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Human Leukocyte Antigens Influence the Antibody Response to Hepatitis B Vaccine

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ABSTRACT

Hepatitis B virus (HBV) infection and its sequelae such as cirrhosis and hepatocellular carcinoma has remained a serious public health problem throughout the world. The WHO strategy for effective control of HBV infection and its complications is mass vaccination of neonates and children within the framework of Expanded Programme on Immunization (EPI). Vaccination with hepatitis B surface antigen (HBsAg) induces protective antibody response (anti-HBs ≥ 10 IU/L) in 90-99% of vaccinees.

The lack of response to HBsAg has been attributed to a variety of immunological mechanisms, including defect in antigen presentation, defect in HBsAg-specific T and/or B cell repertoires, T-cell suppression, increase in the regulatory T cell count, lack of necessary help of T-cells for production of anti-HBs by B cells, defect in Th1 and/or Th2 cytokine production and selective killing of HBsAg-specific B-cells by human leukocyte antigen (HLA)-restricted cytotoxic T lymphocytes. The HLA complex plays an important role in many of these immunological processes.

A variety of HLA class I, II, and III alleles and antigens have been reported to be associated with antibody response to HBsAg vaccination in different ethnic populations. Moreover, some HLA haplotypes were also associated with responsiveness to HBsAg.

In this review the association of the HLA specificities with antibody response to hepatitis B (HB) vaccine is discussed.

Keywords: Hepatitis B vaccine; Hepatitis B antibodies; Human leukocyte antigen

INTRODUCTION

Approximately, one third of the world population shows a previous history of infection with hepatitis B virus (HBV) and more than 350 million individuals have been estimated to be chronically infected.[1] In

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areas with high endemicity, especially in some parts of Africa and south-east Asia, over 8% of individuals are chronically infected and infection is predominantly transmitted vertically during prenatal period from carrier mothers to their neonates.[2] In regions of intermediate endemicity, the patterns of the disease transmission is mixed and disease occurs at all ages, but again the predominant period of transmission seems to be at younger ages.[3]

Therefore, effective control of HBV transmission in regions of high and intermediate endemicity would not be possible without vaccination of the vulnerable groups of the population.[4] The WHO (Word Health Organization) strategy for effective control of HBV infection and its sequelae is mass vaccination of neonates and children within the framework of Expanded Programme on Immunization (EPI). In 1991, the Global Advisory Group of the WHO recommended that all countries integrate hepatitis B vaccine into national immunization by 1997.[5,6] This program has been incorporated in the national immunization scheme in Iran since 1993.[7] More than three decades after the WHO recommendation to implement universal hepatitis B vaccination, many countries have included HB immunization into their national immunization program as a routine vaccine given to all infants.[5, 6]

However, the results obtained from a large number of studies indicate that 1-10% of healthy neonates and adults fail to respond to HB vaccine.[8, 9] The parameters which influence the antibody response to HB vaccine might be overally classified into host and immunization factors. Increasing age, male gender, obesity and short sleep duration have been shown to correlate independently with a decreasing antibody response to the HB vaccine.[10-12] Immunosuppressed groups, such as hemodialysis patients[13] diabetic patients[14] and those on chemotherapy[15] respond poorly to HB vaccination. Smoking and alcohol consumption have adverse effect on antibody response to hepatitis B surface antigen (HBsAg). Moreover, birth weight also influences the immune response to HB vaccine.[11,16] human immunodeficiency virus (HIV), hepatitis C virus (HCV), and schistosoma-infected patients also show poor antibody response to HB vaccine.[17, 18]

Characteristics of the immunization program that influence immunogenicity include type of vaccine,[19] dosage,[8] number and timing of inoculations,[20] storage of vaccine,[21] site and route of inoculations,[22,23] and type of adjuvant which could also influence antibody responses.[24]

Immunologically, the lack of response to HBsAg has been attributed to a variety of mechanisms, including defect in antigen presentation,[25] defects in HBsAg-specific T and/or B cell repertoires,[26,27] T-cell suppression,[28] increase in the regulatory T cell count,[29] lack of T-cell help necessary for production of anti-HBs by B cells,[30] defect in Th1 and/or Th2 cytokine production,[31,32] defect in T cell receptor (TCR) gene repertoire,[33] selective killing of HBsAg-specific B-cells by HLA-restricted cytotoxic T lymphocytes,[34] defectiveantigen presenting cell (APC)/T cell interaction,[35] selective deletion of specific T-cells,[36,37] and over-representation of certain human leukocyte antigen HLA genes and antigens.[36-40] Indeed, the role of HLA seems to be more important, because most of the mechanisms contributing to lack of immune response to a defined antigen are HLA linked.[41-44]

Immunogenicity of HB Vaccine

HBV is an enveloped virus expressing three forms of overlapping surface proteins, including the small, middle and large proteins. These molecules are also known as S, pre-S2 and pre-S1 antigens, respectively. The 'S' antigen (HBsAg) is the predominant form of the surface antigens and constitutes the immunodominant 'a' determinant which is required for induction of protective antibody response in human.[16,45] Therefore, the antibody response against HBsAg (anti-HBs), provides protective immunity against HBV infection.

Despite some differences in national vaccination programs between different countries, triple doses of 10 μg or 20 μg of recombinant hepatitis B surface antigen (rHBsAg) are administered in most countries for vaccination of neonates and adults, respectively.[9,46] Vaccination with rHBsAg induces protective antibody response (anti-HBs≥10 IU/L) in the majority of vaccinees. The results obtained from a large number of studies have indicated that vaccination of healthy neonates and adults with rHBsAg induces a protective antibody response in 90-99% of vaccines.[8,9] In fact, we have previously reported a strong protective antibody response in the majority of healthy vaccinated neonates from Kerman and Urmia cities that are located in southeast and northwest of Iran, respectively.[47] However, a small proportion of vaccinees failed to respond, accounting for 1.7% and 3.9% of Urmian and Kermanian neonates, respectively.[47] It is

noteworthy that identical immunization protocols were employed for the vaccination of neonates in these cities after adjusting the host characteristics such as age, weight, and sex between the two groups. Therefore, the difference in immunogenicity in vaccines from two cities may reflect environmental and/or ethnic differences between the two groups of vaccinees.

Cellular Mechanisms of Anti-HBs Antibody Production

Production of anti-HBs antibody following vaccination or natural infection is a helper T (Th) cell dependent process. $CD4^+$ T lymphocytes recognize different epitopes within the HBsAg that can be presented by certain HLA class II antigens.[48] In general, upon antigenic stimulation Th cells differentiate into several subsets such as Th1, Th2 and regulatory T (Treg) cells which are characterized by the release of distinct cytokines profile. Th1 cells secrete cytokines including interferon-gamma (IFN-γ), tumor necrosis factor-alpha (TNF-α), and Interleukin (IL-)-2, whereas Th2 cells secrete cytokines such as IL-4, IL-5, IL-6, IL-10, and IL-13 which seem to be essential for antibody production.[49] Several studies have been conducted to investigate the precise role of Th1- and Th2-derived cytokines in the immune response to HB vaccination and to get further insights into the cellular basis of unresponsiveness to HBsAg. Different patterns of cytokine production, either predominant Th0 or Th2 related cytokines or Th1 and Th2 type cytokines, have been observed in responder subjects vaccinated with HB vaccine.[31,38,50,51] Accordingly, there are controversial reports regarding the influence of different Th cell subsets on the immune response to this antigen. Analyses of in vitro HBsAg-induced cytokine production have revealed defects in: Th1- [27, 30, 52], Th2- [30] and both Th1 and Th2 cytokines[32, 53, 54] in non-responders. We have previously demonstrated that both Th1 and Th2 responses are defective in healthy neonates who failed to mount a protective antibody response to rHBsAg.[31]

Basically, the differentiation of naive $CD4^+$ Th cells into Th1 and Th2 phenotype is influenced by several factors such as the affinity between the major histocompatibility complex- (MHC)-peptide-TCR complex and the number of MHC-peptide complexes on the surface of APC.[55] While increased affinity of the TCR-MHC-peptide interactions favored Th1 development, high ligand density favored IFN-γ producing cells and lower densities largely resulted in differentiation of IL-4 or mixed responses.[55] It has been demonstrated that there are different immunodominant T cell epitopes within the HBsAg that can be presented by different HLA class II alleles and induce differentially Th0/Th2 responses.[50] Since differences in HBsAg peptides binding affinity between the HLA-DR alleles do not explain the known HLA-DR association and HBsAg vaccination failure, therefore differences in the T cell recognition of peptide/MHC complexes is the critical event in T cell responsiveness to HBsAg.[56] Accordingly, the differences in the TCR affinity for binding to particular HLA-HBsAg-derived peptide may contribute to differential Th1 or Th2 response. HLA antigens may induce insufficient or imbalaced Th1/Th2 response, resulting in inappropriate cellular or humoral immune response to HBsAg, due to the profile of secreted cytokines.[38,53,57]

The association of HLA and Immune Response to HB Vaccine

Genetic background plays a pivotal role in determining the strength of the immune response to HB vaccine. Both HLA and non-HLA genes are involved in regulation of the immune response to infant vaccination.[58,59] Unresponsiveness to HBsAg vaccination has been associated with HLA (MHC) antigens in human and mouse.[36-40, 44, 60-63]

The HLA system is highly polymorphic and many investigators have demonstrated significant associations between certain HLA alleles, antigens or haplotypes with hepatitis B vaccination outcomes. Current data suggest considerable ethnic differences in the HLA antigens is associated with anti-HBs antibody response in adults.[36-40] The frequency of a variety of HLA class-I and class-II alleles and extended haplotypes of HLA have been reported to be either increased or decreased in non-responder vaccinees from different ethnic backgrounds compared with responders [36-40]. Lack of antibody response to HB vaccine was also found to be associated with certain HLA alleles and haplotypes in a group of Iranian non-responder neonates and adults.[64,65]

The Association of HLA Class I Specificities and Antibody Response to HB Vaccine

Non-responsiveness to HBsAg vaccination is reported to be associated with HLA- A1, B15, and B40

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in Indians,[66] HLA- A1, A2, and B8 in German, Belgian, and Spanish,[44, 67-69] HLA- B54 in Chinese,[70] HLA-A10 and Cw4 in Turkish,[71] and HLA A*0602, A*1101, and B*35 in Japanese[72] populations. Moreover, lower response to HBV vaccine is reported to be associated with HLA-B8 in patients with celiac disease from Italy[73] and HLA-A1 and -B8 in hemodialysis patients from Germany.[69] However, high responsiveness is associated with HLA- A1, A19, B5, B27, Cw2, and Cw4 in hemodialysis patients from Germany and Poland.[69] Responsiveness to HB vaccination is also associated with HLA-A11 in Indians[66] and HLA-A2 in hemodialysis patients from Spain.[68] The results of a study from Taiwan showed that the persistence of the long-term immunological memory to HB vaccination was associated with the presence of A*02 and DRB1*08 and the absence of B*15 alleles.[74] However, in our previous study no significant association was observed between antibody response to HBsAg vaccination and HLA class I antigens in healthy Iranian neonates.[64]

The mechanisms by which the HLA class I loci influence the antibody response to HB vaccine is not clear and could be mainly due to their strong linkage disequilibrium with HLA DR locus. As mentioned above, HLA-B8 has been associated with low or non-responsiveness to HB vaccine in several studies and also the presence of this allele has been associated with viral persistence in HBV-infected subjects.[75] For instance, rapid progression of AIDS has been reported in HLA-B8-DR3 positive subjects.[76] Besides, we have recently reported the higher production of Th2-type cytokine (IL-4 and IL-10) by HBsAg-stimulated Peripheral Blood Mononuclear Cell (PBMC)s from HLA-B8^{+} neonates.[41] Furthermore, decreased natural killer cell activity and decreased production of type 1 cytokines, including IL-2, IFN-γ, and IL-12 have also been noted in subjects with this HLA antigen.[77,78] Although the precise mechanisms of these findings have not been elucidated, but we could assume that HLA-B8 allele could determine the outcome of HBV infection by an impairment in cellular immunity which could be due to the effect of Th2-type cytokines.

The Association of HLA Class II Specificities and Antibody Response to HB Vaccine

It has been demonstrated that there is a negative association between HLA- DR7, DR3, and DQ2 antigens and related alleles (including DRB1*0301, DRB1*0701 and DQB1*0201) with responsiveness to HB vaccine, whereas DRB1*0101, DRB1*1301, DRB1*1501, and DPB1*0401 have positive association with strong antibody responses to HB vaccine.[64, 66, 79-83] In a recent study from Turkey, the negative correlations have been reported between HLA-DRB1*04, DRB1*0401, DRB1*11/13, and DRB1*0401-0201 with the responsiveness to HB vaccination but there was a positive correlation with HLA-B13.[84] Like others, we found an over representation of HLA-DR1 and HLA-DQ3 antigens in responder vaccinees, suggesting a positive association between these antigens and anti-HBs antibody production in human [64, 65, 79]. We have observed significantly increased frequencies of the HLA-DR7, DQ2, and DR13 antigens in Iranian non-responder neonate vaccinees.[64] Our finding regarding the increased expression of HLA- DR7 and DQ2 molecules has been also reported in healthy non-responder adults,[36, 37, 44, 62] children,[81] or neonates[85] from different countries. Consistent with these findings, the clinical studies have also supported the association of HLA-DR3 and DR7 with non-responsiveness to HBsAg vaccination. It has been reported that the viral persistence is over-represented in HBV-infected patients with DRB1*0701.[86] Moreover, the HLA-DR*04 and DR*13 alleles showed a significant association with HBV clearance while patients carrying HLA-DR*03 or DR*07 alleles had a significantly increased risk of chronic HBV persistence.[87] Besides, patients with celiac disease who expressed HLA-DR3 and DQ2 displayed a lower response to HBV vaccine.[73]

Other antigens and alleles within HLA class II region have been reported as having positive (such as DQB1*0501, DQB1*0601 and DQB1*0602, DRB1*1301, DRB1*15, DR11, and DQ3) or negative (such as DRw53, DRB1*1302, DQB1*14, and DR16) association with responsiveness to HB vaccine [88-90] (Table 1).

The Association of HLA Class III Specificities and Antibody Response to HB Vaccine

The MHC class III genes can also influence the responsiveness to HBsAg vaccination probably through influencing the B-cell activation. It has been demonstrated that the frequencies of the C4A gene deletions and non-expressed C4AQO alleles were significantly higher in non-responders to HBsAg as compared to responders.[91]

Table 1. The association of HLA with responsiveness to HB vaccine in different studies

Country	Subjects	HLA associated with antibody response to HBsAg	HLA frequency in responders (%)	HLA frequency in non-responders (%)	Association with responsiveness	*P* value	Ref.
Belgium	Healthy adults	DR1	27	2.2	Positive	0.01	97
		DR7	21	54.3	Negative	0.001	
		DQ3	57	32.6	Positive	0.01	
		DQB1 *0201	34	71.7	Negative	0.001	
		DQB1 *0501	27	2.2	Positive	0.001	
Italy	Healthy neonates	DR7-DQ2	11.2	23.5	Negative	0.05	85
		DQB1 *0201	9.9	23.5	Negative	0.05	
Spain	Hemodialysis patients	A2	37.2	7.7	Positive	0.005	68
		DR3	25.7	53.8	Negative	0.05	
		DR7	18.6	53.8	Negative	0.05	
		DQ2	44.1	76.9	Negative	0.05	
Japan	Healthy adults	BW54	14.2	48	Negative	0.001	88
		DR4	34.8	60	Negative	0.05	
		DRw53	53.1	96	Negative	0.001	
		DQA1*0301	9	44	Negative	0.001	
England	Healthy adults	DRB1*07	24.8	52.3	Negative	0.001	82
		DRB1*02	36.8	71.6	Negative	0.001	
		DRB1*0701-DQB1 *0202	12	38	Negative	0.01	
Germany	Healthy neonates	DRB1*1	12.5	42.5	Negative	0.002	36
		DRB1 *13	32.1	14.5	Positive	0.03	
		DRB1*14	1.8	17.7	Negative	0.01	
		DRB1 *15	33.9	12.9	Positive	0.01	
England	Healthy adults	DRB1*0701	38	70	Negative	0.001	44
		DQB1*0202	32	80	Negative	0.001	
French	Hemodialysis patients	DRB1*01	22.9	12.3	Positive	0.02	83
		DRB1*02	22.9	14	Positive	0.05	
		DRB1*03	16.6	32.5	Negative	0.007	
		DRB1*14	3	9.6	Negative	0.008	
Germany	Hemodialysis patients	A1/A1	3.4	52.9	Negative	0.000	69
		B8/B8	0.8	55.9	Negative	0.000	
		DR3/CDR3	0.8	44.1	Negative	0.000	
		DQ2/DQ2	0.8	44.1	Negative	0.000	
		DQ3	60.5	8.6	Positive	0.000	
Sweden	Healthy adults	DQB1*0602	33	11	Positive	0.01	89
		DQB1*0603	22	6	Positive	0.05	
		DQB1*0604	3	21	Negative	0.005	
		DQA1*0101	22	4	Positive	0.02	
		DRB1*1301	22	6	Positive	0.05	
		DRB1*1302	6	25	Negative	0.01	
		DR15	34	11	Positive	0.01	
Germany	Healthy adults	DRB1*3	12.5	42.5	Negative	0.002	36
		DRB1*7	13.2	54.5	Negative	0.002	
		DRB1*13	32.1	14.5	Positive	0.03	
England	Healthy adults	DRB1*0701-DQB1*0202	15	42	Negative	0.001	62
Italy	Healthy neonates	DQB1*02	12	28	Negative	0.05	39
Slovenia	Healthy adults	DRB1*1601	13	32	Negative	0.01	90
		DQB1*0502	6	25	Negative	0.05	
		DQA1*0102	7	31	Negative	0.05	

Iran	Healthy adults	DR7	17.5	58.3	Negative	0.02	[65]
		DQ2	25	66.6	Negative	0.02	
		B8-DR3-DQ2	0	24.9	Negative	0.02	
		DR7-DR53-DQ2	10	41.6	Negative	0.05	
Iran	Healthy neonates	DR1	24	1	Positive	0.05	[64]
		DR7	12	47.8	Negative	0.01	
		DQ2	40	73.9	Negative	0.02	
		DQ3	60	30.4	Positive	0.05	
		B7-DR7-DR53-DQ2	0.0	21.7	Negative	0.05	
		DR13-DR52-DQ2	0.0	21.7	Negative	0.05	

Because the HLA-A1, -B8, -DRB1*0301 haplotype is in strong linkage disequilibrium with C4A gene deletions, association of DRB1*0301 with non-response to HBsAg vaccination may be primarily due to a C4A deficiency.[92] Interestingly, the majority of HBsAg non-responders were heterozygous for C4AQO alleles. This suggests that a selective deficiency in C4A can have severe consequences on the humoral anti-HBs response.[92] Some C4A alleles may contribute to inefficient complement activation and thus failure of B cells to secrete anti-HB antibody.[39, 91] Besides, the mice genetically deficient in C4 demonstrate normal T-cell responses and impaired B-cell responses.[93] C4 is an important component for the formation of the C3-convertase and the cleavage of C3. The attachment of C3d or C4d fragments to antigen results in the binding of antigen to follicular dendritic cells (FDC) and B cells via CD21 and CD35 receptors.[94] Moreover, colligation of the CD21/CD19 receptor complex with the B-cell receptor enhances signal transduction and reduces significantly the amount of antigen required for B cell activation.[94]

Other HLA class III genes including BfF and C4A6 are also associated with responsiveness to HBV vaccination in some populations.[95] Kramer et al studied the TCR/CD3 density in non-responders and responders following vaccination in end stage renal disease (ESRD) patients. Lower density of TCR/CD3 was reported in patients carrying C4A*6 and BfF alleles in comparison to non-carriers. Low TCR/CD3 density is related with non-responsiveness and also associated with HLA A1-B8-DR3 haplotype. It has been reported that the responders who carried HLA-DR3 lacked C4A*6 and BfF alleles.[96] However, controversial results in this area have been reported. For instance, higher antibody response to HBV vaccine has been reported to be associated with C4A*6 and Bf*F alleles in hemodialysis patients from Germany.[69]

The Association of HLA Haplotypes and Antibody Response to HB Vaccine

In our previous study, it has been observed that some haplotypes such as DR7-DR53-DQ2, B7-DR7-DR53-DQ2, DR13-DR52-DQ2, and A2-DR7-DR53-DQ2 were more frequent in non-responder neonates vaccinated with HB vaccine.[64] Molecular analyses have demonstrated that the lack of antibody response to HBsAg was significantly associated with the HLA haplotype DRB1*0701-DQB1*0202 while a second HLA haplotype DRB1*0701-DQB1*0303 was not associated with the lack of antibody response.[82] In Belgian populations HLA DPB1*0201 is more abundant in non-responder to HBV vaccine when it occurs in association with haplotype DRB1*0701/DRB4*0101-DQB1*020*.[97] These findings may indicate a more important role for the DQB1* 0202 allele. Moreover, the importance of increased frequency of other HLA haplotypes such as DQA1*0301-DQB1*0401 in Japanese non-responders to HBsAg vaccine has been elucidated.[98]

Immunological Mechanisms by Which HLA May Influence the Antibody Response to HB Vaccine

HBsAg seems to encompass only a limited set of peptides that are immunogenic at the level of Th cells.[56, 99] It has been demonstrated that the APC from $DR3^+$ and $DR7^+$ non-responders to HB vaccine were able to present HBsAg on their surface, and the expression of accessory molecules such as CD86 were down-regulated after culturing the PBMC with HBsAg.[100]

Thus, it is conceivable that T cells recognizing the dominant epitope(s) of HBsAg in association with certain HLA class II molecules (e.g. DR7 or DQ2) may be absent. The reason could be due to resemblance of these HBsAg-derived peptide-MHC class II complexes with self peptide-MHC class II complexes (molecular

mimicry) which may lead to elimination of specific T cells in the thymus or in the periphery.

Alternatively, the inhibitory effects of these HLA antigens or haplotypes on cytokine secretion may be due to the influence of HLA-DR7 and HLA-DQ2 antigens at the level of antigen presentation. Although defective APC function has not been strongly confirmed, inadequate APC functions have been hypothesized to be responsible for lack or slowness of antibody response to HBV vaccination.[38,100,101] Our findings of diminished IL-12 secretion by PBMC from non responder neonates to HB vaccine strongly suggest contribution of APC dysfunction in unresposiveness to HBsAg.[102]

Furthermore, DRB1*1301 and DRB1*1302 alleles have been associated with responsiveness and unresponsiveness to HBsAg, respectively. There is only one amino-acid difference between the alleles at position 86 in the peptide binding groove. At this position, DRB1*1301 has a valine while DRB1*1302 has glycine.[40] It seems that loss of glycine or existence of valine at position 86 in DRB1 molecules is a determining factor for a positive influence on anti-HBs production. Interestingly, DRB1*1501 and DRB1* 0401 alleles that were also found to be associated with response to HBsAg have a valine at position 86.[40] Association between DRB1*13 alleles with the clearance of HBV and a self-limited course of acute hepatitis B has also been reported.[103-105] Moreover, patients with DR13 can mount a more vigorous $CD4^+$ T cell response to HBV core antigen during acute HBV infection, and the progression to chronic hepatitis B is rare in that group of patients.[105]

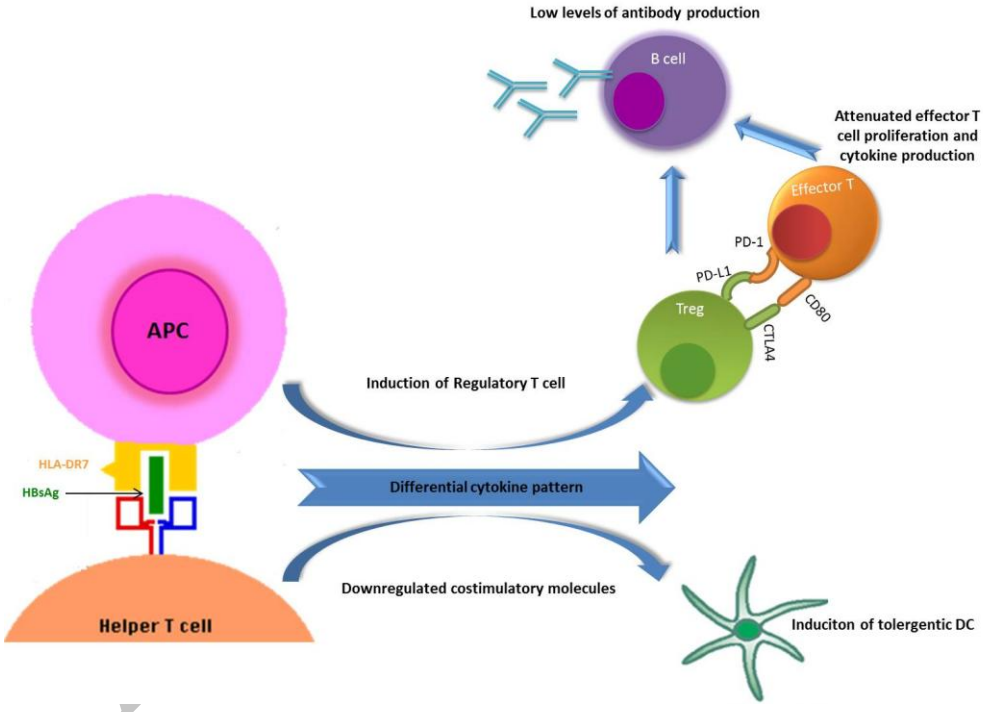

Figure 1. Influence of HLA antigens on HBsAg presentation and immune response to hepatitis vaccination.
Some HLA alleles may negatively influence the immune response to HBsAg. For example, presentation of HBsAg in conjunction with HLA-DR7 may lead to secretion of low levels of IL-12 by APCs and high levels of IL-10 by helper T cells resulting downregulation of costimulatory molecules and induction of tolergenic dendretic cells and regulatory T cells which in turn could attenuate effector T cell proliferation and antibody production by B cells.

We have determined the influence of HLA antigen on cytokine secretion by HBsAg-stimulated PBMCs from healthy neonates vaccinated with recombinant HB vaccine. In turn, these cytokine responses may influence the outcome of both cellular and humoral immune responses to HBV vaccine or infection. Our results demonstrated that the DR7 antigen and some $DR7^+$ haplotypes including DR7-DR53-DQ2, B7-DR7-

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DR53-DQ2, and A2-DR7-DR53-DQ2 are associated with significantly lower secretion of IL-4, IL-10, and IFN-γ by HBsAg-stimulated PBMCs. Besides, inhibition of both Th1 and Th2 responses may cause unresponsiveness to recombinant HB (rHB) vaccine in adult and neonate nonresponders.[32] This inhibitory effect was influenced by those antigens and haplotypes of HLA that were negatively associated with responsiveness to HB vaccine.

Since HLA antigens play a pivotal role in presentation of antigenic peptides to Th cells and induction of their activation, therefore, the composition of HLA antigens is a restrictive element in the quality of T helper responses (Figure 1).

Our previous results suggest involvement of a similar mechanism in nonresponder neonates, as evidenced by production of decreased levels of Th1 and Th2 cytokines. This assumption is supported by our findings indicating expression of similar HLA antigens and haplotypes, particularly DR7 and DQ2, in both adult and neonate nonresponders.[65]

Lack of response could be attributed to other mechanisms such as defect in antigen presentation due to expression of certain HLA antigens and haplotypes.[44,65] However, it has been reported that HLA-DRB1 *0301 non-responder vaccinees are not deficient in their HBsAg-presentation, and the expression of B7 co-stimulatory molecules on their APCs is normal [100]. The HLA complex is central to the T-cell dependent antigen response; therefore, the expression profile of HLA antigens could regulate the immune response through cognate binding of the HLA antigen to the processed antigenic peptides or presentation of the HLA/antigenic peptide complex to T-cell receptors expressed on HBsAg-specific CD4+ T-cells. The latter event could induce either stimulatory or inhibitory signals, depending on the expressed haplotype of HLA. Defective HBsAg-specific T and/or B-cell repertoires have also been demonstrated.[27,36,106] This defect could either be a primary or secondary defect, due to successive destruction of HBsAg-specific B-cells by cytotoxic T-cells.[34] Immunological tolerance[107,108] as well as functional defect in T-cell help necessary for production of anti-HBs antibody by B-cells [27, 30, 52] may also contribute to unresponsiveness to HBsAg.

In conclusion, it should be noted that the non-HLA genes (cytokines, T cell receptors, etc) in addition to HLA genes may influence responsiveness to HBV vaccination. Understanding the genetic factors that influence the responsiveness to HBsAg is important for developing strategies to increase HB vaccine efficacy. Since the profile of HLA gene frequencies in different ethnic populations could influence the response to hepatitis vaccination, large-scale population-based studies may help the development of more effective next-generation vaccine formulations that could improve vaccine immunogenicity and efficacy.

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