Genes in two MHC class I regions control recognition of a single rat NK cell allodeterminant

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Keywords: bone marrow, MHC, NK cells, rodent, transplantation, tumor immunity

Abstract

We have previously presented evidence suggesting that the non-classical class I region of the rat MHC, RT1.C, encodes polymorphic molecules which induce the cytolytic activity of alloreactive NK cells. Those studies used target cells from a panel of MHC congenic rat strains possessing recombed portions of the RT1\textsuperscript{a}, RT1\textsuperscript{1} and RT1\textsuperscript{c} MHC haplotypes. We have now examined in addition a set of rat strains bearing MHC haplotypes recombinant between RT1\textsuperscript{av1} and RT1\textsuperscript{c}, and a more complex picture of the MHC control of rat NK alloreactivity has emerged. The expression of a major NK allodeterminant [the allogeneic lymphocyte cytotoxicity (ALC) determinant 2 or ALC-2, defined operationally using cold-target inhibition assays], appears to be under the control of both the RT1.C and the classical class I RT1.A region. Similarly, the alloreactive repertoires of NK cells from these recombinant strains are influenced by elements encoded within these two MHC class I regions. We present a model in which the classical class I autoantigen RT1.A\textsuperscript{C} exhibits dominant inhibition of NK cytotoxicity specific for the stimulatory determinant ALC-2 shared by the non-classical class I molecules RT1.C\textsuperscript{av1}, RT1.C\textsuperscript{a} and RT1.C\textsuperscript{c}, and also prevents the deletion of NK cells of this specificity during their development.

Introduction

NK cells constitute a distinct population of short-lived cytotoxic lymphocytes with the innate ability to lyse some neoplastic, virus-infected and normal cells (1,2). NK cells neither rearrange TCR genes nor express a TCR on their surfaces, but they nevertheless seem to be closely related to T cells. Both T and NK cells are equipped with receptors for polymorphic MHC molecules (3-5). MHC engagement by T and NK cells, however, elicits cellular responses that appear to be fundamentally different from one another. Whereas T cells in a role are activated by foreign peptide-MHC complexes, NK cells are often inactivated by the presence of class I molecules on target cells (6). The ability of class I molecules to inhibit NK lysis may depend on the presence of certain polymorphic residues in the peptide-binding groove and the surrounding \( \alpha \) helices of the H chain (7,8), and even on the class I-bound peptide itself (9).

Studies on the killing of normal allogeneic and semi-syngeneic leukocytes by NK cells have provided an insight into the role of the MHC in controlling NK cell reactivity (2,6,10). NK cell-mediated elimination of allogeneic leukocytes could be viewed as the failure of allogeneic target cell class I molecules to efficiently engage all the inhibitory receptors on host NK cells. Studies of allorecognition by rat NK cells, however, have provided evidence that allogeneic MHC class I in some instances may provoke, rather than inhibit, NK cytotoxicity (11-14).

In the rat, functional studies have defined at least four distinguishable allotypic target cell determinants encoded in the MHC that induce NK cell-mediated lysis of normal leukocytes both \textit{in vivo} (15) and \textit{in vitro} (13). These determinants are encoded, respectively, in the MHC haplotypes RT1\textsuperscript{av1}, RT1\textsuperscript{a}, RT1\textsuperscript{c}, and RT1\textsuperscript{f}, and here we will refer to them as allogeneic lymphocyte cytotoxicity (ALC) determinants 1, 2, 3 and 4 or ALC-1, -2, -3 and -4. Polyclonal NK cells from one...
Table 1. The genetic constitution of the rat strains used

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<th>Strain</th>
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Recombination point.

Methods

Animals

Breeding pairs from rat strains on PVG background were either obtained from Harlan Olac (Bicester, UK; PVG, PVG.1U, PVG.1AV1, PVG.R1, PVG.R8, PVG.R20 and PVG ru/mu) or from The Babraham Institute [PVG.1L(LEW), PVG.R19 and PVG.R23]. They were reared under conventional conditions in Oslo and screened for common rat pathogens. The rats on LEW background were obtained from the Medizinische Hochschule Hannover. Their genetic constitutions are given in Table 1. The female parent is designated first in interstrain matings.

rat strain of the ALC-4 type, i.e. PVG (RT1\(_{c}\)), discriminate between target cells expressing ALC-1, -2 and -3 (i.e. between RT1\(_{a}\), RT1\(_{b}\) and RT1\(_{c}\)), as established in cold-target inhibition experiments (12). The target elements controlling the expression of these NK-defined specificities (ALC-1, -2 and -3) have been genetically mapped to the non-classical class I region of the rat MHC, RT1.C (12). Thus, ALC-1, -2 and -3 may correspond to distinct target epitopes, encoded within the RT1.C class I locus, which stimulate cytotoxicity by allogeneic (RT1\(_{c}\)) NK cells.

Here, we have extended our studies on the MHC control of NK alloreactivity in the rat by demonstrating that the RT1\(_{b}\), RT1\(_{av1}\) and RT1\(_{c}\) haplotypes appear to encode a common cross-reactive stimulatory epitope in the RT1.C region which activates NK alloreactivity. Moreover, we have shown that molecules expressed from the classical class I region, RT1.A (16), may also have an important influence on NK reactivity and target susceptibility. The present results suggest that the susceptibility of normal lymphoblast targets to allospecific NK lysis may involve a process in which the NK cell interprets coincident inhibitory and stimulatory signals received from classical and non-classical class I molecules on target cells.

Fig. 1. Lysis of RT1\(^{av1}\) lymphoblasts by RT1\(^{a}\) NK cells is controlled by the classical MHC class I region, RT1.A; recessive inheritance of NK susceptibility. Target cells were Con A blasts generated from a panel of intra-MHC recombinant rats (RT1\(^{a}\)-RT1\(^{f}\)) and their respective parental strains as well as some informative F1 hybrids: PVG.1AV1 (\(\ominus\)), PVG.R19 (\(\Delta\)), PVG.R1 (\(\oplus\)), PVG.R20 (\(\bigcirc\)), PVG (\(\uparrow\)) and (PVG.R1×PVG)F\(_{1}\) (\(\times\)). Effector cells were IL-2-activated NK cells from the strains denoted above each graph [P1 represents the PVG.R1, P2 the PVG and F\(_{1}\) the (PVG.R1×PVG)\(_{1}\) F\(_{1}\) animals]. The results are median values from two (A) or three (B-D) experiments.

Fig. 2. Lysis of RT1\(^{av1}\) lymphoblasts by RT1\(^{f}\) NK cells is controlled by the MHC class II-non-classical class I interval, RT1.B/D-RT1.C, semi-dominant inheritance of NK susceptibility. Target cells were Con A blasts from the RT1\(^{f}\)-RT1\(^{av1}\) set of intra-MHC recombinants and their respective parental strains as well as some informative F\(_{1}\) hybrids: PVG.1AV1 (\(\ominus\)), PVG.R23 (\(\bigcirc\)), PVG.R8 (\(\oplus\)), PVG.1U (\(\Delta\)) and (PVG.R23×PVG.1U)F\(_{1}\) (\(\times\)). Effector cells were IL-2-activated NK cells from the strains denoted above each graph [P1 represents the PVG.R23, P2 the PVG.1U and F\(_{1}\) the (PVG.R23×PVG.1U)F\(_{1}\) animals]. The results are median values from two experiments.
classical and non-classical class I molecules, acting on the same NK cell subpopulation. We propose a model whereby RT1.A and RT1.C control of NK alloreactivity by alloreactive NK cells, in agreement with earlier studies of ALC-1 expressed from the classical class I region of the rat MHC, important in determining target susceptibility to RT1.C, are cross-reactive with target determinants from RT1.C regions but not RT1.C* (ALC-1). Effector cells were nylon wool non-adherent spleen cells from PVG mufu rats (11). Target and inhibitor cells were Con A blasts from different panels of intra-MHC recombinants and their respective parental strains: (A to D) PVG (V), PVG.R1 (T), PVG.1AV1 (R), PVG.R23 (O), PVG.R8 (X) and PVG.1U (A). (E and F) PVG (V), PVG.1AV1 (O), LEW.1AV1 (O), LEW.1AD (O), LEW.1WR2 (O), LEW.1WR1 (O) and LEW.1AR2 (X). Labeled target cells are denoted above each graph. Results are presented as medians from two experiments.

**Effectors cells**

IL-2-activated NK cells were generated from spleen cells that had been depleted of T cells with anti-CD3 mAb (G4.18) and complement, and thereafter positively selected with magnetic Dynabeads coated with the anti-NKR-P1 mAb 3.2.3, as described (13). Some experiments made use of unstimulated nylon wool non-adherent spleen cells from PVG mufu rats (11) or of NK cells obtained from the peritoneal cavity of rats implanted 1 week earlier with diffusion chambers containing cultures of IL-2-secreting Chinese hamster ovary cells (17).

**Target cells and cytotoxicity assay**

The generation of concanavalin A (Con A)-activated lymphoblasts as target cells and the 4 h $^{51}$Cr-release assay were performed as described (12). Some experiments made use of the YAC-1, P815 and EL4 cell lines, which were maintained in RPMI 1640 supplemented with 10% FCS and antibiotics. Spontaneous release was usually 5–15% of the total c.p.m. in the cells. The results are presented as median values from triplicates for each effector:target (E:T) or target:inhibitor cell ratio.

**Results and discussion**

In the present study, we demonstrate that molecules expressed from the classical class I region of the rat MHC, RT1.A, in addition to those from the non-classical class I region RT1.C, are important in determining target susceptibility to alloreactive NK cells, in agreement with earlier studies of ALC in vivo (18 and E. Bell, personal communication). Genetic control of NK alloreactivity by RT1.A and RT1.C is strongly suggestive of simultaneous control of allospecific NK lysis by classical and non-classical class I molecules, acting on the same NK cell subpopulation. We propose a model whereby a subset of NK cells from PVG with specificity for an RT1.C encoded stimulatory motif is dominantly inhibited by a classical self-class I antigen from the RT1.A region. The results that have led us to propose this model are presented below and are illustrated in Fig. 5 below.

**Lysis of RT1Av1 lymphoblasts by RT1F and RT1Cp1 NK cells is controlled by MHC determinants in the RT1.A and RT1.B/D-RT1.C regions**

In the strain combination PVG (RT1F) versus PVG.1AV1 (RT1Av1), control of NK alloreactivity maps to the classical class I region RT1.A. Thus, PVG NK cells (RT1.A−1RT1.B/D−RT1.CO or c-c-c) lysed Con A-activated lymphoblasts from PVG.1AV1 (a-a-av1), PVG.R19 (a-a-c) and PVG.R1 (c-c-c) rats, whereas lymphoblasts from PVG.R20 (c-c-c) and PVG (c-c-c) were spared (Fig. 1A). An important further characteristic of this strain combination is that NK susceptibility is inherited recessively. Classical F1 anti-parental responses were high. NK cells from (PVG.R1×PVG)F1 rats (a-c-c/c-c-c) killed PVG.R1 (a-c-c), but not PVG (c-c-c) or (PVG.R1×PVG)F1 Con A blasts (Fig. 1D). Moreover, lymphoblasts from PVG.1AV1×PVG)F1 (a-c-c/c-c-c) and (PVG.R1×PVG)F1 hybrid (a-c-c/c-c-c) lymphoblasts were not lysed by parental PVG NK cells (c-c-c; Fig. 1C and data not shown). This implies that a single dose of RT1Av1 haplotype-derived genes in the RT1.A region is insufficient to impart susceptibility to lysis by PVG and (PVG.R1×PVG)F1 NK cells, confirming the recessive inheritance of NK susceptibility in this strain combination. This pattern of reactivities (13), which resembles those of mouse 'hybrid resistance' phenomena, can be explained on the basis of class I-mediated dominant negative signaling in NK cells, as has been discussed by others (6,10). If in our case we assume that the classical class I molecule RT1.AO from PVG inhibits cytolytic activation...
Co-regulation of rat NK lysis by RT1.A and RT1.C

of PVG and (PVG×PVG.1R1)F1 NK cells, the killing of PVG.1AV1 and PVG.1R1 cells by these effectors could be explained simply by the absence of the inhibitory allele RT1.A in these targets.

Another set of experiments indicate that additional RT1.C av1 target determinants, encoded within the RT1.B/D–RT1.C interval, of the rat MHC stimulate, rather than inhibit NK cell cytotoxicity. In these studies, we began by examining the response of PVG.1U (RT1.C) NK cells to these ALC determinants. NK cells from PVG.1U (u-u-u) effectively lysed Con A blasts from PVG.1AV1 (a-a-av1) and PVG.1R2 (u-a-av1) but not those from either PVG.1R8 (a-u-u) or PVG.1U (u-u-u) (Fig. 2A). Notably, NK susceptibility was inherited non-recursively in this strain combination since semi-syngeneic (PVG.R23×PVG.1U)F1 (a-a-av1/u-a-u) lymphoblasts were also susceptible to lysis by PVG.1U (u-u-u) NK cells (Fig. 2C). This suggested that a single dose of a target molecule expressed from the RT1.B/D–RT1.C regions of the RT1.C av1 haplotype had the ability to transduce signals activating natural killing, in agreement with earlier data (12,13). The anti-parental cytolytic activities, on the other hand, were low. NK cells from (PVG.R23×PVG.1U)F1, hybrid (u-a-av1/u-a-u) rats killed Con A blasts from PVG.R23 (u-a-av1) much less well than did NK cells from the opposite parental strain PVG.1U (u-u-u) (compare Fig. 2D and C, respectively). These data suggest that (PVG.R23×PVG.1U)F1 NK cells are somehow rendered tolerant to the stimulatory RT1.B/D–RT1.C av1 determinant present on parental PVG.R23 (u-a-av1) and syngeneic F1 (u-a-av1/u-u-u) target cells.

RT1.C av1 allospecific NK cells from PVG (RT1.C) display cross-reactivity towards ALC determinants from the RT1.C av1, RT1.C a and RT1.C c, but not the RT1.C r regions.

At this point, therefore, we might have concluded that the RT1.C av1 haplotype possesses two major ALC determinants, one encoded in RT1.A and the other in the RT1.B/D–RT1.C interval. This interpretation was invalidated, however, by experiments making use of cold-target inhibition. Previous experiments had confirmed that RT1.C av1 (PVG.1U) and RT1.C av1 (PVG.1AV1) lymphoblasts express different target specificities (ALC determinants) as evidenced by their relative inability to cross-compete for lysis by RT1.C (PVG) effector cells in cold-target inhibition assays (Fig. 3 and data not shown). The cold-target inhibition assay could therefore be used to compare the NK susceptibility of lymphoblasts from the different recombinant strains bearing portions of the RT1.C av1 haplotype. The surprising outcome of these analyses was that a single major ALC determinant appeared to be shared by susceptible targets of very different MHC constitutions, in a manner strongly suggestive of cross-reactive target specificities within the RT1.C region. Thus, when we used polyclonal NK cells from the PVG mu mouse strain (RT1.P), lysis of radiolabeled PVG.1AV1 (a-a-av1) target cells was inhibited with cold targets from PVG.1AV1 and PVG.R23 (u-a-av1), but not from PVG.R8 (a-u-u) (Fig. 3B), indicating that the RT1.C av1 ALC determinant is different from that of RT1.C av1. In contrast, the PVG effector cells were unable to discriminate between the target determinants expressed from RT1.C av1 and RT1.C av1 since cold targets from PVG.R19 (a-a-c), PVG.R1 (a-c-c) and PVG.1AV1 (a-a-av1) inhibited killing of hot PVG.1AV1 (a-a-av1) targets equally well (Fig. 3B and data not shown). The same was also true when we used PVG.R1 and PVG.R23 targets instead of PVG.1AV1 (Fig. 3C and D).

We used inhibitor cells from the RT1.A/RT1.C av1 recombinant series on the LEW background, to demonstrate that the NK target determinant detected in the canonical RT1.C av1 haplotype is apparently also the same as that in the variant RT1.C av1 haplotype. The RT1.C av1 haplotype is derived from the AWN strain whereas RT1.C av1 is derived from the DA strain and these haplotypes are known to possess differences in the RT1.C region. In this genetic combination, the shared NK determinant could be clearly mapped to the RT1.C region, in agreement with earlier studies (12). Thus, the lysis of LEW.1A (a-a-a) targets by PVG NK cells (c-c-c) was inhibited equally well by unlabeled PVG.1AV1 (a-a-av1), LEW.1AV1 (a-a-av1), LEW.1A (a-a-a), LEW.1WR2 (u-a-a) and LEW.1WR1 (u-a-a) cells, whereas LEW.1AR2 (a-a-u) and PVG control cells (c-c-c) inhibited poorly (Fig. 3E). This pattern was also seen when LEW.1WR1 cells were used as hot targets instead of LEW.1A (Fig. 3F). Overall, these experiments using cold-target inhibition demonstrated that PVG NK cells may cross-react with more than one allele at the RT1.C locus, i.e. with RT1.C av1, RT1.C a and RT1.C c corresponding to the ALC-2 target determinant.

The reactivity of PVG (RT1.C) NK cells against a potentially autoantigenic stimulatory target determinant from RT1.C c is down-modulated by an inhibitory self-determinant from RT1.A c. As shown above, the ALC determinant expressed from the RT1.C av1, RT1.C a and RT1.C c regions (ALC-2) appears to be similar, whereas that from RT1.C av1 is different (Fig. 3). Importantly, this target determinant corresponding to ALC-2 is potentially autoantigenic in the PVG (RT1.F) strain, as can be deduced from Fig. 4(A). The ALC-2 specificity was expressed, but at a somewhat reduced level in (PVG.R8×PVG.1R1)F1 target cells when NK cells from PVG were used. Cold (PVG.R8×PVG.R1)F1 blasts (a-u-u/a-u-c-c) inhibited lysis of PVG.R1 (a-c-c) targets better than did PVG.R8 (a-u-u) cells, but less well than did PVG.R1 (a-c-c) themselves. The semi-dominant inheritance pattern of this target specificity is in agreement with earlier data (12,13) and suggests that a self-determinant encoded from RT1.C c is able to trigger cytotoxicity of PVG NK cells (c-c-c), but only when it is expressed in conjunction with permissive allogeneic RT1.A c genes as in PVG.R1 (a-c-c) and PVG.R19 (a-a-c) (Fig. 4A and data not shown).

Similarly, the ALC-2 stimulatory target determinant could not be detected in the context of autologous genes in the RT1.A region, i.e. RT1.A c. Cold PVG (c-c-c), (PVG×PVG.1AV1)F1 (c-c-cla-a-av1) and (PVG×PVG.R1)F1 (c-c-cla-a-c-c) hybrid lymphoblasts were unable to inhibit killing of PVG.1AV1 (a-a-av1) and PVG.R1 (a-c-c) targets when NK cells from PVG (c-c-c) were used (Fig. 4B and data not shown). The present data are therefore most consistent with the idea that PVG NK cells with specificity for stimulatory RT1.C allos- or autodeterminants (corresponding to RT1.C av1, RT1.C a or RT1.C c genes) was inhibited by the products of the (self) RT1.A c locus.
Expression of the RT1\(^{av1}\) ALC determinant (ALC-2) at the level of the effector cell leads to a down-regulation of the NK allorecognition repertoire

Further strong evidence that RT1.C\(^{av1}\) and RT1.C\(^c\) share the same target specificity, ALC-2, was obtained in experiments examining the influence of self MHC genes on the NK allorecognition repertoire (13). Expression of either RT1.C\(^{av1}\) or RT1.C\(^c\) genes had the same effect on the effector repertoire of alloreactive NK cells from different MHC congenic and recombinant rats. Whereas NK cells from PVG (RT1\(^F\)) and PVG.1U (RT1\(^I\)) were broadly alloreactive against all the MHC incompatible lymphoblast targets tested (Table 2, rows 1 and 7 respectively), NK cells from PVG.1AV1 (RT1\(^{av1}\)) rats displayed a more restricted repertoire of target susceptibilities. These cells only lysed target cells of one allo-MHC type efficiently, i.e. RT1\(^F\) (Table 2, row 4). Notably, NK cells from the recombinant strains PVG.R1 (a-c-c) and PVG.R23 (u-a-a\(^v\)) expressing the ALC-2 target determinant (Fig. 3), displayed target repertoires similar to that of PVG.1AV1 (compare rows 3-5, Table 2). By contrast, the reactivity patterns of NK cells from the PVG.R20 (c-c-a\(^v\)) and PVG.R28 (a-u-u\(^c\)) strains not expressing ALC-2 were different and resembled those of PVG and PVG.1U NK cells respectively (Table 2, rows 2 and 6). The lysis of standard tumor target cells was not affected by the MHC constitution of the effector cells (Table 2, row 1-4).

In order to explain our findings we propose the following model (Fig. 5), (i) The non-classical class I alloantigens RT1.C\(^{av1}\) and RT1.C\(^{C}\) share a stimulatory epitope (corresponding to ALC-2), absent from RT1.C\(^c\), which is recognized by a subset of allospecific NK cells in PVG (RT1\(^F\)). This epitope is also shared by RT1.C\(^c\) where it is potentially autoantigenic for PVG. (ii) The classical class I autoantigen RT1.A\(^e\) is able to down-modulate cytotoxicity by engagement of an inhibitory receptor on the same effector cells. Some other RT1.A alleles, i.e. RT1.A\(^a\) and RT1.A\(^b\), are unable to bring about this inhibition. This inhibitory receptor could either be distinct from that inducing cytolytic activation (two receptor model) or, conceivably, be the same (one receptor model). The latter possibility implies that the ligand threshold for activation and inhibition of cytotoxicity is different and is based on the lower level of expression of RT1.C compared with RT1.A molecules (<10%) (reviewed in 16,19).

One important implication of this model (Fig. 5) is that NK cell reactivity towards normal leukocytes may be determined by more than one type of receptor—MHC ligand interaction and be dependent on the balance between inhibitory and stimulatory signals. Another is that NK cells may express activation receptors for certain MHC autoantigens and that they therefore may be potentially autoreactive cells. Yet, self-tolerance is accomplished by co-expression of inhibitory receptors overriding cellular activation. This model may account for the apparent existence of recessively inherited MHC determinants triggering NK cell lysis both in rats (13), in mice (20) and possibly also in humans (21). It may also be relevant in relation to the discussion of the mechanisms of hybrid resistance. This phenomenon, i.e. the elimination of MHC homozygous leukocytes by semi-syngeneic F1 NK cells, was originally described in mice (22), but has recently been
reproduced also in the rat model (13,15). Originally it was assumed that hybrid resistance was elicited by recognition of recessively inherited Hh-1 alloantigens (22,23). However, more recent results have suggested that rejection takes place on the basis of missing self, i.e. because MHC homozygous parental target cells lack some of the inhibitory class I molecules expressed in the F₁ hybrid (24–26,32). Insight into the missing self model to describe hybrid resistance has been recently provided by the lectin-like Ly-49C/5E6 molecule (26). It was previously thought that Ly-49C was a candidate receptor for the Hh-1<sup>α</sup> allodeterminant because the activity towards Hh-1<sup>α</sup> was confined to the Ly-49C<sup>+</sup> NK cell subset (27). More recent results, however, have shown that Ly-49C may be an inhibitory receptor for the class I antigen H-2K<sup>β</sup> (26). However, as has been discussed previously (28), this result does not prove that the Hh-1<sup>α</sup> phenotype is caused by the lack of K<sup>β</sup> in target cells. The strong association between the expression of the Hh-1<sup>α</sup> phenotype and certain H-2D class I molecules, notably D<sup>β</sup> (29), suggests that there may be an activatory receptor for the autoantigen D<sup>β</sup> in H-2<sup>β/β</sup> F₁ NK cells and that this receptor is co-expressed with Ly-49C preventing autoreactivity upon binding to K<sup>β</sup>, in analogy with the model that we have presented here (Fig. 5). Indeed, experiments using mice transgenic for the H-2D<sup>β</sup> molecule indicate that mouse NK cells may express an activatory alloreceptor for target H-2D<sup>β</sup> (20).

The present results, however, may also be explained by a different model assuming that class I-bound peptides contribute to rat NK allospecificity (13). The gene interaction between RT1.A and RT1.C could be caused by competition for presentation of peptides between RT1.A and RT1.C molecules, more specifically by RT1.A<sup>α</sup> stealing important peptide(s) from RT1.C<sup>α</sup>, RT1.C<sup>α</sup> and RT1.C<sup>β</sup>. Alternatively, RT1.A<sup>α</sup> could contribute with a peptide binding to these RT1.C molecules. However, the dependence of specific peptide in NK recognition has been questioned in some well-studied experimental systems (4,8,30) and this model therefore seems more speculative. It is clear from the present studies that the existence of polymorphisms in MHC class I genes can lead to profound variations of the effective NK repertoire. This provokes the question of whether these polymorphisms have adaptive value with respect to the NK system itself or whether observations like ours are accidental consequences of polymorphisms selected only in relation to T lymphocyte recognition of peptide–MHC complexes.

A diverse receptor system in rat NK cells that can explain the complex MHC recognition patterns observed is awaiting identification. However, the Ly-49 family of molecules which confer MHC specificities upon mouse NK cells may also confer NK allospecificities in the rat. Certain genes whose products appear to activate NK cell cytotoxicity of allogeneic targets map to the rat NK gene complex of lectin-like receptors (31). Work in progress aims to clarify whether the behavior of molecules expressed from this complex may resolve the questions we have raised here.

### Acknowledgements

We thank Dr James C. Ryan for critical readings of the manuscript, and also for valuable comments from Drs Kirsten Fischer-Lindahl, Vinay Kumar and William E. Seaman. This work was supported by The Norwegian Cancer Society and The Nansen Foundation. C. N. and J. T. V. were supported by fellowships from The Norwegian Cancer Research Council.

G.W. B. is supported by the UK Biotechnology and Biological Sciences Research Council.

### Abbreviations

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<td>ALC</td>
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### References

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