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A Comprehensive Review on Helicobacter pylori Infection and Gastric Cancer

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Abstract

Background: The Helicobacter pylori (H. pylori) is a spiral-shaped, gram-negative, motile and microaerophilic bacterium in which the human stomach is the single natural reservoir.
Objectives: This review study indicates the possible contribution of H. pylori infection as one of the recognized vital agents for the development of gastric malignancies.
Methods: Journal online databases such as Science Direct, PubMed, Google Scholar, and Wiley Online Library were investigated through keywords "Helicobacter pylori", "Gastric Malignancy", "Gene therapy" and "Nanotechnology". Studies were subjected to the present review study if they met our relevance and quality criteria.
Results: We will discuss different virulence elements of H. pylori comprising cytotoxin-related gene A, vacuolating cytotoxin A, as well as various outer membrane proteins leading to malignancy through various mechanisms.
Conclusions: We also provide insight into the possible presence and role of a gastric malignancy stem cell in the tumors with the capability to initiate sustain self-renewal and tumor growth and novel strategies against H. pylori such as gene therapy, immunotherapy, immunoinformatics, antibiotic resistance, and nanotechnology aimed to provide a rationale view for new therapeutic approaches that are reviewed in the current study.

Keywords: Gastric Malignancy, Helicobacter pylori, immunoinformatics, Gene therapy, nanotechnology

1. Background

Gastric malignancies caused over 8.2% of all malignancy mortality in the world and Helicobacter pylori led to more than 60% of gastric malignancies, moreover, H. pylori was categorized by the World Health Organization (WHO) as a group1 carcinogen [1, 2]. H. pylori is a spiral-shaped, gram-negative, motile, and microaerophilic bacterium in which the human stomach is the single natural reservoir [4, 5]. It can be recognized by a fast urease test, serological test, histological analysis of biopsy samples, and polymerase chain reaction method. The person-to-person transmission of the bacterium occurs within the fecal-oral or oral-oral route [3, 6]. It is approximated that fifty percent of the human societies in the worldwide is colonized chronically with gastric ulcers, and H. pylori are developed in almost fifteen percent of infected people. Nevertheless, even for the asymptomatic infection, H. pylori infection can result in gastric malignancy and peptic ulcers [7, 8]. According to epidemiological studies, gastric adenocarcinoma is developed in 2 to 3% of H. pylori-infected people, and MALT (mucosa-associated lymphoid tissue) lymphoma is developed in 0.1% [9, 10]. H. pylori enter the gastric mucosa by flagella, in which the bacteria are protected by the mucus layer from the stomach's lower pH [11]. Over twenty percent of the H. pylori strains follow the gastric epithelium cells' surface [12]. H. pylori attached to the gastric epithelium cells via adhesion factors including the adherence-associated lipoproteins (AlpA/B), the blood group antigen-binding adhesin (BabA), sialic acid-binding adhesion (SabA), and outer inflammatory protein A (OipA) [13].

2. Evidence acquisition

Journal online databases such as Science Direct, PubMed, Google Scholar, and Wiley Online Library were investigated through keywords "Helicobacter pylori", "Gastric Malignancy",

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"Gene therapy" and "Nanotechnology". Studies were subjected to the present review study if they met our relevance and quality criteria.

3. Results

3.1. Prevalence of H. pylori infection in pediatrics

H. pylori infection can happen in primary childhood and usually persist for life if left untreated [14, 15]. The situation of H. pylori infection in pediatrics in contrast to mature is not quite discovered because most of them still remain asymptomatic and research is restricted. The diagnostic variety of H. pylori may involve in changeable infection rates in children [16]. The rate of H. pylori infection has decreased in countries which are developed but a calculated totally 33% of healthful or asymptomatic pediatrics were still positive serological in the global [14]. Moreover, high rates of infection include 25.8%, 65.9%, and 40.4% were registered in Nigeria [17], Venezuela [18] and Iran [19], respectively. Among prevalence of symptomatic children assessment in H. pylori infection is significantly different, 3%–76% among diagnostic methods and countries, and the overall universal approximate was 39% [14]. The rates of H. pylori discovery in symptomatic pediatric were usually some higher than those in asymptomatic pediatric. H. pylori seemed to be less usual in pediatric than in mature, exclusively in pediatric of North America, Japan, and Northern Europe. However, it seemed to be more prevalent in pediatric of Asia and South America. On the other hand, the less outbreak amongst youthful persons globally may propose a further decline in the H. pylori infection prevalence and related diseases in the future [20]. An overview in Korea demonstrated that the rate of H. pylori elimination therapy expansed and the rate of sero-positivity among mature decrease oppositely during the past 18 years [21]. With all these descriptions, H. pylori management strategies can help significantly reduce the rate of infection in pediatrics.

3.2. Helicobacter pylori virulence factors

The H. pylori virulence factors implicated in developing gastric malignancy could fall into 3 major classifications such as outer membrane proteins (OMPs), vacuolating cytotoxin A (VacA), and cytotoxin-associated gene A (CagA) (figure 1).

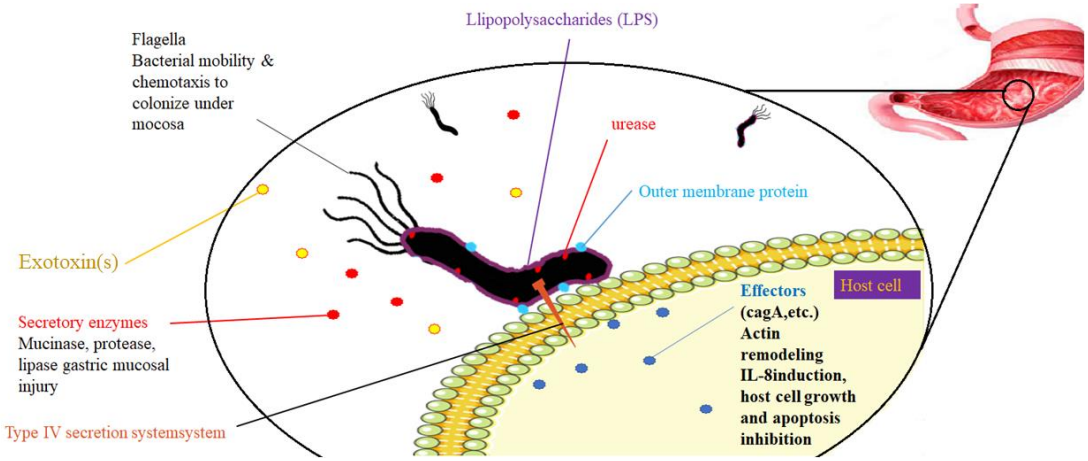

Figure 1. Schematic diagram of H pylori infection and virulence factors

3.2.1. The cag PAI

Among the virulence factors functioning in gastric malignancy is the H. pylori's cag pathogenicity island (cag PAI) [22]. The cag PAI is almost 40 kb DNA insertion element comprising 27 to 31 genes encoding the CagA that making up proteins creating the Cag type IV secretion system (Cag-T4SS) [23]. The CagA is delivered into gastric epithelial cells by Cag-T4SS [24]. CagA can be tyrosine phosphorylated within the host cell, at EPIYA (glutamate-proline-isoleucine-tyrosine-alanine) motifs via host Src/Abl tyrosine kinases [25]. It was reported that phosphorylated CagA interacts with the Src homology 2 domains of SHP2 (Csk (c-terminal Srckinase, SH2 domain-comprising protein tyrosine phosphatase), Crk- (kinase CT10 regulator) proteins, and Grb2 (growth factor receptor-bound protein 2) [26]. Phosphorylated CagA attaches to SH2 domain-comprising protein tyrosine phosphatase to activate this protein. By the activated SHP2, the Ras-ErK signaling path activation is induced resulting in the mitogenic responses [27]. Within the nucleus, by phosphorylating ERK, the transcription activator ELK1 is activated [28]. The activated ELK1 accompanied by serum response factor attaches to serum response elements while inducing the immediate expression of pre-genes such as c-Jun and c-Fos [29–31]. The AP-1 (the activator protein-1) transcription factor is made up by c- Jun and c-Fos inducing cell proliferation and late genes

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genes expression [32]. The transcription of cyclin D is activated by the AP-1 transcription factor [33]. The incremented cyclin D-CDK4/6 (cyclin-based kinase) activity leads to the retinoblastoma protein phosphorylation and induces the E2F release from the pRB-E2F complex [34]. By E2F, the cell cycle's S-phase entry is induced via the cyclin E expression [35, 36]. The DNA replication can be initiated by the activated cyclin-E-CDK2 complex phosphorylating minichromosome maintenance helicase at the replication origin [37]. Abnormal cell proliferation is a key feature of cell transformation [38].

3.2.2. The VacA

Secrete vacuolating cytotoxin A (VacA) is isolated by all H. pylori via the type V secretion system [39]. First, the VacA is created as a 140 kDa protein forming the mature 88 kDa protein comprising p55 (55 kDa) and p33 (33 kDa) followed by a two-step proteolytic cleavage [40]. This protein's p33 domain creates a channel containing 6 VacA subunits for chloride transport, however, the p55 domain is in charge of the binding protein to cell surface receptors such as the epidermal growth factor, sphingomyelin, receptor protein tyrosine phosphatase, lymphocyte-associated antigen, and fibronectin [41-44]. VacA channels are created in the cytoplasmic membrane. They enter then the endosomes' mitochondria and membrane via endocytotic vesicles [45]. The epithelial cells' tight junction can be separated by VacA protein in gastric mucosa, thus, VacA passes within epithelial cells. VacA imposes different impacts on the host cell such as changes in mitochondrial membrane permeability, cell vacuolization, activation cell signaling, and inhibition of T-lymphocyte proliferation and activation [46]. The VacA-induced vacuoles' membranes carry lysosomes and late endosomes markers; thus, vacuoles induced by VacA are extracted from the endosome-lysosome pathways. It was indicated that the activation of ATPase and the creation of VacA anion channels in endosomal membranes results in osmotic swelling and the formation of the vacuoles from late endosomes [47]. The β-catenin signaling pathways are affected by VacA, thus, they may have contributed to the H. pylori oncogenic potential [48]. By VacA, Akt (protein kinase B) is activated through PI3K (phosphatidylinositol 3-kinase) phosphorylating GSK3β (glycogen synthase kinase 3β) [49]. Two protein kinases known as mammalian target of rapamycin complex 2 or mTORC2 and 3- Phosphoinositide-dependent kinase 1 or PDK1 phosphorylate and activate Akt that bind to PIP3 [50]. The cell survival and proliferation are regulated by GSK-3β withdrawn by Akt phosphorylation [51, 52]. GSK3 is active constitutively under resting circumstances [53]. Lack of the ligand causes β-catenin is phosphorylated by GSK3β in a cytoplasmic complex comprising auxin, β-catenin, and the adenomatous polyposis coli protein [54]. Then, ubiquitinating the phosphorylated β-catenin as well as degrading into the proteasome occur [55]. When existing VacA, inactivating GSK3β results in the β-catenin accumulation in the cytoplasm. The β-catenin enters the nucleus act as a LEF (lymphoid enhancer factor) transcription factor and coactivator TCF (T cell factor) to activate transcription of β-catenin-based genes like cyclin D1 [56]. Overexpressing cyclin D1 is related to malignancies in humans [57].

3.2.3. The outer membrane proteins

Gastric malignancy is associated with 3 H. pylori outer membrane proteins (HopH (OipA), HomB, and HopQ) [58, 59]. The precise OipA (outer inflammatory protein antigen) receptor was not recognized [60]. Phosphorylating the signal transducer and transcription 1 (STAT-1) activator are simulated by OipA of H. pylori [61]. The non-receptor tyrosine kinase is related to the cytokine receptor known as Janus kinase (JAK) phosphorylating the STAT. Such a pathway is termed the cytokine-stimulated JAK/STAT signaling path [62]. A homodimer is created by phosphorylated STAT1 in the cytoplasm, it is then transmitted to the nucleus and attached to interferon γ-activated sequence (GAS) while stimulating the interferon γ-triggered genes expression. The phosphorylation STAT3 is also caused by interferon γ signaling, which binds to the GAS element while inducing the expression of the inflammatory genes [63-65]. Nitrogen species and reactive oxygen are created during inflammation for fighting pathogens, however, DNA is also destroyed by such chemicals, which can start mutations and encourage malignancy in turn [66]. The HopQ outer membrane proteins are attached to CEACAM (carcinoembryonic antigen-associated cell adhesion molecule) existing over the gastric epithelial cell's surface enabling the CagA protein transfer into the cell [67]. The HopQ of H. pylori is the main agent of gastric malignancy which facilitates the CagA protein transfer into the cell [68, 69]. H. pylori attach to the gastric epithelial cell through the outer membrane protein HomB related to gastric malignancy [70, 71].

3.3. Gastric Malignancy Stem Cells

Malignancy stem cells can differentiate and self-renew [72]. The gastric malignancy stem cells (CSCs) attracted a huge deal of interest in the CSC hypothesis extensive context. It first emerged more than 100 years ago when some European pathologists found that tumors contained a heterogeneous combination of partly differentiated cell kinds, similar to numerous normal organs. John et al. first revealed the presence of CSCs. They proved that the hypothesis is mostly true for acute myeloid leukemia in humans. The leukemic stem cell determined as specific markers of CD34+/CD38− can reproduce serially the disease in immune-deficient mice. This is in line with their longevity and self-renewal [73].

3.4. Gene therapy for GC

Gene treatment is a new therapeutic method as an alternative option for successfully treating numerous diseases such as malignancies. The clinical outcomes of GC remain unpromising, regardless of the similarity between Gastric malignancy and other malignancies and the progression in the present treatment modalities. Since the oncogenes extreme activity or tumor suppressor genes inactivation is included in the basic molecular alterations in malignancies, gene therapy includes the wild-kind tumor suppressor function reintroduction to the cells with no functioning that gene. Another approach is to silence oncogenes for augmenting the tumor responses to radiotherapy or chemotherapy, conversing resistance to the toxic properties of these cures. Yuan-Gen Fu et al. (2003) represented caspases-3 with the main role in cell apoptosis, to GC cell line SGC7901 through the eukaryotic expression vector pcDNA/Rev-caspase-3. Followed by conducting antisense therapies in these researches, it was

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indicated that gene therapy utilizing such a vector could considerably encourage the gastric malignancy cell line SGC7901 apoptosis possibly as a potential method to gastric malignancy gene treatment [74, 75].

3.5. Immunotherapy for GC

Approaches for immune therapy could be categorized into 3 main classifications such as targeting pro-malignancy inflammation and depleting immune cells reprogramming within the TAM for increasing anti-malignancy immune reactions. Such strategies often are the most effective when providing therapy as an assistant to the present chemotherapy, however, it was proved that others may be more operative as monotherapy. For instance, anti-VEGF agents present some benefits in combination with chemotherapy, however, they provide less effectiveness as monotherapy. Oppositely, immune checkpoint and immunoconjugates inhibitors appear to offer antitumor activity alone or in combination, while adding chemotherapy does not seem to enhance the results in GC. Furthermore, as a result of the reported microenvironments, diversity (gastritis to the tumor) and the potential targets array, tumor characterization, and immune subtyping are vital for the field for moving toward more effective immune-therapies for treating the individuals at risk of GC or treating present malignancy. Ultimately, the drug development procedure such as academia and pharma should be concentrated on identifying representative biomarkers in GC and designing clinical trials with enhanced populations. Hence, we can present GC patients' treatments making a considerable difference in their lives [76, 77]. For example, inhibitory checkpoints including Programmed cell Death-Ligand 1 are a group of molecular mechanisms, which can down-regulate immune responses, thus, they have a key role in the persistence of tumors and chronic infections. PD-L1 is an immune inhibitory checkpoint expressed on T-cells. It was shown that activation of the PD-1 signaling path via PD-L1 dampens T-cells activity. This is vital to keep peripheral tolerance and avoid excessive damage to tissues in removing an infection event when balancing with the co-stimulatory signals. H. pylori infection persistence was related to less responsive T-cells and, however, other mechanisms were presented, PD-L1 expression, choosing a peripheral tolerance status to H. pylori, might have a key role by first, decreasing the CD4+ proliferation level and cytokine generation, second, inducing T-cells apoptosis and their changing naïve T-cells into Tregs. Fascinatingly, PD-L1 expression on H. pylori exposed gastric epithelial cells happens independently of VacA, CagA with no direct contact between them. Its urease B production and increases the probability for the presence of a novel, yet unidentified, virulence molecular determinant [78].

3.6. Immunoinformatic approaches

Recently, immunological works indicated that activation of adaptive T and B cell responses are induced by H. pylori infection, moreover, the Th1/Th17-polarized immune response is needed for its inhibition. A multi-epitope vaccine of H. pylori was designed in some recent works utilizing bioinformatics. Moreover, different advantages have been demonstrated by epitope-based vaccines such as safety, the chance to rationally engineer the epitopes for the incremented potency, antigenicity, and breadth, along with the possibility to concentrate on larger repertoires of immune responses on conserved epitope sequences. Through the several immune-informatics tools we able to investigate H. pylori virulence factors sequences based on vaccine development and design that have altered to produce peptides comprising multi-epitope vaccines in terms of linear arrangements, as an alternative new approach [79, 80, 81, 82]. Zhou et al, in 2009 designed a vaccine including two B cell epitopes and three Th epitopes from the B subunit of urease (UreB) and two B cell epitopes from the HpaA and then expressed in E. coli. Their results showed that oral immunization significantly reduce the colonization of H. pylori compared with control, and the protection was associated with antigen-specific IgG and Th cells and also mucosal IgA antibody responses [83, 84]

3.7. H. pylori's antibiotic resistance

Zhuanghe, Liaoning Province, in northern China (a high-risk area for gastric cancer) includes the higher total H. pylori resistance rates to levofloxacin, clarithromycin, metronidazole, tetracycline, and amoxicillin. The resistance rates to amoxicillin and levofloxacin incremented over time. Clarithromycin resistance was related to iceA and males. vacA was responsible for the resistance of metronidazole. Levofloxacin resistance was related to slyD and cagA and amoxicillin resistance was related to iceA. However, the antibiotic resistance of H. pylori imposes no effect on the gastric disease status [85]. Patients with H. pylori infection can now be treated with a number of antibiotic regimens. The recommendations in the American College of Gastroenterology guidelines in 2007 state that first-line treatment with 10 to 14 days of treatment in three cycles is standard with amoxicillin and clarithromycin, which are a proton pump inhibitor (PPI). In recent years, however, we have seen the development of clarithromycin resistance worldwide, with reduced eradication of H. pylori. Consequently, alternative regimens are necessary to reverse this increase in clarithromycin resistance [86].

3.8. nanotechnology-based treatment approaches against H. Pylori

Nanoparticles (NPs) are small materials that have size ranges from 1 to 1000 nm such as dendrimers, lipid nanoparticles, fullerenes, liposomes, metal NPs, polymeric micelles, polymeric NPs, and ceramic NPs. It appears to be a functional role of metal nanoparticles that act as different mechanisms on bacteria, such as producing oxygenated and reactive species or disrupting cell membranes, genetics, or proteins. It makes these particles a good alternative to conventional antibiotics. The advantages of using nanosystems include increasing the remedial drug's effect can control the distribution of active materials via alteration the surface properties and particle size, and continuous and long-lasting drug delivery, as well as targeted drug delivery to the target areas. In recent years, the use of NPs in infectious diseases has been considered. As with other infectious diseases, the study of the usage of nanoparticle procedures in the H. pylori treatment has also increased. The application of these procedures in the H. pylori treatment can

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reduce the destructive effects of stomach acid on drugs and also allows the drug to be delivered to H. pylori infected areas [87, 88].

4. Conclusions

H. pylori infection is among the most prevalent infections possibly progressing gastric malignancy in humans. Though primary diagnosis of the sickness can obtain higher achievement rates by surgical or endoscopic resection, it often serves late in its inherent course resulting in a lower overall survival rate. H. pylori attaches to gastric epithelial cells via the outer membrane proteins, hence, such proteins are HopQ, HomB, and HopH as the appropriate candidates for developing vaccines. Since VacA and CagA result in gastric malignancy by activation of cell proliferating signaling paths, their inactivation them can be a novel remedial target for further research. In recent works, the presence of CSCs has been elucidated with the exclusive capability at regenerating tumors and differentiation and self-renewal, moreover, they share numerous features with tissue stem cells. The human gastric CSCs origin has yet to be clarified, however, BMDCs was found as a possible source option from data attained from a mouse model of gastric malignancy induced by Helicobacter. According to the gene therapy results, 63.8% of ongoing or accomplished clinical trials on gene therapy have been focused on human malignancies. The immune therapy approaches will be most effective when providing as an attachment to the present chemotherapy. For instance, some benefits are provided by anti-VEGF agents in combination with chemotherapy, however, limited efficacy is offered as mono therapy. In contrast, immune checkpoint inhibitors and immune conjugates appear to present antitumor activity alone or in combination, nevertheless, adding chemotherapy does not enhance the results in GC. Developing an operative vaccine as an alternative has attracted a huge deal of interest, which is still a challenge. Thus, a strategic, rational, and effective vaccine design is essential against H. pylori, in which using the most current bioinformatics instruments can be effective for designing an auspicious new multi-epitope vaccine against H. pylori. To assess the H. pylori antibiotic resistance research, clarithromycin-oriented triple therapy is not yet appropriate in this regard; levofloxacin and metronidazole should be utilized with higher vigilance, and tetracycline and amoxicillin can be utilized as the appropriate candidates for antibiotic therapy. Furthermore, we reviewed the present constraints and novel promising alternatives in H. Pylori treatment, due to the capacity of nanotechnology to dominate the treatment of this infection. Our review study provides valuable information about the H. pylori eradication program and its relation with gastric malignancy for further research in the future.

Footnotes

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