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 *RT1C* Region

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Summary

Lymphocytes from parental strain DA rats can induce potent killer cell responses to atypical antigen systems in F_1 Lewis (L)/DA and DA/L recipients. Here, we describe an antigen system, H, present on homozygous parental target cells, but not on F_1 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 *RT1C* region, and it requires homozygous expression of $RT1C^{av1}$ alleles. This may be another example, this time involving the *RT1C* region, of an MHC gene product antigenically altered by an MHC-linked *trans*-activating modifier gene.

F_1 rats undergoing local GVH reactions, a consequence of footpad inoculation with alloreactive T lymphocytes of parental strain origin, develop CTL responses to unusual antigen systems. In the past, we have shown that priming in vivo with parental cells followed by restimulation in culture with irradiated parental anti-host MLC lymphoblasts generates CTL having lytic specificity for idiotypic markers of alloreactive parental T cells (1). Similar results have been reported from studies in mice (2).

In more recent studies, L/DA rats primed in vivo and restimulated in vitro with DA lymphocytes generate killer cells with lytic specificity for a novel mitochondrial antigen system; it is maternally transmitted, extra-chromosomally inherited, chloramphenicol sensitive, and we have provisionally termed it maternally transmitted antigen (MTA)[1] (see accompanying paper I [3]). This mitochondrial antigen depends on a maternally transmitted factor (MTF) that is present in rats having the genetic backgrounds of the DA, Brown Norway (BN), August 2880 (AUG), and PVG strains, but not the Lewis (L) and Wistar-Furth (WF) strains. In addition, it requires expression of class I $RT1A^a$ gene products for detection by killer cells.

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 F_1 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 *RT1C* 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 F_1 and parental strain DA origin were equally effective in cold target competition assays with labeled DA/L target cells; but that unlabeled F_1 lympho-

[1] *Abbreviations used in this paper:* AUG, August 2880; BN, Brown Norway; CAP, chloramphenicol; Hh, hematopoietic histocompatibility; L, Lewis; WF, Wistar-Furth.

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 F_1 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).

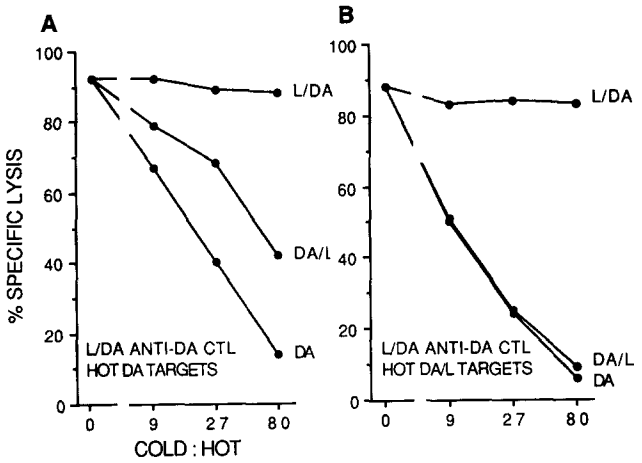

Figure 1. Evidence for a second antigen system detected by L/DA anti-DA CTL on DA target cells. (*A*) Unlabeled DA/L lymphoblasts are less effective than DA lymphoblasts at inhibiting lysis of DA target cells, but (*B*) are equally as effective as cold DA cells in inhibiting lysis of DA/L target cells.

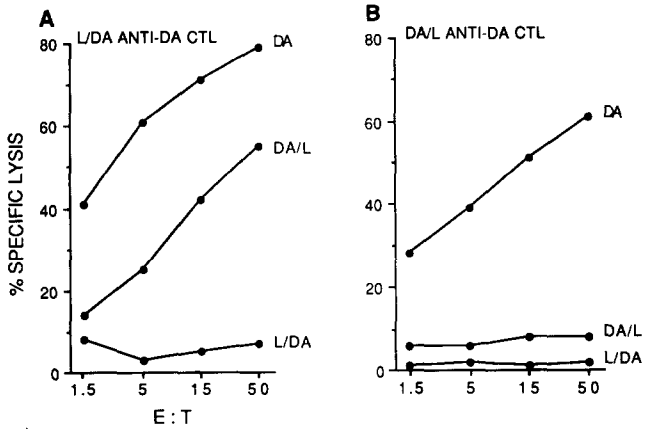

Figure 2. Further evidence for a second antigen system on DA target cells. Comparison of targets lysed (*A*) by L/DA anti-DA CTL and (*B*) by the recriprocal F_1 combination DA/L anti-DA.

CTL Recognition of H Depends on RT1C^{av1}. 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^{av1}* haplotype (DA, PVG-*RT1^{av1}*) are H positive and that class I-like *RT1C^{av1}* gene product(s) are required for expression of H antigen(s). Target cells from congenic and recombinant strain donors expressing the *aaav1*, *ccav1*, and *uaav1* haplotypes are lysed, while those expressing *aac*, *auu*, and *acc* are not. The finding that *aaav1*, *ccav1*, and *uaav1* 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^{av1+}* heterozygous donors (L/DA and DA/L) are H negative. Thus, mere expression of *RT1C^{av1}* 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 $RT1A^a$ molecules, which inhibits CTL recognizing or restricted by $RT1A^a$ (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

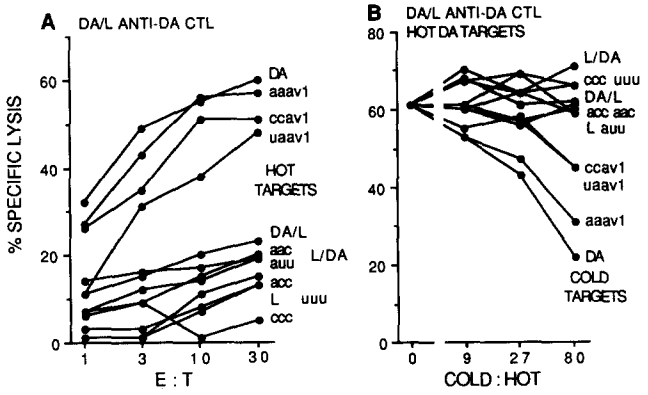

Figure 3. (*A*) direct lysis and (*B*) cold target competition assays with target cells from various MHC congenic and recombinant strains and F_1 combinations showing that the antigen system detected by DA/L anti-DA CTL depends upon expression of the *av1* haplotype of the MHC class I-like *RT1C* region. Note also an apparent requirement for homozygosity of the target cells, since *RT1C^{av1+}* DA/L and L/DA target cells are not lysed nor do they block lysis of labeled targets.

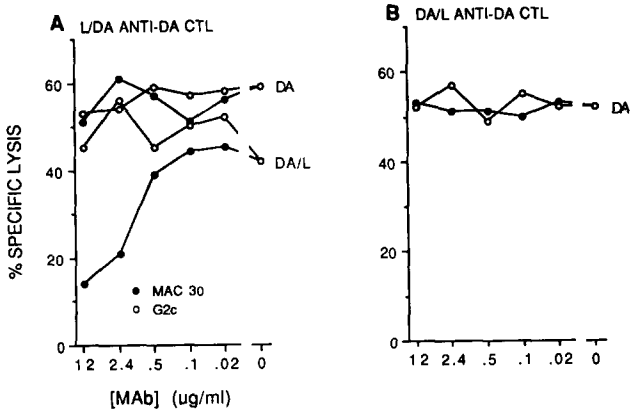

Figure 4. Further evidence that H antigen expression is not dependent upon class I *RT1A*^{a} gene products. MAC 30, a mAb specific for RT1A^a (*A*) blocks MTA-specific lysis by L/DA anti-DA CTL of DA/L targets, which requires *RT1A*^{a} expression, but this antibody does not inhibit lysis of DA target 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.

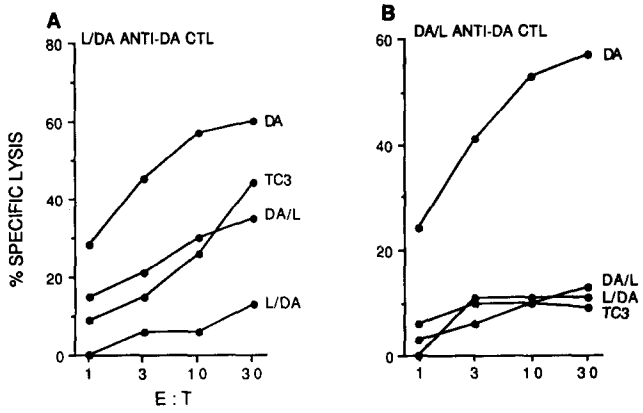

Figure 5. The H antigen does not show a pattern of simple maternal inheritance. (*A*) L/DA anti-DA CTL lyse MTA$^+$ target cells from DA, DA/L, and TC3 donors, but (*B*) DA/L anti-DA CTL lyse target cells by only from the DA strain. TC3 is an MTA$^+$, *RT1*$^{a+}$ testcross donor derived from a mating of an *RT1*$^{av1-}$ DA/WF × WF female and a WF/DA male (see text).

class I MHC gene product. The second, H, is present on parental DA target cells, absent from F_1 cells of L/DA or DA/L origin, and apparently depends upon homozygous expression of *RT1C*^{av1} gene products. The involvement of nonprototypical, class I-like MHC molecules in H expression in the rat raises the possibility that the H antigen may be similar to the mitochondrial Mta antigen of mice, which requires expression of a class I-like gene, *Hmt*, telomeric to the *Tla* region of *H-2* (8).

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 *RT1*$^{av1+}$ testcross animal derived from a backcross mating in which DA was the female grandparent ([DA/WF × WF] *RT1*$^{av1-}$ backcross female × [WF/DA] male). In contrast, DA/L anti-DA CTL (anti-H killers) lyse only DA target cells; target cells from neither of the F_1 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*).

H Antigen 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, *RT1C*^{av1} 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 *aaav1/aaav1*–positive donors (DA, PVG-*RT1*^{av1}) are lysed, while target cells from heterozygous *aaav1/lll* and *lll/aaav1* donors

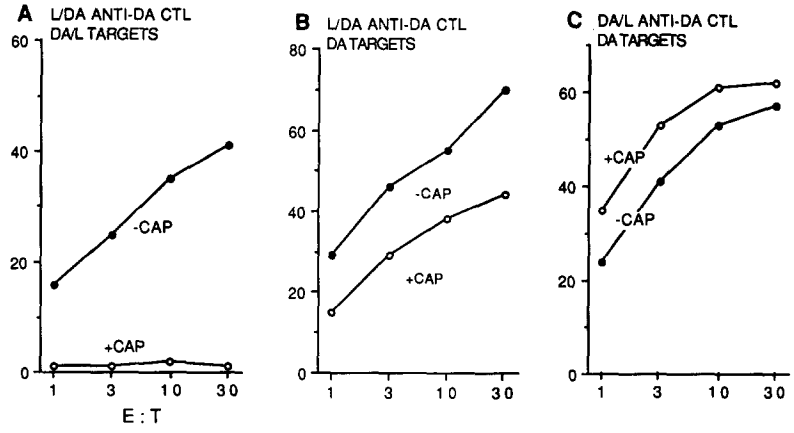

Figure 6. Mitochondrial DNA translation is not required for expression of the H antigen. (*A*) Chloramphenicol treatment of DA/L target cells totally blocks MTA-specific lysis by L/DA anti-DA CTL. (*B*) Similar treatment of DA target cells leads to only partial inhibition of lysis by the same CTL population,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

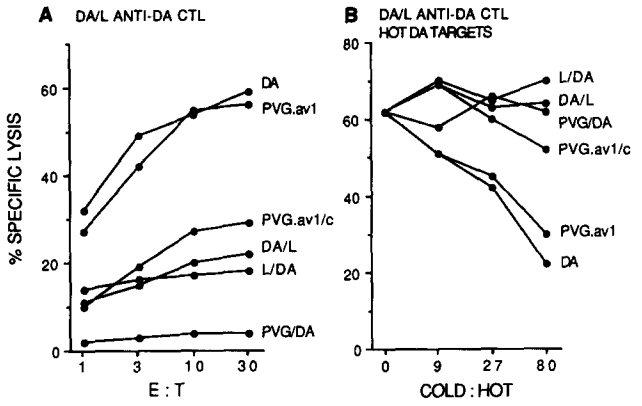

Figure 7. The presence of the H antigen on target cells requires homozygous expression of the *RT1*^{av1} haplotype. (*A*) direct lysis and (*B*) cold target competition assays show that *RT1*$^{av1+}$ target cells from animals heterozygous with respect to MHC are not lysed or are lysed only minimally, and these target cells fail to compete effectively for lysis of labeled DA target cells.

(DA/L and L/DA) are not. Whether this requirement for homozygosity involves the MHC or other loci is shown in a direct lysis and cold competition experiment involving target cells from homozygous PVG-*RT1*^{av1} and (PVG-*RT1*^{av1} × PVG-*RT1*^{c})F_1 hybrid donors (Fig. 7, *A* and *B*). The latter donors are homozygous with respect to their background genes and are heterozygous only at the MHC locus and undefined adjacent regions. Target cells from these congenic F_1 donors show only minimal lysis by H antigen–specific DA/L anti-DA CTL, and as cold targets they cause only minimal inhibition of lysis of labeled H-positive DA target lymphoblasts.

Discussion

Lymphocytes from L/DA F_1 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, extrachromosomally 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 F_1 donors, also present on DA target cells but absent from target cells of F_1 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 F_1 cold target cells fail to compete as effectively as parental cells for lysis of labeled DA target cells (Fig. 1 *A*), but F_1 and parental cells are equally as effective in blocking lysis of labeled DA/L target cells (Fig. 1 *B*); (*b*) the finding that MAC30, a mAb specific for *RT1A*^{a} gene products (7) and that blocks lysis by MTA-specific CTL of DA/L target cells, fails to inhibit lysis of DA target cells (Fig. 4 *A*); 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. 6 *A*), but only partially inhibits lysis of DA target cells by these same CTL (Fig. 6 *B*).

Aside from the unexpected finding of being able to generate F_1 CTL with potent lytic specificity for parental target cells, there are three properties of the H antigen system that distinguish it from more conventional alloantigen systems recognized by CTL. First, target cells must express the *av1* allele 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. F_1 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 F_1 antiparental responses (see below).

H Antigen and RT1A Restriction. The apparent lack of MHC restriction by prototypic class I *RT1A* MHC molecules for CTL recognition of the H antigen depends on the finding that target cells from *aaav1*, *ccav1*, and *uaav1* 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 expression of *RT1A* genes are lysed, but a set of three target cells identical in their expression of *RT1A*^{a} genes are not. This finding can be interpreted as lack of restriction by *RT1A* molecules and dependence in some form on homozygous expression of a particular allele of the *RT1C* region. *RT1C*^{av1} involvement might represent an instance of recognition of an endogenous peptide restricted by a nonclassical MHC molecule expressed only in homozygotes, or it might be recognized 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 Homozygosity. The requirement for MHC homozygosity for expression of the H antigen is unusual. It depends on the finding that PVG$^{av1/c}$ 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*^{a} and *RT1B/D*^{a} 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 possibilities 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 F_1.

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 $RT1A^a$ 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 F_1 antiparental responses. Absence of such an epitope in the F_1 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 $RT1C^{av1}$ molecules in the F_1. F_1 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 F_1 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 F_1 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 F_1 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 F_1 rats, but not BN/DA hybrids, resist marrow grafts from parental BN donors (23), similar nonirradiated F_1 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 F_1 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*^{a} phenomenon (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 F_1 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 F_1 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 F_1 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 *RT1C* 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 *RT1C* gene product imposed by a dominant modifier in a manner analogous to that described earlier for $RT1A^a$ (15). Future investigations will aim to discover whether such *trans*-acting phenomena operate through common or disparate mechanisms.

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