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Review Article

KIR/HLA Interactions and Pathogen Immunity

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The innate immune system is the first line of defence in response to pathogen infection. Natural killer (NK) cells perform a vital role in this response with the ability to directly kill infected cells, produce cytokines, and cross-talk with the adaptive immune system. These effector functions are dependent on activation of NK cells which is determined by surface receptor interactions with ligands on target cells. Of these receptors, the polymorphic killer immunoglobulin-like receptors (KIRs), which interact with MHC class 1 (also highly polymorphic), are largely inhibitory, and exhibit substantial genetic diversity. The result is a significant variation of NK cell repertoire between individuals and also between populations, with a multitude of possible KIR:HLA combinations. As each KIR:ligand interaction may have differential effects on NK cell activation and inhibition, this diversity has important potential influences on the host response to infections. Genetic studies have demonstrated associations between specific KIR:ligand combinations and the outcome of viral (and other) infections, in particular hepatitis C and HIV infection. Detailed functional studies are not required to define the mechanisms underpinning these disease associations.

1. Introduction

Natural Killer (NK) cells are key effector cells of the innate immune system, and as such are crucial in the antiviral immune response. They are multifunctional, with an ability to interact directly with infectious agents, through pattern recognition receptors, with infected cells, via expressed cell surface receptors, and with cells of the adaptive immune system via cell-cell interactions and through secretion of cytokines [1]. Such cytokines are predominantly pro-inflammatory such as interferon (IFN)-γ or tissue growth factor (TGF)-β, but may in some cases be immunoregulatory [2].

NK cell activation is controlled by a complex balance between activating and inhibitory receptors such that the net signal derived from these receptors is integrated to determine whether or not NK cell effector functions are initiated [3–5]. Many of these receptors are monomorphic and expressed on all cells. Furthermore, they are relatively well conserved between human and mice. This particularly applies to the activating receptors, including NKp46 and NKG2D, which have been shown to be especially important in the host-pathogen interaction. The inhibitory receptors, however, fall into two main, although not exclusive, groups: the killer-cell immunoglobulin-like receptors (KIRs) and the NKG2 families. Both have major histocompatibility complex (MHC) class I ligands, but of different types. The NKG2 family, of which NKG2A is the main inhibitory member, is relatively nonpolymorphic and conserved throughout evolution. The functional receptor, a heterodimer of CD94 and NKG2A, binds human leucocyte antigen (HLA)-E plus signal peptides derived from classical HLA class I alleles [6]. Conversely, the KIRs are diverse and polymorphic, with polymorphic HLA class I ligands. Thus, whilst both families may be important in the immune response against pathogens, the KIR family are more likely to be responsible for generating diversity in the immune response to specific pathogens within the human population. They have received much attention as potential disease association markers for a number of infections which have discrete clinical outcomes. The aim of this paper is to summarize our current knowledge of how KIRs and KIR ligand diversity may influence the outcome of a number of key human infections.

2. Structure and Genetics

KIRs exhibit substantial diversity at both the allelic and haplotypic levels. Furthermore, their expression on NK cells is stochastic and variegated [7, 8]. The result is a diverse repertoire of NK cell clones within an individual and also substantial NK cell diversity between populations. Additionally, their HLA class I ligands are extremely polymorphic and this generates a further level of functional diversity. These factors likely synergize to generate varying susceptibility to pathogens and disease.

KIRs are encoded in a 150 kb region on chromosome 19q13.4 within the leukocyte receptor complex (LRC) [9]. There are at least 17 KIR genes or pseudogenes with substantial allelic diversity of many of these genes [10, 11]. Comparison of humans and nonhuman primates has revealed the rapid evolution of this locus, most likely through a combination of gene duplication and nonhomologous recombination [12]. This evolution is thought to be driven by selective pressure from exposure to pathogens, and also by the pressure for reproductive success [13]. The sum total of these effects is substantial genetic diversity at the level of the locus, which has been simplified into two main KIR haplotypes: "A" and "B" based on gene content. The B group of haplotypes are defined by the presence of one or more of the following genes: KIR2DL5, KIR2DS1, KIR2DS2, KIR2DS3, KIR2DS5, and KIR3DS1. Conversely, the group A haplotypes are defined by the absence of all of these genes and the presence of KIR2DS4 [14]. The two haplotypes are thought to have been maintained within the human population by balancing selection; however, the frequency of these haplotypes varies substantially between populations [15, 16]. In general, A haplotypes are associated with an improved response to pathogens, whereas B haplotypes are associated with improved reproductive fitness [17–19].

The KIR proteins are members of the immunoglobulin (Ig) superfamily of receptors. Their nomenclature is based on their structure, where the number of Ig-like extracellular domains (2D or 3D) and the length of the cytoplasmic tail (long, L or short, S) defines the name of the protein. The long cytoplasmic tails contain immunoreceptor tyrosine-based inhibitory motifs (ITIMs) and confer an inhibitory signal when the receptors are engaged with their ligands. The short tailed receptors lack ITIMs and are activating. These activating receptors have a transmembrane lysine residue which allows binding to the immunoreceptor tyrosine-based activating motif (ITAM) containing adaptor DAP12. Thus, KIR2DL1 has two extracellular Ig-like domains, a long intracytoplasmic tail and transduces an inhibitory signal, whereas KIR3DS1 has three extracellular Ig-like domains and a short intracytoplasmic tail and associates with DAP12 to transduce an activating signal. An exception to this is KIR2DL4 which has a long intracytoplasmic tail, but associates with FcεR1γ to transduce an activating signal [20]. There is also diversity in the configuration of the extracellular domains, as for the two Ig domain KIRs the extracellular domains may be in a D1D2 (the majority) or D0D2 (KIR2DL4 and KIR2DL5) configuration. This extracellular domain organisation reflects evolutionary relationships, and thus the D0D2 2Ig domain KIRs comprise the Lineage I KIRs, the 3 IG domain KIRs excluding KIR3DL3 form the Lineage II KIRs and the D1D2 2Ig domain KIRs form Lineage III [21]. Lineage I is the most conserved of the lineages having representative members in the old world monkeys, whereas the Lineage III KIRs are not well conserved even between humans and the common chimpanzees.

3. KIR Ligands

That inhibitory KIRs interact with polymorphic HLA class 1 ligands is well established, and in general the Lineage III KIRs bind MHC-C. Thus, the inhibitory receptors KIR2DL1, 2DL2, and 2DL3 are specific for HLA-C: KIR2DL1 binds alleles of HLA-C with lysine at position 80 (HLA-C2), whereas KIR2DL2 and 2DL3 bind HLA-C alleles with asparagine at position 80 (HLA-C1) [22, 23]. The affinity of these interactions may differ [24], and it is thought that KIR2DL3:HLA-C1 is a relatively weak interaction, whilst KIR2DL2:HLA-C1 and KIR2DL1:HLA-C2 are relatively stronger [25]. Of the Lineage II KIRs, KIR3DL1 recognises HLA-B alleles with the Bw4 serological motif (HLA-Bw4) and also some HLA-A alleles also with the Bw4 motif; KIR3DL2 binds HLA-A3 and -A11 [26, 27]. The specific recognition of HLA class 1 by the activating KIRs is less well defined (Table 1), although sequence homology predicts they should have similar binding specificities as their inhibitory counterparts. Thus, binding of KIR2DS1 to HLA-C is of a similar specificity to that of KIR2DL1, but at a substantially lower affinity [28]. Furthermore, although KIR2DS2 and KIR3DS1 share substantial sequence homology with their inhibitory counterparts, KIR2DL2/3 and KIR3DL1, respectively, binding to the relevant ligands has not been convincingly established. One mitigating factor is that all the inhibitory KIRs tested to date have been shown to have selectivity for the peptide bound by MHC class I, and this implies that specific peptides, either host or viral, may modulate binding of KIRs to their MHC class I ligands. Thus, the absence of a defined HLA specificity may be because key (host or viral) peptides that determine the interaction have yet to be tested, or that they genuinely do lack a ligand [29].

As the gene cluster for HLA class I is located on chromosome 6, inheritance is unlinked to KIRs on chromosome 19. This generates diversity in the number of potential inhibitory interactions that the NK cells from a single individual may have. For instance, an individual with both group 1 and group 2 HLA-C alleles and also an HLA-Bw4 allele has the potential for three inhibitory KIR:HLA interactions, whereas an individual homozygous at the HLA-C locus and with no HLA-Bw4 alleles has only one inhibitory KIR:HLA interaction. Thus, in genetic studies it may be necessary to incorporate the KIR ligand interactions into a biological model, rather than just considering KIRs in isolation.

Within an individual, the KIRs, in combination with the CD94:NKG2A heterodimer, are expressed in a variegated pattern on NK cells. This generates an NK cell repertoire based on inhibitory receptors for self-MHC class I. The patterns of expression are complex, but have recently been segregated into five main types [8]. The relevance of an NK cell

Table 1: KIRs molecules and their HLA ligands.

KIRs	Ligand
2DL1	HLA-C2
2DS1	HLA-C2
2DL2	HLA-C1
2DL3	HLA-C1
2DS2	HLA-C1
2DL4	HLA-G
2DL5	Unknown
2DS3	Unknown
2DS4	HLA-A11, HLA-C
2DS5	Unknown
3DL1	HLA-Bw4
3DS1	HLA-Bw4^{80I}
3DL2	HLA-A3,11
3DL3	Unknown

repertoire may be similar to that of a T-cell repertoire. Thus, if a specific receptor:ligand combination is important for recognizing a host cell infected by a specific virus, then individuals who have a repertoire with more NK cells expressing that specific receptor may have a better immune response to that specific infection. Furthermore, NK cells that do not express a receptor for self-MHC class I appear to be relatively hypofunctional, which implies that they are likely to be less responsive to pathogens [30]. This is thought to be the result of selection and "licensing" processes that are dependent on these receptors during NK cell maturation [31, 32].

Thus, diversity within the KIR system is present at the level of the locus, of the allele, of the ligand, and within their expression patterns. It may be that all these factors can influence the host immune response to infection. We will now focus on how this diversity may impact the outcome some key human infections.

4. Hepatitis C Virus (HCV)

Infection with HCV leads to chronicity in the majority of cases. These individuals remain anti-HCV antibody positive with detectable HCV RNA, as compared to those who clear infection who remain antibody positive long after exposure, but have no detectable HCV RNA. Those with chronic infection have long-term sequelae that include cirrhosis and hepatocellular cancer (HCC). NK cells provide an early line of defence in the host response to HCV [33–35]. Furthermore, functional studies have demonstrated NK cell abnormalities in chronic infection, including decreased levels in the peripheral blood [36] and reduced cytotoxicity [37, 38]. This function can normalise with interferon-based treatment [39], and in patients where cytotoxicity is preserved, progression of liver fibrosis is reduced [36].

The categorization of HCV exposed individuals into those with and without detectable HCV RNA provides a simple variable which can be used to elicit genetic factors associated with protection against HCV. In a study of 1037 exposed individuals the compound KIR:HLA genotype KIR2DL3 and its ligand the group 1 HLA-C (HLA-C1) alleles was associated with resolution of infection. This was in a recessive model in which protection was found in those homozygous for both KIR2DL3 and HLA-C1, and then only in individuals exposed with relatively low inocula such as via intravenous drug use (IVDU) as compared to those exposed through infected blood products [40]. This finding was confirmed in a subsequent study of 160 individuals with IVDU as the risk factor for infection [41]. The finding that inhibitory interactions are protective against a viral infection initially seems counterintuitive. However, natural killer cells are held in check by their inhibitory receptors and, as originally proposed by the missing-self hypothesis, loss of these interactions is a key mechanism to permit NK cell activation [4]. KIR2DL3:HLA-C1 is a lower avidity interaction than KIR2DL2:HLA-C1 and also KIR2DL1:HLA-C2, and therefore the observed correlation with outcome of HCV infection is consistent with the binding data in that lower avidity interactions are more easily overcome than higher avidity ones [24, 25]. Although, HCV does not appear to substantially affect MHC class I expression, it has recently been found that NK cells are unexpectedly responsive to changes in the peptide repertoire of MHC class I through a mechanism of peptide antagonism. Therefore, it may be that this mechanism is more important in perturbing the KIR2DL3:HLA-C1 interaction than wholesale downregulation of MHC class I [42]. Functional data in influenza infection support this inhibitory receptor hierarchy. *In vitro* studies demonstrate that NK cells from individuals with the genotype KIR2DL3:HLA-C1 were activated more rapidly by autologous influenza infected targets than those from individuals with a KIR2DL1:HLA-C2 genotype [43]. The protective effects of KIR2DL3:HLA-C1 homozygosity have also been demonstrated for individuals who are exposed to HCV infection through high-risk behaviour, and do not have antibodies to HCV, or HCV RNA [44]. Furthermore, as KIRs are expressed on NK cells in a variegated manner, homozygosity may be protective because individuals with two copies of this gene have more NK cells expressing the protective KIRs. Indeed individuals that resolve HCV infection do have a higher frequency of NK cells expressing HLA-C-specific KIRs [33]. Additionally, individuals successfully treated with interferon-α-based regimens also have a higher frequency of KIR2DL3:HLA-C1, than those who do not make successful treatment responses [44, 45]. Thus, this gene combination has a consistently protective effect across several different scenarios within HCV exposure and infection. Recently, this protection has been mapped to the allelic level and it has been shown that HLA-Cw*07 (one of the KIR2DL3 ligands) was not protective against chronic infection, nor associated with a successful treatment response. This may be related to the education of NK cells from these individuals, as this allele has been shown to be associated with a "strong educator" phenotype, that is, NK cells from these individuals produce relatively large amounts of IFNγ compared to individuals with other HLA types [8]. Finally, HLA-C1 and also KIR3DS1 were found to be independently protective against the development of hepatocellular carcinoma in individuals with chronic HCV infection [46].

However, this simple model of genetic protection has not been found in all patient populations. KIR2DL3 is found on the "A" group of haplotypes, as is KIR2DS4. Consistent with this, KIR2DS4 has been associated with protection against chronic HCV infection [47]. Similarly, the B group of haplotypes are marked with KIR2DL5, and have been found to be associated with a poor response to treatment for HCV [48]. Finally, KIR2DL3:HLA-C1 was not found to be protective in a cohort of HIV/HCV coinfected individuals, implying that the presence of HIV infection modulates the protective effect of KIRs [49].

Due to the difficulty of obtaining samples in the acute phase of HCV infection, individuals have been studied predominantly in the chronic phase. Thus, it has been difficult to correlate these genetic effects with function. Furthermore, in the acute phase of infection, there are generally lower numbers of $CD56^{dim}$ NK cells which are the KIR expressing subpopulation, suggesting sequestration of these cells to the liver [33, 34]. Indeed, lower frequencies of peripheral blood NK cells expressing the key activating receptors NKp30, NKp46, and NKG2D are found in the acute phase of HCV infection in those that resolve infection compared to those that become chronically infected [33]. During chronic infection with HCV multiple changes in NK cell receptor expression have been observed, but in general KIR expression is low or normal, and NKG2A expression is increased [50–52]. One correlate is that CD107a expression on peripheral NK cells is increased on KIR2DL2/3+ NK cells in acute HCV infection compared to KIR2DL1+ NK cells and also compared to KIR2DL2/3+ NK cells from healthy donors [34].

5. Hepatitis B Virus (HBV)

Like HCV, HBV is a hepatotrophic virus that causes a major global health problem. An estimated 2 billion individuals have been infected with HBV and approximately 350 million are suffering from chronic disease [53]. Of those with chronic infection 25% die of the complications of HCC or cirrhosis, resulting in 600,000 deaths per year. NK cells are activated in the early response to infection, and there is substantial population variability in the rates of HBV infection [54]. Whilst detailed genetic and functional analyses exploring KIR-HLA influences on HBV in large cohorts of HBV are lacking, Lu et al. analysed the KIR genes in 150 patients with chronic HBV infection (CHB), 251 spontaneous resolvers, and 451 healthy controls. They found a lower frequency of the A haplotype, and higher frequency of the B haplotype in patients exposed to hepatitis B compared with healthy controls, implying a susceptibility effect of the B haplotype [18]. A second study, comparing 182 CHB patients with 140 healthy controls, was consistent with this observation [55]. The authors reported that KIR2DL3:HLA-C1 homozygosity was protective, and KIR2DL1:HLA-C2 was associated with susceptibility to HBV infection. Thus, there are important similarities between hepatitis C and hepatitis B infections, despite these viruses being phylogenetically unrelated.

6. HIV

HIV was the first viral infection for which an association of KIRs with outcome was observed. In a seminal study performed by Martin et al. [56], it was shown that the activating receptor KIR3DS1 was associated with a beneficial effect in HIV in combination with HLA-B alleles that have the Bw4 serological epitope with isoleucine at position 80 ($HLA\text{-}Bw4^{80I}$). This epistatic interaction protected against a decline in CD4 count, and hence the development of AIDS. Subsequent work from the same group has also shown that this combination delays the onset of opportunistic infection and is associated with a slightly lower viral load [56–58]. Overall this association forms an attractive model as the activating receptor-ligand interaction could be associated with enhanced NK cell reactivity, and, hence, an improved antiviral immune response. Furthermore, HIV has been shown to selectively downregulate HLA-A and -B, but not HLA-C, implying that it may target this specific interaction [59]. However, to date it has been difficult to demonstrate clearly that KIR3DS1 binds $HLA\text{-}Bw4^{80I}$ alleles in binding assays. This is not unexpected as the avidity of activating KIRs for MHC class I are significantly lower than for the inhibitory KIRs with similar predicted binding specificity [60, 61]. Furthermore, the peptide bound by the MHC class I molecule can profoundly influence the interaction of KIRs with MHC class I [28, 42, 62]. This complexity in binding may be one explanation for differences between these and other studies, such as that of Gaudieri et al. in which KIR3DS1 was not noted to be protective but specific HLA-B alleles were [63]. Additionally, Boulet et al. found a higher prevalence of KIR3DS1 in a cohort of injection drug users that remained HIV seronegative as compared to a matched seropositive cohort [64]. However, they found no association with specific HLA-B alleles in this relatively small cohort. Notwithstanding this, Alter et al. have demonstrated significant inhibition of viral replication in HIV-infected $HLA\text{-}Bw4^{80I}$-positive T cells when cultured with KIR3DS1+ NK cells [65]. This finding was supported in a subsequent study demonstrating increased IFNγ production and CD107a upregulation in HIV-infected individuals with the KIR3DS1, but not specifically the KIR3DS1/$HLA\text{-}Bw4^{80I}$ compound genotype [66].

In addition to a model based on activating receptor-ligand interactions, a hierarchy of inhibitory receptor-ligand interactions may also be associated with outcome of HIV infection. For the most part KIR3DL1 and KIR3DS1 segregate as alleles at a single locus. KIR3DL1 alleles are also extremely polymorphic with more than 50 alleles described [67]. These alleles are associated with different levels of expression of the KIR3DL1 allele and have been correlated with outcome of HIV infection [68, 69]. Martin et al. found that the high-expressing KIR3DL1 alleles combined with HLA-B*57 (a $HLA\text{-}Bw4^{80I}$ allele) was the most protective combination against progression of HIV. In this analysis, it was more protective than KIR3DS1 in combination with $HLA\text{-}Bw4^{80I}$. However, the most protective KIR allele was KIR3DL1*004, which is not expressed at the cell surface. The authors rationalise this on the basis of a potential

intracellular interaction of KIR3DL1*004 either with its ligand, in a manner similar to the endosomal interaction of KIR2DL4 with HLA-G, or with other NK cell receptors [70]. The protective effects of high expressing KIR3DL1 alleles and HLA-B*57 were subsequently independently confirmed at an immunogenetic level, and functional data from this same group has shown that KIR3DL1+ NK cells from IVDUs with a HLA-Bw4 ligand have enhanced functionality, as determined by CD107a expression as well as IFNγ and TNFα secretion [64, 71].

Whilst HLA-B has been associated with the outcome of HIV infection in a number of studies, recent genome-wide association studies have also highlighted the relevance of HLA-C in determining the viral set point and also in defining "elite controllers" of HIV infection [72, 73]. Whilst HLA-C can present HIV-derived peptides to T cells [74], this association may be related to epistatic interactions with KIRs. To date large studies have not defined a protective combination of specific KIRs and HLA-C allotypes, although they have been reported to be protective against HIV-1 transmission in a relatively small study of African sex workers [75]. Nevertheless, the absence of genetic associations does not mean that the HLA-C specific KIRs have no role in controlling HIV infection. If both HLA-C1 and HLA-C2 conferred similar degrees of protection against HIV, their role would not be revealed by the broad consideration of KIRs and HLA-C1 and HLA-C2 interactions. In depth allelic analysis may therefore be required. The -35 C/T polymorphism at the HLA-C locus, identified as protective in the genome-wide association study of Fellay et al., is associated with the level of HLA-C expression, and higher levels of HLA-C expression have also been associated with slower progression to AIDS and improved viral control [72, 76]. This is reminiscent of the effects of KIR3DL1 expression, and it may be that there are differences in NK cell education between high and low HLA-C expressers, which are reflected in their antiviral activity. Alleles of HLA-Cw*07, which are associated with the "strong educator" phenotype, have the nonprotective -35 polymorphism (a "T" allele), are generally expressed at low levels and are associated with the most rapid progression of disease [76]. Conversely, alleles expressed at high levels tend to have the "C" allele and are associated with slower progression. Thus, HIV illustrates the complexity of how KIRs and MHC may interact to determine the outcome of HIV infection, with the potential to generate multiple models to explain the immunogenetic findings.

7. Other Infections

KIRs have been implicated most strongly in HCV and HIV infections, which to some extent reflects the focus of the immunogenetic community on these important diseases. These pathogens cause chronic infection with readily measurable outcomes which can be used to stratify individuals into disease phenotypes. The observation that KIR genotype is important for the response to influenza *in vitro* implies that KIRs may also be important for other viral infections and that they provide a selective advantage against pathogens that may cause acute disease only.

Additionally, NK cells are thought to be particularly relevant for viral infections of the herpes family [77]. Thus, although CMV causes a latent infection in the majority of infected individuals, in immunocompromised individuals it can reactivate, and cause a life-threatening illness. In particular, it can severely compromise individuals undergoing bone marrow transplantation (BMT). Despite substantial variability in protocols for this procedure, a consistent finding appears to be that having more donor activating KIR genes helps to prevent CMV reactivation [78–80].

Activating KIRs genes are also associated with protection against human papilloma virus (HPV) in the relatively unusual setting of recurrent respiratory papillomatosis (RRP), which is due to an impaired immune response to HPV. In one study, protection was associated with KIR2DS1, KIR2DS5, and KIR3DS1 [81]. Interestingly, KIR3DS1 is positively associated with the development of another HPV-associated disease, cervical neoplasia [82]. The authors suggest that the increased activation of NK cells leads to chronic inflammation and, hence, cancer. Thus, these two studies are consistent with each other in that it appears that an absence of KIR3DS1+ NK cells permits active replication of HPV, whereas in cervical neoplasia the activity of KIR3DS1+ NK cells, in the absence of viral eradication, leads to ongoing inflammation.

Like CMV, herpes simplex virus (HSV) causes an asymptomatic infection in the majority of individuals. However, symptomatic infection may occur in relatively immunocompetent individuals. The KIR genes, KIR2DL2 and KIR2DS2, which are in tight linkage disequilibrium, were associated with asymptomatic HSV infection [83]. However, due to this tight linkage, it was impossible to determine whether it was the activating or the inhibitory receptor that was associated with a poor response.

In addition to their role in viral infections, NK cells may also affect the response to protozoa [84], and there may also be a role for KIRs in affecting outcome. In a study of 23 individuals, those with the allele KIR3DL2*002 secreted higher levels of IFNγ in response to Plasmodium falciparum-infected red blood cells [85]. As red blood cells are MHC class I deficient, this may reflect an influence of KIR:HLA on NK cell-macrophage cross-talk, as opposed to any direct interaction between NK cells and infected red blood cells [85, 86]. Alternatively, it may be an effect of a gene in linkage with KIR3DL2*002 or related to differential education of NK cells from individuals with this haplotype. Thus, in these diverse infections KIR genetics have the potential to influence outcome. Larger and more definitive studies are required.

8. Summary

Natural killer cells are important players in an effective antiviral immune response. Their expression of multiple cell surface receptors implies that during different infections different receptors are likely to be important. Many of these receptors are monomorphic and expressed on all NK cells. KIRs have a variegated expression pattern, and their complex genetics coupled with their HLA class I ligands imply that they are involved in generating population diversity in the

antiviral immune response. Tenable models based on both activating and inhibitory receptor-ligand interactions have been generated by detailed genetic studies involving large cohorts. Whilst functional studies have shed some light on these associations, the molecular mechanisms underpinning these genetic models still requires fine tuning.

Abbreviations

NK: Natural killer
IFN: Interferon
TGF: Growth factor
KIRs: Killer immunoglobulin-like receptor
MHC: Major histocompatibility complex
HLA: Human leucocyte antigen
Ig: Immunoglobulin
ITIM: Immunoreceptor tyrosine-based inhibitory motif
ITAM: Immunoreceptor tyrosine-based activating motif
LRC: Leukocyte receptor complex
HCV: Hepatitis C virus
HCC: Hepatocellular cancer
HBV: Hepatitis B virus
HIV: Human immunodeficiency virus
CMV: Cytomegalovirus
HPV: Human papilloma virus
RRP: Respiratory papillomatosis
HSV: Herpes simplex virus.

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