INDUCTION OF T-LYMPHOCYTE RESPONSES TO A SMALL MOLECULAR WEIGHT ANTIGEN

III. T-T Cell Interactions to Determinants Linked Together: Suppression Vs. Enhancement*

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In the preceding paper (1), we have described parameters in guinea pigs for induction of unresponsiveness in T cells specific for the low molecular weight antigen, azobenzene arsonate-chloroacetyl-tyrosine (ABA-T). This unresponsiveness was shown to reflect a state of active suppression by ABA-specific peripheral lymphocytes which had been generated by administration of appropriate doses of ABA-T in an emulsion of incomplete Freund's adjuvant (IFA). Suppressor cells generated in this manner were capable of suppressing development of ABA-specific delayed responses normally induced by ABA-T given in complete Freund's adjuvant (CFA) to unprimed guinea pigs. Such cells were unable, however, to abrogate responsiveness of T cells that had been previously primed to ABA-T.

In view of the (a) well-defined nature of this particular antigen which is capable of stimulating specific T-cell responses; and (b) the evidence obtained by several investigators in earlier studies demonstrating interesting, though ill-explained phenomena of determinant competition, e.g. immunodominance, in responses to hapten-protein conjugates (2-6), we felt that the model of active suppression could be extended to explore various avenues along which cell interactions between T lymphocytes of distinct specificities and possibly distinct subclasses might transpire. The experiments presented in this paper demonstrate not only the existence of such T-T cell interactions in responses to ABA-protein conjugates but also make the intriguing point that the spectrum of T-cell regulation from facilitation (i.e., help) at one end to suppression at the other, which has been well-documented in T-B cell interactions (7, 8), is also followed in T-cell regulation of other T lymphocytes. Moreover, these studies demonstrate that, as is true of T-B cell interactions, the most efficient T-T cell interactions occur to determinants linked together on the same molecule thus supporting the concept that development of effector cell function may involve...

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Abbreviations used in this paper: ABA-T, azobenzene arsonate-chloroacetyl-tyrosine; BSA, bovine serum albumin; CFA, complete Freund's adjuvant; HGG, human gamma globulin; IFA, incomplete Freund's adjuvant; PPD, purified protein derivative of tuberculin.
participation of at least two distinct precursor cells, each of which may convey independent determinant specificities and/or genetic control.

Materials and Methods

The proteins and chemicals reagents, methods for preparation of the antigens, procedures for immunization and skin testing, and the source of Hartley and strain 13 guinea pigs were identical to those detailed in the accompanying paper (1). Strain 2 guinea pigs were obtained from a colony maintained at the New England Regional Primate Center, Southboro, Mass.

Results

Suppression by ABA-Specific Suppressor Cells of T-Cell Responses to Determinants Linked to ABA-T. In the preceding manuscript (1), we demonstrated that the administration of ABA-T in IFA to guinea pigs induced active suppressor lymphocytes which specifically suppressed T-cell responses to subsequent immunization with ABA-T in CFA. In the following experiments, conditions were established for the active suppression by ABA-specific suppressor cells of T-cell responses to protein determinants linked to the ABA-T moiety.

Determination of Optimal Dose of ABA-T Administered in IFA Required to Induce Suppression of Subsequent Responses to Adjacent Protein Determinants. As shown in Fig. 1, groups of random bred Hartley guinea pigs were injected with log-incremental doses (2–200 μg) of ABA-T in IFA in the foot pads and 1 wk thereafter these animals and a group of untreated controls were

![Fig. 1](attachment:image.png)

Fig. 1. Hartley guinea pigs were injected with log incremental doses (2–200 μg) of ABA-T in IFA in the foot pads. 1 wk later, these animals and a group of untreated controls were immunized intracutaneously with 50 μg of ABA-T in CFA. 4 wk later, all animals plus a group of unsensitized controls were injected intradermally with 60 μg of aqueous ABA-HGG, and all animals were skin tested with 10 μg of HGG 1 wk thereafter. The data are presented as the average reaction diameters in millimeters of groups of six guinea pigs recorded 24 h after intradermal sensitization. The vertical lines represent standard errors. The dashed line represents the mean reaction diameters of nonsensitized control guinea pigs skin tested with the same preparation of HGG at the same time. Statistical comparisons of the mean skin reactions to HGG of the various experimental groups to the group receiving only intradermal ABA-HGG yielded the following P values: (a) No treatment, P = 0.37; (b) 2 μg ABA-T (IFA), P = 0.18; (c) 20 μg, P = 0.016; and (d) 200 μg, P < 0.001.
immunized intracutaneously with 50 μg of ABA-T in CFA. 4 wk latter, all animals plus a group of unsensitized controls were injected intradermally with 60 μg of aqueous ABA-HGG. The ABA-specific delayed responses and responses to intradermal testing with purified protein derivative of tuberculin (PPD) were recorded 24 h later. As described in the preceding paper, marked suppression of ABA-specific responses was obtained in animals pretreated with 20 μg or more of ABA-T in IFA without any detectable diminution in PPD responses (1). 1 wk after intradermal administration of ABA-human gamma globulin (HGG), all animals were skin tested with 10 μg of HGG. As shown in Fig. 1, good HGG-specific delayed sensitivity was manifested by guinea pigs which had only received the intradermal injection of ABA-HGG 1 wk earlier. Likewise, comparable responses were observed in the groups that had received either no initial treatment or the lowest dose (2 μg) of ABA-T in IFA. The guinea pigs pretreated with 20 μg of ABA-T in IFA manifested HGG-specific responses of around 50% of the untreated controls, whereas animals treated with 200 μg of ABA-T in IFA were markedly suppressed in their delayed responses to HGG. In subsequent experiments we elected, in general, to use an intermediate dose range of 50 μg ABA-T in IFA to induce suppression.

The experiment illustrated in Fig. 2 was performed to determine whether the suppression of responses to adjacent protein determinants observed in conditions of intradermal sensitization with an aqueous antigen preparation (Fig. 1) would be demonstrable under conditions of more stringent immunization. Groups of inbred strain 2 and strain 13 guinea pigs were treated with 50 lag of ABA-T in IFA, and 4 wk thereafter these animals and groups of untreated controls of each strain were intracutaneously immunized with 10 μg of ABA-HGG administered as an IFA emulsion. Delayed responses to HGG were tested 1 wk later and, as shown in Fig. 2, were depressed by 50% or more in both strains in groups pretreated with ABA-T in IFA as compared to controls.

Evidence for elicitation of a memory response of ABA-specific suppressor cells. With the preceding experiments clearly demonstrating the capacity of ABA-specific suppressor cells to effectively diminish T-cell responses directed against adjacent protein determinants, we next asked the question of whether such suppressor activity would either be diminished or increased by intervening administration of ABA coupled to an unrelated protein under conditions of immunization with CFA. (It should be reiterated that such conditions are highly favorable for induction of T-cell immunity to the protein, but highly unfavorable for ABA-specific T-cell immunity.)

As shown in Fig. 3, two groups of Hartley guinea pigs were injected with 50 μg of ABA-T in IFA. 1 wk later, animals in one of these groups were injected intracutaneously with 10 μg of ABA-bovine serum albumin (BSA) in CFA; the second group was not injected at this time. 2 wk later, both of these groups and a third group of untreated controls were given 10 μg of ABA-HGG in IFA intradermally, and then all animals were skin tested with HGG 1 wk thereafter. As shown in Fig. 3, the HGG-specific delayed responses were significantly suppressed in both groups of guinea pigs pretreated with ABA-T in IFA, but most markedly so in the case of animals that had been subsequently boosted with ABA-BSA in CFA. These results indicate that immunization with ABA-protein
Inbred strain 2 and strain 13 guinea pigs were pretreated with 50 μg of ABA-T in IFA. 4 weeks later, all animals were skin tested with 50 μg HGG. The data are presented as the average reaction diameters in millimeters of groups of three to four guinea pigs recorded 24 h after intradermal sensitization. The vertical lines represent standard errors. The dashed line represents the mean reaction diameters of nonsensitized control guinea pigs skin tested with the same preparation of HGG at the same time. Statistical comparisons of the mean skin reactions to HGG of the respective groups of untreated and ABA-T (IFA)-pretreated guinea pigs yielded P values of 0.21 and 0.003 between the strain 2 and strain 13 groups, respectively.

in CFA, although ineffective in inducing ABA-specific effector T cells, is capable of stimulating a form of memory response in a population of previously induced ABA-specific suppressor cells.

Requirement for determinants to be linked on the same molecule. One of the important aspects of humoral immune responses to hapten-carrier conjugates is the well known fact that the most efficient responses are those elicited by determinants linked together on the same molecule (9-12). This is not however, an absolute requirement since under certain conditions the induction of secondary antihapten antibody responses can be accomplished by administration of hapten and carrier determinants on separate molecules (13, 14). The preferential stimulation of cooperative T-B cell interactions by linked determinants raises the question of whether T-T cell interactions of the type being studied here would follow the same pattern.

Three groups of Hartley guinea pigs were treated with 200 μg of ABA-T in IFA. 1 wk later these groups were injected intradermally, respectively, as follows: (a) a mixture of 10 μg of ABA-BSA and 10 μg of HGG in IFA injected in the same site; (b) 10 μg of ABA-BSA and 10 μg of HGG, each in IFA and injected into separate sites; and (c) 10 μg of ABA-HGG in IFA. An additional group of untreated control guinea pigs were injected with 10 μg of ABA-HGG in IFA. 1 wk later, all guinea pigs were skin tested with 10 μg of HGG. As shown in Table I, HGG-delayed sensitivity was comparable in pretreated groups sensitized with ABA-BSA plus HGG and the untreated controls sensitized with ABA-HGG. The only animals
manifesting suppressed HGG-specific delayed responses were those that had been pretreated with ABA-T in IFA and then sensitized with ABA-HGG. These results not only confirm the specificity of the suppression phenomenon but demonstrate a requirement for linkage between the ABA determinant and the antigenic determinants of the protein groups being secondarily suppressed.

**Failure of ABA-specific suppressor cells to inhibit T-cell responses to linked protein determinants administered in the presence of CFA.** The delayed sensitivity reactions elicited by administration of protein determinants in IFA or in saline have been referred to as cutaneous basophil hypersensitivity or Jones-Mote reactions and have been characterized by the presence of a larger number of basophils in the infiltrate than in the classical tuberculin-type reaction (15). However, we have considered that both types of reactions are manifestations of the general phenomenon of delayed hypersensitivity whereby inflammatory reactions are elicited by products of sensitized T cells reacting with antigen. Typically, the reactions elicited in animals immunized with IFA are less intense than those elicited in animals receiving CFA (15). In order to ascertain the extent to which ABA-specific suppressor cells are capable of exerting a suppressive effect on responses to linked determinants, the following experiment was performed using CFA as the vehicle for sensitization to the ABA-protein conjugate.

Two groups of Hartley guinea pigs were injected with 200 μg of ABA-T in IFA

![Diagram](image-url)
**TABLE I**

Suppression of T-Cell Responses to Adjacent Protein Determinants by ABA-Specific Cells: Requirement for Determinants to be Linked on Same Molecule

| Protocol* | Delayed skin reactions† with HGG (wk 2) |
|-----------|----------------------------------------|
| Group     | Immunization (wk 1)                     |
| A         | None 10 μg ABA-HGG (IFA)                                      22.5 (±2.4) |
| B         | 200 μg ABA-T (IFA) 10 μg ABA-BSA + 10 μg HGG in IFA (same site) 22.7 (±3.9) |
| C         | 200 μg ABA-T (IFA) 10 μg ABA-BSA (IFA) + 10 μg HGG (IFA) (different sites) 20.0 (±2.1) |
| D         | 200 μg ABA-T (IFA) 10 μg ABA-HGG (IFA)                                      5.7 (±3.6) |

* Hartley guinea pigs were pretreated with 200 μg of ABA-T in IFA in the foot pads. 1 wk later, these groups were immunized intradermally with either ABA-HGG, a mixture of ABA-BSA plus HGG, or concomitantly with ABA-BSA and HGG all in IFA as indicated. A control group of untreated guinea pigs was immunized with ABA-HGG in IFA (group A). All guinea pigs were skin tested 1 wk later.

† Skin tests were performed on individual animals in each group using 10 μg of HGG. The data are presented as the average reaction diameters in millimeters of groups of four guinea pigs recorded at 24 h after intradermal sensitization. Numbers in parentheses are standard errors.

Establishment of Conditions to Alter T-Cell Responses to Adjacent Determinants on ABA-Protein Conjugates. The phenomenon of immunodominance of protein determinants in inducing delayed hypersensitivity after injection of hapten-protein conjugates has been recognized for many years (2, 3). Briefly, in the ABA-T system, it happens that whereas immunization of guinea pigs with ABA-T in CFA induces excellent ABA-specific delayed sensitivity, the administration of ABA coupled to a protein will not induce delayed sensitivity to ABA but will do so to determinants of the adjacent protein (4, 5). However, interestingly, the induction of anti-ABA antibody responses follows precisely the reverse requirements, e.g., only ABA-protein conjugates are effective in this regard. Along the same lines, it should be stressed that, as pointed out in the preceding paper (1), induction of ABA-specific delayed responses absolutely requires concomitant administration of bacterial adjuvant products whereas, in contrast, delayed sensitivity to protein determinants can be induced by administering the protein in IFA.
The aforementioned facts thus served as the basis for the next inquiries in the present study, namely to what extent the phenomenon of immunodominance could be manipulated to alter the T-cell responses to adjacent determinants of the same molecule. The experiment in Fig. 4 illustrates the capacity to induce delayed sensitivity to HGG determinants of an ABA-HGG conjugate administered in IFA. Note that over the entire dose range, no sensitivity to the ABA determinant was induced although HGG-specific delayed responses were obtained with doses of ABA-HGG of 2.0 µg or more. This pattern of responsiveness can be substantially altered, however, by several maneuvers which have the effect of diminishing the degree of T-cell responsiveness to determinants of the protein, HGG.

One such experiment is shown in Fig. 5. Hartley guinea pigs were injected with 10 µg of ABA-HGG in IFA, and 2 wk later, these animals and a second group of untreated controls were injected with 10 µg of ABA-HGG in CFA. 2 wk after this immunization, all animals were skin tested for HGG- and ABA-specific delayed sensitivity. The guinea pigs immunized only with ABA-HGG in CFA manifested good delayed responses to HGG but failed to exhibit ABA-specific responses. In contrast, guinea pigs that had initially received ABA-HGG in IFA responded to the second injection of ABA-HGG in CFA by manifesting considerably lower responses to HGG determinants. Most interestingly, this decreased response to HGG was associated with a concomitant increase in the capacity of these animals to develop ABA-specific T-cell responses.

A second type of experiment demonstrating this phenomenon is shown in Fig. 6. Guinea pigs were injected intravenously with 500 µg of either ABA-HGG or

| Protocol* | Group | Pretreatment (wk 0) | Immunization (wk 2) | HGG (10 µg, wk 3) | PPD (20 µg, wk 3) |
|-----------|-------|---------------------|---------------------|-------------------|-------------------|
|           |       |                     |                     | mm               | mm                |
| A         | —     | 10 µg ABA-HGG (CFA) | 18.0 (±1.0)         | 20.5 (±0.5)       |
| B         | —     | 10 µg ABA-HGG (IFA) | 16.3 (±1.0)         | 2.5 (±0.3)        |
| C         | 200 µg ABA-T (IFA) | 10 µg ABA-HGG (CFA) | 16.5 (±1.4)         | 17.8 (±0.7)       |
| D         | 200 µg ABA-T (IFA) | 10 µg ABA-HGG (IFA) | 6.2 (±1.1)          | 2.0 (±0.4)        |
| E         | —     | —                   | 2.0 (±0.0)          | 2.0 (±0.0)        |

*Hartley guinea pigs received foot pad injections of 200 µg of ABA-T in IFA. 2 wk later, these animals and two groups of untreated animals were given intradermal injections of 10 µg ABA-HGG in IFA or CFA. 1 wk later, all animals plus a group of nonsensitized controls were skin tested with HGG and PPD.

†Skin tests were performed on individual animals in each group using 10 µg HGG and 20 µg PPD. The data are presented as the average reaction diameters in millimeters of groups of four guinea pigs (A-D) or two guinea pigs (E) recorded 24 h after intradermal sensitization. Numbers in parentheses are standard errors. Statistical comparisons of the mean skin reactions to HGG yielded P values of <0.001 between groups B and D and P = 0.89 between groups A and C. Comparisons of PPD responses among relevant groups did not reveal significant differences.
Fig. 4. Hartley guinea pigs were immunized with incremental doses (0.08–10.0 μg) of ABA-HGG in IFA in the foot pads. 1 wk later, these animals and a group of untreated controls were skin tested with 50 μg of HGG and 50 μg of ABA-insulin (INS). The data are presented as the average reaction diameters in millimeters of groups of four guinea pigs recorded 24 h after intradermal sensitization. The vertical lines represent standard errors. Statistical comparisons of the mean skin reactions to HGG of the groups of animals immunized with various doses of ABA-HGG with the nonimmunized control group yielded the following P values: (a) 10 μg, P > 0.001; (b) 2.0 μg, P = 0.05; (c) 0.4 μg, P = 0.50; and (d) 0.08 μg, P > 0.50.

Fig. 5. Hartley guinea pigs were injected with 10 μg of ABA-HGG in IFA in the foot pads. 2 wk later, these animals and a second group of untreated controls were injected intracutaneously with 10 μg of ABA-HGG in CFA. 2 wks later, all animals were skin tested with 10 μg of HGG and 10 μg of ABA-guinea pig albumin (GPA) with 10 μg each. The data are presented as the average reaction diameters in millimeters of groups of four guinea pigs recorded 24 h after intradermal sensitization. The vertical lines represent standard errors. The dashed line represents the mean reaction diameters of nonsensitized control guinea pigs skin tested with the same preparations of HGG and ABA-GPA at the same time. Statistical comparisons of the mean skin reactions of the two groups to HGG yielded a P value of 0.0017 and comparisons of the skin reactions of these groups to ABA-GPA yielded a P value of 0.005.
Fig. 6. Hartley guinea pigs were injected intravenously with 500 μg of either ABA-HGG or HGG and then immediately thereafter immunized with 200 μg of ABA-HGG in CFA in the foot pads. 3 wks later, all animals were skin tested with 10 μg of HGG and 10 μg of ABA-insulin (INS). The data are presented as the average reaction diameters in millimeters of groups of three guinea pigs recorded 24 h after intradermal sensitization. The vertical lines represent standard errors. The dashed lines represent the mean reaction diameters of nonsensitized control guinea pigs skin tested with the same preparation of HGG and ABA-INS at the same time. Statistical comparisons of the mean skin reactions of the two groups injected intravenously with ABA-HGG and HGG with the untreated control group yielded the following P values: (a) HGG skin tests, \( P = 0.096 \) and \( P = 0.008 \) for groups treated with intravenously injected ABA-HGG and HGG, respectively; (b) ABA-INS skin tests, \( P = 0.22 \) and \( P = 0.0035 \) for groups treated with intravenously injected ABA-HGG and HGG, respectively.

HGG and then immediately thereafter immunized with a high dose (200 μg) of ABA-HGG in CFA in the foot pads. 3 wk later, the delayed responses to HGG and ABA, respectively, were tested in these animals and an untreated control group that had been immunized with ABA-HGG in CFA at the same time. The control guinea pigs displayed strong HGG-specific delayed responses and weak-to-modest degree of ABA-specific sensitivity. The guinea pigs treated with intravenous HGG or ABA-HGG were suppressed in their HGG sensitivity, the greatest degree of suppression occurring in the group injected with unconjugated HGG, and manifested reciprocally higher levels of ABA-specific sensitivity.

Discussion

The data presented extend the activity of ABA-T suppressor cells, which were shown to specifically suppress the development of delayed hypersensitivity to ABA-T, to T cells responsible for delayed hypersensitivity to protein antigens provided immunization is carried out with ABA conjugates of these antigens. Thus, suppressor T cells acting on the development of delayed hypersensitivity are not limited in their effects to T cells bearing the same specificity but can effectively suppress responses of immunologically unrelated T cells if they are specific for carrier antigens covalently linked to the ABA-T determinant.

The regulation by T cells of delayed hypersensitivity responses resembles, therefore, the regulation of humoral responses in that T-T cell cooperative in-
teractions are most effective when the determinants recognized by the interacting cells are linked on the same molecule. The requirement for linked determinants for most effective interactions in the two systems is best explained by the recent realization that both suppressor and helper factors produced by "regulator" T cells bear, in addition to their postulated regulator or cell interaction moieties (16), combining sites for the antigen which has stimulated their production. Such factors can therefore be effectively concentrated on the specific lymphocyte (T or B), the response of which they regulate, by the specific antigen which the cells have bound.

The demonstration in our experiments that suppressor cells can suppress T-cell responses to linked determinants is of great significance when we consider the broader range of tolerance which can be achieved by this mechanism. In addition to suppressor T-T cell interactions to linked determinants, helper T-T cell interactions have been demonstrated in the same system. Thus, when ABA-T is administered in CFA previous to immunization with ABA protein in IFA, the protein-specific delayed hypersensitivity reactions in ABA-T-sensitized animals are significantly stronger than those observed in animals not previously immunized with ABA-T in CFA (Fig. 1). These findings extend to delayed hypersensitivity reactions, therefore, the previous demonstrations of cooperative T-T cell interactions in other expressions of T-cell functions such as mixed lymphocyte reactions, graft-vs.-host reactions and development of cytotoxic lymphocytes (reviewed in reference 17), and T-T cell interactions in the development of helper T cells involved in humoral immune responses (18).

Another interesting phenomenon explored by these experiments is the well recognized unequal immunogenicity for T-cell responses of different determinants on the same molecule, and the interactions which these responses display resulting in a definite hierarchy according to which different determinants are functionally effective on an antigen. Thus, ABA-T is clearly less immunogenic for the elicitation of delayed hypersensitivity than the determinants of native proteins such as HGG since stimulation of delayed hypersensitivity to ABA-T requires immunization with CFA (4) whereas delayed sensitivity to foreign protein antigens can be observed after immunization by the appropriate route in either saline or IFA (2, 3, 15). Furthermore, immunizations with ABA conjugates of immunogenic proteins always result in strong delayed hypersensitivity responses to the protein determinants and weak or absent ABA-specific responses. This "deviation" of the response from the ABA-T determinant to the protein determinants can be avoided as shown in our experiments and previously by Schwartz and Leskowitz (5) if some degree of tolerance to the protein carrier is induced before immunization with the ABA-protein conjugate in CFA. The mechanisms by which the response to ABA-T is restored in these experiments, and therefore the means by which the immune system exerts discriminating choices between linked determinants, are now understood at present. If, indeed, tolerance to the HGG-carrier molecule, obtained by either administration of HGG in soluble form or of ABA-HGG in IFA previous to injection with ABA-HGG in CFA, is the result of the stimulation of HGG suppressor cells, we are faced with the apparent paradox that ABA-T suppressor cells can suppress delayed hypersensitivity responses to the stronger carrier determinants on such
linked antigens, whereas HGG suppressor cells, although capable of suppressing HGG-specific delayed hypersensitivity reactions, are not only unable to suppress ABA-T responses but also appear to restore these latter responses after immunization with ABA-HGG in CFA.

It is highly probable, however, that we are dealing with the following two distinct phenomena: (a) The suppression of delayed hypersensitivity responses to linked determinants discussed above was not observed when CFA was used for immunization, which is precisely the type of immunization optimal to elicit ABA-specific delayed hypersensitivity irrespective of whether ABA-T or ABA-protein conjugates are used; and (b) The absence of competing immune responses to the HGG determinants in the absence of effective suppression to linked determinants permitted the ABA-specific delayed hypersensitivity response to develop. Moreover, the conclusion can also be drawn from these experiments that suppressor T cells are more effective on T cells of the same specificity than on T cells specific for linked determinants.

Even though we believe we have explained the apparent contradiction discussed above, we cannot offer as yet an unequivocal explanation for the phenomenon of immunodominant determinants or of the hierarchy of determinants on an immunogen. The possibility must be entertained that these phenomena reflect the different frequencies of precursor T cells for these respective determinants or, alternatively, more complex processes involving the balance between the activities of helper and suppressor T cells in T-T cell interactions. It may be relevant to note in this respect that suppressor cells specific for ABA-T (a very weak antigen since it is immunogenic only when administered with powerful bacterial adjuvants) are readily stimulated, very effective, and long lasting in their effects. Similarly, mice genetically nonresponsive to the terpolymer of L-glutamic acid, L-alanine, and L-tyrosine produce preferentially suppressor T cells even when immunized with Bordetella pertussis as adjuvant (19). In both of these situations, the response of weak immunogens is preferentially directed to suppressor cells. A more detailed analysis of the mechanism of T-cell regulation of T-cell responses (as well as B-cell responses) and of the mode of action of bacterial adjuvants on T cells is required for a better understanding of the phenomena of cooperation between determinants and of immunodominant determinants on complex antigens.

Summary

The experiments presented in this paper demonstrate the existence of T-T cell interactions in responses to azobenzenearsonate (ABA)-protein conjugates, and also make the point that the spectrum of T-cell regulation from facilitation (i.e., help) at one end to suppression at the other, which has been well documented in T-B cell interactions, is also followed in T-cell regulation of other T lymphocytes. The data extend the activity of ABA-specific suppressor cells, which were shown to specifically suppress the development of delayed hypersensitivity to ABA-T to T cells responsible for delayed hypersensitivity to protein antigens provided immunization is carried out with ABA conjugates of these antigens. Thus, suppressor T cells acting on the development of delayed hypersensitivity are not
limited in their effects to T cells bearing the same specificity but can effectively suppress responses of immunologically unrelated T cells if they are specific for carrier antigens covalently linked to the ABA-T determinant. Moreover, these studies demonstrate that, as is true of T-B cell interactions, the most efficient T-T cell interactions occur to determinants linked together on the same molecule thus supporting the concept that development of effector T-cell function may involve participation of at least two distinct precursor cells, each of which may convey independent determinant specificities and/or genetic control.

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