ADAPTIVE DIFFERENTIATION OF MURINE LYMPHOCYTES

IV. (Responder × Nonresponder) F_1 T Cells Can Be Taught To Preferentially Help Nonresponder, Rather Than Responder, B Cells*

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Several years ago, we reported that T cells from (responder × nonresponder) F_1 hybrids primed to the synthetic terpolymer, L-glutamic acid, L-lysine, L-tyrosine (GLT),[1] to which responses are governed by *H-2*-linked *Immune response-GLT* genes, were restricted in their ability to provide GLT-specific help for 2,4-dinitrophenyl (DNP)-primed B cells from the respective parental mice in response to DNP-GLT (1). Thus, such F_1 T cells were able to provide normal helper activity for DNP-specific B cells from responder, but not from nonresponder, donor mice. This finding contrasted sharply with the indiscriminant ability of F_1 T cells to interact effectively with partner B cells from either parent when the carrier antigen employed was not one to which responses were governed by a known *Ir* gene. This observation has subsequently been confirmed by others in studies conducted in mice (2, 3) and guinea pigs (4).

These observations were interpreted as an indication that in heterozygous individuals independent subpopulations of interacting T lymphocytes existed, one each corresponding to the respective parental type (1, 5, 6). Hence, we envisaged that stimulation of a (responder × nonresponder) F_1 T-cell population by GLT would sensitize only the population of T cells able to recognize and react with the functional cell-interaction (CI) phenotype of the responder parent; F_1 T cells corresponding to the nonresponder parent CI phenotype would not be stimulated by GLT. This situation would therefore be manifested as the defective ability of F_1 T cells to interact with nonresponder B cells, irrespective of the antigen specificity of the latter. This original interpretation (1, 5, 6) has been reinforced by the subsequent demonstrations of the existence of independent F_1 T-cell subpopulations that are reactive with each respective parental CI phenotype (7-12).

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[1] Abbreviations used in this paper: ASC, *Ascaris suum* extract; CI, cell interaction; DNP, 2,4-dinitrophenyl hapten; GLT, synthetic random terpolymer of L-glutamic acid[57], L-lysine[38], L-tyrosine[5]; *Ir* gene, Immune response gene.

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In this report, we present results of experiments designed to determine whether the normally restricted, cooperating phenotype of (responder × nonresponder) F_1 T cells specific for GLT could be experimentally manipulated to express a different cooperating phenotype. Specifically, we were interested in generating GLT-specific F_1 T cells that might now express cooperative helper activity for nonresponder B cells. We have found that this can, indeed, be done by inducing a transient allogeneic effect during the period of priming of F_1 mice to GLT. Moreover, the conditions in which the allogeneic effect is induced determines, in a critical fashion, the ultimate cooperating phenotype observed with the resulting F_1 GLT-primed helper T cells.

Materials and Methods

The terpolymer poly-α-(L-glutamic acid[57], L-lysine[38], L-tyrosine[5]) (GLT, lot M 72-B), mol wt 50,000, was prepared by polymerization of the α-*N*-carboxyanhydrides of the amino acids (13). After the removal of HBr from the final lyophilized polymer, the reconstituted polymer was dissolved at pH 7.5. All other proteins, hapten-carrier conjugates, animals, methods for determining serum anti-DNP antibody levels or DNP-specific plaque-forming cells (PFC) and for the depletion of T lymphocytes by anti-θ serum plus complement, have been described (1, 14). DNP conjugates employed were $DNP_{2.1}$-*Ascaris suum* (ASC) and DNP_4-GLT. BALB/c, A/J, and (BALB/c × A/J) F_1(CAF_1) donors of DNP-primed B cells were primed with 10 μg of DNP-ASC adsorbed on 4 mg of aluminum hydroxide gel (alum) and then boosted with 10 μg of DNP-ASC in saline, 3–4 wk after primary immunization and again at monthly intervals thereafter. The mice employed in the present studies were so boosted on three occasions and finally used as B-cell donors ≅1 mo after the third saline boost. CAF_1 donors of GLT-primed spleen cells were immunized with 50 μg of GLT emulsified in complete Freund's adjuvant. 10 d after this initial immunization, these mice were injected intravenously with either 25×10^6 A/J or BALB/c spleen cells, or not injected. All mice were boosted on the same day with 50 μg of GLT in saline; spleen cells were obtained from such donor mice 7 d after the transfer of parental cells (or none) and secondary challenge. Mixtures of primed B and T cells were transferred i.v. to 657 R irradiated CAF_1 recipients, which were then secondarily challenged with 50 μg of DNP-GLT in saline i.p.

Results

GLT-Primed (Responder × Nonresponder) F_1 T Cells Help DNP-Primed Responder, but Not Nonresponder, Parental B Cells. Previous studies from this laboratory, which first reported the regulatory influences of allogeneic effects on priming of carrier-specific helper T-cell activity, stressed the importance of the length of the priming regimen as well as the timing of the administration of allogeneic cells (15). Accordingly, the regimen for priming GLT-specific helper T cells in the present study was considerably abbreviated in comparison with the priming method employed in our earlier studies with this antigen (1). We felt it neccessary, therefore, to investigate the patterns of cooperative helper activity manifested by CAF_1 helper T cells primed to GLT (in the absence of any allogeneic effects) according to the schedule used in the present studies. As shown in Fig. 1, it is quite clear that exellent cooperative secondary anti-DNP antibody responses to DNP-GLT could be obtained between F_1 helper cells primed to GLT in this manner and either responder BALB/c (group IV) or F_1 (group VI) B cells. In marked contrast, and consistent with our previous findings (1), F_1 GLT-primed T cells were unable to provide meaningful help for nonresponder A/J B cells (group II).

Helper T-Cell Activity of (Responder × Nonresponder) F_1 Spleen Cells Primed To GLT under the Influence of an Allogeneic Effect. CAF_1 T cells obtained from mice primed to GLT, either in the absence of any allogeneic effect or in the presence of an allogeneic

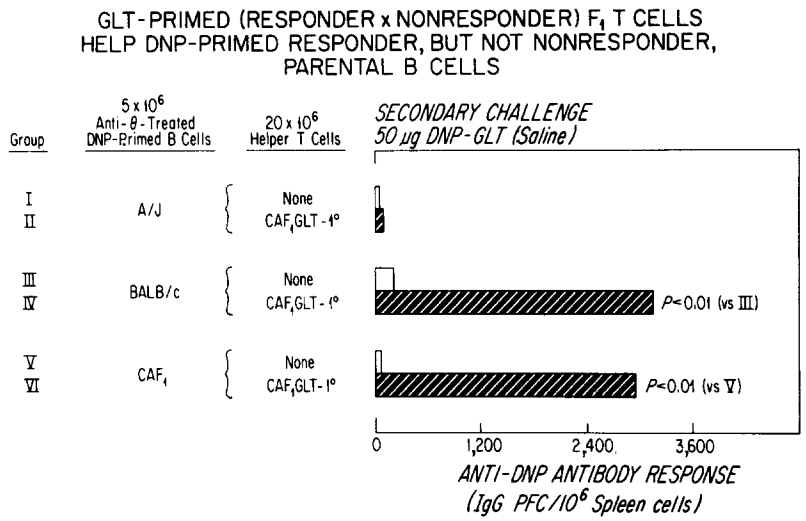

FIG. 1. GLT-primed (responder × nonresponder) F_1 T cells help DNP-primed responder, but not nonresponder, parental B cells.

Irradiated (675 R) CAF_1 mice were injected i.v. with 5×10^6 anti-θ serum-treated B cells from DNP-ASC-primed A/J, BALB/c, or CAF_1 donors, either together with 20×10^6 GLT-primed CAF_1 helper T cells or without any helper cells. Helper T-cell donors were primed with 50 μg of GLT in CFA followed 10 d later by a second injection of 50 μg in saline; spleens were removed from such donor mice 7 d after the second injection to be used as helper cells. All adoptive recipients were secondarily challenged with 50 μg of DNP-GLT in saline. The data presented represent geometric means of individual numbers of IgG DNP-specific PFC per 10^6 recovered spleen cells of groups consisting of five mice each. Statistically significant differences in responses between experimental and control groups are indicated beside the corresponding bar.

effect induced by one or the other parental cell type, display the pattern of cooperative helper activity for DNP-primed B cells from either A/J, BALB/c, or CAF_1 donor mice that is depicted in Figs. 2 and 3. These data are representative of several experiments of this type, all of which utilized a standard adoptive transfer system in which varying numbers of the relevant B and T cells were transferred together to irradiated CAF_1 recipients. The only pertinent difference between the two experiments illustrated in these figures is that 5×10^6 B cells and 10×10^6 helper T cells were transferred in one experiment (Fig. 2), whereas 15×10^6 B cells and 30×10^6 helper T cells were transferred in the other (Fig. 3). The data is presented in terms of numbers of splenic PFC of the IgG class in Fig. 2 and levels of serum anti-DNP antibodies in Fig. 3 to illustrate the fact that the patterns of cooperative activity observed in these studies were the same, irrespective of which type of determination was used.

What these experiments have revealed is that CAF_1 helper T cells, primed to GLT in the absence of an allogeneic effect, provide no help for B cells from A/J mice and variable levels of help for B cells from BALB/c or CAF_1 donor mice depending on the numbers of GLT helper T cells transferred. Note, for example, that 10×10^6 F_1 helper T cells provided only marginal help for F_1, and even less for BALB/c, B cells (Fig. 2), whereas significant levels of helper activity were observed in both cases when 30×10^6 GLT-primed F_1 cells were transferred (Fig. 3).

The remarkable findings are those pertaining to the patterns of F_1 helper activity, for the various B cells, that were generated under the influence of allogeneic effects

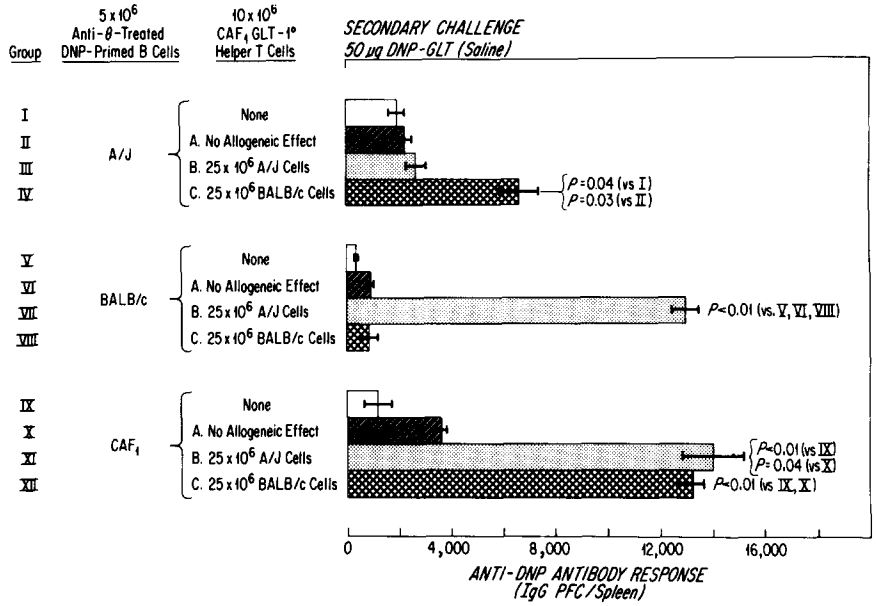

FIG. 2. Helper T-cell activity of (responder × nonresponder) F_1 spleen cells primed to GLT under the influence of an allogeneic effect.

Irradiated (675 R) CAF_1 recipient mice were injected with i.v. with 5×10^6 DNP-primed B cells from either A/J, BALB/c, or CAF_1 donors, either in the absence of helper cells or together with 10×10^6 spleen cells taken from F_1 mice primed to GLT either in the same manner as described in Fig. 1, or under the influence of an allogeneic effect induced by i.v. injection (on day 10 after initial immunization with GLT) of 25×10^6 spleen cells from parental A/J or BALB/c donors. All recipients were challenged with 50 μg of DNP-GLT in saline. The data are presented as geometric mean levels of individual IgG DNP-specific PFC/spleen of groups of five mice each assayed on day 7 after cell transfer and secondary challenge. Horizontal lines represent standard errors and relevant *P* values depicting statistically-significant differences are indicated beside the corresponding bar.

induced by one or the other parental cell type. First, note that F_1 helper T cells, generated under the influence of an allogeneic effect induced by either A/J or BALB/c parental cells, were clearly and significantly enhanced in their levels of cooperative activity for B cells derived from F_1 donors (Figs. 2 and 3, groups XI and XII). This pattern of indiscriminately enhanced F_1 helper T-cell activity as manifested with F_1 B cells did not hold true when such F_1 T cells were assayed for their ability to help nonresponder A/J or responder BALB/c parental B cells. Thus, F_1 T cells, generated under the influence of an allogeneic effect induced by parental BALB/c cells, were clearly capable of providing GLT-specific help for nonresponder A/J B cells (group IV), but were unable to provide detectable help for responder BALB/c cells (group VIII). Conversely, F_1 T cells, generated during an allogeneic effect induced by parental A/J cells, did not display effective helper activity for nonresponder A/J B cells (group III), although exhibiting significantly enhanced helper activity for responder BALB/c B cells (group VII).

It is pertinent to cite certain control experiments that argue against any major role of carry-over of donor parental cells into the final adoptive transfer recipients as contributing significantly to these findings. First, cell mixture experiments in which cells from F_1 mice primed to GLT during an allogeneic effect were analyzed for any

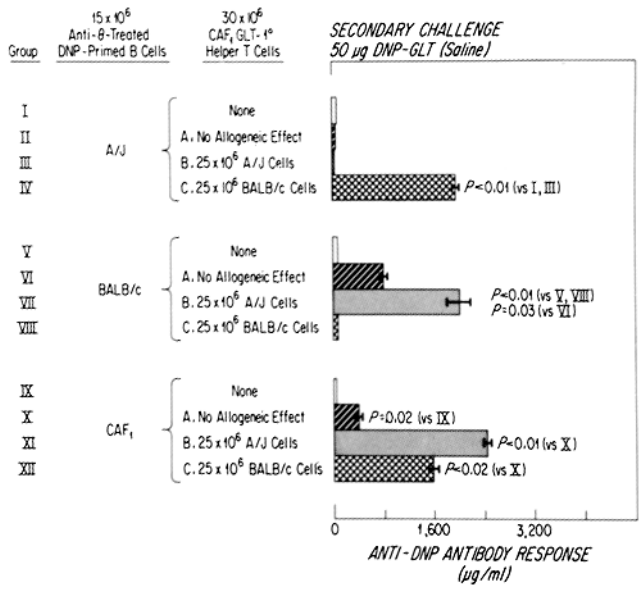

FIG. 3. Helper T-cell activity of (responder × nonresponder) F_1 spleen cells primed to GLT under the influence of an allogeneic effect.

The same protocol as described in Fig. 2 was employed with the only difference being the numbers of transferred B and T cells given to each recipient mouse. The data are presented as geometric mean levels of serum anti-DNP antibodies of individual mice in groups of five mice each bled on day 7 after cell transfer and secondary challenge. Horizontal lines represent the range of standard errors and relevant *P* values of statistically significant differences are indicated.

possible effects on normal cooperative responses between keyhole limpet hemocyanin-primed F_1 T cells and parental A/J, BALB/c, or CAF_1 DNP-primed B cells failed to reveal any such effects. Second, analysis of such cell populations with the relevant anti-*H-2* alloantibodies has revealed little or no contamination of the F_1 donor cell population with detectable parental cells at the time they are removed from GLT-primed mice for the secondary adoptive transfer.

Finally, elimination of F_1 cells by treatment with anti-*H-2* alloantibodies plus complement directed against the opposite parental type as that used for induction of the allogeneic effect, does not leave residual cells in such F_1 populations capable of exerting these effects when cotransferred with mixtures of F_1 T and B cells such as those used in Figs. 2 and 3, group X. Representative data from such an experiment is summarized in Table I. Briefly, it can be seen that F_1 helper T cells, primed to GLT in the absence of an allogeneic effect, provide moderate help for DNP-primed F_1 B cells in adoptive recipients challenged with DNP-GLT (group II). F_1 helper T cells primed to GLT under the influence of an allogeneic effect, induced by parental BALB/c cells, provide enhanced levels of GLT-specific helper activities (group III). Treatment of such helper cells in vitro with either anti-BALB/c or anti-A/J serum + complement before transfer, abrogates the GLT-specific helper activity (groups IV and V). When equal numbers of F_1 GLT-primed spleen cells from donors, primed without or with the influence of an allogeneic effect, are transferred to irradiated recipients together with F_1 DNP-primed B cells, the magnitude of GLT-specific helper activity is essentially additive of the quantities of help exhibited by each individual

TABLE I

*The Effects of F_1 Helper T Cells Primed to GLT under the Influence of an Allogeneic Effect Are Not a Result of Residual Contaminating Parental Cells**

Group	5×10^6 anti-θ-treated DNP-primed B cells	10×10^6 GLT-1° CAF helper T cells	10×10^6 GLT-1° plus allogeneic effect helper T cells**	anti-DNP response† (IgG PFC/spleen)
I	CAF_1	None	None	1,231
II		No allogeneic effect	None	8,957
III		None	BALB/c allogeneic effect (untreated)	15,463
IV			BALB/c allogeneic effect (anti-BALB/c serum—Rx'd)	1,856
V			BALB/c allogeneic effect (anti-A/J serum—Rx'd)	1,420
VI		No allogeneic effect	BALB/c allogeneic effect (untreated)	26,541
VII			BALB/c allogeneic effect (anti-BALB/c serum—Rx'd)	9,923
VIII			BALB/c allogeneic effect (anti-A/J serum—Rx'd)	8,796

* Irradiated (675 R) CAF_1 recipients were injected i.v. with 5×10^6 DNP-primed CAF_1 B cells either in the absence of helper T cells or together with (*a*) 10×10^6 spleen cells from F_1 mice primed with GLT in the absence of an allogeneic effect (Fig. 1) (*b*) 10×10^6 F_1 spleen cells primed to GLT under the influence of an allogeneic effect induced by parental BALB/c cells (Fig. 2) or (*c*) a mixture of the two types of F_1 GLT-primed helper T cells. All recipients were challenged with 50 μg of DNP-GLT in saline.

** F_1 cells primed to GLT under the influence of BALB/c parental cell-induced allogeneic effects were transferred either untreated or after treatment *in vitro* with either A/J anti-BALB/c or BALB/c anti-A/J antiserum plus complement under conditions which gave 100% lysis of each respective parental target cells.

† The data are presented as geometric mean levels of individual IgG DNP-specific PFC/spleen of groups of five mice each assayed on day 7 after cell transfer and challenge.

cell population (group VI). When helper cells from donors primed to GLT under the influence of an allogeneic effect were first pretreated with anti-BALB/c or anti-A/J serum plus complement in vitro, the levels of helper activity obtained reflected essentially the help provided by those cells from donors primed to GLT in the absence of any allogeneic effect (groups VII and VIII). Collectively, these data clearly document the fact that the biological activities of F_1 cells from donors primed to GLT under the influence of an allogeneic effect reflect function of host F_1 cells, and not residual parental cells used for the induction of the allogeneic effect, because alloantibodies directed against either parental cell type were equally effective in abrogating such biological activities.

Discussion

These studies make two important points: (*a*) First, the usually restricted phenotype of (responder × nonresponder) F_1 T cells which typically is permissive only for providing cooperative helper activity for B cells of responder, but not of nonresponder, type, can be changed by inducing an allogeneic effect during the priming of such F_1

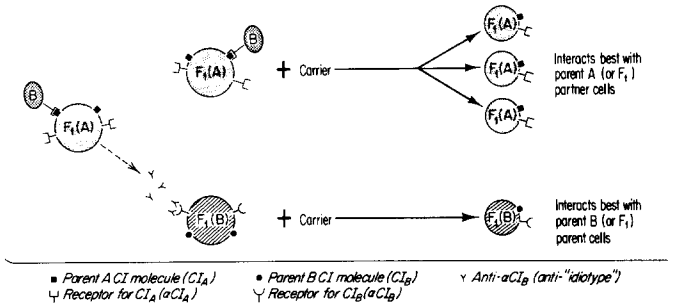

FIG. 4. Influence of parental cell-induced allogeneic effect on differentiation of F_1 lymphocytes. See text for explanation.

mice. This is true provided the allogeneic effect is induced by cells derived from the opposite (i.e. responder) parental type. (*b*) Actually, the ultimate cooperating phenotype of GLT-primed F_1 helper T cells is differentially and reciprocally directed toward B cells of one parental type or the other depending on which parental donor cells are used for inducing the allogeneic effect that takes place during the priming regimen. Thus, F_1 T cells, primed to GLT under influence of an allogeneic effect induced by parental BALB/c cells, now provide effective help for nonresponder A/J B cells, but do not do so for responder BALB/c B cells, and vice versa. On the other hand, F_1 T cells primed to GLT under the influence of an allogeneic effect, induced by either parental cell type, display significantly enhanced levels of helper activity for B cells derived from F_1 donors.

The fact that the allogeneic effect induces such exquisite discriminatory helper activities when F_1 T cells are assayed on parental B cells, but loses this discriminatory aspect when F_1 B cells serve as the partner B cells in the assay, is perhaps the most pertinent aspect of these findings with respect to understanding the regulatory events which these data reflect. Parenthetically, the results with F_1 B cells provide additional arguments against any significant contribution made by contaminating parental B cells that may be carried over in the final assay system; but this possibility has been more directly circumvented (Results).

We believe that these results illustrate the consequences of two interdependent events which are schematically illustrated in Fig. 4: First, the allogeneic effect induced by one parental cell type exerts powerful stimulatory signals which substantially augment the normal differentiation signals induced by immunization with antigen alone; this has been amply documented to occur in many previous studies (16). The consequence of such stimulatory signals is reflected in the significant enhancement of GLT-specific helper T-cell activity provided to B cells from F_1, BALB/c, and A/J donors as shown herein. Of particular note is the capacity of the allogeneic effect, induced by BALB/c cells, to draw out permissiveness of F_1 cells in providing GLT-specific help to the nonresponder A/J B cells. One point that should be clarified is that this finding is by no means directly analogous to either (*a*) our own earlier studies demonstrating that an appropriately timed allogeneic effect would convert the normally tolerogenic effects of DNP-derivatized D-glutamic acid, D-lysine (D-GL) to an immunogenic signal for DNP-primed B cells (17, 18) or (*b*) that of Ordal and Grumet (19) who demonstrated the capacity of an allogeneic effect to permit nonresponder mice to make IgG (as well as IgM) antibody responses to (T,G)-A--L.

In both of the aforementioned instances, the allogeneic effect provided a necessary stimulus to target B cells, thereby replacing a normal interaction step missing in both circumstances. In our present studies, the allogeneic effect has obviously provided the necessary stimulus, in addition to antigen, to encourage the differentiation of the subset of A/J-type T cells capable of interacting with DNP-primed A/J B cells. The reasons for the failure of such cells to differentiate through the helper cell pathway in response to GLT under normal circumstances is, of course, a central question to the whole issue of what role is actually served by *Ir* genes and their products. The present studies certainly do not provide a definitive answer to this question.

It should be pointed out, however, that the fact that the allogeneic effect was effective in inducing GLT-specific helper T cells, presumably of the nonresponder A/J-type subset, must be viewed with serious consideration in the context of the recently mounting speculation that Ir-gene products react specifically with antigenic determinants at the level of the macrophage to orient and display the relevant determinants for recognition by T cells of corresponding specificity (20–22). It is difficult to envisage, for example, how an allogeneic effect could circumvent an absolute requirement for Ir-gene-controlled antigen display by macrophages. Rather, these data seem to argue against any such absolute requirement for macrophage presentation and tend to favor the possibility that the allogeneic effect permits the development of GLT-specific F_1 helper cells capable of interacting with nonresponder B cells by either (*a*) direct stimulation of the A/J-type subset of F_1 GLT-specific T cells to differentiate into effective helper cells, or (*b*) elimination of some type of inherent suppressive mechanism that normally blocks development of GLT-specific helper T cells capable of cooperating with nonresponder B cells.

The second of the two interdependent events, and by far the more difficult to address, pertains to the explanation for the very striking discriminatory aspects of helper activities when F_1 T cells are assayed on parental B cells. Obviously, no direct evidence is presently available to permit conclusions concerning this aspect of our data. Nevertheless, we would like to suggest that aside from the stimulatory consequences of the allogeneic effect in inducing helper T-cell function as discussed above, a second consequence may be the stimulation of an F_1 response against certain of its own receptors which self-recognize native CI determinants (α-CI). Thus, as illustrated in Fig. 4, when parental *B* cells induce an allogeneic effect in an ($A \times B$) F_1, the response within the F_1 would be directed against self receptors for *B*-type CI molecules (anti-α CI_B), and vice-versa. These types of anti-idiotype responses against self-recognizing receptors would be capable of preventing development of helper T cells belonging to the corresponding parental-type T cell subpopulation without adversely affecting the development of helper cells corresponding to the opposite parental-type T-cell subpopulation.

In a sense, these postulated anti-α CI responses are analogous to, but not necessarily the same as, the α-major histocompatibility complex (MHC) idiotype reactions described recently by Bellgrau and Wilson (23) which confer specific resistance to parental cell-induced graft-vs.-host disease in irradiated F_1 rats.

If studies currently in progress demonstrate anti-α CI reactions to be the mechanism responsible for the data presented here, then one wonders (*a*) if responses of this type occur normally in the pathways of immune regulation, (*b*) whether virgin cells and primed cells are similarly susceptible to the effects of such reactions, or not, and (*c*)

what relationship such anti-α CI responses might have to the whole picture portrayed by *Ir* genes and the specificity they appear to display for the antigens under their control.

Summary

Responses to the synthetic terpolymer L-glutamic acid, L-lysine, L-tyrosine (GLT) in the mouse are controlled by *H-2*-linked *Ir-GLT* genes. (Responder × nonresponder) F_1 hybrid mice, themselves phenotypic responders, can be primed with GLT to develop specific helper cells capable of interacting with 2,4-dinitrophenyl hapten (DNP)-primed F_1 B cells in response to DNP-GLT. Unlike the indiscriminant ability of F_1 helper T cells for conventional antigens (i.e. not Ir gene-controlled), which can help B cells of either parental type (as well as F_1) equally well, GLT-primed F_1 T cells can only provide help under normal circumstances for B lymphocytes of responder parent origin; they are unable to communicate effectively with nonresponder parental B cells (1, and the present studies). The present studies reveal, however, that the induction of a parental cell-induced allogeneic effect during priming of F_1 mice to GLT actually dictates the direction of cooperating preference that will be displayed by such F_1 helper cells for B cells of one parental type or the other. Thus, F_1 T cells, primed to GLT under the influence of an allogeneic effect induced by parental BALB/c cells, develop into effective helpers for nonresponder A/J B cells, but fail to develop effective helpers for responder BALB/c B cells, and vice-versa. In contrast, F_1 T cells, primed to GLT under the influence of an allogeneic effect induced by either parental type, display significantly enhanced levels of helper activity for B cells derived from F_1 donors. These results are interpreted to reflect the existence of two interdependent events provoked by the allogeneic effect: one event augments the differentiation of GLT-specific helper T cells belonging to the subset corresponding to the opposite parental type; this would explain the development of increased helper activity provided to partner B cells of opposite parental type (as well as of F_1 origin). The second event, we postulate, involves the production of responses against the receptors which normally self-recognize native cell interaction determinants; this form of anti-idiotype response is restricted against self-recognizing receptors of the same parental type used for induction of the allogeneic effect, hence explaining diminished helper activity of such F_1 cells for partner B lymphocytes of corresponding parental type.

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