

Importance of Different Regions of H-2 for MLC Stimulation¹

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The major histocompatibility complex (MHC) in the mouse is the strongest barrier to allograft survival. One measure of MHC disparity is the mixed leukocyte culture (MLC) test in which lymphocytes from a potential recipient strain, respond to mitomycin C treated lymphocytes of a different donor strain, for example, in the mixture ABm.

The MHC in the mouse can be divided into four different regions (from left to right) (Klein & Shreffler 1972): the H-2K region characterized by the H-2K

locus, alleles of which determine serologically defined (SD) antigens; the immune response (Ir) region which includes at least two loci determining immune responsiveness (McDevitt & Benacerraf 1972, Lieberman & Humphrey 1972); the Ss region marked by the Ss-Slp locus (Passmore & Schreffler 1970); the H-2D region in which the H-2D locus determines a series of SD antigens.

Recent evidence which we have obtained suggests that the strongest MLC activation in the mouse is associated with MHC dis-

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parity for the regions between H-2K and H-2D, although SD differences may in some cases lead to stimulation (Bach et al. 1972). These differences have, to date, not been defined serologically, although they do lead to a lymphocyte response in MLC. We therefore have called these lymphocyte defined (LD) differences. We have considered use of the term "MLC locus" to be parochial since it seems likely that the same differences, determined between the two SD loci, which give rise to an MLC response, also determine a graft-versus-host response as measured by splenomegaly (Livnat et al. 1973).

One form of evidence which leads to the above conclusions is studies with strain combinations which are genetically identical except for the region between H-2K and H-2D. The second line of evidence comes from studies in mouse strain combinations which, for the most part, are congenic - i.e. genetically identical except for

one, two, three or all four of the MHC regions. The level of stimulation in such cases can be correlated with the various MHC regions in an attempt to determine which regions are of greater importance in MLC activation.

We present in this paper a summary of MLC results in 173 mouse strain combinations involving 15 mouse strains. With the exception of AQR and HTG these strains are congenic on a C57BL/10Sn (= B10) background. The results indicate that the strongest stimulation is associated with disparity for the Ir region. It must be remembered, as we have previously discussed, that there may be LD loci associated with the H-2D region; it is thus difficult to conclude whether the SD antigens themselves can cause stimulation in MLC.

The MLC method which we have used in these studies has been briefly described previously (Bach et al. 1972).

In Table 1 are listed the results of mouse

Table 1
Major histocompatibility complex

Responder	Stimulator	K	Ir-1	Ss-Slp	D	No. exp.	Average ratio of stimulation	Range
C57B1/10	B10.Br	K	K	K	K	3	7.3	6.7- 8.3
	B10.D2	D	D	D	D	4	8.7	8.0-11.6
	B10.A	K	K	D	D	4	7.1	3.1-12.7
	B10.A(1R)	K	K	D		3	5.8	4.1- 7.8
	B10.A(2R)	K	K	D		4	8.9	3.4-15.7
	B10.A(3R)			D	D	3	2.9	1.5- 3.9
	B10.A(4R)	K	K			4	7.1	4.2- 9.1
	B10.A(5R)			D	D	3	2.4	2.1- 2.9
	B10.G	Q	Q	Q	Q	2	5.2	4.0- 6.4
	B10.AKM	K	K	K	Q	2	6.5	5.5- 7.5
	HTG	D	D	D		1	7.6	
	AQR	Q	K	D	D	2	7.5	6.4- 8.5
	B10.T(6R)	Q	Q	Q	D	1	10.6	
C3H	K	K	K	K	1	2.3		
B10.Br	C57B1/10	B	B	B	B	3	5.2	4.7- 5.7
	B10.D2	D	D	D	D	3	3.9	3.7- 4.2
	B10.A			D	D	3	1.2	1.1- 1.5
	B10.A(1R)			D	B	3	1.3	1.1- 1.6

(To be continued)

Table 1 (continuation)

Responder	Stimulator	K	Ir-1	Ss-Slp	D	No. exp.	Average ratio of stimulation	Range
B10.Br	B10.A(2R)			D	B	3	1.2	1.1- 1.3
	B10.A(3R)	B	B	D	D	3	5.0	4.2- 6.0
	B10.A(4R)			B	B	3	1.6	1.4- 1.7
	B10.A(5R)	B	B	D	D	2	4.2	2.7- 5.7
	B10.G	Q	Q	Q	Q	1	3.3	
	B10.AKM				Q	1	0.9	
	HTG	D	D	D	B	1	5.5	
	AQR	Q		D	D	1	2.3	
B10.D2	C57B1/10	B	B	B	B	5	7.4	4.4-10.5
	B10.Br	K	K	K	K	3	6.4	5.5- 7.8
	B10.A	K	K			4	5.7	3.9- 7.4
	B10.A(1R)	K	K		B	4	6.4	4.8- 7.7
	B10.A(2R)	K	K		B	4	6.8	3.5- 9.8
	B10.A(3R)	B	B			3	7.0	6.5- 7.3
	B10.A(4R)	K	K	B	B	4	4.6	2.0- 5.9
	B10.A(5R)	B	B			4	7.0	4.2-10.6
	B10.G	Q	Q	Q	Q	2	4.8	3.4- 6.1
	B10.AKM	K	K	K	Q	2	5.6	
	HTG				B	2	1.4	1.2- 1.5
	AQR	Q	K			2	5.0	4.0- 6.0
	B10.T(6R)	Q	Q	Q		1	6.1	
	C3H	K	K	K	K	1	13.1	
B10.A	C57B1/10	B	B	B	B	4	7.0	3.6-12.7
	B10.Br			K	K	3	1.9	1.2- 2.6
	B10.D2	D	D			4	5.0	3.8- 8.3
	B10.A(1R)				B	3	1.5	1.0- 1.4
	B10.A(2R)				B	3	1.7	1.5- 1.9
	B10.A(3R)	B	B			3	5.4	4.4- 6.1
	B10.A(4R)			B	B	4	1.7	0.7- 2.2
	B10.A(5R)	B	B			3	5.4	4.4- 6.1
	B10.G	Q	Q	Q	Q	4	3.0	1.7- 4.5
	B10.AKM			K	Q	4	1.4	1.0- 1.7
	HTG	D	D		B	1	5.8	
	AQR	Q				4	1.4	0.8- 2.0
	B10.T(6R)	Q	Q	Q		3	2.6	1.4- 3.8
B10.A(1R)	C57B1/10	B	B	B		3	5.7	5.4- 6.2
	B10.Br			K	K	3	2.3	1.3- 3.1
	B10.D2	D	D		D	4	5.9	3.8- 8.5
	B10.A				D	3	2.0	1.6- 2.2
	B10.A(2R)					4	1.2	0.6- 1.9
	B10.A(3R)	B	B		D	3	6.0	5.5- 6.6
	B10.A(4R)			B		4	1.2	0.6-2.0
	B10.A(5R)	B	B		D	2	4.6	3.8- 5.3
	B10.G	Q	Q	Q	Q	1	6.7	
	B10.AKM			K	Q	1	1.7	
	HTG	D	D			1	8.0	
	AQR	Q			D	1	3.8	

(To be continued)

Table 1 (continuation)

Responder	Stimulator	K	Ir-1	Ss-Slp	D	No. exp.	Average ratio of stimulation	Range
B10.A(2R)	C57B1/10	B	B	B		4	5.9	5.4- 6.2
	B10.Br			K	K	3	1.8	1.7- 1.9
	B10.D2	D	D		D	4	9.3	4.4-20.5
	B10.A				D	3	1.3	1.0- 1.7
	B10.A(1R)					4	1.3	0.8- 1.6
	B10.A(3R)	B	B		D	3	8.2	4.2-10.6
	B10.A(4R)			B		5	1.3	0.9- 1.7
	B10.A(5R)	B	B		D	3	6.5	5.0- 8.0
	B10.G	Q	Q	Q	Q	1	5.9	
	B10.AKM			K	Q	1	1.9	
	HTG	D	D			1	8.6	
	AQR	Q			D	1	3.1	
B10.A(3R)	C57B1/10			B	B	3	2.3	1.7- 2.8
	B10.Br	K	K	K	K	3	8.5	5.3-10.4
	B10.D2	D	D			3	6.5	4.1- 8.1
	B10.A	K	K			3	5.5	4.0- 6.6
	B10.A(1R)	K	K		B	3	6.1	3.3- 7.8
	B10.A(2R)	K	K		B	3	7.8	5.4-11.1
	B10.A(4R)	K	K	B	B	3	6.1	5.7- 6.4
	B10.A(5R)					2	1.1	0.9- 1.3
	B10.G	Q	Q	Q	Q	1	4.0	
	B10.AKM	K	K	K	Q	1	4.9	
	HTG	D	D		B	1	5.2	
	AQR	Q	K			1	4.6	
B10.A(4R)	C57B1/10	B	B			4	8.9	6.6-11.8
	B10.Br			K	K	3	3.3	2.6- 4.7
	B10.D2	D	D	D	D	4	13.0	5.0-33.6
	B10.A			D	D	4	3.5	1.9- 6.4
	B10.A(1R)			D		4	2.7	1.4- 4.9
	B10.A(2R)			D		5	2.9	1.7- 4.4
	B10.A(3R)	B	B	D	D	3	8.1	7.9- 8.4
	B10.A(5R)	B	B	D	D	3	7.6	6.5- 8.7
	B10.G	Q	Q	Q	Q	2	6.5	4.3- 8.6
	B10.AKM			K	Q	2	3.0	2.1- 3.9
	HTG	D	D	D		1	5.2	
	AQR	Q		D	D	2	5.8	2.9- 8.6
B10.T(6R)	Q	Q	Q	D	1	10.5		
B10.A(5R)	C57B1/10			B	B	4	2.2	1.3- 3.3
	B10.Br	K	K	K	K	2	6.0	3.5- 8.4
	B10.D2	D	D			4	7.9	3.2-18.3
	B10.A	K	K			3	5.2	4.0- 6.8
	B10.A(1R)	K	K		B	2	6.1	5.7- 6.5
	B10.A(2R)	K	K		B	3	6.1	5.5- 7.2
	B10.A(3R)					2	1.2	1.0- 1.3
	B10.A(4R)	K	K	B	B	3	5.6	4.6- 6.1
	HTG	D	D		B	2	9.4	6.4-12.4
	AQR	Q	K			1	5.4	
C3H	K	K	K	K	1	15.6		

(To be continued)

Table 1 (continuation)

Responder	Stimulator	K	Ir-1	Ss-Slp	D	No. exp.	Average ratio of stimulation	Range
B10.G	C57B1/10	B	B	B	B	2	12.2	8.8-15.6
	B10.Br	K	K	K	K	1	7.6	
	B10.D2	D	D	D	D	2	11.7	10.4-13.0
	B10.A	K	K	D	D	4	10.5	6.8-16.0
	B10.A(1R)	K	K	D	B	1	6.5	
	B10.A(2R)	K	K	D	B	1	7.9	
	B10.A(3R)	B	B	D	D	1	12.9	
	B10.AKM	K	K	K	K	4	6.8	5.1- 8.4
	HTG	D	D	D	B	1	11.5	
	AQR		K	D	D	5	10.8	6.6-15.1
B10.T(6R)				D	4	3.3	2.0- 5.4	
B10.AKM	C57B1/10	B	B	B	B	2	6.6	5.9- 7.3
	B10.Br				K	1	2.1	
	B10.D2	D	D	D	D	2	6.9	5.9- 7.8
	B10.A			D	D	3	1.7	1.5- 1.9
	B10.A(1R)			D	B	2	1.8	1.7- 1.9
	B10.A(2R)			D	B	1	2.0	
	B10.A(3R)	B	B	D	D	1	8.5	
	B10.A(4R)			B	B	2	1.5	0.9- 2.1
	B10.G	Q	Q	Q		4	3.4	1.6- 6.3
	HTG	D	D	D	B	1	7.1	
AQR	Q		D	D	4	2.4	1.5- 3.7	
B10.T(6R)	Q	Q	Q	D	3	6.9	1.2-10.6	
HTG	C57B1/10	B	B	B		2	6.5	4.2- 8.8
	B10.Br	K	K	K	K	1	9.5	
	B10.D2				D	2	1.8	1.2- 2.3
	B10.A	K	K		D	1	7.9	
	B10.A(1R)	K	K			1	8.2	
	B10.A(2R)	K	K			1	14.6	
	B10.A(3R)	B	B		D	1	13.4	
	B10.A(4R)	K	K	B		1	9.1	
	B10.A(5R)	B	B		D	2	9.9	8.2-11.5
	B10.G	Q	Q	Q	Q	1	10.9	
B10.AKM	K	K	K	Q	1	10.7		
AQR	Q	K		D	1	12.6		
C3H	K	K	K	K	1	6.8		
AQR	C57B1/10	B	B	B	B	2	4.6	2.8- 6.4
	B10.Br	K		K	K	1	3.4	
	B10.D2	D	D			2	4.7	3.8- 5.6
	B10.A	K				4	1.5	0.8- 2.2
	B10.A(1R)	K			B	1	3.0	
	B10.A(2R)	K			B	1	3.7	
	B10.A(3R)	B	B			1	4.8	
	B10.A(4R)	K		B	B	2	3.0	1.6- 4.3
	B10.A(5R)	B	B			1	5.6	
	B10.G		Q	Q	Q	5	5.8	2.7-13.0
B10.AKM	K		K	Q	4	2.8	1.8- 4.5	
HTG	D	D		B	1	6.5		
B10.T(6R)		Q	Q		5	5.1	3.2- 9.0	

(To be continued)

Table 1 (continuation)

Responder	Stimulator	K	Ir-1	Ss-Slp	D	No. exp.	Average ratio of stimulation	Range
B10.T(6R)	C57B1/10	B	B	B	B	1	4.2	
	B10.D2	D	D	D		1	6.2	
	B10.A	K	K	D		3	7.7	3.6-15.2
	B10.A(4R)	K	K	B	B	1	3.6	
	B10.G				Q	4	1.4	0.8- 2.1
	B10.AKM	K	K	K	Q	3	8.2	5.9-12.8
	AQR		K	D		5	6.4	2.7-12.8
C3H	C57B1/10	B	B	B	B	1	10.7	
	B10.D2	D	D	D	D	1	11.5	
	B10.A(5R)	B	B	D	D	1	10.3	
	HTG	D	D	D	B	1	7.4	

MLC studies; a briefer list of these results is presented elsewhere (Bach et al. 1972).

Each responding cell strain is tested against several different stimulating cell strains. In each combination those regions of the MHC carried by the stimulatory cell which are different from the responding cell are designated with a capital letter.

Table 2
Summary of MLC responses

MHC regions which are different	Ratio of stimulation	
	Range ^a	Average
K, Ir-1, Ss-Slp, D	1.2-33.6	7.2
K, Ir-1, Ss-Slp	1.4-15.7	6.1
K, Ir-1, D	3.3-20.5	7.0
K, Ss-Slp, D	1.5- 8.6	3.3
Ir-1, Ss-Slp, D	2.7-15.1	8.3
K, Ir-1	3.2-18.3	6.6
K, SS-Slp	no experiments	
Ir-1, Ss-Slp	2.7-12.8	5.8
K, D	3.0- 3.8	3.4
Ir-1, D	no experiments	
Ss-Slp, D	0.7- 4.7	2.0
K	0.8- 2.2	1.4
Ir-1	no experiments	
D	0.8- 5.4	1.8
Ss-Slp	0.6- 4.9	2.0
none	0.6- 1.9	1.2

^a These numbers represent the lowest and highest ratios of stimulation noted.

The capital letter refers to the H-2 chromosome carried by the stimulating cell in that region. For instance, in the combination of B10 responding to HTG, the HTG cells carry the H-2^d chromosome in the H-2K, Ir and Ss-Slp regions and the H-2^b chromosome in the H-2D region. The two strains are identical in the H-2D region - both carrying the H-2^b chromosome.

Table 2 summarized results obtained in all experiments; we have combined data obtained from strains differing for the regions of the MHC taken one, two, three or four at a time.

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