Research in Molecular Medicine

Review Article
2014, Vol: 2, Issue: 1, Pages: 1-20
DOI: 10.18869/acadpub.rmm.2.1.1

HLA-KIR Interactions and Immunity to Viral Infections

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Received: 5 Dec 2013

Revised : 10 Jan 2014

Accepted: 26 Jan 2014

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Abstract

Host genetic factors play a central role in determining the clinical phenotype of human diseases. Association between two polymorphic loci in human genome, human leukocyte antigen (HLA) and killer cell immunoglobulin-like receptors (KIRs), and genetically complex infectious disease, particularly those of viral etiology, have been historically elusive. Hence, defining the influence of genetic diversity in HLA and KIRs on the outcome of viral infections has been extensively started in clinically well-defined cohort studies. HLA genes encode molecules which present antigenic peptide fragments to T lymphocytes as central players in adaptive immunity against infectious diseases. KIRs are expressed on natural killer cells which perform a crucial role in innate immunity to pathogen infection. The effector functions of NK cells such as direct killing of infected cells, cytokine production, and cross-talk with adaptive immune system depend on activation of NK cells, which is determined by their surface receptors. Among these receptors, KIRs, which interact with HLA class I, are mainly inhibitory and exhibit substantial genetic diversity. An extensive body of association studies indicates a role for HLA–KIRs interactions in infectious diseases, autoimmune disorders, cancer, transplantation, and reproduction. Various compound HLA-KIR genotypes appear to affect outcome of viral infections that suggests a role for HLA class I diversity in innate immunity as well as adaptive immune responses. The aim of this review is focusing on the impact of HLA and KIR alleles and different combinations of these alleles on clinical outcome of viral diseases to validate this proof-of-concept with respect to the therapeutic interventions.

Keywords: Human leukocyte antigen; Killer cell immunoglobulin like receptor; Viral infection

Please cite this article as: Sabouri Ghannad M, Hajilooi M, Solgi Gh. HLA-KIR Interactions and Immunity to Viral Infections. Res Mol Med. 2014; 2 (1): 1-20

Introduction

Despite advances in therapeutics and vaccines, one of the big challenges for human is life threatening viral infections such as HIV, HBV, and HCV which are still accountable for high morbidity and mortality worldwide (1, 2).

Generally, infectious diseases are thought to be major selection force in the evolution of animals (1, 3). This pathogen-derived selection mainly affects immune response genes particularly human leukocyte antigen (HLA) and Killer cell immunoglobulin like receptors (KIRs) gene loci which are the most numerous and diverse in human genome respectively. This is reflecting the evolutionary advantages of diverse immunological responses to a wide range of infectious pathogens (1, 3). This diversity is more prominent inside major histocompatibility complex (MHC) region and it is generally assumed that resistance to infectious diseases particularly viral infections, exerts evolutionary force that fuels the generation of MHC variation (1, 4).

Variation in MHC molecules (HLA in human) due to extensive polymorphism in this region of genome mainly affects the portion of molecule that involved in peptide presentation and T cell repertoire selection which in turn have a potential to influence the individual's immune response to be susceptible or

resistant against pathogens (5). However, despite the pivotal role of HLA in antigen presentation to the cells of immune system, elucidation of clear association between the HLA genes and major infectious diseases such as HIV/AIDS, hepatitis and tuberculosis is a matter of debate and interestingly the major of these associations are with disease susceptibility rather than protection (1, 3) Susceptibility to most infectious diseases is very complex, especially with regard to polymorphisms at two principal loci involved in the immune response; HLA genes at the heart of acquired immune response and KIRs, a polymorphic set of molecules that modulate natural killer cell activity, in innate immune response (2). The centrality of these two polymorphic loci in determining the inter-individual levels of protection against viral infections have become further imprinted with the discovery of HLA class I as ligands for KIRs (6).

Several mechanisms have been proposed to explain the generation and maintenance of HLA diversity with focus on heterozygote advantage (over dominant selection) as the principle mechanism and rare allele advantage (frequency-dependent selection) as an alternative way (3, 4).

Heterozygous individuals at HLA loci are capable of presenting a wider array of pathogen-derived peptides that lead to a more diverse cytotoxic T lymphocyte (CTL) repertoire and the ability to resist against a greater breadth of infectious pathogens (2,4). Hence, failure of an effective T cell response in some cases of viral infections raises the possibility that certain HLA allotypes present viral epitopes more effectively to T cells than other allotypes (2).

Special features of the MHC genes

MHC locus, the most gene-dense region of the human genome, encompasses ~ 4Mbp on the short arm of chromosome six (6p23.1) and contains 0.6% of identified genes that about 10-20% of these genes have immunological functions (4). A notorious feature of this region is extreme polymorphism so that the number of identified HLA alleles as of May 2010 is more than 4200 accepted alleles and interestingly the numbers continue to rise (4). MHC contingents include genes encoding cell surface glycoprotein that bind peptide fragments from intracellular and extracellular proteins and present those peptides to the immune effecter cells (3, 5, 7).

MHC genes are divided into class-I (Class Ia-classical and class Ib- non-classical), class II and class III molecules based on the structure of encoded protein and their functions (3, 5). Each classical HLA class I (HLA-A, -B and –C) and class II (HLA-DR, DP and DQ) genes alone spans over nearly one third of the mhc region and the remaining part known as class III, contains genes whose products regulate aspects of innate immune responses, notably complement factors C2 and C4B, tumor necrosis factor-α (TNF-α) and Lymphotoxin-α (LT-α). Additionally, the components of this section are either related to the function of HLA antigens or are under similar control mechanisms to HLA genes (Figure 1) (7). Sequence analysis of the MHC region has confirmed the presence of more than 300 loci including over 160 protein-coding genes and 40% of those genes are immune related (8, 9). Totally, over 44000 variations [both single nucleotide polymorphism (SNP) and insertion /deletion] have been identified across this region and the average SNPs diversity varies from 1 to > 60 SNPs per Kb mainly in the class I and II genes (1).

Non-classical HLA Molecules

A growing body of literature emphasizes the diverse roles of MHC class Ib molecules in pathogen recognition, antigen presentation and immunoregulation (10). MHC class Ib genes that are located in MHC locus have few alleles (oligomorphic). Several members have been described for this family including HLA-E, HLA-F, HLA-G, and HFE (HLA-H) in humans (Figure 1). These molecules often exhibit a limited tissue distribution and mainly have a more prominent role in innate immunity. For instance, HLA-E and HLA-G molecules regulate the NK cell activation by acting as a ligand for the CD94/NKG2 and KIR2DL4 receptors respectively (11). In addition, the subset of MHC class Ib molecules such as HLA-E that present peptides to T cells bridges the innate and adaptive immune responses and also is important in regulation of autoimmunity (10).

However, there are MHC class-I-like molecules such as CD1d and MIC-A/MIC-B which are distinct from class Ib molecules and typically do not function in conventional peptide presentation (11). CD1d molecules present lipid antigens for recognition by natural killer T (NKT) cells and MIC (MHC-class I-polypeptide-related–sequence) molecules particularly MIC-A and MIC-B which are stress induced proteins, activate NK cells without the requirement for ligand binding (10, 12). The MIC molecules encoded by polymorphic gene family located within HLA class I part of mhc region which determine polymorphic series of antigens similar to HLA molecules (13, 14).

MHC structure and function

Both class I and class II molecules are heterodimeres consisting of type I transmembrane α and β proteins. Class I molecules composed of a heavy chain known as α (encoded by HLA-A, -B, or –C) and β2-microglobuline (β2M) as a non-MHC encoded

protein (3, 5). Class I α chain is made up of three extracellular (α1, α2 and α3), one transmembrane and one cytoplasmic portion. β2M makes strong non-covalent binding with the extracellular Ig-like membrane-proximal non-polymorphic α3 domain. Assembling of class I subunits (α and β2M) takes place in the endoplasmic reticulum (ER) along with peptide fragments from proteins degraded by proteasome (3). Peptide binding region (PBR) in class I molecules formed by the α1 and α2 domains, the most of the vast polymorphic region, and composed of two α-helics bordering a β-plated sheet (5). PBR binds peptides which are overwhelmingly between 8 and 11 amino acids long. Following the peptide loading, MHC class I molecules released from ER to the cell surface, where it displays the bound peptide fragments for recognition by cytotoxic T lymphocytes (CD8+ CTLs). CTLs can only recognize the foreign peptides for instance those from intracellular pathogens such as viruses in the context of self-class I MHC molecules, a phenomenon known as MHC restriction which demonstrated by Zinkernagel and Doherty for the first time, and then act directly to kill the virally infected cells (3).

Unlike class I molecules which are expressed ubiquitously on all somatic cells, class II molecules (HLA-DR, -DP, -DQ) are confined to professional antigen presenting cells (B cells, macrophages and dendritic cells) and activated T cells. Class II molecule is also a heterodimer consisted of one α chain and a β chain and its PBR is formed by both chains. Peptides bound to class II are typically 11-17 amino acids long that derived from proteins degraded in acidified intracellular vesicles. These multivesicular class II affluent endosomes receive and process antigens derived from outside of the cells, comfort class II peptide loading and export of MHC-peptide complex to the cell surface for presentation to helper T cells (5).

The distribution of mhc polymorphism mainly affects the portion of the molecule involved in peptide presentation, PBR, as well as TCR-contact regions of MHC which in turn affects the binding and presentation of particular peptide epitopes to T cells and consequently the individual's immune response to the pathogens (3, 5).

Some MHC-peptide complexes are likely to induce an effective immune response so conferring an advantage to the host. Conversely, poor binding and/or presentation of certain viral or bacterial antigens may lead to an insufficient immune response or even unresponsiveness of the host. In other words, different alleles of MHC are associated with various outcomes of infection (3, 5).

However, the host immune response involves a complex interaction between the innate and adaptive immunity, which determines outcome of infection by pathogenic organisms. The HLA class I and II genes encode molecules that lie at the heart of specific immune response against infectious diseases. With regard to the viral infections, HLA class I molecules are essential not only to the adaptive immune response but also in innate immunity as ligands for the KIRs, which modulate natural killer cell activity (2).

Natural killer cells (NKCs) receptors

Natural killer cells (NKCs) are crucial effecter cells of the innate immunity that perform a vital role in an effective antiviral immune response as well as in defense against tumor-transformed cells (15, 16). The ability of these killer cells in direct killing of infected cells, cytokine production and interaction with adaptive immune system indicates that these multifunctional cells are more efficient than simple innate killers and involved in adaptive immunity to infections, cancer and transplantation as well (15-17).

Activation of NK cells is determined by a complex balance between stimulatory and inhibitory receptors following interaction with ligands on target cells. Several gene families encode NK receptors such as KIRs, C-type lectin like receptors (e.g. CD94/NKG2 heterodimers), leukocyte immunoglobulin like receptors (LILRs) and natural cytotoxicity receptors (NKp46, NKp30 and NKp44) that trigger inhibitory or activating functions (15-16).

There are two main types of inhibitory receptors including KIRs and CD94/NKG2A which are specific for HLA class I (A, B, C) and HLA-E as a non-classical HLA class I molecule respectively. Every mature NKC expresses at least one receptor for self HLA class I to ensure the turning NK cells off against normal HLA Class I expressing cells (missing self-hypothesis). NKG2 family is consisted of five genes designated NKG2A, C, D, E and F which express on the cell surface as a heterodimers with CD94 glycoprotein. CD94/NKG2A heterodimer recognize the HLA-E and delivers the inhibitory signal to the NK cell whilst, CD94/NKG2C, E (also recognize HLA-E) and NKG2D homodimer which is specific for stress inducible proteins MICA/ MICB or UL16 binding protein (ULBP) on tumor cells or infected cells trigger NKC activation (Figure 2) (18-20).

Among NK receptors family, only the KIRs, which interact with class I HLA molecules, exhibit substantial genetic diversity and therefore the possible KIR-HLA combination may have differential effects on NK cell activation and inhibition which in turn has potential influences on the host response to viral and other infections (15-16). The interplay between stimulatory and inhibitory KIRs and their corresponding HLA ligands is likely to play a role in outcome of viral infection (such as Hepatitis C virus), which leads to

either chronic viremia or spontaneous viral clearance (21).

Genetic and function of Killer cell immunoglobulin like receptors (KIRs)

The KIR gene cluster spans a 150kb region on chromosome 19q13.4 within the leukocyte receptor complex (LRC) and is not linked to the HLA loci on chromosome 6p 21.3 (15-16). Fourteen functional KIR genes as well as two pseudogenes have been identified in humans. The encoded receptors can deliver inhibitory signal (3DL1-3, 2DL1-3 and 2DL5) or activating signal (3DS1, 2DS1-5) or both (2DL4) to the NK cells (Figure 3) (15-17, 22).

Based on the gene content on each chromosome, 2 main KIR haplotypes have been defined; group A haplotypes are characterized by the absence of all stimulatory receptors and the presence of 2DS4 and group B haplotypes which are defined by the presence of one or more of following genes: KIR2DS1-3, KIR2DS5, KIR3DS1 and KIR2DL5 (17). Haplotypes of the KIR locus vary in the number and type of KIR genes present. To date over 30 distinct KIR haplotypes with distinct gene content have been characterized by genomic analysis (15, 16). The inhibitory KIR2DL2/2DL3 and 2DL1 recognize HLA-C1 allotypes which has asparagines at position 80 (Cw1, Cw3, Cw7, Cw8, Cw12, Cw13 and Cw14 alleles) and HLA-C2 allotypes with lysine at position 80 (Cw2, Cw4, Cw5, Cw6, Cw15 and Cw17 alleles) respectively. The activating receptors KIR2DS2, 2DS1 and 3DS1 have similar Ig-like domains to the corresponding inhibitory counterparts and hence, they are thought to exhibit similar ligand specificity, although their interactions are much weaker. KIR2DS4 has ligand specificity for subsets of HLA-C allotypes (C1 or C2 groups) and HLA-A11 molecules. A subset of HLA-A (HLA-A23, 24, 25 and 32) and HLA-B molecules that carry either Bw480I or Bw480T epitopes bind to KIR3DL1 receptor. Interestingly, the interaction of KIR3DL1 with Bw480I is thought to be stronger than that with Bw480T. KIR3DL2 receptor binds to HLA-A3 and HLA-A11 allotypes. The ligand specificity for KIR2DL5, 2DS3, 2DS5 and 3DL3 remain elusive (Figure 4) (6). In addition to ample variation in gene contents across haplotypes, all KIR genes show considerable allelic polymorphism so that until April 2011 a total of 614 nucleotide sequences encoding 321 different proteins have been documented in IPD-KIR database [http://www.ebi.ac.uk/ipd/kir] (16).

This extraordinary degree of genetic diversity results in significant variation of NK repertoire among individuals and also between populations with many possible KIR/HLA combinations which in turn may induce inhibition or activation of NK cells and consequently affect the host responses to infectious agents (16). Associations between these polymorphic loci and genetically complex infectious diseases have been historically elusive, in contrast to the more obvious HLA associations with autoimmune diseases (2).

As the KIRs and HLA genes are in different human chromosomes (19q13.4 and 6p23.1) and based on the substantial diversity for both loci, a wide variety in the number and type of KIR-HLA combination is possible which probably contributes to overall immune competency. Consistently, certain combinations of KIR-HLA variants have been associated with susceptibility to autoimmune diseases, viral infections and cancer (15).

The aim of this review is to summarize the effects of variation within the polymorphic HLA and KIR loci as well as HLA / KIR combinations on anti-viral immunity and outcomes of viral infections. This will help us to validate this proof-of-concept and to find out the role of different viral infections in exhibition of different expression of HLA and KIRs genes. Better classification of this genetic makeup can help to expect immune responses and provide information to improve understanding the potential role of HLA and KIR in resistance or susceptibility to viral diseases. This will also confirm the need for finding novel vaccination policies and therapeutic methods in viral infectious diseases.

Data for this review were obtained from Medline. Search terms which applied were "HLA", "KIR ", "therapy","resistant" and also the specific viral terms, including HBV, HCV, HIV, HSV, EBV, HCMV, HTLV-1, measles, mumps, rubella, influenza, rabies, papilloma, polyoma, and parvoviruses, are discussed in this review. It should be noted that just English-language papers were included in this review.

HLA/KIRs and viral hepatitis

Hepatitis B virus (HBV), a double stranded DNA virus from hepadnaviridae family, and Hepatitis C virus (HCV), a single stranded RNA virus as a member of flaviviridae family, are the major causes of liver related morbidity and mortality with 70% of the global load of liver diseases (23). The clinical outcomes of infection of hepatitis B and C viruses are different, from the resolution of infection to chronic viral persistence, cirrhosis, and hepatocellular carcinoma (HCC) which is typically correlated with HBV and HCV infections (1). A research in chronic hepatitis B patients and asymptomatic HBV carriers showed that the frequencies of HLA-DQB1*0503 and DQB1*0303 alleles in chronic hepatitis B patients were significantly lower than asymptomatic HBV carrier people. In that report, HLA-DQB1*0503 and DQB1*0303 alleles were determined as resistant genetic factors to chronic hepatitis B infection (24).

Furthermore, other studies have shown that HLA-Bw480I allele which binds KIR3DL1 with higher affinity than HLA-Bw480T allele and consequently stronger inhibition of NK cells may involve in increasing the risk of HCC incidence. This indicates that activated NK cells may have a role in HBV-associated HCC progress (25), which in turn shows a position for host's genetic backgrounds of KIR and HLA loci in HBV infected patients under interferon therapy (25). Moreover, HLA-C group 1 homozygote, HLA-Bw480I and combination of KIR2DS4 (KIR2DS4/1D) have been reported to be correlated with HCC incidence (26). An association study performed by Lu et al. demonstrated a lower frequency of A haplotype for KIRs and higher presence of the B haplotype in patients exposed to hepatitis B virus compared to healthy controls (27). Another study showed that KIR2DL3: HLA-C1 homozygosity was protective against HBV infection while KIR2DL1: HLA-C2 was correlated with susceptibility to HBV infection (28). It could be due to stronger inhibition of NK cells following interaction of KIR2DL1 with HLA-C2 which is difficult to overcome by simultaneous activating signals whereas, weaker KIR2DL3-HLA-C1 interaction can be overridden easily by activating signals, resulting in lyses of the target (6).

Also, the role of HLA-DRB1*1302 and HLA-A*0301 alleles in clearance of infection and HLA-B*08, HLA-B*44 alleles and HLA-DQA1*0501/ DQB1*0301/DRB1*1102 haplotype in HBV persistence have been confirmed by other studies (Table 1) (29-31).

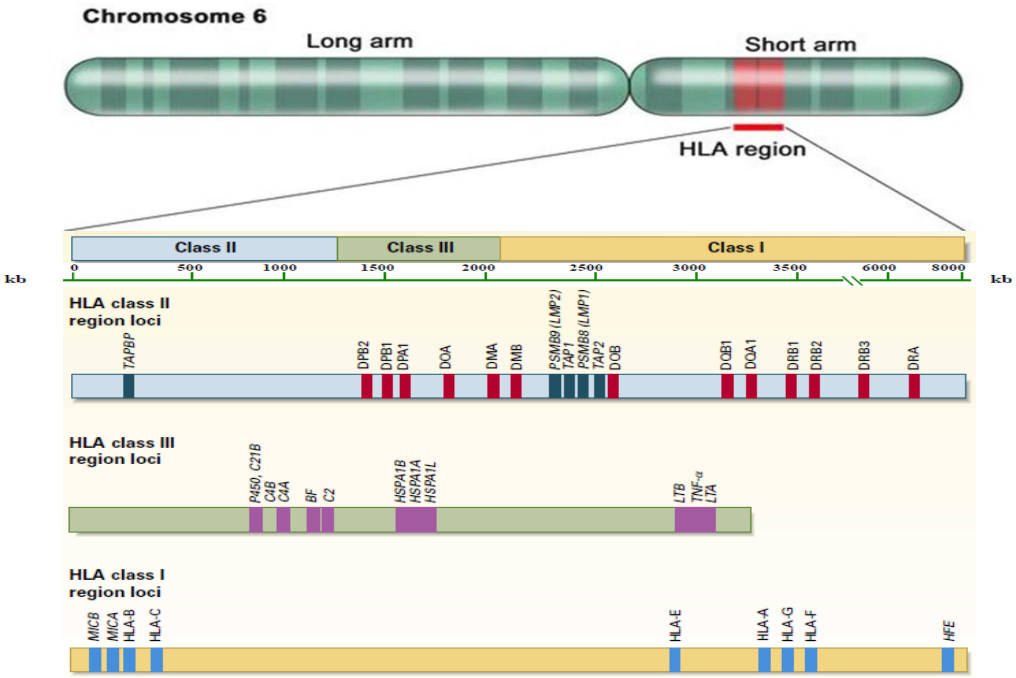

Figure 1. Genomic organization of the HLA Complex on chromosome 6p23.1 in human. The encoded genes by three regions of this complex (HLA-class I, class II and class III) as well as non-classical HLA genes (e.g. HLA-G, HLA-E, HLA-F, HFE, MICA, and MICB) have been depicted in different colors [Adopted and modified from Klein et al. (7)].

An *in vitro* study by Bertoletti et al. demonstrated that the optimal amino acid sequence recognized by cytotoxic T cells from HLA-A2 positive patients is a 10-mer peptide (residues 18 to 27) containing the predicted peptide-binding motif for HLA-A2 and this peptide can stimulate cytotoxic T cells which are able to recognize endogenously synthesized hepatitis B core antigen. Since patients with chronic hepatitis B virus infection fail to induce an efficient anti-HBV-specific CTL response, this epitope (HbcAg18-27) might serve as the starting point for the design of synthetic peptide-based immunotherapeutic strategies to terminate persistent viral infections (32).Another worldwide problem is hepatitis C virus infection. The mechanisms by which HCV can escape the host immunity have remained as a matter of debate (33). It has been reported that HCV infection course and also treatment efficacy are influenced by the patient's factors including HLA genes. Correlation between HLA molecules and chronic hepatitis C treatment

with interferon has attracted the attention of the researchers (34). A research in Taiwanese patients with chronic HCV infection showed that HLA-A11, B51, Cw15, and DRB1*15 alleles were positively related with sustained response to interferon (IFN)-alpha treatment. Contrarily, it appears that HLA-A24 allele was associated with response to IFN-alpha, in the cases of cirrhosis, pretreatment viral load, and viral genotype. Additionally, HLA-DRB1*15/DQB1 *05 haplotype was shown to be related with response to IFN-alpha therapy. Persistent response was also correlated to HLA-A11/DRB1*15 (35) and HLA-B44/DRB1*03 haplotypes (36). Another research which performed on Brazilian patients with chronic HCV infection revealed that the HLA-DRB1*07 allele was connected with chronic HCV infection (37). However, It has been reported that one of the KIR2DL3 ligands (HLA-Cw*07) has not any protecting effect against chronic infection (38).

On the other hand, the role of HLA DQB1*0301 in predicting spontaneous resolution of HCV following acute infection has been reported (39). Clearance of HCV infection have been also reported in association with HLA-DRB1*0101, *0401 and *15 alleles (40), DRB1*1101/DQB1*0301 haplotypes (30), HLA-A*1101, *03, B*57, B*27 and Cw*0102 alleles (41). On the other hand, persistence of infection was associated with HLA-DRB1*0701, A*2301 and Cw04 alleles and A3/B8/C7/DRB1*0301 /DQB1* 0201 and Cw4/B53 haplotypes (40-42). Preliminary experiences showed that the recurrence and development of hepatitis C disease in liver transplant recipients are related to KIR genotype and KIR/HLA-C ligand compatibility (43).

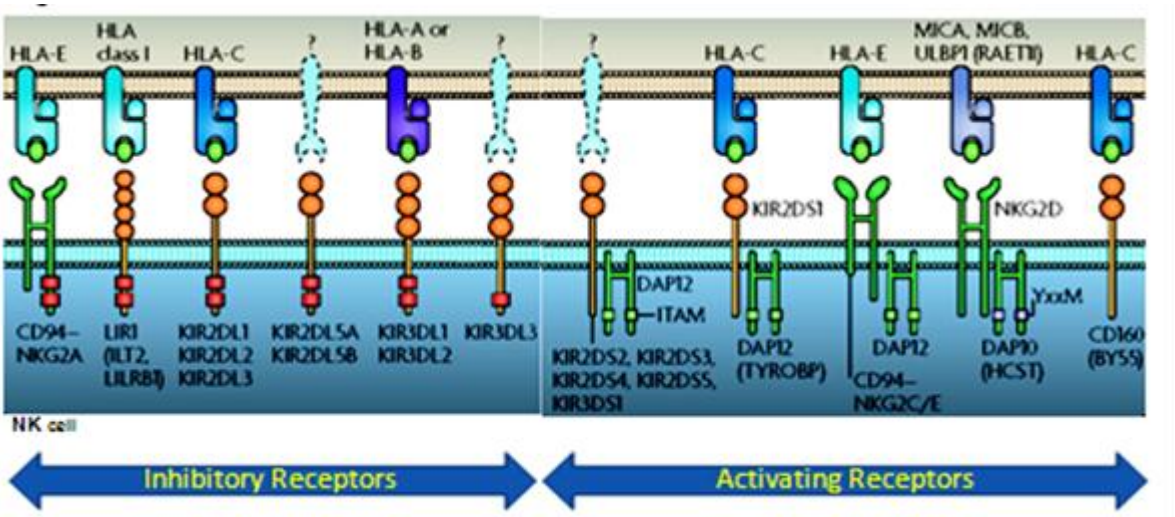

Figure 2. NK cell receptors for HLA class I and class I like molecules. (Modified from http://www.nature.com/nri/posters/nkcells).

Also, the genetic interactions of KIRs and HLA-C ligand along with class II HLA alleles in relation to antiviral response to HCV infection has been reported (21). In the cases of spontaneous clearance of HCV infection, association between DRB1*1201 with KIR2DL3/ 2DL provides an indication that both class II alleles and KIRs are implicated in the spontaneous resolution of HCV infection (21). Moreover, KIR2DL3 and its ligand, HLA-C group 1 alleles (Cw1, Cw3, Cw7, Cw8, Cw12, Cw13 and Cw14), were shown to be correlated with spontaneous clearance of HCV infection in those people who were faced through blood products, intravenous drug use (IVDU) or through high-risk behavior without having antibodies to HCV or HCV RNA (44). In people with spontaneous clearance of HCV infection, a higher frequency of NK cells expressing HLA-C-specific KIRs has been reported (45). KIR2DL3: HLA-C1 has Also been shown to have the protective effects in patients with HCV infection but without anti-HCV antibodies (38). Nevertheless, KIR2DL3: HLA-C1 has not been found to be protective in HIV/HCV co-infected patients indicating that the HIV infection changes the defensive effect of KIRs (38). Additionally, a higher frequency of KIR2DL3: HLA-C1 has been shown in the patients who were successfully treated with interferon-α-based regimens in compare with those who have not made successful treatment responses. KIR2DL3 as well as KIR2DS4 are found in group "A" haplotype (46) and KIR2DS4 is correlated with protection against chronic HCV infection (44). On the other hand, KIR2DL5 as a group "B" haplotype has been shown to be associated with poor response in HCV treatment (46). Of interest was the observing non-protective role of KIR2DL3: HLA-C1 in HIV/HCV co-infected patients.

This indicates modulation of the protective features of KIRs by HIV (15).

Preclinical studies have shown that one peptide from HCV1b core protein (residues 30-39) can induce *in vitro* peptide-specific CTL response from patients with HLA-A11, -A31, and -A33 alleles (47). Additionally, other residue from this protein, positions 35-43, as well as positions 918-926 of the non-structural protein 2 has been shown to induce peptide-specific CTLs from the PBMCs of HLA-A11 and -A33 patients. Therefore, the peptide at positions 30-39 of the core protein could be an appropriate target molecule of specific immunotherapy for all HLA- A11, -A31, and -A33 positive patients with HCV1b infection (48). Also, several peptide motifs in HCV2a have been found to efficiently induce specific CTLs response *in vitro* in HLA-A2 positive patients with HCV2a infection (49).

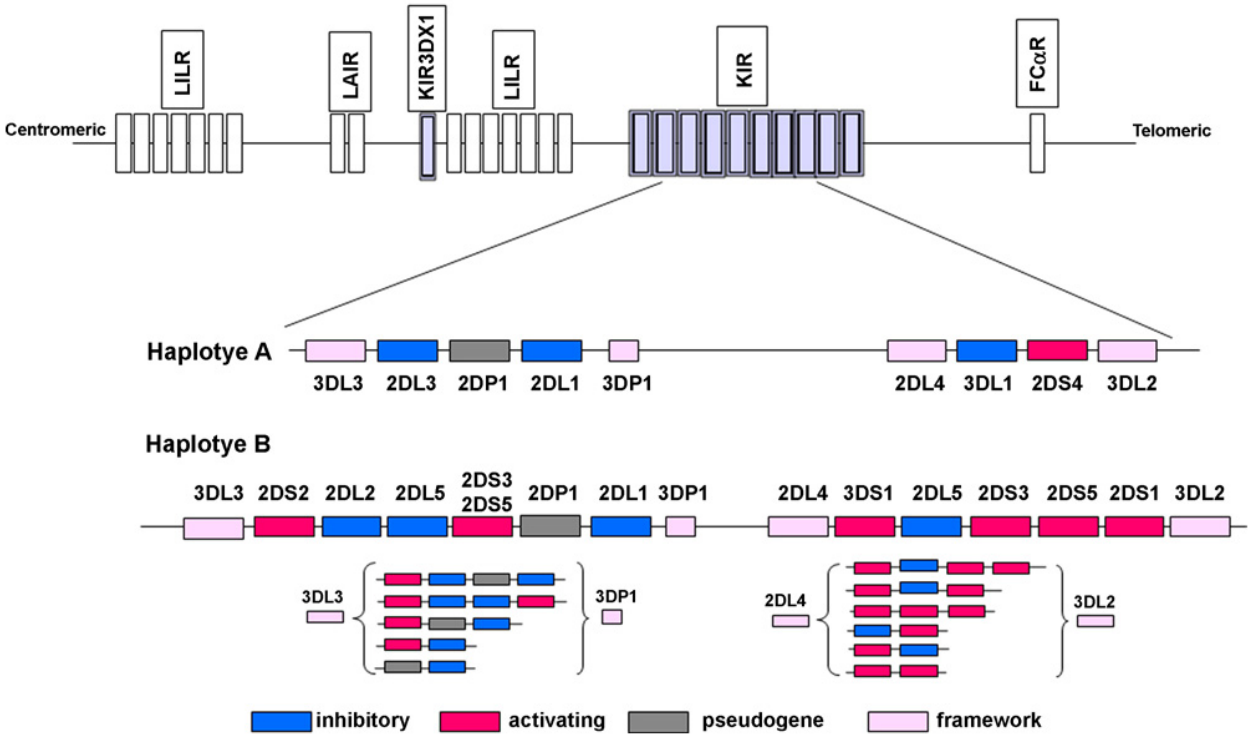

Figure 3. Genomic organization of the KIR gene cluster within the leukocyte receptor complex on chromosome 19q13.4 in human. KIR haplotypes are composed of centromeric and telomeric halves and vary extensively in gene content. The centromeric half is demarcated by 3DL3 and 3DP1, while the telomeric half is demarcated by 2DL4 and 3DL2. There are two main KIR haplotypes. The A haplotype is fixed in terms of gene content, but the B haplotypes are characterized by variable gene numbers (shown in parentheses).Framework genes (pink boxes) are present on all haplotypes. The ancestral KIR gene 3DX1 is also shown. [With permission from Carrington M. (6)]

Similarly, it has been shown that, amino acid changes in HCV genotype 2b from patients with sustained biochemical response (sBR), normal biochemical values despite persistent viraemia, during interferon therapy were mainly located in the binding motifs of HLA class I molecules. These results depicted that the greater amino acid changes of HCV arising during interferon therapy are associated with the establishment of sBR and these escape mutations of HCV genome from immune responses were suggested to be related to reduced hepatocyte injury. Hence, understanding the mechanisms of sBR that facilitate the prediction of sBR before IFN therapy probably in the context of HLA variations could be important for clinical treatment as well as basic research (50). Taken together, a complex and substantial role for host's genetic background particularly HLA and KIRs genes is suggested for clinical outcomes of HBV and HCV infections. In this line, peptide binding analysis of some HLA molecules revealed that patients with HLA-A2 and HLA-A11can induce more efficiently a peptide – specific CTL response against certain epitopes of HBV and HCV which can be probable candidates for peptide based immunotherapy strategies.

HLA/KIRs and Human Immunodeficiency virus

Human immunodeficiency virus (HIV), a single stranded RNA virus from retroviridae family, is still an agent of sanitation problem all over the world. During the twenty-first century, the virus was the cause of more than 5% of mortality worldwide (51).

As the most related researches confirm, the definition of clinical phenotype is vital for HIV infection management (1). For instance, host genetic factors which contribute in HIV infection including MHC genes, provide identification of overall susceptibility or resistance to infection (52, 53). Published data have shown the intense effects of HLA restriction on HIV variants that escape from immune responses. The HIV/HLA researches have also presented mechanistic view of the interaction between HLA molecules and NK cell receptors (1).

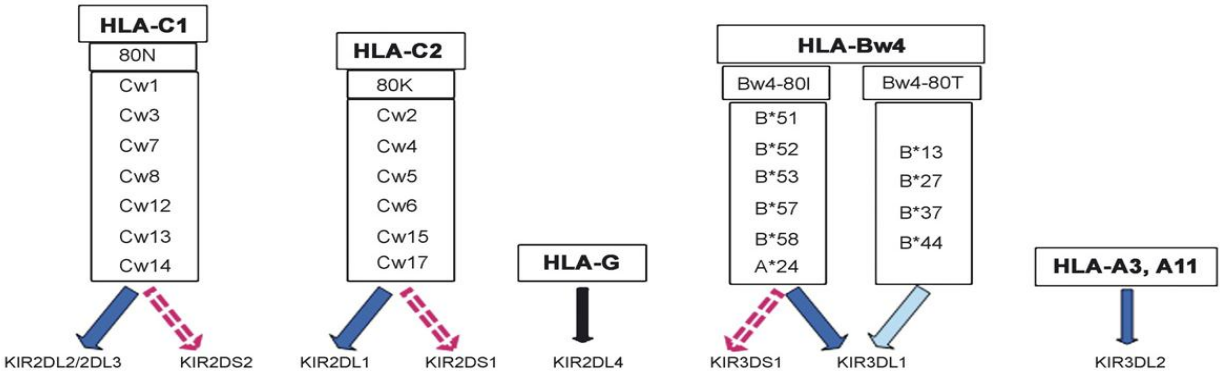

Fig 4. KIR receptors bind to distinct HLA class I allotypes. The inhibitory KIR2DL2/2DL3 and 2DL1 recognize HLA-C1 allotypes which has asparagine at position 80 and HLA-C2 allotypes with lysine at position 80 respectively. The activating receptors KIR2DS2, 2DS1 and 3DS1 are thought to exhibit ligand specificity similar to the corresponding inhibitory counterparts, although their interactions are much weaker (depicted as smaller red broken arrows). The interaction of KIR3DL1 with Bw4 80I (dark blue arrow) is thought to be stronger than that with Bw4 80T (light blue arrow). KIR2DS4 has ligand specificity for subsets of HLA-C allotypes (C1 or C2 groups) and HLA-A11 molecule (Not shown here). Ligands for KIR2DL5, 2DS3, 2DS5 and 3DL3 have not been identified [With permission from Carrington M. (6)]

The role of different HLA alleles in HIV infection has been reported as controversial results. Several DQB1 alleles including DQB1*050301, DQB1* 0603, DQB1*0609, and DQA1*010201/ DQB1*0603 haplotype have been reported to be associated with resistance to HIV-1 infection (54). Also, significant presence of DQB1*0602 allele and DQA1*010201/ DQB1*0602 haplotype in the HIV-1 resistant patients have been demonstrated. Other haplotypes including DQA1*0504/DQB1*0201, DQA1*010201/DQB1*0201, DQA1*0402/DQB1*0402 and DQA1*0402/DQB1* 030101 were reported in HIV-1 positive subjects. Moreover, protective effect of HLA-B27 and B57 alleles against development of HIV infections have been documented (55). Hence, controversial results have been concluded with regard to correlation between HLA and resistance to HIV infection. One study showed that the relation between DQ alleles and haplotypes and susceptibility or resistance to HIV-1 infection were independent of HLA-DRB1*01, HLA-A*2301 and HLA-A2/6802 alleles, whereas previous study had confirmed this relationship (54). In view of ethnic groups, HLA-DRB1*04 presented a protective role against HIV-1 infection in Caucasians. These data indicated that there is HLA class II alleles connected with protection of HIV-1 infection which varies among ethnic groups (47). On the other hand, the correlation between DQ alleles and haplotypes with resistance and Susceptibility to HIV-1 suggests the significant role of HLA-DQ and CD4 in anti-HIV-1 immunity (54). Serum level of soluble HLA-A, -B, -C (sHLA-A, -B, -C) molecules have been reported to be increased in HIV-infected patients and be decreased following therapy. These findings suggest that the serum levels of sHLA-G and sHLA-A,-B, -C molecules may characterize a useful indicator to observe virological interactions and immune responses in HIV-positive patients (56).

Another report indicated the association between HLA-B57 and B*5801 alleles with increased recognition and control of the same Gag epitope of HIV (57). Some functional studies have been able to verify the importance of NK cells in controlling HIV-1 infection. These data revealed that HIV can escape from NK-cell-mediated immune responses via sequence polymorphisms in KIRs genes (58). KIR3DL1/S1 is the unique KIR gene which encodes both inhibitory (KIR3DL1) and activating (KIR3DS1) receptors (59). KIR3DS1 together with HLA-B, Bw4–80I, was shown to be related with slow progression to AIDS. Of note, neither KIR3DS1 without Bw4–80I nor Bw4–80I without KIR3DS1 had any consequence on development of disease. Interestingly, highly expressed KIR3DL1 alleles (KIR3DL1*h) combined with HLA-B*57 (an HLA-Bw480I allele) have been reported to be effective against AIDS progression and viral replication which highlights more protective role in comparison to the combined KIR3DS1/HLA-Bw480I. Moreover, HLA-

B*27 alleles which contain the Bw480T motif, showed greater protection against AIDS progression in the presence of KIR3DL1*l (low expressed alleles), suggesting that B*27 alleles might have greater affinity for one or more of the KIR3DL1*l allotypes (59). It has been suggested that Bw4 allotypes with threonine at position 80 (Bw480T) particularly HLA-B*2705, are better ligands for other KIR3DL1 subtypes (59). Noteworthy, expression of HIV nef (negative factor) protein down regulates some HLA class I molecules including HLA-B, this could be sensed via inhibitory KIRs, KIR3DL1. In addition, the stronger interaction between KIR3DL1 and HLA-B molecule will ensure that more dearly HLA-B will be missed by NK cells in this recognition of "missing self". In other words, the activation potential of the NK cell pool is expected to correlate with the level and frequency of KIR3DL1 expression and its affinity for the available HLA class I ligands (59).

Recent reports have shown the relationship of HLA-B with the outcome of HIV infection and HLA-C as elite controllers of HIV infection (60, 61). This relationship may be due to the role of HLA-C in presenting HIV-derived peptides to T cells (62) or correlated to epistatic connections with KIRs. Slower progression to AIDS and also enhanced viral control has also been connected with higher levels of HLA-C expression. In conclusion, understanding the molecular nature of the interaction between HLA, KIRs and HIV represent a high priority goal which might be included and considered in rational therapeutic strategies which needs to be applied in HIV infected patients (59, 63).

HLA / KIRs and Human T-lymphotrophic virus type-1

Human T-lymphotrophic virus type-1 (HTLV-1) belongs to retroviridae family and infects about 15–20 million people globally (64). Most infected people are considered as asymptomatic carriers (65). Nevertheless, infection in both cases of symptomatic and asymptomatic subjects may lead to severe illnesses such as cancer although the factors which ascertain outcome are still unclear. A report showed that in patients who are infected to HTLV-1, inheritance of the KIR2DL2 gene intensifies both protective and detrimental HLA class I-restricted anti-viral immunity. This research also indicated that inhibitory KIRs alongside with T cells are believed to be as major determinative factors for outcome of persistent HTLV-1 infection (65).

HLA / KIRs and Herpes Simplex Virus (HSV)

Herpes simplex virus type 1 (HSV-1) is a double stranded DNA belongs to Herpesviridae which causes cold sore, gingivostomatitis and herpetic whitlow. Non-classical human MHC class I molecules, HLA-G and HLA-E, are able to support viral evasion from immune system and also are contributed in viral tolerance (66). It has been reported that the HSV-1 as a neurotropic virus induces neuron latency and chronic infection and is able to induce HLA-G (66) mostly HLA-G3 and HLA-G5 expression in human neurons (67) but does not up-regulate HLA-E expression (66). It has been suggested that neither HLA-G nor HLA-E can contribute to viral latency of HSV-1 (66). Moreover, there is also evidence supporting the view that HSV-1 infection may decrease the expression of invariant chain (Ii) strongly which in turn impairs configuration of SDS-resistant DR-peptide complexes (45).

HSV triggers NK cell cytotoxicity via down-regulating HLA-C molecules which are involved in induction of KIRs signals (68). Furthermore, association of KIR genes, KIR2DL2 and KIR2DS2, with asymptomatic HSV infection has been documented (15). Thus, a role for KIRs in detection of virally infected cells might be considered. This is in consistence with down-regulation of MHC class I which can render infected cells with herpes viruses to be vulnerable to killing by NK cell (68).

An *in vitro* study by Sievers et al. demonstrated that a six amino acid sequence from HSV-1 (strain 17) glycoprotein B (gB) is identical to a sequence of MHC class II-associated invariant chain (Ii) and interestingly, this gB sequence is adjacent to a highly conserved HLA-DR1 binding motif which in turn mediates binding of gB to DR heterodimers. Two viral sequences consisting of a MHCII groove binding segment and a promiscuous binding site together resemble the class II binding site of human Ii. Additionally, there was an association between cloned gB, a virus envelop protein, and three HLA-DR allotypes. By using chimeric Ii/gB fusion proteins, it was shown that some parts of gB sequences mediate promiscuous or allotype-specific binding to the HLA-DR peptide-binding domain. Mutations of two Lysine residues in the viral segment of chimeris Ii/gB abrogate promiscuous binding to HLA-DR heterodimers. This finding indicates that promiscuous binding of virus sequence to HLA-DR molecules and suggests a potential for HSV-1 to manipulate MHC class II pathway of antigen processing and presentation (69).

HLA / KIR and Epstein Barr Virus (EBV)

EBV as a member of Herpesviridae may cause mononucleosis, Burkett's lymphoma, and naso-pharyngeal carcinoma. One study showed that the presence of HLA-B7 and HLA-A2 were related to increased and decreased levels of IgG antibody against viral capsid antigen (VCA) of Epstein Barr virus respectively (70).

On the other hand, HLA-A*02 allele expression has been reported most important in the chronic patients with high viral loads (80%) in comparison to patients who resolve EBV infection. In contrast, the prevalence of HLA-B*08 allele has been reported in people who recovered from EBV infection. Inclusively, in the chronic carriers with high viral loads, EBV gene expression is different from those that resolve infection and therefore, it seems to be related partly with HLA polymorphisms (71). Moreover, underlying mechanism that HLA genes affect the pathogenesis of multiple sclerosis (MS) is still a matter of debate although, it may partly involve in immune control of EBV infection (72). Several studies indicate that in a small percentage of MS patients, decreased HLA class II expression on B cells may harm cytotoxic T cells (CTL) reaction to EBV by decreasing the CD4+ T cell help (73). EBV may cause a disease entitled EBV-infected T/NK-cell (74). Moreover, KIR2DS5 may be probably involved in promoting the susceptibility to Epstein-Barr virus in association with hemophagocytic lymphohistiocytosis disease (75).

It has been shown that HLA-A*11 molecule presents an immunodominant epitope derived from the EBV nuclear antigen 4 (NA-4) to EBV-specific cytotoxic T-lymphocytes. In addition, subpicomolar concentrations of a synthetic nanomer peptide corresponding to residues 416-424 of the EBV NA-4 sequence, IVTDFSVIK, can sensitize phytohemag- glutinin-stimulated lymphoblasts to be lysed by EBV-specific HLA-A11-restricted CTLs. It was also shown that micromolar concentrations of this peptide induce biosynthesis and surface expression of HLA-A11 in an A11-transfected sub line of the peptide transporter mutant cell line T2. Using the IVTDFSVIK peptide and a series of synthetic nonamer peptides with single amino acid substitution, specific motifs were determined for HLA-A11 peptide binding groove. More importantly, the presence of a hydrophobic amino acid in position 2, small side chains amino acids in positions 3 and 6, and a lysine in position 9 was predictable in this motif. Using this motif, a peptide in the carboxyl-terminal end of wild-type p53, ELNEALELK, was identified to be able to induce HLA-A11 biosynthesis as efficiently as the IVTDFSVIK viral peptide (76).

HLA / KIRs and Human cytomegalovirus

Human cytomegalovirus (HCMV) is a Herpesvirus with double stranded DNA and expresses US11 and US2 proteins that dislocate human MHC class I molecules from the lumen of endoplasmic reticulum to cytosol, location where degrades the class I heavy chains quickly (77). In the majority of infected people, CMV makes an asymptomatic infection and it can be reactivated in immunocompromised patients particularly in transplant recipients which consequently cause a life-threatening illness (15, 78). Some studies indicate that a subset of CMV-specific CD4 T cells is regulated by HLA class I-specific KIRs (47). Therefore, the down-regulation of HLA class I stimulated by CMV might increase CMV-specific CD4 T cell memory responses controlled by HLA class II molecules (47, 79). With regard to the role of CMV in transplantation outcomes, a study has performed to find any association between CMV infection, HLA tissue type, and acute graft-versus-host disease (aGVHD) after allogeneic hematopoietic stem cell transplantation (HCT). The results showed a higher frequency of HLA-A30, HLA-B40, and HLA-DRB1*15 in seropositive patients without aGVHD but with post-transplant CMV infection compared to those without CMV infection. It can be concluded that certain HLA alleles can have either a predisposing or defensive function in CMV reactivation, which may be useful in estimating the risk of aGVHD and convincing the specialized therapy in each individual (80).

In view of escaping from NK cell-mediated reaction, HCMV may interfere with the expression of NKG2D ligands in virally infected cells. Moreover, the virus may keep NK inhibitory receptors involved in preserving HLA class I molecules or showing class I surrogates (81). In general, data obtained from studies appear to be in consistence with NKG2D function as a co-stimulatory receptor in HCMV-specific CD4 T lymphocytes (47). Therefore, it might have a position diathesis against infected HLA class II cells which express NKG2D ligands (82, 83). A study in USA has shown a correlation between elevated expression of both KIR2DS2 and KIR2DS4, and a 7-fold raise in risk for HCMV reactivation in HCT recipients (44). It was speculative that, elevated KIR expression in those CMV positive recipients might be coincidental with factors that active CMV or initiated by CMV or cellular defense mechanism against CMV reactivation (44). Altogether, NK cells as important players in innate immunity are thought to be especially relevant to viral infections of the herpes family including CMV, HSV and EBV (15). A consistent finding seems to be association between protection against viral infections and presence of more activating KIR genes, although further researches are needed to clarify the exact relationship between NK receptors and different viral infections.

Regarding to the immunodominant peptides, one investigation suggested that a nonomer peptide derived from CMV immunogenic matrix protein pp65 protein, QYDPVAALF, is one of the HLA-A24-restricted CTL epitope and may be of therapeutic value in peptide-based immunotherapy

against CMV infection in bone marrow transplantation (BMT) patients (84).

Table 1. HLA and KIR alleles and various combinations of HLA/KIRs that affect the outcome of viral infection.

Virus	HLA alleles or haplotypes association/Disease outcome	KIRs alleles and KIR–HLA combinations/Disease outcome
HBV	HLA-DRB1*1302/Clearance [29] HLA-DQA1*0501-DQB1*0301- DRB1*1102 haplotype/ Persistence [31] HLA-A*0301/ Clearance [29], [30] HLA-B*08 and HLA-B*44 / Persistence [29], [30] HLA-DQB1*0503,*0303/ asymptomatic HBV carrier [24] HLA-Bw4^{80I}/ increased HCC incidence [26]	2DS4 (2DS4/1D) / HCC incidence [26] KIR2DL3/ HLA-C1 homozygote. / Protective against infection [28] KIR2DL1 / HLA-C2 homozygote / Increased susceptibility [28]
HCV	HLA-DRB1*0101, DRB1*0401 and DRB1*15 alleles /Clearance [40] HLA-DRB1*1101-DQB1*0301 haplotypes/ Clearance [30] DRB1*07/ chronic infection [37] HLA-DRB1*0701 Persistence [42] HLA-A*03-B*08-Cw*07-DRB1*0301- DQB1*0201 /Persistence [41] DQB1*0301/ spontaneous resolution [39] HLA-A*2301, HLA-Cw*04 allèles and HLA-Cw*04- B*53 haploype /Persistence [40] HLA-A*1101, *03, B*57, B*27 and Cw*0102 alleles /Clearance [41]	KIR-HLA-C ligand compatibility / Recurrence and development of hepatitis C disease in liver transplant recipients [43] KIR2DL3-HLA-C1 homozygote / Spontaneous clearance and successful IFN therapy [44] KIR2DS4 / Protective agains chronic infection[44] KIR2DL5 / Poor response in HCV therapy[46] 2DL3/2DL3/DRB1*1201 And 2DL3/ HLA-C1/C1 / HCV spontaneous clearance [21]
HIV	HLA- A,-B,-C homozygosity / Accelerate AIDS [59] HLA-B*35/ Accelerate AIDS [50] [59] HLA-B*57, HLA-B*27/ Delay AIDS [55] HLA-A*01-B*08-DRB1*03/ Accelerate AIDS [55] HLA-DRB1*13-DQB*06/ Maintenance of viral suppression in patients treated early [47] DQB1*050301, *0602,*0603 and *0609 alleles/ Resistance to infection [54] DQA1*010201-DQB1*0603 and DQA1*010201-DQB1*0602 haplotypes/ Resistance to infection [54] HLA-DRB1*04/ Protection in ethnic groups [47]	3DS1 + Bw4^{80I} / Delays progression to AIDS [59] 3DL1 + B*57 (Bw4^{80I} allele) / Delays progression to AIDS [59] 3DL1 + B27 (Bw4^{80T} allele) / Delays progression to AIDS [59] 2DL2 / 2DS2 / Faster rate of CD4 T cells decline and accelerates progression to AIDS [59]
EBV	HLA-B*08 / Clearance of infection [71] HLA-A*02 / Chronic infection [71]	KIR2DS5 / Increased susceptibility in association with heomophogocytic lymphohistiocytosis [75]
HCMV	HLA-A30, B40 and DRB1*15/ Seropositive for infection and low risk of aGvHD [80]	2DS2/ 2DS4 / CMV reactivation after hematopoietic cell transplantation [44]
Influenza	Up regulation of HLA-G/ Evading from immune system [103]	3DL1/3DS1 ligand-negative pairs, 2DL1 ligand-negative pairs and 2DL2/2DL3 ligand-positive pairs / Sever response to H1N1/09 infection in ICU patients [106], [107]
Papiloma (HPV) and Polyoma	DRB1*13 allele/DRB1*13-DQB1*06 haplotype / protective in risk to HPV infection and cervical cancer [111] HLA-B*07-DQB1*0301/ Susceptible [111] DRB1*15 allele/DRB1*15-DQB1*06 haplotype / susceptibility to HPV infection, cervical cancer, precancerous expansion [111] DRB1*04 allele/DRB1*04-DQB1*03 haplotype / predisposition to cervical precancerous lesions [111]	3DS1 and 2DS1 / protect against increasing risk of the severe form of recurrent respiratory papillomatosis [112] HLA-Cgrp2/Bw4^{1} and no 3DS1 / Decreased risk of cervical neoplasia [15] Genotype 10^{2} and 2DL5* 002 / Increased risk of CIN [114] KIR2DS1, KIR2DS5 and KIR3DS1 / protection against HPV [15] KIR3DS1 / development of HPV related disease, cervical neoplasia [15]
HSV	HLA-G and HLA-E/ evasion from immune system/Viral tolerance [66] Induction of HLA-G3 and HLA-G5/ latency and chronic infection [66]	2DL2 and 2DS2 / asymptomatic HSV infection [15]
HTLV-1	HLA class I / anti-viral immunity [65]	KIR2DL2 / Protective and detrimental effect of anti-viral immunity [65]
Parvoviruses	HLA-DR4, HLA-Cw4 / susceptibility to RA [116],[117] HLA-DRB1*01, DRB1*04, and DRB1*07/ symptomatic infection [62]	2DS4 / HLA-Cw4 / Association with RA [117] 2DL2 / 2DS2 / Improved response to anti TNF-α therapy [118] Different HLA-C / KIRs genotypes / Variable responses to anti TNF-α therapy [118]
Measles	HLA-B*08, B*13, B*44, DRB1*03, DQA1*0201 alleles and HLA-B44, and B58 supertypes * A*24/C*03/B*15, DRB1*07/DQB1*03/DPB1*04 & DRB1*07/DQB1*02/DPB1*02 haplotypes* HLA-B*07, DRB1*08, DQA1*0104, DPA1*0202 alleles, HLA-B7 supertype and DRB1*15/16-DQB1*06-DPB1*04 haplotype** A*26/C*12/B*38 and DRB1*03/DQB1*02/DPB1*04 haplotypes ** DRB1*04/DQB1*03/DPB1*03 haplotype ***	

Mumps	DRB1*0101, *0301, *0801, *1001, *1201, *1302 alleles, DQA1*0101, *0105, *0401, *0501 alleles and DQB1*0201, *0402, *0501 alldes → variations in lymphoproliferative responses to mumps vaccine [92]	
virus	**HLA alleles or haplotypes association/Disease outcome**	**KIRs alleles and KIR–HLA combinations/Disease outcome**
Rubella	DPB1*0301, DPB1*0401, DPB1*1301, DPB1*1501 alleles and HLA-B*2705, B*4501, Cw*0303 and Cw*0704 alleles →antibodies induction by rubella vaccine [95] DPB1*0301, DQB1*0501, DRB1*0101, DRB1*1104, HLA-B*3503 and HLA-Cw*1502 alleles→ increased stimulation rubella-specific lymphoproliferative indices [96] DPB1*0401, DPB1*1001, DPB1*1101, DQB1*0202, DRB1*0701 and HLA-B*3901 alleles → negatively related to rubella-specific lymphoproliferation [96]	

*: Decreased humoral response against measles vaccine [90, 91], **: Increased antibody response or higher specific cellular immune responses to measles and mumps vaccine [90, 91] ***: high lymphoproliferative responses to measles and rubella antigens [90, 91], **** variations in lymphoproliferative responses to mumps vaccine [92]
§: antibodies induction by rubella vaccine [95], **§§:** increased stimulation rubella-specific lymphoproliferative indices [96].
[1]Bw4 refers to HLA-B Bw4 alleles.
[2]Genotype 10; KIR2DL1, KIR2DL2, KIR2DL3, KIR2DL4, KIR3DL1, KIR3DL2, KIR3DL3, KIR2DS4.
CIN: Cervical intraepithelial neoplasia, HCC: Hepatocellular carcinoma

HLA and Measles, Mumps and Rubella viruses

Measles and Mumps are single stranded RNA viruses from Paramxoviridae family and Rubella virus is also a single stranded RNA member of Togaviridae Family. All three viruses are used in a combination form as live-attenuated vaccine known MMR (46). One study has indicated that measles virus H protein has a significant role in induction of CD8+ T cells in addition to antibody responses in HLA-A2-positive people (85). Consistently, the role of HLA-DRB1 alleles as the main restriction molecules in presenting measles virus-N and P antigens to T cells has been documented (86). Another research showed the relations between interleukin-2 (IL-2) cytokine production and expression of DPA1*0201 and DPA1*0202 alleles. Also, the presence of DQB1* 0302, DQB1*0303, DQB1*0502, DRB1*0701, DRB1 *1103, DRB1*1302, DRB1*1303, DQA1*0101, and DQA1*0201 alleles have been reported to be strongly associated with measles-induced IL-10 secretion (87). Furthermore, correlation between specific DQA1* 0505 alleles and measles-specific IL-12p40 secretion has been confirmed which indicates that cytokine responses to measles antigens are mainly influenced by HLA class II genes (87).

An *in vitro* study by Marttila et al. depicted that only a few T cell epitopes of the measles virus nucleoprotein which mainly restricted to HLA-DRB1*1501 or DRB1*1201 alleles are important in establishing cellular immunity to measles virus. This information could be applicable in the development of new vaccines and in elucidating the immuno-pathological complications associated with MV infection (88).

Some studies have attempted to clarify the role of HLA haplotypes and their genotypic combinations in immune status following measles vaccination. An investigation on measles vaccinated seropositive and seronegative subjects depicted a correlation between presence of different HLA alleles and antibody response which may clarify the vaccine non-respondents phenomenon (46). Another study showed HLA supertypes, such as A3, B7, B44, B58, B62, and DR may have a viewpoint in regulating immune responses to the measles constituents of MMR vaccine (89). Accordingly, Poland et al. study demonstrated that HLA-B*08, B*13, B*44, DRB1*03, DQA1*0201 alleles and also HLA-B44, and B58 supertypes are associated with decreased humoral response against measles vaccine. Conversely, the HLA-B*07, DRB1*08, DQA1*0104, DPA1*0202 alleles and HLA-B7 supertype were associated with increased antibody response. In that study, significant associations were also found between A*24/C*03/ B*15, DRB1*07/DQB1*03/DP B1*04 and DRB1*07/ DQB1*02/DPB1*02 haplotypes and decreased IgG antibody responses against measles antigens. On the other hand, people with DRB1*15/16-DQB1*06-DPB1*04 haplotype showed an increased antibody response to measles virus but presented low levels of IgG antibody to rubella virus (90-91).

Additionally, the presence of A*26/C*12/B*38 and DRB1*03/DQB1*02/DPB1*04 haplotypes have been significantly associated with higher specific cellular immune responses to measles and mumps vaccine viruses. Whereas DRB1*04/DQB1*03/DPB1*03 haplotype has been correlated with high lympho-proliferative responses to measles and rubella antigens and lower levels of IgG antibody against rubella virus (90-91) In Ovsyannikova et al. study, class I A*29-Cw*16-B*44 haplotype was shown to be associated with lower levels of immunoglobulin G (IgG) antibody to both measles and mumps antigens (91). Another study by Ovsyannikova et al. demonstrated significant associations between the

HLA-DQB1*0303 alleles and lower mumps-specific antibody titers. Additionally, alleles of DRB1 (*0101, *0301, *0801, *1001, *1201, and *1302), DQA1 (*0101, *0105, *0401, and *0501), and DQB1 (*0201, *0402, and *0501) loci were correlated with significant variations in lymphoproliferative responses to mumps vaccine (92).

An experiment performed in human B-lymphoid cell-line Akata and in the human chronic myelogenous leukaemia cell line K562, showed that the expression of MHC class-I antigen was extensively decreased in the infected cell lines with mumps virus in compare with uninfected cells (93). This result showed the role of mumps virus in decreasing MHC class-I antigen expression. Also, *in vitro* model of synovial cells infected by mumps virus has shown that cells containing viral antigens do not express HLA-DR in reaction to interferon-gamma and they also do not show up-regulation of ICAM-1 expression as well. Lack of neoantigen expression on infected cells may be considered as an essential viral plan for mumps virus to escape from detection and suppression by the immune system which causes joint inflammation (94).

With respect to the correlation between rubella virus and HLA genes, it was shown that the DPB1*0301, DPB1*0401, DPB1*1301, DPB1*1501 alleles and HLA-B*2705, B*4501, Cw*0303 and Cw*0704 alleles are connected with antibodies induced by rubella vaccine (95, 96). Alleles which are suggested of being positively correlated with the stimulation rubella-specific lymphoproliferative indices are DPB1*0301, DQB1*0501, DRB1*0101, DRB1*1104 (95) and also HLA-B*3503 and HLA-Cw*1502 (96). Contrarily, the DPB1*0401, DPB1*1001, DPB1*1101, DQB1*0202, DRB1*0701 (95) and HLA-B*3901 (96) alleles are negatively related to rubella-specific lymphoproliferation (95). Another study by Ovsyannikova et al. on finding association between cellular immune responses and HLA haplotypes and supertypes following two doses of rubella vaccine in 738 healthy children revealed some class I supertypes (A1, A2, A3, and B7) have potential associations with IL-10 ELISPOT counts and rubella-specific IL-2, IL-10, TNF-α, and IL-6 cytokine secretion levels (97). In that study, the supertype A3 was correlated with increased IL-2 and slightly decreased IL-10 production and generally, higher levels of cytokine secretion was associated with A2 and A3 supertypes that could be considered as favorable HLA supertypes in rubella immunity (97). The involvement of several alleles of the HLA-DQA1 and HLA-DQB1 loci in rubella-specific IL-2 cytokine discharges has been reported as well (98). Furthermore, the vaccination of measles-mumps-rubella (MMR) has indicated the increased proportion of CD56 (47) natural killer (NK) cells after vaccination (99). As the recent investigations have revealed significant associations between vaccine responses and HLA alleles, variety in vaccine-induced humoral immune responses among individuals and between populations seems reasonable and these variations may also hold the key for development of future generations of vaccines (100). Accordingly, better characterization of such HLA profiles could apprise and improve the design of novel epitope-based vaccines that are recognized by T cells restricted to special HLA alleles. This in turn could be helpful to predict protective immune responses at the individual and population level. (89, 91). Taken together, HLA haplotypes and supertypes may be important in induction of effective immunity to measles, mumps and rubella viruses although, further investigation of the roles of both HLA haplotypes and supertypes and probably NK cells receptors in MMR vaccine-induced immunity should be pursued.

HLA and Influenza

Influenza virus as a segmented RNA virus belongs to orthomyxoviridae family and is able to hamper MHC class I-restricted presentation of cell-related antigens (101). Influenza infection leads to exhibition of 3-6 viral peptides derived from the internal viral nucleoprotein and internal viral polymerase subunit which are presented by HLA class I molecule B*0702 and whereby CTL recognize consistently presented influenza ligands (102). It has been reported that different strains of influenza virus type A may up-regulate the HLA-G expression in alveolar epithelial cells. Therefore, the viral virulence and evading from immune system is proposed to be induced by the ability of diverse viral strains in up-regulation of HLA-G expression (103). Moreover, influenza vaccination in cancer patients increased monocyte HLA-DR expression in conservatively-treated patients versus those undergoing surgical therapy (104). Regarding to the role of NK cell receptors in flu viral infection, it should be noted that NKp46 has a possible binding site for influenza hemagglutinin which is placed near the region that mediates ligand binding in KIR molecules.

The similarity of NKp46 structure to related inhibitory KIRs has raised the possibility that similar receptors are occupied in ligand recognition and this structural similarity may have implications for how NK cells balance activating and inhibitory signals (105).

An exploratory study by La D, et al. (106) on the role of NK cells in immune response to H1N1/09 infection among intensive-care unit patients showed that severe responses to H1N1/09 may be dependent on 3DL1/S1, 2DL1, and 2DL2 ligand interactions, at

least in the case of aboriginal patients. In that study, enrichment of 3DL1*00101, 3DL1*01502, and 3DL1*029 alleles was shown to be associated with rigorous responses to H1N1/09 virus in aboriginal ICU patients, whereas 3DL1*00401 and 3DL1* 01502 allels were enriched in non-aboriginals ICU patients. Also, higher proportion of the ligand-negative pairs KIR3DL1/S1^{+}Bw6^{+}Bw4^{-} and KIR2DL1 C2^{-}C1^{+}, and ligand-positive pair KIR2DL3 C1^{+} were observed in ICU patients compared to healthy St. Theresa controls. This study showed that enrichment of specific KIRs allotypes and imbalanced distribution of cognate HLA class I ligands are probably factors that mediated NK cell dysfunction in ICU patients with overactive immune responses to H1N1/09, leading to severe disease (107).

It has been reported that most of influenza A infected patients who have HLA-A*0201 allele, develops a M58-66-specific CTL response consequent of presentation of this peptide from matrix protein, M58-66, by HLA-A*0201 molecules. It was suggested that M58-66-specific CTL clones bear conserved T cell receptor (TCR) alpha and beta gene segments. More importantly, the expression of V beta 17 during the development of M58-66-specific CTL lines in 21 unrelated HLA-A*0201 subjects were observed significantly. TCR V beta 17 was the dominant V beta segment used and clonal expansion of CD8+ T cells with V beta 17 correlated with M58-66-specific lysis. Additionally, Limiting dilution analysis from five subjects showed that up to 85% of the matrix peptide (M58-66)-specific CTLs used the V beta 17 gene segment. Sequence analysis of thirty eights M58-66-specific V beta 17 transcripts from 13 subjects revealed extensive conservation particularly for an arginine-serine motif in the CDR3 region. These findings indicate that HLA-A*0201-restricted cytotoxic T lymphocyte recognition of influenza A virus is dominated by T cells bearing the V beta 17 gene segment (108). Concisely, it is highly speculative that HLA/KIRs compound genotypes affect the outcome of viral infections. As, *in vitro* model of influenza A virus infection revealed functional differences in human NK cell activity to distinct KIR/HLA genotypes. These studies provide functional proof for differential NK cell responsiveness depending on KIR/HLA genotype and may supply useful insights into differential innate immune responsiveness to viral infections such as influenza A virus.

HLA and Rabies

Rabies virus is a member of Rhabdoviridae family which has a tropism to human neurons. It has a single stranded RNA. The over expression of HLA-G or B7-H1 molecules in the infected nervous system induced by Rabies virus (RABV) can prevent neuronal cell death (109). It has been found that the RABV, up-regulates HLA-G expression (66) including mostly HLA-G1 and also HLA-G5 isoforms (67) in infected human neurons and neighboring uninfected cells (66). It has also been shown that RABV as a neuronotropic virus, up-regulates HLA-E expression. However, it could not be detected on the surface of RABV-infected (66). Altogether, a correlation has been observed between HLA-G and not HLA-E and the immune evasion of RABV (66). The capability of HLA-G and HLA-E to mediate killing by NK cells is accomplished through interaction with inhibitory receptor, KIR2DL4, and binding to NKCD94/NKG2A receptors respectively (66). With regard to unusual characteristic of HLA role in vaccinated people with rabies vaccine, it should be noted that semple rabies vaccine which is a derivative product from brain tissue infected with rabies virus causes autoimmune encephalomyelitis (SAE) in immunized persons. The researches have been provided valuable information about the pathogenesis of SAE. The allele frequencies of HLA-DRB1*0901 and HLA-DRB1*0301 have been increased in SAE patients in comparison with unvaccinated and also with vaccinated controls. Moreover, further clarification of the allele frequency of HLA-DQB1*0301 has been revealed decreasing rate of this allele in SAE patients compared with vaccinated and unvaccinated controls. The data already presented is generally thought to confirm the role of genetic susceptibility correlated with MHC class II alleles that might speculate in the pathogenesis of SAE (110).

HLA, Papilloma and Polyoma

Papilloma and Polyoma as double stranded DNA viruses belong to papillomaviridae family. There is a report which reveals that the DRB1*15 allele/DRB1*15-DQB1*06 haplotype can show susceptibility for human papilloma virus **(**HPV) infection or cervical cancer/precancer expansion (111). Also, the DRB1*04 allele/DRB1*04-DQB1*03 haplotype can display a predisposition to cervical precancerous lesions. On the other hand, the DRB1*13 allele/DRB1*13-DQB1*06 haplotype has been shown to be protective in risk to HPV infection and also cervical cancer. This shows the implication of HLA DR-DQ polymorphisms in genetic vulnerability to HPV infection or cervical cancer (111). Moreover, Simian virus 1 (SV-1) as a member of Polyoma genus binds to the MHC class II, HLA-DM (DM), HLA-DR (DR), and invariant chain (Ii) molecules (55). It has reported that activating KIRs, 3DS1 and 2DS1 make capablity to protect against increasing risk of the severe form of recurrent

respiratory papillomatosis (112). Activating of KIRs genes appears to be also connected with immunity against human papilloma virus (HPV) in the recurrent respiratory papillomatosis (15). One study showed that protection against HPV was probably correlated with KIR2DS1, KIR2DS5 and KIR3DS1 (15). Interestingly, KIR3DS1 has been also implicated in the development of HPV related disease, cervical neoplasia (113). Absence of KIR3DS1+ NK cells helps to active replication of HPV, while activity of KIR3DS1+ NK cells can be attributed to ongoing inflammation in cervical neoplasia (15). Another study on Swedish women demonstrated a significant association between increased risk of cervical intraepithelial neoplasia and presence of genotype 10 from KIRs haplotype A in these patients (114).

Generally, presence of activating KIRs are associated with increased risk of developing cervical neoplasia, indicating that KIR/HLA interactions mediate a various immune response against chronic HPV infection which may contribute to HPV pathogenesis in the cervix (2).

Activation of helper T cells is a prerequisite for the function of cytotoxic T lymphocytes (CTL) and development of B cell response. Because of the probable shared epitopes which recognized by these lymphocytes, E2 protein of human papillomavirus (HPV) type 16 was examined to identify specific epitopes for helper T cells. Four major epitopes mapping between residues 11-25, 141-155, 191-205 and 231-245 and adjacent to B cell epitopes were found. The first peptide-defined epitope (RLNV) 11CQDKILTHYENDSTD25 overlapped five putative HLA-I binding motifs including HLA-A1 (CQDKILTHY), HLA-A2 (RLNVCQDKI), HLA-A*0205 (NVCQDKIL), HLA-A3 (RLNVCQDK) and HLA-A11 (RLNVCQDK). Additionally, this epitope is part of an N-terminal alpha-helix which may form specific agretopes for HLA class II molecules (DR2, DR4, DR7& DR8) recognizable by the T cell receptor. The second epitope 141EEASV TVVEGOVDYY155 (GLYY) overlapped the putative HLA-A1 and HLA-Bw37 binding motifs (VVEGQVDYY/QVDYYGLYY and EEASVTVV respectively), and two HLA class II specific agretopes (DR1 & DR3). The third and fourth epitopes were not correlated with more than one putative CTL epitope each. Only the first epitope shared significant amino acid homology with corresponding regions of other genital HPV types (115). It can be concluded that identification of specific shared epitopes from HPV which is recognizable by T cells, could be promising approach for defining specific peptide-based immunotherapy strategies.

HLA and Parvoviruses

Parvoviruses are the single stranded DNA and known as the smallest DNA viruses. Among parvoviruses, the prevalence of parvovirus B19 infection has been reported considerably high in patients with Rheumatoid Arthritis (RA). There have been the plausible mechanisms between HLA-DR4 and parvovirus B19 DNA for susceptibility to RA (116). Following human parvovirus infection, HLA-DR4 positive people have been shown more susceptible to expand joint complications (60). Moreover, a correlation between the HLA-DRB1 alleles including HLA-DRB1*01, DRB1*04, and DRB1*07 alleles (61) and symptomatic parvovirus B19 infection have been shown (62). Inclusively, the role of parvovirus B19 infection in susceptibility to RA has been confirmed in the context of HLA system (116). Moreover, the relationship of RA with KIR 2DS4 in the presence of HLA-Cw4 has been reported in a group of Taiwanese patients (117). On the other hand a research in UK indicated that KIR and HLA-C genotype were associated with response to anti-TNF-α therapy in RA patients (118). In this regard, a significantly higher frequency of KIR2DS2/KIR2DL2 was seen in patients responded to therapy with anti-TNF-α (118).

Conclusion

An extensive body of literature has reported that genetic diversity in HLA and KIR loci is correlated with variability in outcome of viral infections. Such results have been generally thought to be a hypothesis which supports the allele-specific overdominance in humans (119). HLA appears to play multiple roles in viral infections. Effect of human leukocyte antigen on infectious diseases justifies the requirement for allele-specific determination which still remained wide open for further investigation. In other words, linking MHC to infectious disease susceptibility via known immunological mechanism remains the central goal.

Understanding the exact role of HLA-KIR interactions in control of viral infections will underlie specific features of the individual course of viral infections. This can control the development of drug-resistant viruses which may help to find strategies to improve therapeutic methods in viral infected people. More importantly, it may help to design peptide-based immunotherapy approaches using well known immunodominant HLA alleles. In this regard, functional significance of HLA-A2 and/or A11 molecules in induction of efficiently CTL responses against HBV, HCV, EBV, influenza, measles, rubella and papiloma viruses, greater protection against progression to AIDS in the presence of HLA-B57 and B27 in combination with KIR3DL1/S1 and clinical significance of HLA-A24 in more potent immunity to CMV in transplant patients have been well

documented. In addition, considering the HLA and KIRs alleles may help clinicians to have new insights for assessing the clinical response to therapy. In consistent with the hypothesis, this will also serve as a practical implication model for other pharmaco-genomics research, mainly those that intended to reduce the rates of severe drug hypersensitivity reactions in clinical observations (120).

Taken together, the influence of host genetic variations particularly in two polymorphic loci, HLA and KIRs, in viral infectivity and disease outcomes is becoming increasingly well accepted among infectious immunity researchers. Several mechanisms have been shown in different studies which implicate the central role of these two molecules in anti-viral immunity, For instance, controlling the level of cytokine production and antibody responses, increasing the memory specific CD4+T cell responses, impairing the CD8+ T cell reactions which increases recognizing and controlling the viral proteins and predicts the autonomous resolution of viral infections.

Further efforts in determining the exact role of HLA/KIRs interaction in viral infections and understanding the molecular nature of this interaction with respect to the viral antigens as well as defining additional probable associations between HLA/KIRs and other viral diseases will greatly enhance our ability to find out the real place of immunogenetics in viral infections and to apply potentially this knowledge clinically.

Conflict of interest

All authors have read and approved the manuscript and there is no conflict of interest to declare.

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