

FURTHER INVESTIGATIONS ON THE ASSOCIATION BETWEEN EQUINE LEUCOCYTE ANTIGENS (ELA) AND SUSCEPTIBILITY TO SARCOID IN HORSES

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SUMMARY

Twenty internationally accepted ELA antigens were determined in 140 sarcoid diseased horses. The typing results were computed breed for breed and these compared with control groups. In all 3 evaluated warmblooded horse breeds, ELA W13, a representative of the 2nd series of serologically detectable ELA antigens, occurred with increased frequency in the sarcoid groups (Swiss and French: $P < 0.0001$, Irish bred horses: 0.02). Further analysis of sarcoid affected animals lacking ELA W13 antigen showed an alternating increased occurrence of ELA A5 in Swiss and ELA W19 in Irish bred horses.

The results show that the susceptibility to sarcoid is strongly associated with or linked to the ELA system in horses.

INTRODUCTION

Equine sarcoid is a cutaneous, fibroblastic growth and the most common tumor in the horse. It appears singly or multiply on various regions of the body. Invasive growth is characteristic for sarcoid but it does not metastasise into organs other than the skin. Recurrence after conventional surgical treatment is frequent; radiotherapy and cryosurgery have contributed to a lowering of recurrence rates. A viral aetiology is strongly suspected but never been formally proven. The gross and microscopic lesions caused by sarcoid, as well as aetiological considerations have been discussed by Ragland et al. (1970).

In recent years an allelic series of serologically definable Class I equine leucocyte antigens (ELA) has been described and identified by Lazary et al. (1980a,b), Bailey (1980) and Antczak et al. (1982) as part of the gene products of the major histocompatibility complex (MHC) in the equine species. To date, serological data from 12 laboratories have been evaluated in four international comparison tests and 17 allelic specificities have been internationally accepted; ELA A1-A10 and W14-W20. Furthermore, three other alloantigenic structures W12, W13 and W21 were defined as part of the MHC but not allelic to the first series of the Class I antigens (Fourth International Comparison Test, Lexington, 1985). Recently, a case of recombination was observed between ELA A5 and W13 specificities by Lazary et al. (1985). These findings demonstrate the existence of a second series of allelic ELA antigens.

The first study by Lazary et al. (1985) on the ELA distribution in sarcoid diseased animals demonstrated that the predisposition of crossbred warmblooded horses to sarcoid is associated with or lin-

ked to the MHC. The study on the ELA system and predisposition to sarcoid in Thoroughbreds by Meredith et al. (1985) resulted in similar finding i.e. a strong relationship exists between the equine MHC and predisposition to sarcoid.

We report here our extended study on the association between MHC and the predisposition of horses to sarcoid.

MATERIAL AND METHODS

One hundred and forty Swiss, French and Irish warmblooded hunter-type horses with clinically and partly histologically diagnosed sarcoid were typed for their ELA. The age of the animals ranged from 2 to 18 years. The 415 control horses had the same age and sex distribution. They represented the same breeds as the groups of affected horses but there were no detectable sarcoids, nor was there a history of previous sarcoid affection.

ELA specificity determination was performed by the microcytotoxicity test according to Lazary et al. (1980a). The following specificities were determined: A1 to A10 and W14 to W20. These 17 specificities belong to the first series of the ELA Class I antigens. Furthermore the ELA W12, W13 (representing the second series of ELA antigens) and W21 were also determined.

The typing results were computed according to Svegaard et al. (1983) for each ELA specificity and breed for breed. The following formulae were used:

$$\text{Relative Risk (RR)} = \frac{a \times d}{b \times c}$$

$$\text{Etiologic Fraction (EF)} = \frac{\text{RR} - 1}{\text{RR}} \times \frac{a}{a + b}$$

where a = antigen present-affected; b = antigen absent-affected; c = antigen present-unaffected; d = antigen absent-unaffected. RR indicates the risk that an antigen carrier will develop the disease, expressed in multiples of the risk in horses lacking the antigen; EF indicates "how much of a disease is due to the disease associated factor".

$$\chi^2 = \frac{n(ad-bc)^2}{(a+b)(c+d)(a+c)(b+d)}$$

RESULTS AND DISCUSSION

The calculations showed that the frequencies of the ELA antigens in the controls of the three breeds are substantially identical (results not shown). As shown in the Table 1, the antigens A5 in Swiss bred and W19 in Irish bred affected horses occurred with significantly increased frequencies. ELA A3 was also overrepresented (statistically significantly) in all three breeds in the diseased groups but always in haplotype linked to the ELA W13 antigen, which belongs to the second ELA series. As the Table shows, affected animals of all three breeds share the ELA W13 antigen with significantly increased frequencies. Combination of the res-

pective data from the three breeds resulted in a RR of 3.8 and χ^2 value of 41.5 ($P = 10^{-9}$) and an EF of 0.48. High associations between the ELA W13 specificity and predisposition of the carriers to equine sarcoid were reported previously (Lazary et al. 1985), and in the investigation by Meredith et al. (1985), studying the ELA distribution in sarcoid affected Thoroughbreds.

ELA W19 in the diseased Irish bred horses was never linked to W13; on the other hand, in Swiss and French bred horses with ELA A5 or W15, these specificities may occur as haplotype together with ELA W13. In all breeds, when W13 was missing, the second series allele remained undefined.

Further studies in families with multiple sarcoid cases showed that the predisposition is inherited with ELA A5 (without W13) as with haplotypes containing the W13 antigen (Dubath et al. in preparation). Of particular interest are an Arab and a Trakhener family each with 3 affected members. In these two families the predisposition was inherited together with ELA W20 antigen and without W13.

CONCLUSION

At least one factor predisposing the horses to sarcoid is linked to or associated with the MHC region. The W13 antigen, a representative of the second allelic series of the ELA system shows the strongest association with susceptibility to sarcoid in the investigated breeds, but the inheritance of predisposition in multiple-case families not sharing the W13 antigen also shows strong association with particular haplotypes. It remains to clarify if some of the MHC genes i.e. Class II genes or separate susceptibility gene(s), linked to the MHC are involved in the pathogenesis of the equine sarcoid.

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Table 1

Distribution of sarcoid-associated antigens
in French, Swiss and Irish Warmblooded horses

Breed	Affected	n Controls	ELA	Antigen frequency (%)		RR	EF	χ^2	P
				Affected	Controls				
French	24	101	A 5	29	22	1.48	0.09	0.59	n.s.
			W 13	83	29	12.4	0.77	24.27	<0.0001
			A 5 and/or W 13	88	48	7.7	0.76	12.53	0.0004
Swiss	87	193	A 5	38	19	2.7	0.24	12.00	<0.001
			W 13	56	23	4.4	0.44	30.38	<0.0001
			A 5 and/or W 13	75	42	4.1	0.57	25.76	<0.0001
Irish	29	121	W 19	24	5	6.1	0.27	10.87	<0.0001
			W 13	62	39	2.6	0.38	5.14	0.02
			W 19 and/or W 13	79	44	4.8	0.62	11.26	<0.0001

RR Relative risk

EF Etiologic fraction