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MATURATION OF THE FILARIA *LITOMOSOIDES SIGMODONTIS* IN BALB/c MICE; COMPARATIVE SUSCEPTIBILITY OF NINE OTHER INBRED STRAINS [1]

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SUMMARY

When inoculated subcutaneously, the infective larvae of *L. sigmodontis* undergo complete development and produce a patent microfilaraemia in mice of the BALB background (BALB/c, BALB/K and BALB/B, with respectively the $H\text{-}2^d$, $H\text{-}2^k$ et $H\text{-}2^b$ haplotypes). The most susceptible strain is BALB/c with all mice harbouring adult filariae and 47 % of mice presenting with a patent microfilaraemia. Mice with the B10 background (B10, B10Br and B10D2, with respectively the $H\text{-}2^b$, $H\text{-}2^k$ et $H\text{-}2^d$ haplotypes) are almost completely resistant to infection.

Adult filariae were recovered from all mice of the CBA/Ca, CBA/HN, C3H/HeN, DBA/2N strains. However, the site and structural development of the parasite varied in each strain. Absence of microfilaraemia is associated with absent or abnormal spicules, reduced number of female filariae and small size of female filariae.

These results show that the Major Histocompatibility Complex only modulates the developmental pattern of filariae within the limits imposed by background genes.

Male CBA/HN and C3H/HeN were more susceptible to infection than female mice. Inverse phenomenon was observed with strains BALB/c; and, no host sex effect was seen in DBA/D2N.

RÉSUMÉ : **Développement complet de la filaire *Litomosoides sigmodontis* chez la souris BALB/c; comparaison avec neuf autres souches consanguines.**

Après inoculation sous-cutanée des stades infestants, la filaire *L. sigmodontis* effectue son développement complet chez les souris de souche BALB/c, BALB/B et BALB/K ayant respectivement les Complexes Majeurs d'Histocompatibilité $H\text{-}2^d$, $H\text{-}2^b$ et $H\text{-}2^k$. La souche BALB/c est la plus sensible avec 47 % de souris à microfilaires sanguines et 100 % de souris avec des filaires adultes, 2 mois après l'inoculation. A l'opposé, les souches B10, B10Br et B10D2, ayant respectivement les haplotypes $H\text{-}2^b$, $H\text{-}2^k$ et $H\text{-}2^d$, sont presque complètement résistantes. Dans les souches CBA/HN, CBA/Ca, C3H/HeN, DBA/2N, il y a 96 à 100 % de souris avec des filaires adultes, mais pas de souris à microfilaires sanguines; le développement parasitaire présente différentes anomalies, qui sont cumulées ou non : spicules anormaux, femelles très petites, sex ratio déséquilibré, forte proportion des femelles dans la cavité abdominale alors que la localisation normale est thoracique. Les souris mâles CBA/HN et C3H/HeN sont plus sensibles à la filaire que les souris femelles; avec la souche BALB/c, la microfilarémie est supérieure chez les souris femelles; avec les DBA/2N, les résultats sont semblables dans les deux sexes. La comparaison des lignées congéniques BALB d'une part et B10 d'autre part montre que la région *H-2* du Complexe Majeur d'Histocompatibilité module la réponse au parasite, dans les limites imposées par le fond génétique.

INTRODUCTION

Filaria/mouse experimental models are necessary for the study of mechanisms of immunity and genetics of filarial infections. As indicated in *Table I A and B,* there have been many attempts to develop such models (the numbers in this table refer to papers quoted below).

Most work has been carried out using *Brugia* filariae. Results obtained indicate that subcutaneous inoculation of infective larvae (L3) can give rise to a patent microfilaraemia only in nude mice *(Table I)* (5, 6, 8, 14) or thymectomised mice (7). Intraperitoneal inoculation of L3 results in patent microfilaraemia only using the neonate male Swiss mice (11) although microfilariae can be found in the peritoneal cavity of BALB/c mice (9, 22), CBA/Ca (13) and, asplenic DH mice (9) following this route of inoculation.

The rodent filaria *Acanthocheilonema viteae* is also used in mice but surgical implantation of adult filariae are performed to obtain a microfilaraemia (25, 29).

Recently, we have found that *Litomosoides galizai* Bain

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TABLE I A and B. — *Filaria/mouse models; A: mice inoculated with infective larvae; B: mice infected by transplantation of various stages, excluding infective larvae.*

TABLE I A.

Ref	FILARIA	MICE	INOC.	d- NECR.	F/L3	Mf	AUTHORS
1	L.sigmodontis	White mice	IN	-	-	+	HAWKING, BURROUGHS, 1946
2	B. malayi	White mice	SC 25L3	180	0	0	LAING et al.,1961
3	B. pahangi	White mice	SC	6-115	0	0	AHMED,1967
4	L.sigmodontis	Mus sp	IN	>65	-	+	PATRA, BASU, 1970
5	B.pahangi	BALB/c,CBA/Ca,AKR	IP 50L3	90	0	0	SUSWILLO et al.,1980
	=	T.O (outbred)	=	=	0	0	
	=	outbred (nu/nu)	IP 86-100L3	150	4	+	
	=	= (nu/+),(+/+)	IP 86-100L3	=	0	0	
6	B.pahangi	C3H/HeN (nu/nu)	SC 100L3	80-240	-	+	VINCENT et al. ,1980
	=	= (nu/+),(+/+)	=	50-72	0	0	
7	B.pahangi	CBA/H-T6T6 thymecto.	SC 100L3	166	1.2	+	SUSWILLO et al., 1981
	B.pahangi	=	IP 100L3	=	25.8	+	
8	B.pahangi	C3H/HeN(nu/nu)	IP 200L3	163	16	-	VINCENT et al.,1982
	=	=	SC 10-100L3	-	-	+	
	=	=	SC 100L3	160	14.3	+	
	=	C3H/HeN(nu/+)	=	=	0	0	
	=	=	SC 25-50L3	40	0	0	
	=	=	IP 100L3	160	-	0	
9	B.pahangi	BALB/c	IP 50L3	28	19.2	+IP	HOWELLS et al., 1983
	=	CBA/Ca	=	=	12.2	-	
	=	C3H/He	=	=	5.2	-	
	=	B10	=	=	9.6	-	
	=	101	=	=	8	-	
	=	Asplenic (DH/+)	=	=	38	+IP	
	=	Normal (+/+)	=	=	2.5	-	
10	B.pahangi	C3H/HeN(nu/nu)	SC 50L3	40	14.6	-	VICKERY et al.,1983
	=	= (nu/+)	=	=	0	-	
11	B.pahangi	Neonate Swiss male	IP 100L3	100-140	7	+	FURMAN et al., 1983
	=	= female	=	=	7.4	0	
	=	= male	SC 100L3	=	3.7	0	
	=	= female	=	=	3.9	0	
12	B.malayi	BALB/c	IP 100L3	14	23	-	HAYASHI et al.,1984
	B.pahangi	=	=	=	26	-	
13	B.pahangi	CBA/Ca	IP 100L3	84	1	+IP	MACKENZIE et al., 1985
14	B.malayi	C3H/HeN(nu/nu)	SC 50L3	>60	-	+	VICKERY et al.,1985
	B.patei	=	=	>60	-	+	
	B.pahangi	=	=	>60	-	+	
15	B.pahangi	BALB/c	IP50L3	29-32	10-42		DEVANEY et al.,1985
16	B.pahangi	BALB/c male	IP 50L3	49	>	-	NAKANISHI,1987
	=	= female	=	=	<	-	
17	B.malayi	BALB/c	IP 50L3	30	2	-	CARLOW, PHILIPP,1987
18	L.galizai	Swiss	SC 25L3	>60	-	+	DIAGNE et al., 1989
	=	BALB/c	=	>60	-	+	
19	B.pahangi	BALB/c male	IP 100L3	15	1.7	-	SAKAMOTO et al., 1989
	=	= female	=	=	4.8	-	
	=	C3H/He male	=	=	1.8	-	
	=	= female	=	=	6.8	-	
	=	C57BL6 male	=	=	9.1	-	
	=	= female	=	=	3.7	-	
	=	ICR male	=	=	17	-	
	=	= female	=	=	10.8	-	
20	B.pahangi	C57BL6 male	IP 50L3	15	52	-	NAKANISHI et al., 1989
	=	= female	=	15	29	-	
21	B.malayi	BALB/c	IP DC20L3	21	65	-	ABRAHAHM et al.,1989
22	B.malayi	BALB/cCR male,female	IP 100L3	140-316	1.1	+IP	LI YUTANG et al., 1989
	=	BALB/cJ male	=	=	1	+IP	
	=	= female	=	=	0	0	

TABLE I B.

Ref	FILARIA	MICE	INOC.	Mf	AUTHORS
23	A.viteae	CBA/H	IV Mf	short	THOMPSON et al., 1979
	=	CBA/N	=	long	
24	B.pahangi	BALB/c	IP 50L3	+IP	SUSWILLO et al.,1980
	=	CBA/Ca; AKR; T.O	=	0	
	=	BALB/c	IP L4	+IP	
	=	CBA/Ca; AKR; T.O	=	0	
	=	BALB/c; CBA/Ca; AKR; T.O	IP Adult	+IP	
25	A.viteae	BALB/c	Adult	high, long	HAQUE et al., 1980
	=	C3H/He	=	intermediate	
	=	C57BL6	=	low, short	
26	B. malayi	CBA/H	SC Mf	short	THOMPSON et al., 1981
	=	CBA/N	=	long	
27	O.lienalis	BALB/c; DBA/2; CBA/H-T6T6	SC Mf	>50	TOWSON, BIANCO,1982
	=	C57BL; A+; BKW$_{\beta}$ AKR	=	>36<43	
	=	BK/TO; C3H; sh/sh; T.O	=	30<	
28	B. malayi	CBA/CaJ; C3H/HeJ; DBA/1J	IV Mf	low, short	FANNING, KAZURA, 1983
	=	AuSs/J; A.Sw/Sn;	=	=	
	=	BALB/cJ; C57Br/cdJ; AKR/J;	=	high, long	
	=	C57BL/6J; 129/J; DBA/2J	=	=	
	=	B10D2/NSn, OSn; SJL/J	=	=	
		Susceptible X Resistant F1		low, short	
29	A.viteae	BALB/c; BALB/B; BALB/K	Adult	high, long	STOREY et al., 1985
	=	B10; CBA; C3H	=	low, short	
	=	BALB/c X (B10)F1	=	low, short	
30	B.malayi	SMMC/B	IV Mf	high, long	LIU et al.,1987
	=	BALB/cCR; LACA; ICR/JCL	=	low, short	

Ref.: number of the reference given in the text. FILARIA: species of *Litomosoides* (L.), *Brugia* (B.), *Acanthocheilonema* (A.) and *Onchocerca* (O.). MICE: outbred stocks and inbred strains of mice (code symbols *in* Festing, 1987 and Lyon and Searle, 1989). INOC.: in *Table A,* number of L3 inoculated and way of inoculation, IN: by vectors, SC: subcutaneously, IP: intraperitoneally, and DC: within diffusion chamber; in *Table B,* IV Mf, SC Mf: microfilariae inoculated intravenously or subcutaneously; L3, L4, adults: different post-infective stages. d-NECR.: time in days between inoculation and necropsy. F/L3: percentage of infective larvae developed into adult filariae. Mf: in *Table A,* presence (+) or absence (0) of microfilariae in the blood, or peritoneal cavity (IP); in *Table B,* level (high, low) and duration (long, short) of microfilaraemia; for *O. lienalis* microfiladermia expressed by the number of Mf/g of ear-skin. In each column, —: no data.

et al., 1989 may develop a patent microfilaraemia following subcutaneous inoculation of L3 in Swiss and BALB/c mice (18). More recently, more successful mouse infections were achieved using the closely related *L. sigmodontis* Chandler, 1932 (= *L. carinii, in* Bain *et al.,* 1989). The observation that *L. sigmodontis* can undergo complete development in the mouse is not new (1, 4) but possibly due to greater interest shown in *Brugia* spp., the seminal works of Hawking and Burroughs (1) and Patra and Basu (4) have been largely forgotten.

It has been claimed that *Litomosoides* spp. are of little interest because this genus is zoologically distant from human filarial species. However, the Phasmidian nematodes realise a very homogeneous group (Chabaud, *in* Grassé, 1965) which exhibit extensive immunological cross-reactivity. Furthermore, *Litomosoides, Brugia, Wuchereria* and *Onchocerca* belong to the same subfamily (see Key of filariae, by Anderson and Bain, 1977).

The *L. sigmodontis* large size and ease of recovery free of host tissues make it a useful study system. In anticipation of immunological and genetic studies, the quantitative and morphological characteristics of its development have been studied in 10 inbred and congenic mouse strains with three objectives:

1 — To identify susceptible and resistant strains of mice.

2 — To assess whether or not host sex affect the *L. sigmodontis* development.

3 — To determine a possible role of the Major Histocompatibility Complex (MHC).

MATERIALS AND METHODS

INFECTION OF MICE

L. sigmodontis is maintained in *Meriones unguiculatus* and cyclically passaged through the mite *Bdellonyssus bacoti* (*in* Diagne *et al.,* 1989). The infective larvae were recovered from mites by dissection in RPMI 1640 containing 20 % calf serum. Mice were infected by subcutaneous inoculation of 25 infective larvae into the right side of the lumbar area of one month old animals.

MOUSE STRAINS

Ten strains of mice were used with different genetic backgrounds and different *H-2* regions of the MHC (code sympols in Festing, 1987 and Lyon and Searle, 1989):

1 — 3 congenic strains of the BALB background, with three different *H-2* haplotypes: BALB/c *(H-2^d)*, BALB/B *(H-2^b)* and BALB/K *(H-2^k)*.

2 — 3 congenic strains of the B10 background (= C57BL/10): B10D2 *(H-2^d)*, B10Br *(H-2^k)* and B10 *(H-2^b)*.

3 — 2 strains of the CBA background: a line of CBA/HN *(H-2^k)* which has the mutation *Xid* (a defect of IgM and IgG 3 in both mouse sexes), and CBA/Ca *(H-2^k)*.

4 — C3H/HeN *(H-2^k)*.

5 — DBA/2N *(H-2^d)*.

Both sexes of the BALB/c, CBA/HN, C3H/HeN and DBA/2N strains were inoculated. Only male mice of the other strains were inoculated.

TABLE II. — Litomosoides sigmodontis *in ten inbred and congenic strains of mice.*

MICE						FILARIA				
STRAIN	S	Mf	%Mf	%F	N	%TC	Fm	Ff	F	F/L3
BALB/c (d)	m	2.3(a)	41	100	58	75.7 ±11.3	2.8 ±0.2	2.9 ±0.2	5.7 ±0.3	23
	f	6.7(a)	62	100	21	79.6 ±13.3	2.3 ±0.3	2.3 ±0.4	4.6 ±0.5	18
BALB/K (k)	m	1.2	28	100	18	82 ±13.2	1.9 ±0.3	1.8 ±0.3	3.7 ±0.4	15
BALB/B (b)	m	0.6	6	100	18	94.9 ±5.2	2.4 ±0.3	2.4 ±0.4	4.8 ±0.6	19
CBA/HN (k)	m	0	0	100	10	90.6 ±8.2	4.3(b) ±0.9	3.9(c) ±0.4	8.2(d) ±0.9	33
	f	0	0	100	9	90.4 ±13.1	1.9(b) ±0.3	2(c) ±0.4	3.9(d) ±0.6	16
CBA/Ca (k)	m	0	0	100	10	93.7 ±14.1	3.4 ±0.6	3.6 ±0.8	7 ±1.3	28
C3H/HeN (k)	m	0	0	100	5	61.8 ±26	2 ±0.7	3 ±0.6	5 ±0.8	20
	f	0	0	100	16	62.3 ±6.6	1.9 ±0.3	3.4 ±0.4	5.4 ±0.3	22
DBA/2N (d)	m	0	0	96	24	63.3 ±19.1	2.2 ±0.4	0.3 ±0.1	2.5 ±0.4	10
	f	0	0	100	6	42.6 ±18	2.2 ±0.4	0.8 ±0.2	3 ±0.4	12
B10 (b)	m	0	0	28	18	-	0.2 ±0.1	0.1 ±0.1	0.3 ±0.1	1
B10Br (k)	m	0	0	12	16	-	0.1 ±0.1	0.1 ±0.1	0.2 ±0.1	1
B10D2 (d)	m	0	0	6.7	15	-	0.1 ±0.1	0	0.1 ±0.1	0.4

The haplotype *H-2* of the major histocompatibility complex is written in brackets, under the name of each strain. In the column MICE, S: mouse sex (m: male; f: female); Mf: mean microfilaraemia of the mouse sample, expressed for 10 mm³ of blood; % Mf: percentage of mice with microfilaraemia; % F: percentage of mice with adult filariae; N: number of mice in the sample. In the column FILARIA; % TC: percentage of the adult filariae recovered in the thoracic cavity; Fm and Ff: number of male or female filariae; F: total number of filariae; F/L3: percentage of infective larvae developed into adults. ±: standard deviation. The paired values which are significantly different are followed by one lower case letter (a, b, c or d).

PARASITOLOGICAL ANALYSIS

The following assessments were performed two months after inoculation:

1 — Measurement of microfilaraemia *(Table II):* the microfilaraemia was determined in 10 mm³ of blood collected from the retro-orbital sinus, stained with Giemsa. When mice had no microfilariae but adults worms, 10 mm³ were collected from the heart for control. The mean microfilaraemia of a given strain of mice (and a given mouse sex) was calculated on the whole sample, including amicrofilaraemic mice.

2 — Number of adult filariae and localisation in thoracic or

TABLE III. — *Morphology of* Litomosoides sigmodontis *recovered from the mice strains and, for comparison, from* Meriones unguiculatus *(M. U.).*

The strain B10D2, which is almost totally resistant, is not in the Table.

MICE			FEMALE FILARIA						MALE FILARIA			
STRAIN	S	N	L ±s	W ±s	UE	DE	Mf	nF NF	L ±s	W ±s	Sp. an.	NF
BALB/c	m	7	58.7 6.1	200 17.1	+++	++	+	8 15	15.8 2.9	109 21	0%	12
	f	7	55.5 8.9	210 5.7	+++	++	+	6 11	18.8 ±2.3	116 ±8.9	42%	12
BALB/K	m	14	59 11.6	181 39.3	+	+	+	3 26	17.1 2.7	103 18.7	0%	16
BALB/B	m	9	58.1 10.6	189 31.6	+++	+	±	1 16	17.6 2.2	112 12	13%	8
CBA/HN	m	5	44.2 14.7	171 35.5	+	+	0	0 11	15.9 1.9	105 19	58%	12
	f	6	40 10	196 5.5	±	±	0	0 5	16.8 1.6	110 7	20%	5
CBA/Ca	m	4	56.8 6.9	189 31.6	+++	++	±	1 14	16 1.9	95 11.5	75%	12
C3H/HeN	m	4	62.6 10.1	206 9.1	+++	++	++	3 8	18.8 0.8	120 28.2	0%	5
	f	5	58.1 9.2	184 36.3	++	+	0	0 16	18.5 0.5	109 11.2	75%	8
DBA/2N	m	5	60.6 8.1	180 52.9	++	0	0	0 3	18 1.2	108 8.3	40%	5
	f	2	62	200	++	0	0	0 1	16.2 2.2	108 21.6	100%	5
B10	m	5	30 -	150 -	0	0	0	0 1	15 3	102 4.4	40%	5
B10Br	m	1	51 -	190 -	0	0	0	0 1	17	120	0%	1
M.U	m/f	2	83.6 11.3	242 8.4	++++	++++	++++	5 5	21.6 1.1	156 5.5	0%	5

N: number of rodents from which a sample of filariae were randomly studied; in BALB/c, K, B strains, respectively 3/7, 3/14 and 0/9 of the mice had blood microfilariae. In the column FEMALE FILARIA: L: body length, in mm. W: body width, in µm. UE, DE, Mf: respectively, mean densities of undivided eggs, divided eggs and uterine microfilariae in the female filariae. nF and NF: number of female filariae with uterine microfilariae and number of studied female worms. In the column MALE FILARIA: Sp. an.: percentage of studied male filariae with abnormal or no spicules. Nf: number of male filariae studied.

abdominal cavities; sex ratio: number of males/number of females filariae *(Table II)*.

3 — Presence and localisation of filarial cysts.

4 — Morphological analysis of filariae *(Table III)*: measurement of length (L in mm), width (W, in μm); analysis of female genital apparatus: estimation of number of undivided eggs, divided eggs and uterine microfilariae; morphological abnormalities in male filariae: the right, or more often the left spicules were abnormal; sometimes, one or both spicules were absent.

In each strain, the morphological analysis was performed on filariae randomly sampled from several mice. In the 3 BALB strains, which show patent microfilaraemia, filariae were sampled from mice with and without microfilariae.

Statistical analysis

To compare adult worm burden, microfilaraemia and size of the worms in the different mouse strains, two non-parametric tests were used: test U of Mann-Whitney and test H of Kruskal-Wallis. Confidence intervalle to 95 %.

RESULTS

The pattern of development of the filariae in the different mouse strains *(Tables II and III)* enable these to be divided into those in which a microfilaraemia does or does not develop. Among the last group, a further division can be made into those strains with 96-100 % of inoculated mice harbouring filariae and those in which less than a third of them have filariae.

In each strain, filarial cysts were observed, these were principally localized in the thoracic cavity; the mean number per mice was nearly 1, with extremes of 0.3 in CBA/Ca and 1.7 in DBA/2N.

1 — Mouse strains presenting with blood microfilariae

These are mice of the BALB background. They have the following features in common: all mice harbour filariae, with a mean of 3.7 to 5.4/animal; the filariae are primarily localised in the thoracic cavity; the filarial sex ratio is normal; the female worms measure 58-59 mm in length; and, the males measure 16-17 mm.

The BALB/c strain is the most susceptible with nearly one in two animals presenting with a microfilaraemia (79 mice examined); half the female filariae possess microfilariae in their uteri. Some differences linked to the sex of the mouse are seen; in male mice, microfilaraemia is lower: 2.3 vs. 6.7/10 mm³ and no spicular abnormalities are seen in the twelve male filariae studied; but in female mice, 5 of 12 have abnormal spicules.

In the BALB/K strain, the mean microfilaraemia is 1.2/10 mm³; 28 % of mice were microfilaraemic (18 examined) and three of twenty-six female filariae contained microfilariae in their uteri; the density of divided and undivided eggs in uteri was low.

The BALB/B strain is rarely microfilaraemic (one of eighteen mice), the mean microfiraemia was 0.6 mf/10 mm³; one in sixteen female filariae had uterine microfilariae at a low density; a small proportion of male filariae had abnormal spicules (one in eight).

2 — Mouse strains presenting without blood microfilariae

A — *Strains with 96 to 100 % of mice harbouring adult filariae*

These are the CBA, C3H and DBA strains. All have a high percentage of abnormal males.

All CBA mice harboured adult filariae, generally localized in the thoracic cavity; the sex ratio was normal; the male filariae were around 16 mm long and some of them had spicular abnormalities. Female filariae were short and without uterine microfilariae in both sexes of the CBA/HN *Xid* mice, although the mean recovery of filariae differed: 8.2 and 3.9 filariae respectively in male and female mice. In the CBA/Ca mice, female filariae were 56.8 mm long and one female filaria in fourteen had microfilariae in their uteri.

In the C3H/HeN strain, all the mice had adult filariae, with a mean number of five, but only 62 % were found in the thoracic cavity; the length of the female and male filariae were around 60 and 18.5 mm respectively, whatever the mouse sex. In male mice, spicule development was normal and three in eight female filariae had uterine microfilariae, with an exceptionally high density (similar to that observed in *Meriones unguiculatus*). In female mice, 75 % of male filariae had abnormal spicules and no female filariae had uterine microfilariae (sixteen examined).

In DBA/2N mice the mean number of adult filariae was *nearly* three; some mice were negative; the filariae were equally distributed between the thoracic and abdominal cavities; filarial sex ratio was equal to 5; the length of the female and male filariae were around 60 and 17 mm respectively. No female filaria in the four examined was found with uterine microfilariae or divided eggs, but undivided eggs were present.

B — *Strains with less than 30 % of mice harbouring adult filariae*

These are mice of the B10 background. These strains harboured a maximum 0.3 filariae per mouse and the percentage of L3 which develop into adults was less than 1 %. The uteri of the rare filariae were totally empty.

In the B10 strain the only female filaria recovered measured 30 mm in length. Three of five male filariae were partly degenerated with their head invaginated; they measured 15 mm in length and their spicules were abnormal.

In the B10Br strain, the only female and male filariae recovered measured 51 mm and 17 mm respectively; spicules were normal.

In the B10D2 strain, the spicules of a single degenerated male were normal.

DISCUSSION

1 — Patterns of development of *L. sigmodontis* related to the genetic strains of mice

Different patterns of development are seen. Patent microfilaraemia is associated with a high percentage of filariae in the thoracic cavity (≥ 75 %), a length of females ≥ 58 mm, a normal sex ratio, the presence of divided eggs and microfilariae in the uteri; spicules are often normal but not always.

In the strains from which recovery of adult filariae was good but no microfilaraemia was detected, there is no common pattern of development. It may be similar to that seen in strains that become microfilaraemic, such as in C3H/HeN male mice; alternatively it may present developmental abnormalities such as a high percentage of male filariae with abnormal spicules (male CBA/HN, male CBA/Ca, female C3H/HeN, female DBA/2N), female filariae very short and consequently without uterine microfilariae (CBA/HN *Xid*); and low proportion of female filariae compared to the males (DBA/2N).

In the resistant mouse strains, the rare filariae recovered are small and degenerated.

These patterns may be related to the genetics of mice.

A — Mice genetic backgrounds and susceptibility or resistance to *L. sigmodontis* infection

Mice of the BALB background are susceptible while mice with the B10 background are almost resistant to infection with *L. sigmodontis*; strains with other backgrounds (CBA, C3H, DBA) are intermediate *(Table II)*.

B — Host-sex effect on *L. sigmodontis* infection

The effect of host sex was different in the four strains examined *(Table II)*. The microfilaraemia was higher in female mice in BALB/c, although spicular abnormalities was seen in this mouse sex and not in the male mice.

In CBA/HN strain, male mice had twice the number of adult filariae compared to female mice. In C3H/HeN stain, male mice had higher mean density of uterine microfilariae and no spicular abnormalities.

In DBA/2N, no clear effect of host sex was seen.

C — MHC-linked effect on *L. sigmodontis* infection

Comparison of the pattern of infection and development of *L. sigmodontis* in mice of similar *H-2* haplotype on the 5 different genetic backgrounds did not reveal any MHC linkage independent of background genes *(Table II)*.

In the congenic BALB mice, where samples are sufficient for statistical analysis, a presumed MHC linkage (see Festing and Blackwell, 1988, p. 24) was shown: microfilaraemia was respectively 5 mfs, 1.2 mfs, 0.6 mfs/10 mm^3 in BALB/c, BALB/K, and BALB/B mice; this is related to the frequency of female filariae with uterine microfilariae: 8/15, 3/26 and 1/16 from BALB/c, BALB/K and BALB/B mice respectively. If female mice are not considered, spicular abnormalities are seen only in the BALB/B line.

2 — Comparison with the patterns of development of other filarial species

A — Strains of mice susceptible or resistant to filarial infections

Comparison of models has proved difficult for three main reasons. First, about forty mouse strains have been employed but often only once. Second, in order to obtain a patent microfilaraemia, immunodeficient mice and different routes of inoculation of infective larvae or other filarial stages have been used; and third, the time between the inoculation of parasites and their recovery from mice varies greatly *(Table I)*. Nevertheless, it seems possible to identify some common features with *L. sigmodontis*.

BALB/c mice appear to be more susceptible to filarial infections than the B10 strains both following intraperitoneal inoculation of *B. pahangi* infective larvae *(Table I)* (9), or transplantation of *Acanthocheilonema viteae* adult filariae (29). BALB/c mice are also more susceptible than the CBA/Ca mice to infection with *B. pahangi* following inoculation of infective larvae (9) or transplantation of developed L3 and L4 (24); and to *B. malayi* following intravenous inoculation of microfilariae (28).

B — Host-sex effect on parasite development

In many case male mice were found to be more susceptible to infection with filariae. Similar observations have been frequently reported, both in experimental animal infections (Ash, 1971; Denham, 1974) (ref. 1, 16, 18 in *Table I*) and also in human filariases (cf. Nelson, 1962; Brabin, 1990). It has been suggested that testosterone may favour development of the parasites (Wesley, 1973; Nakanishi *et al.*, 1989). In the case of *L. sigmodontis,* the relative susceptibility of female versus male is dependent upon the mouse strain.

C — MHC-linked effect on parasite development

The MHC-linked effect (*H-2* region) on filarial development, has been studied using *A. viteae* in three congenic lines of the BALB and B10 backgrounds (ref. 29 in *Table I*) and using *B. malayi* in C3H mice and C57BL mice (28). In these experiments, mice were infected by surgical implantation of adult filariae (29) or inoculation of microfila-

riae (28). Comparison of levels and duration of microfilaraemia did not revealed any effects of MHC, in contrast to the *L. sigmodontis* data.

CONCLUSION

In some parasitic groups, such as leishmaniasis or trichinellosis, the experiments with mouse models have succeeded in demonstrating that some developmental phases of the parasite may be controlled by two or even a single genes, which are associated or not to the MHC (reviewed *in* Wakelin and Blackwell, 1988). Less precise knowledge has been obtained in filariasis, due to the difficulty in obtaining complete development of filaria in mice.

With *L. sigmodontis,* infective larvae inoculated subcutaneously develop into adults and give rise to a patent microfilaraemia in immunologically normal mice. The wide diversity of developmental patterns, shown by several quantitative and morphological characters, and the identification of inbred strains of mice which are susceptible or resistant to this filaria provide a convenient and practical model for the study of immunology and genetics of filarial infections.

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