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Immunology

Physiological regulation of antigen binding to T cells: Role of a soluble macrophage factor and of interferon

(major histocompatibility complex)

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ABSTRACT **A soluble product of macrophages (MF) and mouse viral interferon (IF) increase both major histocompatibility antigenic determinants and the number of antigen-binding cells in nonstimulated T cell-enriched mouse lymphocyte cultures. MF increases *Ia* and not *H-2* antigens; IF increases *H-2* but not *Ia* antigens. The increased antigen binding due to MF can be inhibited by anti-*Ia* but not by anti-*H-2* sera, whereas IF-induced binding is sensitive to anti-*H-2* but not to anti-*Ia* sera. The specificity of IF- or MF-induced binding of branched synthetic polypeptides by T cells is different from that of B cells and similar to the specificity of the *Ir* gene regulation. MF increases antigen binding only in *Ir* high-responder animals. The IF-induced antigen binding is not dependent on the *Ir* genotype. MF-reactive cells express the Ly-1 marker, and the IF-reactive antigen binders express the Ly-2 phenotype. It is suggested that MF and IF are physiological mediators of antigen binding by T cells.**

We have recently observed that availability of murine T cell surface antigenic determinants controlled by portions of the major histocompatibility complex is increased in the presence of a humoral macrophage factor (MF) or mouse viral interferon (IF). MF increased *Ia* antigenic determinants and IF increased *H-2* antigenic determinants. Concomitant to this increase in the expression of antigenic determinants, we have observed that the number of antigen binding cells in T-cell enriched cultures of normal mouse lymphocytes is also increased. Because products of the major histocompatibility complex were shown to be involved in antigen recognition by T cells (1–5), we have interpreted these observations to indicate a physiological regulation of antigen binding by T cells (6). Indeed, macrophages are obligatory in various T cell-dependent immune responses (7), and viral and immune interferon were shown to influence immune responses (8).

Here we report experiments that clarify (*i*) whether antigen binding to T cells is regulated by the putative mediators MF and IF, (*ii*) whether antigen binding to T cells is under *H-2* linked genetic control, (*iii*) whether this binding follows the same specificity pattern as *Ir* gene-regulated T cell proliferation (1, 9), and (*iv*) whether surface products of the *H-2* complex are involved in antigen binding. Finally, we also demonstrate the Ly-classes of antigen-binding T cells regulated by MF and IF.

MATERIALS AND METHODS

Antigens. The following branched synthetic polypeptide antigens were used: poly(L-Tyr,L-Glu)-poly(DL-Ala)—poly(L-Lys) [(T,G)-A—L] batch 598; poly(L-His,L-Glu)-poly(DL-Ala)—poly(L-Lys) [(H,G)-A—L] batch 925; poly(L-Phe,L-Glu)-poly(DL-Ala)—poly(L-Lys) [(Phe,G)-A—L] batch 1501; poly(L-Tyr,L-Glu)-poly(L-Pro)—poly(L-Lys) [(T,G)-Pro—L] batch 952. Immune responsiveness to these antigens is under different *H-2* linked genetic control, but antibodies produced to (T,G)-A—L are crossreactive with all members of the series (10). Natural proteins, TEPC-15, an IgA myeloma protein [the immune responsiveness to which is under *H-2* linked control (11)], and ovalbumin were also used.

Animals. The following congeneic mouse strains bred in our colony were used: C3H/DiSn, C3H.SW, C57BL/10, B10.A, B10.BR, C57BL/6, B6-Ly-1.1, and B6-Ly-2.1.

Factors. MF was produced in nonstimulated mouse peritoneal exudate cell cultures. The cells were plated in tissue culture medium [RPMI-1640 with 1% fresh mouse plasma, penicillin (100 units/ml) streptomycin (100 μg/ml), 2 mM glutamine, 20 μM 2-mercaptoethanol, and 25 mM *N*-2-hydroxyethylpiperazine-*N'*-2-ethanesulfonate (Hepes buffer)] at a density of 5×10^6 cells per ml. The nonadherent cells were removed, and the adherent cells were cultivated for 24 or 48 hr. Cell-free supernatant of such cultures was used as MF. MF could be stored at −80° for several months. IF, was prepared from mouse fibroblasts infected with Newcastle disease virus, and contained 3.2×10^6 viral interferon units per ml. This IF preparation was a gift from I. Gresser (I.R.S.C., Villejuif, France).

Treatment of Cells. Thymocytes, spleen cells, and T or B cell-enriched spleen cells [nylon wool filtration (12)] were incubated at a density of 2×10^7 cells per ml with the factors in tissue culture medium at 37°, with 7% CO_2 for 2 or 20 hr. After incubation, the cells were collected, and erythrocytes and dead cells were removed by the Ficoll-Hypaque method. The cell composition of the enriched cells was tested with anti-Thy-1.2 serum and complement. Only preparations with <15% cross contamination were used.

Alloantisera. Anti-Thy-1.2 (A.Thy-1.1 × AKR-H-2^b)F1 against A.SL1 tumor cells; anti-H-$2K^k$ [A.TL × B10.A(5R)]F1 against B10.A; anti-H-$2D^k$ (A.TL × B10.A)F1 against BB10.BR; anti-Ia^k (A.TH) against A.TL; anti-I-A^k, -I-B^k, -I-J^k (B10.HTT × A.TH)F1 against A.TL; anti-I-E^k, -I-C^k, -S^k, -H-$2G^k$ (C57BL/10 × A.TH)F1 against B10.HTT; anti-Ly-1.1 (B6 × BALB/c)F1 against B6-Ly-1.1; and anti-Ly-2.2 (C3H/HeJ × B6-Ly-2.1)F1 against C57BL/6 lymphoid cells were produced in our laboratory. The antisera were tested in a double-step microcytotoxicity test with trypan blue staining of the dead cells and selected adsorbed rabbit serum as complement source.

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Abbreviations: MF, soluble factor of normal mouse peritoneal macrophages; IF, mouse viral interferon; *Ir* genes, *H-2* (*I* region) linked immune response genes; *Ia* antigens, antigens controlled by the *I* region; (T,G)-A—L, poly(L-Tyr,L-Glu)-poly(DL-Ala)—poly(L-Lys); (H,G)-A—L, poly(L-His,L-Glu)-poly(DL-Ala)—poly(L-Lys); (Phe,G)-A—L, poly(L-Phe,L-Glu)-poly(DL-Ala)-poly(L-Lys); (T,G)-Pro—L, poly(L-Tyr,L-Glu)-poly(L-Pro)—poly(L-Lys).

Table 1. Effect of MF and IF on lymphocyte membrane antigens, adsorption experiments

Exp.	Strain	Cells,* type and no.	Treatment	Alloantiserum	50% titer after adsorption with lymphocytes: Control	Treated	Control / Treated
1	B10.A	Th 10^7	MF^{C3H} 1:60	anti-Ia^k	1:420	1:160	2/63
		B 10^7	MF^{C3H} 1:60	anti-Ia^k	1:200	1:220	0/91
		Th 10^7	$MF^{B10.S}$ 1:60	anti-Ia^k	1:380	1:120	3/16
		Spleen 5×10^6	MF^{C3H} 1:60	anti-Ia^k	1:400	1:120	3/33
		Spleen 5×10^6	MF^{C3H} 1:60	anti-H-$2K^k$	1:60	1:55	1/09
		Spleen 5×10^6	MF^{C3H} 1:60	anti-Thy-1.2	1:1200	1:1320	0/91
2	B10.A	T 10^7	MF^{C3H}-through anti-Ia^k-Sepharose column, 1:60	anti-Ia^k	1:410	1:120	3/42
3	C3H	Spleen 5×10^6	MF^{C3H} 1:80	anti-Ia^k	1:420	1:110	3/81
		Spleen 5×10^6	MF^{C3H} 1:80	anti-I-A^k,I-B^k,I-J^k	1:70	1:30	2/33
		Spleen 5×10^6	$MF^{C}3H$ 1:80	anti-I-E^k,I-C^k,S^k,H-$2G^k$	1:160	1:75	2/13
		Spleen 5×10^6	MF^{C3H} 1:80	anti-H-$2D^k$	1:48	1:50	0/96
4	C3H	Th-10^7	IF, 4000 units/ml	anti-Ia^k	1:160	1:160	1/0
		Th-10^7	IF, 4000 units/ml	anti-H-$2K^k$	1:100	1:25	4/0
		Th-10^7	IF, 4000 units/ml	anti-H-$2D^k$	1:15	1:36	4/2
		Th-10^7	IF, 4000 units/ml	anti-Thy-1.2	1:400	1:360	1/1

* Th, thymocytes; B, nylon wool-purified B cells; T, nylon wool-purified T cells.

Autoradiography. Previously described techniques were used (13, 14). The antigens were labeled with ^{125}I by the chloramine-T method. The specific activity ranged from 5 to 10 μCi/μg. Labeled antigen, 0.1 ml (3–5 μg/ml), was added to cells (2×10^6 in 0.1 ml) previously treated with the factors. After 30 min at 37°, the cells were washed three times by centrifugation, and smears were prepared for autoradiography. The emulsion (Ilford, K.5, Essex, England) was exposed for 2 weeks. The cells were counted under ×1000 magnification; 5 grains per cell was regarded as positive. Two or three slides were counted in each group, and 4000 individual cells were counted on each slide in code. In experiments in which the effect of alloantisera on antigen binding was studied, the alloantisera were added to the cells in a 1:15 final dilution for 15–30 min before addition of the radiolabeled antigen. The cells were then incubated for an additional 30 min.

Anti-*Ia*-Sepharose Columns Coupled with Cyanogen Bromide. The columns used were tested for adsorbing specific T cell factors (15) and in their capacity to remove proteins of molecular weight 26,000 and 33,000 from a Nonidet P-40 extract of [^{3}H]leucine-labeled spleen cells after elution from a lentil lectin column and before precipitation with anti-*Ia* serum and acrylamide gel electrophoresis.

RESULTS

Changes in Cell Surface Antigens. Different lymphocyte preparations were incubated in the presence of MF or IF for 20 hr. Change in the amount of cell surface antigens was tested in adsorption experiments. The sera were adsorbed either on different numbers of cells treated with MF or IF and titered directly on fresh spleen cells (quantitative adsorption), or a serum dilution was adsorbed on 5 to 10×10^6 cells and further diluted in doubling dilutions before titration on spleen cells.

On lymphocytes treated with MF, the amount of *Ia* antigens (*I-A*, *I-B*, and *I-C* subregion specificities), and not that of *H-2* antigens, increased whereas on IF-treated cells, *H-2K* and *H-2D* increased but not *Ia*. Both factors increased the amount of the respective antigenic determinants on spleen cells, splenic T cells, or thymic lymphocytes. MF had no effect on B cell-enriched preparations. No effect could be observed on the Thy-1 determinant with either of the two factors (Table 1). Neither the MF- nor the IF-treated cells adsorbed noncrossreactive alloantisera (B10.S cells and anti-Ia^k or anti-H-$2K^k$, not shown here), suggesting that the treatment did not enhance the nonspecific adsorption to these cells.

The genetic origin of MF did not influence its effect. When B10.A (H-2^a) cells were treated with MF from B10.S (H-2^s) macrophages, a significant adsorption of the anti-Ia^k serum, which does not crossreact with the *Ia* specificities of the *s* haplotype, was observed (Exp. 1, Table 1), Moreover, adsorption of *Ia* antigens from a C3H-MF preparation on Sepharose-anti-Ia^k columns did not influence its activity (Exp. 2, Table 1).

The increase of antigenic determinants due to either MF or IF was approximately 2- to 4-fold. This was confirmed also in quantitative adsorption experiments in which 9.6×10^6 MF-treated or 25×10^6 incubated control C3H spleen cells were necessary for a 50% decrease in the cytotoxicity of an A.TH anti-A.TL serum. We think that the increased amount of *Ia* antigens after MF treatment and the increased amount of *H-2* antigens after IF treatment are not due to selective survival or multiplication, because these effects could be observed as soon as 2 hr after incubation. The number of Thy-1, Ly-1, and Ly-2 positive cells did not change even during a 20-hr incubation. Moreover, no cell multiplication was observed (unpublished data).

Effect of MF and IF on Antigen Binding. In 30 autoradiographic experiments we observed that the number of T cells that bind antigen, from genetic high-responder animals, significantly increased (3- to 10-fold) after treatment with either MF or IF. No increase was observed when B cell-enriched populations were tested (Table 2). In addition, the increased antigen binding was observable at 2 hr of incubation. In all further experiments to be shown, the shorter incubation time was used.

To investigate whether the increased antigen binding was specific, C3H.SW (high-responder) T cells were treated with MF or IF and the binding of ^{125}I-labeled (T,G)-A—L was determined in the presence or absence of 100-fold molar excess of different nonlabeled antigens (Table 3). Although unlabeled (T,G)-A—L significantly competed with radioactive (T,G)-A—L, the unrelated ovalbumin had no effect, suggesting that

Table 2. Effect of MF and IF on the binding of ^{125}I-labeled (T,G)-A—L to high-responder T and B cells

Cells	Treatment	Antigen-binding cells per 10^4 cells* At 2-hr incubation	At 20-hr incubation
	Strain C3H.SW		
T	None	ND†	28 ± 6
T	$MF^{C3H.SW}$ 1:60	ND	137 ± 12
B	None	ND	60 ± 14
B	$MF^{C3H.SW}$ 1:60	ND	80 ± 9
	Strain C57BL/10		
T	None	25 ± 4	25 ± 8
T	MF^{B10} 1:40	75 ± 4	85 ± 2
T	IF, 4000 units/ml	105 ± 12	105 ± 7
B	None	30 ± 4	50 ± 8
B	MF^{B10} 1:40	30 ± 4	65 ± 2
B	IF, 4000 units/ml	40 ± 4	53 ± 1

* Data shown as mean ± SEM.
† ND, not determined.

the binding is specific. (H,G)-A—L and (T,G)-Pro—L did not influence the binding of labeled (T,G)-A—L to T cells, but (Phe,G)-A—L almost completely inhibited it. Because *H-2^b* mice are low responders to (H,G)-A—L but high responders to both (T,G)-A—L and (Phe,G)-A—L, the cellular specificity of antigen binding by T cells, as it is shown in Table 3, seems to be strikingly similar to the specificity of the *Ir* gene control (2, 9, 10, 13, 16).

Influence of the *Ir* Genotype on Antigen Binding by T Cells. This question was investigated in an experiment in which T cell-enriched spleen cultures of C57BL/10 and B10.BR mice were treated with either MF or IF. The MF was prepared from C57BL/6 macrophages. MF- or IF-treated cells were exposed to one of two radiolabeled antigens, (T,G)-A—L (C57BL/10 high-responder; B10.BR low-responder) or TEPC-15 (C57BL/10 low-responder; B10.BR high-responder). Although cells of the low-responder genotype did not reveal increased numbers of antigen binders after MF treatment, IF treatment did increase the number of antigen binders in both the high- and in the low-responder genotype (Table 4). The effect of allogeneic MF and IF was also revealed in this experiment. B10.BR cells have the *k* haplotype, different from that of the origin of the MF used (C57BL/6, *H-2^b*); nevertheless, these T cells responded with increased antigen binding when the antigen to which they are high-responders was presented to them. The IF used in this study was prepared from L fibroblasts of C3H (*H-2^k*) origin. This IF also influenced both syngeneic and allogeneic T cells. It can be assumed therefore that the activity of MF and IF is not subject to an "allogeneic barrier."

Table 3. Specificity of binding of ^{125}I-labeled (T,G)-A—L to C3H.SW T cells: Competition with 100-fold molar excess of nonlabeled antigen

Unlabeled antigen	MF-treated cells Binding*	% inhibition	IF-treated cells Binding*	% inhibition	Cross reactivity
Control	20 ± 1		23 ± 1		
Factor	91 ± 4		90 ± 7		
Factor (T,G)-A—L	22 ± 3	76	20 ± 8	78	+
Factor Ovalbumin	88 ± 6	3	85 ± 5	6	−
Factor (H,G)-A—L	84 ± 1	8	90 ± 2	0	−
Factor (Phe,G)-A—L	17 ± 2	81	8 ± 2	91	+
Factor (T,G)-Pro—L	80 ± 7	12	73 ± 9	19	−

* No. antigen binding cells per 10^4 cells, shown as mean ± SEM.

Table 4. Expression of the Ir phenotype in antigen binding by T cells

Strain	Factor	^{125}I-Labeled antigen	Binding*
C57BL/10†	None	(T,G)-A—L	25 ± 8
	MF	(T,G)-A—L	75 ± 4
	IF	(T,G)-A—L	93 ± 5
	None	TEPC-15	45 ± 2
	MF	TEPC-15	43 ± 1
	IF	TEPC-15	160 ± 12
B10.BR‡	None	(T,G)-A—L	25 ± 4
	MF	(T,G)-A—L	35 ± 2
	IF	(T,G)-A—L	79 ± 7
	None	TEPC-15	40 ± 2
	MF	TEPC-15	130 ± 2
	IF	TEPC-15	138 ± 9

* No. antigen binding cells per 10^4 cells, shown as mean ± SEM.
† *H-2^b*, high-responder to (T,G)-A—L, low-responder to TEPC-15.
‡ *H-2^k*, low-responder to (T,G)-A—L, high-responder to TEPC-15.

Taken together, the data in Table 4 suggest that (*i*) the MF-induced increased T cell antigen binding depends on the *H-2* genotype of the T cell, (*ii*) the increased antigen binding induced by IF is not under *H-2* linked control, and (*iii*) the genetic origin of MF and IF does not influence their activity.

Effect of Anti-*H-2* and Anti-*Ia* Sera on Antigen Binding by T Cells. The MF-induced antigen binding was inhibited by anti-*Ia* but not by anti-*H-2* sera; IF-induced antigen binding was inhibited by anti-*H-2K* or anti-*H-2D* but not by anti-*Ia* sera (Table 5). In other experiments (data not shown), the serological specificity of the antisera was confirmed on antigen binding cells of noncrossreactive *H-2* haplotypes. The finer specificity of the inhibition of anti-*Ia* sera on MF-induced antigen binders was investigated also, and it was found that sera reactive with *Ia* specificities assigned to the *I-A* and *I-C* subregions are inhibitory to a comparable extent.

These experiments suggest that major histocompatibility determinants are associated with antigen binding by T cells. Because MF and IF affected different *H-2* complex products, and because the *Ir* genotype of the T cells influenced only the MF-induced antigen binding (Table 4), we investigated whether MF and IF act on different lymphocyte classes.

Effect of Ly Phenotype of Antigen Binding T Cells. This was investigated on MF- or IF-treated T cells of B6-Ly-1.1, B6,

Table 5. Effect of anti-*H-2* and anti-*Ia* sera on antigen binding to T cells*

Alloantiserum	Control binding†	MF treatment Binding†	% inhibition	IF treatment Binding†	% inhibition
None	28 ± 3	95 ± 3	—	90 ± 3	—
α H-2K^k	—	110 ± 10	0	47 ± 2	48
α H-2D^k	—	108 ± 5	0	27 ± 5	70
α Ia^k	—	22 ± 2	77	120 ± 3	0

* Strain B10.BR, *H-2^k*; antigen was TEPC-15.
† No. of antigen binding cells per 10^4, shown as mean ± xxx.

Table 6. MF-responsive and IF-responsive T cells belong to different Ly classes

Antiserum used for elimination	T cells		Factor	Binding*	% decrease
	Strain	Ly genotype			
None	B6-Ly-1.1	Ly-1.1; Ly-2.2	None	17 ± 1	—
	B6-Ly-1.1	Ly-1.1; Ly-2.2	MF	90 ± 4	—
	B6-Ly-1.1	Ly-1.1; Ly-2.2	IF	95 ± 4	—
	B6	Ly-1.2; Ly-2.2	None	25 ± 2	—
	B6	Ly-1.2; Ly-2.2	MF	105 ± 1	—
	B6	Ly-1.2; Ly-2.2	IF	98 ± 1	—
	B6-Ly-2.1	Ly-1.2; Ly-2.1	None	22 ± 3	—
	B6-Ly-2.1	Ly-1.2; Ly-2.1	MF	80 ± 1	—
	B6-Ly-2.1	Ly-1.2; Ly-2.1	IF	80 ± 4	—
α-Ly-1.1	B6-Ly-1.1	Ly-1.1; Ly 2.2	MF	27 ± 1	70
	B6-Ly-1.1	Ly-1.1; Ly 2.2	IF	75 ± 1	21
	B6	Ly-1.2; Ly-2.2	MF	88 ± 2	16
	B6	Ly-1.2; Ly-2.2	IF	85 ± 2	13
α-Ly-2.2	B6-Ly-1.1	Ly-1.1; Ly-2.2	MF	85 ± 7	6
	B6-Ly-1.1	Ly-1.1; Ly-2.2	IF	5 ± 0	95
	B6-Ly-2.1	Ly-1.2; Ly-2.1	MF	75 ± 2	6
	B6-Ly-2.1	Ly-1.2; Ly-2.1	IF	78 ± 1	3

* No. antigen binding cells per 10^4 cells, shown as mean ± SEM.

and B6-Ly-2.1 mice. The cells were treated with anti-Ly-1.1 or anti-Ly-2.2 antiserum and complement, after which the dead cells were removed and the remaining cells were cultured with the appropriate factor. The experiment was planned so that, with each serum, cells of both the homologous and the opposite Ly allele were tested as an internal control (Table 6). The results demonstrate that elimination of cells expressing the Ly-1 phenotype specifically decreases the MF-responsive antigen binding in the remaining cell population; in contrast, removal of the Ly-2 phenotype causes the loss of the IF-responsive antigen binders. This experiment was repeated several times. In some experiments, a 40–50% increase of the IF-responsive antigen binders was observed after treatment with the anti-Ly-1.1 serum. There are two possible interpretations of these results according to the current understanding of Ly-t types (17): the MF-responsive cells may belong specifically to the Ly-1^+, 2^-, 3^- (helper, MLR proliferative) class or to the Ly-1^+, 2^-, 3^- and to the Ly-1^+, 2^+, 3^+ classes; the IF-responsive antigen binders may belong to the Ly-1^-, 2^+, 3^+ (suppressor, killer) class exclusively or to the Ly-1^-, 2^+, 3^+ and Ly-1^+, 2^+, 3^+ classes of T cells.

DISCUSSION

Our experiments indicate that the binding of soluble antigens to T cells is under physiological control. On the basis of our findings it is tempting to suggest that the Ly-1 helper T cells are controlled by the macrophage which is probably the first immunocyte to come into contact with antigen, whereas Ly-2.3-suppressor or killer cells may be influenced by interferon. Interferons can be released by immunocytes in their reaction to antigen or by prospective target cells during virus infection. Moreover, these experiments suggest that antigen binding to the MF-reactive Ly-1 cells is connected to *Ia* antigens, and that antigen binding to the IF-sensitive Ly-2.3 cells is connected to *H-2* antigens. The binding involving *Ia* antigens was shown to depend on the *Ir* type of the T cells, suggesting that, for the antigens used in these studies, antigen binding to helper T cells may be under *H-2* linked genetic control. This connection between the genetic control of immune responsiveness and the physiological control of antigen binding could provide a mechanism for the regulatory function of T cells in the immune response (18).

The frequency of antigen-binding T cells of nonimmunized animals after MF or IF treatment was surprisingly high in these experiments. It was indeed close to that found in immunized animals (ref. 13; unpublished data). The understanding of this phenomenon and its correct interpretation require further investigation.

T cells respond to a complex recognition signal involving antigens as well as elements of the major histocompatibility complex. In delayed-type hypersensitivity to certain antigens, T cells of the Ly-1 class respond to the antigen combined with *Ia* on the surface of macrophages (19). Cytotoxic T cells of the Ly-2.3 class recognize a signal formed by *H-2* and the antigen on the target cells (20, 21). In our experiments, the binding of soluble antigens through highly specific receptors was found to be connected with *Ia* on the surface of Ly-1 T cells and with *H-2* on the surface of Ly-2.3 T cells. The concordance in the elements of the *H-2* complex that are present in the recognition signals as well as on the respective recognizing T cell is striking.

The role of major histocompatibility complex products in antigen binding by T cells is not known. In preliminary experiments we have found that the anti-idiotype serum specifically inhibited both the MF- and the IF-controlled antigen binding, suggesting that both major histocompatibility determinants and anti-idiotype reactive molecules are involved in antigen binding by T cells.

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