**TABLE 372e-10 ASSOCIATION OF KIRs WITH DISEASE**

| Disease | KIR Association | Observation |
|---|---|---|
| Psoriatic arthritis | KIR2DS1/KIR2DS2; HLA-Cw group homozygosity | Susceptibility |
| Spondylarthritides | Increased KIR3DL2 expression | May contribute to disease pathology |
| | Interaction HLA-B27 homodimers with KIR3DL1/KIR3DL2; independent of peptide | May contribute to disease pathogenesis |
| Ankylosing spondylitis | KIR3DL1/3DS1; HLA-B27 genotypes | Susceptibility |
| Rheumatoid vasculitis | KIR2DS2; HLA-Cw*03 | Susceptibility |
| | Increased KIR2L2/2DS2 in patients with extraarticular manifestations | Clinical manifestations may have different genetic backgrounds with respect to KIR genotype |
| Rheumatoid arthritis | Decreased KIR2DS1/3DS1 in patients without bone erosions | Susceptibility |
| | KIR2DS4; HLA-Cw4 | Susceptibility |
| Scleroderma | KIR2DS2+/KIR2DL2– | Susceptibility |
| Behçet's disease | Altered KIR3DL1 expression | Associated with severe eye disease |
| Psoriasis vulgaris | 2DS1; HLA-Cw*06 | Susceptibility |
| | 2DS1; 2DL5; haplotype B | Susceptibility |
| IDDM | KIR2DS2; HLA-C1 | Susceptibility |
| Type 1 diabetes | KIR2DS2; HLA-C1 and no HLA-C2, no HLA-Bw4 | Increased disease progression |
| Preeclampsia | KIR2DL1 with fewer KIR2DS (mother); HLA-C2 (fetus) | Increased disease progression |
| AIDS | KIR3DS1; HLA-Bw4Ile80 | Decreased disease progression |
| | KIR3DS1 homozygous; no HLA-Bw4Ile[80] | Increased disease progression |
| HCV infection | KIR2DL3 homozygous; HLA-C1 homozygous | Decreased disease progression |
| Cervical neoplasia (HPV induced) | KIR3DS1; HLA-C1 homozygous and no HLA-Bw4 | Increased disease progression |
| Malignant melanoma | KIR2DL2 and/or KIR2DL3; HLA-C1 | Increased disease progression |

***Abbreviations:*** HCV, hepatitis C virus; HLA, human leukocyte antigen; HPV, human papillomavirus; IDDM, insulin-dependent diabetes mellitus; KIR, killer cell immunoglobulin-like receptor.

***Source:*** Adapted from R Diaz-Pena et al: Adv Exp Med Biol 649:286, 2009.

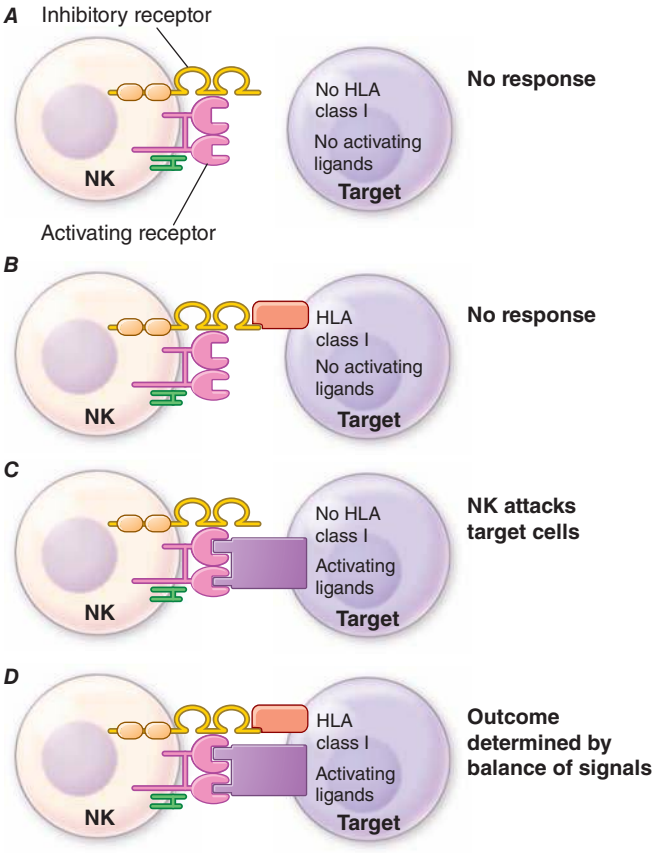


**FIGURE 372e-4 Encounters between NK cells: potential targets and possible outcomes.** The amount of activating and inhibitory receptors on the NK cells and the amount of ligands on the target cell, as well as the qualitative differences in the signals transduced, determine the extent of the NK response. ***A.*** When target cells have no HLA class I or activating ligands, NK cells cannot kill target cells. ***B.*** When target cells bear self-HLA, NK cells cannot kill targets. ***C.*** When target cells are pathogen infected and have downregulated HLA and express activating ligands, NK cells kill target cells. ***D.*** When NK cells encounter targets with both self-HLA and activating receptors, then the level of target killing is determined by the balance of inhibitory and activating signals to the NK cell. HLA, human leukocyte antigen; NK, natural killer. *(Adapted from L Lanier: Annu Rev Immunol 23:225, 2005; reproduced with permission from Annual Reviews Inc. Copyright 2011 by Annual Reviews Inc.)*

In general, cytokines exert their effects by influencing gene activation that results in cellular activation, growth, differentiation, functional cell-surface molecule expression, and cellular effector function. In this regard, cytokines can have dramatic effects on the regulation of immune responses and the pathogenesis of a variety of diseases. Indeed, T cells have been categorized on the basis of the pattern of cytokines that they secrete, which results in either humoral immune response ($T_H2$) or cell-mediated immune response ($T_H1$). A third type of T helper cell is the $T_H17$ cell that contributes to host defense against extracellular bacteria and fungi, particularly at mucosal sites (Fig. 372e-2).

*Cytokine receptors* can be grouped into five general families based on similarities in their extracellular amino acid sequences and conserved structural domains. The *immunoglobulin (Ig) superfamily* represents a large number of cell-surface and secreted proteins. The IL-1 receptors (type 1, type 2) are examples of cytokine receptors with extracellular Ig domains.

The hallmark of the *hematopoietic growth factor (type 1) receptor* family is that the extracellular regions of each receptor contain two conserved motifs. One motif, located at the N terminus, is rich in cysteine residues. The other motif is located at the C terminus proximal to the transmembrane region and comprises five amino acid residues,

**TABLE 372e-11 EXAMPLES OF MEDIATORS RELEASED FROM IMMUNE CELLS AND BASOPHILS**

| Mediator | Actions |
|---|---|
| Histamine | Smooth-muscle contraction, increased vascular permeability |
| Slow reacting substance of anaphylaxis (SRSA) (leukotriene $C_4$, $D_4$, $E_4$) | Smooth-muscle contraction |
| Eosinophil chemotactic factor of anaphylaxis (ECF-A) | Chemotactic attraction of eosinophils |
| Platelet-activating factor | Activates platelets to secrete serotonin and other mediators: smooth-muscle contraction; induces vascular permeability |
| Neutrophil chemotactic factor (NCF) | Chemotactic attraction of neutrophils |
| Leukotactic activity (leukotriene $B_4$) | Chemotactic attraction of neutrophils |
| Heparin | Anticoagulant |
| Basophil kallikrein of anaphylaxis (BK-A) | Cleaves kininogen to form bradykinin |