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The Proteins of Type IV Secretion System as Promising Candidates for Helicobacter Pylori Vaccine

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Abstract

Helicobacter. pylori is a component of class 1 carcinogens and there is a close association between the incidence of gastric cancer and high prevalence of infection with this bacterium. The risk of gastric cancer associated with H. pylori infection in industrialized and developing countries is estimated to be 80

Index terms—

The Proteins of Type IV Secretion System as Promising Candidates for Helicobacter Pylori Vaccine Azad Khaledi ? , Abbas Bahador ? & Davoud Esmaeili ? Abstract-Helicobacter. pylori is a component of class 1 carcinogens and there is a close association between the incidence of gastric cancer and high prevalence of infection with this bacterium. The risk of gastric cancer associated with H. pylori infection in industrialized and developing countries is estimated to be 80% and 70% respectively. CagA is the important virulence factor in this bacterium and all of the strains involved in gastric cancer are CagA positive. This factor is secreted into host cells by type IV secretion system. CagA and type IV secretion system in H. pylori encoded by the cag pathogenicity islands (cag PAI) that encodes 30 proteins which are necessary for the pilus formation and function of type IV secretion system, so regarding to the role of this secretion system in secreting CagA and its function in pathogenesis and cancer development in humans and the role of different proteins of this secretion system such as canal and pilus formation and their necessity for function of these structures, it is possibly they are be appropriate candidates for design vaccine, because with inhibiting these proteins can stop canal and pilus formation and finally hinder CagA secretion into the host cells.

1 I. Review

elicobacter pylori is a spiral-shaped gramnegative bacillus that it colonizes half the world's population (1). Chronic infection with this bacterium causing an increased risk for several infectious diseases such as gastritis, duodenal ulcers, hyperplasia, neoplasia and ect (2).

H. pylori is one of the ancient microorganisms and its spread between human societies is return to sixty thousand years ago (3). H. pylori colonize the human gastric for years and even decades without anyadverse consequence (4). The risk factors for acquiring H. pylori are including poverty, the use of common sleeping devices, living in very crowded sittings such as boarding houses which raise the possibility of infection (5). H. pylori is component of the family of class 1 carcinogen and there is a high correlation between the incidence of gastric cancer and high prevalence of infection with this bacterium (6). Gastric cancer is the second common cancer worldwide and the fourteenth cause of death in the world and it is considered as a main epidemiological problem in the 21st century (7). The risk of gastric cancer associated with H. pylori infection in industrialized and developing countries are estimated to be 80%, and 70% respectively (8). H. pylori infection is usually asymptomatic chronic gastritis and between infected people the rate of chronic gastritis or gastric ulcer are 10%-15 % (8). H. pylori infection, exposure to nitrosamines, high-salt diet, smoking and low consumption of fruits and vegetables are major risk factors for gastric cancer. The high prevalence of H. pylori infection in the world and its role in gastric cancer and other diseases, and the emergence of antibiotic resistance strains have caused different therapeutic and prevention methods recommended against infection with bacterium (9) . It should be

noted, only patients with symptoms are treated and asymptomatic patients are at risk of serious problems such as atrophic gastritis and gastric cancer as well after cure, recurrence or reinfection might be take place (10), particularly in developing countries (11). Thus the need for vaccines in general that can control infection is felt.

The immune mechanisms against H.pylori is mediated by innate and adaptive immunity, the innate immunity is including gastric acidity, gastric peristalsis, loss of gastric epithelial cells, gastric mucosa, saliva and etc (12). In total, acquired immunity is consists of the cellular and humeral immunity. Despite stimulate antibody production, clearance and complete protection against H. pylori infection is caused by cellular immunity (13). So to eradication of this bacterium, The strong Th1 response to protection (IFN? production is necessary for protection) and Th2 response (IL-10) to reduce inflammation during H. pylori infection is required (13).

Some H. pylori native and recombinant antigens such as urease, Heat Shock proteins, CagA, VacA, HP-NAP, catalase (14) HpaA (15), SOD (16) are used as vaccine and the efficacy of therapeutic and prophylactic immunization of these antigens have been shown. several studies tried to discover more protective antigens in mice including Hp0410 (neuraminyllactosebinding hemagglutinin HpaA homologue) (17), Tpx (thiol peroxidase) (18) outer membrane proteins, alkyl **??**9), but other studies have attempted to use from proved previous protective antigens in new forms to show their treatment aspect and prophylaxis efficiency in mice (20). The first evidence of the efficacy of protection against H. pylori has been provided by urease immunization in mouse model and showed that the both types of recombinant vaccines UreB or UreA are effective when they used in the oral forms (21). The protective role of HP-NAP has been evaluated in mouse model, in orally the mice with recombinant HP-NAP along with LTK63, LTK63 nonmutant strains as adjuvant were immunized and following challenge with H. pylori showed protection against gastric colonization of the majority of vaccinated mice (22). The protective efficacy of native purified VacA given along with LTK63 as an adjuvant was proved in oral immunization in mice (23). Other studies demonstrated the same (24). Recombinant CagA in companying with was used in mice and the results showed this combination to be protective against gastric colonization upon consequence H. pylori trial intragastrically challenge (25). Combination of CagA, VacA and HP-NAP was used as a therapeutic vaccine in the model of H. pylori experimental infection of beagle dog and presented good efficacy without any sideeffects owing to immunization. Following challenge, the decrease in H. pylori colonization and gastric inflammation was observed in vaccinated dogs (26). A study revealed recombinant vaccine proteins CagA + VacA + HP-NAP has been immunogenic and safe in clinical phase (27). The emphasis of all studies on that protection against H. pylori would be acquired by vaccination through animal models; but unfortunately complete protection is seldom achieved, it appear that this depend on optimization of the antigen mixture, adjuvant and route and regimen of immunization and to get this aim the appropriate combination is very important (28). In addition, efficiency in animals is not essentially indicative of efficacy in humans (28). Due to inadequate knowledge upon mechanisms of protective immunity against H. pylori till this moment there has been no licensed vaccine against H. pylori, Until now there has been no licensed vaccine against H. pylori. The reasons for this are: inadequate knowledge about the mechanisms of protective immunity against H. pylori, thus extensive research is needed to identifying the mechanisms of protective immunity against H. pylori and the vaccine formulations should be known to be able to preventing and treatment of infection (28), regarding known role of CagA and other main carcinogens factors, the supposition is that the vaccine should be targeting specifically these factors (28). In other words, a vaccine is valuable for us to prevent gastric cancer rather than prevent colonization of H. pylori in human (28). The studies upon new vaccine candidates, efficient adjuvants, regimens and routes of application is go on yet (28).

In continue we want to explain in this brief about type IV secretion system and introduce its proteins as good candidates for vaccine. In several gram-negative bacteria, such as Neisseria gonorrhoeae, Bordetella pertussis, Agrobacterium tumefaciens and Brucella suis have type IV secretion system and in these bacteria this system is used to transfer macromolecules (such as DNA, nucleic acid and protein complexes), (29). Type IV secretion system in H. pylori encoded by the cag pathogenicity islands (cag PAI) that encodes 30 proteins which are necessary for the pilus formation and function of type IV secretion system (29). Type IV secretion system is a molecular pump that facilitates the interaction between host and pathogen or injects toxins into the host cells (30). According to the medical literature in the human H. pylori species, type IV secretion system is divided into three different groups, first group (Tfs3, group 1) which plays an important role in shaping the genome plasticity of bacterium, the second group is called Com B system which plays an important role in insertion and integration of environmental DNA fragments into the itself genome. At last the third group there is only in H. pylori pathogenic strains which play role in translocation of protein effectors (such as CagA) into the eukaryote cells (27). CagA toxin and type IV secretion system is encoded by cag PAI, this pathogenicity island is a 40 kDa fragment of DNA and transfer of it occurs horizontally (31). Based on the nomenclature used for A. tumefaciens T4SS, this system generally contains 12 protein which these proteins are called Vir (30). The H. pylori cag PAI encoding T4SS (Cag-T4SS) initially have been identified by comparing the sequence with those of the VirB /D A. tumefaciens (30). These proteins assemble together to form three interlinked subparts: a cytoplasmic ? inner membrane complex, a double membrane -spanning channel and an external pilus (32). The cytoplasmic ? inner membrane complex is consists of three NTPases (HP0544, HP0532 , HP0524), HP0529 and HP0530; the trans-membranes pore complex (HP0532, HP0528, HP0527; as well as called 'the core complex') creates a channel from the inner to the outer membrane; the HP0546 and HP0539 proteins create external pilus (32).

Other components are crucial for the creation of the T4SS compound: the role of HP0523 is insertion of the system in the periplasm and finally HP0544, with the unknown role, is frequently related to HP0544 (32).

Regarding to the role of type IV secretion in secretion of CagA and its role in pathogenesis and cancer formation in humans and the role of different proteins of type IV secretion such as canal and pilus formation and their necessity for function of these structures, it is possibly they are be appropriate candidates for design vaccine, because with inhibiting these proteins can stop canal and pilus formation and finally can prevent of CagA secretion into the host cells, of course these proteins should be used in combination [1]

Figure 1:

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Figure 2:

with H.pylori virulence factors in multi-component vaccines.

.1 II. Acknowledgement

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.2 Conflict of interest

None declared.

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