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No evidence for specificity between host and parasite genotypes in experimental *Strongyloides ratti* (Nematoda) infections

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Abstract

A key requirement for several theories involving the evolution of sex and sexual selection is a specificity between host and parasite genotypes, i.e. the resistance of particular host genotypes to particular parasite genotypes and the infectivity of particular parasite genotypes for particular host genotypes. Determining the scope and nature of any such specificity is also of applied relevance, since any specificity for different parasite genotypes to infect particular host genotypes may affect the level of protection afforded by vaccination, the efficacy of selective breeding of livestock for parasite resistance and the long-term evolution of parasite populations in response to these control measures. Whereas we have some evidence for the role of specificity between host and pathogen genotypes in viral and bacterial infections, its role in macroparasitic infections is seldom considered. The first empirical test of this specificity for a vertebrate–nematode system is provided here using clonal lines of parasite and inbred and congenic strains of rat that differ either across the genome or only at the major histocompatibility complex. Although significant differences between the resistance of host genotypes to infection and between the fitness of different parasite genotypes are found, there is no evidence for an interaction between host and parasite genotypes. It is concluded that a specificity between host and parasite genotypes is unlikely in this system.

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1. Introduction

Interest in the consequences of genetic diversity in host and parasite populations has been stimulated by our recognition of the potential of parasitism as a major force in evolution and ecology. Thus, the antagonistic interaction between hosts and parasites is central to several theories to explain the evolution of sex (Jaenike, 1978; Hamilton, 1980), patterns of sexual selection in host populations (Hamilton and Zuk, 1982) and the maintenance of genetic diversity in both host and parasite populations (Haldane, 1949; Seger, 1988) through the sustained, dynamic interaction of host and parasite genotypes. These theories are predicated on a specificity between host and parasite genotypes (Haldane, 1949); i.e. the ability of a particular parasite genotype to infect one host genotype better than other host genotypes and, conversely, the ability of a particular host genotype to resist infection by one parasite genotype better than other parasite genotypes. This specificity between host and parasite genotypes means that the fitness of a particular host genotype depends on the parasite genotypes to which it is exposed (and that of a parasite genotype depends on the host genotypes that are available). An applied consequence of any such specificity is that selective breeding programmes for increased parasite resistance may result in the selection of host genotypes resistant to a more limited range of parasite genotypes than those found naturally occurring in the field. Similarly, a specificity between host and parasite genotypes may affect the degree of protection afforded by immunization according to both the parasite antigens used in a vaccine and the genotype of the host (Morrison, 1996).

There is now a large body of empirical evidence demonstrating genetic variation in resistance of hosts to a variety of parasite species (Wakelin, 1975; Hill, 1998;

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Pemberton et al., 2004). Equally, we are beginning to build a picture of the role of genetic variation in determining the infectivity of different parasite strains (Wakelin and Goyol, 1996; Moss et al., 2002; Paterson and Viney, 2003). Some notable studies provide evidence for a specificity between host and parasite genotypes: in some invertebrate pathogens, such as microsporidian infections of crustacea (Ebert, 1994; Carius et al., 2001) and trematode infections of snails (Lively, 1987; Dybdahl and Lively, 1998; Lively and Dybdahl, 2000); in some viral infections of humans, such as HIV and influenza; and in Theileria parva infections of cattle (Goddeeris et al., 1990; Morrison, 1996). In general, however, the range of such studies is limited, particularly for parasitic infections of vertebrates and (at least to the author's knowledge) no studies have investigated specificity between host and parasite genotypes in nematode infections.

In vertebrates, the major histocompatibility complex (MHC) is, a priori, a likely source of specificity between host and parasite genotypes. First, the molecular function of genes within the MHC is to present foreign antigen to the immune system (Benacerraf, 1981). They do this by binding short peptides within their antigen presenting site (APS). Although each MHC molecule is able to bind a wide range of peptides, they are restricted in that each bound peptide must have specific 'anchor' residues to enable strong binding (Bjorkman et al., 1987; Bjorkman and Parham, 1990). Second, loci within the MHC are extremely polymorphic, with much of this polymorphism encoded within the APS, which generates functional variation between MHC alleles in the anchor residues required for effective peptide binding (Hedrick, 1994). Third, population and quantitative trait loci (QTL) mapping studies repeatedly highlight associations between MHC variation and resistance/susceptibility to a range of parasitic diseases (Else and Wakelin, 1988; Hill, 1998; Paterson et al., 1998; Wegner et al., 2003). However, few studies have so far attempted to look for associations between MHC variation and resistance to particular parasite genotypes (Penn et al., 2002) rather than resistance to a parasite species.

This study tests for genetic specificity between parasitic nematodes and their vertebrate hosts. Parasitic nematodes are widespread infectious agents, with a high prevalence of infection in most natural vertebrate populations (Shaw and Dobson, 1996), and nematode infections are generally accompanied by morbidity effects such as stunting of growth and loss of condition (Hudson and Dobson, 1995; Stephensen, 1999). These morbidity effects have particular economic importance for cattle and sheep due to the losses in productivity that they can cause. Strongyloides ratti is used here as a model of infection (Viney, 1999). This nematode is a natural parasite of rats and has the feature that clonal lines can be generated from a single individual and maintained thereafter either sexually or asexually [where asexual reproduction occurs without genetic recombination or inbreeding (Viney, 1994)]. This system is used to assay the fitness of defined parasite genotypes in host genotypes

that differ either across their entire genomes or only at the MHC.

2. Materials and methods

2.1. Study system

Strongyloides ratti is a parasitic nematode that naturally infects rats (Dawkins, 1989). Infection is by skin penetration, followed by migration through muscle, lungs, nasopharyngeal region and finally the small intestine, where the adult parasites mature and reproduce. Parasitic stages are female only and produce eggs by mitotic parthenogenesis (Viney, 1994), which are passed in the faeces and can then develop by one of two developmental routes (Viney, 1996; Harvey et al., 2000). In homogonic development, eggs develop directly into infective third stage larvae (iL3s). In heterogonic development, eggs develop into free-living males and females, which mate and produce eggs that develop into iL3s. All parasite lines used were generated from a single iL3 and thus are known as isofemale lines (Tindall and Wilson, 1988; Viney, 1996) and were maintained by serial passage in Wistar rats. The lines ED5, ED43 and ED132 were maintained homogonically, and ED248 and ED321, heterogonically. Thus, for lines maintained homogonically, no genetic recombination occurs and all parasites are identical to each other and to the original wild isolate. For heterogonic lines, genetic recombination will occur in the free-living adults with the consequence that any loci heterozygous in the original wild female will segregate in the laboratory line. Further details on the lines used can be found in Paterson and Viney (2003).

2.2. Experiment 1

Hosts that differ across their entire genome were used to test for an interaction between host and parasite genotypes in the dynamics of experimental infection. Commercially supplied female rats (Harlan, UK), approximately 100 g, were used. These were of inbred strains PVG, Lewis and LOU/C. Groups of rats were infected by s.c. injection of iL3s and faeces collected twice weekly following patency on day 5 p.i. Faeces were cultured and viable eggs counted as described previously (Paterson and Viney, 2003) to assay the reproductive output of these infections through time. PVG and Lewis rats were tested against S. ratti lines ED43 and ED321 in a factorial design consisting of four groups of six rats each infected with 1,000 iL3s. Infections were monitored until day 27 p.i. PVG and LOU/C rats were then tested against S. ratti lines ED5 and ED132 in a factorial design consisting of four groups of six rats each infected with 100 iL3s. Two blocks were used in this design; infections were monitored until day 32 p.i. in the first block and until day 45 p.i. in the second block.

2.3. Experiment 2

Hosts that differ only at loci within the MHC were used to test for an interaction between host and parasite genotypes in the dynamics of experimental infection. Commercially supplied female rats (Harlan, UK), approximately 100 g, were used. These were of congenic strains derived from a PVG background that differed across the MHC region (called the RT1 region in rats). The original PVG strain was used, which is of RT1 genotype c/c, and congenic strains of genotype u/u (found in the LOU/C strain used in Experiment 1) and av¹/av¹. All rats were infected with 100 iL3s and the reproductive output of these infections monitored as for Experiment 1. In the first block of this experiment, five PVG RT1-c/c rats were infected with ED5 and five PVG RT1-c/c rats with ED132; two PVG RT1-u/u rats with ED5 and two PVG RT1-u/u rats with ED132; three PVG RT1-av¹/av¹ rats with ED5 and three PVG RT1- av^{1}/av^{1} rats with ED132. Infections were monitored until day 43 p.i. In the second block of this experiment, three PVG RT1-c/c rats were infected with ED248 and three PVG RT1-c/c rats with ED132; three PVG RT1-u/u rats with ED248 and three PVG RT1-u/u rats with ED132; four PVG RT1-av¹/av¹ rats with ED248 and four PVG RT1-av¹/av¹ rats with ED132. Infections were monitored until day 29 p.i.

2.4. Statistical analysis

Repeated measure analysis was performed in R (http:// www.r-project.org) using a linear mixed effects model, with $\log_e + 1$ transform of reproductive output (Paterson, 2001; Paterson and Lello, 2003). Preliminary analysis indicated that this method provided a better fit to the data than generalised linear mixed models with a Poisson response. Each of the two experiments were analysed separately. Individual rats were fitted as random effects since observations were grouped on each rat. Experimental block, time, host genotype and parasite genotype, and interactions between these terms were fitted as fixed effects. Models were fitted using the maximum likelihood method in R and model selection conducted by standard AIC methods that progressively delete terms using models containing all possible third order terms as a starting point (Lindsey, 1999). Where a higher order term is found to be significant, all lower order terms marginal to that term are retained. Indicative significance levels for each term in the resulting minimal model were determined by deletion testing of each term in turn and comparison of twice the resulting change in likelihood against a χ^2 distribution.

Power analyses were conducted to determine the size of effects that could be detected as significant from the data using a bootstrapping approach. Simulated datasets were generated by combining: the fixed effects estimated in the minimal model from the observed data; a simulated fixed effect for a host by parasite genotype interaction; random effects generated from a normal distribution with variance equal to that estimated in the minimal model; and the residuals from the minimal model resampled without replacement across all data points. Effect sizes for the interaction between host and parasite genotypes—corre sponding to the expectation of the coefficient fitted for this term—ranging from 0.1 to 1, in 0.1 increments, were tested using 1,000 simulated datasets for each effect size.

3. Results

For Experiment 1 (a comparison of rat genotypes that differ across the genome), the minimal models, which contain only significant terms, are summarised in Table 1a,b and displayed in Fig. 1. Infections within this experiment used doses of either 100 or 1,000 iL3s in order to broaden the range of infection regimes used since it is known that the strength of the immune response to S. ratti (as measured by its effect on survivorship and fecundity) increases with infective dose (Paterson and Viney, 2002). However, infections at these two infective doses did not give qualitatively different results. In all comparisons, significant differences between host genotypes on the reproductive output of infections were found (PVG more resistant than Lewis rats, P < 0.001; PVG more susceptible than LOU/C, P < 0.001). Significant differences between parasite genotypes in their reproductive output (P < 0.01, for all pairwise comparisons) were also found, either as main effects or as interaction effects with time. Some differences between blocks were observed (indicated by second and third order interaction terms), particularly with respect to the dynamics of the two parasite genotypes through time. Thus, in the first block the reproductive output of ED5 was consistently lower than that of ED132 throughout, whereas in the second block the reproductive output of ED5 declined more rapidly through time than that of ED132. The interaction term between host and parasite genotype was not significant for either PVG and Lewis rats infected with ED43 and ED248 $(\chi^2 = 1.13, d.f. = 1, P = 0.29)$ or for PVG and LOU/C rats infected with ED5 and ED132 ($\chi^2 = 0.001$, d.f. = 1,

Table 1a			
Minimal model for Experiment	1, PVG and	Lewis inbred	l rats

Fixed terms	Coefficient	$\Delta 2 \times \log$	P value
		likelihood	
Intercept ^a	12.082		
Parasite genotype (ED43)	-0.264	68.348	< 0.001
Host genotype (PVG)	-0.498	16.806	< 0.001
Time	-0.176	3.527	0.060
(Time) ²	-0.008	38.162	< 0.001
Parasite genotype (ED43)×	0.162	86.382	< 0.001
Time			
Random term; rat, $\sigma = 0.004$			
Log likelihood = -232.388			

^a Contrasts are made against Lewis rats infected with ED321. Time is measured in days p.i.

Table 1b Minimal model for Experiment 1, PVG and LOU/C inbred rats

Fixed terms	Coefficient	∆ 2×log likelihood	P value
Intercept ^a	7.259		
Parasite genotype (ED5)	-1.791	7.273	0.007
Host genotype (PVG)	0.794	24.668	< 0.001
Block	-1.395	6.483	0.0109
Time	-0.045	34.697	< 0.001
(Time) ²	-0.00344	0.0481	0.8263
Parasite genotype (ED5) \times	-0.0416	0.831	0.3621
Time			
Parasite genotype (ED5) \times	2.525	15.471	< 0.001
Block			
Block×Time	-0.0811	7.788	0.0053
$Block \times (Time)^2$	0.00418	16.086	< 0.001
Parasite genotype (ED5) \times	-0.0673	14.281	< 0.001
Block×Time			
Random term; rat, $\sigma = 0.369$			
Log likelihood = -752.501			

^a Contrasts are made against LOU/C rats infected with ED132 in block 1. Time is measured in days p.i.

P=0.97). Such an interaction is predicted if a specificity exists between host and parasite genotypes. Significant third order interactive effects involving host and parasite genotypes were not found. Using a bootstrap approach, the power of this analysis to detect an interaction between



Fig. 1. Reproductive output (viable eggs per day) of *Strongyloides ratti* lines ED5 (top panel) and ED132 (bottom panel) in PVG (solid line and squares) and LOU/C (dashed line and circles) female rats. Data from the first block is shown. Lines represent predicted values from the minimal model (Table 1a,b) and markers the actual data.

host and parasite genotypes was determined. The size of this effect corresponds to the coefficient that the model attempts to estimate for the interaction term between host and parasite genotypes. It was determined that an interaction between host genotypes PVG and Lewis and parasite genotypes ED43 and ED248, having an effect of size 0.7 would be detected as significant at the 5% level on 80% of occasions. [In Table 1a, for example, this would correspond to the inclusion of a term for parasite genotype (ED43) \times host genotype (PVG) with a coefficient of 0.7]. For an interaction between host genotypes PVG and LOU/C and parasite genotypes ED5 and ED132, an effect size of 0.8 would be detected as significant on 80% of occasions. Thus, the effect sizes that could be detected for an interaction between host and parasite genotypes are of similar magnitude to the effect sizes that were observed for host and parasite genotypes as main effects (Table 1a,b).

For Experiment 2 (a comparison of rat genotypes that differ only at the MHC), the minimal model is summarised in Table 2 and displayed in Fig. 2. Significant differences between host genotypes on the reproductive output of infections were found as interaction terms with block. As shown in Table 2, genotype u/u appeared the most resistant to infection of the three host genotypes tested in the second block, but this result was not found in the first block. Significant differences between parasite genotypes were observed, with ED5 exhibiting lower reproductive output than ED132, and ED248 lower than either ED5 or ED132. We found no evidence of an interaction between host and parasite genotypes ($\chi^2 = 4.96$, d.f. = 4, P = 0.29). Using a bootstrap approach, it was determined that an interaction between host and parasite genotypes, having an effect of size 0.5 would be detected as significant at the 5% level on 80% of occasions. This effect size is smaller than those observed for host and parasite genotypes as main effects.

 Table 2

 Minimal model for Experiment 2, MHC congenic rats

Fixed terms	Coefficient	$\Delta 2 \times \log$ likelihood	P value
Intercept ^a	7.915		-
Parasite genotype (ED248)	-1.715		-
Parasite genotype (ED5)	-1.088	66.068	< 0.001
Host genotype $(RT1-av^{1}/av^{1})$	-0.155		-
Host genotype (RT1-u/u)	0.736	1.179	0.5547
Block	0.418	1.141	0.2854
Time	-0.157	39.657	< 0.001
(Time) ²	0.000240	2.002	0.1571
Host genotype $(RT1-av^{1}/av^{1}) \times$	-0.0663		-
Block			
Host genotype (RT1-u/u)×Block	-1.359	20.685	< 0.001
$Block \times (Time)^2$	-0.000713	3.335	0.0678
Random term; rat, $\sigma = 0.0185$			
Log likelihood = -600.410			

^a Contrasts are made against PVG RT1-c/c rats infected with ED132 in block 1. Time is measured in days p.i.



Fig. 2. Reproductive output (viable eggs per day) of *Strongyloides ratti* lines ED5 (top panel) and ED132 (bottom panel) in congenic female rats having a PVG background and MHC genotypes RT1-c/c (solid line and squares), RT1-u/u (dotted line and triangles) and RT1-av¹/av¹ (dashed line and circles). Data from the first block is shown. Lines represent predicted values from the minimal model (Table 2) and markers the actual data.

4. Discussion

Functional differences were found between host and parasite genotypes with respect to host resistance and parasite reproductive output in experimental nematode infections. These findings are in line with a large body of work on resistance of laboratory mice to Heligmosomoides polygyrus and Trichuris muris infections (Wakelin, 1975; Else and Wakelin, 1988; Menge et al., 2003) and support previous work on the infection dynamics of different S. ratti lines in experimental infections (Gemmill and West, 1998; Paterson and Viney, 2003). Crucially, however, no evidence was found for a specificity between the genotype of a host and its susceptibility to a particular parasite genotype using rats that exhibit genetic differences across either their entire genome or localised to the MHC. Given that the design of these experiments readily detected host and parasite genotypes as main effects, and power analyses indicate that interactive effects of a similar magnitude could be detected, there can be some confidence that a strong interaction between host and parasite genotypes could have been detected had such an interaction existed. Clearly, the use of more host and parasite genotypes and under a greater range of infection doses and host nutritional status would be desirable to extend the scope of these findings (Ing et al., 2000; Paterson and Viney, 2002). However, this study examined five host genotypes and five parasite genotypes, in a total of 15 combinations and failed to find any evidence for

an interaction between host and parasite genotypes. Given this, it seems reasonable to conclude that a strong, widespread specificity between host and parasite genotypes is unlikely to exist in this system-albeit that the potential for specificity between host and parasite genotypes under some conditions cannot be excluded. These results are also in line with the failure to demonstrate acquired immune responses that are specific to individual S. ratti genotypes rather than infection with S. ratti per se (Paterson and Viney, 2003), and the finding that facultative sexual reproduction in S. ratti can be produced in response to stress imposed by the immune response but not as a response to genotype-specific immunity (West et al., 2001). If these results are applicable to a wider range of nematode species, the medical and veterinary implications are encouraging and would suggest that selective breeding for host resistance and the development of potential anti-nematode vaccines are unlikely to be compromised by heterogeneity in protection due to specific host-parasite interactions.

These results are based on a nematode model of infection and caution needs to be exercised before extending the lack of specificity between host and parasite genotypes found here to other pathogens. Parasitic nematodes are amongst the largest of pathogens to infect vertebrates (in terms of both physical size and genome size) and undoubtedly provide a far larger number of potential antigens than do viruses or bacteria (Parkinson et al., 2003) (although what proportion of these potential antigens actually elicit an effective immune response remains unclear; Kennedy et al., 1990; Frank, 2002). Given this, there may be little relative difference between two nematode genotypes in the number of antigens that they present to the immune system or in the number of antigenic peptides derived from these antigens that will bind to any particular MHC molecule. Thus the scope for specificity between host and parasite genotypes may be inversely related to the complexity of the parasite, with the relatively much simpler virus pathogens exhibiting greater specificity to host genotype than more complex eukaryotic parasites. In support of this, adaptation to host MHC type (i.e. the MHC-restricted cytotoxic T-lymphocyte repertoire of a host) has been documented in HIV/AIDS progression in human patients (Goulder et al., 2001) but a similar effect was not observed in experimental passage of the pathogenic fungus Cryptococcus neoformans through different MHC genotypes in mice (McClelland et al., 2004).

While many theoretical models for the evolution of sex and sexual selection consider the coevolutionary dynamics of host and parasite genotypes, very few models take into account the fact that an individual host is likely to be infected with more than one species of parasite (although see Hamilton, 1986; Frank, 1994). The evolutionary consequences of infection by multiple parasite species may differ markedly from infection by multiple genotypes within a single parasite species. Thus, it is reasonable to hypothesize that—for a single host species infected with a single parasite species and given a specificity between host and parasite genotypes-the frequency of host alleles will shape the frequency of corresponding parasite alleles (and vice versa). However, it is unclear the extent to which the density of different parasite species will be driven by the frequency host alleles, rather than by environmental and ecological factors such as host density, climate, vector abundance, etc. Further empirical work is required to determine whether, in the wild, variation in genes underlying host resistance are driven primarily by a single, virulent parasite species or by a combination of several parasite species (Wegner et al., 2003). Equally, further theoretical work is required to understand the processes able to maintain variation in resistance following exposure to multiple pathogens in a spatially and temporally heterogeneous environment and whether such variation is characterised predominantly by heterozygosity within individuals or by temporal dynamics in gene frequencies within a population (Peters and Lively, 1999; Penn et al., 2002; Nuismer and Otto, 2004).

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