

# ANTIGEN-SPECIFIC T-CELL FACTOR IN CELL COOPERATION: PHYSICAL PROPERTIES AND MAPPING IN THE LEFT-HAND (K) HALF OF *H-2*\*

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We have previously shown that mouse thymocytes educated to a synthetic polypeptide antigen, poly(tyrosyl,glutamyl)-polyDLalanyl--polylysyl, [(T,G)-A--L],<sup>1</sup> and subsequently cultured briefly *in vitro*, release a soluble factor capable of replacing thymus-derived (T) cells in the thymus-dependent antibody response to (T,G)-A--L of bone marrow-derived (B) cells in irradiated recipients (1). This factor was not removed by anti-immunoglobulin sera (antimouse Fab), but was completely adsorbed by alloantisera raised against the *H-2* type of the strain producing the factor (2). We now report further characterization and mapping of this T-cell factor.

## Materials and Methods

**Antigens.** The immunogen used throughout this work was the multichain synthetic polypeptide, polyL(tyrosyl, glutamyl)-polyDLalanyl--polyLlysyl, [(T,G)-A--L] batch no. 1,383. A related polypeptide is used in the hemolytic plaque-forming cell assay (below), namely polyL(tyrosyl,glutamyl)-polyLpro--polyLlysyl, [(T, G)-Pro--L] batch no. 935. Both materials were kindly supplied by Dr. Edna Mozes, Department of Chemical Immunology, The Weizmann Institute of Science, Rehovot, Israel. Their synthesis, characterization, and properties have been extensively described (3-6).

**Animals.** In the majority of experiments, congenic strains of mice derived from C57BL/10.ScSn(B10) were used, namely B10 itself, B10.BR, B10.D2, and B10.A. The *H-2* types of these strains are *H-2<sup>b</sup>*, *H-2<sup>k</sup>*, *H-2<sup>d</sup>*, and *H-2<sup>a</sup>*, respectively. In some experiments, BALB/c (*H-2<sup>d</sup>*) mice were used. Animals were obtained from the Laboratory Animal Centre, Carshalton, England, and were bred at the Department of Pathology, University of Cambridge.

Particular use has been made in this work of the fact that the *H-2<sup>a</sup>* haplotype, as in B10.A, is a recombinant between *H-2<sup>b</sup>* and *H-2<sup>d</sup>*. Since extensive reference to this will be made below, a genetic map of the *H-2<sup>a</sup>* haplotype is shown in Fig. 1. It will be seen that the *H-2<sup>a</sup>* complex contains the K, *Ir-1A*, and *Ir-1B* genes of *H-2<sup>k</sup>*, and the Ir-C, Ss, and D genes of *H-2<sup>d</sup>*.

**Preparation and Test of T-Cell Factor.** The production and activity of the specific cooperative T-cell factor have been described in detail in previous reports (1, 2). In brief, "educated" T cells were

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<sup>1</sup> *Abbreviations used in this paper:* BSA, bovine serum albumin; MIF, migration inhibition factor; SMAF, specific macrophage-arming factor; (T,G)-A--L, poly(Tyr,Glu)-polyDLAla--polyLys; (T,G)-Pro-L, polyL(Tyr,Glu)-polyL-Pro--polyLlys.

prepared by transferring  $10^8$  thymocytes into each of a group of irradiated (800 R) syngeneic recipients, and immunizing each animal intraperitoneally 1 day later with  $10 \mu\text{g}$  (T,G)-A--L in complete Freund's adjuvant. 7 days after immunization, the spleens of these mice, containing the educated T cells, were removed and cell suspensions prepared in Hepes-buffered minimal Eagle's medium. The suspensions contained 2-3 spleen equivalents/ml. (T,G)-A--L to a concentration of  $1 \mu\text{g}/\text{ml}$  was then added and the suspensions cultured in small petri dishes under an atmosphere of 5%  $\text{CO}_2$  at  $37^\circ\text{C}$  for 6-8 h, with continuous gentle rocking. At the end of this time, the cells were removed by centrifugation, and the supernate, containing the T-cell factor, was mixed with bone marrow cells and (T,G)-A--L and transferred into irradiated (800 R) recipients, syngeneic for the bone marrow donors. Each recipient received one spleen equivalent of the supernatant T-cell factor,  $10^7$  bone marrow cells, and  $10 \mu\text{g}$  (T,G)-A--L in solution, inoculated into a tail vein. 12 days after transfer, the recipients were killed and their spleens removed and assayed for direct plaque-forming cells (below).

In general, the T-cell factor is tested for activity with syngeneic B cells. In some of the experiments described here, namely those in which the factor was produced by animals of  $H-2^k$  or  $H-2^d$  strains, it was not possible to test it with syngeneic B cells since these strains are low responders to (T,G)-A--L. Nevertheless, educated T cells of these animals produced cooperative factor to (T,G)-A--L with high efficiency, and this was tested in irradiated high responder recipients such as B10 ( $H-2^d$ ) with syngeneic, i.e. B10, bone marrow cells. It may be noted that there is no evidence for any nonspecific "allogeneic" effect when factor of one strain is tested with B cells of another (see also reference 7).

**Hemolytic Plaque-Forming Cell Assay.** Plaque-forming cells (PFC) to (T,G)-A--L are estimated most efficiently using sheep red blood cells coated with (T, G)-Pro--L. No inaccuracy is involved since the antibody response to (T,G)-A--L is almost wholly directed to the (T,G) determinants. (T,G)-Pro--L was attached to sheep red blood cells (SRBC) by incubating equal volumes of packed SRBC, chromium chloride (10 mg/ml), and (T, G)-Pro--L (10 mg/ml) for 5 min at room temperature. After coating, the SRBC were washed three times in saline and diluted to a final concentration of 10%. Direct splenic PFC were determined, using the method of Jerne and Nordin (8).

#### Antisera

**ANTI-IGM.** Antiserum to the IgM ( $\mu$ ,  $\lambda$ ) myeloma MOPC 104E was raised by repeated inoculation in sheep.

**ANTI-Fv.** Rabbit antiserum to the Fv fragment of the myeloma MOPC 315 (9) was the kind gift of Professor P. J. Lachmann.

**ANTI-H-2 SERA.** All alloantisera were raised in congenic B10-derived strains, by repeated weekly inoculations of spleen cells, using the following combinations: (a) anti- $H-2^d$ -DBA/2 spleen cells inoculated into B10.BR; (b) anti- $H-2^k$ -CBA into B10.D2; (c) anti- $H-2^k$  (K, Ir-1A, Ir-1B)-A/J ( $H-2^d$ ) into B10.D2; and (d) Anti- $H-2^k$  (I-C, Ss, D)-CBA into B10.A ( $H-2^d$ ). Reference to Fig. 1 makes it clear that antisera (c) and (d) will only react with part of the products of the  $H-2$  complex, as indicated. (e) In addition, anti- $H-2^k$ , prepared as in (b), was rendered specific for the right-hand side (I-C, Ss, D) of  $H-2$  by absorbing three times with B10.A spleen cells ( $10^8$  lymphocytes/ml serum absorbed).

**Immunoabsorbents.** Adsorbents were prepared by coupling the following reagents to CNBr-activated sepharose (10). (g) (T,G)-A--L: 5 mg (T,G)-A--L were coupled to 1 g (dry weight) activated sepharose. The extent of the reaction was monitored with trace-labeled ( $^{125}\text{I}$ ) (T,G)-A--L. (b) Anti-immunoglobulin and anti- $H-2$  sera: Gamma globulin fractions were prepared by ammonium sulphate precipitation and coupled to activated sepharose after removal of ammonium sulphate. Where necessary, anti- $H-2$  sera were adjusted to equivalent cytotoxicity before coupling. T-cell factor was tested immediately after preparation by passage over the immunoabsorbents in the form of short columns, and was then mixed with B cells and (T,G)-A--L and transferred into irradiated recipients as already described above.

### H-2 complex

<u>H-2K</u>	<u>Ir-1A</u>	<u>Ir-1B</u>	<u>I-C</u>	<u>Ss</u>	<u>H-2D</u>
k	k	k	d	d	d

FIG. 1.  $H-2$  map of the  $H-2^d$  haplotype (27, 28).

*Sephadex Chromatography.* 10 ml BALB/c factor was concentrated to 1 ml by ultrafiltration through a UM10 membrane after addition of 10 $\lambda$  heat-inactivated BALB/c serum. A small aliquot was removed as an activity control and the rest was separated on a G100 Sephadex column (35 cm  $\times$  1.7 cm) equilibrated in HEPES-buffered minimal Eagle's medium containing 1% BALB/c serum. Internal markers, [<sup>125</sup>I] bovine serum albumin (BSA) and [<sup>125</sup>I]Na were included; blue dextran and ovalbumin were run separately as external markers. Fractions were pooled as shown in the results and tested for activity.

## Results

*Binding of Factor by Antigen-Coated Column.* It has been previously shown that both the production in vitro and activity in vivo of the factor are antigen specific (1). Thus, factor produced to (T,G)-A--L did not cooperate with B cells in the response to SRBC (1). In order to establish that the factor possesses a specific antigen-binding site, it was passed through a (T,G)-A--L-sepharose immunoadsorbent. Table I shows that such an adsorbent completely removed all activity.

TABLE I  
*Binding of T-Cell Factor by Antigen-Coated Column*

Factor	Immunoabsorbent	PFC/spleen*
—‡		2.281
BALB/c	—	4.209
	Ig-sepharose§	4.101
	(T,G)-A--L-sepharose	2.315
	Standard error	0.184

\* Log<sub>10</sub> geometric means anti-(T,G)-A--L direct PFC, five mice per group.

‡ Control: B cells and (T,G)-A--L transferred into irradiated recipients with T-cell factor.

§ Control for nonspecific adsorption, rabbit immunoglobulin-coupled sepharose.

*Attempts to Remove Factor with Anti-Immunoglobulin Adsorbents.* Previous attempts to remove the T-cell factor with an anti-immunoglobulin immunoadsorbent (sheep antmouse Fab) were unsuccessful (2). This finding has now been extended using sheep antmouse IgM and rabbit antmouse Fv. Neither of these were able to remove factor activity (Table II). These results would appear to exclude the possibility that the cooperative T-cell factor is any known class or fragment of conventional immunoglobulin.

*Adsorption of Factor by Alloantisera-Coated Columns.* In contrast to the failure to remove the factor on anti-immunoglobulin columns, adsorbents prepared from alloantisera consistently removed activity. We have previously demonstrated this using alloantisera raised against the whole *H-2* complex of the strain in which the factor was produced (2). In order to determine whether the factor was coded for by genes in the K or D half of *H-2*, use was made of the recombinant haplotype *H-2<sup>a</sup>*. As shown in Fig. 1, this is a recombinant between

$H-2^k$  and  $H-2^d$ , and possesses the K region, *Ir-1A*, and *Ir-1B* genes ("K side") of  $H-2^k$ , and the I-C-, Ss-, and D-region genes ("D side") of  $H-2^d$ .

In the first experiments, factor to (T,G)-A--L was prepared from  $H-2^a$  (B10.A) T cells and tested either unadsorbed or after passage through anti- $H-2^k$  or anti- $H-2^d$  immunoadsorbents. Table III shows that anti- $H-2^k$  but not anti- $H-2^d$  removed the activity completely, even though the same anti- $H-2^d$  adsorbent successfully removed factor produced by  $H-2^d$  T cells (2). Thus, the factor is coded by, or carries the antigens of, the left-hand (K) side of the  $H-2$  complex.

Confirmation of this is shown in Tables IV and V. Factor was prepared from  $H-2^k$  (B10.BR) T cells and adsorbed with alloantisera prepared either against the whole  $H-2^k$  haplotype, or raised specifically against the K or D sides of  $H-2^k$ . Once again, only the antisera which contained anti-K side specificity successfully removed the cooperative activity of the factor (Table IV). Finally, the anti- $H-2^k$  alloantiserum was itself adsorbed with  $H-2^a$  (B10.A) spleen cells to remove anti-K side antibodies, before coupling to sepharose. Anti- $H-2^k$  adsorbed in this way no longer had the ability to remove  $H-2^k$  factor (Table V). These results

TABLE II  
*Attempts to remove T-Cell Factor with Anti-Immunoglobulin Adsorbents*

Factor	Immunoadsorbent	PFC/spleen*
—‡		1.431
B10.BR	—	4.008
	Anti-IgM	4.064
	Anti-Fv	4.033
	Standard error	0.124

\* Measured in B10 (high responder) recipients;  $\log_{10}$  geometric means anti-(T,G)-A--L direct PFC, five mice per group.

‡ Control: B cells and (T,G)-A--L transferred into irradiated recipients without T-cell factor.

TABLE III  
*Adsorption of T-Cell Factor by Alloantisera Adsorbents*

Factor	Immunoadsorbent	PFC/spleen*
—‡		1.462
$H-2^a$ (B10.A)	—	2.875
	Anti- $H-2^k$	1.301
	Anti- $H-2^d$	2.740
	Standard error	0.142

\* Measured in B10.D2 recipients;  $\log_{10}$  geometric means anti-(T,G)-A--L direct PFC, five mice per group.

‡ Control: B cells and (T,G)-A--L transferred into irradiated recipients without T-cell factor.

TABLE IV  
Adsorption of T-Cell Factor by Alloantisera Adsorbents

Factor	Immunoabsorbent	PFC/spleen*
—‡		1.431
<i>H-2<sup>k</sup></i> (B10.BR)	—	4.338
	Anti- <i>H-2<sup>k</sup></i>	1.301
	Anti- <i>H-2<sup>k</sup></i> (K, <i>Ir-1A</i> , <i>Ir-1B</i> )	1.732
	Anti- <i>H-2<sup>k</sup></i> (I-C, Ss, D)	4.380
	Standard error	0.212

\* Measured in B10 (high responder) recipients; log<sub>10</sub> geometric means anti-(T,G)-A--L direct PFC, five mice per group.

‡ Control: B cells and (T,G)-A--L transferred into irradiated recipients without T-cell factor.

TABLE V  
Adsorption of T-Cell Factor by Alloantisera Adsorbents

Factor	Immunoabsorbent	PFC/spleen*
—‡		1.431
<i>H-2<sup>k</sup></i> (B10.BR)	—	4.338
	Anti- <i>H-2<sup>k</sup></i>	1.301
	Anti- <i>H-2<sup>k</sup></i> absorbed with <i>H-2<sup>a(k-d)</sup></i> spleen cells	4.398
	Standard error	0.210

\* Measured in B10 (high responder) recipients; log<sub>10</sub> geometric means anti-(T,G)-A--L direct PFC, five mice per group.

‡ Control: B cells and (T,G)-A--L transferred into irradiated recipients without T-cell factor.

demonstrate that this cooperative factor for (T,G)-A--L contains a product of the K, *Ir-1A*, or *Ir-1B* genes of *H-2*.

*Sephadex Chromatography of T-Cell Factor.* T-cell factor for (T,G)-A--L was concentrated and passed through a Sephadex G100 column. Pooled fractions were tested for cooperative activity. As shown in Fig. 2 active factor was eluted immediately after BSA marker, corresponding to a mol wt of about 50,000.

## Discussion

These results describe some of the properties of a cooperative T-cell factor. Of key importance is specificity for antigen. This has been demonstrated by binding of the factor to antigen-coated columns, and confirms the functional specificity of the factor in vivo (1). Although this clearly suggests that the factor possesses a binding site for antigen, it is equally clear that it is nonimmunoglobulin in nature. Thus, the factor has an approximate mol wt of 50,000, and is not adsorbed by anti-immunoglobulin reagents. On the other hand, alloantisera,

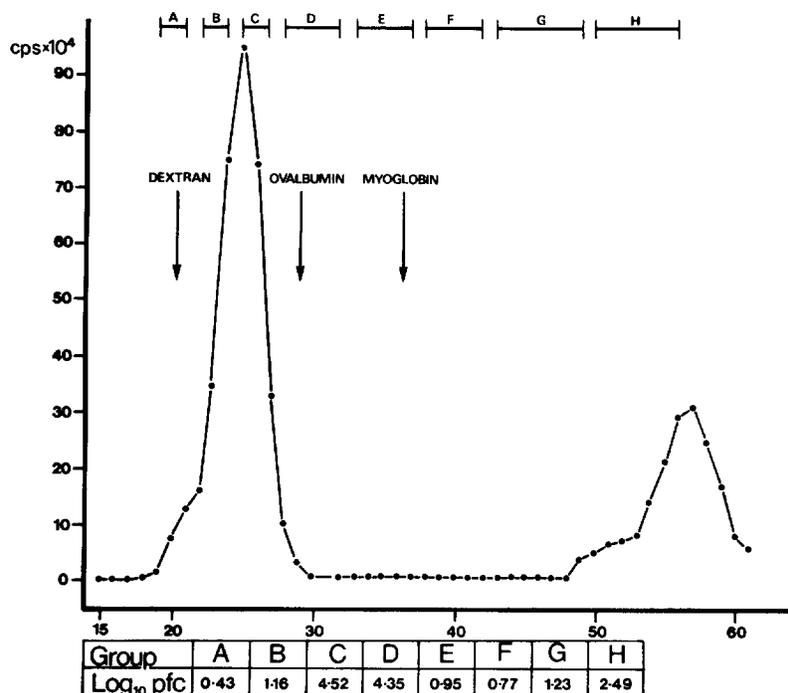


FIG. 2. Chromatography of T-cell factor on G100 Sephadex. The graph shows the elution pattern of [<sup>125</sup>I]BSA and [<sup>125</sup>I]Na. The table shows the activity of pooled fractions (log<sub>10</sub> geometric means).

immobilized as immunoadsorbents, removed the factor with great efficiency, provided the sera were directed against the *H-2* antigens of the strain producing the factor. It appears, therefore, that the factor is an antigen-specific product of the *H-2* complex. The latter contains several genetic regions—*K*, *Ir*, *Ss*, and *D*—and by the use of the recombinant *H-2<sup>a</sup>* chromosome it was possible to show that the factor is a product of genes in either the *K* or *Ir* regions, or both. (This result does not exclude the presence also of products of genes outside *H-2*.)

These properties distinguish this T-cell factor from other T-cell products capable of stimulating a response in B cells. Various factors produced as a result of stimulation of T cells by antigen are not antigen-specific in their effect on B cells (11–13), and specific collaborative factors have usually been immunoglobulin in nature (14). One exception to the latter is antigen-specific macrophage migration inhibition factor (MIF) (15), reported to have collaborative properties (16), and which in common with the *H-2*-derived factor described here has a mol wt of about 50,000. Another specific T-cell product of similar molecular size, though of unknown collaborative potential, is specific macrophage-arming factor (SMAF) (17). It would be important to discover whether MIF and SMAF are also derived from the major histocompatibility complex.

It seems very likely that the antigen-specific *H-2*-derived T-cell factor is closely related to, if not identical with, the T-cell receptor for antigen. The conclusion that the T-cell receptor is coded by *H-2* genes is in basic agreement

with the ability of alloantisera to inhibit T-cell recognition of antigen (18-20). Other workers have found evidence for immunoglobulin on the surface of T cells (21-24), though the possibility that T cells absorb immunoglobulin from serum (25) makes interpretation of these results ambiguous.

The exact nature of the T-cell factor is still unclear. Thus far, the data are strongly in favor of the factor containing a K- or *Ir*-gene product(s). It is obviously relevant here that the response to (T,G)-A--L is controlled by the *Ir-1A* gene (26-28). One possibility, therefore, which has already been suggested (26-28), is that the *Ir* gene controls the specificity of the T-cell receptor, and our data would accord with this view. A dilemma arises in the interpretation of the defect in low responder strains. Although it would be logical to assume that T cells of these strains lacked the genes necessary to produce specific T-cell cooperative factor for (T, G)-A--L, this is demonstrably not always the case. It has been shown elsewhere (7), and repeated here with other strains, that low responder T cells of some strains are apparently as efficient at producing T-cell factor for (T, G)-A--L as high responders. In short, in this case the *Ir*-gene-controlled defect is apparently not reflected in T-cell function. The implication is that genes of the *Ir* region are functionally expressed on other cells as well as on T cells, for example, B cells or macrophages. On the latter cell types, their role could be to receive the T-cell signal.

### Summary

Mouse thymus cells, educated to poly(tyrosyl,glutamyl)-polyDLalanyl--polylysyl [(T,G)-A--L], release an antigen-specific factor on brief culture in vitro. The factor cooperates with bone marrow cells in the antibody response to (T,G)-A--L in irradiated recipients. Its mol wt determined from Sephadex G100 chromatography is in the region of 50,000. The factor is removed by specific antigen-coated columns, but not by anti-immunoglobulin (anti-Fab, anti- $\mu$ , anti-Fv) adsorbents. The factor is removed by alloantisera directed against the *H-2* haplotype of the strain in which it is produced. Moreover, only antisera with specificity for the K side of *H-2* were successful in removing the factor activity.

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