Generation of T Cells with Lytic Specificity for Atypical Antigens. II. A Novel Antigen System in the Rat Dependent on Homozygous Expression of Major Histocompatibility Complex Genes of the Class I-like RTIC Region

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Summary

Lymphocytes from parental strain DA rats can induce potent killer cell responses to atypical antigen systems in F1 Lewis (L)/DA and DA/L recipients. Here, we describe an antigen system, H, present on homozygous parental target cells, but not on F1 cells. This antigen system is unusual in several respects: it does not involve class I RT1A gene products usually used by killer cell responses in the rat, it maps to the major histocompatibility complex (MHC) class I-like RTIC region, and it requires homozygous expression of RTIC" alleles. This may be another example, this time involving the RTIC region, of an MHC gene product antigenically altered by an MHC-linked trans-activating modifier gene.

In this paper, we demonstrate a second antigen system (H), present on homozygous parental DA target cells, that is detectable with L/DA anti-DA CTL as well as with CTL generated from the reciprocal F1 combination DA/L anti-DA. This antigen system is more conventional in that it is inherited chromosomally and insensitive to chloramphenicol, thus, not of mitochondrial origin, but it is unusual in that it depends on homozygous expression of MHC gene products, in particular those of the rat RTIC class I-like region. Lytic T cells specific for most antigen systems in the rat are restricted by gene products of the RT1A region (4).

Materials and Methods

All procedures, methods, animals, and reagents are the same as described earlier (see accompanying paper I [3]). As before, the female parent in interstrain matings is designated first.

Results

Evidence for a Second Antigen System Present on DA Target Cells. During the course of our studies of MTA in rats, which is detected by L/DA anti-DA CTL, we noticed that unlabeled lymphoblasts of DA/L F1 and parental strain DA origin were equally effective in cold target competition assays with labeled DA/L target cells; but that unlabeled F1 lympho-
blasts were always less effective than DA lymphoblasts in inhibiting lysis of labeled homozygous DA target cells (Fig. 1, A and B). This finding is consistent with the possibility of a second antigen system detected by these killer cells present on parental strain lymphoblasts, but absent from F₁ target cells.

To explore further the structure of this second antigen system on parental DA target lymphoblasts, we generated CTL from progeny of reciprocal DA/L matings; unlike L/DA anti-DA CTL, which lyse both DA and DA/L target cells (Fig. 2 A), DA/L anti-DA CTL lyse only targets from homozygous DA donors (Fig. 2 B). Provisionally, we refer to this antigen system as H. Evidence that the killer cells that detect this antigen system are T cells is provided by the finding that lysis is completely inhibited in the presence of R73 (see accompanying paper III [5]), a mAb specific for TCR-α/β heterodimers of the rat (6).

**Figure 1.** Evidence for a second antigen system detected by L/DA anti-DA CTL on DA target cells. (A) Unlabeled DA/L lymphoblasts are less effective than DA lymphoblasts in inhibiting lysis of DA target cells, but (B) are equally as effective as cold DA cells in inhibiting lysis of DA/L target cells.

**Figure 2.** Further evidence for a second antigen system on DA target cells. Comparison of targets lysed (A) by L/DA anti-DA CTL and (B) by the reciprocal F₁ combination DA/L anti-DA.

**Figure 3.** (A) Direct lysis and (B) cold target competition assays with target cells from various MHC congenic and recombinant strains and F₁ combinations showing that the antigen system detected by DA/L anti-DA CTL depends upon expression of the aVL haplotype of the MHC class I-like RT1C region. Note also an apparent requirement for homozygosity of the target cells, since RT1C<sup>aVL</sup> DA/L and L/DA target cells are not lysed nor do they block lysis of labeled targets.

CTL Recognition of H Depends on RT1C<sup>aVL</sup>. Direct lysis (Fig. 3 A) and cold target competition assays (Fig. 3 B) with DA/L anti-DA CTL and target cells from various sources, including the PVG MHC congenic and recombinant strains, shows quite clearly that homozygous strains of the RT1<sup>aVL</sup> haplotype (DA, PVG-RT1<sup>aVL</sup>) are H positive and that class I-like RT1C<sup>aVL</sup> gene product(s) are required for expression of H antigen(s). Target cells from congenic and recombinant strain donors expressing the aaavl, ccavl, and saavl haplotypes are lysed, while those expressing aac, auu, and acc are not. The finding that aaavl, ccavl, and saavl targets are lysed to a comparable degree suggests that prototypical class I RT1A gene products are not involved in the recognition of H antigen by CTL.

A second finding of interest is that target cells from RT1<sup>aVL</sup> heterozygous donors (L/DA and DA/L) are H negative. Thus, mere expression of RT1C<sup>aVL</sup> gene products is not sufficient for expression of H antigen(s); there is a requirement for homozygosity at one or more loci within this region.

Further evidence that classical RT1A MHC gene products are not involved in recognition of the H antigen system is provided by the finding that MAC 30, a mAb specific for RT1A<sup>+</sup> molecules, which inhibits CTL recognizing or restricted by RT1A<sup>+</sup> (7), fails to block lysis of H-positive target DA cells by both L/DA anti-DA and DA/L anti-DA CTL (Fig. 4, A and B). This finding supports the conclusion drawn above that the MTA and H antigen systems, both present on DA target cells, are different.

The H Antigen Is Not of Mitochondrial Origin. The experiments presented above indicate the existence of two antigen systems detectable with L/DA anti-DA CTL. One, MTA, is of mitochondrial origin and is present on both DA/L and DA target lymphoblasts, and is restricted by the major
Further evidence that H antigen expression is not dependent upon class I RT1A+ gene products. MAC 30, a mAb specific for RT1A+ (A) blocks MTA-specific lysis by L/DA anti-DA CTL of DA/L targets, which requires RT1A+ expression, but this antibody does not inhibit lysis of DA target cells by the same CTL population. (B) MAC 30 does not block lysis of DA target cells by DA/L anti-DA CTL. G2c is another mAb (R3-40) of the same isotype; it has no effect.

The results of two different experiments argue against this possibility. First, the H antigen does not show a pattern of simple maternal inheritance. Target cells from DA, DA/L, and TC3 are all lysed by L/DA anti-DA CTL (anti-MTA killers; Fig. 5 A). TC3 is an RT1ac+ testcross animal derived from a backcross mating in which DA was the female grandparent ([DA/WF x WF] RT1ac- backcross female x [WF/DA] male). In contrast, DA/L anti-DA CTL (anti-H killers) lyse only DA target cells; target cells from neither of the F1 animals nor from the TC3 donor are lysed (Fig. 5 B).

A second experiment indicating the nonmitochondrial origin of the H antigen is that its expression is not extinguished by treatment of target cells with chloramphenicol (CAP), an inhibitor of mitochondrial, but not of nuclear, RNA translation (9). In this experiment, CAP treatment completely inhibits lysis of DA/L targets (Fig. 6 A) and partially inhibits lysis of DA targets (Fig. 6 B) by MTA-specific L/DA anti-DA CTL. In addition, CAP treatment of DA targets fails to inhibit any lysis by H antigen-specific DA/L anti-DA CTL (Fig. 6 C).

HAntigen Requires Homozygous MHC Expression. The results presented in Fig. 3, A and B indicate the importance of the RT1C region in expression of the H antigen, in particular, RT1Ca+ gene products. It should also be noted that these data display a requirement that the target cells be from homozygous donors; target cells from homozygous aaavl/aaavl- positive donors (DA, PVG-RT1a+) are lysed, while target cells from heterozygous aaavl/ll/aaavl donors of the F1 animals.

Figure 5. The H antigen does not show a pattern of simple maternal inheritance. (A) L/DA anti-DA CTL lyse MTA+ target cells from DA, DA/L, and TC3 donors, but (B) DA/L anti-DA CTL lyse target cells by only from the DA strain. TC3 is an MTA+, RT1ac+ testcross donor derived from a mating of an RT1ac- DA/WF x WF female and a WF/DA male (see text).

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Figure 6. Mitochondrial DNA translation is not required for expression of the H antigen. (A) Chloramphenicol treatment of DA/L target cells totally blocks MTA-specific lysis by L/DA anti-DA CTL. (B) Similar treatment of DA target cells leads to only partial inhibition of lysis by the same CTL population, and (C) fails to inhibit lysis by H-specific DA/L anti-DA CTL.

Figure 4. Further evidence that H antigen expression is not dependent upon class I RT1A+ gene products. MAC 30, a mAb specific for RT1A+ (A) blocks MTA-specific lysis by L/DA anti-DA CTL of DA/L targets, which requires RT1A+ expression, but this antibody does not inhibit lysis of DA target cells by the same CTL population. (B) MAC 30 does not block lysis of DA target cells by DA/L anti-DA CTL. G2c is another mAb (R3-40) of the same isotype; it has no effect.
A), but F₁ and parental cells are equally as effective in
by several lines of evidence, involving experiments with L/DA
but absent from target cells of F₁ origin. The conclusion
reciprocal DA/L F₁ donors, also present on DA target cells
pretreatment with chloramphenicol, and, unlike a simi-
chromosomally inherited, extinguished on target cells by
mitochondrial origin; it is maternally transmitted, extra-
Discussion
Lymphocytes from L/DA F₁ rats undergoing local GVH
reactions, resulting from inoculation with parental strain DA
lymphocytes, can be stimulated in culture with parental strain
lymphoblasts to generate potent CTL with lytic specificity
for unusual antigen systems. A previous study in this series
demonstrates that one of these antigen systems, MTA, is of
mitochondrial origin; it is maternally transmitted, extra-
chromosomally inherited, extinguished on target cells by
pretreatment with chloramphenicol, and, unlike a similar
mitochondrial antigen system in mice (10), its recognition by
CTL is restricted by class I MHC molecules of the RT₁A
region (see accompanying paper I [3]).

H Antigen. Here, we describe a second antigen system,
H, detected by these same CTL as well as by CTL from
reciprocal DA/L F₁ donors, also present on DA target cells
but absent from target cells of F₁ origin. The conclusion
that H and MTA are different antigen systems is supported
by several lines of evidence, involving experiments with L/DA
anti-DA CTL, which also recognize MTA: (a) the finding
that DA/L F₁ cold target cells fail to compete as effectively
as parental cells for lysis of labeled DA target cells (Fig. 1A),
but F₁ and parental cells are equally as effective in
blocking lysis of labeled DA/L target cells (Fig. 1B); (b) the
finding that MAC30, a mAb specific for RT₁A⁺ gene prod-
ucts (7) and that blocks lysis by MTA-specific CTL of DA/L
target cells, fails to inhibit lysis of DA target cells (Fig. 4A);
and (c) experiments showing that chloramphenicol, which
extinguishes expression of MTA on target cells, completely
inhibits lysis of DA/L target cells by L/DA anti-DA CTL
(Fig. 6A), but only partially inhibits lysis of DA target cells
by these same CTL (Fig. 6B).

Aside from the unexpected finding of being able to generate
F₁ CTL with potent lytic specificity for parental target cells,
there are three properties of the H antigen system that dis-
inguish it from more conventional alloantigen systems rec-
ognized by CTL. First, target cells must express the av₁ al-
lee of the class I-like RT₁C region; second, prototypical class
I gene products of the RT₁A region appear not to be involved,
neither as target structures nor as restricting elements; and
third, the targets must derive from donors homozygous with
respect to the MHC locus. F₁ antiparental CTL with lytic
specificity for an MHC-linked antigen system limited to
homozygous target cells have been noted previously in mice
(11–14), but there appear to be important differences between
the mouse and rat F₁ antiparental responses (see below).

H Antigen and RT₁A Restriction. The apparent lack of
MHC restriction by prototypic class I RT₁A MHC mole-
cules for CTL recognition of the H antigen depends on the
finding that target cells from aaav₁, ccav₁, and aaav₁ donors
are recognized by anti-H CTL, but target lymphoblasts from
aac, auu, and acc donors are not (Fig. 3). Thus, target cells
from three different donors differing with respect to expres-
sion of RT₁A genes are lysed, but a set of three target cells
identical in their expression of RT₁A⁺ genes are not. This
finding can be interpreted as lack of restriction by RT₁A
molecules and dependence in some form on homozygous expres-
sion of a particular allele of the RT₁C region. RT₁C⁺⁺ in-
volve might represent an instance of recognition of an
endogenous peptide restricted by a nonclassical MHC mole-
cule expressed only in homozygotes, or it might be recog-
nized as a native class I-like MHC antigen that is somehow
expressed differently on target cells homozygous with respect
to this region.

H Antigen and MHC Heterozygosity. The requirement for
MHC homozygosity for expression of the H antigen is un-
usual. It depends on the finding that PVGav₁/c target cells,
from donors homozygous in their genetic background but
heterozygous with respect to MHC, are either not, or only
poorly lysed by anti-H CTL (DA/L anti-DA); similarly, cells
from these MHC heterozygous donors do not compete for
lysis of labeled DA target cells in cold target competition assays
(Fig. 7, A and B). This finding indicates the necessity for
homozygosity with respect to MHC, and, since RT₁A⁺ and
RT₁B/D⁺ are unimportant for expression of the H antigen
(Fig. 3, A and B), it is apparent that the homozygous locus is
within the RT₁C region.

Why homozygous gene expression in the RT₁C region
is required for the H antigen is not clear; a range of possibili-
ties can be considered. Perhaps the most trivial, the failure
to recognize the H antigen on heterozygous target cells could
be a reflection of diminished density compared with H expression on homozygous target cells. While this remains a possibility, we consider it an unlikely one. In the absence of any other information, one would assume that H antigen density on homozygous target cells is only twofold greater than on heterozygous target cells; it seems unlikely that a twofold difference in the density of antigen expression could be the basis for an all-or-nothing difference in lytic susceptibility. This simple quantitative argument is not only a problem at the level of target susceptibility but also at the level of self-tolerance of the responding DA/L F1.

Precedent exists in both rats and mice for a more interesting explanation of MHC homozygosity and H antigen expression. One of our groups has described a trans-acting MHC-linked gene (cim) telomeric to the rat RT1A region whose alleles determine post-translational alterations both in the antigenic structure and restriction specificity of class I RT1A molecules (15). Also, Qa-1 in the mouse can be modified by an H-2-linked, trans-dominant gene that alters epitopes detected by some monoclonal CTL lines (16, 17). Still other studies have shown that Qa-1 molecules occur in several allelic forms, some of them with epitopes that depend on N-linked glycosylation (18). The evidence to date from these studies seems to indicate that antigenic alterations brought about by genes of these modifier loci are post-translational effects, rather than changes in the primary protein sequence of MHC molecules. Such effects might involve differences in intracellular assembly or transport of MHC molecules and/or differential glycosylation events.

The H antigen could result from a similar circumstance. If it is an epitope of an RT1C gene product expressed in homozygous animals of some strains, but lacking in MHC heterozygous animals, this would account for some F1 antiparental responses. Absence of such an epitope in the F1 might reflect the existence of an MHC-linked modifier gene, the other parental allele of which could exert a dominant trans-regulatory effect that alters the expression of RT1Cm molecules in the F1. F1 animals would then express an epitope(s) on RT1C molecules different from that (those) expressed in parental animals.

Other Antigen Systems. The unusual features of the H antigen system — mapping to the RT1C region, lack of involvement of RT1A region gene products, and the requirement for MHC homozygosity — raise questions concerning its uniqueness and if it is related to antigens that have been previously described. The finding that H maps to the RT1C region (Fig. 3) might suggest that it is similar to the class I-like Qa, TL, and Hmt molecules that have been described for both mouse and man (19). These molecules are encoded by genes telomeric to the prototypic class I and class II MHC loci; some are thought to have a limited tissue distribution, a lower level of expression, a limited degree of polymorphism, and do not usually serve as restriction elements for CTL responses to environmental antigens. Recent genetic and functional studies have indicated that they are codominantly expressed in F1 individuals and that they can sometimes function as antigen-presenting molecules for recognition by both TCR-α/β and TCR-γ/δ T cells (20). While mapping to the RT1C region, the most potent argument against the notion that the H antigen is the rat version of the murine class I-like Qa, TL, or Hmt molecules is that it is not expressed on F1 target cells; it behaves like the product of a recessive allele.

To what extent is the H antigen here described in rats similar to hematopoietic histocompatibility (Hh) antigens associated with hybrid resistance in mice, a phenomenon involving rejection of parental marrow grafts by heavily irradiated F1 recipients (21)? Trans-regulatory modifier genes have been implicated in control of Hh gene expression as well (21, 22). While rats have been used only infrequently for genetic and mechanistic studies of hybrid resistance, examples in this species have been reported. Irradiated WF/BN and L/BN F1 rats, but not BN/DA hybrids, resist marrow grafts from parental BN donors (23), similar nonirradiated F1 recipients resist engraftment with promyelocytic leukemia cells of BN origin (24), and SV40-transformed BN strain fibroblasts were shown to be more sensitive to lysis by F1 hybrid spleen cells than by cells from BN donors (25). The nature of the effector cells in these rat hybrid resistance models is totally unknown. In addition, the cim/RT1A- phenotype (15) is known to mediate an effect akin to hybrid resistance exhibited by resistance to the induction of conventional popliteal GVH reactions (26; G.W. Butcher, unpublished results).

While NK cells and macrophages have been implicated most frequently as effector cells in in vivo mouse models of hybrid resistance (21), a useful culture model involving the induction of CTL with lytic specificity for homozygous target cells expressing presumptive Hh-like antigens has been described (12–14). C57BL/6 × DBA/2 F1 spleen cells cultured for 5 d with irradiated B6 or DBA parental spleen cells generate lytic activity specific for target cells or stimulator origin. Despite similarities, there are some important differences between this murine Hh model and the rat H antigen that suggest that they may be quite different systems. In the mouse model, priming of the F1 donor with parental cells is not required and, in fact, it inhibits the appearance of lytic cells upon secondary stimulation, the effector cells are T cells, and their lytic activity is limited to homozygous target cells although it can be inhibited in cold target competition assays with F1 cells (14). In contrast, the rat H antigen system described above requires priming to generate killer, the effector cells are T cells (see accompanying manuscript III [5]), and lytic activity against homozygous target cells cannot be inhibited with unlabeled cells from heterozygous donors.

A final consideration is whether the H antigen system is related to the CT antigen system, which we described in rats several years ago (7, 27–29). This is a polymorphic system of medial histocompatibility antigens linked to MHC that are targets for unrestricted CTL responses raised between rat strains sharing similar, but not identical, MHC alleles. The common features of H and CT antigens are that they both map to the RT1C region and both appear to be recognized by CTL independently of prototypical class I MHC gene products. Aside from the donor/recipient combinations used to generate the CTL populations that detect them, these two antigen systems differ in the homozygosity requirement for
H expression. This difference, however, could be accounted for by the modification locus model discussed above. At present, we favor the interpretation that gene products of the RTIC region might be considered as functionally underutilized homologues of murine Qa, TL, and Hmt molecules, and that the H antigen represents a post-translational structural alteration of an RTIC gene product imposed by a dominant modifier in a manner analogous to that described earlier for RTLA (15). Future investigations will aim to discover whether such trans-acting phenomena operate through common or disparate mechanisms.

We thank Ms. Kim Schroder for her excellent technical assistance, Ms. Annette Feinstein for her help in preparing the manuscript, and Dr. K. Fischer Lindahl and C. Cowing for helpful and provocative discussions.

This study was supported by National Institutes of Health grants AI-24526 and AI-22519, and the Agricultural and Food Research Council, Cambridge, UK.

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Received for publication 27 November 1990 and in revised form 3 January 1991.

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