Commentary

Hybrid Resistance and the Ly-49 Family of Natural Killer Cell Receptors

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The phenomenon of hybrid resistance occurs when irradiated F1 hybrid mice reject bone marrow cells (BMC) donated by either parent (1). Hybrid resistance is of major interest in immunology because it violates the classical laws for solid tissue transplantation, upon which the MHC was defined. (F1 hybrid mice normally accept solid tissue donated by either parent.) Recent studies, including those published in this issue (2, 3), have yielded significant insight into the relationship between NK cells and this perplexing biological phenomenon, providing a means to determine the molecular basis for NK cell specificity for their targets.

Initially described on the basis of an apparently innate ability to kill certain tumor cells, termed natural killing, NK cells are now also known to be surface immunoglobulin-negative lymphocytes that are important in early host defense against infections and in regulating the subsequent specific immune response to intracellular pathogens by producing cytokines (4). NK cells closely resemble T cells with regard to display of cell surface molecules, cytolytic mechanisms to kill their cellular targets, and cytokine production profiles. It is not surprising, therefore, that they may share an immediate common progenitor (5, 6).

NK cells clearly must use a mechanism to discriminate between cells that they kill and those that they spare, such as normal cells. However, NK cells differ from T cells in target recognition mechanisms in two important ways. First, NK cells do not express the TCR/CD3 complex (7). Indeed, NK cells do not rearrange TCR genes and appear to be normal in mice with genetic abnormalities in TCR gene recombination, such as *scid*, and targeted RAG-1 or RAG-2 deficiency (8–10). Second, by contrast to MHC class I–restricted T cells, NK cells do not require the expression of MHC class I molecules on targets for natural killing (11). In fact, NK cells kill better when their targets do not express MHC class I. To explain this, Kärre postulated the "missing self" hypothesis, suggesting that NK cells survey tissues for MHC class I expression that is nearly ubiquitously expressed (12). With abnormal expression of MHC class I, the NK cell is released from this inhibitory influence and the target is killed. Certainly, there is now ample in vitro and in vivo evidence to support the general tenet of the hypothesis that MHC class I inhibits target killing. Although these findings were initially controversial because they were difficult to reproduce, more recent studies have shown that not all MHC class I molecules were capable of conferring resistance to targets. Selective resistance has been surprisingly mapped to the peptide binding domains of MHC class I molecules (13), suggesting that NK cells may discriminate between MHC class I molecules by recognition of the MHC class I epitopes that are also recognized by T cells, but in a TCR-independent manner.

In hybrid resistance, NK cells have been identified as the host elements that reject parental BMC (1). Hybrid resistance can occur in the apparent absence of immunoglobulin and T cells because it occurs in hosts with the scid mutation. Although the presumption is that NK cells are directly cytotoxic against BM precursors, the ability of NK cells to produce cytokines, such as interferon-γ, TNF-α, GM-CSF, etc. (4), which may influence bone marrow engraftment raises the possibility that differential cytokine production may be another mechanism. Nevertheless, even this latter possibility suggests that NK cells must be specifically triggered (or inhibited, see below) to manifest hybrid resistance.

Parental Determinants Recognized by Host NK Cells. Recipient NK cells mediate BMC rejection by recognizing parental determinants encoded by genes that have been mapped to the MHC (1). Moreover, an H-2^b mouse transgenic for H-$2D^d$ resembles the (H-2^b × H-2^d)F1 hybrid with regard to hybrid resistance (14). In addition, host NK cells in otherwise syngeneic hosts reject MHC class I–deficient BMC derived from mice with a targeted mutation in the β_2-microglobulin gene (15, 16). This rejection is thus highly reminiscent of hybrid resistance. Taken together, the data strongly suggest that NK cells in F1 hybrid animals mediate hybrid resistance against parental BMC cells that do not express the full complement of MHC class I molecules that would be codominantly expressed on F1 hybrid cells.

Other considerations, however, have prevented a consensus on this interpretation. The Bennett and Kumar group suggest that NK cells recognize parental determinants termed "hematopoietic histocompatibility" (Hh-1) antigens that can be distinguished from MHC molecules for several reasons (1). Their extensive studies of MHC-congenic mice demonstrated that the specificity of rejection could not be conveniently grouped according to MHC class I haplotypes of either the donor or recipient (17). Moreover, there is significant overlap between the groups. This analysis, however, has required interpretation without knowledge of putative NK cell receptors that presumably also affect the specificity. Analyses of MHC recombinant congenic mice have also suggested that

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Hh-1 genes can be separated from the H-2D subregion and reside in a region centromeric to H-2D (17). Although the Hh-1 gene may modify or regulate the expression of MHC class I molecules, this separation is confined to a small number of recombinant congenic mice with cross-over points near H-2D. It remains possible that the H-2D genes in these mice may be mutated. Nevertheless, the available data appear to contain discrepancies concerning the nature of the parental determinants for hybrid resistance.

How can these issues be resolved? In vitro systems resembling hybrid resistance (18) coupled with analysis of the specificity of NK cell clones or subsets have provided significant insight into NK cell receptors. In humans, several groups have made extraordinary progress indicating that NK cell clones are specifically inhibited by certain MHC class I molecules, depending on expression of putative MHC class I–specific NK cell receptors (19, 20). This has been recently reviewed in this journal (21) and elsewhere (22). In the mouse, however, it has only recently been possible to produce NK cell clones (23) and the available clones demonstrate an MHC class I–independent specificity that is not readily apparent in hybrid resistance. Nevertheless, it has become clear that murine NK cells are heterogeneous with respect to expression of certain cell surface molecules; several are involved in MHC class I–associated specificity.

With particular relevance to hybrid resistance, the Dallas group produced an mAb, SW5E6, that recognizes a disulfide-linked dimer, composed of 54-kD subunits, on a subpopulation of NK cells (24). Although $5E6^+$ and $5E6^-$ NK cells appeared to have similar lytic capacity in vitro, injection of mAb SW5E6 into F1 hybrid mice abrogated rejection of $H\text{-}2^d$ but not $H\text{-}2^b$ BMC. This study was among the first to demonstrate specificity of murine NK cell subsets, and it raised the possibility that the 5E6 molecule itself was involved in conferring this specificity. No direct evidence, however, has been presented to show the direct involvement of the 5E6 molecule itself in NK cell recognition, and the structure of the 5E6 antigen remained undefined.

In this issue, the Dallas group describes the cloning of a cDNA encoding the molecule recognized by mAb SW5E6 (2). Surprisingly, the 5E6 molecule (from C.B-17/*scid/scid* mice; C.B-17 is congenic to BALB/c) is identical in sequence to a member of the Ly-49 family of molecules, specifically Ly-49C, previously cloned from BALB/c mice (25). (There is one codon difference but this may result from sequencing artifacts.) To evaluate the implications of Ly-49C in hybrid resistance, it is useful to first review what is known about the Ly-49 family of molecules.

The Ly-49 Family of NK Cell Receptors. The Ly-49A molecule is a disulfide-linked homodimer that has the characteristics of a type II integral membrane protein with an external carboxyl terminus that is homologous to the C-type lectin superfamily (26). The gene encoding Ly-49A is clustered with a family of highly related genes on distal mouse chromosome 6. Based on cDNA cloning studies, at least eight members (Ly-49A through Ly-49H) are transcribed primarily in NK cells (27, 28). Some of the transcripts produce molecules with varying degrees of in-frame deletions consistent with alternative splicing. The Ly-49 gene family is genetically linked to another cluster of genes encoding the NKR-P1 family of molecules (26). Though distinct by nucleotide sequence and genetic linkage analysis, the NKR-P1 genes encode molecules that share structural features with the Ly-49 family (disulfide-linked homodimers, type II integral membrane orientation, C-type lectin homology) and selective expression and functional activity on NK cells. Hence, this genomic region has been termed the NK gene complex.

A current model for NK cell specificity involves activation receptors and MHC class I–specific inhibitory receptors (29). NKR-P1 molecules activate NK cells by apparently interacting with carbohydrate residues on targets (30), whereas Ly-49A globally inhibits NK cell cytolytic activity when targets express certain murine MHC class I molecules, specifically $H\text{-}2D^d$ or $H\text{-}2D^k$ (31). Transfection and expression of $H\text{-}2D^d$ on an otherwise susceptible target inhibited natural killing by $Ly\text{-}49A^+$ IL-2–activated NK cells. Moreover, these targets could not be killed even when $Ly\text{-}49A^+$ effector cells were stimulated through activation pathways that are not physically associated on the cell surface and that trigger distinct proximal signaling events. Thus, this global inhibition of NK activity is consistent with the hypothesis that Ly-49A delivers an inhibitory signal upon engagement.

Recent evidence supports a direct physical interaction between Ly-49A and $H\text{-}2D^d$. Experiments demonstrated binding only between transfected cells expressing high levels of Ly-49A by DNA amplification and $H\text{-}2D^d$, respectively (32). $Ly\text{-}49^+$ tumor cell lines also bound to immunopurified D^d molecules (33). Binding was blocked by mAbs specific for Ly-49A or the $\alpha1/\alpha2$ domains of D^d. Similar interpretations are possible from in vivo studies of Ly-49A expression in MHC congenic, recombinant congenic, and transgenic mice on the C57BL/6 or B10 background (34). Ly-49A expression was markedly diminished, in mice expressing $H\text{-}2D^d$ or D^k. It was normally expressed in mice transgenic for soluble $H\text{-}2D^d$, indicating that membrane-bound MHC class I was required for this effect. Studies with BM chimeric mice strongly suggested that downregulation resulted from extracellular engagement of Ly-49A with host MHC class I molecules (35). This did not appear to be a result of negative selection (clonal deletion), however, because Ly-49A could be detected at very low levels on highly purified NK cells (34). Thus, there is in vitro and in vivo evidence for physical interaction between Ly-49A and its MHC class I ligands, consistent with the role of Ly-49A as an MHC class I–specific receptor.

These findings are not confined to Ly-49A. In this issue, Mason et al. (3) corroborate major aspects of the Ly-49A–$H\text{-}2D^d$ paradigm with their studies on the LGL-1 molecule, another disulfide-linked homodimer expressed on an NK cell subset. They isolated a cDNA encoding LGL-1 in C.B-17/*scid/scid* mice; the deduced polypeptide is 98% identical to Ly-49G2 from C57BL/6 mice (27). Inasmuch as there is generally <90% amino acid identity between Ly-49 family members in a single inbred strain (27), the LGL-1 and Ly-

49G sequences probably represent allelic forms in BALB/c and C57BL/6 mice, respectively. This is also consistent with the distinct grouping of BALB/c and C57BL/6 strains, based on RFLP variants (36). Functional experiments indicated that LGL-1 expression could be correlated with target cell specificity; H-2^d targets were not killed by LGL-1^+ NK cells (3). Moreover, mAbs with apparent specificity for private determinants on H-$2D^d$ or L^d mAb each abrogated this resistance, suggesting that LGL-1 directly interacts with either MHC class I molecule. If, however, LGL-1 is acting as an inhibitory receptor specific for either ligand, binding to only one ligand should continue to protect because both MHC molecules are expressed on the target. It is therefore inconsistent that either anti–MHC class I mAb could restore killing to the level seen with anti–LGL-1, raising the possibility that simultaneous binding to both MHC class I molecules is required for inhibition by LGL-1. Further analyses with cell or physical binding experiments are necessary. Nevertheless, Ly-49 family members appear to be inhibitory MHC class I–specific NK cell receptors that significantly influence NK cell specificity.

Ly-49C: Implications for Understanding Hybrid Resistance. The finding that Ly-49C can be correlated with NK cell specificity in hybrid resistance is therefore a significant advance because it is a major clue to understanding the complexities in hybrid resistance. Although it is formally possible that Ly-49C is coexpressed with another molecule that is instead involved in determining specificity, it seems most plausible to hypothesize that Ly-49C itself is directly responsible by its ability to engage specific ligands, presumably MHC class I molecules. Two obvious functional consequences could occur after Ly-49C contacts its putative ligands. To result in graft acceptance, it could decrease NK cell cytolytic activity, analogous to Ly-49A, and/or change its cytokine production profile by producing cytokines that facilitate bone marrow growth or decrease the production of inhibitory cytokines. Absence of MHC class I molecules on BMC would then result in increased NK cell cytotoxic activity or production of inhibitory cytokines and/or decreased production of stimulatory cytokines. There seems to be less experimental support for the opposite functional consequence when Ly-49C contacts its MHC ligand, i.e., direct activation resulting in rejection, but this remains formally possible particularly since it has been suggested that Ly-49G (LGL-1) can act as an activation receptor under certain circumstances (3). Moreover, in the rat, NK cells appear to be stimulated by (nonclassical) MHC class I determinants (37). The previous studies of Ly-49C, therefore, may be interpreted as having a role as either an activation or inhibitory receptor.

To distinguish between these possibilities, it is critical to determine the ligand specificity of both allelic forms of Ly-49C in not only functional experiments, but also binding experiments. Based on previous findings with Ly-49A, and consistent with previous data in hybrid resistance, the ligand for Ly-49C is likely to be a specific MHC class I molecule. Interestingly, Stoneman et al. (2) describe preliminary data from functional experiments suggesting that Ly-49C interacts with H-2^d and H-$2K^b$, imparting inability to kill targets expressing these MHC class I molecules. These results are confusing in light of mapping data placing the genes for parental determinants near H-2D rather than H-2K subregion (1, 17). Moreover, specificities of Ly-49C for both H-2^d and H-2^b haplotype molecules were not predictable from the in vivo experiments with mAb SW5E6 (24). To date, cell binding experiments corroborated the interaction of Ly-49C (BALB/c allele) with cells from H-2^b and H-2^d haplotypes, but also indicated binding to cells from H-2^k and H-2^s haplotypes (28). The specific MHC class I molecules involved have not been identified and the specificity for a C57BL/6 form of Ly-49C has not been determined. It is also unclear whether mAb SW5E6 binds both allelic forms and inhibits recognition of MHC class I to an equal extent. Stoneman et al. (2) also refer to preliminary data implying differential cytokine production by different Ly-49C subsets in the context of different MHC class I molecules. Yet, human NK cell clones appear to directly kill BMC rather than to regulate their growth by cytokine production (37). Analysis of this possibility will also be aided by a more precise definition of the ligand specificity of Ly-49C alleles.

Definition of Hh-1 Determinants. Precise identification of the putative MHC class I ligand for Ly-49C will make it feasible to begin addressing previous discrepancies in defining parental determinants in hybrid resistance. It is noteworthy that Ly-49A appears to interact with the $\alpha1/\alpha2$ domains of H-$2D^d$, based on functional, binding, and in vivo expression analyses (31–34). Ly-49A is thus reminiscent of the MHC class I–restricted TCR rather than the CD8 molecule that binds to the $\alpha3$ domain of MHC class I molecules, consistent with the mutational analysis of protective HLA molecules (13). The apparent involvement of the peptide binding domains in interaction with Ly-49A predicts that other Ly-49 members also interact with similar MHC class I domains. In the context of hybrid resistance, this could mean that bound peptides may play a role in determining the parental determinants and could be encoded by genes influencing Hh-1 determinants. Recent studies, however, indicate only a general role for peptides in inducing the correct assembly, expression, and conformation of MHC class I molecules because all tested peptides for H-$2D^d$ could confer the resistant phenotype (39). More extensive analysis with a broader panel of peptides may reveal other interpretations, but the current data suggest that Ly-49A molecules do not bind peptides directly, seemingly arguing against the possibility that Hh-1 determinants result from specific MHC class I–bound peptides.

Another implication that would arise from a definition of the MHC class I ligand for Ly-49C is related to the observation that Ly-49 family members resemble Ca^{2+}-dependent lectins (27). Moreover, Ly-49A has an apparent carbohydrate specificity (40). The specificity of Ly-49C, therefore, could involve glycosidic residues, perhaps on specific MHC class I or on bound peptides. Such modifications could be regulated by genes linked to Hh-1. Alternatively, relevant epitopes on MHC class I molecules may be regulated in other ways as previously suggested (1).

The involvement of the Ly-49 family in hybrid resistance

raises another distinct possibility: Hh-1 determinants may be MHC class I molecules, as defined by the specificity of promiscuous NK cell receptors. Ly-49A binds H-2D^d and D^k in functional, binding, and in vivo expression studies (31–34), yet H-2D^d and D^k do not share general features such as structural or peptide motif, and they are distinct in sequence and serologic analysis. On the other hand, they are both encoded in the H-2D subregion, the genetic area linked to Hh-1, and may share as yet undefined epitopes involved in Ly-49A binding. Similarly, Ly-49G2 appears to be specific for H-2D^d and L^d (3), unrelated except for derivation from H-2D subregion (and in this case, the H-2^d allele). This promiscuity is also compatible with the overlapping specificities of the Hh-1 groups (1). Classification of MHC class I determinants with regard to the specificity of NK cell receptors, such as the Ly-49 family members, may therefore be revealing in understanding Hh-1 specificities, as determined by in vivo hybrid resistance assays.

Expressed Functional Repertoire of Ly-49 Molecules on NK Cells. Available data strongly indicate that an individual NK cell may simultaneously express more than one Ly-49 family member. Compounding the difficulty of this analysis, these molecules may have overlapping specificities. For example, both Ly-49A and Ly-49G2 (LGL-1) appear to have specificity for H-2D^d, and also D^k and L^d, respectively (2, 31–34). In addition, multiple allelic forms for each Ly-49 family member are predicted from analysis of RFLP variants (36). It remains unclear whether each allelic form has the same specificity. These issues are highly relevant to discussion of hybrid resistance because the F1 hybrid is heterozygous with respect to MHC and to allelic forms of Ly-49 family members. This raises the additional prospect that F1 hybrid NK cells may express heterodimers between allelic forms of individual Ly-49 family members (normally homodimers on cells transfected with single cDNAs) and/or between family members, altering specificity for their ligands. Yet, apparently only one allelic form of Ly-49C is expressed in F1 hybrids, presumably because of allelic exclusion (2). This important observation indicates that not all pair combinations of Ly-49 alleles may be expressed, limiting the expressed diversity of these receptors. Recent data also suggest that the function (41) and expression (34) of Ly-49A molecules may be influenced by host MHC class I molecules. Thus, further dissection of hybrid resistance will require detailed understanding of the expression and function of Ly-49 molecules on F1 hybrid NK cells in the context of different host MHC class I molecules.

Finally, the Ly-49C molecule is expressed only on a subset of NK cells and only this subset has the apparent specificity for H-2^d but not H-2^b BMC (24). Why are Ly-49C$^-$ NK cells not involved in mediating hybrid resistance in this strain combination? In addition to the considerations above involving other Ly-49 family members with overlapping specificity with Ly-49C, perhaps other recognition mechanisms are involved, similar to the apparent Ly-49–independent specificity of recently described mouse NK cell clones (23). Further analysis of hybrid resistance therefore promises to enhance our understanding of, not only MHC class I–associated specificity and the Ly-49 family, but of NK cell specificity in general.

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