Chapter 7

Unveiling the Intricacies of *Helicobacter pylori*-Induced Gastric Inflammation: T Helper Cells and Matrix Metalloproteinases at a Crossroad

Avisek Banerjee**, Asish K. Mukhopadhyay**, Sumit Paul, Arindam Bhattacharyya and Snehasikta Swarnakar

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1. Introduction

For most of the 20th century, the human stomach has been considered an environment that is inhospitable for the growth of any bacteria. But the first isolation of a curved, microaerophilic, gram-negative bacterium, *H. pylori* by Marshall and Warren in 1982 is responsible for provoking a rupture in contemporary popular medical doctrines, thereby enforcing changes in global conceptions of gastroduodenal disorders. *H. pylori* is of growing concern today because of its crucial role in the pathogenesis of chronic gastritis, peptic ulcer diseases and in the multi-step carcinogenic processess of gastric cancer, a fourth most common cancer worldwide while the second cause of cancer related deaths. Epidemiologically, more than 50% of the world population is infected by this bacterium and develops persistent inflammation in their stomachs, which lasts for decades unless treated with antibiotics. About 60-95% of peptic ulcer diseases are thought to be idiopathic and *H. pylori* is one of the causative agents of nearly all of these cases in adults. About 15% of infected individuals become symptomatic for peptic ulcer (duodenal or gastric) as a long-term consequence of infection. The apparent paradox suggests that the mere presence of *H. pylori* in the stomach is insufficient to cause gastric disease, rather requiring additional conditions. Beside bacterial genetics, host genetic factors, hygiene, microbiome, medication, food habits along with life-style might be additional reasons for *H. pylori*-induced pathogenecity.

Progression of gastric inflammation by long term association of *H. pylori* in stomach can broadly be viewed in two ways. The first being the antigenic stimulation of *H. pylori* and

the second one is the host immune response to microbe that is necessary for bacterial clearance yet causing injury to the host. Besides, *H. pylori* must bear an arsenal of specific virulence factor such as the cytotoxin-associated gene-pathogenicity island (*cag*-PAI), vacuolating associated cytotoxin gene A (*vacA*), outer membrane protein A (*oip*A), blood group antigen binding adhesin (*bab*A), lipases and lipopolysaccharides (LPS) be potentially toxigenic to initiate the process of inflammation in the host gastric tissues. These antigens can interact with specific host proteins, initiating a cascade of signaling processes which ultimately affect many abnormalities like loss-of-function of tumour suppressor genes, gain-of-function of oncogenes, dysregulation of miRNAs and several defects in cytoskeleton and cell-cell junctions.

On the other hand, the host immune response is characterized by the cardinal signs of inflammation. Both innate and adaptive immune systems are activated by inhabiting *H. pylori*. The principal mechanism of innate immunity includes complement activation, phagocytosis and the inflammatory response. The adaptive immune response is guided mainly by T cells including T regulatory cells (Tregs), T helper (T_H1) cells and more recently reported T_H17 cells and their corresponding cytokines. *H. pylori* has evolved with unique features to evade immune response. It also exhibits multiple strategies to reside within the host yet escaping host immune response (refer Box 1). Thus, it remains a mystery as to why some infected patients are susceptible to disease manifestation compared to others who remain asymptomatic throughout their lives in spite of infection.

- *Acidic milieu:* Gastric niche is acidic, while *H. pylori* grow normally at neutral pH but fails to grow at pH below 4. To overcome this problem, the bacteria secrete urease, which breaks urea into water and ammonia. This property has been successfully exploited for disease diagnosis known as urea breath test.
- *Non-Adherence:* For successful colonization, the bacterium has to successfully adhere to the gastric wall, but the peristaltic movements of the stomach provide a hostile barrier. However, *H. pylori* possess spiral shaped polar flagella, which permit proficient hydrodynamic movement within gastric mucous. About 20% bacterial population adheres to gastric epithelial cells but majority remains within mucous layer. *H. pylori* express several outer membrane proteins (OMPs) which bind to their receptors on gastric epithelial cells. For example, BabA is an adhesion molecule that binds to the fucosylated Lewis ^{b} receptor, SabA binds to sialyl Lewis^X receptor and OipA not only adhere onto gastric epithelial cells but also triggers β-catenin activation and secretion of proinflammatory cytokines.
- *Host Immune Response:* Activation of host immune system results in inflammation. Interestingly, this gram-negative bacterium has evolved with anergic lipopolysaccharide (LPS) and flagelin due to its modification of lipid a component that has about 10^3 times less endotoxin activity in comparison to LPS of other gram-negative bacteria. Moreover, *H. pylori* can acquire molecular mimicry by taking cholesterol from its host into its own membrane. Furthermore, Tregs upregulation following infection may suppress antibacterial immune response.

Box 1. Barriers overcome by *H. pylori* for colonization and infection in host.

It is known from several studies that MMP, a family of zinc-dependent endopeptidases that selectively degrade or remodel most of ECM components and other structural molecules are intimately associated to different diseases including gastric ulcer and cancer. At present,

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both *in vivo* and *in vitro* studies have established the activation of several MMPs during *H. pylori* association. However, very few studies have been made till date dissecting the significant role of T_H cell subsets and MMPs during the progression of *H. pylori* related gastric inflammation. In this review, we aim at to highlight the influence of T_H cells on modulation of MMPs activity during *H. pylori* induced gastric inflammation that further open up new avenues both in research and clinical perspectives in future. Since the present scenario failed to generate much hope on *H. pylori* vaccination we will emphasise on how *H. pylori* behave within gastric niche and how do they trigger inflammation?

2. Gastric inflammation: An overview

Persistent association of microaerophilic, gram-negative enteric bacteria results in chronic gastric inflammation which in turn leads to gastric cancer. Accumulating evidences suggest that *H. pylori*-induced inflammation is initiated both by host and bacterial factors. In addition, environmental factors also play potent role in disease progression. However, the actual pathogenesis behind chronic inflammation is not well understood. *H. pylori* enter inside stomach via fecal-oral route mainly by contaminated food and water (Klein et al., 1991, Hopkins et al., 1993). The most probable mode of transmission is via direct contact with the infected patient within the family or a common source of contaminated water or food of a locality (Hopkins et al., 1993) (Nurgalieva et al., 2002).

Gastric inflammation is accompanied by induction of oxidative stress by reactive oxygen species (ROS), inducible nitric oxide synthase (iNOS) and subsequent secretion of proinflammatory cytokines like interleukin (IL)-1β, IL-6 and tumor necrosis factor (TNF)-α (Yamaoka et al., 1996). Gastric epithelial cells also secrete IL-8 (Jung et al., 1997) which attracts the polymorphonuclear (PMN) cells. Local inflammation is also associated to reduced prostaglandin synthesis and increased infiltration of mast cells, neutrophils, macrophages and *H. pylori* specific IgA and IgG antibodies (Warren, 2000). The dendritic cells (DCs), which are present in the epithelial layer, present the antigens with their Toll-like receptors (TLRs) to naïve T cells and thereby initiate humoral immune response. Moreover, *H. pylori* infection stimulates iNOS and other enzymes including myeloperoxidases, NADPH oxidases, eosinophil peroxidases. These enzymes trigger ROS and reactive nitrogen species (RNS) production, which induce DNA damage (Wang et al., 2005).Therefore, *H. pylori*-mediated inflammation is complex and no single factor can be targeted for successful clinical therapy. For example the study on mast cell-deficient $Kitl^{Sl}/Kitl^{Sl\text{-}d}$ mice reported that mast cells also contribute to neutrophil recruitment and inflammatory response due to *H. pylori* infection thereby contributing a part though are not essential for vaccine-induced immunity (Ding et al., 2009).

Over-secretion of pro-inflammatory cytokines and growth factors promote neovascularisation, which cause invasion and metastasis. Vascular endothelial growth factor (VEGF), the main mediator of angiogenesis is reported to be over-expressed in 54% of severe gastric cancer patients with lymph node and liver metastasis (Saukkonen et al., 2003). Along with

VEGF, other pro-angiogenic factors like IL-6, IL-8 and iNOS are also upregulated in tumor cells. IL-8 promotes angiogenesis in gastric tumor by interacting with its receptors CXCR1 and CXCR2, present on surface of endothelial cells. Over expression of iNOS has been observed in both primary tumors as well as lymph node metastases compared to normal mucosa (Wang et al., 2005). Excess nitric oxide increases the activity of VEGF thereby promoting blood flow, vascular permeability and endothelial cell proliferation and migration (Wang et al., 2005). Other than stimulating angiogenesis, iNOS promotes gastric carcinoma through various ways including inhibiting DNA repair enzymes, inducing oxidative DNA damage, oncogene expression and apoptosis deregulation (Ohshima et al., 2003). The niche of *H. pylori* colonization is also a determinant factor for the severity of the disease. For example; chronic corpus-predominant gastritis leads to mainly gastric adenocarcinoma, in contrast antrum-predominant gastritis may promote duodenal ulceration. Also patients with *H. pylori* infection in the distal part (antrum) of the stomach may develop duodenal ulcer but are somewhat protective from gastric cancer. Thus, duodenal ulcer may have a protective role from development of gastric adenocarcinoma (Saukkonen et al., 2003).

In cancer tissues, there is very less information available regarding the association between a specific factor and methylation of a gene. Aberrant DNA methylation is frequently associated with different human cancers. DNA methylation is involved with change in gene expression pattern, which can be confirmed by measuring the mRNA levels of the corresponding genes. Nakajima *et al,* in human gastric cancer cell lines showed that DNA methylation pattern due to *H. pylori* infection was conserved in the promoter region of 48 genes. Interestingly, this methylation pattern remained in gastric cancer patients; who were previously infected with *H. pylori* but later eradicated (Nakajima et al., 2009). Similarly from *Mongolian gerbils* (Niwa et al., 2010) 10 CpG islands showed specific methylation pattern after *H. pylori* infection, which sustained the inflammatory response of the host towards *H. pylori* infection rather than *H. pylori* itself. Therefore with reduction of inflammation, there was reduction in DNA methylations, even as *H. pylori* load remained unchanged. So, long term *H. pylori* infection induces chronic inflammation, the later maintain epigenetic changes inside host's genome.

From evolutionary view point, the successful adaptability of *H. pylori* within the host can be attributed to their versatile genetic diversity, which has specifically evolved for a habitat, population or geographical locations. The virulence of *H. pylori* depends on what specific antigens they possess. Interestingly, nature selected both Cag A^+ (high virulence) as well as $CagA^-$ (less virulent) bacteria during the course of evolution. Possibly, high-virulence implies successful host attack; while less-virulence implies their innovative masking strategy from host's immune response. So, diversity seems to help bacteria to keep the host alive even with infection, in turn preserving them. Therefore, one of the most intriguing aspects of *H. pylori* is its genetic diversity, the biological significance of which is enigmatic (Covacci and Rappuoli, 1998, Logan and Berg, 1996). The bacteria colonize the gastric mucus layer and persist livelong in close vicinity with epithelial cells. Though bacterial colonization depends on their secreting system, which they use as molecular syringes to inject their virulent component into the host (Kamada et al., 2012), yet competition also play crucial role for *H. pylori* colonization inside the gut and hence, the gut microbiota is often referred to as the for-

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gotten organ (Sperandio, 2012). The human gastrointestinal tract hosts bacterial cells as many as 10 times more than total number of cells of human body (Hooper and Gordon, 2001). These bacteria compete with pathogens like *H. pylori* for food source. Therefore, changes in microenvironments like high salt-intake, change in life-style or food-habits give stress on normal gut microbiota and helping *H. pylori* to proliferate and induce infection.

3. Genetics of *H. pylori* and gastropathy

H. pylori are a highly heterogeneous bacterial species, both genotypically and phenotypically, and are highly adapted for survival in the gastric niche. The genomic diversity of *H. pylori* parallels that of its host species, consistent with colonization of the earliest humans and co-migration out of east Africa at least 60,000 years ago (Censini et al., 1996). *H. pylori* colonize the stomach for almost the entire lifetime of the host. *H. pylori* colonization of the gastric mucosa typically occurs in early childhood and may persist for decades or for life, unless eradicated by antimicrobial treatment.

The clinical outcome of *H. pylori* infection is determined by multiple factors, including host genetic predisposition (especially certain cytokine polymorphisms (Amieva and El–Omar, 2008), *H. pylori* strain heterogeneity and environmental factors such as dietary salt intake (Fox et al., 1999, Beevers et al., 2004, Hwang et al., 1994). *H. pylori* heterogeneity and the association with *H. pylori* virulence factors have been intensively investigated over the past two decades (Covacci et al., 1993, Atherton et al., 1995, Argent et al., 2004). One possible problem that has complicated the identification of definite disease-specific *H. pylori* virulence factors is the considerable geographic diversity in the prevalence of *H. pylori* virulence factors. The major *H. pylori* candidate virulence factors include cagA, vacA, babA and dupA.

cagA was the first reported gene that varies in *H. pylori* strains and considered as a marker for the presence of cag-PAI, which include a number of other genes associated with increased virulence (Broutet et al., 2001). The gene that encodes CagA is part of a ~40 kb horizontally acquired DNA segment in the *H. pylori* genome known as cag-PAI (Censini et al., 1996). The cag-PAI also contain genes encoding a type IV secretion system, to ensure efficient translocation of the CagA protein into the host epithelium.The CagA also disrupts the tight junctions and causes loss of apical-basolateral polarity in epithelial cells (Amieva et al., 2003).

The extent of biological activity of CagA is directly associated with the number of phosphorylation sites or the number of EPIYA motifs present at the C-terminal region of CagA (Higashi et al., 2002b, Azuma, 2004, Azuma et al., 2004). Thus, molecular weight of the CagA protein varies from 128 kDa -148 kDa and the *cagA* gene shows extensive length polymorphism at the 3′ end. Several attempts were made to type the distinct CagA proteins and the *cagA* genes on the basis of its length polymorphism at the C-terminal and 3' ends, respectively (Argent et al., 2005, Dong et al., 2002, Owen et al., 2003). Mutational analyses revealed that the first two EPIYA motifs (Y1 and Y2 positions) have little, if any, biological function while the other motifs are responsible for the CagA phosphorylation and CagA-SHP-2 complex formation (Higashi et al., 2002a). Moreover, the amino acid sequences, which are repeated among the third, fourth and

fifth EPIYA motifs differ among strains isolated from west and east Asia. Accordingly, CagA was typed as Western-CagA-specific sequences (WSS) and East Asian-CagA-specific sequences (ESS) and this difference may account for differences in disease outcome between the two geographical regions. Recent study suggested that EPIYA motifs as well as the spacer sequence units were present as distinct insertions and deletions, which possibly have arisen from extensive recombination events (Chattopadhyay et al., 2012). Moreover, several new CagA types have been identified, a new typing system has been proposed. It is hypothesized that a *cagA* gene encoding higher number EPIYA motifs may perhaps have arisen from *cagA* genes that encode lesser EPIYA motifs by acquisition of DNA segments through recombination events (*refer figure 1a)*. Chattopadhyay *et al* also described that carrying a particular type of CagA is not the only determinant for the disease outcome especially in the developing countries like India, where multiple infections with different CagA primary structures are possible. Recent study regarding the multiple infections and microdiversity among the colonies from individual patient in Indian population suggested that most of the patients have acquired *H. pylori* due to repeated exposure to this pathogen with different genetic make-up, which may increase the possibility of super infections(Patra et al., 2012). Genetic exchanges between these unrelated *H. pylori* strains may support certain *H. pylori* variant to grow better in a given host than the parental strain and thereby increasing the possibility for the severity of the infection (Patra et al., 2012) (*refer figure 1)*. Additional isolates of the sequenced *H. pylori* strain J99 from its human source patient after a 6-year interval was analyzed in another study (Israel et al., 2001). Patterns of genetic diversity were distinct among the additional J99 isolates, both when compared with each other and to the original prototype isolate. Their results indicated that within an apparently homogeneous population remarkable genetic differences existed among single-colony isolates of *H. pylori*. Direct evidence that *H. pylori* has the capacity to lose and possibly acquire exogenous DNA is consistent with a model of continuous microevolution within its cognate host (Israel et al., 2001).

Soon after *H. pylori*'s discovery, it was reported that a protein in *H. pylori* broth culture filtrates could cause the formation of large intracellular vacuoles in cultured mammalian cells (Leunk et al., 1988). The *H. pylori* protein responsible for this effect (designated VacA) is encoded by a chromosomal gene known as *vacA.* The *vacA* gene encodes a precursor protein of 140 kDa (Cover et al., 1994, Telford et al., 1994, Lupetti et al., 1996). Proteolytic processing of the protoxin during secretion yields the mature toxin (~90 kDa). Secreted VacA can be further processed into an N-terminal fragment of 33 kDa (p33) and a C-terminal fragment of 55 kDa (p55), but cleavage does not seem to be necessary for VacA activity. Although the p33 domain exhibits pore-forming activity necessary for vacuole formation (McClain and Cover, 2003), and the p55 domain is responsible for target cell binding (Reyrat et al., 1999), Several families of *vacA* alleles can be distinguished on the basis of diversity near the 5′ terminus of *vacA* (which is known as the s-region s1a-c and s2), the intermediate region (i1, i2) and in the mid-region of the gene (known as the m-region m1, m2) (Atherton et al., 1995, Rhead et al., 2007). Most strains with s1/m1 genotype and some of the s1/m2 express the cytotoxin while strains with s2/m2 genotype do not express a toxic VacA (Cover and Blanke, 2005). Studies have shown that VacA contributes to *H. pylori* colonization, persistence and disease outcome *in vivo*. *H. pylori* strains that contain *vacA* alleles of the s1 type are associated with an in-

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creased risk for development of peptic ulcer disease and gastric cancer compared with strains containing *vacA* alleles of the s2 type (Atherton et al., 1995, Van Doorn et al., 1999, van Doorn et al., 1998, Figueiredo et al., 2002). However, east Asian strains are almost universally s1/m1 and are not associated with any specific clinical outcome (Ito et al., 1997, Ito et al., 1998).

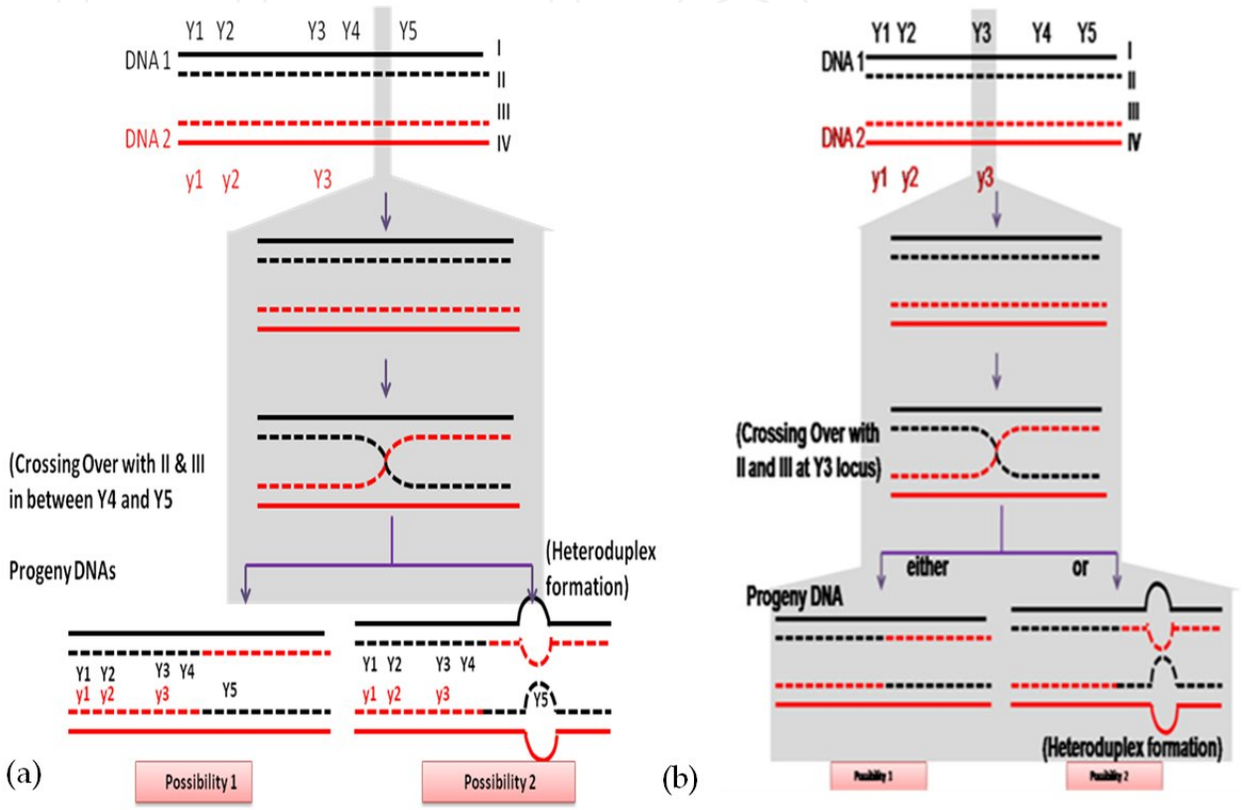

Figure 1. Schematic representation of generation of genetic diversity in cagA gene involving EPIYA motifs (Ys): (a) genetic diversity arise within a cagA gene from another cagA gene that encode lesser EPIYA motifs by acquisition of DNA segments through homologous recombination events or **(b)** genetic variation within a cagA gene may also result from crossing over within any particular EPIYA motif (for example Y3 as shown in the figure). In all the events, crossing over can also happen involving DNA strands I and IV, as mentioned above and therefore can generate more genetic variation within cagA gene. It is to be noted that DNA 1 and 2 are genetically different. The rationale behind making the two strands of a DNA dissimilar due to acquision of new mutations is highlighted.

Approximately 4% of the *H. pylori* genome encodes a diverse repertoire of outer membrane proteins (OMPs), the largest of which is the 21-gene Hop family. Several of the Hop proteins have been identified as adhesins, the best studied of which is BabA (Ilver et al., 1998, Guruge et al., 1998). It is an adherence factor expressed in a subgroup of *H. pylori* strains and binds to difucosylated Lewis b (Leb) blood group antigens found on gastric epithelial cells. The *babA* gene was cloned initially from strain CCUG17875, which contains a silent *babA1* gene and an expressed *babA2* gene. The sequence of these two genes differs only by presence of a 10bp deletion in the signal peptide sequence of *babA1* that eliminates its translational initiation codon (Prinz et al., 2001). Initial studies indicated that *H. pylori babA2*$^{+}$ strains are associated with an increased risk of peptic ulcers and distal gastric adenocarcinoma, whereas *babA2*$^{-}$ strains are

more often associated with uncomplicated forms of gastritis (Gerhard et al., 1999, Prinz et al., 2001). *babA2*-genopositive *H. pylori* usually coexists with other disease-related *H. pylori* virulence-factor genes, such as *vacA s1* and *cagA.* Tripositive strains, which have *cagA*$^{+}$, *vacA s1*, *babA2*$^{+}$in a single *H. pylori* species, further increase the risk of developing gastroduodenal ulcers and distal gastric cancer(Prinz et al., 2001, Gerhard et al., 1999).

Recent studies have proposed the possibility of using genetic markers in the plasticity zone as indicators of pathogenicity for *H. pylori* infection, in spite of a lack of credible knowledge regarding the functions of the putatively encoded proteins in this cluster. It seems that these determinants may play a key role in determining the virulence capacity of *H. pylori* strains either directly or by encoding factors that may lead to varying clinical outcomes. The association between some of the ORFs in the plasticity zone and various disease categories has been previously reported. For instance, Occhialini *et al.* (Occhialini et al., 2000) found that two single ORFs (*jhp0940* and *jhp0947*) were more prevalent in strains isolated from patients with gastric adenocarcinoma in Costa Rica. However, Santos *et al.* (2003) (Santos et al., 2003) showed the association between *jhp0947* and duodenal ulcer (DU) as well as gastric cancer in Brazilian patients. This was once more confirmed for *jhp0947* and *jhp0949* genes in DU patients from the Netherlands (de Jonge et al., 2004).

Recently, a novel duodenal ulcer promoting gene (*dupA*) was described, which consists of two ORFs *jhp0917* and *jhp0918* and form one continuous gene by the insertion of a base T or C after the position 1385 of the *jhp0917* in the 3' region (Lu et al., 2005). This gene (homologues to *virB*4) is located in the plasticity region and is associated with increased risk of DU and protective against gastric atrophy, intestinal metaplasia and gastric carcinoma in Japan and Korea (Lu et al., 2005). However, the role of *dupA* as a virulence marker is still controversial. Some researchers have supported the interpretations of Lu *et al.* (2005) (Lu et al., 2005) but others did not find any association. Hussein *et al.* (2008) (Hussein et al., 2008) have reported that *dupA* gene is associated with peptic ulcer but they did not find any negative association with gastric cancer in Iraqi population. In Chinese and north Indian populations significant association of *dupA* with DU was established (Arachchi et al., 2007). In contrast, Argent *et al.* (2007)(Argent et al., 2007) showed no association of *dupA* gene with DU in population from Belgium, South Africa, China and the United States. Meta-analysis based study by Shiota *et al.* (2010) (Shiota et al., 2010) has shown that the presence of *dupA* gene was significantly associated with DU. Another systematic review confirmed that *dupA* was associated with gastro duodenal diseases (Hussein, 2010). Study in southeast Indian population demonstrated that *dupA* gene was 6.5 times more prevalent in duodenal ulcer patients than non-ulcer patients (Alam et al., 2012). Infection with the *dupA*-positive *H. pylori* increased the risk for DU overall and this evidence was significant in Indian study (Alam et al., 2012). The discrepancy of *dupA* association with diseases outcome could be related to the limitation of PCR techniques for detecting the intact *dupA* gene or may be a consequence of the genetic diversity of *H. pylori*, which is at a level as yet unseen among other bacterial pathogens (Covacci and Rappuoli, 1998, Logan and Berg, 1996, Blaser 1998).

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4. Immunobiology of host and *H. pylori* interaction in both *in vivo* and *in vitro*

Through evolution, *H. pylori* have gradually developed highly sophisticated adaptation for successful colonization and better adaptation inside the host's microenvironment. Interestingly, humans too show some tricky adaptation to check *H. pylori* colonization inside the stomach. The *in vitro* studies documented (Linden et al., 2009) that human gastric cell-surface mucin MUC1, a large glycoprotein, prevents the adhesion of the bacterium with the epithelial layer. *H. pylori* usually bind to MUC1 through their cell surface receptor BabA and SabA adhesion proteins, but the human gastric cells shed these MUC1 glycoproteins by MUC1 sheddases ADAM17 and MMP-14. Similarly, in murine model too, MUC1 prevents *H. pylori* colonization (McGuckin et al., 2007).

After entering the gastric milieu, most of the bacteria remain in the gastric mucosa and only about 10% *H. pylori* bind with the gastric epithelial cells (Oh et al., 2005, Semino-Mora et al., 2003). So it becomes difficult to eradicate the bacteria with antibiotics. *H. pylori* adhere via BabA (Ilver et al., 1998) with histo-blood group antigen Le^b expressed over gastric epithelial cell surface. The other protein that significantly contribute stable adherence of *H. pylori* is sialic acid-binding adhesion protein (SabA) which bind to $Lewis^X$ (Mahdavi et al., 2002), a glycosphingolipid that is significantly expressed during gastric dysplasia (Hansson et al., 1993).

The genetic study in relation to the virulence factor has been extensively studied in relation to *cagA* and *vacA* (Peek and Crabtree, 2006). CagA positive *H. pylori* strains impart higher risk for gastric cancer (GC) than infection of strains that devoid of *cag*PAI (Parsonnet et al., 1997, Enroth et al., 2000). After stable adherence, *H. pylori* with its type IV secreting system translocate CagA into the gastric epithelial cells (Segal et al., 1999). Once inside, Cag A is differentiately phosphorylated at its specific tyrosine residues in their EPIYA (Glu-Pro-Ile-Tyr-Ala) motifs located at the C-terminal region of the protein (Higashi et al., 2002a). This phosphorylation is carried out by host's Src and Abl family kinases (Selbach et al., 2002, Poppe et al., 2007). A variety of tyrosine phosphorylation motifs results in difference in virulence and consequently host infection(Higashi et al., 2002a).This overall difference in phosphorylation of the tyrosine motifs may be the reason for diversity of GC incidence in the global scenario (*refer figure 1)*. Phosphorylated CagA can interact with several other host proteins and ultimately targets specific proteins including oncoprotein, tumor suppressing protein, junction proteins, cell cycle regulators and several other transcription factors. These collectively affect the cell's normal physiology and propel the cells toward carcinoma. The phosphorylated CagA protein binds to SH2 domain of tyrosine phosphatase and increases its phosphatase activity (Higashi et al., 2002b, Hatakeyama, 2004). SHP-2 is an important component involved in intracellular signaling during development and haematopoiesis whose gain-of-function lead to lymphoid and myeloid malignancy (Tartaglia and Gelb, 2005). Due to the intrinsic membrane tethering property of CagA the CagA-SHP-2 complex localizes to the plasma membrane of the host epithelium (Higashi et al., 2002b), leading to deregulation of the SHP-2. This event is necessary and sufficient to change the gastric epithelium to a transformed epithelium, which is characterized by altered cellular proliferation,

migration and elongated cell morphology known as hummingbird phenotype (Higashi et al., 2002b, Yamazaki et al., 2003). So, transgenic expression of CagA also manifest gastrointestinal as well as hematopoietic abnormalities (Ohnishi et al., 2008). *H. pylori* having a functional *cag* PAI also stimulate cultured gastric epithelial cells to secrete the pro-inflammatory cytokine or chemokine IL-8 (Crabtree et al., 1995). CagA binds to SHP-2 and induces 'humming bird phenotype' in AGS cell line involving extracellular signal-regulated kinase (Erk), mitogen-activated protein (MAP) kinase pathway and dephosphorylating focal adhesion kinase (FAK) (Tartaglia and Gelb, 2005) (Higashi et al., 2004). Cag A also interacts with Crk and thereby promotes loss of adhesion in gastric epithelial cells (Suzuki et al., 2005). In addition, Cag A also interacts with other factors including c-Met and Grb2 (Churin et al., 2003, Mimuro et al., 2002). In addition to the above components, *H. pylori* also secrete nucleotide-binding oligomerization domain-1 (NOD1), a specific peptidoglycan of gram-negative bacteria (Viala et al., 2004), a potent molecule involved in stimulating the host innate immune response (Fox and Wang, 2007).

The other virulence factor in *H. pylori* is VacA. The intra-luminal environment of VacA-induced vacuoles is acidic, and the vacuoles are endocytically active (Cover et al., 1991, Papini et al., 1994). A current model to explain the mechanism by which VacA induces vacuole formation proposes that VacA binds to the plasma membrane of cells, is internalized by cells, forms anion-selective channels in endosomal membranes and alters the permeability of these compartments. Within 10 minutes of addition of VacA to a human gastric adenocarcinoma cell line (AZ-521), two classes of mitogen-activated protein kinases (p38 and ERK1/2) and the activating transcription factor 2 (ATF2) signalling pathway are activated (Nakayama et al., 2004). Within 30–60 minutes of the binding of VacA to BHK-21 cells expressing receptor protein tyrosine phosphatase β (RPTPβ, also known as Ptprz), tyrosine phosphorylation of G-protein-coupled receptor kinase interactor (Git1) can be detected (Fujikawa et al., 2003). In another model system, binding of of VacA to a mast cell line (RBL-2H3) cells results in a rapid change in cytosolic calcium concentrations (de Bernard et al., 2005). VacA is also reported to induce pro-inflammatory effects. It stimulates the production of TNF-α and IL-6 by mast cells and induces chemotaxis and degranulation of these cells (de Bernard et al., 2005). Moreover, VacA treatment stimulates expression of cyclooxygenase-2, a proinflammatory enzyme, in neutrophils and macrophages (Boncristiano et al., 2003). Thus, the effects of VacA on immune cells are complex and are characterized by both immnostimulatory and immnosuppressive actions.

5. Role of T cells in *H. pylori* infection

Very limited information is available on how the host immune system; particularly the adaptive immune system is modulated by *H. pylori* infection to promote gastric diseases. Chronic inflammation associated to *H. pylori* infection is known to promote gastric cancer in some individuals (Suerbaum and Michetti, 2002, El-Serag and Rudolph, 2007). In contrast to earlier notion that T cells generate antitumor responses, as supported by the fact that $Rag^{-/-}$ mice and mice with mutated interferon signaling promote more tumor development, recent

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advances establish new insights into T cells particularly TH17 response in aggravating gastric cancer due to *H. pylori* colonization (Erdman et al., 2003, Dunn et al., 2006).

Bacterial chemotaxis is their inherent property by which it can migrate from a harsh environment towards more favorable environment. Genetically modified *H. pylori* (Che^-) cannot respond to environmental stimulus although they retain power of locomotion. In animal models, they manifest marginal colonization abnormalities and relatively less inflammation severity. Interestingly, Che^- *H. pylori* fail to colonize epithelial cells and gastric glands vigorously. This support the fact that chemotaxis helps the bacteria to successfully cross the thick mucus layer with their unipolar flagella and adhere to gastric epithelial cells which are resident of antigen presenting cells (APCs); thus promoting antigen presentation to naïve T cells (Rolig et al., 2011). In the process, epithelial cells also secrete chemokines for recruiting APCs like DCs. DCs with their Toll-like receptors recognize specific antigens of the bacteria; and in turn presents those antigenic peptide fragments to T cells to promote class switching and differentiation in TH1 subsets, T regs or more recently classified TH17 cells (*refer figure 2)*. Specific cytokines secreted by these cells regulate host immune response leading towards chronic inflammation.

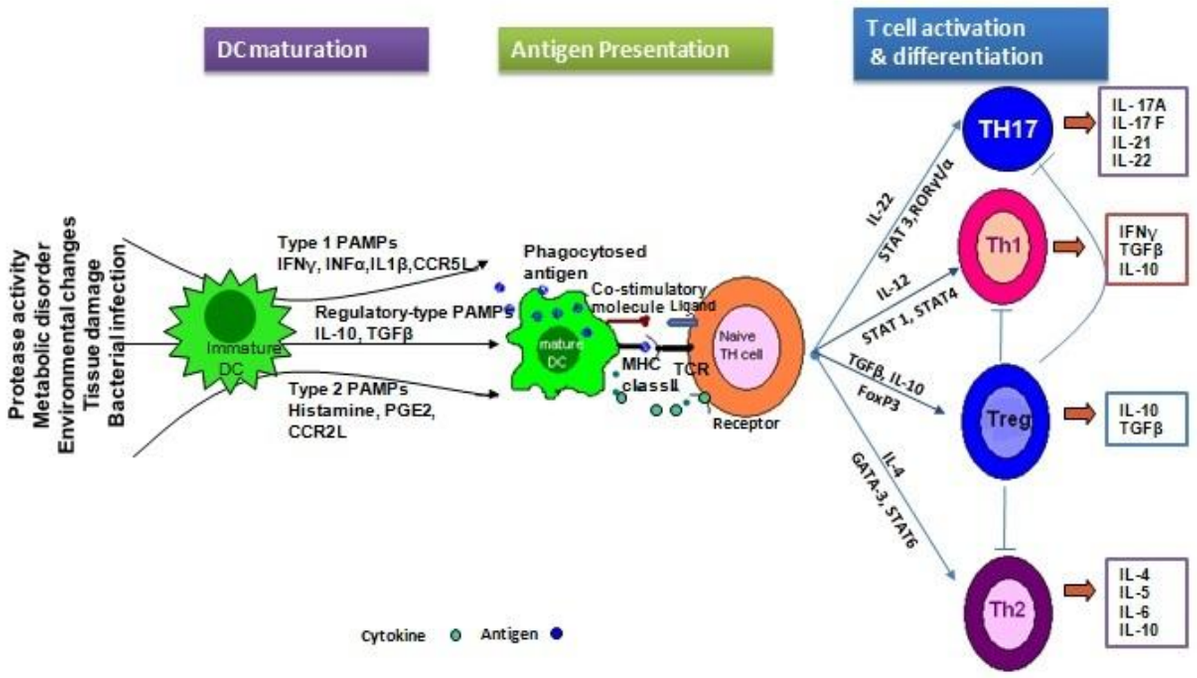

Figure 2. Maturation of DC and formation of T cell subsets following exogeneous stimuli: Maturation of dendritic cell (DC) occurs under the influence of different pathogen-associated molecular patterns and specific host cytokines.Various physiological and environmental factors also trigger DC for successful antigen presentation. Upon maturation, DC expresses MHC II and co-stimulatory molecules including cytokines and growth factors which enhance antigen presentation, naïve T cells activation followed by differentiation into TH1, TH2, TH17 and regulatory T cell (Treg). Each T cell subtypes has its own signature cytokines which perform effector functions as well as maintain balance among various other T cell subtypes.

The mechanism underlying differentiation of T cell has been intensively investigated: Stat1 and Stat4 signaling drive TH1 response; Stat6 signaling promotes TH2 whereas Stat3 signaling drives TH17 responses. IL-2 drives TH1 responses and results in (interferon) IFNγ production; that may have carcinogenic effect. However, role of TH2 and TH17 are not well known (Dunn et al., 2006) until recent reports suggest that TH17 may play a pivotal role in *H. pylori*-mediated gastric cancer (Rolig et al., 2011). In addition, nuclear transcription factors, NF-κB are normally activated during *H. pylori* infection. This is not unusual since conditional knock-out mice have shown that NF-κB not only signals epithelial cells to undergo transformation but also myeloid cells which are source of inflammation (Greten et al., 2004, Karin and Greten, 2005). NF-κB in turn promotes IL-6 expression and contribute to carcinogenesis (Naugler and Karin, 2008). Key features that appear to be IL-6 specific are triggering proliferative, pro-angiogenic and anti-apoptotic genes including Stat3 (Yu and Jove, 2004). Under Stat3 signaling, the role of TH17 in case of an enteric bacteria like *H. pylori* become significant. Recent studies have focused on the post-transcriptional modification within naive T cells that are ultimately primed by APCs for proliferation and differentiation into effecter T cell subtypes. Posttranscriptional regulation rather repressions of target genes may be responsible for development of T cell subtypes. On this account miRNA has received much attention in various diseases including cancer. miR-155 is expressed in variety of immune cell type's namely DCs, macrophages, TH1 and TH17 cells. In myeloid cells, miR-155 is induced by TLR and TNFα that in turn activate AP-1 and NF-κB transcription factors (Oertli et al., 2011). miR-155$^{-/-}$ mice show TH2 bias development, signifying miR-155 mediated TH1 response. miRNA is also reported to be involved in TH17 differentiation (O'Connell et al., 2010). It was demonstrated that miR-155$^{-/-}$ mice were incapable of spontaneously arresting *H. pylori* load, lacked vaccine-induced protective immunity and failed to induce infection-associated preneoplastic pathology (Oertli et al., 2011).

The role of Tregs in modulating host immune response during *H. pylori* infection has been speculated for quite a sometime. Tregs are a subset of T cells that suppresses the host immune response and are associated with cancer and parasite infection. These specialized T cells express markers like CD4, CD25, and FoxP3. Tregs increase the tolerance towards self-antigens and at the same time facilitates the growth of tumors through immunosupression. Once differentiated Tregs proliferate and maintain their population through autocrine signaling pathway and starts secreting immunosuppressive cytokines like IL-10 and TGFβ (Joetham et al., 2007). Reports indicate that reduction of Tregs can actually stimulate the immune response against other microbial infections (Belkaid et al., 2002). In recent years, the observation shows that the rate of Treg infiltration in human stomach is proportionate to the degree of inflammation and *H. pylori* density. Interestingly, this study also concluded that Treg infiltration parallels the increased expression of programmed cell death 1(PD-1), a negative regulatory molecule belonging to CD28/B7 family (Wu et al., 2001).

It has been hypothesized that better hygiene in Europe and America has inversely proportional with the rise of asthma, due to lack of early exposure to microbial antigens. Arnold *et al* reported that prior infection with *H. pylori* in neonatal mice increases the number of long lived Treg cells in the airways and thereby checks the development of asthma. In support, the experi-

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ments were performed to sensitized mice with ovalbumin to generate primary T cell response, following feeding virulent *H. pylori* to both neonatal and adult mice prior to application of aerosolized allergic antigens. This showed *H. pylori* infected neonatal mice have reduced airway hypersensitivity and less number of immune cells in bronchoalveolar lavage in compared to the control; even to adult mice infected with *H. pylori* (Papatriantafyllou, 2011).

H. pylori induced gastric inflammation relates to both TH1 and TH2 mediated phenomena. *H. pylori* infection was looked out as predominantly TH1 mediated inflammatory pathway. But recent reports show deviation from the earlier notion. Kido et al (2010) demonstrated that in humans, an epithelial derived cytokine, thymic stromal lymphopoitein (TSLP), induces DC-mediated TH2 inflammatory response and thereby triggering B cell activation in *H. pylori*-induced gastritis. *H. pylori* infection results in mixed T cell response. Several studies established the upregulation of TH1 (Bimczok et al., 2011), TH2 (Kido et al., 2010), Treg (Mitchell et al., 2012), TH17 (Shi et al., 2010) subtypes suggesting seems a host immunomodulatory balance for inflammation. TH17 followed by TH1 (Shi et al., 2010) upregulation may promote acute inflammation via IL-17 and gelatinase activity (*refer figure 3)*. The above inflammatory condition is counter balanced by Treg's IL-10 to promote chronic infection by partial immunosuppression. Thus, TH17 plays a significant role to develop inflammation due to *H. pylori* infection, though better understanding of how TH17 is activated during post infection along with its exact role during infection remains open for further investigation. However, post infection when inflammation begin the order of T cell subset activation may be first through TH17, TH1 lymphocytes (Shi et al., 2010) and finely counterbalanced by immunosuppressive Treg activation. Thus, the frequency of tumor-infiltrated Th17 cells decreases in advanced disease human patients. In contrast, tumor-infiltrated Treg increases compared with early disease human patients. Therefore, maintenance of fine tune balance between Treg and TH17 seems crucial (Kao et al., 2010, Maruyama et al., 2010).

6. Tracking the matrix metalloproteinases during infection

Proteinase are a class of enzymes capable of hydrolysing peptide bonds. These biocatalysts are largely classified into two major groups: exopeptidases and endopeptidases, depending on the site of cleaving a peptide bond either proximal or distal to the amino or carboxy termini of the substrate respectively. They are further subdivided into serine proteases, threonine proteases, cysteine proteases, aspartate proteases, metalloproteases, glutamic acid proteases based on their catalytic properties (Hartley, 1960). Source of proteases are mainly restricted to stomach, pancreas and small intestine; where they are utilized for digestion of protein. Matrix metalloproteinases (MMPs) are Zn-requiring endopeptidases, the essential player for ECM remodeling of tissues. The function of MMPs are tightly regulated at several levels by via different mechanisms including synthesis in zymogen, localization in cellular compartments like granules or lysosomes, inhibition by protease inhibitors and inactivation in response to change in pH and/or temperature. However, virulent bacteria colonizing the gut sometime secrete proteases that can directly activate host MMPs, thereby increasing their biochemical efficiency to degrade host's ECM (Löwer et al., 2008). Therefore, disba-

lance of proteases and/or protease inhibitors play decisive role in chronic inflammation and cancer (Wex et al., 2004). In this chapter we will limit our discussion to MMPs as their role in gastric inflammation as well as in gastric cancer is just relevant (Knapinska and Fields). MMPs comprise more than 29 different proteases that differ in the expression profile, substrate specificity, subcellular localisation and functional implications (Birkedal-Hansen et al., 1993). Among them, gelatinases, (MMP-2 and MMP-9) and stromelysin-1 (MMP-3) collectively cleave gelatins (types I and V), collagens (type IV, V, VII, IX and X), elastin, fibronectin, laminin and proteoglycan core proteins. The activities of MMPs are regulated by the endogenous tissue inhibitors of metalloproteinases (TIMPs), while cytokines, growth factors, tumour promoters and transcription factors including nuclear factor NF-κB and activator protein AP-1 modulate their gene expressions. The balance between MMPs and TIMPs is a critical factor for diverse cellular functions including cellular proliferation, migration, adhesion and apoptosis (Somerville et al., 2003). Based on the important role of certain members of MMPs in cancer, including gastric cancer, they have been studied to a large extent in chronic gastritis and premalignant lesions in the stomach (Pender and MacDonald, 2004, Schuppan and Hahn, 2000).

To explore the role of host proteinases during *H. pylori* infection, *in vivo* models are essential. Although, a majority of *H. pylori* strains do not colonize mouse, the few that do have substantially contributed in understanding the pathogenic mechanism of this bacterium and helped largely in the development of therapeutic strategies against it (Kundu et al., 2011). Because of the ease with which gelatinases MMP-2 and -9 can be assayed in a zymography, host MMP-9 and MMP-2 activities were reported to be first up regulated in *H. pylori* infected gastric mucosa (Kundu et al., 2006, Mori et al., 2003, Kubben et al., 2007). However, reports regarding the expression of TIMP-1 and TIMP-2 in course of *H. pylori* infection are not straightforward. Several studies have reported unchanged or even increased expression of both TIMP-1 and TIMP-2 (Cheng et al. 2012) while a few others claimed decreased expression of TIMP-1 in course of *H. pylori* infection and augmentation of TIMP-1 expression following a course of *H. pylori* eradication therapy (Kundu et al., 2006, Kundu et al., 2011). Reports of other studies soon followed and workers identified several other MMPs including MMP-3, MMP-7, MMP-1, MMP-13 and MT1- MMP as target genes in *H. pylori* infection (Schuppan and Hahn, 2000). While ascribing functionality to these enzymes, localization of MMP-9 expression was observed in the macrophages infiltrating the gastric mucosa that elicited the inflammatory response in the host through activation of cytokine networks (Kundu et al., 2011). A correlation was observed between the expression of MMP-7 and bacterial virulence factor CagA and functionally the MMP-7 upregulation was shown to be involved in the degradation of insulin-like growth factor binding protein-5, leading to higher insulin-like growth factor-II levels that explained epithelial hyper proliferation and stromal expansion in *H. pylori*-infected subjects (Steele et al., 2007). An increasing pool of evidence suggested the increased expressions of several pro-inflammatory cytokines and in *H. pylori*-associated gastro duodenal disorders. Among them, TNF-α and IL-1β are essentially involved in the activation of NF-κB in gastric epithelial cells (Münzenmaier et al., 1997), which in turn induces several inflammatory genes including IL-8, iNOS and several MMPs (Wroblewski et al., 2003). Reports suggested that IL-1β was a key mediator for the induction of

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MMP- 1 and -3 in gastric adenocarcinoma (AGS) cells (Wallasch et al., 2002), whereas MMP-9 induction was regulated via the NF-κB pathway(Kundu et al., 2011). Using the ADAM-17 deficient mice, it was shown that this protease is essential for the *H.pylori*-dependent activation of epithelial growth factor receptor (EGFR) and downstream pathways including ERK 1/2 and MMP-7 production(Lee et al., 2003). In addition to the epigenetic dysregulation of MMPs in *H. pylori* infection, several gene polymorphisms in MMP-1, 3, 7 and 9 have been identified to be associated with ulcer disease or gastric cancer (Matsumura et al., 2005, Zhang et al., 2004, Alakus et al., 2010, Dey et al., 2012).

Another way of exploring host-pathogen interaction is to co-culture the parasite and the host cell that it infects. In this regard AGS cell lines co-cultured with *H. pylori* provide a good model to intensely investigate the function of bacterial as well as host secreted MMPs. The functions of bacterial MMPs are currently the focus of investigation. A typical *H. pylori* bacterium has around 1500-1600 genes in its genome, out of which at least 20 are proteases. Notably, a 200 KD zinc-dependent endopeptidase was isolated from *H. pylori* and found to be localized on the bacterial outer membrane and like other MMPs it was also secreted into the conditioned medium. *H. pylori* also co-cultured with AGS cells also expressed MMP-3 like enzyme and TIMP-3 like protein. Moreover, expression of bacterial MMPs and TIMPs suggested the involvement of bacterial type IV secretory system which might transfer Cag A protein into gastric epithelial cells allowing *H. pylori* to modulate host MMP and TIMP mobilization which could trigger the onset of *H. pylori* mediated insult in the host (Windle and Kelleher, 1997, Göõz et al., 2001, Sokolova et al., 2012, Oliveira et al., 2006).

7. Th-17 governs matrix metalloproteases: A pertinent query in clinical therapy

Upon *H. pylori* infection different T cell subtypes in the host having specific surface marker, cytokine profile and transcription factor, arise from CD4+ T cells (Reiner, 2007).The pathways involved in tissue damage during gastritis or gastric adenocarcinoma are complex. However, disruption of tissue architecture is deeply associated with a class of proteases namely MMPs. MMPs are capable of cleaving almost all ECM proteins and connective tissues (Nagase and Woessner, 1999). It has been observed earlier that *H. pylori*-induced gastric ulcer and gastrointestinal diseases are associated with regulation in MMP expression profile and activity profile involved in gastric tissue (Saarialho-Kere et al., 1996, Pender and MacDonald, 2004, Hellmig et al., 2006). The major source of MMP in stomach is gastric epithelial cells (Pillinger et al., 2005, Mori et al., 2003). Several studies were mainly focused on reporting the basic changes occurring on MMPs during infection and the cell signaling cascade associated with it. At the same time, significant reports were published from the immunological perspective upon *H. pylori* infection on the host. However, the story may not complete if we don't connect the two ends of the stick. On a broader view, there are accumulating evidences that T cell secreted cytokines primarily regulate MMP secretion from the gastric epithelial cells (MacDonald et al., 1999),though *in vitro* studies support *H. pylori* can alone stimulate gastric epithelial cell lines to secrete MMPs (Crawford et al., 2003, Bebb et

al.), which are collectively responsible for disrupting tissue architecture. The general view is that once *H. pylori* antigen is taken up and presented by antigen presenting cells (APCs) to naïve T cell, the later start to differentiate into specific effecter T cell subsets. These specialized subtypes of T cells start secreting specific cytokines, which ultimately activate gastric epithelial cells to produce specific MMPs.

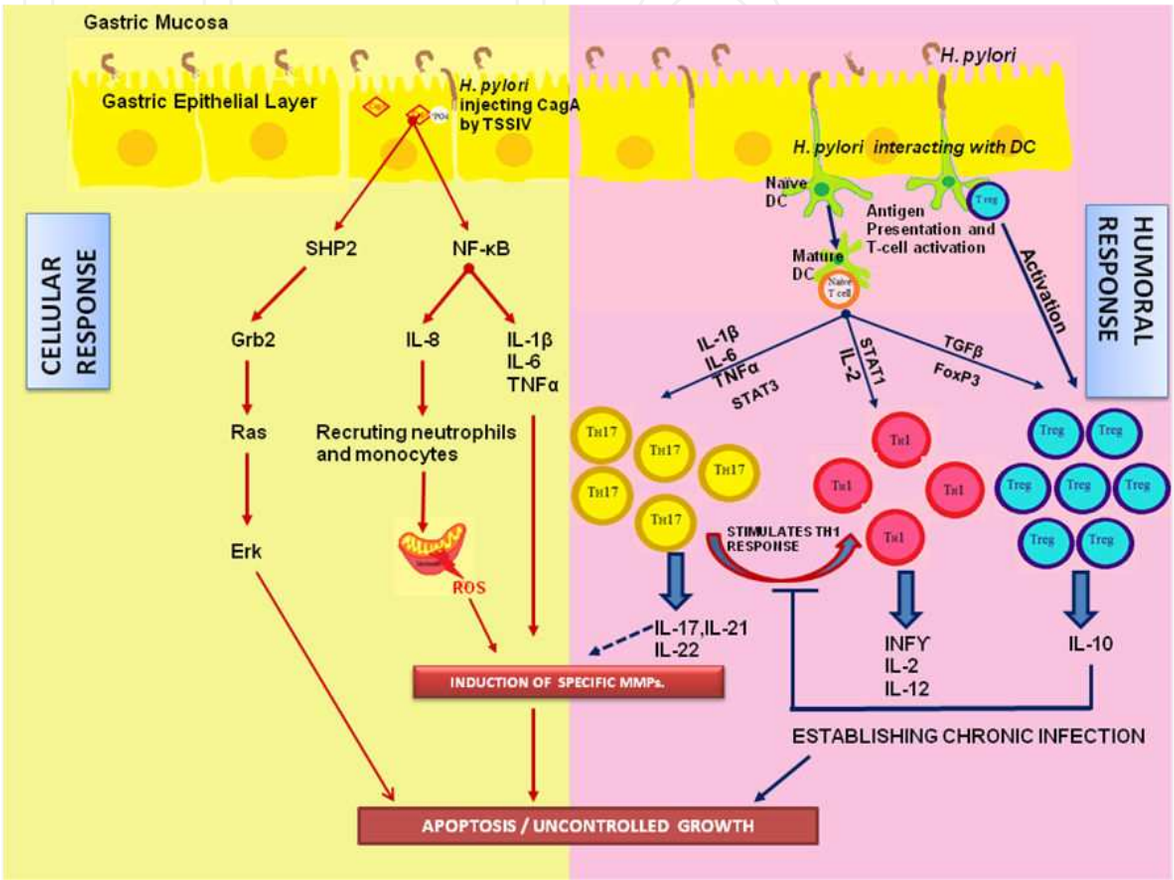

Figure 3. Schematic view of Helicobacter pylori infection and MMPs induction involving both cellular and humoral components. Cellular response: During infection H. pylori injects CagA with their type IV Secretion System (TSSIV) into the gastric epithelial cells. CagA phosphorylation occurs by host's Src/Abl kinases and phosphorylated CagA activates a series of signaling molecules including inflammatory cytokines, ROS, MMPs leading to aberrant cellular function. **Humoral response**: H. pylori prime the host immune system by various lymphocyte subsets through dendritic cells (DC)-mediated antigen presentation to naïve T cell. Under the influence of specific cytokines and foreign antigens the naïve T cells start class switching and differentiate into effector T subtypes via signature transcription factors. TH17 and TH1 promote while Treg arrests inflammatory response by secreting immunosuppressive cytokines; thereby maintaining H. pylori load inside gastric mucosa. TH17 stimulates MMPs through IL-17 and IL-21.

Studies using *in vitro* system document that *H. pylori* infection can induce apoptosis and stimulate release of chemokines from the infected gastric epithelial cells (Cover et al., 2003, Yamaoka et al., 1998, Bhattacharyya et al., 2002). Interestingly, *H. pylori* infection in lymphocyte deficient mice fails to develop gastric inflammation. However, administration of T cells into these animals induces severe gastric ulcer, suggesting T cell mediated inflammatory response play the dominant role in *H. pylori*-mediated mucosal damage (Eaton et al., 1999, Ea-

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ton et al., 2001, Smythies et al., 2000). *H. pylori* infection has a strong Th1 response which is mediated by Th1 cytokines including IFN-γ, IL-12, and TNF-α (Ernst and Gold, 2000, D'Elios et al., 1997, Crabtree, 1998, Monteleone et al., 1999, Pender et al., 1997).

Activated CD4+ T cells secrete IL-21, which regulates the growth and functional properties of T cells, B cells, NK cells and DC (Leonard and Spolski, 2005). Of late, it is reported that IL-21 secretes from TH17 in Stat-3 dependent manner and in turn IL-21 can induce IL-17 production the maintaining TH17 cell population in an autocrine manner(Wei et al., 2007). In contrast, IL-21 is also reported as a TH2 secreted cytokine which prevents the differentiation of naive CD4+ T cells into TH1 cells (Wurster et al., 2002). Therefore the role of IL-21 though appears complex, yet it's a crucial cytokine which promotes gelatinase activities during *H. pylori* infection (Caruso et al., 2007). The other studies by Shi et al demonstrated that IL-17 stimulates MMP activity (Shi et al., 2010). Thus, TH17 acting as an initiator of inflammation and MMPs which inturn carry out the effecter function of inflammation. Though, it is yet to be understood on the backdrop of *H. pylori* infection but from the above documents a strong correlation of IL-17 and MMPs is plausible and the TH17-MMP pathway may evolve as one of the crucial one during *H. pylori*-mediated gastric inflammation (*refer figure 3)*.

8. Management of *H. pylori* infection and future avenues

As, much greater percentage of the world's population are infected with *H. pylori* compared to the actual number of people developing symptoms so, it may be plausible that host's inflammation due to food habits, hygiene and lifestyle contribute to bacterial susceptibility. In view of this, host's prior inflammatory history may be a dominant issue over virulence of *H. pylori* in the development of gastric diseases. *H. pylori* are known to induce atrophic gastritis and achlorhydria. The later is associated with loss of parietal cells which leads to reduced gastric acid secretion (Fox and Wang, 2007). The rise of intragastric pH above 4.0 accelerates the growth of a range of bacterial species in gastric juice including *H. felis* (Williams and McColl, 2006). In addition to the finding of Cai X *et al*., that *H. felis*-infected wild type mice developed antral gastric cancer, after prolonged achlorhydria along with undetectable *H. pylori*; Ekstroma *et al* reported the difficulty in detecting *H. pylori* from patients with severe achlorhydria (Ekstrom et al., 2001) (Cai et al., 2005), even though achlorhydric mice develop pathophysical manifestation like gastrin-deficient ones. (Zavros et al., 2005, Zavros et al., 2002).Therefore, *H. pylori*-induced atrophic gastritis and achlorhydria, though progression to severe gastric diseases may be partly contributed by other bacteria including *H. felis*, remain open for further investigation.

The study on tribal populations in India reported that biopsy samples contain strains having *cag* PAI and putatively toxigenic s1 alleles of *vacA*, which contribute to virulence when active, and this is in accord with the high abundance (about 90%) of this strain type in mainstream Indian populations (Mukhopadhyay et al., 2000, Chattopadhyay et al., 2002, Datta et al., 2003). This abundance is also remarkable, in light of the apparent absence of *H. pylori*-associated gastrointestinal disease in these populations suggesting that *H. pylori* infections

on an average are less virulent in these ethnic minorities than in mainstream Indians. Such virulence might be due to subtle features of bacterial strains or intricacies of the human host environment. For example, lesser virulence of the *H. pylori* strains themselves might be ascribed to subtle (e.g., point) mutations that affect levels of expression of virulence genes or the potencies of their products, which do not, however, affect outcomes of diagnostic PCR tests (Kersulyte et al., 1999, Philpott et al., 2002).

Antibiotics along with proton pump inhibitors (PPIs) known as 'Triple therapy' have been used for *H. pylori*-infected patients by most physicians for high effectiveness and negligible side effects However, long term 'Triple therapy' in *H. pylori*-infected patients may increase atrophic gastritis (Kuipers et al., 1996). Omeprazole, the potent PPI used to treat reflux esophagitis in *H. pylori*-infected patients, increase the proportion of atrophic gastritis compared to those patients receiving alternative treatments (Berstad et al., 1997, Eissele et al., 1997, Klinkenberg-Knol et al., 2000). In addition, omeprazole initiates dysplasia in *H. felis*-infected mice with over expressed gastrin (Takaishi et al., 2005). Therefore, the effect of long-term PPI treatment over gastric microbiome needs further investigation. Antibiotic treatments not only remove *H. pylori* but also other bacteria from gut microbiota some of which may exacerbate disease condition. In theory, screening and treating patients for *H. pylori* eradication by antibiotics would be economical; only if the probability of reducing gastric disorder is 30% or more (Parsonnet et al., 1996). Studies involving *H. pylori* eradication by antibiotic treatment have shown reduced risk for tumor recurrence (Uemura et al., 1997), or development of gastric cancer (Uemura et al., 2001, Wong et al., 2004) though little or no significant improvement of gastric atrophy with *H. pylori* eradication has been reported (Ruiz et al., 2001). In contrast, even increasing gastro-esophageal reflux is reported after *H. pylori* eradication (Labenz et al., 1997), though other studies do not agree (Moayyedi et al., 2001, Schwizer et al., 2001, Kuipers et al., 2004, Vaira et al., 2003). Therefore, antibiotic treatment to eradicate *H. pylori* in early infected patients may prevent the development of disease; though it still remains unclear whether patients with advanced stages of the disease can benefit from antibiotic intervention. In addition, long-term use of antibiotics kills the beneficial bacteria thereby changing gut microbiota. The later would in turn affect host's metabolic and immunological functions, which may disrupt gut, liver and brain functions (Nicholson et al., 2012). Moreover, the consequence in disease progression yet remains to be explored in the context of modalities of *H. pylori* treatment. Therefore, gut microbiota influence significantly on the host immune system and vice versa (Hooper et al., 2012).

Although, 'Triple therapy' is successful in individual cases, yet the recurrence of bacterial infection especially in highly endemic countries makes vaccination as an alternative approach to standard therapy. However, till date vaccination against *H. pylori* has not shown much promise. Vaccination in various clinical trials of either preventive or therapeutic has failed to generate successful immune response. Vaccination has been tested in many ways. Firstly, intra-gastric immunization has been used in some studies to could efficiently stimulate gastrointestinal immune response. However, this method requires large amount of antigen and adjuvant injection in gastric milieu which potentially raises other side-effects (Wu et al., 2008). Secondly, intranasal immunization against *H. pylori* prove ineffective as it fails

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to stimulate immune system in stomach and intestine. Moreover, it increases the chance of infection of olfactory bulb of brain (van Ginkel et al.). Finally, sublingual immunization emerges as another approach, in which the vaccine or antigen do not enter the brain (Song et al., 2008). Indeed, sublingual immunization against *H. pylori* strongly induces IFNγ, IL-17 along with increased expression of various integrins and chemokines facilitating the migration of lymphocytes into stomach mucosa (Raghavan et al.).

Though large-scale research is going around the world in relation to *H. pylori* infection, yet day by day the result is becoming exhaustive without a conclusive direction. The bacteria colonize the gastric mucus layer and are continuously faced with harsh physiological conditions and a vigorous immune response. The need for adaptation to the extremely changing micro-environment and to individual hosts (Van Vliet et al., 2002) is probably the cause of a high degree of inter strain genetic variation observed in the *H. pylori* population worldwide. (Blaser, 1994). So, identification of subpopulations at high risk of developing deleterious *H-pylori*-related diseases remains a mainstream challenge for clinicians and basic researchers. In relation to treatment, nothing absolute promising therapeutic has yet arrived in the market. So, the fundamental question that arises is should we treat infection or inflammation with more priority? Since neither antibiotic treatment nor vaccine development have shown much promise in recovery of infected patients. The approach of reducing inflammation may arrest the development of gastric diseases. Epigenetic studies reveal that changes in the DNA methylation pattern during infection are due to inflammation. One possibility entails concurrent infection with particular parasites that may down regulate inflammatory responses to infection, as has been documented in a mouse infection model (Martin et al., 2000). Features of human host genotype might also determine resistance to pathogenic effects of putatively virulent *H. pylori* strains (Ferrero and Fox, 2001, Ferrero and Jenks, 2001). Also, inflammatory cytokines generates ROS within the cells and activate several MMPs that further aggravate the inflammatory response leading towards disease progression. Finally, while many studies have investigated the host genetic factors involved in gastric carcinogenesis (Hishida et al.), but there is an urgent need for extensive studies that will investigate the genetic traits associated with the risk of gastric precancerous conditions. Particularly, studies on polymorphism in the genes involved in host immunity against *H. pylori* infection or the genes essential for the development/ differentiation of the gastric epithelial cells, are the need of the time.

Abbreviations

H. pylori: *Helicobacter pylori*

MMP: matrix metalloproteinase

ECM: extracellular matrix

ROS: reactive oxygen species

TSSIV: type IV Secretion System

IL: interleukin

IFNγ: interferon gamma

DC: dendritic cell

NK cell: natural killer cell

APC: antigen presenting cell

TIMP: tissue inhibitor of metalloproteinase

EGFR: epidermal growth factor receptor

Erk: extracellular signal-regulated kinase

iNOS: inducible nitric oxide species.

NF-κB: nuclear factor kappa B

AP-1: activator protein 1

Treg: regulatory T cell

TH: T helper cell

TGF-β: transforming growth factor beta

miRNA: micro-RNA

SabA: sialic acid-binding protein

VacA: vacuolating associated cytotoxin gene

CagA: cytotoxin-associated gene A

Cag-PAI: cytotoxin-associated gene-pathogenicity island

NOD1: nucleotide-binding oligomerization domain-1

FAK: focal adhesion kinase

dupA: duodenal ulcer promoting gene

BabA: Lewis blood group antigen binding adhesin

ORF: open reading frame

VEGF: vascular endothelial growth factor

TNFα: tumor necrosis factor alpha

GC: gastric cancer

DU: duodenal ulcer

MAPK: mitogen-activated protein kinase

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Author details

Avisek Banerjee**[1], Asish K. Mukhopadhyay**[2], Sumit Paul[1], Arindam Bhattacharyya[3] and Snehasikta Swarnakar[1*]

*Address all correspondence to: snehasiktas@hotmail.com

1 Drug Development Diagnostics and Biotechnology Division, CSIR-Indian Institute of Chemical Biology, Jadavpur, Kolkata, India

2 National Institute of Cholera and Enteric Diseases, Kolkata, India

3 Immunology Lab, Department of Zoology, University of Calcutta, Kolkata, India

**These authors contributed equally to this work.

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