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Review

Host genetic factors respond to pathogenic step-specific virulence factors of *Helicobacter pylori* in gastric carcinogenesis

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ABSTRACT

The interindividual differences in risk of *Helicobacter pylori* (*H. pylori*)-associated gastric cancer involve significant heterogeneities of both host genetics and *H. pylori* strains. Several recent studies proposed a distinct sequence for *H. pylori* exerting its virulence in the host stomach: (i) adhering to and colonizing the surface of gastric epithelial cells, (ii) evading and attenuating the host defense, and (iii) invading and damaging the gastric mucosa. This review focuses on several key issues that still need to be clarified, such as which virulence factors of *H. pylori* are involved in the three pathogenic steps, which host genes respond to the step-specific virulence factors, and whether and/or how the corresponding host genetic variations influence the risk of gastric carcinogenesis. Urease, BabA and SabA in the adhesion-step, PGN and LPS in the immune evasion-step, and CagA, VacA and Tipα in the mucosal damage-step were documented to play an important role in step-specific pathogenicity of *H. pylori* infection. There is evidence further supporting a role of potentially functional polymorphisms of host genes directly responding to these pathogenic step-specific virulence factors in the susceptibility of gastric carcinogenesis, especially for urease-interacting *HLA* class II genes, BabA-interacting *MUC1*, PGN-interacting *NOD1*, LPS-interacting *TLR4*, and CagA-interacting *PTPN11* and *CDH1*. With the continuous improvement of understanding the genetic profile of *H. pylori*-associated gastric carcinogenesis, a person at increased risk for gastric cancer may benefit from several aspects of efforts: (i) prevent *H. pylori* infection with a vaccine targeting certain step-specific virulence factor; (ii) eradicate *H. pylori* infection by blocking step-specific psychopathological characteristics of virulence factors; and (iii) adjust host physiological function to resist the carcinogenic role of step-specific virulence factors or interrupt the cellular signal transduction of the interplay between *H. pylori* and host in each pathogenic step, especially for the subjects with precancerous lesions in the stomach.

Contents

Abbreviations: BabA, blood-group antigen binding adhesion A; CagA, cytotoxin-associated antigen A; cagPAI, cag pathogenicity island; CD74, HLA II-associated invariant chain; CLR, C-type lectin receptor; IL, interleukin; FUT4, fucosyltransferase 4; HLA II, human leukocyte antigen class II molecule; *H. pylori*, *Helicobacter pylori*; iE-DAP, γ-D-glutamyl-meso-diaminopimelic acid; Le^b, Lewis b; Le^x, Lewis x; LPS, lipopolysaccharide; LRR, leucine-rich repeats; MUC, mucin; NCL, nucleolin; NLR, NOD-like receptors; NOD1, nucleotide binding oligomerization domain containing protein 1; PAMP, pathogen-associated molecular pattern; PGN, peptidoglycan; PRR, pattern recognition receptors; PTPN11, protein-tyrosine phosphatase, nonreceptor-type 11; RLR, RIG-like receptors; RPTP, receptor-like protein tyrosine phosphatase; SabA, sialic acid-binding adhesion A; Tipα, TNF-α inducing protein; T4SS, type IV secretion system; TNF-α, inducing protein; TLR, Toll-like receptor; VacA, vacuolating cytotoxin; VNTR, variable number tandem repeat.

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1. Introduction

Stomach carcinogenesis involves independent and/or combined effects of host genetics and *Helicobacter pylori* (*H. pylori*) infection. The variability of host response to *H. pylori* with specific virulence may determine the divergent clinical outcomes of *H. pylori* infection [1,2]. *H. pylori* uses a set of secreted and translocated proteins as virulence factors to mediate its pathogenicity in the host stomach [3,4]. Several recent studies revealed that at least three distinct and sequential steps are required for *H. pylori* to exert its virulence on the colonized stomach: (i) adhering to and colonizing the surface of gastric epithelial cells, (ii) evading and attenuating the host defense, and (iii) invading and damaging the gastric mucosa [5,6]. It is beginning to emerge that the joint effects of *H. pylori* virulence factors and the corresponding gastric epithelial receptors in each pathogenic step may demonstrate a set of step-characteristic abnormalities that could partially explain why cancer occurs. Which virulence factors are involved in the three pathogenic steps (see Table 1), which host genes respond to the step-specific virulence factors (see Table 2), and whether and/or how the corresponding host genetic variations influence the risk of gastric carcinogenesis are the main questions addressed in this review (see Table 3). With the deepening clarification of these issues, *H. pylori* infection may be effectively prevented and/or eradicated by blocking step-specific physiopathological characteristics of virulence factors in the host. Furthermore, personalized prevention of *H. pylori*-associated gastric cancer may also be achieved by adjusting the host physiological function to resist the pathogenic effect of virulence factors in each step and/or directly by interrupting the step-specific carcinogenic role of *H. pylori*.

2. Adherence- and colonization-step virulence factors and their interacting host genes

Adhering to and colonizing gastric epithelial cells is the initial and indispensable step for *H. pylori* to induce cancer, although this step is not sufficient to cause cancer, per se. Adaptation of *H. pylori* to the hostile environment of the host's stomach relies on a set of proteins including secreted extracellular enzymes and outer membrane adhesins, of which urease, BabA (blood-group antigen binding adhesion), and SabA (sialic acid-binding adhesion) are the most prominent pathogenicity factors with known receptors in the host gastric epithelium (Fig. 1).

2.1. H. pylori-*urease interacting host* HLA *(human leukocyte antigen) class II genes*

The release of abundant urease from *H. pylori* into the stomach lumen is a crucial trait that promptly protects the bacterium from lethal gastric acidity, and adapts the microbe to the continuously changing mucous layer [7,8]. The two distinct subunits of urease (urease A and urease B) interact with host HLA class II molecules and CD74 (alternatively named HLA II-associated invariant chain), respectively, on gastric epithelial cells [9,10]. HLA class II molecules are well-known as the key signaling molecules in the regulation of specific immune response by presenting foreign antigenic peptides to CD4+ T cells, while CD74 plays a coordinated role in this antigen processing.

The genes encoding for HLA class II molecules, *HLA-DP*, *HLA-DQ*, and *HLA-DR*, are the most genetically variable coding loci in the human genome. Over 100 variant alleles have been detected in these three loci in humans. Several studies have shown associations of specific HLA class II alleles with the risks of gastric cancer and *H. pylori* infection. The *HLA-DQB1*0301* allele is one of the frequently reported alleles, but its association with gastric cancer or *H. pylori* infection risk has proved to be inconsistent [11–13]. For example, a positive association of **0301* with gastric cancer was first reported by Lee et al. in a study of Caucasians [11], but this association was not replicated in a subsequent study in Japanese patients [12]. Paradoxically, the study of Wu et al. demonstrated an inverse correlation of this allele with gastric cancer in a Taiwanese population [13]. Nevertheless, the presence of the *HLA-DQB1*0301* allele was consistently reported to be associated with lower seropositivity of *H. pylori* infection [11,13]. In addition, the **0401* and **0602* alleles of *HLA-DQB1* have been linked with increased risk of *H. pylori* infection and gastric cancer in European or Indonesian populations [14,15], and *HLA-DQA1*0102* was associated with lower risk of *H. pylori* infection, atrophy, and carcinoma in Swedish and Japanese [16,17]. Studies also showed positive relationships between *HLA-DRB1*0404*, **0405*, and **1601* alleles with gastric cancer development in Korean and Japanese [16,18,19]. A previous study by our research group investigated *HLA-DPB1* polymorphisms in Chinese populations at high- and low-risk of gastric cancer but found no statistical association of any *HLA-DPB1* allele with gastric cancer or *H. pylori* infection [20]. Currently, no *HLA-DP* allele has been linked with susceptibility to gastric cancer [12,20].

Significantly increased expression of HLA II molecules in *H. pylori*-infected gastric mucosa tissue not only functions as an anchoring point for *H. pylori* in the host [21,22], but also plays an indispensable role in the induction of epithelial cell apoptosis triggered by the urease released by *H. pylori* [9,23]. Immunization of mice with a urease vaccine revealed that HLA class II restrictive immunity determined the protection of vaccinated mice against *H. pylori* [24]. In spite of no apparent difference of binding ability of urease to different alleles of *HLA-DQ* and *HLA-DR*, reported by Fan et al. [9], this experiment was conducted in B cell lines, which cannot preclude the biological effects of *HLA-DQ* and *HLA-DR* alleles in gastric epithelial cells or in humans. Together, the available information indicates that the variant alleles in different members of the *HLA II* genes may play an important role in

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