

The Association of the Human Leukocyte Antigen (HLA) with the Pathogenesis of *Helicobacter pylori*

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H. pylori pathogenesis is related to various virulence factor which some of them involved to adhesions. Urease as a main pathogenecity factor to attach to HLA-II is expressed on the surface of Gastric Epithelial Cells (GECs). Apoptosis induced by caspase3 activation as a result of urease effects on Spermine-Spermidine cycle. There is a contribution of HLA-DQA1 gene to the host's response against *H. pylori*. HLA allele type as an immune-genetic factors are related to host susceptibility to *H. pylori*. HLA-DQA1 might be contributed to the susceptibility or resistance to *H. pylori* infection. Based on the existed evidences the current review aimed to evaluate the results obtained by different studies carried out so far on correlation of human HLA and the pathogenesis of the *H. pylori* in gastric epithelial cells.

Key words: Human Leukocyte Antigen, Pathogenesis and *Helicobacter pylori*.

Among the host cell structures to which *H. pylori* have been shown to bind some sites include sialic acids, fucose-containing blood group antigens, membrane lipids, mucin, and several basement membrane constituents are mentioned (Boren, 1993; Piotrowski, 1993).

Urease is present on the outer membrane surface of *H. pylori* (Phadnis, 1996) which capable of binding to human MHC-II and inducing apoptosis (Fan, 2000; Gobert, 2002). The bacteria attachment to the epithelial cells induces actin polymerization and the phosphorylation of cellular proteins by phospho-Cag.A, and also Vac.A effects on mitochondrial transmembrane potential that leads to release of cytochrome.C, activation of caspase8 and caspase9 and apoptosis induction. (Wroblewski, 2010) (Bauer, 2011).

GECs apoptosis has been increased in the infected mucosa (Moss, 1996) and this damage could lead to ulcer formation or gastric atrophy.

HLA class II

HLA is capable of binding tumor peptides, and recognition of this combined by T-cell might provoke an effective antitumor immune response or repress this immune response (Takahashi, 1995).

Regards to previous reports about HLA-DQA1 gene contribution with susceptibility or resistance to *H. pylori* infection, the association of DQA1*0102 allele is presumed with gastric atrophy and intestinal type gastric adenocarcinoma that is happened after *H. pylori* infection. While, absence of DQA1*0102 might be a risk factor for *H. pylori*-related atrophic gastritis and gastric adenocarcinoma (Azuma, 1998).

H. pylori eradication by HLA-DR expression attenuation on GECs and inflammation reduction (Archimandritis, 2000). *H. pylori* could up-regulate the expression of HLA class II on epithelial cells and possibly activation of Toll-like receptors (TLs) induce apoptosis.

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Through *H. pylori* infection, GECs acquire HLA-DR and co-stimulatory molecules as properties of an antigen presenting cell (APC). And also, Macrophages in the lamina propria play role as APC in infected gastric mucosa (Archimandritis, 2000; Kountouras, 2004). As was mentioned earlier the secreted products such as urease from *H. pylori* make a rise in expression of HLA-DR and B7-2 on monocytes and GECs, though interferon- γ (IFN- γ) also has such effects (Harris, 1996; Ye, 1997).

Dendritic Cells stimulation by *H. pylori*

Dendritic Cells (DCs) are professional Antigen Presenting Cells (APCs) with critical roles in the initiation and progression of immunity (Banchereau, 2000) which involved in the response to *H. pylori* infection (Bimczok, 2010; Andres, 2011) (Kao, 2010).

Galgani et al. reported that the expression of cag.E could induce of IL-1, IL-12, and TNF in DCs (Galgani, 2004; Chomvarin, 2008). Cag.E is related to *H. pylori* type IV secretion system and placed on the cag PAI. Both strains of *H. pylori* can completely induce DCs activation and maturation.

In addition, DCs maturation is not essentially controlled by the viability of the bacteria (Gebert, 2003; Kranzer, 2004). The evaluation of maturation markers of Monocyte-Derived Dendritic Cells (MDDCs) lead to activation of p38 MAPK and NF- κ B signaling pathways which is concomitant with the decreased trimethylated H3K9 and the increased acetylated H3 could be accounted for the association between the *H. pylori* and the IL-10 expression (Chang, 2012).

Histone acetyltransferase and methyltransferase inhibitors in *H. pylori* infection significantly suppressed the up-regulation of IL-10 expression in *H. pylori*-pulsed MDDCs (Li.B, 2007). The impaired DC function contributes to the less effective innate and adaptive immune responses against *H. pylori* in gastric cancer patients. IL-10 production through different pathways could be up-regulated by Toll-like and DC-SIGN receptors recruiting, p38 MAPK signaling and the transcription factors NF- κ B activation, and modulates histone modification (Chang, 2012).

Outer membrane proteins (OMPs) and *H. pylori* Antigen (Hpa)

Omps are proteins which located on the outer plasma membrane of *H. pylori* and plays various roles such as ion transporter, adherence factors, structural and osmotic stabilizers, and bacterial virulence. And also might be an antigenic elements. Previous, proteome analysis of *H. pylori* outer membrane proteins indicated there is a strong serological reaction toward Hpa.A (TIGR HP0797) and Omp.18 (TIGR HP1125). (Volland, 2003)

Results shown that the recombinant Hpa.A (rHpa.A) and Omp.18 (rOmp.18) strongly stimulated MHC-II and CD83 expression 7-10 fold on isolated DCs. While, these recombinants Omps could not stimulate Monocytes to secrete IL-8 but of IL-12 and IL-10 secretion from DCs significantly were increased (Guiney, 2003; Volland, 2003). According to the results obtained by these studies the above mentioned proteins are expressed in all strains tested and have a surface localization (Lundstrom, 2001).

Pathogenesis of *Helicobacter pylori*-induced autoimmunity

H. pylori induces IL-12, which selects for IFN- γ -producing Th₁ cells in situ by which aberrant MHC class II expression occurs on nonprofessional antigen presenting cells (gastric epithelium). (Applemilk, 1998). Increased MHC class II in turn results in increased presentation of auto-antigens such as gastric H₁K₁-ATPase which induces activation of auto-reactive T cells (CD41 Th₁, e.g. H₁K₁-ATPase-specific). T-cell helper induces auto-antibodies and the auto-reactive T cells destruct glands, e.g. by Fas-FasL apoptosis (atrophy). Then epitope-spreading to other auto-antigens such as IF and PG occurs. Increased corpus atrophy parallels loss of *H. pylori* and normalization of antrum and finally the T cells become *H. pylori*-independent and an autoimmune response perpetuates (AIG/PA) (Ye. G, 1997; Applemilk 1998).

HLA and *H. pylori* resistant

It has been demonstrated that prevention of the *H. pylori* disease development may correlate with host resistance controlled genetically by the immune system. Azuma *et al.* have reported that patients who carry a particular HLA-DQA gene show resistance to *H. pylori* infection (Hirota, 2001). Also, efficient induction of *H. pylori*-specific antibodies and T-cells may contribute to host resistance against *H. pylori* infection. Recent

Table 1. Chronologically table of selected studies

Researchers	Year	Study design	Aim of study	Sample size	Results	Conclusion
1. Xuejun Fan <i>et al.</i> ,	2000	Clinical trial	<i>H. pylori</i> Urease binds to class II MHC on Gastric Epithelial Cells and Induces Their Apoptosis	<i>In vitro</i> experiment	<i>H. pylori</i> use class II epithelial cells as receptors and IFN- γ increased expression of class II MHC expression.	Attachment of bacteria to GECs MHC on gastric induces actin polymerization and the phosphorylation of cellular which may be reductive of the stimulation of signaling mechanism that transduce apoptotic but these signals were unknown.
2. Dino Veneri, <i>et al.</i> ,	2002	Case-	HLA class II alleles infection, and <i>H. pylori</i> Idiopathic thrombocytopenic purpura	39 patients 160 control Control	There is little evidence of an association between MHC-II and ITP. A higher prevalence of other class II alleles and ITP patients has been described in some human races, although other studies failed to demonstrate a statistically significant association.	By contrast, in our study the HLA class II allele pattern seems to identify 2 groups of ITP patients with a different incidence of <i>H. pylori</i> infection and, possibly, with different pathogenetic mechanisms.
3. Kranzer <i>et al.</i> ,	2004	Clinical trial	<i>H. pylori</i> Release of Human Dendritic Cells by Induction of Maturation and cytokine	<i>In vitro</i> experiment	Cell lyses or death induce IL-8 release in the remaining viable cells. While, IL-12, IL-10, and IL-6 release depends on cell	<i>H. pylori</i> stimulates DC maturation despite its ability to inhibit phagocytosis and induces IL-10 and IL-12 production

4.	Lydia et al.,	2010	Review	<i>H. pylori</i> and Gastric Cancer Factors that Modulate Disease risk	:	<p>vitality, as cytokine production decreases and cell death increases with MOIs of >50.</p> <p>The effects of VacA, leads to mitochondrial transmembrane potential cytochrome c release, caspase-8 and caspase-9 activation, and finally apoptosis induction.</p> <p>The bacteria attachment to the epithelial cells induces actin decrease, polymerization and the phosphorylation of cellular proteins by phospho-CagA, and also VacA effects on mitochondrial transmembrane potential that leads to apoptosis induction</p> <p>Apoptosis of macrophages could be induced by VacA. Host cell molecules such as plasminogen and cholesterol by coating the surface of bacteria protects <i>H.pylori</i> from recognition. In this its absence situation, genetic adhesive mechanisms.</p> <p>In the presence of <i>H. pylori</i>, TLR/DC-SIGN positively regulates maturation and IL-10 cytokine production via the p38-MAPK signaling and histone modification. These signals leads to apoptosis</p>
5.	Bianca Bauer	2011	Review	The Human Gastric Pathogen <i>Helicobacter pylori</i> and Its Association with Gastric Cancer and Ulcer Disease		<p><i>H. pylori</i>-encoded auto-transporter proteins such as BabA, SabA, AlpA, have main role in adherence.</p> <p>However, There is no individual molecule has been shown to be essential to adhere, that indicate redundancy of</p>
6.	Lin-Li, et al.,	2012	Clinical trial	Impaired dendritic cell maturation and IL-10 production following <i>H. pylori</i> stimulation and in gastric cancer patients	<i>In vitro</i> experiment	<p><i>H. pylori</i> induces IL-10 production via DC-SIGN, TLR2, MD DCs TLR4 receptors in MDDC's</p>

published papers indicated that the frequencies of HLA-DQA*0301 allele are higher in *H. pylori* positive cases while allele frequencies of DQA*0102 are higher in negative cases.

This result suggested that HLA-DQA gene polymorphism could be contributed to susceptibility or resistance to *H. pylori* infection (Azuma, 1994; Azuma 1994). More recent literatures have demonstrated that polymorphisms in various cytokine genes might act an important role in the susceptibility or resistance to *H. pylori* infection, such as IL-1 β , TNF- α , Lewis Blood group (Le) and Secretor (Se) genes (Oba-Shinjo, 2004; Zhang, 2008).

These results shown although there has been no study that directly mentioned this issue that genetic factors play a role in *H. pylori* re-infection, especially after successful eradication, (Zhang, 2008). In addition, The correlation with the HLA-DR⁻/ICAM-3⁻ phenotype and survival rate reduction and in contrast the HLA-DR⁺/ICAM⁺/PECAM⁻ phenotype, with survival rates increase reported, recently.

Emilia *et al* studied the HLA-DR/-DQ antigens frequency among 39 Idiopathic Thrombocytopenic Purpura (ITP) patients and compared with 150 healthy bone marrow donors (Study groups were matched for sex and age). Obviously, the frequency of HLA-DRB1*11,*14 and -DQB1*03 alleles were significantly lower in *H. pylori*-negative patients whereas the HLA-DRB1*03 frequency were considerably higher than in positive ones.

This seems the observed low frequency of HLA-DRB1*11 and of -DQB1*03 in ITP patients must be a typical feature of *H. pylori*-negative cases (Hirota, 2001). There did not observed any major differences in any of the class II alleles in *H. pylori*-positive patients as compared with controls. (Emilia, 2001)

These researchers found that the HLA-II allele pattern can identify two groups of ITP patients with different incidence of *H. pylori* infection and pathogenetic mechanisms (Veneri, 2002). *H. pylori* infection susceptibility increasing and *H. pylori* re-exposure are proposed to be the major necessities to occur re-infection.

As mentioned previously, genetic factors as a main important element of *H. pylori* infection susceptibility had difference dissemination in the

population. Result of a study on two groups of monozygotic and dizygotic twins pairs which *H. pylori* infection was higher in monozygotic pairs (81%) than in dizygotic pairs (63%), shown the genetic might have influence in the *H. pylori* acquisition because of strong similarities within the monozygotic twin pairs (Malaty, 1994; Zhang 2008).

CONCLUSION

The *H. pylori* colonization by employed adhesions lead to consequently signaling in cell as mentioned (Wroblewski, 2010; Bauer, 2011). The result of this effect is HLA expressing on GECs, DCs maturation. *H. pylori* virulence factors such as urease (Gobert, 2002), ompA and Hpa.A beside host factor like IFN- γ induce HLA expressing. The induction of HLA expressing may be related to Ulcer forming or gastric cancer developing. (Azuma, 1998; Archimandritis, 2000; Kountouras, 2004) HLA-II polymorphism has strongly association with resistant or susceptibility to *H. pylori* infection (Azuma, 1998; Veneri, 2002; Zhang, 2008). This funding shown a relationship between the role of HLA in *H. pylori* infection therefore more studies are needed to clarify HLA-II polymorphism and its potential to treatment or prevention.

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