Natural Killer (NK) cells are a subset of innate lymphoid cells specialized for cytotoxicity and production of inflammatory cytokines such as IFN-γ. As such, they are presumed to be important for early control of infections with intracellular pathogens and anti-tumor immunity. In addition, NK cells may help to regulate placentation. The activation of effector functions is controlled by the integration of signals from multiple receptors, including not only activating and inhibitory NK cell receptors but also receptors for cytokines such as IL-12, -15, -18. The Killer cell Immunoglobulin-like Receptors (KIR) make up the largest and by far most polymorphic human NK cell receptor family. Underscoring the importance of KIR, their genetic variation is associated with resistance to viruses such as HCV and HIV, autoimmune diseases and reproductive success. To understand how KIR influence health and reproduction, it is critical to know what molecules they interact with. In this topic, leading experts provide an up-to-date overview of the known ligand specificities of specific KIR.

Cresswell and deMars first showed in 1989 that transfection of HLA class I molecules into class I-deficient cell lines reduced their susceptibility to NK cell lysis (Harel-Bellan et al., 1986; Quillet et al., 1988; Shimizu and DeMars, 1989; Storkus et al., 1989). In this fashion, several HLA-B and -C alleles were identified as potential ligands for inhibitory NK cell receptors (Ciccone et al., 1992; Colonna et al., 1993; Cella et al., 1994; Mandelboim et al., 1996). Certain antibodies to NK cell surface molecules were able to restore lysis of these HLA class I transfectants by NK cell clones, allowing the definition of specificities of the receptors that were blocked by the antibodies. Most of the antibodies (GL183, EB6, CH-L, DX27, HP-3E4) bound 58 kDa receptors for HLA-C variants characterized by either an Asparagine (C1) or a Lysine (C2) at position 80 of their alpha-chains (Ciccone et al., 1992; Moretta et al., 1993; Mandelboim et al., 1996), others (DX9, Z27) a 70 kDa receptor for HLA-B (and some HLA-A) alleles carrying the “Bw4-motif” (Litwin et al., 1994; Gumperz et al., 1995), and a few (Q66, DX31) bound a 140 kDa homodimeric receptor for HLA-A3 and -A11 (Pende et al., 1996). In many individuals the antibodies recognizing inhibitory, 58 kDa receptors for HLA-C also bound 50 kDa proteins from NK cell clones that acted as activating receptors. Some of these receptors also bound HLA-C, although weakly (Moretta et al., 1995).

Molecular cloning revealed that these receptors carried 1–3 immunoglobulin-like extracellular domains that were very similar between different receptors (Colonna and Samaridis, 1995; D’Andrea et al., 1995; Wagtmann et al., 1995). The main differences between activating and inhibitory receptors were found in their cytoplasmic tails. While the inhibitory receptors had a long cytoplasmic tail with two ITIMs, allowing inhibitory signaling (Burshtyn et al., 1996; Olcese et al., 1996), the activating ones had a short cytoplasmic tail and a positively charged residue in their transmembrane domain, allowing association with the ITAM-bearing, signaling adapter DAP12 (Olcese et al., 1997; Lanier et al., 1998). As scientists generally would rather share toothbrushes than nomenclatures, for a while nomenclatures from different laboratories co-existed. However, since the receptors from different loci had remarkably high sequence similarity, in some cases over 97%, and clearly belonged to the same receptor family, it made sense to use a unified nomenclature that reflected the receptors’ structures (Long et al., 1996). The receptors were named KIR. KIR2D (50, 58 kDa) and KIR3D (70, 140 kDa), refer to receptors with two or three IgSF domains, respectively. Furthermore, L stands for receptors having long and S for those having short cytoplasmic tails, consistent with the presence or absence of ITIM motifs, respectively. Each KIR subfamily is designated by an individual number, for example KIR2DS1 (Uhrberg et al., 1997; Valiante et al., 1997). The different KIR loci can be found, together with discontinued names, on the EBI-website: http://www.ebi.ac.uk/ipd/kir/genes.html (Robinson et al., 2010).

Molecular cloning of the KIR paved the way for more detailed genetic analyses. In the first instance, novel KIR were cloned from cDNA libraries by homology. In this way KIR2DL4 (Selvakumar et al., 1996), a receptor for HLA-G (Rajagopalan and Long, 1999; Rajagopalan et al., 2005), was identified. The KIR locus, located on chromosome 19q13.4, turned out to be densely packed with KIR genes, oriented in a head-to-tail fashion (Martin et al., 2000; Wilson et al., 2000). While some KIR haplotypes contained few KIR genes, others had many. These efforts also revealed the existence of additional KIR genes KIR2DL5A, KIR2DL5B, KIR2DS5, KIR3DL3 (Vilches et al., 2000; Gomez-Lozano et al., 2002), as well as several pseudogenes (KIR2DP1, KIR3DP1, KIR1D). Common to virtually all haplotypes is the presence of KIR3DL3 at the centromeric end of the locus, KIR2DL4 roughly in the center, and KIR3DL2 at the telomeric end. It also quickly became clear that individual KIR genes display extensive and functional polymorphism (O’Connor et al., 2007).
The total number of functional KIR genes is 15, and well over 50 alleles for individual genes have been described (http://www.ebi.ac.uk/ipd/kir/alleles.html).

All this sequence information allowed the design of primer sets to rapidly determine the presence or absence of specific KIR genes (or alleles) in individuals (Uhrberg et al., 1997), which in turn allowed genetic association studies. The first report of this kind showed that the presence of KIR2DS2 was associated with vasculitis in rheumatoid arthritis patients (Yen et al., 2001; Majorczyk et al., 2007). Subsequent studies indicated a role for KIR in psoriatic arthritis (Martin et al., 2002b; Nelson et al., 2004; Williams et al., 2005), type I diabetes (van der Slik et al., 2004), success (Hiby et al., 2004, 2010).

Natal KIR and fetal HLA-C appeared to influence reproductive outcomes as well as homodimers of HLA-B27 heavy chains. These binding profiles are supported in some cases by structural studies (Boyington et al., 2000; Fan et al., 2001; Campbell and Purdy, 2011; Vivian et al., 2011). Of the six activating KIR, only KIR2DS1 has a clearly defined specificity: C2 (Stewart et al., 2005). In this topic, leading experts discuss the state of the art in ligand identity for several KIR, in an effort to shed light on the contribution of KIR-ligand interactions to disease (Cisneros et al., 2012; Korner and Altfeld, 2012; Moesta and Parham, 2012; Rajagopalan and Long, 2012; Shaw and Kollnerber, 2012).

Even though these studies demonstrated an important role for KIR and KIR-HLA interactions in various diseases, the underlying mechanisms are only beginning to be understood (Anfossi et al., 2006; Alter et al., 2007, 2009; Ahlenstiel et al., 2008; Hiby et al., 2010; O’Connor et al., 2011; Tarek et al., 2012). A critical gap in our knowledge is the fact that ligands for many activating, and some inhibitory, KIR are unknown. Of the eight inhibitory KIR, five have well-characterized HLA specificities. Generally, KIR2DL1, KIR2DL2, KIR2DL3 together cover all HLA-C alleles, KIR3DL1 binds a subset of HLA-B alleles, and KIR3DL2 binds HLA-A3/A11 loaded with specific peptides as well as homodimers of HLA-B27 heavy chains. These binding profiles are supported in some cases by structural studies (Boyington et al., 2000; Fan et al., 2001; Campbell and Purdy, 2011; Vivian et al., 2011). Of the six activating KIR, only KIR2DS1 has a clearly defined specificity: C2 (Stewart et al., 2005). In this topic, leading experts discuss the state of the art in ligand identity for several KIR, in an effort to shed light on the contribution of KIR-ligand interactions to disease (Cisneros et al., 2012; Korner and Altfeld, 2012; Moesta and Parham, 2012; Rajagopalan and Long, 2012; Shaw and Kollnerber, 2012).

**REFERENCES**

Ahlenstiel, G., Martin, M. P., Gao, X., Carrington, M., and Rehermann, B. (2008). Distinct KIR/HLA compound genotypes affect the kinetics of human antiviral natural killer cell responses. *J. Clin. Invest.* 118, 1017–1026.

Alter, G., Martin, M. P., Teigen, N., Carr, W. H., Suscovich, T. J., Schneidewind, A., et al. (2007). Differential natural killer cell-mediated inhibition of HIV-1 replication based on distinct KIR/HLA subtypes. *J. Exp. Med.* 204, 3027–3036.

Alter, G., Rihn, S., Walter, K., Nolting, A., Martin, M., Rosenberg, E. S., et al. (2009). HLA class I subtype-dependent expansion of KIR3DS1+ and KIR3DL1+ NK cells during acute human immunodeficiency virus type 1 infection. *J. Virol.* 83, 6798–6805.

Anfossi, N., Andre, P., Guia, S., Falk, C. S., Roertynck, S., Stewart, C. A., et al. (2006). Human NK cell education by inhibitory receptors for MHC class I. *Immunology* 25, 331–342.

Boyington, J. C., Motyka, S. A., Schuck, P., Brooks, A. G., and Sun, P. D. (2000). Crystal structure of an NK cell immunoglobulin-like receptor in complex with its class I MHC ligand. *Nature* 405, 537–543.

Burshyun, D. N., Scharenberg, A. M., Wagtmann, N., Rajagopalan, S., Bermada, K., Yi, T., et al. (1996). Recruitment of tyrosine phosphatase HCP by the killer cell inhibitor receptor. *Immunity* 4, 77–85.

Campbell, K. S., and Purdy, A. K. (2011). Structure/function of human killer cell immunoglobulin-like receptors: lessons from polymorphisms, evolution, crystal structures and mutations. *Immunology* 132, 315–325.

Cella, M., Longo, A., Ferrara, G. B., Strominger, J. L., and Colonna, M. (1994). NK3-specific natural killer cells are selectively inhibited by Bw4-positive HLA alleles with isolucine 80. *J. Exp. Med.* 180, 1235–1242.

Ciccone, E., Pende, D., Viale, O., Thian, A., di Donato, C., Oreno, A. M., et al. (1992). Involvement of HLA class I alleles in natural killer (NK) cell-specific functions: expression of HLA-Cw3 confers selective protection from lysis by alloreactive NK clones displaying a defined specificity (specificity 2). *J. Exp. Med.* 176, 963–971.

Cisneros, E., Moraru, M., Gomez-Lozano, N., Lopez-Botet, M., and Vilches, C. (2012). KIR2DL5: an orphan inhibitory receptor displaying complex patterns of polymorphism and expression. *Front. Immunol.* 3:289. doi: 10.3389/fimmu.2012.00289.

Colonna, M., Borsellino, G., Falco, M., Ferrara, G. B., and Strominger, J. L. (1993). HLA-C is the inhibitory ligand that determines dominant resistance to lysis by NK1- and NK2-specific natural killer cells. *Proc. Natl. Acad. Sci. U.S.A.* 90, 12000–12004.

Colonna, M., and Samaridis, J. (1993). Cloning of immunoglobulin-superfamily members associated with HLA-C and HLA-B recognition by human natural killer cells. *Science* 268, 405–408.

D’Andrea, A., Chang, C., Franz-Bacon, K., McClanahan, T., Phillips, J. H., and Lanier, L. L. (1995). Molecular cloning of NK1B. A natural killer cell receptor for HLA-B allotypes. *J. Immunol.* 155, 2306–2310.

Dring, M. M., Morrison, M. H., McSharry, B. P., Guinan, K. J., Hagan, R., O’Farrelly, C., et al. (2011). Innate immune genes synergize to predict increased risk of chronic disease in hepatitis C virus infection. *Proc. Natl. Acad. Sci. U.S.A.* 108, 5736–5741.

Fan, Q. R., Long, E. O., and Wiley, D. C. (2001). Crystal structure of the human natural killer cell inhibitory receptor KIR2DL1–HLA-Cw4 complex. *Nat. Immunol.* 2, 452–460.

Gomez-Lozano, N., Gardiner, C. M., Parham, P., and Vilches, C. (2002). Some human KIR haplotypes contain two KIR2DL5 genes: KIR2DL5A and KIR2DL5B. *Immunogenetics* 54, 314–319.

Gumperz, J. E., Litwin, V., Phillips, J. H., Lanier, L. L., and Parham, P. (1995). The Bw4 public epitope of HLA-B molecules confers reactivity with natural killer cell clones that express NKBI, a putative HLA receptor. *J. Exp. Med.* 181, 1133–1144.

Hiby, S. E., Ffps, R., Sharkey, A. M., Farrell, L. E., Gardner, L., Mulder, A., et al. (2010). Maternal activating KIRs protect against human reproductive failure mediated by fetal HLA-C. *J. Clin. Invest.* 120, 4102–4110.

Hiby, S. E., Walker, J. J., O’Shaughnessy, K. M., Redman, C. W., Carrington, M., Trowsdale, J., et al. (2004). Combinations of maternal KIR and fetal HLA-C genes influence the risk of preeclampsia and reproductive success. *J. Exp. Med.* 200, 957–965.

Khakoo, S. I., Thio, C. L., Martin, M. P., Brooks, C. R., Gao, X., Astemborski, J., et al. (2004). HLA and NK cell inhibitory receptor genes in resolving hepatitis C virus infection. *Science* 305, 872–874.

Knapp, S., Warshaw, U., Hegazy, D., Brackenbury, L., Guha, I. N., Fowell, A., et al. (2010). Consistent beneficial effects of killer cell immunoglobulin-like receptor
Long, E. O., Colonna, M., and Lanier, L. L. (1996). Inhibitory MHC class I receptors on NK and T cells: a standard nomenclature. 

Moesta, A. K., and Parham, P. (2012). Diversity function among NK cell receptors for the C1 epitope of HLA-C: KIR2DS1, KIR2DL2, and KIR2DL3. Front. Immunol. 3:336. doi: 10.3389/fimmu.2012.00336

Moretta, A., Sivori, S., Vitale, M., Pende, D., Morelli, L., Augugliaro, R., et al. (1995). Existence of both inhibitory (p58) and activitory (p50) receptors for HLA-C molecules in human natural killer cells. J. Exp. Med. 182, 875–884.

Moretta, A., Vitale, M., Bottino, C., Orreno, A. M., Morelli, L., Augugliaro, R., et al. (1993). P58 molecules as putative receptors for major histocompatibility complex (MHC) class I molecules in human natural killer (NK) cells. Anti-p58 antibodies reconstitute lysis of MHC class I-protected cells in NK clones displaying different specificities. J. Exp. Med. 178, 597–604.

Nelson, G. W., Martin, G. E., Gladman, D., Wade, J., Trovisolo, J., and Carrington, M. (2004). Cutting edge: heterozygoyt argument in autoimmune disease: hierarchy of protection/susceptibility conferred by HLA and killer Ig-like receptor combinations in psoriatic arthritis. J. Immunol. 173, 4273–4276.

O’Connor, G. M., Guinan, K. J., Cunningham, R. T., Middleton, D., Parham, P., and Gardiner, C. M. (2007). Functional polymorphism of the KIR3DL1/S1 receptor on human NK cells. J. Immunol. 178, 235–241.

O’Connor, G. M., Yamada, E., Rampersaud, A., Thomas, R., Carrington, M., and McVicar, D. W. (2011). Analysis of binding of KIRDS1*014 to HLA suggests distinct evolutionary history of KIRDS1. J. Immunol. 187, 2162–2171.

Olcese, L., Cambiaggi, A., Semenzato, G., Bottino, C., Moretta, A., and Vivier, E. (1997). Human killer cell activatory receptors for MHC class I molecules are included in a multimeric complex expressed by natural killer cells. J. Immunol. 158, 5083–5086.

Olcese, L., Lang, P., Vely, F., Cambiaggi, A., Marquet, D., Bleyr, M., et al. (1996). Human and mouse killer-cell inhibitory receptors recruit FcTP1C and FcPT1D protein tyrosine phosphatases. J. Immunol. 156, 4531–4534.

Pende, D., Biassoni, R., Cantoni, C., Verdiani, S., Falco, M., Di Donato, C., et al. (1996). The natural killer cell receptor specific for HLA-A allotypes: a novel member of the p58/p70 family of inhibitory receptors that is characterized by three immunoglobulin-like domains and is expressed as a 140-kD disulphide-linked dimer. J. Exp. Med. 184, 505–518.

Quillet, A., Presse, F., Marchiol-Fournirault, C., Harel-Bellan, A., Benhumn, M., Ploegh, H., et al. (1988). Increased resistance to non-MHC-restricted cytototoxicity related to HLA A, B expression. Direct demonstration using beta 2-microglobulin-transfected Daudi cells. J. Immunol. 141, 17–20.

Rajagopalan, S., Bryceson, Y. T., Kuppusamy, S. P., Geraghty, D. E., Meir, A. V., Joosten, I., et al. (2002). Activation of KIR2D1/L2/L3 by an endocytosed receptor for soluble HLA-G. PLoS Biol. 4:e9. doi: 10.1371/journal.pbio.0040009

Rajagopalan, S., and Long, E. O. (1999). A human histocompatibility leukocyte antigen (HLA)-G-specific receptor expressed on all natural killer cells. J. Exp. Med. 189, 1093–1100.

Rajagopalan, S., and Long, E. O. (2012). KIR2DL4 (CD158d): an activation receptor for HLA-G. Front. Immunol. 3:258. doi: 10.3389/fimmu.2012.00258

Robinson, J., Mistry, K., McWilliam, H., Lopez, R., and Marsh, S. G. (2010). IFP~the immuno polymorph-ism database. Nucleic Acids Res. 38, D686–D696.

Selvakumar, A., Steffens, U., and Dupont, B. (1996). NK cell receptor gene of the KIR family with two Ig domains but highest homology to KIR receptors with three Ig domains. Tissue Antigens 48, 285–294.

Shaw, J., and Kollnberger, S. (2012). New perspectives on the ligands and function of the killer cell immunoglobulin-like receptor KIR3DL2 in health and disease. Front. Immunol. 3:339. doi: 10.3389/fimmu.2012.00339

Shimizu, Y., and DeMars, R. (1989). Demonstration by class I gene transfer that reduced susceptibility of human cells to natural killer cell-mediated lysis is inversely correlated with HLA class I antigen expression. Eur. J. Immunol. 19, 447–451.

Stewart, C. A., Laugier-Anfossi, F., Vely, F., Saulquin, X., Riedmuller, J., Tisserant, A., et al. (2003). Recognition of peptide-MHC class I complexes by activating killer immunoglobulin-like receptors. Proc. Natl. Acad. Sci. U.S.A. 102, 13224–13229.

Storkus, W. J., Alexander, J., Payne, J. A., Dawson, J. R., and Cresswell, P. (1989). Reversal of natural killing susceptibility in target cells expressing transfected class I HLA genes. Proc. Natl. Acad. Sci. U.S.A. 86, 2361–2364.

Tarek, N., Le Luduec, J. B., Gallagher, M. M., Zheng, J., Venstrom, J. M., Chamberlain, E., et al. (2012). Unlicensed NK cells target neuroblastoma following anti-GD2 anti-body treatment. J. Clin. Invest. 122, 3260–3270.

Uhbrig, M., Valiente, N. M., Shum, B. P., Shilling, H. G., Lienert-Weidenbach, K., Corllis, B., et al. (1997). Human diversity in killer cell inhibitory receptor genes. Immunity 7, 753–763.

Valiente, N. M., Uhbrig, H. G., Lienert-Weidenbach, K., Arnett, K. L., D’Andrea, A., et al. (1997). Functionally and structurally distinct NK cell receptor repertoires in the peripheral blood of two human donors. Immunity 7, 739–751.

van der Sluk, A. R., Alizadeh, B. Z., Koelman, B. P., Roep, B. O., and Giphart, M. J. (2007). Modelling KIR-HLA genotype disparities in type 1 diabetes. Tissue Antigens 69(Suppl. 1), 101–105.

van der Sluk, A. R., Koelman, B. P., Verduijn, W., Bruiining, G. J., Roep, B. O., and Giphart, M. J. (2003). KIR in type 1 diabetes: disparate distribution of activating and inhibitory natural killer cell receptors in patients versus HLA-matched control subjects. Diabetes 52, 2639–2642.

Vilches, C., Rajalingam, R., Uhbrig, M., Gardiner, C. M., Young, N. T., and Parham, P. (2000). KIR2DL5, a novel killer-cell receptor with a D0-D2 configuration of Ig-like domains. J. Immunol. 164, 5797–5804.

Vivian, J. P., Duncan, R. C., Berry, R., O’Connor, G. M., Reid, H. H., Beddoo, T., et al. (2011). Killer cell immunoglobulin-like receptor 3DL1-mediated recognition of human leukocyte antigen B. Nature 479, 401–405.

Wagtmann, N., Biassoni, R., Cantoni, C., Verdiani, S., Malnati, M. S., Vitale, M., et al. (1995). Molecular clones of the p58 NK cell receptor reveal immunoglobulin-related...
molecules with diversity in both the extra- and intracellular domains. *Immunity* 2, 439–449.

Williams, F., Meenagh, A., Sleator, C., Cook, D., Fernandez-Vina, M., Bowcock, A. M., et al. (2005). Activating killer cell immunoglobulin-like receptor gene KIR2DS1 is associated with psoriatic arthritis. *Hum. Immunol.* 66, 836–841.

Wilson, M. J., Torkar, M., Haude, A., Milne, S., Jones, T., Sheer, D., et al. (2000). Plasticity in the organization and sequences of human KIR/ILT gene families. *Proc. Natl. Acad. Sci. U.S.A.* 97, 4778–4783.

Yen, J. H., Moore, B. E., Nakajima, T., Scholl, D., Schaid, D. J., Weyand, C. M., et al. (2001). Major histocompatibility complex class I-recognizing receptors are disease risk genes in rheumatoid arthritis. *J. Exp. Med.* 193, 1159–1167.