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MHC (RT1) restriction of the antibody repertoire to infection with the nematode *Nippostrongylus brasiliensis* in the rat

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SUMMARY

It might be expected that infections with transmissible agents will elicit an immune response to all of their exoantigens and that immune response (Ir) gene control of responses to individual epitopes on a given parasite component would be obscured by reaction to the molecule as a whole. Humans infected with parasitic nematodes, however, mount antibody responses which are selective for certain parasite components. This was modelled in inbred rats infected with the parasitic nematode *Nippostrongylus brasiliensis* and their responses to secreted antigens analysed by immunoprecipitation and SDS–PAGE. No strain responded to all the potential antigens and only those of identical major histocompatibility complex (MHC) had similar recognition profiles. This MHC-restricted response applied to whole molecules synthesized by the parasite, rather than merely to epitopes thereon and is, therefore, contrary to expectation. Moreover, the response patterns of F_1 hybrid animals were not merely summations of parental responses. This suggests defective antigen presentation of particular parasite components by certain MHC class II molecules and/or cross-tolerance with background gene products.

INTRODUCTION

Immune response (Ir) gene control of the specificity of B- and T-cell responses is well-established but has been mainly defined using model antigens which have no relevance to infection. These include phylogenetically conserved antigens such as insulin (Keck, 1975a, b; Rosenwasser *et al.*, 1979), myoglobin (Berkower *et al.*, 1984; Infante, Atassi & Fathman, 1981), cytochrome c (Solinger *et al.*, 1979; Schwartz, 1985) and artificial amino acid co-polymers (Klein, 1986). The former are likely to have fewer non-self epitopes than might be expected on a similarly-sized component of an infective agent and self-epitopes might lead to down-regulation of responses to otherwise antigenic regions of molecules concerned (Schwartz, 1984; Vidovic & Matzinger, 1988). Artificial co-polymers probably also give a misleading picture because their restricted amino acid composition and repeating structures are likely to provide only a limited scope for epitope diversity. The situation is probably quite different for responses to transmissible disease agents, whose antigens are likely to comprise several unrelated epitopes per molecule. Ir gene effects would, however, still control recognition of individual determinants, but non-responsiveness to a given epitope would probably be obscured by responses to others on that component.

Abbreviation: ES, excretory/secretory antigen; MW, molecular weight.

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For viral, bacterial and protozoan pathogens, Ir gene control of expressed B- and T-cell repertoires has been described (Graham *et al.*, 1989; Barnett *et al.*, 1989; Ivanyi & Sharp, 1986; Lamb *et al.*, 1988; Niiyama *et al.*, 1987; Elson & Ealding, 1987; Harris *et al.*, 1989; Del Giudice *et al.*, 1988; Togna *et al.*, 1986; Good *et al.*, 1987) although, in most cases, this applies to epitopes on a given antigen and does not necessarily extend to non-recognition of whole molecules. In contrast to microparasites, there is a paucity of information on genetic control of responses to the antigens of the multicellular and antigenically more elaborate helminth parasites such as the nematodes, particularly for natural host–parasite combinations. Here we show that major histocompatibility complex (MHC)-linked Ir genes place limits on the antibody repertoire in rats infected with the nematode *Nippostrongylus brasiliensis* and that this leads to responsiveness or non-responsiveness to whole molecules of the parasite.

MATERIALS AND METHODS

Animals and parasites

Rats of all strains except WLEP were obtained from Harlan Olac Ltd, Bicester, Oxon, U.K. The WLEP rats are of an inbred line derived from Wistar stock and have been typed to $RT1^u$ (Christie *et al.*, 1990). The RT1 haplotypes of all the strains used are listed in Table 1. Cultures of the rat nematode *N. brasiliensis* were obtained from the Moredun Research Institute, Edinburgh, U.K. and passaged by standard methods. In the experiments described, the rats were infected subcutaneously at

Table 1. MHC (RT1) haplotypes of the rat strains used

Strain	RT1 haplotype
AUG	c
PVG	c
AGUS	l
LEW	l
PVG-RT1[l]	l
BN	n
WKY	k
AO	u
LOU	u
WLEP	u

8–10 weeks of age with 2000 infective stages, at which dose range the adult parasites will be rejected from the intestine by an immunological mechanism within approximately 15 days of infection (Woodbury *et al.*, 1984). Blood was sampled from individual animals by cardiac puncture following each of three or five infections. Parasite antigen was obtained as supernatant from *in vitro* culture of adult parasites for 4 hr, as described previously (Haig *et al.*, 1982), except that a richer culture medium was used (Kennedy & Qureshi, 1986). This type of preparation is conventionally referred to as excretory/secretory (ES) material.

Radio-iodination, immunoprecipitation and SDS-PAGE

Parasite antigen was iodinated extrinsically with the IODOGEN reagent and immunoprecipitated in a protein A-based assay, as described previously (Kennedy & Qureshi, 1986). This assay was modified as necessary to detect antibodies of isotypes

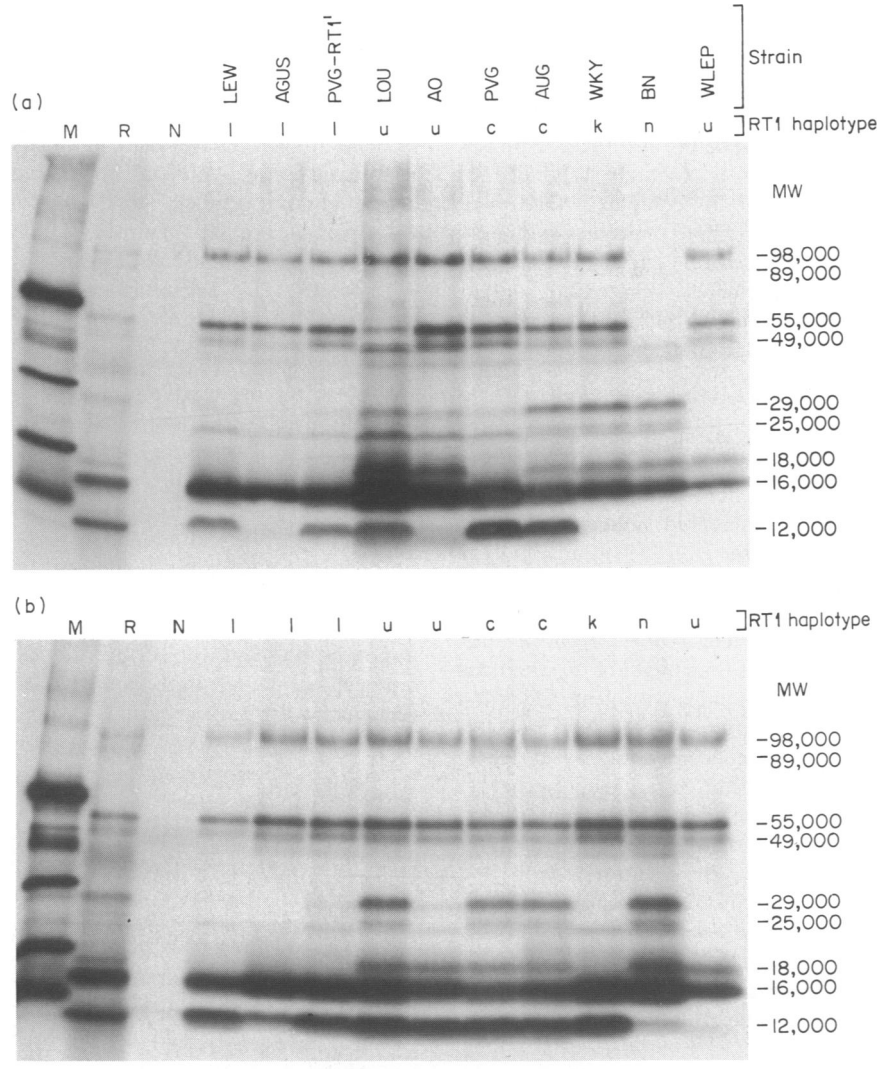

Figure 1. MHC-restricted antibody repertoire to infection with the nematode *N. brasiliensis*. Rats were infected three time (a) or five times (b) with 2000 infective stages, and bled 14 days later. Sera were pooled from six animals per group and assayed by protein A-based immunoprecipitation assay using ^{125}I-labelled secreted materials and the precipitates analysed by SDS–PAGE, under non-reducing conditions, and autoradiography. In (b), the *Staphylococcus aureus* immunosorbent was pre-coated with antibody to rat Ig. The tracks are as follows: iodinated molecular mass marker proteins (Pharmacia 17- 0446-01; Uppsala, Sweden) (M), ^{125}I-labelled parasite secretions (R), immunoprecipitates with normal serum (N) and, in the remaining tracks, sera from the strains indicated.

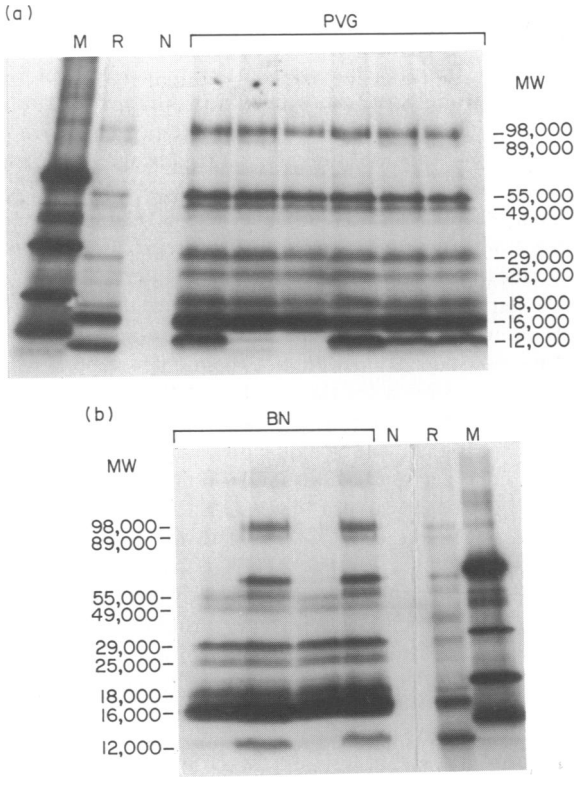

Figure 2. Differences in antigen recognition patterns between individuals within a strain. (a) Serum taken from individual PVG rats taken 14 days after the last of three infections. (b) Serum taken from individual BN rats, 14 days after the last of five infections. Marker proteins (M) and reference antigen (R) are as for Fig. 1.

other than those which bind to protein A by precoating the *Staphylococcus aureus* bacteria immunosorbent with excess sheep anti-rat gamma globulin (Scottish Antibody Production Unit, Carluke, Lanarkshire, U.K). SDS–PAGE was performed with 0·7-mm thick 5–25% acrylamide gradient gels, which were autoradiographed to pre-flashed X-ray film at −70°.

RESULTS

MHC restriction of antibody repertoire to nematode infection

Figure 1 shows the reactivity of pooled sera from a range of different rat strains that had been infected with *N. brasiliensis* on three (a) or five (b) occasions. There were clear MHC-associated differences between the various strains in the components of the parasite to which they responded. RT1^{l} strains were consistently negative for antibody to the 18,000 MW molecule and were the weakest responders to those of 25,000 MW and 29,000 MW. RT1^{u} strains responded variably to the 25,000 and 29,000 MW molecules, the WLEP and LOU strains being weak and strong responders, respectively. This could have been due to differences in the isotype bias in antibody between RT1-identical strains, but modification of the immunoprecipitation procedure to broaden the range of isotypes assayed did not alter the immunoprecipitation profiles of sera taken after either three or five infections.

Comparison of the response patterns on the two occasions showed that the overall recognition profiles of MHC-identical strains remained remarkably similar, although there were some differences in detail. First, more strains responded to the 12,000 MW component after five infections than responded after three. Second, responses to some components faded in spite of further boosting. Third, the BN strain was remarkable in its poor responses to the higher MW molecules after three infections but, after five, it mounted a substantial response to them. These disparities were possibly due to differences in the kinetics of responses in different strains and between individuals within a strain.

Differences between individuals within a strain

Individuals of all strains were screened for differences in antigen recognition and the results from PVG and BN rats, which represented the extremes of similarity or heterogeneity within a particular strain, are illustrated in Fig. 2. Following three infections of PVG animals, the only substantial heterogeneity was in the recognition of the 12,000 MW entity (Fig. 2a), although the profiles became identical after five infections (not shown). A similar situation applied in the AGUS strain. After three infections, individuals of the BN strain were all found to have recognition patterns essentially as in Fig. 1a, but distinct differences became apparent between individuals after five exposures (Fig. 2b).

Unexpected repertoires in F_1 animals

The response phenotypes of F_1 animals can provide some indication of the mechanism of non-responsiveness to certain antigens. Figure 3 illustrates the recognition profiles of two F_1 hybrid combinations in which the responses of the hybrids were not merely summations of parental profiles. The most notable instance involved the 18,000 MW component, responses to

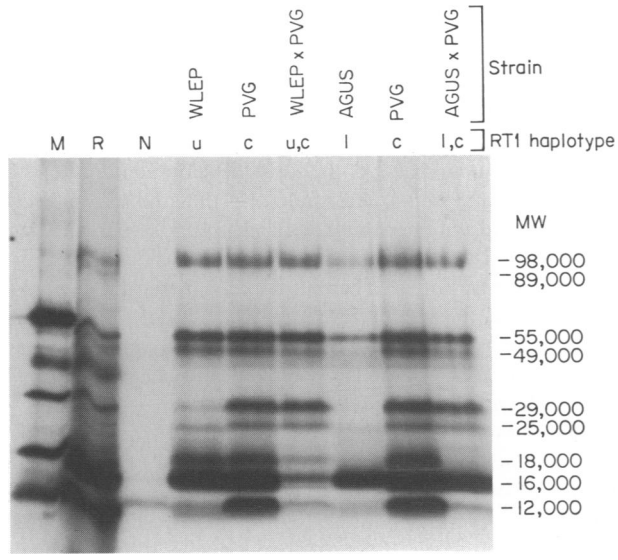

Figure 3. Antibody repertoires of F_1 hybrid animals are not merely summations of parental response phenotypes. Parental and F_1 hybrids were infected three times, and bled 14 days after the last infection. Serum was pooled from six animals per group. Marker proteins (M) and reference antigen (R) are as for Fig. 1.

which were recessively inherited in the (AGUS × PVG)F_1 hybrid. This was also true for the 12,000 MW molecule, but responses to this entity varied too much between individuals and with time for this to deserve emphasis. The same hybrid also provided the clearest example of dominant inheritance, this time involving the 29,000 MW molecule.

DISCUSSION

The secreted materials of several species of parasitic nematode contain protective antigens (Maizels & Selkirk, 1988), and differential immune recognition of these exoantigens is potentially crucial to protective immunity. Of equal significance is the fact that nematode products are known to contain allergens and to stimulate immune T cells to produce mast cell differentiation factors *in vitro*, *N. brasiliensis* being a case in point (Haig *et al.*, 1982, 1983; Petit, Pery & Luffau, 1980). Nematode infections are also potent potentiators of IgE responses to bystander antigens (Jarrett & Miller, 1982) and their secreted materials are claimed to encompass this activity (Stromberg, 1980).

Perhaps the most surprising finding of the present study was that the MHC-restricted recognition of *N. brasiliensis* antigens applied to molecules as large as 98,000 MW. This could have occurred if the antigens concerned comprised repeating structures and that the Ir effects were directed against a limited array of epitopes in each case. Internal repeats in protein sequences are known for several antigens of the malarial parasite *Plasmodium* (Kemp *et al.*, 1986), for example, and it has been argued that these repetitive structures are involved in immune evasion (Anders *et al.*, 1986). There is no such information yet available for nematode exoantigens, but *N. brasiliensis* along with other nematodes is known to secrete a range of active enzymes (Maizels & Selkirk, 1988). Functional constraints on these would probably limit the degree to which repetitive structures could be incorporated without disrupting their biochemical function. Alternatively, immune selection might have resulted in the evolution of biochemically active exoantigens which are of poor immunogenicity or only subject to immune recognition in certain members of the definitive host species.

MHC control of the antibody repertoire has previously been described for nematode infection of mice (Kennedy *et al.*, 1987; Tomlinson *et al.*, 1989), but that work used a parasite which does not progress beyond its early developmental stages in rodents. It could be argued, therefore, that the findings were artifactual and unrepresentative of natural host–parasite combinations. This criticism cannot apply to the definitive host–parasite combination used here. It is likely, therefore, that MHC restriction of the antibody repertoire applies in nematode infections in general and would certainly explain the heterogeneity in antibody response specificities to such infections in humans (Kennedy *et al.*, 1990).

Two possible mechanisms for MHC-restricted recognition of *N. brasiliensis* antigens are the inability of certain class II proteins to present processed peptides of a particular antigen and/or cross-tolerance with self-components (Schwartz, 1985; Vidovic & Matzinger, 1988; Matzinger, 1981). The former is probably the case for the 29,000 and the 25,000 MW molecules to which $RT1^l$ animals were all poor responders, regardless of genetic background. Cross-tolerance is an unlikely explanation for this because hybrids between the non-responder AGUS and the responder PVG were responders to both these entities. In contrast, the variable responses of $RT1^u$ strains to the 25,000 MW, and 29,000 MW molecules is suggestive of cross-tolerance. Of the three strains of this haplotype examined, only LOU rats responded strongly, AO rats occupied an intermediate position, and the WLEP were consistently faint responders, even after five infections. On the other hand, the recognition of these molecules was dominantly inherited in the (WLEP × PVG)F_1, which argues against cross-tolerance in the WLEP parent. The explanation might, therefore, lie in T-cell repertoire potential of the various $RT1^u$ strains used.

Of particular note is the response to the 18,000 MW molecule in which F_1 hybrids between the non-responder AGUS and the responder PVG were not themselves responders. The immediate possibility for this would be tolerance to a component in the AGUS background, which is absent in the PVG, but carried over to the F_1. It would be predicted, therefore, that the $RT1^l$ haplotype might be a responder on the PVG background but this was not the case for the PVG-$RT1^l$ strain (Fig. 1). This indicates that if the effect were due to tolerance, then either tolerance specificities are under MHC control in this case or that the cross-reactive self-component is tightly linked to the MHC. Self-components fulfilling the latter criterion include MHC proteins themselves or C2, C4 or Factor B of the complement system, all of which are polymorphic (Rittner & Schneider, 1989).

The variability in the response patterns between members of the same strain deserves some comment. The possibility that this was due to variability in the infective dose or the genetic composition of the parasites themselves would seem unlikely in view of the numbers given. An alternative might be imperfection in the inbred strains of rat used. While homozygosity most probably pertains in the MHC of these strains, it would be difficult to exclude residual heterogeneity at other loci (McLaren & Tait, 1969). Any such heterogeneity in background loci would then affect cross-tolerance in individuals at an individual level and lead to variability in the expressed repertoire.

The MHC-restricted effects found here were manifest after multiple exposures to the parasite. It is likely, however, that few if any adult parasites developed from the later infections. The observed effects might, therefore, be due to carry-over antibody from earlier infections, or boosting by young adults which managed to establish before immunological expulsion occurred and/or cross-reactivity between adult and larval antigens. Also, several exposures might be necessary to allow the repertoire differences to become apparent. For instance, in a previous study with a different host–parasite combination, MHC effects have been considered subordinate when only primary infections were studied (Else & Wakelin, 1989). It could be argued, therefore, that multiple infection studies are the more relevant to nematodiases of humans because these infections can persist virtually throughout the lifetime of an individual, during which there is continual loss and recruitment of parasites (Anderson, 1986). Lastly, we have unpublished evidence from infections of rats with *N. brasiliensis* and mice with *T. spiralis* that the MHC-controlled repertoire is established as early as the primary infection. The strength of the primary response is, however, not usually sufficient in our hands to permit accurate characterization of the repertoire.

Whether MHC restriction of the antibody repertoire to nematode antigens has any relevance to protective immunity against nematodes remains to be seen. MHC effects have,

however, been firmly established in protective responses to experimental infection in mice (Wassom *et al.*, 1984, 1987) (although non-MHC genes can be the more influential) and in preliminary epidemiological studies in humans (Bundy, 1988). Moreover, the fact that nematode secretions contain allergens means that genetic restriction of immune repertoire could have implications for hypersensitivity responses to parasite infection and to IgE-based immune expulsion mechanisms (Miller, 1984).

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