

Recognition of Major Histocompatibility Complex Class I Antigens by Natural Killer Cells

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Natural Killer (NK) cells are cytotoxic lymphocytes that, in the absence of prior stimulation, lyse a variety of target cells, including tumor cells, virus-, or intracellular bacteria-infected cells, and, in some cases, normal cells (1). Thus, NK cells represent a first line of defense to infections, tumor growth, or other pathogenic alterations of tissue homeostasis. Unlike T or B lymphocytes, NK cells do not express molecularly rearranged receptors and, in particular, neither rearrange nor express on their surface any of the four genes encoding the T cell receptor (TCR). Activation of NK cells results not only in cytotoxicity but also in rapid secretion of cytokines, particularly interferon- γ (IFN- γ), granulocyte/macrophage colony-stimulatory factor (GM-CSF), and tumor necrosis factor (TNF) (1). The ability of NK cells to recognize and destroy target cells has been considered nonspecific and possibly mediated by multiple adhesionlike receptors recognizing an altered pattern of expression of surface molecules on pathological target cells.

The best characterized receptor able to activate NK cell cytotoxicity and cytokine production is the receptor for Fc of IgG type IIIA (Fc γ RIIIA or CD16). CD16 is associated with dimers of the ζ chain of CD3/TCR or of the γ chain of Fc ϵ RI, and mediates signal transduction with similar mechanisms as those observed via the TCR/CD3 complex (1). Through CD16, NK cells recognize IgG antibody-coated target cells and mediate antibody-dependent cytotoxicity (ADCC). However, CD16 does not appear to be involved in the induction of cytotoxicity in the absence of antibodies (1). Other cytotoxicity-triggering receptors have been described on NK cells, but their ligands on target cells and their role in cytotoxicity have not been elucidated.

Although the activity of NK cells has been considered nonspecific and, unlike CD8⁺ cytotoxic T lymphocytes (CTL), does not require the expression of major histocompatibility complex (MHC) antigens on target cells, evidence suggesting specificity in NK cell recognition has been accumulating for many years. Kiessling et al. (2) demonstrated that NK cells were the effector cells responsible for the rejection of parental bone marrow grafts in irradiated F1 mice (hematopoietic hybrid resistance) indicating a genetic specificity in NK cell action. The major locus responsible for this resistance, Hh-1, was mapped to the H-2DL region and studies with H-2D^d transgenic mice strongly suggested that the product of the class I allele D^d is a major determinant governing the genetic specificity of NK cells (3). In rats, NK cells rapidly eliminate in vivo allogeneic lymphocytes as well

as bone marrow cells (allogeneic lymphocyte cytotoxicity, ALC), and alloreactive NK cells were also generated in vitro (4). The genetic elements controlling this alloreactivity are in a class I region (RT1-C) of the rat MHC, but, unlike murine hybrid resistance in which the susceptibility to rejection was always inherited as a recessive trait (and resistance as a dominant one), susceptibility to both rejection and lysis by rat alloreactive NK cells was found to segregate dominantly, although rarely, in some strain combinations (4).

In several experimental systems, the susceptibility of target cells to NK cell-mediated lysis is inversely proportional to their expression of class I MHC antigens (5). One of the hypotheses to explain the ability of NK cells to recognize class I low target cells is the "missing self hypothesis" that postulates that one function of NK cells is to recognize and eliminate cells that do not express MHC class I molecules (5). This hypothesis needs to be modified, however, to accommodate findings suggesting that NK cells may be affected not only by the presence or absence of class I molecules, but also by the nature of MHC-bound peptide fitting, either because, similarly to T cells, they might directly sense the combination of peptide and MHC, or because they recognize changes in molecular conformations of the MHC molecules induced by the peptide binding (6). The peptide-binding class I $\alpha 1/\alpha 2$ domains have been shown to be necessary for NK cell recognition, and single amino acid substitutions in the peptide-binding groove of the class I molecules alter the ability of the molecules to protect target cells from NK cells (6). It has also been suggested that alteration of endogenous peptides by external peptide loading or by virus infection abrogates class I-mediated resistance of target cells and makes them susceptible to NK cell cytotoxicity (7).

Two hypotheses have been proposed to explain the mechanism of class I recognition by NK cells: (a) the effector inhibition hypothesis postulating that the presence of class I (or particular conformations of class I) on the target cells delivers a negative signal to the NK cells, which prevents the activation of cytotoxicity; or (b) the target interference hypothesis postulating that class I antigens or their peptides sterically mask recognition of an NK target structure on the target cells (5). Although many of the experimental data can be explained on the basis of either hypothesis, or through intermediate interpretations, several recent lines of evidence, discussed below, appear to favor the effector inhibition hypothesis.

The first receptor identified on murine NK cells that is probably involved in recognition of class I MHC is the Ly-49

antigen. Ly-49 is expressed in 15–20% of NK cells in C57BL/6 mice (8). Both the Ly-49⁺ and Ly-49⁻ subsets of NK cells have similar cytotoxic activity against NK-sensitive cell lines, but the Ly-49⁺ subset, unlike the Ly-49⁻ one, is unable to lyse target cells expressing H-2D^d or H-2D^k (8). The following observations suggest that interaction of Ly-49 with class I MHC D^d or D^k delivers a negative signal to the NK cells: (a) anti-Ly-49 or anti-class I $\alpha 1/\alpha 2$ domain antibodies restore lysis of H-2D^d or D^k target cells by Ly-49⁺ NK cells (8); (b) Ly-49⁺ cells bind to purified D^d or D^k molecules and this binding is prevented by anti-Ly-49 antibodies (9); and (c) the Ly-49⁺ NK cells binding to a H-2D^d or D^k target cell are globally inactivated and can not mediate ADCC against the same target cells (8). Ly-49 is a homodimeric type II integral membrane protein with COOH-terminal extracellular domains homologous to members of the C-type lectin superfamily. In addition to the Ly-49 gene, there are several genes highly homologous to Ly-49 (10) that may encode receptors recognizing class I antigens, possibly with a different specificity, and account for the class I-mediated protection of target cells against the majority of NK cells which are Ly-49⁻ (10). The Ly-49 multigene family is encoded by a cluster of genes, the NK gene complex, which are in the distal portion of mouse chromosome 6, associated with the genes encoding the NK1.1, NKR-P1, and CD69 antigens, which are all disulfide-linked dimers of type II integral membrane proteins with type C lectin homology (10). The human CD69 antigen is encoded by a gene in the chromosome 12p13 near the NKG2 gene cluster, encoding other still uncharacterized type II integral membrane molecules preferentially expressed in NK cells (10). Although these lectinlike molecules have a specificity for carbohydrates, they might also bind to polypeptide or conformational sequences, as shown by the fact that CD23, one of the members of this family, binds to IgE independently of carbohydrates, whereas it binds to the carbohydrate structure of CD21 (11). It is noteworthy that many members of this receptor family, e.g., NK1-1, NKR-P1, and CD69, are triggering molecules on NK cells, inducing cytotoxicity and cytokine production (10). Thus, structurally similar molecules are responsible for negative or positive signaling upon ligand interactions. Although the ligands for NK1.1, NKR-P1, and CD69 are not known, it can not be excluded that they also recognize class I MHC and that interaction of different NK receptors with class I or of the same receptor with different conformations of class I might deliver either blocking or triggering signals. The data from alloreactive rat NK cells (4), indicating that in certain strain combinations the susceptibility to lysis by NK cells cosegregates with MHC class I in a dominant way, indeed suggest the possibility that at least in some instances NK cell cytotoxicity may be activated by direct recognition of class I MHC.

Because the NK receptors recognizing class I appear to be clonally distributed or at least clonally heterogeneous, the studies using polyclonal NK cell preparations are only of limited value for the analysis of NK cell specificity. Moretta et al. (12) have extensively analyzed the ability of NK cell clones to lyse allogeneic normal cells (PHA blasts). A small proportion of CD3⁻ human NK clones was found to be

cytotoxic for PHA blasts from certain allogeneic donors. Five different specificity groups were defined, and for most of them the character resistance to lysis dominantly cosegregated within families with the HLA complex, whereas susceptibility to lysis segregated recessively (12). These findings, which are reminiscent of the genetic control of hybrid resistance in mice, suggested that single HLA class I antigens are responsible for conferring resistance to the NK cells in a clone specific fashion. Moreover, experiments of transfection of class I genes in mouse target cells or in class I-deficient human cells demonstrated that the expression of HLA-Cw3 or Cw4 confers target cell resistance to group 2 (specificity NK2) or to group 1 NK clones (specificity NK1), respectively (12). Colonna et al. (13) demonstrated that NK1-specific NK cell clones are inhibited by the presence on the target cells of HLA-C alleles encoding Asn-77-Lys-80 (including HLA-Cw4, -Cw5, and -Cw6), whereas NK2-specific NK cell clones are inhibited by HLA-C alleles encoding Ser-77-Asn-80 (including HLA-Cw1, -Cw3, -Cw7, and -Cw13). Thus, alloreactive NK clones, unlike T cells, do not recognize fine differences among highly polymorphic HLA alleles, but rather supertypic (public) differences shared by several alleles. The fact that NK-recognized haplotypes correspond to ancestral haplotypes (14) may indicate that the class I recognition mechanisms of NK cells precedes evolutionarily the more finely tuned recognition mechanism of T cells. The analogy with other class I molecules suggests that amino acid positions 77 and 80 in HLA-C are in the peptide-binding cleft, implicating again MHC-bound peptides in NK cell recognition.

Putative NK cell receptors for HLA-C are identified by two monoclonal antibodies, GL183 and EB6, that identify four subsets of NK cells and react with similar but distinct molecules of 55–58 kD on the NK cell surface, most probably forming noncovalently linked hetero- or homodimers (15). The existence of other members of this family, defined p58, possibly able to form dimers with GL183 or EB6, is suggested by immunoprecipitation experiments with antibodies recognizing common determinants of the p58 family. Several lines of evidence suggest that the p58 molecules might represent receptors for class I HLA-C on NK cells (15). The specificity of alloreactive NK clones is closely correlated with their p58 phenotype. In particular, virtually all group 1 specificity clones (unable to lyse Cw4⁺ target cells) are EB6⁺ GL183⁻, whereas the group 2 clones (unable to lyse Cw3⁺ target cells) are EB6⁺ GL183⁺. Similar to Ly-49, both the EB6 and GL183 antibodies restore lysis of Cw3⁺ cells by group 2 NK clones and the EB6 antibody restores lysis of Cw4⁺ cells by group 1 NK clones (15). Furthermore, when the IgG anti-p58 antibodies are added in a lytic assay using p58⁺ NK clones and FcR⁺ murine P815 target cells, inhibition of lysis is observed (15). The interpretation of these results is that the anti-p58 antibodies in soluble form block the interaction of p58 with HLA-C and prevent delivery of a negative signal, whereas, when cross-linked by the FcR on the target cells, they inhibit lysis by delivering a negative signal, analogous to that delivered upon interaction of p58 with the HLA-C ligand. The heterodimer EB6/GL183 would be a receptor for a group of HLA-C molecules including Cw3,

whereas a dimer of EB6 with another member of the p58 family (or possibly a homodimer) would be a receptor for a group of HLA-C molecules including Cw4 (12). Other p58 molecules could be specific for other class I molecules. Unlike the Ly-49 molecules, direct binding of p58 to HLA class I molecules to fully support this interpretation remains to be demonstrated.

It is surprising that molecules different in structure from Ly-49 have quite similar functions. Unlike Ly-49, the p58 molecules do not form covalently linked homodimers and they are linked to dimers of either the ζ chain of CD3 or the γ chain of Fc ϵ RI and are associated with the protein tyrosine kinase p56^{lck}. Although cross-linking of p58 induced a Ca²⁺ flux, in contrast to CD3/TCR or CD16 triggering, phosphorylation of the associated CD3 ζ chain was not observed (12 and Moretta, A., personal communication). The putative negative signal delivered by p58 is reminiscent of that observed with Ly-49 in that not only is the lysis of the target cells carrying the appropriate class I molecule prevented, but a global inactivation of the NK cells is observed as measured by an inability to mediate ADCC or antibody-redirected lysis against the same target cells (15). However, this inactivation is directional, because susceptible target cells are lysed in the presence of cold target cells carrying the protective class I molecules (15).

Analysis of alloreactive NK cells for their ability to lyse PHA blasts identified only a limited number of clones, whereas the large majority of clones appeared not to have allospecificity. However, by analyzing the ability of individual HLA-A, -B, or -C molecules transfected into class I negative target cells to protect them from lysis mediated by unselected human NK clones, Litwin et al. (16) showed that the large majority of clones recognize multiple HLA-A, -B, or -C alleles, of both autologous and allogeneic origin, and that simple patterns of recognition were difficult to identify. These results, which are reminiscent of the earlier results with polyclonal NK cells, suggest that the receptor for class I antigens on NK cells have broad specificity and are heterogeneously distributed at the clonal level, so that each clone may express more than one receptor type in different combinations. Because PHA blasts express all six HLA-A, -B, and -C alleles and each one of them might react with class I receptors with broad specificity on NK cells, clones able to lyse allogeneic PHA blasts are rare and characterized by the expression of only one or a very limited number of receptors for class I. Thus, these alloreactive NK cell clones, unlike the majority of NK clones with possible multiple receptors, display simple patterns of target specificity, including the reactivity of two out of five specificity groups specifically with certain HLA-C molecules (12).

The study of NK clones lytic for allogeneic PHA blasts represented a useful tool for defining the characteristics of class I protection of target cells at the clonal level and for identifying at least some of the NK cell receptors for HLA-C molecules (12). It remained, however, to identify the receptors for HLA-A and -B and to determine their contribution to the specificity of NK cells both at the clonal and polyclonal level. Two papers in this issue of *The Journal of Experimental*

Medicine, by Moretta et al. (17) and by Litwin et al. (18) identify the putative receptors on NK cells for two distinct groups of HLA-B alleles; surprisingly, these two receptors are not only molecularly different from the p58 receptor for HLA-C, but are also quite different among themselves. Moretta et al. (17) identify Kp43 (CD94), a homodimeric molecule belonging to the family of type II lectinlike transmembrane proteins, as the receptor on NK clones responsible for target cell protection induced by HLA-B7, -B8, and -B14. Although Kp43 is expressed on all NK clones at least at low density and was previously characterized as a marker of both resting and activated NK cells, it is expressed at high density only on those NK clones that are inactivated by the presence of HLA-B7 on target cells (17). Similar to other anticlass I receptor antibodies, the anti-Kp43 antibody in soluble form restores lysis of HLA-B7⁺ target cells by the Kp43^{high} NK clones, whereas when IgG antibodies are cross-linked on FcR⁺ target cells, the spontaneous as well as the antibody-dependent cytotoxicity of Kp43^{high} NK clones is blocked, suggesting that the Kp43 molecule in this condition delivers a negative signal (17). Litwin et al. (18) characterize a single chain glycoprotein of 70 kD (NKB1, recognized by antibody DX9) that appears to be the NK receptor for the HLA-B*5101, -B*5801, and -B*2705, but not for HLA-B7 or any HLA-A or -C allele tested. The DX9 antibody restored the ability of NKB1⁺ NK clones to lyse target cells expressing the relevant HLA-B antigens, suggesting that NKB1, similarly to Kp43, p58, or Ly-49, recognizes class I molecules and delivers a negative signal preventing lysis (18). It is of interest to note that the alleles recognized by the Kp43 receptor express the supertypic specificity Bw6 whereas those recognized by NKB1 the supertypic specificity Bw4 (17, 18). It is therefore likely that, as in the case for the receptors for HLA-C, the receptor for HLA-B on NK cells also recognizes a public and probably primordial polymorphism on the class I molecules and not the fine polymorphic differences detected by antibodies or T cells.

Although the receptors for every class I molecule on NK cells have not been identified, the present evidence suggests that NK cells, rather than using somatic gene recombination for generating receptor diversity, have used receptors of quite different molecular structure for developing a relatively restricted repertoire of specificity for class I, with similar biological effects upon ligand interaction. This convergent evolution in specificity and function of different receptors involves possibly primitive lectinlike molecules (Ly-49 and Kp43), heterodimers associated with the CD3 ζ homodimers (p58) that are reminiscent of the TCR/CD3 complex, and the still poorly characterized NKB1 70-kD glycoprotein.

Little is known of the mechanism of the putative negative signaling. In most cases, the inhibition of cytotoxicity appears to be global, with inactivation of both spontaneous and antibody-dependent cytotoxicity, but also directional, because lysis of a third party target cell is not affected (8, 15, 17, 18). The negative signal does not prevent NK-target cell adhesion and early signals such as Ca²⁺ flux or formation of inositol phosphates (19). Therefore, the lateral signaling resulting in membrane molecule modification and adhesion is not

prevented, whereas the vertical signaling, leading to granule secretion and cytotoxicity is blocked. These effects appear analogous to those initiated by class I or class II antagonistic peptides that also determine a directional partial inactivation of TCR signaling with abrogation of cytotoxicity or proliferation, but only partial inhibition of early signaling and no effect on binding (20). However, in the case of antagonistic peptides, both the positive and putative negative signaling are primarily mediated by the TCR, whereas in NK cells the inhibitory and the triggering receptors may, but not necessarily, be different molecules. It is also possible that the negative signal may depend on alternative signal transduction pathways interfering with the cytotoxicity triggering pathway: e.g., antibody-induced cross-linking of the CD27 molecule inhibits T cell proliferation and NK cell cytotoxicity presumably by increasing intracellular cAMP levels (21).

NK cells may be selectively expanded or deleted during differentiation to avoid the presence of autoreactive NK cells. NK cell clones are not lytic for autologous normal cells, probably because they carry receptors for at least one autologous class I allele, as indicated by the ability of certain anti-HLA class I antibodies to restore the lysis of autologous normal target cells (22). Therefore, it is likely that NK clones that do not have a receptor for at least one autologous class I allele are eliminated or inactivated during differentiation to prevent the presence of autoreactive NK cells *in vivo*. Cells from β_2 -microglobulin-deficient mice, which do not express complete class I MHC antigens, are particularly sensitive to NK cell-mediated lysis, both *in vitro* and *in vivo*; NK cells from these animals have a strongly reduced lytic activity, although they are not reduced in number or in their ability to produce cytokines, suggesting that NK cells might be subjected to negative selection mechanisms (23). However, because of the broad specificity of the class I receptor and the presence of multiple receptors on NK cells, only a small proportion of NK cells are expected to be autoreactive; these few cells may not represent a significant risk for the organism, because upon interaction with target cells, NK cell cytotoxicity and proliferation are rapidly downregulated (1). The presence of receptors for autologous class I on NK cells would prevent this downregulation maintaining their cytotoxic potential and allowing them to expand in response to appropriate stimuli. The best evidence for negative selection of NK cell clones is that the EB6⁺ GL183⁻ subset, which recognizes Cw4, is almost completely absent from individuals negative for the protective HLA-C alleles and thus susceptible to the lysis mediated by the EB6⁺ GL183⁻ NK cells (15). The interpretation of

these data is not simple, because most of the EB6⁺ GL183⁻ NK cells probably also express other receptors for HLA-A or -B alleles, that should have allowed them to escape deletion. The distribution of Ly-49 is also paradoxical; Ly-49 is present in ~20% of NK cells in C57BL/6 mice, which do not express the protective D^d or D^k alleles, whereas it is absent in H-2^d or H-2^k strains, in which Ly-49 prevents autologous cell lysis (8). Recent studies (24), however, showed that Ly-49 is expressed on NK cells from H-2^d or H-2^k mice, although at a density ~fivefold lower than in C57BL/6 mice.

The physiological importance of the class I receptor on NK cells is probably not the need to avoid lysis of autologous cells or to recognize missing self, a task that could have been accomplished with a much simpler receptor system. Rather, the presence of receptors on each NK cell clone, able to recognize both autologous and allogeneic class I alleles, suggests that NK cells might be poised to recognize major changes in conformation of class I antigens, which may take place, e.g., during infection by viruses or other intracellular pathogens. Because NK cells recognize class I alleles and do not need class II-restricted helper T cells or professional antigen-presenting cells, they might be able to detect pathological alteration in most tissue cells, including at least all hematopoietic cells and endothelial cells. Importantly, the negative signal mediated by class I receptors prevents both cytotoxicity and cytokine production by NK cells (25). Thus, activation of NK cells in the absence of negative signals may result in both cytotoxicity of the altered tissue cells and production of cytokines. IFN- γ and GM-CSF, produced by NK cells, are potent activators of phagocytic cells, contributing to the inflammatory processes and making the NK cells an important component of the primordial mechanisms of innate resistance (1). The same cytokines are also strong activators of antigen-presenting cells, by upregulating MHC class II and costimulatory molecules. The early NK cell response during infection has profound effects on the characteristics of the ensuing antigen-specific adaptive immune response, and it is required for optimal response of type I T helper cells (26). Thus, NK cells appear to have evolved to play an important role in modulating the antigen-specific adaptive response of helper and cytotoxic T cells (26). It should also be noted that several of the receptors expressed on NK cells are expressed on some T cells, often on subsets of CD8⁺ cells, with distinct functions or cytokine production patterns. Whether some of these receptors play a functional role in T cell functions remains to be investigated.

I thank Ermanno Ciccone, Jenny Gumperz, Vinay Kumar, Lewis Lanier, Alessandro Moretta, Lorenzo Moretta, William Seaman, and Nick Valiante for discussions.

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