ANTIGEN-SPECIFIC HELPER T CELLS REQUIRED FOR
DOMINANT PRODUCTION OF AN IDIOTYPE (ThId) ARE
NOT UNDER IMMUNE RESPONSE (Ir) GENE CONTROL*

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Anti-hapten antibody responses to hapten-protein conjugates have been shown to
involve the cooperative interaction of hapten-specific B lymphocytes and helper T
(Th) lymphocytes specific for the protein carrier molecule (1). In addition to
specificity for the carrier, helper T cells display specificity for self determinants
encoded in the I-region of the major histocompatibility complex (MHC), such that
eye collaborate efficiently only with B lymphocytes also bearing these determinants
(2-4). Also mapping in the I-region of the MHC are a family of genes known
collectively as immune response (Ir) genes that control the immune response to many
protein and synthetic polypeptide antigens (5, 6). When antigens under the control of
Ir genes are used as carriers, only B cells from responder animals can be activated to
produce antibody by T cells from mice which themselves are responders (7, 8).

Recently, it has been shown that certain antibody responses require two distinct
sets of antigen-specific helper T cells (9-12). For instance, dominant production of the
idiotype associated with the BALB/c phosphorylcholine (PC) binding myeloma
protein TEPC 15 (T15) involves two sets of helper T cells (11, 12). One set is specific
for carrier, requires a physical linkage of hapten and carrier molecules, and activates
hapten-specific B cells independent of idiotype. The other set, also specific for antigen,
does not require physical linkage of the hapten and the carrier. These latter helper T
cells are deficient in mice having low levels of circulating antibody bearing the T15
idiotype (11-13). Optimal activation of PC-specific B cells bearing the T15 idiotype
by such Th cells occurs only in the presence of the other Th cell set (12). This finding
that B cell activation can involve helper signals from two distinct sets of antigen-
specific T cells raises the question of whether both types of helper T cells recognize
antigen in the context of I-region-encoded determinants, or more specifically are both
under the control of MHC-linked Ir genes. This question seems particularly relevant
in the case of the idiotype-recognizing helper T cell set as these cells appear to have

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Abbreviations used in this paper: CFA, complete Freund's adjuvant; DTH, delayed type hypersensitivity;
GLPhe, poly-(L-glutamic acid, L-lysine, L-phenylalanine); HRPO, horse radish peroxidase; KHL, keyhole
limpet hemocyanin; MHC, major histocompatibility complex; NP, 4-hydroxy-3-nitrophenyl acetyl; OVA,
ovalbumin; PC, phosphorylcholine; PFC, plaque-forming cell; (T,G)-A--L, poly(Tyr,Glu)-poly(DL-Ala)--
poly-L-Lys; T15, TEPC 15; Th, helper T cell(s).
A T-HELPER CELL (Thld) IS NOT UNDER Ir GENE CONTROL

specificity both for antigen and for self idiotypic determinants, and it would seem unlikely that they bear a receptor for yet another specificity.

In order to approach this question, the synthetic polypeptide antigen poly-(L-glutamic acid, L-lysine, L-phenylalanine) (GLPhe) was used. Responsiveness to GLPhe in inbred mice has been shown to be under the control of Ir genes mapping in the I region of the MHC (14, 15). Effective T-B collaboration in response to hapten conjugates of GLPhe has been shown to require that both the B cell and the T cell be derived from responder animals (8). In the present experiments, responder and nonresponder mice were primed with GLPhe. T cells from these animals were analyzed by adoptive transfer for both types of helper activity needed for a T15 dominated anti-PC response. Although conventional GLPhe-primed T cells helping via a hapten-carrier linkage were found only in responder animals as expected (8), GLPhe-primed helper Th acting selectively on T15-bearing B cells in the presence of GLPhe were found equally in both responder and nonresponder animals. This demonstrates that responses of these antigen-specific idiotype-recognizing helper T cells are not regulated by the same Ir genes as are the conventional helper T cells.

Materials and Methods

**Mice.** BALB/cByJ mice were obtained from The Jackson Laboratory, Bar Harbor, Maine, and were used between 8 and 12 wk of age. BALB.B and BALB.K mice were provided by the core mouse breeding facility in the Comprehensive Cancer Center at Yale, New Haven, Conn. by Dr. D. B. Murphy.

**Antigens.** The preparation of antigens used in these experiments has been described previously (11, 16). The preparation of GLPhe utilized in these studies was prepared and analyzed as previously described (14).

**Antisera.** The preparation, purification, and testing of anti-T15 idiotype antibodies have been described previously (11, 16). Hybridoma anti-Thy-1.2 was kindly provided by Dr. J. Sprent, Wistar Institute, Philadelphia, Pa.

**Anti-μ-treated Mice.** Anti-mouse μ-chain-antibody-treated mice were generously supplied by Dr. C. A. Janeway, Jr., Yale University School of Medicine, New Haven, Conn. These mice were injected three times weekly starting within 24 h of birth with ammonium-sulfate-precipitated anti-μ-chain antibody prepared in a goat. This antibody reacted only with IgM in normal mouse serum by immunoelectrophoresis. The anti-μ-treated mice had no surface-immunoglobulin-positive cells in their spleens and no circulating T15 idiotype at the time of killing (12).

**Immunizations.** BALB/c and BALB.B mice to be used as B cell donors were immunized with 100 μg of PC-horse radish peroxidase (HRPO) in complete Freund's adjuvant (CFA). Mice to be used as T cell donors were immunized with either 50 μg ovalbumin (OVA), keyhole limpet hemocyanin (KLH), or GLPhe in CFA.

**Isolation of Spleen Cell Populations and Adoptive Transfer.** This was carried out as previously described (11, 16). Briefly, graded numbers of primed T and B cells, 25 μg of PC-KLH, and, as appropriate, 25 μg OVA or 50 μg GLPhe were injected intravenously into syngeneic irradiated recipients. Their spleens were assayed for plaque-forming cells (PFC) 8 d after cell transfer.

**Hemolytic PFC Assay.** Spleen cells were assayed for direct anti-PC PFC by the modified Jerne hemolytic plaque technique (17). The proportion of anti-PC PFC of the T15 idiotype was determined by inhibition of plaque formation using rabbit anti-T15 antibodies in the agarose suspension medium. Only PFC that could be inhibited by 10⁻³ M PC-Ficoll were considered to be PC specific.

Results

It has been previously established that the dominant production of T15 idiotype in the antibody response to PC-proteins requires two distinct Th (11, 12). One Th cell
set is present in both carrier-primed normal mice and mice treated from birth with anti-μ antibody. This T cell set induces an anti-PC response which is mainly non-T15 in nature and requires the hapten PC to be physically linked to the carrier. The second Th set is present in normal BALB/c mice but lacking in carrier-primed anti-μ suppressed mice, and it is necessary for predominant production of the T15 idiotype. The missing T cell set necessary for T15 production in anti-μ suppressed BALB/c mice can be restored by adding carrier-primed T cells from normal BALB/c donors along with the priming antigen (12).

To approach the question of whether or not Irf genes influence carrier recognition and subsequently T-B interactions, the ability of both helper cell sets to be activated by GLPhe and to induce PC-specific B cells to produce antibody was determined both in responder BALB/c mice and nonresponder BALB.B mice.

**Helper Activity for the T15 Idiotype from BALB/c Responder Mice Primed with GLPhe.** The experiments represented in Table I (lines 1–4) demonstrate again that T cells from KLH-primed, anti-μ-treated mice were unable to induce PC-primed syngeneic B cells to produce a T15-dominated anti-PC response (line 1). The missing Th cell set needed for predominant T15 production could only be restored by transferring T cells from KLH-primed, anti-μ-treated mice along with T cells from OVA-primed normal BALB/c mice and boosting with PC-KLH plus OVA (lines 2–4). It can be seen that whereas the Th cell set needed for predominant T15 production existed among the OVA-primed T cell pool, it required activation by the addition of the appropriate priming antigen, in this case OVA. Neither KLH nor GLPhe could activate this cell (lines 2 and 4). It should be noted that the activity of the idiotype-specific Th cells did not require that the hapten (PC) be linked to the priming carrier (OVA) (line 3).

| T cells from donors* | Geometric mean PC-PFC/spleen† | Antigen boost | Total | T15* | T15± | T15
|---|---|---|---|---|---|---|
| Anti-μ | Normal | Normal | GLPhe | | | |
| KLH | OVA | | | | | |
| 1. | 2 | — | — | — | 1,774 (1.28) | 682 (1.58) | 1,002 (1.16) | 38
| 2. | 2 | 2 | — | — | 1,772 (1.15) | 772 (1.57) | 913 (1.18) | 44
| 3. | 2 | 2 | — | — | 4,772 (1.25) | 3,531 (1.01) | 1,214 (1.11) | 74
| 4. | 2 | 2 | — | — | 2,361 (1.21) | 1,062 (1.32) | 1,403 (1.29) | 45
| 5. | — | — | 5 | — | 1,465 (1.12) | 1,204 (1.17) | 251 (1.31) | 82
| 6. | 2 | — | 5 | — | 4,169 (1.12) | 3,251 (1.37) | 811 (1.23) | 78
| 7. | 2 | — | 5 | — | 1,480 (1.09) | 715 (1.17) | 726 (1.21) | 48

* 5 × 10⁶ B cells from PC-primed BALB/c donors were transferred along with T cells from anti-μ treated, KLH-primed, and normal OVA and GLPhe-primed BALB/c donors into 500-rad irradiated BALB/c recipients.

† The number of PC-specific PFC was determined on day 8 after cell transfer. The proportion of anti-PC PFC shown to be T15* was determined by plaque inhibition with rabbit anti-T15 antibodies. The number of T15* PFC was determined by subtracting the T15* PFC response from the total anti-PC response. The background PFC response of Tand B cells transferred alone was subtracted.

§ The total number of PC-PFC represents only those PFC inhibited by 10⁻³ M PC and therefore considered to be PC specific.
To determine whether or not both helper cell sets needed for $T^{15+}$ anti-PC antibody production could be primed to the synthetic antigen GLPhe, the helper activity of $T$ cells from GLPhe-primed normal BALB/c mice was evaluated. It can be seen in Table I, line 5 that $T$ cells from GLPhe-primed BALB/c responder donors could effectively collaborate with PC-primed $B$ cells to generate a $T^{15}$-dominated anti-PC response to PC-GLPhe. It is clear that even though it takes a greater number of GLPhe-primed $T$ to generate a substantial anti-PC response, GLPhe-like large protein carriers can induce an anti-PC antibody response dominated by the $T^{15}$ idotype in responder BALB/c mice. This confirms that at least the helper $T$ cell requiring hapten (PC) and carrier (GLPhe) linkage is present in BALB/c mice primed with GLPhe. Likewise, $T$ cells from GLPhe-primed donors were tested directly for their ability to replace the helper cell set required for predominant $T^{15}$ production and missing in anti-$\mu$ treated, KLH-primed BALB/c mice. The results shown in Table I, lines 6 and 7 indicate that $T$ cells from GLPhe-primed donors do include a $T$ cell set, which in the presence of $T$ cells from anti-$\mu$ treated, KLH-primed BALB/c mice. The helper cells for $T^{15}$ idotype production are activated only when the system is boosted with PC-KLH and GLPhe (compare lines 6 and 7).

These results indicate that priming of responder BALB/c mice with GLPhe activates both helper cell subpopulations involved in an optimal $T^{15}$ dominated anti-PC antibody response. Furthermore, this provides further evidence as to the antigen-specificity of the helper $T$ cell required for dominant $T^{15}$ idotype production, in that OVA, KLH, and GLPhe are all discriminated by such $T$ cells.

Helper Activity for the $T^{15}$ Idiotype from BALB.B Nonresponder Mice Primed with GLPhe. Previous studies have shown that the immune response to GLPhe is under the control of MHC-linked Ir genes at the $T$ helper cell level (8). Because both $T$ cell subsets involved in an optimal anti-PC antibody response were found to be present in GLPhe-primed BALB/c responder mice, it was of interest to determine whether or not the same Ir genes controlled the ability of the two distinct helper $T$ cells to collaborate effectively with PC-primed $B$ cells. To do this, helper activity was evaluated in BALB.B mice primed with GLPhe, an antigen to which they are nonresponders. The results obtained using BALB.B mice are similar to those found using BALB/c mice in that anti-$\mu$ treated, KLH-primed BALB.B mice are missing a $T_h$ cell set needed for dominant $T^{15}$ production (Table II, line 1) and this cell set can be replaced by addition of OVA-primed $T$ cells from normal BALB.B mice provided the recipients are boosted with both PC-KLH and OVA (line 2). By contrast, $T$ cells from GLPhe-primed BALB.B donors were unable to induce PC-specific $B$ cells to produce antibody to PC-GLPhe (line 3), thus confirming previous studies demonstrating ineffective T-B collaboration when the carrier molecule used to prime nonresponder $T$ cell donors is under Ir gene control (7, 8). More important, however, is the finding that $T$ cells from GLPhe-primed BALB.B donors were able to provide effective antigen-specific helper activity to $T^{15}$-idiotype-producing $B$ cells when transferred along with $T$ cells from anti-$\mu$-treated, KLH-primed donors in the presence of PC-KLH and GLPhe (line 4). The findings in lines 5 and 6 demonstrate the specificity of this added helper $T$ cell for the immunizing and boosting antigen GLPhe. In some experiments the total PC-PFC response increases when a mixture of $T$ cells from anti-$\mu$, KLH-primed, and normal GLPhe-primed donors is transferred along with PC-
Table II

| T cells from donors* | Geometric mean PC-PFC/spleen§ |  
|---------------------|-------------------------------|  
|                      | Anti-μ KLH | Normal OVA | Normal GLPhe | Antigen♭ boost | Total | T15* | T15− | T15  |
| × 10⁶               |             |             |             |                | mean ×/± relative SE % |
| 1. 2 — —            | —           | —           | —           | PC-KLH         | 2,261 (1.28) 855 (1.34) 1,401 (1.23) | 38 |
| 2. 2 2 —            | —           | —           | —           | PC-KLH + OVA   | 9,465 (1.22) 7,968 (1.21) 1,372 (1.47) | 84 |
| 3. — — 6            | 6           | —           | —           | PC-GLPhe       | 0 0 0 | 0 |
| 4. 2 — 4            | —           | 4           | —           | PC-KLH + GLPhe | 7,095 (1.24) 5,741 (1.46) 1,226 (1.30) | 81 |
| 5. 2 — 4            | —           | 4           | —           | PC-KLH + OVA   | 4,591 (1.03) 1,965 (1.04) 2,498 (1.02) | 43 |
| 6. 2 — 4            | —           | 4           | —           | PC-KLH         | 2,430 (1.07) 842 (1.07) 1,564 (1.15) | 35 |

* 5 × 10⁶ B cells from PC-primed BALB.B donors were transferred along with T cells from anti-μ treated, KLH-primed, and normal OVA- and GLPhe-primed BALB.B donors into 500-rad irradiated BALB.B recipients.

♭ Each recipient received 25 μg of PC-KLH or 50 μg PC-GLPhe intravenously plus 25 μg OVA or 50 μg GLPhe, as appropriate.

§ See footnotes to Table I.

KLH plus the inappropriate carrier, OVA (line 5). Although the reason for this finding is unclear, there is no selective activation of those B cells bearing the T15 idiotype. The finding shown in lines 3 and 4 demonstrates that T cells requiring a hapten-carrier-linkage are under the control of MHC-linked Ir genes, whereas antigen-specific activation of those helper T cells that selectively activate idiotype-bearing B cells and that do not require a hapten-carrier linkage is not under the control of the same Ir genes. Similar results have been obtained in the H-2k nonresponder strain BALB.K (data not shown).

Discussion

It has been clearly demonstrated that determinants encoded by the I-region of the major histocompatibility complex have an important restrictive role in interactions between T lymphocytes and macrophages and between T lymphocytes and B lymphocytes (2–4, 18–20). Many studies have indicated that the ability of helper T cells to recognize antigen and subsequently activate B cells depends on I-region, particularly I-A, similarity between the cell types (2–4). Furthermore, studies evaluating the role of MHC-linked Ir genes in regulating specific immune responses to a variety of antigens have shown that these genes can control T-dependent immune responses, and also play a role in T-B interactions in such responses (7, 8, 14, 15, 20).

In this context, the studies reported here have shown that the activity of one of the two distinct sets of helper T cells involved in B cell responses to PC is indeed under the control of specific Ir genes that have been shown to be in the I-A and I-E/C subregions of the MHC (8, 15). By contrast, the second T helper cell set required for predominant T15 production is either independent of Ir gene control or under the control of genes distinct from those regulating conventional helper T cell activation.

These observations were obtained in a system that has allowed an examination of two Th required for a T15 dominated anti-PC response. As shown previously (12), helper T cells from mice suppressed from birth with anti-μ antibody provide effective
help for anti-PC PFC responses, but lack a helper T cell required for dominant production of anti-PC antibody bearing the T15 idiotype. The helper T cell set present in anti-μ-treated mice is identical to the carrier specific Th cells described by Mitchison (1) in that the optimal activity of these cells depends on the hapten being physically linked to the carrier. These conventional helper cells have been shown to be I-region restricted (2-4) and under Ir gene control (7, 8). In the present in vivo studies, T-B collaboration for an anti-PC response requires the presence of this cell set. The failure of the conventional Th cells from anti-μ-treated mice to induce an idiotype-dominated anti-PC response can be reconstituted by adding Ly-1+ T cells from normal antigen-primed donors, provided the appropriate priming antigen is also given to the recipients (11, 12). From these and previous studies, it has been concluded that the helper T cells that selectively activate T15-bearing B cells are also antigen-specific, but their activation does not require that PC be coupled to the carrier. The present experiments extend these studies and clearly demonstrate that the antigen-specific responses of this unique set of helper T cells are not under the control of known Ir genes, in that both responder and nonresponder mice can provide such helper T cell activity to syngeneic responder or nonresponder B cells after priming with GLPhe, an antigen that is under MHC-linked Ir gene control. The same GLPhe-primed T cells were shown to behave as nonresponders when tested for their ability to help syngeneic nonresponder B cells make an anti-PC antibody response to PC-GLPhe. In addition, the use of both protein and synthetic polypeptides as antigen in these studies renders unlikely the possibility that idiotype-recognizing helper T cells are activated by each of these antigens through a resemblance of the antigen either for the hapten PC or for the T15 idiotype. These results lend additional weight to the concept that idiotype-recognizing helper T cells bear a distinct recognition unit for the antigen.

It can be envisioned that the antigen-specific T cell population needed for predominant T15 production selectively activates T15-bearing B cells through the use of an anti-idiotypic receptor. Previous studies have demonstrated that T cells activating B cells bearing a particular idiotype can be depleted on plastic plates coated with idiotypic molecules, suggesting that idiotype-specific Th cells can bind idiotype directly (21, 22). Therefore, it seems reasonable to conclude that such helper T cells recognize at least two distinct specificities: antigen and the T15 idiotype.

One can propose several possible explanations for the inability of known Ir genes to regulate the antigen-specific response of idiotype-recognizing Th to GLPhe. The interpretation we favor is that idiotype-recognizing helper cells do not bear recognition sites for self I-region determinants (in this case Ir gene products), but rather bear recognition sites for self idiotypic determinants. This would lead one to predict that the Th idiotype (ThId) cell set would not recognize antigen in the context of MHC-linked Ir gene products, and would therefore not be under the control of known Ir genes, as was indeed found in these experiments. The present results would favor the notion that Id-recognizing Th cells bear receptors only for antigen and for self idiotype. Alternatively, the activity of the Id-specific Th cell set may be regulated either by an as yet undescribed set of Ir genes or by other genes encoded in the MHC. This would suggest that this cell set either has three specificities (Id-, antigen-, and MHC-encoded determinants), or that there are two interacting T cells responsible for the specificities determined for this cell population. We believe the latter possibility
Table III
Characteristics of Th Involved in the T15-dominated Anti-PC Response

| Characteristic                              | ThMHC | ThId | Reference          |
|--------------------------------------------|-------|------|--------------------|
| Antigen specificity                        | +     | +    | (this paper; 11, 12) |
| Antigen recognition under Ir gene control  | +     | -    | (this paper)       |
| Selective activation of T15+ B cells        | -     | +    | (this paper, 11, 12) |
| Requirement for hapten-carrier linkage     | +     | -    | (this paper, 11, 12) |
| Presence in low T15 idiotype strains       | +     | -    | (11-13)            |
| Cell surface antigens                      |       |      |                    |
| Lyt-1                                      | +     | +    | (12)               |
| Lyt-2                                      | -     | -    | (12)               |
| Activates B cells by itself                 | ?     | -    | (this paper)       |

If one accepts the argument that ThId cells are indeed not MHC-recognizing, then one can propose a general framework within which to consider such helper T cells. Because both sets of Th cells recognize antigen, it is convenient and informative to describe these cells in terms of the known self specificity each recognizes during responses to antigen. Therefore, one can refer to those helper T cells that recognize antigen in the context of self MHC gene products (in this case the products of Ir genes) as ThMHC, and those helper T cells that selectively activate B cells bearing the T15 idiotype as ThId. Table III lists the salient characteristics of each of these types of helper T cells as revealed in studies of the anti-PC antibody response. The ThMHC and ThId cell sets have some striking similarities. For instance, both cell sets are Lyt-1-, 2-, both have a specificity for self and a specificity for antigen, and both have the ability to activate B cells. These similarities have suggested (23) that the development of these two Th sets may be analogous. It has been shown that ThMHC cells are selected for recognition of self MHC specificities by radioresistant elements of the thymus, and the selected cells are subsequently expanded by contact with the same MHC specificities in the periphery (24). Although nothing is known about the role of the thymus in the ontogeny of ThId cells, it is clear that peripheral contact with idiotype is required for their development. This has been shown by noting the absence of ThId cells in mice with low levels of circulating T15 idiotype (11, 12).

Studies from other laboratories have also demonstrated anti-idiotypic T cells involved in helper (21, 22, 25-27) and suppressor (28-33) cell activity. It might be envisioned that the anti-idiotypic T cell population could be divided into two distinct groups based on differences in the immunization procedures used to induce these cells and ultimately on differences in the specificity of the T cells. Several studies have
demonstrated that immunization with idiotype-bearing antibody generates Th cells specific for the idiotypic determinants (25-27). In vivo, such cells have been shown to function as carrier-specific Th cells activating hapten-specific B cells only when the hapten is linked physically to idiotype-bearing antibody (26, 27). Moreover, these idiotype-specific Th cells are capable of activating B cells to secrete antibody in vivo (26, 27) and in vitro (25). It might be speculated that Th cells immunized with idiotype recognize idiotypic determinants in association with MHC-encoded antigens, as has been shown for other antigen-specific Th cells (2-4). Although this question has not been resolved for such anti-idiotypic Th cells, the function of effector-phase suppressor T cells involved in 4-hydroxy-3-nitrophenylacetyl (NP)-specific delayed type hypersensitivity (DTH) responses depends on cells which are both anti-idiotypic and MHC-restricted (33). In the case of helper T cells, this class of idiotype-immunized anti-idiotypic Th cells may most likely be MHC restricted and may recognize Id by the use of an anti-idiotypic antigen receptor.

By contrast, anti-idiotypic Th cells involved in selective activation of B cells bearing germ-line idiotypes are normally present in mice (11, 12, 21, 22) and can be shown to function only in the presence of conventional Th cells (ThMHC) (11, 12, 21). These cells can be activated by immunization with antigens unrelated to the idiotype in question (11, 12, 21) and have been shown to be antigen (11, 12) and idiotype (21, 22) specific. The ability of these anti-idiotypic cells to recognize idiotypic determinants appears not to involve the receptor for antigen, and, furthermore, it might be proposed that this recognition involves a receptor for self determinants. Further experiments are planned to test this hypothesis. Clearly, T cells bearing anti-idiotypic receptors can be generated in a variety of ways and can be demonstrated to have differing functions. Further studies should resolve the question of whether specificity and function are related in such cells.

Although the influences of Ir genes on carrier recognition by the conventional helper T cell has been well documented (7, 8, 15, 20), certain T cell responses to Ir-controlled antigens, in addition to those described in this paper, have been generated in nonresponder strains. Both proliferating T cell (34) and DTH responses (35) could be elicited by haptenated Ir-controlled antigens in nonresponder strains if the nonresponders were first primed with hapten conjugated to an immunogenic carrier. There seems to be little similarity between these cells and the ThId cell set, because responses of proliferating and DTH cells could be elicited but could not be primed in nonresponder strains, whereas ThId could be primed and shown to function in a nonresponder environment. Furthermore, T cells from low- and high-responder strains have been shown to produce antigen-specific T cell factors in response to poly(Tyr,Glu)-poly(Ala-Ala)--poly-L-Lys [(T,G)-A--L] (36). By contrast with the Th activity of GLPhe-specific ThId cells, these factors will only trigger high-responder and not low-responder B cells to produce antibody. The relationship between the ThId cell set and such T cell factors, both of which can be generated in nonresponder strains, is not known.

These experiments do not specifically address the possible physiological role of the ThId cell set. It seems most likely, however, that ThId cells function specifically early in an immune response, to activate those B cells most frequently represented; namely, those bearing germ-line encoded idiotypes. Several studies have shown that the expression of germ-line idiotypes may be only dominant early in an antibody response
Furthermore, experiments using helper T cells from normal and anti-μ-treated mice demonstrate that the Ig-dependent T cells were only active early during an anti-DNP response (9). Taken together, these data lend support to the concept that preferential activation of frequently represented B cells may be a result of the Th1d cell set. Furthermore, the shift from idiotype dominance to a more heterogeneous response seen with some antigens could be explained by suppression of Th1d function as the response proceeds. Thus, Th1d would play a critical role in protective immunity, causing the early activation of B cells with receptors bearing frequently represented idiotypes. Current experiments are aimed at confirming this role of Th1d cells in the anti-PC antibody response.

Summary

Responder and nonresponder mice primed with poly-(L-glutamic acid, L-lysine, L-phenylalanine) (GLPhe), the response to which is under the control of immune response (Ir) genes, were used as a source of both types of helper T cells required for a T15 idiotype dominated T-dependent anti-phosphorylcholine (PC) response. It was found that the activity of one of the helper T cells needed for an anti-PC response was under major histocompatibility complex (MHC)-linked Ir gene control, and only GLPhe-primed responder mice could be used as a source of these cells. These T cells (ThMHC) whose presence is required for in vivo T-B collaboration are found in normal and anti-μ-treated mice, and their activity depends on the hapten being physically linked to the carrier molecule. By contrast, the activity of the second helper T cell (Th1d) required for a T15-dominated anti-PC response was present in both GLPhe-primed responder and nonresponder mice. The Th1d cell set that is missing or deficient in anti-μ treated mice can be restored by the addition of T cells from normal, carrier-primed donors and restimulating with the priming carrier. When T cells from GLPhe-primed donors are used as a source of Th1d cells, both responder and nonresponder donors provide helper cells capable of inducing syngeneic B cells to produce a T15 dominated anti-PC response. These results are interpreted to suggest that idiotype recognizing helper T cells (Th1d) recognize antigen independent of known Ir gene products.

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