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Pathogenesis of *Helicobacter pylori*: An Overview of Bacterial Virulence Agents and the Mechanism of Occurrence Disease

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إمراضية بكتيريا *Helicobacter pylori*: نظرة عامة على عوامل الضراوة البكتيرية وآلية حدوث المرض

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ABSTRACT

Helicobacter pylori is believed to be a main reason of stomach diseases in addition to the occurrence of infections that may end in cancer, there may be new virulence factors and as a result of the genetic analysis of this bacteria, which shows a wide view of the genome of this bacteria, so we hope to discover a new generation of genetic sequencers to verify the presence of new virulence agents. Studying the function of virulence factors possessed by *H. pylori* that increase its susceptibility to disease will lead to the possibility of developing treatments and vaccines. This review focuses on virulence factors and their role within pathogenesis of *H. pylori* contagion. This review contributes for development about new prevention and treatment methods based on an understanding of the role of cagA, vacA, ureE-H, and ureI proteins in increasing the susceptibility of bacteria to colonize the host digestive system in addition cause damage of host tissue.

Keywords:

Helicobacter pylori; pathogenesis; virulence agents; stomach ulcer; stomach cancer

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الخلاصة

يُعتقد أن بكتريا *Helicobacter pylori* سبب رئيسي لأمراض المعدة بالإضافة إلى أن حدوث الالتهابات قد ينتهي بالسرطان ، وقد تكون هناك عوامل ضراوة جديدة ونتيجة للتحليل الجيني لهذه البكتيريا والذي يظهر رؤية واسعة لجينوم هذه البكتيريا ، لذلك نأمل في اكتشاف جيل جديد من أجهزة التسلسل الجيني للتحقق من وجود عوامل ضراوة جديدة. ستؤدي دراسة وظيفة عوامل الضراوة التي تمتلكها البكتريا الحلزونية والتي تزيد من قابليتها للإصابة بالمرض إلى إمكانية تطوير علاجات ولقاحات. تركز هذه المراجعة على عوامل الفوعة ودورها في التسبب لعدوى الحلزونية البوابية. تساهم هذه المراجعة في تطوير طرق جديدة للوقاية والعلاج تستند إلى فهم دور بروتينات cagA و vacA و ureE–H وurel في زيادة قابلية البكتيريا لاستعمار الجهاز الهضمي المضيف بالإضافة إلى التسبب في تلف الأنسجة المضيفة.

الكلمات المفتاحية:

بكتريا الحلزونية البوابية,الامراضية, عوامل الضراوة ,قرحة المعدة ,سرطان المعدة.

1. *H. pylori* Contagion and Pathogenesis

Helicobacter pylori is a widespread bacterium that cause infection to nearly most of the world's people, as contagion for this bacterium varies of one country into another [1]. It was found that infection with bacteria leads to many diseases of the digestive system, including peptic ulcer, gastritis, duodenal ulcer and stomach cancer, and there are many bacterial, environmental and host agents that contribute to the increase in disease events [2]. *H. pylori* is a scientifically proven carcinogenic bacterium, it lead to stomach cancer. The disease occurs as an outcome of the complicated interaction among host and bacteria[3]. It is worth noting that in spite of elevation spread of contagion with this bacterium in Africa in addition to South Asia, Prevalence of stomach tumor in these regions is decreased compared to other areas, where clinical reports have shown that environmental factors, diet and host influence the intensity of the immune response in addition to the virulence bacteria[4].

When *H. pylori* passes into the host's gastric, it utilizes its urease enzyme for conserve herself from the acidic medium of the digestive tract at beginning about the infection of the stomach, after which it moves by the flagella towards the epithelium of the host's stomach, then the bacteria attaches to the receptors of the host cells, leading to colonization and infection, then the bacteria releases a lot of proteins in addition to toxins inclusive cytotoxic related gene A, excretion cytotoxic A that lead to host tissue harm. The stomach epithelium releases chemokines for start

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natural immunity , stimulates neutrophils in addition to causing gastritis diseases[2]. *H. pylori* is able to adapt to the acidic environment of the host's gastric by arranging the action of urease. Urease gene collection is consist of 7 genes, inclusive catalytic subunits ureA/B, an acid-gated urea canal ureI, in addition to additional aggregation proteins ureE-H [5].

For heterodimer urease action, the mineral cofactor nickel has to be integrated into the Apo enzyme by the activity of the four additional proteins, for example *ureE* show to be a significant metallochaperone [6]. The secretion of urease enzyme is regulated by proton-gated urea duct *ureI* that found in internal envelope, which permits urea arrival just down acidic situations to prohibit deathly alkalization[7] . *H. pylori* is able to pass safely through the stomach juice when the ammonium hydroxide produced by the breakdown of urease is neutralized to hydroxide and combined with the ammonia secreted by the bacteria [7,8]. The use of antibiotics as a treatment for *H. pylori* has become less effective as a result of its increased resistance to antibiotics. It is worth noting the possibility of eliminating this bacteria by inhibiting the activity of the enzyme urease [9].

2. The Virulence Agents

2.1. External Envelope Sac

H. pylori virulence agents are dissoluble, binding above exterior of the cell and inserted inside the host cells through style four excretion system. *H. pylori* produces outer membrane sac which have a function in the distribution of bacterial antigens, *H. pylori* produces many biologically active compounds that are found in the outer membrane vesicles of host cells that lead to the death of stomach epithelial cells in addition to immune cells, resulting in the strengthening or weakening of immune responses [10]. *H. pylori* produces α- carbonic anhydrase (CA) in outer membrane vesicles in addition to the enzyme urease, which has a role in reducing the acidity of gastric juice [11].

2.2. Vacuolating Cytotoxin (VacA)

The toxicity of vacuolating cytotoxin A (vacA) is concerned with virulence agents, where the ammonia produced by bacterial enzyme urease increases the secretion of the cytotoxin vacA[12]. The subtypes of vacA: $s_1as_1bm_2$, s_1a_1b, and s_2m_2, are linked to the infection of the inside layer of the stomach. Dispersal of VacA s1m1 strains may for rise danger of transport of this gastric

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bacterium in addition to the total danger of a gaining contagion. Examination data of phylogenetic indicates the prevalence of rise genetic diversity in India [13].

2.3.Other Agents Related with Virulence Agents

The interactivity of *H. pylori* and stomach epithelial cells stimulate various indicative transportation lanes inside the host. After a short time of linking the human gastric adenocarcinoma cell-line with *H. pylori*, this leads to lower the stages of metabolites of krebs cycle, while in the long period time cultivated of stomach cells with *H. pylori* which leads to high levels of metabolites of the krebs cycle and amino acid metabolism [14]. CagA and vacA are two of the virulence genes and have the potential to cause stomach disease, while the genes *homA* and *homB* are not yet confirmed for their role [15]. Lipopolysaccharide of *H. pylori* in Western and Asian areas was various in the kind of attachment in the midst core oligosaccharide Glc,Gal,Hep,III,Hep,II,Hep,I,KDO and connected 3-saccharide GlcNAc,Fuc,Hep, *H. pylori* strains in western areas, a stringy glucan- heptan attachment through two sections of Lipopolysaccharide was specified. existence of another attachment inside Lipopolysaccharide about Asian isolates in addition this function in *H. pylori* diseases were indicated in order to contagion by *H. pylori* is acute in addition signaling in Asia in contrast with Western areas[16].

3. Protein A Stimulating by Neutrophil

Neutrophil stimulating protein A of *H. pylori* is associated with the proteins that keep DNA under famished cases, from white blood cells, it was known for the first time to activate high manufacturing of oxygen radicals. Which leads to the loss of topical tissues, in addition to enhance white blood cells cohesion to endothelial cells in the time of bacteria contagion [17]. Neutrophil stimulating protein A prompt cohesion is based on the procuration of a rising-attraction case of β2 integrin on the white blood cells exterior envelope [18]. The prompting of reactive oxygen species output, Neutrophil stimulating protein A stimulates the expression in addition to freeing of IL-8, macrophage inflammatory protein through white blood cells [18]. So, Neutrophil stimulating protein A is very related together the feature of persistent inflammation of the lining of the stomach, in addition to permeation of neutrophils and mononuclear cells into the stomach mucosa, due to *H. pylori* contagion.

On the neutrophil exterior the glycosphingolipids which exist, act as an essential receptor to react together Neutrophil stimulating protein A explicated on bacterial surface [18]. For

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survey *H. pylori* establishing in mice injured together the wild-type and Neutrophil stimulating protein A mutant strains, in an animal survey explains the degree of permanence of the Neutrophil stimulating protein A mutant was present to be much down than that of the wild-type strain [19]. Many studies have shown that neutrophil stimulating protein A can keep deoxyribonucleic acid of *H. pylori* from loss, because of its capability to connect deoxyribonucleic acid, therefore to deny deoxyribonucleic acid from exposure by free radicals or its iron isolating capability to decrease the oxidative stress created in ferrous ion through Fenton interactions [19,20].

Interestingly, neutrophils or monocytes was activated by neutrophil stimulating protein A to raise the expression of IL-12, and prompt T helper cells to distinguish to T helper 1 phenotype [21]. So, Neutrophil stimulating protein A has been indicated as an immunotherapeutic anticancer factor in addition to helping in to inoculation within clinical implementations.

4. Blood Group Antigen-Binding Adhesion

Novel researches explained the medicine relation of the blood group Ag-linking adhesion BabA, converted through babA2 gene. The strains have babA2 were connected with sore illness in addition to stomach cancer [22]. BabA is a cohesion agent expressed in a subgroup of *H. pylori* strains and connects to difucosylated Lewisb blood group present above epithelial cells [23]. The effect of BabA on bacterial habitation is not understood. Previous studies have proved which happing of bacterial colonization is affected through capability of bacteria to connect to epithelial cells [24,25]. Cohesion bacteria are presumed to have evolution features depend on closeness to the epithelium.

BabA seems to be a main rising colonization intensity. Therefore, this cohesion agent succeeded in creation of a nonspecific immune response by indirect technique. The existence of babA2 was related with sore illness in addition to cancer, that seems the genetically sensitivity might impact disease progression again once bacterial colonization is building up[26].

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CONCLUSIONS

We conclude through this review that the pathogenicity of *H. pylori* can be controlled by knowing the mechanism of disease events and identifying virulence agents and their function in the occurrence of pathogenesis. The mechanism of carcinogenesis by *H. pylori* can be understood through the development of screening methods.

Conflict of interests.

There are non-conflicts of interest.

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