The importance of the interactions between KIRs and HLA ligands in the development of human autoimmune and viral diseases

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Abstract

Killer immunoglobulin-like receptors (KIRs) regulate the activation of natural killer cells through their interaction with human leucocyte antigens (HLA). KIR and HLA loci are highly polymorphic, and certain KIR/HLA combinations have been found to protect against viral infections or to predispose to autoimmune disorders. In particular, some activating KIR profiles may be detrimental in autoimmune pathogenesis, and specific KIR genes may be particularly aggressive in the clearance of different microorganisms, protecting individuals in the control of a given pathogen. Here we reviewed a growing body of evidence purporting the influence of KIR polymorphism and KIR-HLA interaction in the development of the main human autoimmune and viral diseases.

Key words

Autoimmune diseases, HLA ligand, KIRs, Viral infections.

State of the art

Killer immunoglobulin-like receptors (KIRs) are surface receptors specific for allelic forms of human leukocyte antigen (HLA) class I molecules, which are expressed by natural killer (NK) cells and a subset of CD8 T lymphocytes. The polygenic nature of the KIR locus is particularly consequential in a functional sense because KIR genes encode receptors that can either inhibit or activate both cell types [Campbell & Purdy, 2011].

The KIR gene cluster consists of a segment of about 150 kb situated on chromosome 19q13.4 within the leukocyte receptor complex. To date, 15 KIR genes and 2 pseudogenes have been described. However, variability in gene content at the KIR locus appears largely due to gene duplication and non-allelic homologous recombination [Martin et al., 2003].

KIR genes are organized in two basic haplotypes that have been defined on the basis of gene content, and are termed A and B. Haplotype A is uniform in terms of gene content and is composed of five inhibitory genes (KIR2DL1, 2DL3, 3DL1, 3DL2 and 3DL3), one activating gene (KIR2DS4), and KIR2DL4, which may have both inhibitory and activating capacity. Interestingly, many A haplotypes possess null variants of both KIR2DS4 and KIR2DL4 that are not expressed on the cell surface [Hsu et al., 2002; Witt et al., 2000]. Accordingly with this, these haplotypes do not have functional activating KIR.

The B haplotypes contain variable numbers of activating and inhibitory receptors and are the primary contributors to the extraordinary differences in gene profiles observed in distinct ethnic populations. Although at different frequency, A and B haplotypes have been maintained within the human population, suggesting the occurrence of a balancing selection. A haplotypes seem to be associated with improved responses to pathogens, whereas B haplotypes with improved reproductive fitness [Moffett & Loke, 2006; Parham, 2005; Rajagopalan & Long, 2005].

Much of the variability among KIR haplotypes derives from the presence or the absence of activating KIR, because most of the inhibitory KIRs are present on all or nearly all haplotypes [Uhrberg et al., 1997]. The inhibitory KIR family is characterized by cytoplasmic immunoreceptor tyrosine-based inhibition motifs (ITIMs), which recruit the SHP-1/2 tyrosine phosphatases preventing NK cells activation. On the contrary, the activating KIRs have short cytoplasmic tails lacking ITIMs (i.e., KIR2DS and

KIR3DS), which interact with DAP12; this is an adaptor molecule that contains immunoreceptor tyrosine-based activation motifs (ITAMs) linked to protein tyrosine kinase activation pathways [Parham & Moffett, 2013]. The activating KIRs stimulate NK/CD8 T lymphocytes cytokine secretion and target cell cytolysis may be generally beneficial in response to microorganisms and tumor cells. Not all inhibitory or activating receptors are present on the surface of NK or CD8 T cells and it is the balance of these signals that modulates NK cells cytotoxicity and cytokine release.

Most inhibitory KIRs specifically recognize sets of HLA class I (i.e., HLA-A, -B, and -C) allotypes; yet, the ligands for some of them (e.g., KIR2DL5) and for most activating KIRs are unknown.

HLA class I genes map to chromosome 6. These genes are extremely polymorphic, determining functional diversity, and generating variable susceptibility in response to pathogens and other diseases.

The inhibitory KIR2DL1, 2DL2, and 2DL3 recognize HLA-C ligands, that belong to one of two ligand groups based with a dimorphism at position 80: group 1 (HLA-C1), which has asparagine, and group 2 (HLA-C2), which has lysine at position 80 [Winter & Long, 1997]. KIR3DL1 is known to bind HLA-B allotypes with the Bw4 motif, although some low affinity binding with Bw6 has also been reported [Carr et al., 2005; Cella et al., 1994; Gumperz et al., 1995]. Other receptor–ligand relationships among KIRs and HLA include KIR2DL4 specificity for HLA-G, which is primarily expressed on foetal trophoblasts, thymic endothelial cells and cornea, and KIR3DL2 specificity for HLA-A3 and A11 [Dohring et al., 1996; Rajagopalan & Long, 1999].

The activating receptors KIR2DS1, 2DS2 and 3DS1 share sequence similarity in their extracellular domains with their corresponding inhibitory counterparts (KIR2DL1, 2DL2-2DL3 and 3DL1, respectively) and are thought to share HLA ligand binding specificities as well [Kulkarni et al., 2008].

Combinations of HLA and KIR genes have been associated with several diseases such as infectious diseases, autoimmune/inflammatory disorders, cancer and reproduction. Emerging functional data supports a mechanism based on a continuum of inhibition to activation through various compound KIR/HLA genotypes in diseases [Kulkarni et al., 2008]. Moreover, allelic variation also plays a role in determining the strength of the interaction [Yawata et al., 2006]. The diversity of KIR haplotypes, which likely imparts a continuum from relatively strong inhibition to

strong activation, suggests the pleiotropic nature of KIR on different diseases in that a given KIR genotype affording protection against one disease may actually predispose to another unrelated disorder.

In this regard, activating KIR profiles might be detrimental in autoimmune pathogenesis, potentially aggravating the disease process, although, this may be true for only certain autoimmune diseases and quite the opposite for others [Baxter & Smyth, 2002; Flodstromet et al., 2002a]. KIR associations with susceptibility to autoimmune conditions point to the short chain of the activating KIR. Moreover, the NK cell control of viral infections has been the subject of excellent reviews [Brandstadter & Yang, 2011]. Specific KIR genes may be particularly aggressive in the clearance of some microorganisms, and their presence in only a fraction of individuals (as well as their allelic polymorphism) could explain differences observed among individuals in their ability to control a given pathogen.

KIR/HLA association and autoimmune diseases

Currently about 5% of the population of the developed countries is affected by various types of autoimmune diseases [Flodstrom et al., 2002b]. The background of autoimmune diseases is multifactorial and remains unclear. However, the robust associations between the highly polymorphic HLA class I/class II loci and autoimmune diseases are strong [Matzaraki et al., 2017]. It would not be surprising if the strongest effects of KIR variation were also observed in autoimmune diseases. Some previously determined HLA associations with autoimmune diseases might actually be explained by synergistic interactions between KIR and alleles encoding their HLA class I ligands. On the other hand, NK cell activation may be protective against some autoimmune disorders by suppressing or eliminating dendritic cells and monocytes [Geldhof et al., 1998], cells known to stimulate the generation of cytotoxic T lymphocytes (see Table 1 for an overview).

A number of studies have investigated KIR expression in rheumatoid arthritis (RA). RA was the first disease in which an effect of KIR genotype was observed. In RA patients, where $CD4^{+}$ $CD28^{null}$ T cells are expanded and cause endothelial damage, it was showed that these cells expressed KIR2DS2 in the absence of inhibitory KIR2DL2 [Namekawa et al., 2000]. Further, the frequency of KIR2DS2 was increased in RA patients with vasculitis in comparison to normal controls and RA pa-

tients without vasculitis [Yen et al., 2001]. HLA-Cw*03, an HLA-C1 allotype, and therefore a putative ligand for KIR2DS2, was also increased in subjects with vasculitis, although this was not true for other C1 alleles [Yen et al., 2001]. Thus, it is possible that KIR2DS2 recognizes a specific HLA-Cw*03-peptide complex generated during RA vasculitis.

Activating B haplotypes of KIR [Suzuki et al., 2004] and KIR2DS1 alone [Luszczek et al., 2004] or in combination with HLA-Cw6 (a C2 ligand for KIR2DS1) have been reported to associate with psoriasis [Holm et al., 2005]. Based on the data, a model was proposed in which a gradient of more activating to more inhibitory compound genotypes of KIR2DS and HLA-C appear to influence susceptibility to psoriatic arthritis. So, genotypes conferring highest activation (KIR2DS1 and/or KIR2DS2 with either HLA-C1 or C2 homozygosity) are associated with greatest susceptibility, whereas the genotypes conferring maximum inhibition (absence of activating receptors KIR2DS1 and KIR2DS2 and presence of both the inhibitory ligands, such as HLA-C1 and C2) were protective.

Moreover, the association between KIR gene polymorphisms and systemic lupus erythematosus (SLE) risk has been investigated by many case-control studies, but findings are not always consistent. SLE is a multifactorial and highly polymorphic systemic autoimmune disease that predominantly afflicts women in child-bearing age. It is a complex interaction result of genetic, environmental., and hormonal factors, companying a global loss of immune tolerance [Maselli et al., 2016]. In 2007, Pellett et al., first reported that the frequency of KIR2DS1 was significantly increased in SLE patients compared with controls [Pellett et al., 2007]. In addition, a recent meta-analysis shows that KIR2DL1 might be a potential risk factor for SLE in Caucasians and KIR2DL3, KIR2DL5 might be protective factors for SLE in Asians [Liang et al., 2017], indicating that the association between KIR polymorphisms and the risk of SLE may be different in different ethnic populations. In addition, activating KIR profiles, like KIR2DS2/KIR2DS5/KIR2DS1 were significantly higher in SLE patients as compared to healthy persons; however, it was seen that various ethnic and environmental factors might influence susceptibility to disease, which is consistent with previous studies [Pedroza et al., 2016].

An increasing stream of studies has been designed with systemic sclerosis (SSc) and ankylosing spondylitis (AS) patients to investigate the re-

lation between autoimmunity and KIR. SSc is a chronic disease of the connective tissue characterized by the fibrosis of the skin associated with the structural and functional damages of various organs such as the gastrointestinal system, lungs, heart, kidneys. It is a global disease and affects all races, and women are more susceptible than men [Romano et al., 2011]. It was seen that KIR2DS2 was more frequently highlighted in these studies. In fact, it was reported as a risk factor in the absence of KIR2DL2 in SSc patients. Moreover, the KIR2DS3 gene was more frequent in SSc patients than in controls, instead the KIR2DL3 gene was detected more frequently in controls while KIR2DS3 gene was more frequent in the patient group when SLE and SSc were combined [Tozkir et al., 2016].

In AS strong epidemiological evidence of significant genetic associations with HLA has been convincingly identified. AS is a chronic inflammatory disease which primarily affects the sacroiliac joint and is characterized by strong genetic association with HLA-B27 [Mathieu et al., 2008]. HLA-B27 interactions with KIR have been implicated in the pathogenesis of AS, with consistent differences among populations. KIR3DL1, for example, and possibly KIR3DS1, interact with classical B27, whereas KIR3DL2 binds B27 heavy chain dimers [Cauli et al., 2014]. Moreover, it was suggested that reduced HLA-Bw4 genotype with and without its inhibitory receptor KIR3DL1, may influence the inhibitory effect of NK cytotoxicity leading to continued injury in AS.

Further work in this area will help to establish the role of KIR/HLA association in autoimmune disease development.

Table 1. KIR-HLA associations in autoimmune diseases.

Disease	KIR–HLA ligand pair	Effect
Rheumatoid arthritis	KIR2DS2/HLA-Cw*03	Susceptibility
Psoriasis	KIR2DS1/HLA-Cw*06 KIR2DS1; KIR2DL5; KIR haplotype B	Susceptibility Susceptibility
Systemic lupus erythematosus	KIR2DS2; KIR2DS5; KIR2DS1	Susceptibility
Systemic sclerosis	KIR2DS2 in the absence of KIR2DL2 KIR2DS3	Susceptibility Susceptibility
Ankylosing spondylitis	KIR3DL1/ HLA-B27	Susceptibility

KIR/HLA association and viral diseases

Several epidemiological studies have associated KIR/HLA genotypes with susceptibility to some infectious diseases such as human immunodeficiency virus (HIV), human cytomegalovirus (CMV), and hepatitis C virus (HCV) [Cook et al., 2006; Di Bona et al., 2014; Khakoo et al., 2004; Hadaya et al., 2008; Martin et al., 2002; Martin et al., 2007; Stern et al., 2008]. So far, there are limited data on the relationship between KIR genes and their HLA ligands and the outcome of hepatitis B virus (HBV) infection (see Table 2 for an overview).

HIV prevalence is increasing worldwide because people on antiretroviral therapy are living longer, although new infections decreased from 3.3 million in 2002, to 2.3 million in 2012. New insights into the mechanisms of latent infection and the importance of reservoirs of infection might eventually lead to a cure. The role of immune activation in the pathogenesis of non-AIDS clinical events (major causes of morbidity and mortality in people on antiretroviral therapy) is receiving increased recognition [Sharp & Hahn, 2011]. In individuals infected with HIV, the combination of KIR3DS1 with its putative ligand HLA-Bw4-80I was associated with slower progression to AIDS, lower mean viral load, and protection against opportunistic infections [Martin et al., 2007; Qi et al., 2006]. Moreover, a study of 25 HIV exposed uninfected intravenous drug users from Vietnam found transcription of KIR3DS1 to be significantly higher than KIR3DL1 in KIR3DS1/3DL1 heterozygous individuals and there was expansion of NK cells expressing KIR2DL3 in HLA-C1/C1 individuals who were KIR2DS2^{-}/2DL2^{-} [Ravet et al., 2007]. KIR3DS1 homozygosity was also found to be significantly increased in HIV exposed seronegative intravenous drug users and HIV negative partners of sero-discordant couples [Boulet et al., 2008]. These individuals also had an increase in KIR AB haplotypes, which are characterized by increased numbers of activating KIR.

Also the variability in the association of host innate immune response to HCV infection requires the possible role of host KIR and HLA genotypes in HCV-related disorders. The World Health Organization estimates that about 3% of the world population is infected with HCV, and 3 to 4 million individuals are newly infected each year. Although new antiviral treatments are very promising, today

only a minority of patients successfully clear up HCV infections, and the remaining patients (60–85%) develop chronic infection [Afdhal et al., 2014]. NK cells have also been reported to play a role in HCV clearance [Cheent & Khakoo, 2011]. In particular, NK cells were demonstrated to mediate the inhibition of HCV-replication and to exert a targeted cytotoxic action against targeted cells given that NK cells isolated from healthy donors kill HCV-replicating cells and secrete IFN-γ [Larkin et al., 2006; Stegmann et al., 2010].

HLA-C1/KIR2DL3 in homozygosis has been associated with HCV clearance in several studies but the occurrence of this association was not always observed. At the same time, HLA-C1/KIR2DL3 has also been associated with sustained virus response to anti-HCV therapy.

Moreover, a protective role for HLA-Bw4/KIR3DS1 against liver disease progression has been proposed [De Re et al., 2015]. Previous data have also suggested that KIR2DL1/HLA-C2 may confer stronger inhibitory responses than does KIR2DL3/HLA-C1 [Ahlenstiel et al., 2008].

CMV is a member of the herpes virus family (type 5) that is ubiquitous in human populations, reaching a prevalence of 100% in Africa and Asia, and approximately 80% in Europe and the United States, depending on socioeconomic status. Clinically, primary CMV infection is assumed to be asymptomatic in the immunocompetent host, but a minority of subjects (<10%) exhibit symptoms of the infection, such as malaise, fever, sweating, and abnormal liver function [Cannon et al., 2010]. There is increasingly compelling evidence that NK cells play a crucial role in host defence against CMV infection. In order to evade the immune system, CMV encode several proteins that interfere with MHC class I expression, potentially rendering infected cells more susceptible to attack by NK cells [Lin et al., 2007]. In a case study of a child with a novel immunodeficiency syndrome and recurrent CMV infection, the entire population of NK cells from this patient expressed KIR2DL1 and the child also possessed the KIR2DL1 ligand, HLA-C2, raising the possibility that the strongly inhibitory KIR2DL1/HLA-C2 combination crippled NK cell activity and prevented the cells from mounting a protective response against CMV [Gazit et al., 2004]. Recent reports have also documented a role for activating KIRs in the control of CMV infection after hematopoietic stem cell or kidney transplantation, showing that the CMV reactivation rate in patients homozygous for the KIR A haplotype (virtually without activating KIRs) is higher than in patients with the B

haplotype (with a variable number of activating KIRs), suggesting the importance of activating KIRs in the immune surveillance against CMV [Cook et al., 2006; Hadaya et al., 2008; Stern et al., 2008]. Moreover, it was showed that immunocompetent subjects carrying the homozygous A haplotype or the HLA-Bw4^{T} allele are at higher risk of developing symptomatic disease after primary CMV infection. The frequency of the homozygous A haplotype (only KIR2DS4 as activating KIR) was higher in symptomatic patients than controls. By logistic regression, the risk of developing symptomatic disease was associated with the homozygous A haplotype and the HLABw4^{T} allele [Di Bona et al., 2014].

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 have the chronic disease. NK cells are activated in the early response to infection, and there is substantial population variability in the rates of HBV infection [Custer B et al., 2004]. Although detailed genetic and functional analyses exploring KIR influences on HBV in large cohorts are lacking, accumulating evidence supports that NK cell activation contributes to inflammation and liver injury during HBV infection both in HBV transgenic mice and in HBV infected patients [Chen et al., 2007; Dunn et al., 2007; Kakimi et al., 2001]. However, in a Turkish cohort, the rate of inhibitory KIR2DL3 and 3DS1 were higher in the healthy group than in the group composed of chronic HBV patients and patients with spontaneous remission. There were no statistically significant differences between the rate of AA and Bx genotypes of chronic HBV patients and patients with spontaneous remission and the control group. Moreover, a case-control study showed that more copies of HLA-C1 alleles, which resulted in inherently more potent NK cells, were associated with disease progression towards hepatocellular carcinoma (HCC) (one copy associated with cirrhosis; two copies associated with HCC) in HBV-infected patients, suggesting that NK cell activation may play a role in HCC development [Pan et al., 2011]. Finally, in a recent study, the authors compared the frequencies of KIR and HLA gene families in subjects with chronic hepatitis B (CHB) and subjects with resolved infection [Di Bona et al., 2017]. The inhibitory KIR2DL3 gene was less frequent in CHB (81%) than in subjects with resolved infection (98%). The only other KIR gene expressed differently between CHB and subject with resolved infection was the KIR2DS4-Del, which codes

for an inactive receptor. No difference was reported in the frequency of KIR haplotypes between the groups, suggesting that activating receptors likely do not play a role in the control of the infection. These results suggest that a combination of KIR/HLA gene/alleles is able to predict the outcome of HBV infection.

These data suggest that specific KIR and HLA gene segregations were likely the result of a pathogen selective pressure.

Table 2. KIR-HLA associations in viral infections.

Disease	KIR–HLA ligand pair	Effect
HIV	KIR3DS1/HLA-Bw4-80I KIR3DL1*004/HLA-Bw4 KIR3DS1	Slower progression Slower progression Reduced risk of infection
CMV	KIR2DL1 expression on all NK cells >1 activating KIR in donor in bone marrow transplantation KIR A haplotype/HLA-Bw4^{T}	Recurrent CMV infection Protection from CMV reactivation in the recipient Higher risk of developing symptomatic disease
HCV	KIR2DL3/HLA-C1 homozygosity	Resolution of infection
HBV	KIR2DL3; KIR3DS1 KIR2DL3/HLA-A-Bw4 and HLA-C2	Lower in chronic HBV patients Development of chronic hepatitis B

Discussion

Combinations of HLA class I and KIR variants have been associated with pathologies as autoimmunity, viral infections, pregnancy-related disorders and cancer [Parham, 2005; Khakoo & Carrington, 2006]. Thus, interactions between KIR and HLA class I polymorphisms have probably been involved in human during incidences of epidemic infections and have affected reproduction and population expansion. These types of selection pressures might explain the functional coevolution of KIR with diverging HLA class I molecules and why KIR sequences, like the HLA loci, are highly polymorphic and rapidly evolving [Guethlein et al., 2007; Martin et al., 2007].

Multiple factors complicate the interpretation of KIR-HLA disease association, including the extensive polymorphism of the KIR and HLA class I ligands, the incomplete knowledge of KIR ligands, the oversimplification of the structural complexities of their interactions, and limited understanding of KIR gene expression control [Traherne, 2008].

In general., KIR-HLA combinations with a tendency towards stronger NK cell activation or lower levels of inhibition are associated with increased risk of autoimmune diseases but tend to be protective against infectious diseases.

The reviewed data are consistent with the idea that disease susceptibility is modified by specific KIR-HLA ligand interactions. For this reason several studies have examined KIR and HLA class I combinations in disease association studies. Such studies will need to be large, with well-controlled populations, in order to be adequately powered.

Conclusion

In NK cell education, KIR/HLA interactions are required to establish self-tolerance and to shape the KIR repertoire of fully functional NK cells. It is clear that the association of activating KIR genotypes increases risk of autoimmune diseases and decreased risk of some infectious disease outcomes. Further efforts and incremental experiments are necessary to define the role of KIR-HLA interaction in human disease, and in turn, to potentially apply this knowledge clinically, and to define a common threads of KIR involvement across diseases that share some etiological characteristics.

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