

# Autoimmune rheumatic diseases and their association with killer immunoglobulin-like receptor genes

Patricia Hartstein Salim<sup>1</sup>, Mariana Jobim<sup>2</sup>, Luiz Fernando Jobim<sup>3</sup>, Ricardo Machado Xavier<sup>4</sup>

## ABSTRACT

Killer Immunoglobulin-like Receptor (KIR) genes express as receptors that activate or inhibit Natural Killer (NK) cells. The NK cells are part of the innate immune response and, through their KIR receptors, they identify target cells that have modified or different HLA (Human Leukocyte Antigen) molecules, inducing their lysis. The KIR receptors result from the expression of KIR genes (19q13.14) on the cell membrane of NK cells, which are polymorphic, and form haplotypes. The diversity of the frequency of KIR haplotypes in certain populations suggests that some individuals have different levels of protection against some diseases. The balance between cell inhibition and activation enables the NK cell to help the organism in immunological surveillance. In addition, there is evidence of the association of activating KIR genotypes with an increased risk for autoimmune disease.

**Keywords:** autoimmunity; KIR receptors; systemic sclerosis

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## GENETIC EVIDENCE IN AUTOIMMUNE DISEASES

There are several mechanisms to explain the participation of Natural Killer (NK) cells in autoimmunity, one of them being the Killer Immunoglobulin-like Receptors (KIR) genes. The diversity of the frequency of KIR haplotypes in certain populations suggests that some individuals have different levels of protection against some diseases. The balance between cell inhibition and activation enables the NK cell to help the organism in immunological surveillance. Some studies have shown that KIR activators recognize HLA (Human Leukocyte Antigen) class I

molecules that contain peptides related to some pathologies or even other types of ligands that serve to identify abnormal cells.

## FUNCTION OF NATURAL KILLER CELLS

The NK cells are part of the innate immune response, being the first line of defense against virus, bacteria, tumors, and microorganisms.<sup>1</sup> They represent a cell line different from that of monocytes, granulocytes, and B cells, sharing the hematopoietic progenitor with T cells, and maintaining some ancestral characteristics of plasticity and versatility.<sup>2</sup> Unlike

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Services of Rheumatology and Immunology of the Hospital de Clínicas de Porto Alegre (HCPA), Medical School, Universidade Federal do Rio Grande do Sul (UFRGS), Brazil.

1. PhD candidate in Medical Sciences at the UFRGS; Master in Medicine (Medical Sciences) at the HCPA/UFRGS

2. PhD candidate in Medical Sciences; Master in Medicine (Medical Sciences), Medical School, HCPA/UFRGS; Physician of the Service of Immunology of the HCPA/UFRGS

3. Associated Professor of the Department of Internal Medicine of the UFRGS; PhD in Medicine; Immunologist; Head of the Service of Immunology of the HCPA/UFRGS

4. Adjunct Professor of the UFRGS; Head of the Service of Rheumatology of the HCPA/UFRGS; PhD in Immunology at the Shimane Medical University

Correspondence to: Ricardo Machado Xavier, Serviço de Reumatologia do Hospital de Clínicas de Porto Alegre. Rua Ramiro Barcelos, 2.350, sala 645. CEP: 90035-003, Porto Alegre, RS, Brazil. E-mail: rmaxavier@hcpa.ufrgs.br.

T and B cells, NK cells do not express a single well-defined antigen, and are phenotypically characterized as CD3<sup>-</sup>CD2<sup>+</sup>CD16<sup>+</sup>CD56<sup>+</sup>CD14<sup>-</sup>CD19<sup>-</sup>. They are low-density, large granular lymphocytes that develop and differentiate mainly in the bone marrow, being then released into blood stream.<sup>3</sup> The development and differentiation of NK cells can also take place in the thymus, spleen, tonsils and lymph nodes.<sup>4</sup>

Because of their different sites and development pathways, NK cells are heterogeneous regarding their phenotypic characteristics and functional capacities.<sup>5</sup> They comprise 10%-15% of the circulating mononuclear cells in the blood. In response to pro-inflammatory stimuli, which can be induced by a viral infection, NK cells migrate to several tissues and organs.<sup>2</sup>

The maturation of NK cells takes place in the bone marrow from CD34<sup>+</sup> progenitor cells in the presence of cytokines, such as IL-15. In the initial stage of maturation, those cells (still immature) do not express inhibitory receptors, although they express activating receptors and an efficient cytolytic activity.<sup>6</sup>

The NK cells can be divided into two large subsets based on the CD56 expression level,<sup>7</sup> as well as on the presence or absence of CD16.<sup>8</sup> Both markers are usually expressed reciprocally in those cells. The two subsets, CD56<sup>high</sup>CD16<sup>low</sup> and CD56<sup>low</sup>CD16<sup>high</sup>, represent 10% and 90% of the NK cells in peripheral blood, respectively. In the two subsets, the cells differ in their proliferative potential, functional capacities, and response to different cytokines.<sup>9</sup>

The cells in the first subset express receptors with high affinity with IL-2 (IL-2R), proliferate in response to picomolar concentrations of cytokines, produce mainly cytokines after activation, and have low cytotoxic potential. They express few KIR genes and migrate preferentially to secondary lymphoid organs (lymph nodes and tonsils). In the lymph nodes, most of NK cells are CD56<sup>high</sup>.<sup>10</sup> The CD56<sup>low</sup>CD16<sup>high</sup> cells express low affinity with IL-2R, proliferate in response to nanomolar concentrations of IL-2, express KIR, and are highly cytotoxic.<sup>11</sup> Those NK cells migrate to inflamed tissues in response to chemotactic stimuli. Because of the CD16 expression, they are also efficient mediators of antibody-dependent cell-mediated cytotoxicity (ADCC). The subset CD56<sup>high</sup> is less cytotoxic as compared with the subset CD56<sup>low</sup>, probably due to its lower expression of perforin.<sup>12</sup>

During the immune response, the NK cells can directly attack the target-cells and interact with dendritic cells in peripheral tissues with inflammatory processes,<sup>13</sup> by using two different cytolytic mechanisms. The first is through apoptosis activated by granules, which depends on the synergic action of the perforin and granzyme proteins.<sup>14</sup> The second is through

apoptosis induced by the Fas/FasL interaction.<sup>15</sup> An indirect attack to the target cells, through characteristics of the adaptive immune response, can occur.<sup>16</sup>

The cytolytic activity of NK cells and their production of cytokines are regulated by the activation or inhibition of receptors on cell surface. The receptors comprise different families of proteins: with lectin-type domains (CD94/NKG2A, HLA-E ligand with inhibitory function; and NKG2D, MICA ligand with activating function)<sup>17</sup> and with immunoglobulin-type domains (-KIR).<sup>18</sup> The receptors of leukocytes with immunoglobulin-type domain (leukocyte Ig-like receptors - LILR) are also expressed in B and T cells, and, thus, are not specific for NK cells.

The NK cells express at least one inhibitor receptor, and the interaction of the expression of HLA class I molecules with inhibitory receptors in NK cells represents an important and well-known checkpoint in controlling the activation of those cells,<sup>19</sup> thus preventing autoaggression.<sup>20</sup>

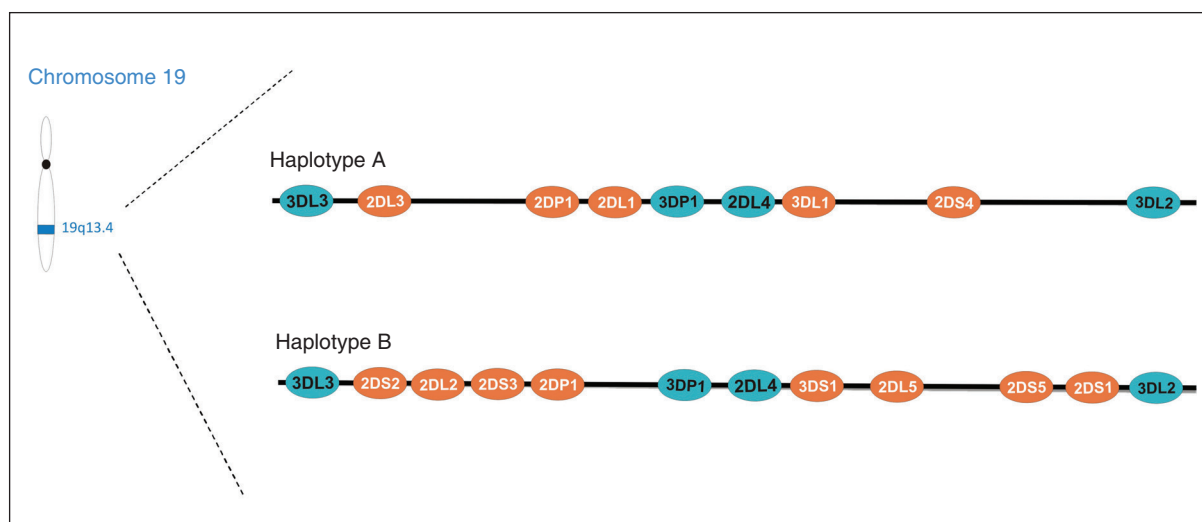
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## STRUCTURE OF KIR GENES

The KIR receptors are members of the immunoglobulin family present on cell surface, expressed in NK cells<sup>21</sup> and some T lymphocytes (NKT).<sup>22</sup> So far 17 genes have been identified in chromosome 19q13.4.<sup>23</sup> One typical KIR gene contains nine exons<sup>24</sup> that encode leader sequences (exons 1 and 2), the extracellular domains (D0, D1 and D2, which correspond to exons 3, 4 and 5, respectively), the tail (exon 6, between the extracellular domain and the membrane), the transmembrane domain (exon 7), and the intracytoplasmic tail (exon 8 and 9)<sup>25</sup> of the molecule of those receptors.

The KIR receptors result from the expression of that polymorphic gene system and are divided into inhibitory and activating functional groups.<sup>26</sup> The receptors with inhibitory intracellular signal prevent the lysis of the target cell.<sup>27</sup> They have a long cytoplasmic tail, and, thus, were attributed the letter "L" in their denomination (English, long). The letter "S" (English, short) was attributed to the receptors with short tail, which have an activating intracellular signal and cause the lysis of the target cell.<sup>28</sup>

The extracellular domains are responsible for the recognition of the target cell. Some have two immunoglobulin domains (denominated 2D) and others have three (denominated 3D)<sup>29</sup> identified as D0, D1, and D2. The 2D receptors can be of two different types: type 1, which possesses the D1 and D2 domains (KIR2DS1/2/3/4/5 and KIR2DL1/2/3), due to the removal of exon 3; and type 2, which possesses the D0 and D2 domains (KIR2DL4/5), due to deletion of exon 4.<sup>30</sup>



**Figure 1**

Haplotypes of the KIR genes.

[P1] Haplotype A has nine genes: one is the activator, five are inhibitory, and three are structural genes, which are present in haplotypes A and B.

[P2] Two proteins are involved in the activation: Zap 70 and Sv4. During inhibition, dephosphorylation of those substrates occurs.

[P3] Each individual has two HLA class I alleles. More than four KIR receptors can exist in NK cells, differently from the HLA antigens, which are extremely specific.

## HAPLOTYPE DIVERSITY OF KIR GENES

All KIR genes are grouped in the region of the leukocyte receptor complex (LRC),<sup>31</sup> and each KIR gene has approximately a 2-kb interval. They form haplotypes, which are a set of genes in the same chromosome, transferred as a block from generation to generation. The order of the genes in that region has been deduced from the sequencing of KIR haplotypes, as well as from segregation analyses. The KIR haplotypes vary in human beings regarding the number of activating and inhibitory genes and their allele forms. Because of such variations, a large number of KIR haplotypes has been identified and classified as A and B haplotypes.<sup>32</sup>

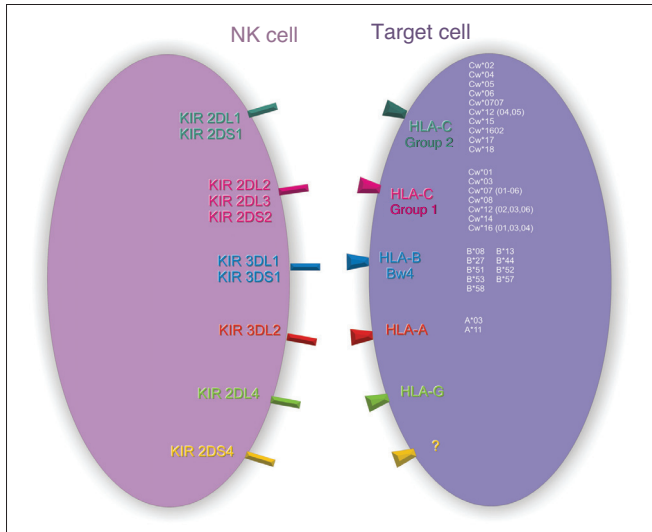
The A haplotype has nine KIR genes, and only one is an activator (2DS4). This gene, which is often not expressed, has a deletion of 22 pairs of bases in exon 5. Approximately 80% of the Caucasians have that suppression. Usually that haplotype contains five inhibitory genes, the other three being structural genes (Figure 1-P1). The B haplotypes have a high diversity of genes, both activators and inhibitors (Figure 1). The frequency of those two haplotypes varies significantly in different populations.<sup>33</sup>

Four KIR genes are present in all (or almost all) haplotypes: 3DL3, 3DP1, 2DL4, and 3DL2. They are called structural or “framework” genes, because they suggest certain stability regarding gene recombination.<sup>34</sup> The centromere region contains the KIR 2DL3, 2DP1, 2DL1, 2DS2, 2DL2, and 2DS3 genes, while the telomere region contains the KIR 3DL1, 2DS4, 2DL5, 2DS5, 3DS1 and 2DS1 genes. The 3DP1 and 2DL4 genes are located between those two regions, the KIR3DL3 is next to the centromere, and the KIR3DL2 is next to the telomere.<sup>27</sup>

## KIR RECEPTOR LIGANDS

The NK cells recognize a foreign cell through the bonding of KIR receptors expressed on their membrane with the class I human leukocyte antigen (HLA) present in the target cell. The KIR receptor binds to the top of the  $\alpha$ -helix and to the exposed regions of the peptide in HLA. The specificity of that interaction is defined by a dimorphism of HLA-Cw in position 80 and a corresponding dimorphism in position 44 of the KIR receptor.<sup>26</sup>

The dimorphism in positions 77 and 80 of the amino acid sequence defines two serologically different HLA-Cw allotypes: group 1 (C1), which has a serine residue in position 77 (Ser77)



**Figure 2**  
KIR receptors and their respective ligands.

and asparagine in position 80 (Asn80); and group 2 (C2), which has an asparagine residue in position 77 (Asn77) and lysine in position 80 (Lys80). Those two groups have differentiated during the evolution. In the first phase of human evolution, C1 group ligands were formed, while, in the second phase (after the separation of their ancestors, orangutan and chimpanzee), mutation of the Asn80 to Lys80 occurred in the HLA molecule of the C1 group, producing the first ligand of the C2 group.<sup>28</sup> Thus, Lys80 is a specific characteristic of HLA-C, while Asn80 is also present in HLA-B and other HLA class I molecules.

The KIR receptors can also differentiate in two groups of ligands. The first group has a lysine residue in position 44 of the D1 domain, and corresponds to the KIR2DS2, KIR2DL2 and KIR2DL3 receptors that recognize the C1 allotype of HLA-Cw. The second group (KIR2DS1 and KIR2DL1) has one methionine in that position, recognizing the C2 allotype of HLA-Cw (Figure 2). KIR3DL1/KIR3DS1 interact with HLA-Bw4 (that differs from Bw6, because of a polymorphism in positions 77 and 80).<sup>26</sup> The HLA-Bw4 with the amino acid isoleucine (Ile) in position 80 causes a strong inhibition through KIR3DL1.

The KIR-HLA interaction is differentiated by the intensity of the bonding and affinity between the receptors and their respective ligands. The receptors bind weakly to the antigens of group C1 and strongly to those of group C2.<sup>30</sup> The inhibitory receptor has greater affinity than the activating receptor. The biological relevance of low affinity has not been totally clarified, it might exist to attenuate the inhibitory receptors in

situations in which inhibition is not advantageous or avoid the aggression of NK cells against other cells in the organism.<sup>27</sup>

## MECHANISM OF ACTION OF KIR RECEPTORS

The receptors of NK cells with long cytoplasmic chains transmit inhibitory signals. Those receptors usually have two Immunoreceptor Tyrosine-based Inhibitory Motifs (ITIMs), except for KIR2DL4, which has only one ITIM in its cytoplasmic tail and one amino acid (arginine) in the transmembrane region, making the interaction with DAP-12 easier, the reason why it can transmit inhibitory or activating signs, or both.<sup>27</sup>

When the recognition of their ligands occurs, the tyrosine residues in ITIMs become phosphorylated, and associate with the SHP-1 and 2 molecules (Src-homology domain-bearing tyrosine phosphatase). Those phosphatases dephosphorylate many of the substrates involved in the NK cell activation cascade, inhibiting cytolytic activity and activating the secretion of cytokines (Figure 1-P2).<sup>31</sup>

The receptors with short cytoplasmic chain are activators. Such receptors lack ITIMs; however, they have a positively modified amino acid (lysine) in the transmembrane region. By use of that amino acid, the receptors associate non-covalently with a dimer of the adaptor protein DAP-12. Each DAP-12 has Immunoreceptor Tyrosine-based Activating Motifs (ITAMs) in its cytoplasmic chain. The tyrosine residues in ITAMs are phosphorylated and recruit several tyrosine kinases (ZAP-70/Syk), transmitting the activating signal so that the NK cell can exert its lytic activity on the target cell and secrete cytokines.<sup>28</sup>

## KIR GENES AND SUSCEPTIBILITY TO RHEUMATOLOGIC DISEASES

In Systemic Sclerosis (SSc), two studies, one Brazilian and another German, have reported an association with the presence of the activating KIR2DS2 and the absence of the inhibitory KIR2DL2. Salim *et al.*<sup>35</sup> have reported that, in addition to the KIR2DS2+/KIR2DL2- combination, the inhibitory KIR2DL2 was significantly less frequent in patients than in controls. However, the presence of both KIR2DS2 and KIR2DL2 (KIR2DS2+/KIR2DL2+) was more frequent in controls than in patients, suggesting a protective effect of KIR2DL2 over KIR2DS2. Momot *et al.*<sup>35</sup> have only observed the combination of the presence of the activating 2DS2 with the absence of inhibitory 2DL2. Another study carried out in patients with SSc was controversial, because it reported that SSc was associated with the presence of KIR2DS1 and the absence of KIR2DS2.<sup>36</sup>



Regarding systemic lupus erythematosus (SLE), a study has shown that the KIR2DL5 gene was significantly associated with a reduced risk of SLE, as well as with an increased risk of infectious events in general in patients with SLE.<sup>37</sup> Another study has reported 27 new genetic combinations in patients with SLE, who showed a higher KIR2DL2 and KIR2DS1 gene frequency than healthy individuals. The results of that study have suggested that a genetic disorder in the activating and inhibitory KIR genes might be one of the major underlying factors of the SLE pathogenesis.<sup>38</sup> In 2011, a study suggested that the predisposition to SLE is associated with the presence of the KIR2DS2+/KIR2DS5+/KIR3DS1+ profile and with the GTGT deletion at the SLC11A1 3'UTR.<sup>39</sup>

Regarding ankylosing spondylitis (AS), an association with the KIR3DS1 gene has been demonstrated by most studies performed. Jiao *et al.*<sup>40</sup> have reported that the KIR2DL5 gene has also been more frequent in AS, but the KIR3DS1 gene has shown to be more susceptible to trigger continuous lesions of arthrosis. The imbalance between activating and inhibitory KIR, as well as HLA-C of the groups 1 and 2, has been suggested as a key factor in the pathogenesis of AS. Another study has suggested that susceptibility to AS can be determined by the global balance between activation and inhibition of the compound genotypes KIR-HLA, showing that the 3DS1 allele is associated with B27.<sup>41</sup> In the Chinese population, an increase in KIR3DS1, KIR2DS5 and KIR2DL5 has been observed in patients with AS similarly to that reported in the Thai population.<sup>42</sup> In addition, the KIR2DL1 and KIR2DL5 frequencies were significantly higher in patients than in controls. Individuals with AS have shown a higher frequency of HLA-Cw \* 08.<sup>43</sup> However, Harvey *et al.*<sup>44</sup> have reported no association between the KIR genes and AS.

A deeper study carried out by Díaz-Peña *et al.*<sup>45</sup> has shown that the KIR3DS1 \* 013 allele was the sole responsible for the increase in the frequency of the activating receptor KIR3DS1 in patients with AS as compared with healthy HLA-B27-positive controls. The increased frequency of that allele in patients with AS is clearly independent from the presence of the HLA-Bw4I80 epitope, but the presence of inhibitors, such as KIR3DL1 004, has shown a negative association in patients with AS in the presence of HLA-Bw4I80. Consequently, the influence of the KIR genotypes on the susceptibility to AS would be mediated by an imbalance between activation/inhibition. However, in addition to the HLA and KIR genotype, KIR expression levels can also be involved in the pathogenesis of AS.<sup>46</sup>

Regarding rheumatoid arthritis (RA), in 2007, Majorczyk *et al.*<sup>47</sup> carried out a study and reported that the KIR frequencies

of patients with RA were similar to the frequencies observed in controls. However, the KIR2DL2 and KIR2DS2 genes were significantly more frequent in patients with extra-articular manifestations and in their subgroup with vasculitis than in controls and patients without those complications. In addition, the KIR2DS1 and KIR3DS1 frequency was lower in patients with no bone erosions as compared with healthy individuals. The relations between the presence or absence of autoantibodies and the frequency of the KIR gene have also been assessed, but no significant differences have been found. That study suggests that certain clinical manifestations of RA can have different genetic origins regarding the KIR genotype. However, that association has not yet been well established, because another study with patients with RA has shown that such association between RA and the KIR genes was not significant.<sup>48</sup>

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#### ACTIVATION OF NK CELLS THROUGH THEIR KIR RECEPTORS IN AUTOIMMUNE DISEASES

The NK cells can express the KIR receptor, to which the specific ligand is not present. This occurs because the KIR locus is located in chromosome 19, while the HLA genes are in chromosome 6. Thus, the two loci segregate independently.

When the expression of HLA class I antigens is reduced or deficient, such as during a viral infection or tumor transformation, the inhibitory signal is weakened and the NK cell is activated, thus inducing the target cell to death. The NK cells are always apt to develop their lytic activity, because they are part of a continuous immune surveillance process, checking if all cells are correctly expressing the class I HLA.<sup>1</sup> In the affirmative case, the inhibitory receptors will play their role and the target cells will be preserved (the inhibitory receptor suppresses the signals of intracellular activation). However, on the surface of NK cells, there are more than four KIR receptors, and they are activators and inhibitors (Figure 1-P3).<sup>26</sup>

When an organism expresses the 2DS2 and 2DL2/3 receptors (that recognize C1 ligands) on NK cells, and at the same time expresses homozygous antigens of the C2 group, cell activation occurs, causing autoaggression (Figure 3). When the activating receptor does not recognize any of its ligands, it generates a signal to the NK cell to exert its lytic activity. The inhibitory receptor does not activate the signal, because it does not recognize the ligands either. The same occurs in an organism homozygous for the C1 group in the presence of 2DS1 and 2DL2 receptors.<sup>20</sup>

However, in the presence of heterozygosity for the C1 and C2 groups, the NK cell recognizes the other as one of

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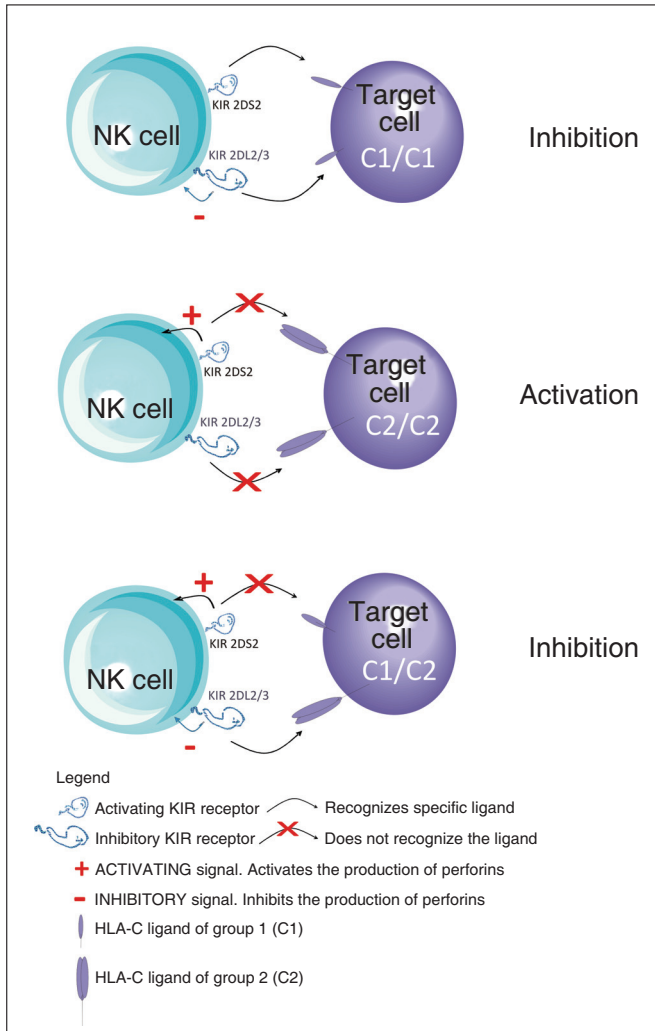
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**Figure 3** Activation and inhibition of NK cells through the recognition of their receptors with their respective ligands.

its own. Thus, there are two possibilities: a) the activating receptor recognizes its ligand (not generating a signal) and the inhibitory receptor does not recognize the ligand (not generating a signal), resulting in lack of cell activation, because the receptor responsible recognizes the cell as one of its own; b) the activating receptor does not recognize the ligand (generating a signal to the NK cell to lyse the target cell) and the inhibitory receptor recognizes the ligand (generating a signal to the NK cell NOT to lyse the target cell). In this case, the inhibitory signal predominates over the activating signal, canceling its effect.<sup>26</sup>

### CONCLUSION

The presence of many polymorphisms of the KIR genes might contribute to the risk of developing a rheumatologic disease, while a single polymorphism might have a limited impact. In addition, the identification of additional genes or the characterization of the functional mechanisms involved in the interaction of the molecules of the activating or inhibitory KIR receptors during the process of NK cell activation contributes to understanding the pathogenesis of autoimmune rheumatologic diseases. Studies of clinical association conducted with large populations, and particularly in families, can provide better identification of the genetic associations of rheumatologic diseases, promoting the development of diagnostic tools, identification of genetic markers, and establishment of strategies of treatment.