



Current status of *Helicobacter pylori* associated human gastric cancer and the therapeutic approaches – A Review

Partha Pal

Assistant Professor, Department of Zoology, Scottish Church College,
1 & 3 Urquhart Square, Kolkata - 700006, India

E-mail address: parthapal_iicb@yahoo.co.in

Phone: 91-33-2350-3862

ABSTRACT

In the recent years one of the common causes of cancer related deaths in humans is associated with the development of gastric carcinoma leading to gastric cancer. It had long before reported that the potent agent that is intimately related with the gastric cancer is the infection of the bacterium *Helicobacter pylori* (*H. pylori*). *H. pylori* infection in humans is characterised by the development of acute peptic ulcers which creates a lots of gastroenterological symptoms. Co-existence of *H. pylori* in the human gastric environment is well adapted by the pathogen by evading the immune responses of the host. Gastric biopsy in patients suffering from *H. pylori* infection reported the development of gastric lesions having the chance to proceed towards development gastric cancer. Recently it was reported that eradication of the *H. pylori* colonization is not possible even after continued current antibiotic treatment over long periods and even combined regimes are unsuccessful. Moreover alterations of the genetic background of the host gastric cells were also reported along with infection of *H. pylori*, the primary concern for the evolution of the genetically transformed cells which is the hallmark for the development of malignancy. Clinical studies have reported the limited efficacy in decreasing the incidence of gastric carcinoma even after the eradication therapy has been completed for the bacterial colonization. Research based on the biopsy specimens obtained from conventional gastric endoscopy of affected patients has revealed some genetic or epigenetic alterations in the gastric mucosa. The cause of concern to human life lies in the fact that the number of sporadic cases of primary or metachronous gastric carcinoma has increased after successful eradication. The purpose of the present review is to assess the current status of the research based on the concept of development

of gastric carcinoma in association with *H. pylori* infection in humans and to throw some light in the remedial measures against the pathogen which is a chronic burden in the well-being of the human society.

Keywords: *Helicobacter pylori*; Gastric carcinoma; Peptic ulcers; Antibiotic treatment

1. INTRODUCTION

Novel cancers are emerging and about 2 million cases of malignancy each year worldwide are associated with infectious agents [1]. Among the numerous pathogenic microorganisms namely Hepatitis viruses, papillomavirus, and *Helicobacter pylori* are the causative agents of responsible for most of these malignancies in liver, cervix, and stomach, respectively. It has been reported that *H. pylori* is the only bacterium known till now to be a sole agent responsible for the development of gastric cancer. Epidemiological investigations have reported that *H. pylori*-infected persons are more prone to development of gastric cancer isthan *H. pylori*-negative persons. It was also reported that *H. pylori* infection precedes the development of gastric cancer [2-4]. Colonization of *H. pylori* in the stomach triggers a gastric mucosal inflammatory response commonly referred to as “gastritis” in humans which signifies the beginning of the development of peptic ulcers. Establishment of the bacterial infection leads to local inflammation that can persist for long period if antimicrobial treatment is not ensured. Chronological studies indicate that gastritis is one of the first symptomatic changes in patients infected with *H. pylori* and in a cascade of cellular alterations leading to histologic abnormalities that can ultimately results in gastric cancer along with the detectable changes including inflammation, gastric atrophy (loss of specialized cell types such as parietal cells and chief cells), intestinal metaplasia (presence of intestinal-type epithelium in the stomach), and dysplasia [5,6].

The chronic inflammation which is one of the major hallmarks of the infection contributes to the pathogenesis of many types of malignancy [7]. The bacterial growth in stomach alters the internal milieu of the normal acidic environment and it is characterised by DNA damage, activation of gastric stem cells, changes in cell proliferation and apoptosis, changes in epithelial differentiation and polarity, degradation of tumor suppressors, and impaired gastric acidification, leading to bacterial overgrowth with species not found in the normal acidic stomach [5,6]. The genomic plasticity of the *H. pylori* genome resides on the remarkable genetic as well as phenotypic diversity of the microorganism. Thus *H. pylori* can acquire resistant genotypes, and rapidly acquire the MDR (multi resistant drug) property which is a major concern in accurate management of the pathogen [8-10]. The virulence factors of the bacterial pathogen is attributable to the cytotoxin-associated gene A antigen (CagA) and vacuolating cytotoxin which play an important role in *H. pylori* related gastric disorders [11,12].

The *CagA* gene is part of the *cag* pathogenicity island and is largely responsible for triggering the signalling pathways that activates the carcinogenic development [13,14]. The entry of the pathogen within the gut is facilitated by the fact that the toll-like receptors present on the epithelial and inflammatory cells of the gastric mucosa are in direct contact with the external environmental milieu [15,16]. The long-term colonization by *H. pylori* was reported to cause an environment of chronic inflammation along with reductions in acidity as well as in

the level of antioxidant enzymes in the gastric juice [15,17]. Although 50% of world population carries *H. pylori*, most infections are asymptomatic and 10-15% of the *H. pylori* infected individuals develop chronic inflammation leading to atrophic gastritis, peptic ulcer as well as gastric adenocarcinoma [18].

According to World Health Organization classification *H. pylori* has been assigned as a group I carcinogen with significant risk of gastric cancer [19]. So, in case of infection, eradication of *H. pylori* is the most effective treatment for *H. pylori* associated diseases. Recently eradication of *H. pylori* infection is usually carried out by treatment with “Triple therapy” (TT) including two anti-microbial agents either clarithromycin and amoxicillin or metronidazole along with a proton pump inhibitor which is recommended by several workers [20]. However, such multiple therapy regimens have not been very successful in clinical practice due to their misuse and side effects.

2. MOLECULAR BASIS OF PATHOGENESIS OF *H. pylori*

H. pylori upon entry into human host utilizes certain special adaptive defensive mechanisms against the host immune responses for persistent colonization in human body, including disruption of epithelial junctions, stimulation of cytokine production, apoptosis, over-proliferation, DNA damage and cell transformation. *H. pylori* disrupts intercellular epithelial tight junctions through binding to specific cellular receptors and stimulating the specific signalling pathways which are responsible for maintaining the integrity of gastric epithelial barrier as well as performing the normal cellular functions [21].

More or less 70% of *H. pylori* strains from western world and nearly 100% of East Asian strains express virulent protein CagA [22-24]. Genomic analyses of *H. pylori* genome have detected the presence of *cag* pathogenicity island (PAI) harbouring the genes encoding the strongest virulence factors [25]. The type IV secretion system (T4SS) pathway components are encoded by CagA which is a highly immunogenic protein, positioned at one end of the *cag* PAI [25]. The other component encoded that participates in T4SS includes the CagL protein which binds to and activates the integrin $\alpha 5 \beta 1$ receptor on gastric epithelial cells and activates CagA delivery into the target cells [26]. Several proteins of this secretory pathway are CagM, along with CagX and CagT, forming an outer membrane associated T4SS subcomplex [27] along with CagX and CagT which interact directly [28].

Transportation into epithelial cells through T4SS is followed by the interaction of CagA with junction proteins namely E-cadherin and ZO-1 resulting in the alteration of the tight or adherence junctions [29, 30]. Previous study reported that E-cadherin, a transmembrane protein, localizes at cell-to-cell junctions and interacts with β -catenin to form the E-cadherin/ β -catenin complex playing a major role in interaction of epithelial cells and stabilization of cellular architecture [30]. Infection with *H. pylori* causes the destabilization of the complex mainly by translocated CagA in a phosphorylation independent manner [30]. It was also reported that CagA translocation is involved in mislocalization of ZO-1 in epithelial cells [31,32]. Recent study showed a different aspect of *H. pylori* pathogenesis in that infection of the pathogenic bacteria diminished acid-induced tightening of cell junctions, affected the response of epithelial cells to acid, which are manifested in inflammatory response and alteration of the barrier function [33]. Infection of *H. pylori* in gastric epithelial cells induces the disruption of the polarity of the cells through interaction with PAR1/MARK

kinase [34] which is affected by targeting the epithelial adhesion receptors like E-cadherin and β 1-integrin to modulate formation of cytoskeleton [35]. Studies reported that an atypical protein kinase C (PKC) has a critical role in the disaggregation of PAR1 from tight junctions by phosphorylation of PAR1 at the junctions [34] and PAR1b binding to CagA restrains PAR1b activity and phosphorylation by a PKC to promote disintegration of cellular polarity [32,34]. Recent study also confirmed that *H. pylori* infection resulted in rapid association of the virulence factor CagA with the c-Met receptor, activation of signaling and epithelial proliferation [36].

The production of CagA varies in different isolates of *H. pylori*. Recent studies showed that the risk of development of premalignant lesions in persons infected with the pathogenic strains is related with production high levels of CagA compared to strains producing a lower level of CagA protein [37,38].

According to further genomic studies it was noted that *H. pylori* secretes a protein known as vacuolating toxin VacA through an autotransporter or type V secretion pathway [39-41]. Previously the VacA protein was recognized based on its capacity to cause vacuolation of epithelial cells [42] but recent studies reported that the protein was known to have a much broader range of activities [39-41]. The amino acid sequence, structure, and cellular effects of VacA are unique among other known bacterial toxins [43]. The VacA-induced cellular damage is related to its capacity for pore formation in cell membranes [39-41]. Similar to CagA protein all *H. pylori* strains contain a *vacA* gene and nearly all secrete a VacA protein, but there is considerable variation in strain specific VacA-induced host cellular alterations which is associated with the levels of production and secretion of the VacA protein [44].

The outer membrane proteins (OMPs) in *H. pylori* genome are encoded by approximately 60 genes including BabA and SabA proteins like adhesins mediating the binding of the pathogen to gastric epithelial cells. It was reported that BabA binds to the fucosylated Lewis b histoblood group antigen on host cells, and SabA binds to the sialyldimeric Lewis x glycosphingolipid [45,46]. Moreover SabA can function as a sialic acid-dependent hemagglutinin and has a role in nonopsonic activation of neutrophils [47]. Thus from different studies based on the genomic analyses of different strains of *H. pylori* it can be concluded that the genome is highly heterogeneous and suitably adapted to colonise in the human gastric epithelial cells and cause infection.

3. DEVELOPMENT OF GASTRIC CANCER IN ASSOCIATION WITH *H. pylori* INFECTION

H. pylori upon entry into human host penetrate the thick mucus layer by adhering to the gastric mucosal surface which is facilitated by the presence of unipolar sheathed flagella and colonises in favourable condition. In contrast the non-motile isolates fail to colonize suitably in the stomach of gnotobiotic piglets [21,48]. In the usual manifestation of infection of *H. pylori* results in development of inflammatory immune responses after colonization of the pathogen. In contrast chronic infection in certain individuals leads to induction of gastric inflammation and ultimately the atrophy of gastric mucosa due to destruction of normal gastric glands as well as replacement of intestinal-type epithelium. It was also reported that subjects having lower gastric secretion are more prone to the development of atrophic gastritis

depending on pattern as well as extent of distribution of chronic active inflammation [49]. The extent of severity of atrophy has been correlated with the reduction in gland size and level of intestinal metaplasia which were associated with rise in gastric cancer risk by 5- to 90-folds [50]. Experiments on animal models including Mongolian gerbil reported *H. pylori* infection induces atrophic gastritis followed by gastric cancer [51-53].

In another study a small number of human volunteers for research purposes were deliberately infected with pathogenic *H. pylori* strain and individuals developed acute inflammation of gastric mucosa with neutrophilic infiltration [54,55]. It was also reported that the volunteers after several decades when exposed repeatedly to intragastric pH-electrodes contaminated with *H. pylori* developed conditions called “epidemic hypochlorhydria” [55] and the corresponding gastritis can either resolve spontaneously or change into chronic gastritis.

It was previously suggested that integrity of gastric epithelial barrier along with maintenance of essential cellular functions depends on the intercellular apical junctions of epithelial cells [56]. The hallmark of *H. pylori* leads to disruption of the epithelial tight junctions through binding to specific cellular receptors and stimulating the signaling pathways. The entry into host epithelial cells is facilitated through T4SS. The proteins which play a key role in this entry process include the CagA that interacts with junction proteins like E-cadherin and ZO-1. The mechanism underlying *H. pylori*-related gastric carcinogenesis was related with CagA interacting with E-cadherin thereby deregulating β -catenin signal transduction and promoting gastric and intestinal epithelial cells trans-differentiation [57].

The translocation of CagA intracellularly and simultaneously binding to PAR1 results in the destruction of cellular junctions and polarity and ultimately initiates carcinogenesis [58]. Experimental studies conducted on genetically optimised mice strains expressing CagA showed development of gastric and hematological carcinoma [59]. Genetically modified *H. pylori* strains having the merozygous condition *cagA+vacAsI+vacAmI+* promoted pathogenesis of intestinal metaplasia and gastric carcinoma [60]. Further genomic analyses revealed that *H. pylori* regulate expression of toll-like receptors (TLR) including TLR4 and TLR9 in epithelial cells during gastric carcinogenesis [61]. Recent evidences support that TLRs are known to be involved in both recognition of the pathogen and gastric carcinogenesis as well as the detection of polymorphisms in genes involved in the TLR signalling pathways modulating the onset of gastric oncogenesis [62]. Moreover it was also reported that in addition to TLR, peroxisome proliferator-activated receptors are also involved in *H. pylori*-related gastric carcinogenesis [63].

The site for *H. pylori* colonization is not only restricted to the mucus layer covering gastric mucosa, but also invasion in the gastric epithelial cells and even in the immunocytes are also reported [64]. Autophagy of epithelial cells and phagocytes are induced upon *H. pylori* infection which is facilitated by VacA exposure. In contrast the prolonged exposure to the toxin disrupts autophagy by preventing maturation of the autolysosome [64]. This particular event in *H. pylori* infection has supported the finding that suppression of autophagy facilitates intracellular survival of this bacterium and generates an environment favouring carcinogenesis [65]. Moreover it was also reported that *H. pylori* disrupts the balance of the proliferation and turnover of gastric epithelium to facilitate its survival [66]. *H. Pylori* regulates the balance of epithelial cell apoptosis, which plays a key role in tissue homeostasis [67] and proliferation for its reproduction and survival in the host [68,69]. It has also been reported that *H. pylori* adhering to the epithelial surface also stimulate cellular apoptosis [70].

Studies on human gastric epithelial cells infected with *H. pylori* showed susceptibility to TRAIL-mediated apoptosis by regulation of cellular FLICE-inhibitory protein activity and assembly of death-inducing signalling complex [71].

4. STRATEGIES FOR COMBATING *H. pylori*

In the present decade *H. pylori* has emerged as one of the potential microorganism capable of causing gastric cancer and other severe gastro-duodenal diseases when it infects human host and colonises suitably [72]. Thus therapeutic approaches in the eradication of the pathogen are an effective procedure for the prevention of gastric cancer as well as cure for peptic ulcers [73-75]. Till date antibiotics are best choice for the clinicians in eliminating the pathogen since the alternative strategies are not effective enough as a tool for treatment against *H. pylori* [76-78]. But the current trend of the bacterium acquiring antibiotic resistance calls for a different approaches including the development of probiotics as well as vaccines against the pathogen [79].

4. 1. Antibiotic based therapeutic approach

Antibiotics were long before been known as a potent bactericidal agent dating back from the era of penicillin effective in eradication of *Streptococcus* [80,81]. The random use of antibiotics in the control of microbes infecting and causing diseases in humans over many decades opened up another problem of development of resistant bacterial strains and thus it is difficult to manage those disease causing microbes in the era [82,83]. Following the rule of other pathogenic bacterial strain *H. pylori* was also well known to have acquired the characteristics of antibiotic resistance and posed a great challenge to the scientists to design the best approach in combating the pathogen [74,84-89]. Several approaches including the use of combination of different antibiotics consisting of amoxicillin + clarithromycin +proton pump inhibitors (PPI) is the most widely applied therapy against *H. pylori* [90]. Concomitant use of clarithromycin in respiratory as well as gastric diseases randomly raised resistance against the drug decreasing the efficacy of the drug [78, 83]. The failure of this approach led to the development of quadruple treatment consisting of bismuth salicylate, metronidazole, tetracycline, and PPI [90,91]. Moreover Levofloxacin-based therapy showed a satisfactory efficacy as second line therapy [92]. Failure of the second line therapy calls for the third line therapy and the antibiotic of choice is the rifabutin which showed a high eradication rate of the bacterium [91,93,94]. Antibiotic treatment for elimination of the microorganism is only possible in symptomatic patient but it is difficult to eradicate in asymptomatic individuals leading to serious gastric problems and eventually leading to gastric cancer. Another important aspect of antibiotic therapy is that even if the infective strain has been eradicated after a complete antibiotic course there are possibilities of re-infection [79].

4. 2. Alternative therapeutic approaches

4. 2. 1. Probiotics

According to World Health Organization (WHO) [95] probiotics are beneficial bacterial species when administered into host body survive in the gastric mucosa altering the microbiota composition. The antibiotic induced diarrhoea is a common after effect in the

treatment of *H. pylori*. Probiotics are prescribed in the control of such drug induced diarrhoea [96,97]. Recently the probiotics are often used as a useful agent for enhancing the immune response of the host against the infective bacterium, decreasing the gastric pH which hinders bacterial growth, as a competitor for other bacterial species in the host body [98-100].

The most commonly used bacterial species as probiotics is the *Lactobacilli* which have shown promising results as an effective adjuvant in the control of *H. pylori* [74,93]. The protective effectiveness of probiotics in the control of *H. pylori* has been thoroughly investigated [101-103].

4. 2. 2. Vaccination

The control of *H. pylori* bacterium has posed great challenge in the scientific world. The short comings of both the antibiotic therapy and lack of utilization of the alternative therapies including the probiotics the search for a suitable weapon for combating the pathogen is an indeed a great requirement since complete eradication of the microorganism is not possible in either of the therapies [76,91,104-106]. The reliable effective and protective tool is the search for proper vaccines and recently certain researches on vaccine designing for *H. pylori* have been initiated [107-110].

4. 2. 3. Curcumin as an alternative therapeutic agent

Curcumin since long time is well known for its property suppress the growth of a variety of microorganism/organism including parasite, bacteria and pathogenic fungi. The antimicrobial effect of curcumin has also been noted in a variety of disease causing parthogenic strains belonging to species such as *Helicobacter pylori*, *Bacillussubtilis*, *Plasmodium falciparum* etc [111].

The potent antimicrobial properties of a compound include anti-oxidant, anti-inflammatory, anti-carcinogenic and pro-apoptotic properties. Curcumin contains chemical compound that has all the major antimicrobial as well as anti-cancer properties and several studies reported that it acts as an effective anti-inflammatory agent [112]. The strong anti-oxidant and anticancer properties of curcumin is reflected in regulating the expression of genes coding for activator protein (AP1) and NF- κ B and suppression of TNF [113]. The anti-cancer effect of Curcumin has been recorded in several animal model experiments where carcinogenic growth has been effectively prevented in certain cancers including oral, oesophageal, stomach, duodenal and colon cancer [114].

The apoptotic effect Curcumin was investigated by Irving *et al.*, [115] and the signalling pathways were elucidated adequately. Another study reported that Curcumin as a potent stimulator of caspase-3 and not only that it can also increase the activation of caspase-7, 8 as well as releases cytochrome-C [116]. In the year 2002 it was first reported that Curcumin has direct effect on the control of *H. pylori* [117].

According to recent report several studies confirmed that curcumin as an effective therapeutic agent which can be used judiciously as a natural clinical compound in the control of *H. pylori* related gastric disorders ultimately leading to the development of gastric carcinoma in different experimental protocols encompassing both *ex vivo* as well as *in vivo* and even clinical trials [118].

5. DISCUSSION

H. pylori induced gastric cancer progression is initiated from chronic inflammation along with atrophic gastritis and intestinal metaplasia. One of the dangerous aspects of *H. pylori* related gastric cancer is the fact that eradication of the bacterium from the host does not rule out the possibility of the development of gastric carcinoma in patients who have developed atrophic gastritis which was envisaged by previous studies [119].

Studies on the development of gastric cancer indicated that the process is multifactorial and depended on hosts' genetic make-up and production of inflammatory cytokines as for example IL-1. Moreover the polymorphism in the genes involved in cytokine production is related with *H. pylori* infection since the production of cytokine is associated with gastric acid secretion and inflammation. Certain bacterial protein factors including the VacA and CagA associated with the *H. pylori* infection augment the development of gastric cancer in individuals having polymorphic cytokine encoding genes for IL-1 and TNF [120].

The remedial measures for the control of the bacterial infection have been widely studied by different groups including the antibiotic profiles as well as the probiotic therapy. Zeng *et al.*, [121] reported the production of an oral vaccine having good prophylactic aspects in the elimination of the pathogen [79]. Another study using the useful component of Curcumin reported that it acts as a useful drug in the prevention of different types of cancerous growth in pre-clinical trials particularly the gastrointestinal cancers. Thus over a decade scientists are working on the effect of Curcumin in the control of cancerous growth associated with *H. pylori* infection although the potentiality of Curcumin was authenticated mostly in *in vitro* studies as well as in small animals [118].

6. CONCLUSIONS

The purpose of the present review is to ascertain the current status of *H. pylori* associated development of gastric cancer which is a highly lethal disease. The establishment of *H. pylori* as a risk factor for this malignancy is based on an approach to identify infected persons' genetic makeup as well as environmental cues they are in who are at an increased risk of acquiring gastric carcinoma. However, infection with this organism is extremely common, and most persons colonized with the pathogen never develop cancer. Thus search for suitable techniques to identify high-risk subpopulations utilizing other biological markers are of utmost importance in combating the disease. Conclusions based on different recent studies on *H. pylori* related gastric cancer, it is apparent that cancer risk is the outcome of amalgamation of the genomic polymorphic nature of the infective bacterial strain population in the host, the host genotype itself and environmental effects, individually affecting the level of long-term interactions between *H. pylori* and humans gastric layer. Recent molecular biological based analytical tools including genome sequences information of both *H. pylori* and human, measurable phenotypic expression including CagA phosphorylation and practical animal models, which may be used to dissect out the biological basis of *H. pylori*-associated neoplasia, which should have direct clinical applications. As for example, persons with polymorphisms associated with high levels of IL-1 β expression and who are colonized by *cag*⁺ strains may be most likely to derive benefit from *H. pylori* eradication and as such suitable treatment could result in a substantially reduced cancer risk. Although antibiotics,

probiotics as well as natural treatment for *H. pylori* eradication exists still it is important to gain more insight into the molecular basis of pathogenesis of *H. pylori*-induced gastric adenocarcinoma. Researches based on the development of more effective treatments for this common cancer and to search for paradigm for the role of chronic inflammation in the genesis of other malignancies that arise within the gastrointestinal tract is the utmost need in the present era for the protection of humans from *H. pylori* associated gastric carcinoma.

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