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Killer Immunoglobulin-Like Receptors and Their Ligands

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1. Introduction

In immunology, the concept of alloreactivity is universally linked to the mechanism of T-cell recognition, where the T cell receptors (TCR) may interact with peptides mounted on major histocompatibility complex (MHC) molecules. The mechanisms responsible for the generation of TCR specificity and thus for the T cell activation depend on the repertoire of the genes coding for T cell receptor following the gene rearrangements of their variable regions and on the development and maturation of T-cells (Felix & Allen, 2007). Alloreactivity is not only important in the regulation of the adaptive immune responses, but it is also involved in the function of a major component of the *innate immune system* represented by the Natural killer (NK) cells (Ciccone et al., 1988, 1992; Kärre et al., 1986), and the rationale of this phenomena has been shown useful in some leukemia treatments (Ruggeri et al., 2005). NK cells are known to play a major role in the rejection of viral-infected or tumour-transformed cells (Herberman et al., 1975; Kiessling et al., 1975) following the “missing self” mechanism (Ljunggren & Kärre, 1990). Their function is controlled by a multifaceted collection of receptors able to deliver either inhibitory or activating signals. Differently than T lymphocytes, NK cells display receptors encoded by germline loci, and some of them are able to interact specifically with particular alleles of the MHC class I.

In humans and in primates these molecules are the killer immunoglobulin-like receptors (KIR) that display a clonal and stochastic distribution on the cell surface and are encoded by a multigene family. In particular, NK cells are known to express at least a one dominant self class I inhibitory receptor responsible for the self-tolerance (Moretta et al., 1996, Biassoni et al., 2009a). The activation of NK cells is based on continuous surveillance for MHC class I expression on autologous cells by inhibitory KIR cell surface receptors and by a balance of functions depending by integration of activating and inhibitory receptors responses (Biassoni, 2009b). All conditions that alter the surface expression level of the MHC class I on target cell, such as virus infection or tumour-transformation, are sufficient to trigger NK-mediated cytotoxicity.

In humans, higher primates and cattle, the inhibition of NK cell function depends by the expression of KIR encoded by a multigene family evolved in the last 135 million years from the two *KIR3DL* and *KIR3Dx* ancestral gene loci (Parham et al., 2011). Humans and higher primates have generated the KIR repertoire from the ancestral *KIR3DL* gene, while in cattle NK receptors have evolved from the other ancestral gene locus *KIR3Dx*, that is still

conserved in primates genomes as remnant of genes evolution during speciation. The human KIR genes map on chromosome 19q13.42, in the telomeric region of Leukocyte Receptor complex (LRC). Rodents and other species conversely evolved a completely different set of MHC class I-specific NK receptors, the Ly49 multigene family, which encode for type II transmembrane proteins belonging to the C-type lectin molecules.

Also the CD94/NKG2A receptor, conserved during speciation, is involved in the negative-control of NK cell function. In humans and in mice, it is specific for the HLA-E or Qa-1 molecules able to bind conserved peptides derived from the processing of different MHC class I leader sequences. Thus, CD94/NKG2A receptors sense the expression of different HLA class I molecules at once, indirectly monitoring the overall presence and level of expression of MHC class I alleles, making it particularly sensitive to any modification induced in transformed cells (Borrego et al., 2006).

KIR and HLA loci are both highly polymorphic and within this review we discuss the vast polymorphism of the KIR gene complex, which rivals that of the HLA complex. Indeed, one of the purposes of this chapter is to summarize our current knowledge of how KIR and their ligand diversities may influence the outcome of a number of key human diseases. For this reason, it is imperative for the accurate and reliable typing to determine the presence/absence of specific KIR genes, since the interactions of specific KIR and specific ligands have important roles in several diseases.

2. Killer immunoglobulin-like receptors (KIR)

KIR receptors vary in length from 306 to 456 amino acid residues and are characterized by immunoglobulin-like (Ig-like) domains on their extracellular regions, by a transmembrane and cytoplasmic region that are functionally relevant as they define the type of signal which is transduced by a defined NK cell (Colonna & Samaridis, 1995; D'Andrea et al., 1995; Wagtmann et al., 1995).

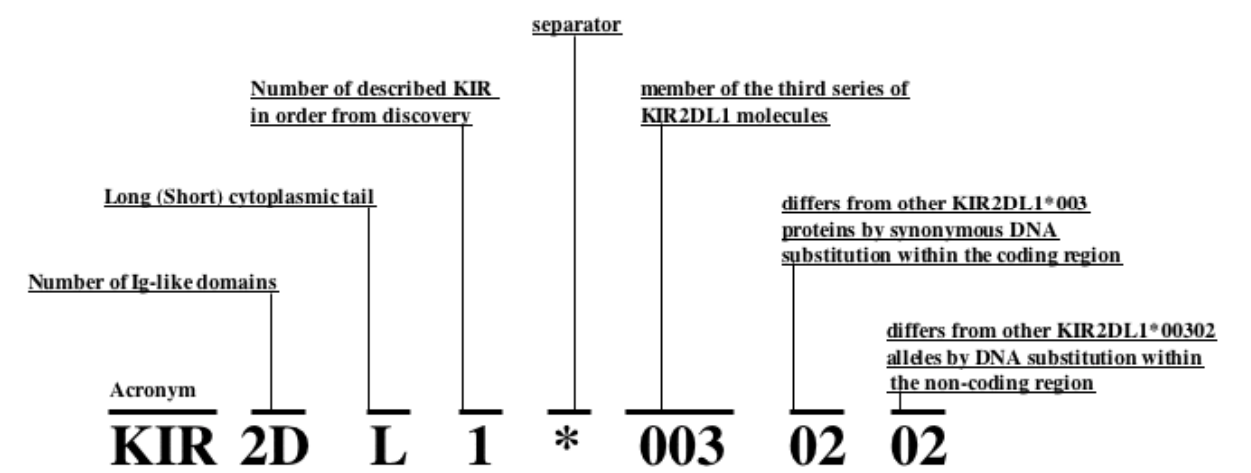
KIR proteins are classified by the number of extracellular Ig-like C2-type domains (2D or 3D) by the presence of a long (L) or short (S) cytoplasmic tail represented as KIR2DL and KIR2DS, respectively (Anfre' et al., 2001). *Inhibitory* KIR have a transmembrane region containing only hydrophobic amino acids and a long cytoplasmic tail (KIR2DL and KIR3DL) containing Immune Tyrosine-based Inhibitory Motifs (ITIM) involved in negative signalling. Upon ligand recognition ITIM are phosphorylated and lead to the association with the intracellular Src homology-2 (SH2) domain-containing phosphatases 1 or 2 (SHP1 or SHP2), which are responsible for turning off locally all triggering signalling pathways induced by activating NK cell receptors.

In contrast, some KIR are known to induce triggering of NK cell functions displaying a transmembrane region characterized by a positively charged amino acid (lysine) involved in the association with ITAM-bearing subunits and by a short cytoplasmic tail (KIR2DS, KIR3DS). Intracytoplasmic signalling and activation induced by these receptors are linked to the DAP12 receptor-associated signalling molecules that form a multichain immune recognition receptor (Sigalov, 2010). Different from all the other members of the KIR family, KIR2DL4 exhibits low polymorphism and high conservation, being one of the KIR framework genes. Although, it is characterized by a long cytoplasmic tail containing a single N-terminal ITIM, a feature shared with KIR3DL2 and KIR3DL3, KIR2DL4 transduces weak

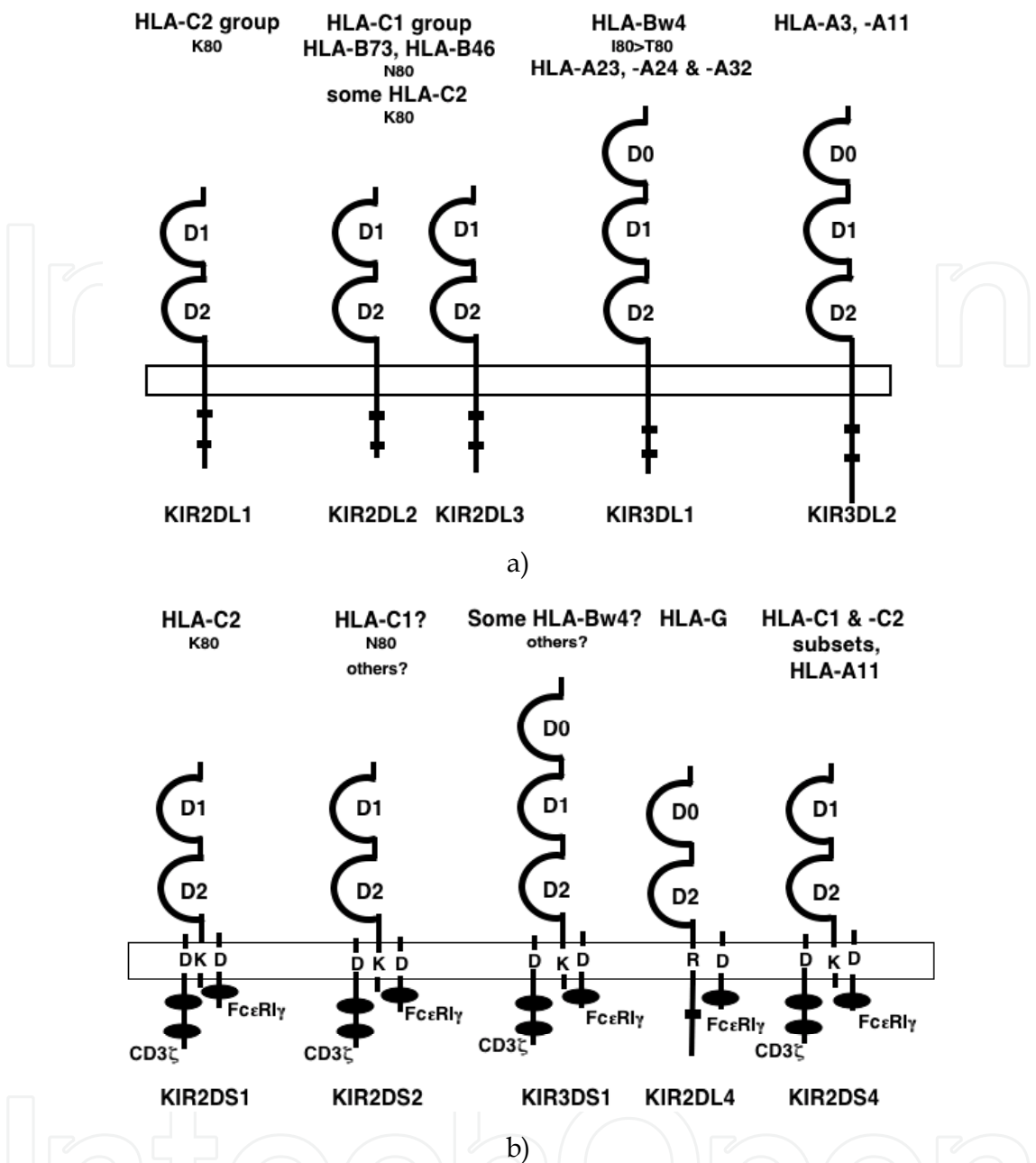
triggering signals mainly associated with cytokine releases rather than cytolysis (Cantoni et al., 1998; Faure & Long, 2002; Kikuchi-Maki et al., 2003; Rajagopalan et al., 2001; Selvakumar et al., 1996). The activating function depends by the association with FcεRIγ-chain, as signalling adapter molecule, instead of the DAP12, due to the positively charged arginine residue present in the transmembrane region (Kikuchi-Maki et al., 2005).

2.1 Organization of Killer immunoglobulin-like gene loci

The KIR genes are polymorphic, although highly homologous and are found in a region of 150 kb on chromosome 19q13.4 within the 1 Mb leukocyte receptor complex (LRC). The KIR loci and the genes coding for the Human Leukocyte Antigens (HLA) class I molecules reside on different chromosomes so they segregate independently and probably constitute the most diverse loci in the human genome. Indeed, the polygenic region coding for KIR has underwent rapid evolution and selection through mechanisms of homologous recombination, domain shuffling, and point mutations (Rajalingam et al., 2004); finally its diversity is achieved from the polymorphism of KIR genes and by the numbers of genes present in a haplotype. In detail, there are at least fifteen KIR genes and 2 pseudogenes (*KIR3DP1*, *KIR2DP1*) exhibiting substantial allelic diversity (Figure 1). Among them we may find 4 frameworks KIR genes/pseudogene present in nearly all individuals (*KIR2DL3*, *KIR3DP1*, *KIR2DL4*, *KIR3DL2*). Overall, KIR genes encode eight inhibitory receptors (*KIR2DL1*, *KIR2DL2*, *KIR2DL3*, *KIR2DL4*, *KIR2DL5A*, *KIR2DL5B*, *KIR3DL1*, *KIR3DL2*), six activating molecules (*KIR2DS2*, *KIR2DS3*, *KIR2DS5*, *KIR3DS1*, *KIR2DS1*, *KIR2DS4*), and two pseudogenes (*KIR2DP1*, *KIR3DP1*). Genes coding for KIR molecules, vary in length from 4 to 16 kb and may contain from four to nine exons, and with signal peptides encoded by sequences present in the first two exons. KIR genes are classified as belonging into either Type I (Cw Group I, 80 Asn) (*KIR2D*), Type II (Cw Group II, 80 Lys) (*KIR2D*), or *KIR3D* grouping. These depend on the presence of pseudoexon-3, partial or complete deletion of coding regions, and by the homology of the sequences encoding the immunoglobulin like (Ig-C2) domains. In detail, *KIR3D* genes encode proteins with three extra-cellular Ig-like domains (termed D0, D1 and D2), while *KIR2D* receptors are encoded by either



EMBL-EBI/IPD-KIR database at the following address, <http://www.ebi.ac.uk/ipd/kir/>
Fig. 1. Nomenclature Killer cell Immunoglobulin-like Receptors (KIR) genes and alleles.



Panel A: Inhibitory KIR named on the bottom and the relative HLA-ligand recognized by the same receptors (shown on the top). D0, D1 and D2 Ig-like domain structures are shown. Cell membrane is shown as an open rectangle. Small black-filled parallelograms represent ITIM in the cytoplasmic tail of the receptors.

Panel B: Activating KIR named on the bottom and the relative HLA-ligand recognized by the same receptors (shown on the top). D0, D1 and D2 Ig-like domain structures are shown. Cell membrane is shown as an open rectangle. Small black-filled parallelogram represent ITIM in the cytoplasmic tail of the KIR2DL4. Small black-filled ovals represent ITAM in the cytoplasmic tail of the associated chains. These signal transducing molecules are associated with the receptors through a polar interaction, inside the hydrophobic transmembrane environment, involving either lysine (K) or arginine (R) present in the cytoplasmic tail of triggering KIR with an aspartic acid residue (D) in the cytoplasmic tail of the signalling transducing molecules.

I80>T80: indicates the affinity of interaction with KIR3DL1

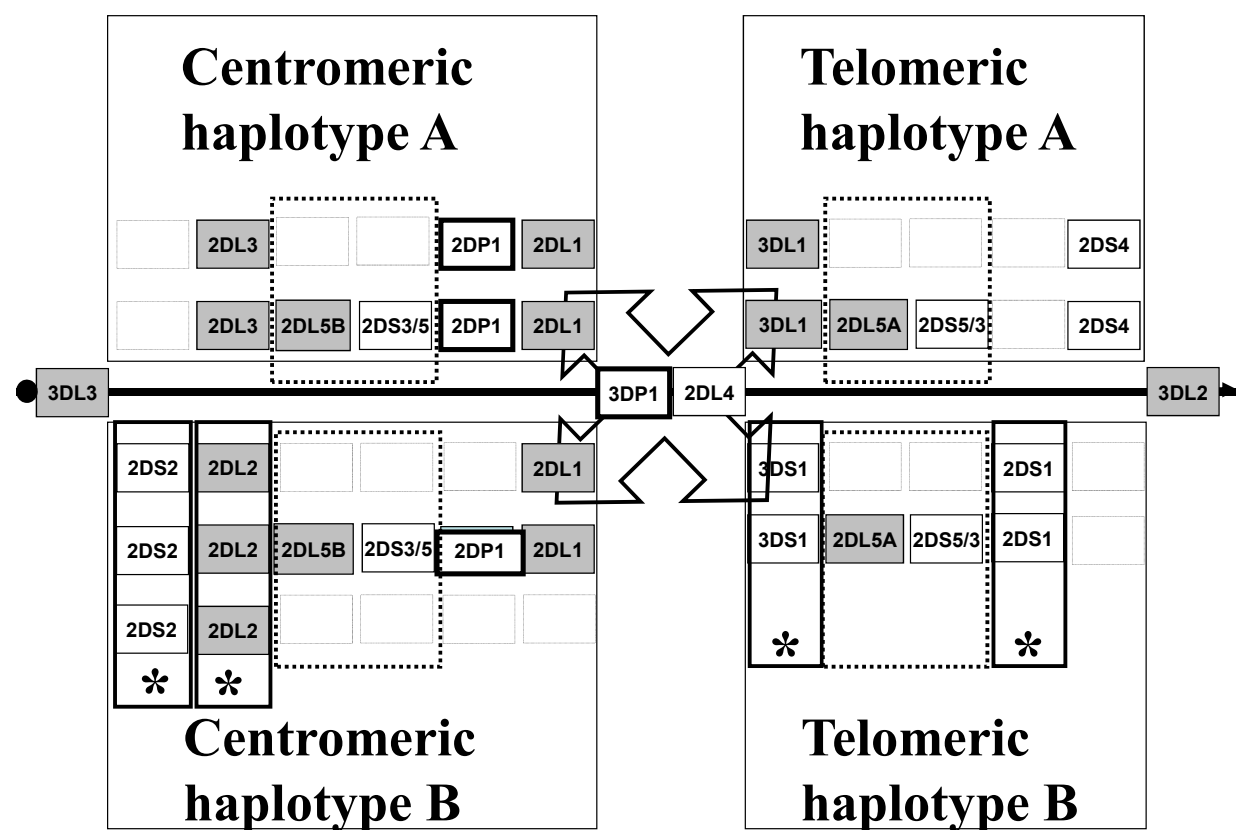
Fig. 2. Structural representation of either inhibitory (A) or activating (B) KIR.

Type I KIR2D genes characterized by the presence of pseudoexon 3 and displaying two extra-cellular domains with a D1 and D2 conformation or Type II KIR2D genes, which encode two extra-cellular domain proteins with a D0 and D2 conformation having deleted the corresponding region of exon 4 (Figure 2). Type I KIR2D genes (*KIR2DP1*, *KIR2DL1-3* and *KIR2DS1-5* genes) are all characterized by eight exons and by the presence of pseudoexon 3, that it is inactivated due to a nucleotide substitution located on the intron 2-exon 3 splice-site. The nucleotide sequences of pseudoexon 3 share a high-degree of nucleotide identity with to KIR3D exon 3 corresponding sequences. Within the Type I KIR2D group of genes, *KIR2DL1* and *KIR2DL2* have an additional identical partial deletion in exon 7, a characteristic of these genes, only. *KIR2DS1-5* differ from the other type I KIR2D genes only in the length of the coding sequences for the cytoplasmic tail in exon 9. Finally, the *KIR2DP1* pseudogene structure shows a shorter exon 4 sequence due to a single base pair deletion. Type II KIR2D genes (*KIR2DL4*, *KIR2DL5A* and *KIR2DL5B*) have a translated exon 3 and a deletion of exon 4 sequence. Within the Type II KIR2D genes, *KIR2DL4* is further differentiated from *KIR2DL5A/B* and from all other KIR genes, on the base of the length of its exon 1 sequence. In *KIR2DL4*, exon 1 was found to be longer by six nucleotides displaying a different initiation codon, interestingly in better agreement with the 'Kozak transcription initiation consensus sequence' than those present in the other KIR genes. KIR3D genes are characterized by nine exons and include the structurally related *KIR3DL1*, *KIR3DS1*, *KIR3DL2* and *KIR3DL3* genes, where the *KIR3DL2* locus has the longest genomic nucleotide sequence among all KIR genes (16,256 bp). Within the KIR3D group the genes differ in the length of exon 9, so that the cytoplasmic tail encoded sequences vary in length from 23 to 116 amino acid residues in *KIR3DS1* or in *KIR2DL4*, respectively. Moreover, *KIR3DS1* differs from *KIR3DL1* or *KIR3DL2* loci for the presence of a short exon 8 sequence, while *KIR3DL3* is lacking exon 6. Finally, *KIR3DP1* shares a high degree of sequence identity to *KIR3DL3* sequences, but it lacks sequences from exon 6 to exon 9, and occasionally also exon 2.

2.1.1 KIR haplotypes

The assortment of KIR genotypes may vary significantly in different subjects due to duplication or deletion of gene loci that have occurred during evolution. This has lead to two major groups of haplotypes, "A" or "B", based on the relative KIR gene content. Members of haplotype B are characterized by a higher number of genes coding for activating receptors than members of the haplotype A group. Immunogenetic analyses of different ethnic populations show significant differences in terms of the distribution of group A and B haplotypes. The linkage disequilibrium analyses of the centromeric and telomeric regions clearly indicate the evolutionary histories of these regions, which may have undergone different gene assortment and may also have been inherited separately during evolution. Thus, the complexity of haplotypes is such that the genomic region belonging to the KIR complex is structurally organized having as centromeric boundaries the gene *KIR3DL3* and at the telomeric ends the *KIR3DL2* locus (Figure 3). In addition it is possible to define separate partial haplotypes since a centromeric portion distinct from the telomeric one is structurally separated by the two framework genes *KIR3DP1* and *KIR2DL4* (Figure 3). Based on this classification, members of the haplotype "A" group needs to display both centromeric (CenA) and telomeric (TelA) genotype organization A/A (Uhrberg et al., 1997). We have also to consider that KIR gene inheritance is the result of distinct diploid combinations of genotypes so that haplotype A is only the result of Cen A/A and

Tel A/A combinations, i.e., both parents having CenA and TelA, and both parents passing both sets to their offspring who then has CenAA/TelAA (Cooley et al., 2010). Thus in this situation *KIR2DL3*, *KIR2DP1*, *KIR2DL1* loci are typically present in the centromeric portion while a single activating gene (*KIR2DS4*) could be present in its telomeric region together with *KIR3DL1* (Figure 3). All other haplotypes are described as members of the B haplotype, which is the more variable in terms of genotype, having at least one of the following genes: *KIR2DL5A/B*, *KIR2DL2*, *KIR2DS1*, *KIR2DS2*, *KIR2DS3*, *KIR2DS5* and *KIR3DS1*. Interestingly, *KIR3DL1* and *KIR3DS1* segregate as alleles of the same gene locus, the former associated with TelA haplotype, while the latter with TelB group of genes; in addition, the unexpressed *KIR2DL5B* variant is usually present together with *KIR2DS3* or more rarely with *KIR2DS5* that conversely is frequently present with *KIR2DL5A*. It is of note that in



The framework 3DL3, 3DP1, 2DL4 and 3DL2 gene loci are drawn on the line representing chromosome19q13.42 region oriented from centromer (left) to telomer (right). Inhibitory receptors (shown gray boxes), activating ones (unfilled boxes) and pseudogenes (boxed with thicker line) are indicated. The genomic organizations of centromeric and telomeric regions are boxed with continuous line trait. The genes defining A haplotype are drawn on top, while the ones typical for B haplotype on the bottom. Boxes represented with dotted lines indicate gene regions frequently deleted, in detail *KIR2DL5B* is more frequently, but no exclusively associated with *KIR2DS3* and on the opposite the gene telomeric to *KIR2DL5A* is *KIR2DS5* and rarely *KIR2DS3*. The *KIR3DP1* may be also present as *KIR3DP1* Δex2. Centromeric and/or telomeric haplotype B need to have at least one of the genes indicated with *. The four ways arrow indicate possible combination of centromeric and telomeric regions to determine CenAA-TelAA, CenAA-TelAB, CenAA-TelBB, CenAB-TelAA, CenAB-TelAB, CenAB-TelBB, CenBB-TelAA, CenBB-TelAB, CenBB-TelBB.

Fig. 3. Simplified genomic organization defining the KIR haplotypes

KIR	Aliases	Ligand	Function
2DL1	CD158a, cl-42, 47.11,nkat1, p58.1	HLA-C2 ^{Lys80} (Biassoni et al., 1995; Colonna et al., 1995; Wagtmann et al., 1995 ; Winter & Long, 1997)	Inhibition
2DS1	CD158h, EB6Actl, EB6Actll	HLA-C2 ^{Lys80} (weak) (Biassoni et al., 1997)	Activation
2DL2	CD158b1, cl-43, nkat6	HLA-C1 ^{Asn80} , HLA-B*73, -B*46, some HLA-C2 (Biassoni et al., 1995; Moesta et al., 2008)	Inhibition
2DL3	CD158b2, cl-6, nkat2, nkat2a, nkat2b, p58	HLA-C1 ^{Asn80} , HLA-B*73, -B*46 (Moesta et al.,2008; Winter et al., 1998)	Inhibition
2DS2	CD158j, 183Actl, cl-49, nkat5	HLA-C1 ^{Asn80} (weak) (Stewart et al., 2005)	Activation
2DL4	CD158d, 15.212, 103AS,	HLA-G	Activation Inhibition ?
2DL5A/B	CD158f, KIR2DL5.1/KIR2DL5.2,KIR2DL5.3, KIR2DL5.4	Unknown	Inhibition
2DS3	nkat7	Unknown	Activation
2DS4	CD158i, cl-39, KKA3, nkat8	Various HLA-C1 and HLA-C2 alleles, HLA-A*11(Graef et al., 2009)	Activation
2DS5	CD158g, nkat9	Unknown	Activation
3DL1	CD158e1, cl-2, cl-11, AMB11, nkat3, NKB1, NKB1B	HLA-Bw4 ^(I80>T80) except HLA-B*13:01/02 (Foley et al., 2008) HLA-A*23,-*24,-*32 (Stern et al., 2008; Thananchai et al., 2007) HLA-A*25 (Foley et al., 2008 : but not by Stern et al., 2008)	Inhibition
3DS1	CD158e2, nkat10	HLA-Bw4 ?	Activation
3DL2	CD158k, cl-5, nkat4, nkat4a, nkat4b	HLA-A*3,-*11 (weak) (Pende et al., 1996; Hansasuta et al., 2004)	Inhibition
3DL3	CD158z, KIR3DL7, KIR44, KIRC1	Unknown	Inhibition

I80>T80: indicates the affinity of interaction with KIR3DL1

Definition of KIR-mismatch in the case of HSCT

- **ligand-ligand model:** incompatibility between the donor KIR ligand and recipient KIR ligand is based on the “missing-self” hypothesis. Thus a ligand-ligand mismatch is possible if the donor has a ligand that is absent in the recipient (Ruggeri et al., 2002).
- **missing ligand model:** the above ligands-ligand paradigm is complicated by the fact that not all the individual genomes contain the complete set of KIR genes. Thus, you have to take in consideration that incompatibility between the donor KIR and recipient KIR ligand (receptor-ligand mismatch) is true if the donor has an inhibitory receptor for which the cognate ligand is absent in the recipient (Leung et al., 2004; Hsu et al., 2005). Thus to avoid this problem a KIR genotypic and phenotypic analysis is required.
- **receptor-receptor model:** it is known as KIR-haplotype incompatibility between the donor KIR and recipient KIR and it is valid if the donor has a receptor that is absent in the recipient (Gagne et al., 2002; McQueen et al., 2007)

Table 1. KIR ligand specificity

group A the haplotype diversity is primarily associated at the allelic polymorphism, while the group B haplotypes have greater diversity in gene content exhibiting only a moderate allelic polymorphism. In particular an analysis based on the genotype of only the four KIR2DL1, 2DL3, 3DL1 and 3DL2 loci showed at least 22 different haplotype A members with only 0.24% of unrelated individuals sharing an identical genotype (Shilling et al., 2002). The different B haplotypes may have mixed "B/x" genotypes (CenAA/TelAB, CenAB/TelAA, CenAA/TelBB, CenAB/TelAB, CenBB/TelAA, CenAB/TelBB, or CenBB/TelAB), which display all genes typical of group B plus at least an additional KIR group A gene, or may have a pure B/B genotype, without any A genes, CenBB/TelBB (Figure 3) (Cooley et al., 2010; Gourraud et al., 2010; Hsu et al., 2002; Middleton & Gonzelez, 2010; Pyo et al., 2010).

2.2 Ligand(s) of the Killer immunoglobulin-like receptors

On human NK cells, the KIR family of receptors participates in the complex regulation of NK cell responses through recognition of specific human leukocyte antigen (HLA) class I molecules on target cells. Both the KIR receptor and its cognate HLA ligand must be expressed in order to regulate NK cell activity. In fact each KIR interacts directly with distinct groups of expressed HLA alleles and the NK-mediated responses are governed by the avidity of interaction with HLA class I α 1-helix around amino acid residue-80 (Figure 2). Thus, this α 1-helix region is directly responsible for defining the different NK alloreactivities. In particular, inhibitory KIR2DL1, KIR2DL2 and KIR2DL3 receptors, and to a lesser extent the activating KIR2DS1 and probably KIR2DS2 are able to discriminate between two essentially non-overlapping groups of HLA-C alleles (Table 1). KIR2DL1 and KIR2DS1 (weaker) are specific for HLA-C alleles belonging to C2-group sharing V⁷⁶, N⁷⁷ and K⁸⁰ residues (essentially the majority of HLA-Cw2, 4, 5, 6 and some other alleles) (Figure 2A) (Table 1). In contrast, KIR2DL2 and to a lesser extent KIR2DL3 recognize HLA-C alleles (C1-group) characterized by V⁷⁶, S⁷⁷ and N⁸⁰ amino acids (mainly defined by HLA-Cw1, 3, 7, 8 and some other alleles). Additionally, some rare or geographically localized HLA-B allotypes (B73 and B46, respectively) containing a functional C1 epitope, originated by recombination events and sharing amino acids 66–77 with HLA-Cw3 alleles, and therefore interact with KIR2DL2 and KIR2DL3 (Biassoni et al., 1995; Abi-Rached et al., 2010) (Figure 2A). In addition, both KIR2DL2 and KIR2DL3 have also been described in having weak alloreactivity against some C2 allotypes (Moesta et al, 2008; Pende et al, 2009), probably due to allelic differences within the C2 subgroup (Figure 2A) (Table 1) (Moesta et al., 2008). Intriguingly, NK cell biology evolution drove to dominance in the recognition of HLA-C loci, where in humans at least 3 inhibitory and 2 activating receptors are able to sense the dimorphisms covering all known HLA-C alleles. It is known that MHC-C evolved only recently in humans and great apes (at least in orangutans), and not before. Apparently, the KIR and C1 loci evolved before the KIR-C2 since in Orangutans neither MHC-C2 alleles nor C2-specific KIRs could be detected (Older Aguilar et al., 2010). KIR3DL1 loci encode specific receptors for HLA-B alleles that share the public epitope Bw4 corresponding to amino acids 77-83 on the HLA class I α 1-helix with the exception of HLA-B*13:01 and HLA-B*13:02 (Foley et al., 2008), and for some HLA-A alleles characterized by Bw4-supertypic specificity like A23, A24, , and A32 (Stern et al., 2008; Thananchai et al., 2007). An additional paper suggested that also HLA-A*25 alleles may be recognized by KIR3DL1 (Foley et al., 2008) although these data have not been confirmed by others (Stern et al., 2008).

KIR3DL1 has been described to strongly interact with target cells expressing homozygous Bw4 alleles sharing Isoleucine-80, and weakly with homozygous Bw4 Threonine 80 (Figure 2A) (Table 1). KIR3DL2 has been reported to be specific for HLA-A3 and -A11 allotypes, but with a limited ability to inhibit NK-mediated lysis (Döhrring et al., 1996; Pende et al., 1996) (Figure 2A) (Table 1).

Among activating KIR receptors, the direct HLA binding was demonstrated only for KIR2DS1, where the weaker avidity of interaction was been found to be dependent on the dimorphism of amino acid residue 70 (Biaassoni et al., 1997) (Figure 2B). In contrast, evidence that KIR3DS1 may be associated with HLA-B recognition has been hypothesized, since it was found to be responsible for the delay of AIDS progression, but direct binding could not be demonstrated (Martin et al., 2002a; Gillespie et al., 2007). Recently a single KIR3DS1 allele (KIR3DS1*014), selected on the basis of critical D1-domain residues associated with Bw4-specificity (Figure 2B) (Norman et al., 2007), and carrying glycine-138 instead than tryptophan, was found to have direct HLA-Bw4 binding capability (O'Connor et al., 2011). The non-synonymous mutations in the extracytoplasmic domain linked with HLA-specific interaction are typical on activating KIR molecules (Biaassoni et al., 1997; O'Connor et al., 2011), and also experimental shuffling of 2DS2 residue 45 from tyrosine to phenylalanine typical of 2DL2 receptor were found to enhance the affinity of the KIR2DS2 for HLA-C1 ligand (Winter et al., 1998). These observations may be the results of evolution followed by selection pressure, since activating KIR may have evolved from ancestral inhibitory receptors (Abi-Rached & Parham, 2005). Further, it is likely that the triggering ones have evolved to decrease the affinity of HLA-recognition probably to avoid autoimmune phenomena, but with time, they acquired the potential to recognize HLA class I molecules presenting peptides of viral origin (Khakoo et al., 2000; Vilches & Parham, 2002; Abi-Rached & Parham, 2005). Class I MHC tend to present peptides of ~9 amino acids in length in their binding groove bounded by the $\alpha 1$ - and $\alpha 2$ -helices. The amino acid residue at position 8 of the peptide in the MHC class I binding groove may be governing KIR/HLA class I-interactions. Interestingly, this amino acid in position 8 is localized near the residue 80 amino acid of the $\alpha 1$ -helix. In particular, the KIR2DL/HLA-C and KIR3DL1/HLA-Bw4 interactions are affected by the presence of P8-residues either bearing strong negative or positive charges (Malnati et al., 1995; Peruzzi et al., 1996; Rajagopalan & Long, 1997). The relevance of pathogen derived-peptide is known to be associated with the positive association of both KIR3DS1 and Bw4 gene loci in HIV-infected subjects thus suggesting a possible role for HIV-associated peptides and by the fact that EBV infection is able to influence the KIR2DS1 HLA-C2 group interaction (Figure 2B) (Stewart et al., 2005). Pathogens present in the environment may have participated in the shaping of genetic loci of activating KIR thus explaining the hypothesis of recurrent acquisition and loss of activating KIR loci during evolution. In addition, the role of peptide in the KIR-mediated HLA class I recognition is known, since KIR3DL2 have a strong dependence from EBV-derived peptides presented by HLA-A3 and A11 alleles, and by that the presentation of particular self-peptide via HLA-Bw4 alleles were found to be protective from NK cell mediated lysis (Hansasuta et al., 1997; Malnati et al., 1995). Finally, KIR2DL4 binds to the non classical MHC class I HLA-G molecules (Ponte et al., 1999; Rajagopalan & Long EO, 1999), while KIR2DS4, probably originated from a gene conversion event with KIR3DL2 sequences, binds specifically to subsets of HLA-C1 and HLA-C2 group of alleles, and to HLA-A11 (Figure 2B) (Table 1) (Graef et al., 2009). Different analyses have demonstrated that KIR and their ligands may influence the outcome of a number of key human diseases. It is therefore obvious that accurate and

reliable molecular typing, to determine the assortment of KIR genes together with HLA class I genes, is imperative. This is necessary to define the KIR-ligand associations in order to determine possible interactions associated either in the positive or negative responses to several diseases and pathologic states.

3. Molecular typing techniques

Accurate typing methods to discriminate HLA class I alleles and KIR genotypes is of great interest to establish the associations of KIR/HLA, and their activation or inhibition potentials. Due to the extraordinary polymorphism of the Human Leukocyte Antigen complex, it is recognized that serological HLA typing techniques are inadequate for this task. The correct assignment of HLA class I alleles relies on molecular typing techniques (Harville, 2009). The introduction of Polymerase chain reaction (PCR) has allowed the development of more advanced techniques for molecular typing of HLA alleles. Additional methods dedicated in the HLA typing of group of alleles relevant in the NK-mediated function have been published using either RT-PCR or pyrosequencing on genomic DNA (Shilling et al., 2002; Ugolotti et al., 2011). At present for the identification of KIR genotype there is a tendency to use methods familiar to laboratories, such as the sequence-specific primers (SSP-PCR) and sequence-specific oligonucleotide probes (SSOP). In fact, traditional KIR genotyping methods utilize SSP-PCR and requires that genomic DNA must be amplified using a collection of primers in separate reactions in order to define the various loci or alleles and to be detected by fragment lengths using gel electrophoresis. However, there are drawbacks to utilizing the SSP method for higher-throughput analysis of KIR loci in populations. Furthermore, the SSP method includes the problem of sample amplification failure, which could be due to either general PCR failure, or an as of yet undefined variant sequence. The first problem could be partially overcome using different primer combinations to amplify the same KIR locus, and if the same primer set is able to amplify different KIR loci (Martin & Carrington, 2008; Kulkarni et al., 2010). Unfortunately, the inability to detect variant KIR alleles due to primer mismatch is without a practical solution. Accordingly, amplification failure could result in erroneous KIR genotyping results. An alternative KIR genotyping assay uses sequence-specific oligonucleotide probes (SSOP) developed for locus-specific resolution of 14 KIR gene loci. The SSOP assay requires a smaller quantity of genomic DNA than SSP techniques. Although generally more efficient than SSP methods, genotyping analysis by SSOP assays is still cumbersome and may have similar pitfalls in the detection of previously unreported variants (Middleton & Gonzeles, 2010). Some groups use sequencing for the KIR allele determination, whereas others have used mass spectrometry, or real-time reverse transcription-polymerase chain reaction, which not only could prove useful for allele determination but also for determining copy number of either gene or allele (Cooley et al., 2009; Du et al., 2008; Norman et al., 2007). Recently, the possibility to discriminate the KIR alleles by the technique of high-resolution melting (HRM) has been reported (Gonzales et al., 2009).

More recently, KIR haplotypes have been completely sequenced using Next Generation Sequencer (NGS), different patents using NGS have been filed (De Re et al., 2011), and some of sequenced haplotypes are present on the EBI database (http://www.ebi.ac.uk/ipd/kir/sequenced_haplotypes.html). Further, commercial kits are available for KIR typing in the clinical setting.

4. KIR/HLA class I genotypes and their implication in disease progression

As noted, an accurate typing system to discriminate groups of HLA class I alleles of a subject together with the analysis of KIR genotypes is of great interest to establish the association KIR/HLA, and their possible involvement in different pathologic or disease states. Another issue is to accurately define the sub-population of effector cells responsible for the immune responses. In this regard, an important issue is that KIR receptors are not only expressed by NK cells, but also by a subpopulation of CD8⁺ T lymphocytes. In this context, the role of this latter subpopulation may mask, or may actually be, the principal subject in any association between pathologic states and KIR/HLA interactions.

4.1 Human immunodeficiency virus (HIV)

HIV was the first viral infection for which an association between specific KIR and HLA class I ligands was observed. In detail, it has been reported that specific combinations between the activating receptor KIR3DS1 and HLA-Bw4 alleles, characterized by isoleucine at position 80 (HLA-Bw4^{I80}), have a protective effect against AIDS progression (Martin et al., 2002a). In fact, the interaction between HLA-Bw4^{I80} alleles and the activating receptor KIR3DS1 could be associated with enhanced NK cell reactivity that improves antiviral immune responsiveness. Moreover, this combination was found to confer protection against the onset of opportunistic infection during AIDS (Qi et al., 2006). Additionally, others found that KIR3DL1 alleles are correlated with the outcome of HIV infection in combination with HLA-B57, also an HLA-Bw4^{I80} allele. It has been found to be more protective than the KIR3DS1/HLA-Bw4^{I80} interaction (Martin et al., 2002a). It has to be stressed that the most protective KIR allele was KIR3DL1*004, which is not expressed on the cell surface, thus suggesting that absence of inhibition, or the better the enhanced KIR/HLA triggering potential, play roles in the immune-response against HIV (Rajagopalan et al., 2006). These data may not be in contrast though, since KIR3DS1 and KIR3DL1 are allelic form of the same gene present in haplotype B or A, respectively, thus representing different aspects of a complex system of interactions.

As expected, since the KIR complex has a multiloci ligand system, in some subject not only HLA-B alleles, but also HLA-C ligands appear to play roles in the control of HIV infection. A higher expression of HLA-C has also been associated with a slower AIDS progression (Fellay et al., 2007; Jenness et al., 2006; Thomas et al., 2009). While the HLA-C*07 alleles (C1-group), which are generally less expressed probably due to a mutation in the -35 residue (C>T), are associated with the most rapid progression of disease. Whereas alleles expressed at high levels (characterized by the -35 "C" allele), are associated with slower progression (Fellay et al., 2007; Thomas et al., 2009). These data may suggest the existence in these subjects of activating KIR(s) with C1-group specificity. Recently, a correlation of NK cell responses against HIV1-derived peptides has been associated with the presence of activating KIR(s) characterized by such C1-group specificity (Tiemessen et al., 2011).

4.2 Hepatitis C virus (HCV)

KIR/HLA combinations, suggesting a weak inhibitory potential, or better suggesting a triggering interaction, are been also found to be relevant in the viral clearance in hepatitis C virus (HCV) infection. This pathogen is common worldwide and is the direct cause of

chronic diseases such as cirrhosis and hepatocellular carcinoma in 85% of infected subjects due to non-efficient immune-responsiveness. Among the high number of patients with chronic infection, 17% develop complications such as cirrhosis, and 2% due the most serious progression of disease like hepatocellular carcinoma. The factor leading to these different outcomes are not clear yet, although the route of infection, size of inoculums, and the viral genotype may play major roles. Interestingly, it is known that a particular MHC polymorphism is associated with the spontaneous clearance, or a self-limited HCV infection. Thus, subjects characterized by weaker KIR-mediated inhibitory interaction (KIR2DL3/HLA-C1 group) would be protective. Probably, it is because this inhibition could be more easily overridden by activating receptors, which generate a more efficient viral clearance than a stronger inhibitory interaction such as that triggered from KIR2DL2/HLA-C1 group or KIR2DL1/HLA-C2 group. In detail, analyses on more than 1000 subjects revealed that 350 recovered spontaneously without treatment for HCV infection. The more common characteristics among them were the homozygous inheritance of the KIR2DL3 locus and of its relative HLA-C1 group ligand (Khakoo et al., 2004). When a KIR does not efficiently suppress immune cells, the cells can be more easily activated to eliminate infected cells. Another retrospective study was performed in 151 donor-recipient pairs, evaluating the KIR/HLA genotypes and the relapse of HCV disease, and its progression after liver transplantation. Liver biopsies were obtained from the recipients 1, 3, 5, 7 and 10 years post-transplant to determine when hepatitis relapsed, the degree of fibrosis, and the progression to cirrhosis (Espadas de Arias et al., 2009). They found that hepatitis was more at risk to recur when the KIR/HLA-C interacting ligands are “staggered” between donor and recipient. In addition, the presence of KIR2DL3 in the recipient was related to the progression of liver fibrosis. In general, a simple model of genetic protection has not been found in all patient populations. KIR2DL3 is found in the “A” group of haplotypes, as it is true for KIR2DS4. Consistent with this, KIR2DS4 has also been associated with protection against chronic HCV infection. Similarly, the B group of haplotypes marked with KIR2DL5, but without the presence of both KIR2DL3 and KIR2DS4, have been found to be associated with a poor response to treatment for HCV (Carneiro et al., 2010). Finally, the KIR2DL3/HLA-C1 group interaction was not found to be protective in a cohort of HIV/HCV co-infected individuals, implying that the HIV viral infection might modulate the protective effect of KIR3DL3.

4.3 Hepatitis B virus (HBV)

The same rationale of weak inhibition by the homozygous KIR2DL3 and HLA-C1/C1 group genotype has been also indicated in the protection from hepatitis B (HBV) viral infection, while the presence of KIR2DL1 in combination with HLA-C2 group ligand (stronger interaction), conferred the susceptibility to chronic hepatitis B (Gao et al., 2010). Chronic hepatitis B (CHB) is an inflammatory disease of the liver caused in 10% of people who become infected with hepatitis B virus (HBV). Many of those with chronic infection may be asymptomatic, thus increasing the risk of viral transmission. Chronic infection with hepatitis B may increase the chance of permanent damage to the liver, including cirrhosis and liver cancer. Chronic hepatitis B (CHB) affects more than 350 million persons in the world. Another study, has also investigated on the KIR gene polymorphisms in a large cohort of 150 chronic hepatitis B patients, 251 subjects with resolution of infection, and 412 healthy controls. These authors found a correlation between KIR2DS2 and

KIR2DS3 as HBV susceptible genes able to induce a persistent weak inflammatory reaction that results in continuous injury of live tissues, and thus to chronic hepatitis; whereas, KIR2DS1, KIR3DS1, and KIR2DL5 may act as protective genes that facilitate the clearance of HBV (Zhi-ming et al., 2007).

4.4 Human Cytomegalovirus (HCMV)

Human Cytomegalovirus (HCMV) is the cause of latent infections in the majority of infected individuals. In infected immuno-compromised subjects, this virus may reactivate causing life-threatening infection. Again, activating KIR genes are thought to be important for the control of CMV reactivation after haematopoietic stem cell transplantation (HSCT), and KIR2DS2 together with KIR2DS4, or a total of at least 5 loci coding for activating KIR present, could be associated with reduced CMV infection after transplantation (Zaia et al., 2009).

4.5 Human papilloma virus (HPV)

Activating KIR genes are associated with recurrent respiratory papillomatosis (RRP), a rare disease caused by human papilloma virus (HPV). In this context, activating KIR3DS1 and KIR2DS1 receptors have been found to be involved in the triggering of an effective early immune response against HPV-infected targets to establish resistance to RRP development (Bonagura et al., 2010).

4.6 Herpes simplex virus (HSV)

In the case of infections sustained by herpes simplex virus (HSV) it has been found that both KIR2DL2 and KIR2DS2 genes could be associated in all asymptomatic cases (Estefania et al., 2007). However, at present it was impossible to determine whether the inefficient responses to HSV could be associated to one of the gene loci coding for the activating or the inhibitory receptor. The uncertainty is because these genes are in tight linkage disequilibrium since they are expressed as different adjacent loci of the B-haplotypes.

4.7 Psoriasis

There is a strong genetic basis associated with the development of the chronic inflammatory condition of the skin known as psoriasis. The MHC class I region that includes HLA-A, -B, -C, and -E genes has been found associated with psoriasis (Bowcock & Krueger, 2005; Nair et al., 2000). Among them, HLA-Cw6 appears to be one of the loci most associated with psoriasis (Nair et al., 2006; Tiilikainen et al., 1980). At least 3 additional loci, an allele with a HLA-Bw4 epitope (Feng et al. 2009), HLA-E alleles representing the ligand for type II heterodimeric receptors (NKG2A/CD94, and NKG2C/CD94), and stress-induced MICA molecules, representing the ligand for the NKG2D triggering receptor (Cerwenka & Lanier, 2003; Cheng et al., 2000) may be involved in disease. Data about which KIR may be involved in psoriasis are still unresolved, since some researchers have found KIR2DS1 associated in the development of disease (Holm et al., 2005; Luszczek et al., 2005; Suzuki et al., 2004), while others could not find any association (Chang et al., 2006; Williams et al., 2005). The findings about a possible association between KIR2DS1 and psoriasis is intriguing, since this receptor may recognize the HLA-Cw6 alleles (C2-group) as ligands, making these data very

attractive, although a consensus on the biological significance of this association is still without an unanimous consensus. Another study pointed out the KIR2DL5 locus as the locus associated with the development of psoriasis (Suzuki et al., 2004). KIR2DS1 and KIR2DS2 have been found to be associated with psoriatic arthritis (PsA) (Williams et al., 2005), but without the expression of their associated HLA-C ligands (Martin et al., 2002b), or conversely, in presence of their ligands (Nelson et al., 2004). Altogether, the variability of the data published on psoriasis and PsA, indicate the absence of consensus, either because the numbers of patients analyzed were too low, or because the data on KIR/HLA association could be epiphenomenon and not the real cause of disease.

4.8 Inflammatory bowel disease (IBD)

In chronic inflammatory diseases of the gastrointestinal tract (IBD), Crohn's disease (CD) and ulcerative colitis (UC), the frequency of KIR2DL1 and KIR2DL3 is lower in patients than in healthy donors. It is of note that, the KIR2DL1/HLA-C2 group interaction is less frequent in IBD patients than with controls (Zhang et al., 2008). Therefore, the data suggest that poor inhibition through the KIR/HLA interaction contribute to the genetic susceptibility of IBD, and may be the direct cause of the chronic inflammation.

4.9 Use of NK cell activity in hematopoietic stem cell transplantation (HSCT)

NK cells have been used in adoptive immunotherapy as alloreactive natural killer (NK) cells for treatment of hematologic malignancies, in particular the myeloid leukemias. The knowledge acquired have made possible the use of NK cell alloreactivity (donor-versus-recipient) for eradication of leukemia cells using KIR/HLA haplotype-mismatched transplants ('haploidentical') or haploidentical hematopoietic stem cell transplantation (haplo-HSCT) (Pende et al., 2009; Velardi, 2008). This immunotherapy is based on the selection of donor NK cell expressing appropriate KIR repertoire (Table 1). The selection of KIR mismatches in HLA-matched donors by KIR genotyping is fundamental in the clinical treatment approach to define a donor selection strategy for improving transplant outcomes (Table 1) (Leung, 2011; van der Meer et al., 2008).

4.10 Reproduction

The interaction between NK cells and uterine trophoblasts is an active process for blood vessel enlargement, and in remodelling during placentation, in order to have a more efficient blood supply to the fetus during pregnancy. Defective invasion of uterine trophoblasts is one cause of abnormal placental development, which may occur in disorders such as pre-eclampsia. In this pathological condition there is incomplete enlargement of blood vessels, which is often associated with high blood pressure, ending up in poor fetal growth, or in recurrent miscarriages. Much evidence indicates that interactions between fetal trophoblasts and maternal uterine NK cells are important in human placentation, with abnormal interaction resulting in increased risk for developing pre-eclampsia. This situation arises in a mother displaying homozygosity for KIR haplotype A (essentially absence of activating KIRs) and presence of HLA-C2 group alleles in the fetal tissues (Hiby et al., 2004). These data suggest that strong KIR inhibitory signals may be associated with a reduction of vessel enlargement, resulting in poor implantation, and increasing the risk of recurrent spontaneous abortions. More

interestingly, also the HLA-C typing of the father was found to be crucial in miscarriages, where an increased frequency of HLA-C2 group alleles in both the mother and the father, associated with the lack of KIR2DS1 in the mother, seems to increase the risk of abortion. These data are the first evidence of a male factor that increases the risk in spontaneous abortions (Hiby et al., 2008). Others have found that mothers with recurrent miscarriages showed an increase of KIR2DS1 frequency, together with a decrease of HLA-C2 group alleles, in comparison with mothers without recurrent spontaneous abortions, while the expression of KIR2DL1, the inhibitory receptor for HLA-C2 group, was unchanged (Wang et al., 2007). In addition, trophoblast cells express on their cell surface the non-classical MHC class I, HLA-G, while decidual NK cells express the HLA-G-specific KIR2DL4 receptor. Thus, the HLA-G-specific KIR2DL4 receptors could play an important role in pregnancy outcome though the interaction between decidual NK cells and trophoblasts. Indeed several studies showed that higher cell surface expression of KIR2DL4 is associated with successful pregnancy (Yan et al., 2007). These data are not in conflict with the idea that activating KIR likely support placentation, since KIR2DL4 is known to have triggering potential. While KIR/HLA interactions, including maternal and paternal HLA and KIR alleles, between NK cells and trophoblasts are involved in preservation or loss of pregnancies, they do not represent the only set of factors. For example, women who are missing KIR2DL4 have had successful pregnancy outcomes (Nowak et al., 2011).

5. Conclusion

Killer Ig-like receptors (KIR) expressed by NK cells and by some CD8⁺ T lymphocytes are known to have important roles in normal immune protection, and certain pathological conditions, such as cancer, infectious diseases, loss of pregnancy, and autoimmunity. NK cells and some CD8⁺ T lymphocytes, which express KIR, also express multiple other receptors on their cell surface able to modulate/regulate their function and thus influence host immune-responses through a complex matrix of intra-cytoplasmic signals. All the knowledges gathered in the last 15 years about the structure of KIR, their function, as well as defining their ligand specificity, although still not completed, have made some clinical applications possible. It is currently possible via specific HLA matching and KIR mismatching to use NK cells to kill tumor cells. It can be envisioned that via knowledge of KIR associations with specific pathogen-infected cells, directed NK cell therapy, activation and inhibition, can be utilized to result in eradication of the virus, rather than chronic infection. All of these approaches are based on the correct KIR genotyping, performed together with the determination of the HLA class I allele. And, is ultimately based on the specific residues determining the KIR specificity, and interaction with HLA. Since NK cells and a subpopulation of CD8⁺ T lymphocytes express KIR, efforts continue to require addressing which is the correct cell population associated with the process under investigation. In addition, due to differential KIR levels of expression and haplotypic expression, studies must consider the presence, an increase, or a decrease of expression of certain KIR locus in the analyzed population versus the control population for valid assessment of the obtained results. At the current time, published information is lacking on the relative expression levels of KIR in different populations of people. In conclusion, an accurate evaluation of KIR/HLA interaction, taking in consideration the complexity of the KIR and HLA gene systems, together with a sufficient number of subjects analyzed is needed to define the KIR involvement in natural immunity and in different disease states.

6. References

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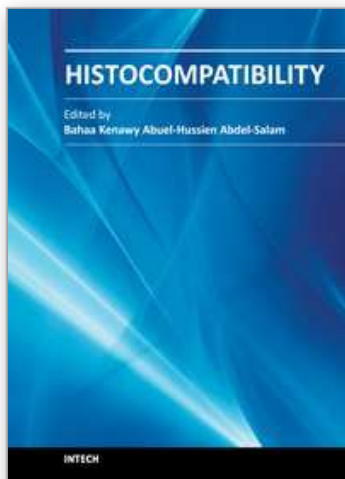
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