Acta Veterinaria (Beograd), Vol. 45. No. 2–3, 115–126, 1996.

UDK 619:616.995.132:636.4.082

MHC (SLA) CLASS I ANTIGEN PHENOTYPE AND RESISTANCE TO T. SPIRALIS INFECTION IN SWINE: A POTENTIAL RELATIONSHIP

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(Received, 19. January 1996)

A possible relationship between parasite specific immune response and swine leukocyte antigen (SLA) class I phenotype was investigated in outbred domestic swine experimentally infected with Trichinella spiralis. The immune response was monitored by analysing the changes in peripheral blood mononuclear cell subsets, the development of a humoral anti-parasite response and muscle larvae (ML) burden. Potentially important differences in the capacity to resist the infection were seen in swine whose cells express the determinant recognized by monoclonal antibody (mAb), 2. 12. 3; this mAb reacts with an allele of the swine major histocompatibility, or SLA, complex class I antigen. The frequency of pigs which express the 2. 12. 3 phenotype in two Yugoslav swine breeds was 0.56 and 0.33. Evidence suggests that 2.12.3-positive swine exhibit a lower burden of T. spiralis muscle larvae in tongue and/or diaphragm, as well as a delayed development of an antibody response to T. spiralis ML excretory-secretory antigens, after a low level primary infection. These results indicate a genetic basis for resistance to primary T. spiralis inoculation. Further experiments will be necessary to confirm whether such a linkage can be established; this would facilitate selection and identification of T. spiralis resistant swine for breeding and prophylactic purposes.

Key words: Trichinella spiralis, MHC phenotype, resistance

INTRODUCTION

Animals infected with *Trichinella spiralis* exhibit varying degrees of resistance/susceptibility to infection. Genetically- determined differences exist both between particular strains of a host species and between individuals within strains that are genetically heterogeneous. In rodent models, genes within and outside the major histocompatibility complex (MHC) have been shown to be associated with resistant phenotypes in both primary and secondary infection with *T. spiralis.*

The association between murine MHC (H-2) haplotypes and the degree of resistance/susceptibility to primary infection with *T. spiralis,* as measured by the muscle larvae (ML) burden 30 days after inoculation, was first described by Wassom et al. (1979). Further studies with recombinant H-2 strains identified two MHC associated genes, terued Ts-1 and Ts-2, that regulate murine responses to *T. spiralis* inoculation (Wassom et al. 1983a; 1984a). In addition, Bell et al. (1984) identified an autosomal dominant gene (The-1), not linked to the MHC, which appears important in the manifestation of gut expulsion.

Studies using NIH minipigs, inbred pigs defined at their MHC or swine leukocyte antigen (SLA) complex, have demonstrated MHC-associated differences in immune responses to both primary and secondary inoculation with *T.spiralis.* $SLA^{c/c}$ (*cc*) minipigs developed a 50% lower ML burden than *aa* or *dd* pigs following primary infection with *T. spiralis*, which correlated with earlier serum antibody reactivity and augmented cellular blastogenesis to *T. spiralis* antigens (Lunney and Murrell 1988). Primary infection of *aa*, *cc* and *dd* pigs induced a strong concomitant immunity, but, after challenge infection, only *aa* minipigs exhibited a highly significant reduction in the encysted ML burden (Madden et al. 1990). Detailed analyses revealed that 47% of the minipigs bearing at least one dose of the SLA^{a} genotype expressed a "responder phenotype", characterized by a 50-90% reduction in encysted ML remaining from a primary infection (Madden et al. 1993).

For identification of genes associated with disease resistance, especially in outbred pigs, populations of swine can be analysed for the resistance/susceptibility and data correlated with SLA gene inheritance, or swine with known resistance can be analysed for their SLA genes. Such analyses are dependent on having reagents that specifically identify each unique locus product, such as monoclonal antibodies (mAbs) that react with private determinants of specific alleles of SLA antigens. MAbs that react with polymorphic determinants of SLA class I antigens have been produced; mAbs 2.12.3. and 2.32.1. recognize alleles of one SLA locus product, which is expressed on murine fibroblasts transfected with the cloned SLA class I PD14 gene, while another mAb, 2.28.1, reacts with a second SLA locus, represented by the cloned SLA class I PD1 gene (Ivanoska et al. 1991). With these mAbs, analyses of potential relationships between parasite responses and SLA class I phenotypes were examined in outbred domestic swine experimentally inoculated with *T. spiralis.* The specific immune response to the parasite was monitored by analysing the changes in peripheral blood mononuclear cell (PBMC) subsets and the development of a humoral antibody response and ML burden.

MATERIALS AND METHODS

Animals and Experimental Protocol: Domestic Yugoslav meat breed and Yugoslav Landrace pigs were used in two experiments. Cells

from each pig were individually typed with specific anti-SLA class I mAbs. For each experiment groups of pigs of either sex were matched for age and weight and treated to be helminth free. For inoculation, *T. spiralis* (a strain isolated from infected swine muscle at a Belgrade slaughterhouse in 1976 and maintained by regular passage in Wistar rats) infective ML were prepared from carcasses of infected rats and inoculated by oesophageal intubation. For analysis of the potential relationship between parasite response and SLA class I phenotype only weight and *T. spiralis* dose-matched animals were included. In experiment A, 7 Yugoslav meat breed pigs received 12.0 ± 2.2 ML/kg or 357 ± 57 total *T. spiralis* ML recovered by hydrochloric acid-pepsin digestion from infected rat muscle. Each animal was weighed and bled at the start of the experiment (day 0), and then on days 15, 21, 41 and 60 for analyses of PBMC subpopulations and serological testing. Starting from day 47, the pigs were gradually killed and parasitologically examined by enzymatic digestion of their diaphragms for ML recovery. In this experiment, final ML burden was determined in 100 g of diaphragm tissue and since diaphragm weights were not available, the ML burden is reported as LPG (larvae per gram) of diaphragm. In experiment B, 9 Yugoslav Landrace pigs, received an oral inoculation of 300 *T. spiralis* ML (9.6 ± 0.4 ML/kg) and 4 pigs an oral inoculation of 5000 ML (76.8 ± 5.3 ML/kg) at day 0. Each pig was bled at the beginning of the experiment and then on days 21, 42, 63 and 84 for serology and analysis of PBMC subset dynamics.On days 21 and 42 post infection 0.2-0.4 g biopsies were obtained from the tongues after appropriate local anesthesia. Pigs were sacrificed on days 108 and 125 post infection for the lower and higher dose inoculation group, respecively, and their tongues and diaphragms excised for evaluation of ML burden. Final ML burdens were determined in at least 40 g of each tissue and total ML recovered calculated. The lower final larval burdens (LPG) in animals used in exp. B as compared to pigs in exp. A after similar low dose inoculation (app. 10 ML/kg) may be due to the mode of nutrition, since the experimental procedure was the same in both experiments, except that pigs from exp. B were fed *ad libitum* whereas pigs in exp. A were placed on a special restricted diet before and immediately after inoculation.

Monoclonal Antibodies: The characterization and preparation of Abs 2.12.3. (anti-class I, PD14 gene product); 2.32.1 (anti-class I, PD14 gene product); 2.28.1 (anti-class I, PD1 gene product); PT85 (anti-class I, monomorphic); 74-12-4 (anti-CD4); 76-2-11 (anti-CD8); 40D (anti-class II, SLA-DR); TH16 (anti-class II, SLA-DQ) and 74-22-15 (anti-macrophage, granulocyte) has been descibed previously (Davis et al. 1984; Ivanoska et al. 1991; Lunney and Pescovitz 1988; Pescovitz et al. 1984). MAbs were used in specific dilutions either as culture supernatants or ascites preparations.

Fluorescence Analysis: PBMC were separated from whole heparinized blood by density gradient centrifugation on a Ficoll-Ronpacon. For indirect immunofluorescent test, cells were stained with aliquots of murine mAbs specific

for swine lymhocyte antigens, followed by a FITC-conjugated anti-mouse IgG reagent (INEP, Zemun). FITC-conjugated sheep anti-swine IgG (INEP, Zemun) was used to directly label surface immunoglobulin-positive B cells. Immunostained cells were analysed by flow cytometry (EPICS CS Flow Cytometer) or under an ultraviolet microscope.

T. spiralis Antibody ELISA. Serum samples were obtained from each pig at various time points and 1:10 and 1:100 dilutions of each serum analysed for antibody reactivity to *T. spiralis* ML excretory-secretory (ES) antigens by ELISA (Čuperlović et al. 1987). For antibody-positive animals, serum titres were determined as the dilution that gives 50% of the maximum ELISA OD value for the corresponding sample.

RESULTS

Murine anti-SLA class I mAbs 2.12.3, 2.28.1, 2.32.1 and PT85 were used as phenotyping reagents on cells from two breeds of outbred swine, Yugoslav meat breed and Yugoslav Landrace pigs (Table 1).

Table 1. Results of analysis of preparation of anti-SLA class I mAbs in Yugoslav Meat Breed and Yugoslav Landrace pigs

mAb	Frequency Batch I	Frequency Batch II	Total Frequency
2.12.3	0.56 (9/16)	0.33 (5/15)	0.45
2.28.1	1.0 (16/16)	0.53 (8/15)	0.77
2.32.1	N.T.	0.8 (12/15)	0.80
PT85	N.T.	1.0 (15/15)	1.00

Batch I - Yugoslav Meat Breed pigs (16 animals)
Batch II - Yugoslav Landrace pigs (15 animals)
N. T. - not tested

In these two breeds, the reaction patten of 2.12. 3 mAb was the most restricted, since the frequencies in Yugoslav meat breed and Yugoslav Landrace pigs were 0.56 and 0.33, respectively. Although mAb 2.28.1 reacted with cells from all Yugoslav meat breed pigs, it reacted with cells from only about 50% of Yugoslav Landrace pigs (freq. 0.53). MAbs 2.32.1 and PT85 were used only to phenotype Yugoslav Landrace pigs. In this breed, PT85 mAb detected all animals as expected, whereas 2.32.1 reacted with 80% of the tested animals.

The parasite specific immune response was followed for 9 weeks after primary *T. spiralis* inoculation in Yugoslav meat breed (experiment A) and Yugoslav Landrace (experiment B) pigs. In both experiments differences in parasitological and serological findings were seen in 2.12.3-positive swine. In experiment A, 7 Yugoslav meat breed swine infected with 12 ML/kg were compared.

Table 2. Comparison of *T. spiralis* larval recovery from 2.12.3-positive and 2.12.3-negative swine in experiment A.

2.12.3	Pig. N°	Final		
		day p.i.	LPG	Mean
+	104	136	1.36	
+	305	125	1.11	1.19
+	503	47	1.09	
+	505	133	1.19	
—	303	47	10.20	
—	304	96	3.03	6.62
—	504	70	6.64	

Yugoslav meat breed pigs received an oral inoculation of 12.0 ± 2.2. *T. spiralis* ML/kg (357±57 total ML) at Day 0. Pigs were sacrificed on different days post inoculation (p.i.) and 100 g of diaphragms digested. Final ML burdens are expressed as larvae per gram (LPG) of diaphragm tissue.

The results shown in Table 2 revealed that 2. 12. 3-positive swine had lower larval burdens than 2. 12. 3- negative pigs. Since the animals were sacrificed on different days post infection the uniformity of these parasite findings might be questioned, since decreases in ML densities were observed in pigs infected with *T. spiralis* with increasing time after primary inoculation (Murrell 1985).

Table 3. Comparison of *T. spiralis* larval recovery from 2. 12. 3- positive and 2. 12. 3-negative swine in experiment B

Dose ML/kg	2.12.3	Pig N°	Final					
			day p.i.	T+D weight (g)	LPG	Mean	total ML	Mean
9.6	+	004	108	862	0.075	0.075	61.9	61.9
	—	002	108	623	0.15		93.5	
	—	003	108	839	0.15	0.13	125.7	99.0
	—	005	108	779	0.10		77.9	
76.8	+	012	125	681	5.35	5.35	3643	
	—	011	125	719	22.1		15890	
	—	014	125	890	16.1	35.1	14329	25329
	—	015	125	682	67.1		45770	

Yugoslav Landrace pigs received an oral inoculation of 300 (9.6 ± 0.4 ML/kg) or 5000 (76.8±5.3 ML/kg) *T. spiralis* ML at Day 0. Pigs were sacrificed on days 108 and 125 post inoculation (p. i.) for the lower and higher dose inoculation groups, respectively, and at least 40 g of the tongues and diaphragms digested (larvae per gram of combined tissue - LPG). The total ML recovered in tongue and diaphragm (T + D) was calculated for each pig.

In the second trial (exp.B) 4 Yugoslav Landrace pigs that were inoculated with a low dose (9.6 ML/kg) of *T. spiralis* ML were killed at 108 day post infection and ML burden assessed; higher ML burdens were again observed in 2.12.3-negative pigs (Table 3). Since the other 5 low dose-infected swine were subject

to challenge infection on day 42 post primary infection, their final ML burdens were not included in this study. However, to follow the course of the infection in all animals, in this experiment ML burdens were also assessed by examination of tongue biopsies at weeks 3 and 6 post infection.

All 3.2.12.3-positive swine had no detectable parasite burden at biopsy whereas the majority of 2. 12. 3-negative pigs tested (3 out of 4) had ML in biopsy samples on day 42 post infection (Table 4). Even in pigs infected with a high dose *T.spiralis* ML inoculum (76.8 ML/kg) diffrences in ML recovered from either day 21 and 42 biopsy samples or from tongue and diaphragm tissues after sacrifice were observed between 2. 12. 3-positive and 2. 12. 3-negative swine (Table 3 and Table 4).

Table 4. Assessment of *T. spiralis* ML densities in tongue biopsies of 2. 12. 3-positive and 2. 12. 3-negative swine in experiment B

Dose ML/kg	2.12.3	Pig N°	Biopsy LPG	
			day 21	day 42
9.6	+	004	0	0
	+	006	0	0
	+	007	0	0
	—	002	0	N.T.
	—	003	0	N.T.
	—	005	0	2.5
	—	008	0	10.0
	—	009	0	3.3
	—	010	0	0
76.8	+	012	0	3.3
	—	011	3.3	16.7
	—	014	3.3	3.3
	—	015	3.3	16.7

At three week intervals post inoculation (day 21 and day 42) 0.2 - 0.4 g biopsies were performed on the tongues of low - and high-dose infected animals. LPG - larvae per gram; N.T. - not tested.

The development of antibody responses to *T. spiralis* ML ES antigens was analysed by ELISA (Table 5). One of the nine 2. 12.3-negative pigs that received the low dose (~ 10 ML/kg) inoculum was seropositive as early as 21 days post infection; 100% were positive on day 42 post infection. In 2. 12.3-positive swine, antibodies were not detected on day 21. They were first detected on day 42 post infection in 4 out of 7 pigs (57%) but it was not until day 60 post inoculation that all 2. 12. 3-positive pigs exhibited antibody responses to ES antigens. Differences in antibody titres were not observed within groups for antibody positive animals. In pigs given the high dose inoculum, no differences were seen in the development of antibody responses to ML ES antigens between groups.

Table 5. The appearance of antibodies to *T. spiralis* ML ES antigens in the circulation of 2. 12. 3-positive and 2. 12. 3-negative swine

Exp.	Dose ML/kg	2.12.3	Day 0	Day 21	Day 42	Day 60
A	12.0	+	0/4	0/4	2/4	3/3
		—	0/3	0/3	3/3	2/2
B	9.6	+	0/3	0/3	2/3	3/3
		—	0/6	1/6	6/6	6/6
	76.8	+	0/1	0/1	1/1	1/1
		—	0/3	0/3	3/3	3/3

Data are presented as number of seropositive/number of total tested sera for 1:100 diluted serum samples analysed by ELISA.

Sequential changes in PBMC subsets were also analysed during the course of these porcine *T. spiralis* infections. The analysis revealed no differences in cellular subset dynamics between 2. 12. 3-positive and 2. 12. 3-negative pigs (data not shown). Swine from each group exhibited a persistent elevation in both CD4+ and CD8+T cell subsets. No significant differences over time or between groups were found in the number of circulating monocytes/macrophages, B cells or PBMC expressing MHC (SLA) class II antigens.

DISCUSSION

Monoclonal antibodies reactive with polymorphic and monomorphic SLA class I determinants (2. 12. 3, 2. 28. 1, 2. 32. 1 and PT85) were used to phenotype individual outbred domestic pigs. Due to the differences in SLA haplotypes inherited within the breeds each mAb had different reactivities; mAb 2. 12. 3 exhibited frequencies 0.56 and 0.33 in Yugoslav meat breed and Yugoslav Landrace pigs, respectively, while 2.28.1 mAb reacted with cells from all Yugoslav meat breed pigs, but only from a portion of Yugoslav Landrace animals (freg. 0.53). MAb PT85 reacted with cells from all Yugoslav Landrace swine while 2.32.1 exhibited a frequency of 0.80 with cells from Landrace pigs. These frequencies are consistent with previous observations in US outbred swine as well as with the broader analyses on various outbred swine breeds in Denmark and France (Kristensen et al. 1992). From the later studies it was evident that mAb PT85 detects a monomorphic determinant in all tested breeds whereas the other mAbs (2.12.3., 2. 28.1, 2.32.1) detected polymorphic SLA class I determinants. MAb 2.28.1 detects a broadly polymorphic specificity found in several breeds but which is expressed in some haplotypes only on one SLA locus (PD1) product (Ivanoska et al. 1991; Kristensen et al. 1992). For 2. 12. 3 and 2. 32. 1 mAbs (PD14 gene product specific) it was shown that they primarily detect specificity SLA W9 in outbred swine; in addition, mAb 2. 12.3 may also recognize specificity W16. Due to their broad reaction pattern in Yugoslav swine breeds, the association of genotype and *T. spiralis* reactivity was not assessed for mAbs 2.28.1 and 2.32.1 (freq. 0.77 and 0.80, respectively). The reactivity of mAb 2. 12. 3 was more

restricted and thus more useful as an SLA phenotyping reagent in our populations.

After experimental infection with *T. spiralis*, a potential relationship between SLA class I phenotype and immunological and parasitological parameters of the infection was found. The 2.12.3-positive animals exhibited lower larval burdens and delayed development of an antibody response to *T.spiralis* ML ES antigens. Previous experimental findings, both in mice and in inbred NIH minipigs (Jungery and Ogilvie 1982; Lunney and Murrell 1988) have shown that lower ML burdens were correlated with earlier antibody reactivity. However, delayed reactivity to *T. spiralis* ML ES products is not required for the lower larval burdens, since different outbred pigs were used in this study. In addition, the antibodies to *T. spiralis* ML ES products are only a minor component of swine protective immunity and their levels are not necessarily correlated with parasite burdens, since anti-newborn larval antigen responses appear to be more important for swine reactivity against primary *T. spiralis* infections (Marti et al. 1987).

T cell responses may be the most important regulatory factors involved in host resistance/susceptibility to *T. spiralis* infecition since genes both with ih and outside of the MHC have been well demonstrated in rodent and swine models (Bell et al. 1984; Wakelin and Donachie 1983; Wassom et al. 1979; 1983a; 1983b; 1984a; 1984b; 1987; Lunney and Murrell 1988; Maden et al. 1990; 1993). However, the immunogenetic mechanisms underlying swine resistance/susceptibility to *T. spiralis* infection are currently unknown. Various mechanisms could be involved: T cell recognition of foreign antigen in conjunction with self structures encoded by the genes of the MHC and differential presentation of selected *T. spiralis* antigens; differential cell subset stimulation; or differential cytokine production.

The encysted stage of *T. spiralis* is actually a dramatically transformed host myofibril (nurse cell), so presentation of stimulatory *T. spiralis* antigen(s) in conjunction with class I SLA molecules present on virtually all cells could be a possible mechanism mediating the host immune response. In mice, Wassom et al. (1987) have reported an association between resistance/susceptibility to infection with *T.spiralis* and the expression of class MHC (I-E) molecules in different mouse strains. They suggested that presentation of *T.spiralis* antigens in the context of I-E molecules either prefentially induces T suppressor cells or stimulates different T helper subsets.

Differential induction of CD4+helper T cell subsets, Th-1 and Th-2, with their different cytokine secretion patterns, has also been implicated in resistance/susceptibility to *T. spiralis* infection in several murine models (Pond et al. 1989; 1992; Grencis et al. 1991; Kelly et al. 1991; It is not yet clear whether pigs have such defined CD4 subsets or an organ specific secretion pattern, but selective activation of a particular CD4 subset could be a mechanism correlated with resistance/susceptibility to *T. spiralis*. In addition, the presence in pigs of unique circulating T cell subpopulations (excess of CD8+ T cells and a high percentage of CD4+CD8+ double positive T cells) and, in swine infected with *T. spiralis*, the observed elevated levels of CD8+T cells (Ivanoska et al. 1990) and of CD4+CD8+ lymphoblasts after *T. spiralis* antigen stimulation (Dillender and

Lunney 1992) may further alter cellular interactions due to differential cytokine production. This is especially relevant since murine and human CD8+ T cells secrete the Th-1 pattern cytokines (Fong and Mosmann 1990; Kemeny et al. 1994) and human CD4+CD8+ T cell clones have been demonstrated to produce IL-2, IFN and TNF (Patel et. al. 1989). Thus, further analysis of these unique pig T cell subsets, their function and cytokine production may indicate mechanism(s) associated with the anti-parasite immune response and, thus, with resistance/susceptibility to infection.

In this study no differences in PBMC subsets were observed between 2.12.3-positive and 2.12.3-negative pigs. Similar observations were made in inbred pigs, lymphoid cell subsets and expression of activation associated surface markers did not correlate with responder/nonresponder status of aa pigs (Madden et al. 1993). In addition, *T.spiralis*-specific T cell lines were established from PBMC of responder and nonresponder aa pigs (Dilender and Lunney 1992), but unfortunately, they exhibited similar cell surface phenotypes after antigen stimulation. Results of compartmentalization of the IFN versus IL-5 producing lymphoid cells to the spleen and mesenteric lymph nodes, respectively, of *T.spiralis* infected mice (Kelly et al. 1991), and the lymphoid organ-dependent, *T.spiralis*-induced differential cytokine secretion profiles observed in resistant and susceptible mice (Pond et al. 1992; Grencis et al. 1991) revealed the importance of analysis of local tissue responses, since PBMC may not be representative of local immune events.

In summary, in domestic outbred swine, certain preliminary associations between SLA class I phenotype and *T. spiralis* ML. burdens, as well as the appearance of ciruclating anti-parasite antibody, were observed. However, further experiments with a larger number of animals are necessary to confirm whether this apparent "resistance" of 2.12.3-positive swine to *T. spiralis* infection really exists. At this moment it is hard to say whether true MHC (SLA)-associated differences in immunity exist in these pigs, or whether these are just linked characteristics, similar to correlations that have been proposed between levels of resistance to infection and hemoglobin type in sheep (Altaif and Dargie 1978; Čuperlović et al. 1978). In any case if a linkage can be established that might facilitate selection for breeding or identification for prophylaxis.

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POVEZANOST SLA KLASA I FENOTIPA I PRIJEMČIVOSTI SVINJA NA INFEKCIJU SA T. SPIRALIS

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SADRŽAJ

Povezanost između parametara imunskog odgovora i SLA klasa I fenotipa proučavana je kod genetski ne-srodnih svinja eksperimentalno inficiranih sa *Trichinella*-om *spiralis*. Imunski odgovor je praćen analizom promena zastupljenosti imunokompetentnih ćelija periferne krvi, pojavom antitela u cirkulaciji i nalazom parazita u mišićima. Potencijalno važne razlike u otpornosti/prijemčivosti na infekciju ustanovljene su kod svinja čije ćelije su eksprimirale determinantu koju prepoznaje monoklonsko antitelo 2.12.3; ovo monoklonsko antitelo reaguje sa alelom gena klase I glavnog histokompatibilnog kompleksa svinja (SLA). Frekfenca svinja koje su eksprimirale 2. 12. 3 fenotip kod dve rase svinja bila je 0,56 i 0,33. Preliminarni rezultati ukazuju da 2.12.3-pozitivne svinje imaju niži nalaz parazita u mišićima i sporiju pojavu antitela u cirkulaciji. Ovi rezultati ukazuju na genetsku kontrolu prijemčivosti svinja na primarnu infekciju sa *T. spiralis*. Ukoliko dalja istraživanja potvrde postojanje *genetske regulacije* imunskog odgovora, to može olakšati selekciju i identifikaciju *T. spiralis*-otpornih svinja za odgoj ili profilaksu.