate T cells in different ways, being capable of inducing either a Th1 or Th2/regulatory T cell (Treg) response by generation of IL-12 or IL-10, respectively (Fig. 1).[54-56] Toll-like receptors' independent mechanisms seem to predominate in

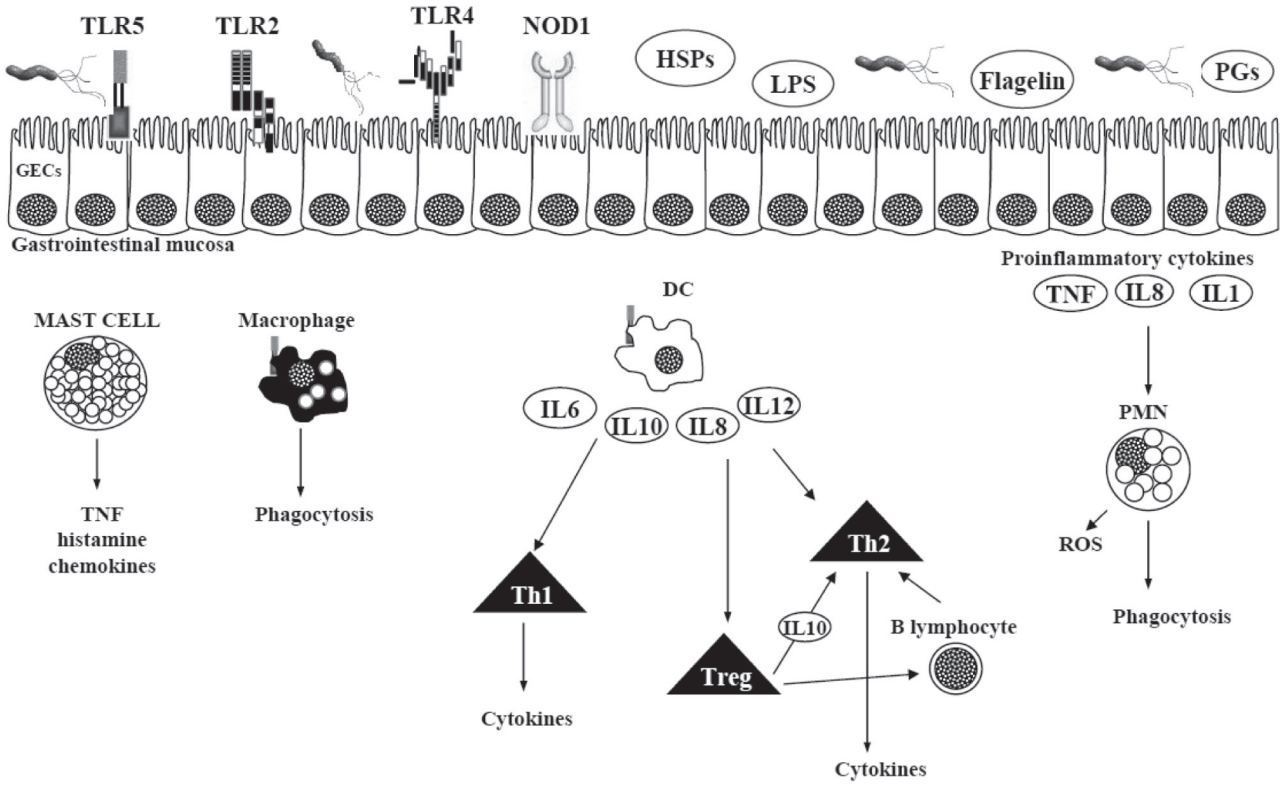

FIGURE 1. Innate and adaptive immune response against Helicobacter pylori. Innate immune recognition of Helicobacter pylori (Hp), mediated in part through Toll like receptors (TLRs) such as TLR2, TLR4, TLR5, and TLR9, leads to the production of proinflammatory cytokines by macrophages, dendritic cells (DCs), mast cells and gastric epithelial cells (GECs). In addition, Hp peptidoglycan (PG) can be recognized by intracellular nucleotide-binding oligomerization domain (NOD) receptors such as NOD1. Production of interleukin 8 (IL-8) by GECs leads to recruitment of neutrophils (polymorphonuclear leukocytes [PMNs]), which can phagocytose opsonized bacteria and produce reactive oxygen species (ROS). Direct interactions between Hp and GECs or Hp constituents can also activate polymorphonuclear (PMN) cells and/or macrophages, which further amplifies the T-cell response to this pathogen. Dendritic cells can penetrate the epithelial barrier in vivo and sample Hp antigens directly, leading to an activation of T cells in different ways, being capable of inducing either a T helper 1 (Th1), or a Th2/regulatory T cell (Treg), response by generation of IL-12 or IL-10, respectively. The activation of mast cells results in degranulation and production of proinflammatory cytokines and chemokines.

the activation of the innate response against Hp. For example the recognition of the bacterial heat shock protein (Hsp) 60 is not mediated via these TLRs.[57] The intracellular peptidoglycan, transferred into the cytoplasm by cag (cytotoxin associated genes) pathogenicity island (cag-PAI)-mediated contact between the epithelial cell and the bacterium, may be a key activator of the innate response against Hp. This intracellular peptidoglycan is recognized by Nod1, a member of the recently discovered Nod family also known as CARD4 (Caspase-activating domain 4) and such recognition probably contributes to initiation of an innate immune response in vivo.[58]

Helicobacter pylori has recently been shown to decrease production of specific heat shock proteins (HSPs) in vitro and within colonized gastric mucosa.[59] Since HSPs can modulate both innate and adaptive immune responses, inhibition of HSP production may represent an additional mechanism of immune evasion that promotes long-term colonization. Helicobacter pylori also has the capacity to use cholesterol from its host and incorporate this into its membrane which could facilitate molecular mimicry.[60] Moreover, Hp is capable of inhibiting phagocytosis by macrophages resulting not only in reduced anti-Hp activity of the macrophages but more importantly in decreased and altered processing of Hp antigens by activated macrophages.[57,61-64]

CONCLUSION

Helicobacter pylori (Hp) is one of the most widely spread pathogens in humans. Mechanisms that allow Hp to cause a life-long infection involve modulation of the immune response and host cellular processes. The interaction between bacterial

effectors, environmental factors and factors that modulate the host's response, have been shown to influence the clinical outcome of Hp infection either towards peptic ulcer and/or cancer.[66] Future studies directed toward understanding interactions between Hp and immune cells in vivo may lead to the development of novel therapeutic approaches for eradication of Hp.

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