THE ANTIBODY RESPONSE TO SPECIFIC IMMUNE
COMPLEXES IS UNDER GENETIC CONTROL AND
CORRELATES WITH THE EXPRESSION OF A RECURRENT
IDIOTYPE

BY MICHAEL J. CAULFIELD, KATHLEEN J. LUCE, DIANA SHAFFER AND
JEFFREY P. LAKE*

From the Department of Molecular and Cellular Biology, Cleveland Clinic Foundation,
Cleveland, Ohio 44106; and the *Department of Pathology, The Jewish Hospital of St. Louis,
St. Louis, Missouri 63110

In the natural selection theory of antibody formation (1), Jerne proposed that
the “antigen is solely a selective carrier of spontaneous circulating antibody to a
system of cells which can reproduce the antibody.” Although proposed before
the nature of the antigen-reactive cell was known, the hypothesis has proved to
be remarkably accurate in its predictions. Central to the theory is the prediction
that natural antibody exists prior to exposure to an antigen, and that the
subsequent response is composed of antibody that is identical to that which
interacts with the antigen in the first place. This study was undertaken to test
this prediction by examining the antigen-specific antibody response to preformed
immune complexes. Specifically, we wished to determine whether the response
to the antigen is influenced by allotypic or idiotypic determinants on the antibody
used to form the immune complex. Our approach has been to examine the
immunogenicity of preformed antigen/antibody complexes in strains of mice
that have different immunoglobulin heavy chain allotypes and in strains that
express either high or low levels of the relevant idiotype.

In the network theory, Jerne suggested (2) that recognition of self-idiotopes
forms the basis of an immunoregulatory network. Indeed, there is a great deal
of evidence showing that immune responses can be regulated by anti-Id antibody
or with Id-specific T cells. However, in most cells, the anti-Id responses were
activated under nonphysiological conditions, such as repeated injection of Id-
bearing antibody in adjuvant (3), or with Id artificially coupled to cells (4).
Nevertheless, certain investigators have demonstrated (5) that the injection of
physiological concentrations of Id-bearing antibody caused a marked change in
the expression of that Id in a subsequent response to antigen. Furthermore,
Klaus (6) has shown that Id are highly immunogenic when presented in the form
of antigen/antibody complexes. In spite of such findings, however, there remains
skepticism of the importance of Id recognition in immune regulation (7, 8).

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of Ohio.
Previously (9), we examined the Id profile of the antibody response of BALB/c mice to immune complexes formed in antigen excess. The complexes were prepared using the TEPC-15 myeloma protein and the PC-containing polysaccharide antigen (PnC). The antibody response to this antigen in BALB/c mice is dominated by the T15 family of Id that are expressed on the TEPC-15 myeloma protein (10, 11). Our previous results (9) showed that the TEPC-15/PnC complexes readily induced an antigen-specific PFC response that was equal to the response induced by free antigen; however, the Id profile of the response to the complex was more restricted than that of the response to the free antigen (9). Thus, the proportion of Id-specific PFC (as determined by plaque-inhibition with the AB1-2 (11) anti-T15 mAb) was greater and more variable in individual mice immunized with PnC vs. those injected with TEPC-15/PnC complexes.

The above results were obtained using BALB/c mice, a strain in which the response to PnC is dominated by a major or recurrent Id. This study was undertaken to examine the response to TEPC-15/PnC complexes using mouse strains in which the T15 (AB1-2) Id is not dominant. The results show that the response to TEPC-15/PnC complexes is under genetic control, and that responsiveness to the complex correlates with the level of T15 (AB1-2) Id produced in response to immunization with free antigen (PnC). The results suggest that the antigen-specific response to immune complexes is Id-restricted and, therefore, that the recognition of Id is important in regulating the immune response.

Materials and Methods

Animals. Female mice of the following strains were purchased from The Jackson Laboratories, Bar Harbor, ME: BALB/cByJ, C3H/HeJ, C3H.SW, and C3H.OH, SEC/1ReJ, A/J, AKR/J, C57/J, and (BALB/cByJ × C3H/HeJ)F1. BALB.B and BALB.K mice were obtained from the Animal Resources Facility of Jewish Hospital of St. Louis. CB-20 mice were the generous gift of Dr. Jan Cerny of the University of Texas Medical branch at Galveston. All mice were used between the age of 8 and 14 wk.

Antigens. PnC was extracted from *Streptococcus pneumoniae* R36a as described by Anderson and McCarty (12). The concentration of PnC was based on the weight of dialyzed, lyophilized material. Sheep and burro red blood cells (RBC) were obtained from Cleveland Scientific (Cleveland, OH).

mAb and Myeloma Proteins. The AB1-2 (anti-T15) hybridoma cell line was generously provided by Dr. John Kearney, University of Alabama, Birmingham, AL. The AB1-2 mAb and the TEPC-15 myeloma protein were partially purified from ascites fluid as described elsewhere (13).

Plaque-forming Cell Assay. A microscope slide modification of the Jerne-Nordin hemolytic plaque assay was used (14). The PnC antigen spontaneously binds to RBC in the absence of phosphates. Thus, the RBC target cells were coated with PnC by incubating 1 vol of burro RBC (washed three times in 0.85% saline) with 4 vol of PnC (0.1 mg/ml in 0.85% saline) at 37°C for 1 h. The coated RBC were washed twice with saline, then resuspended to a 15% suspension in HBSS (Gibco Laboratories, Grand Island, NY). For the plaque assay, the following ingredients were added to tubes containing 0.2 ml of molten 0.5% agarose (Sea Plaque: FMC Maine Colloids, Rockland, ME) at 37°C: RBC, 0.04 ml of a 15% suspension; complement, 0.04 ml of a 1:3 dilution of guinea pig serum (preadsorbed with the target RBC); and spleen cells, 0.1 ml (various cell numbers). For plaque-inhibition assays, AB1-2 mAb was added at a final concentration of 1:300. The contents of the tubes were poured onto glass slides ( precoated with a 0.1% solution of

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1 Abbreviations used in this paper: GAMIgM-AP, goat anti-mouse IgM-alkaline phosphatase; PnC, cell wall polysaccharide extracted from *Streptococcus pneumoniae* R36a.
agarose) and incubated at 37°C for 2 h in a sealed, humid chamber. The number of plaques was scored with the aid of a magnifying glass. The results are expressed as the geometric mean of the number of PFC/spleen from 3-5 mice/group, assayed in duplicate.

**Assay for Serum Antibody and Id.** The serum IgM antibody response specific for PnC was measured by an ELISA as previously described (15). The serum concentration of IgM antibodies expressing the T15 Id defined by the AB1-2 mAb was determined by ELISA as follows: Polyvinyl chloride 96-well microtiter plates (Dynatech Laboratories, Alexandria, VA) were coated with 50 µl of a 10 µg/ml solution (in 0.05 M Tris and 0.15 M saline, pH 9.5) of the IgG mAb, AB1-2 (17), which had been prepared from ascites fluid by ammonium sulfate precipitation. After 4 h at 37°C, the plates were blocked with 0.05% gelatin in PBS, then washed three times with 0.15 M saline with 0.05% Tween 20 (polyoxyethylene sorbitan monolaurate; Sigma Chemical Co., St. Louis, MO). Serial fivefold dilutions of serum, in PBS-0.05% Tween with 0.05% gelatin (PBS-T), were made in consecutive wells of the coated plates in a final volume of 0.1 ml, and the plates were incubated overnight at 4°C. A T15 Id + IgM mAb (41-H11) specific for PnC that was prepared in this laboratory was used as a standard. After the second incubation period, the plates were washed three times with saline-Tween and then 50 µl of a 1:1,000 dilution of alkaline phosphatase-conjugated goat anti-mouse IgM (GAMIgM-AP) (Southern Bio-technology Associates, Birmingham, AL) was added to each well. After an overnight incubation at 4°C, the plates were washed three times with saline-Tween and then 50 µl of phosphatase substrate (p-nitrophenyl phosphate, 1 mg/ml in Tris-saline with 1 mM magnesium chloride, pH 9.5) was added to each well and incubated for 30 min at room temperature. The reaction was stopped by adding 50 µl of 3 M NaOH to each well. The optical density at 405 nm in each well was determined using an MR580 MicroELISA Auto Reader (Dynatech Laboratories), and antibody concentrations were determined relative to the standard using a computer program as previously described (15).

**Preparation of Immune Complexes.** Initially, complexes were prepared at various ratios to determine the equivalence zone. The complexes were incubated at 37°C for 30 min, and then at 4°C overnight or until used. The complexes were centrifuged at ~800 g, and the supernatants were removed and tested for the presence of excess antigen or antibody. Excess antibody was detected by ELISA as described elsewhere (15), and excess antigen was detected by ELISA as follows: plates were coated as described above with the IgA myeloma protein, TEPC-15, and then samples to be tested for PnC were titrated in consecutive wells of the coated plates. An IgM anti-PnC mAb (41-H11) was then added at 1 µg/well. Finally, GAMIgM-AP was added to each well, and the reaction was developed with p-nitrophenyl phosphate. The antigen concentration of the unknown samples was determined relative to a known standard.

Once the equivalence zone had been determined, complexes were prepared in antigen excess by adding a 10-fold excess of PnC to a standard amount of TEPC-15. Before use, the complexes were washed twice with 0.85% saline, an aliquot was dissolved in 0.1 N NaOH, and the protein concentration was determined as described previously (13). The amount of complex used was based on the concentration of protein in the complex.

**Results**

The results shown in Table I show that the injection of TEPC-15/PnC complexes (formed in antigen excess) into BALB/c mice elicits a PnC-specific antibody response that is comparable to that induced with antigen alone. On the other hand, immunization of C3H mice with TEPC-15/PnC complexes resulted in a weak response that was 10-fold less than the response to PnC alone. The results also show that the PnC-specific response of BALB/c mice is dominated by the T15 (AB1-2) Id, whereas the response of C3H mice is AB1-2-negative, confirming the results of others (11). Thus, the response to the complex appears to be genetically restricted.

Since the restriction appears to be mediated by the antibody (TEPC-15) used
TABLE I

C3H Mice Are Low Responders to TEPC-15/PnC Complexes Formed in Antigen Excess

| Responder strain | Immunogen (μg) | PnC-specific response |  |
|------------------|----------------|-----------------------|---|
|                  |                | PFC/spleen            | % | T15 Id* |
|                  |                | Control               |   | PFC (%) |
| BALB/c           | PnC (1)        | 15,690 (1.19)         | 51|       |
|                  | TEPC-15/PnC (10) | 20,520 (1.30) | 130 | 98 |
| C3H              | PnC (1)        | 15,700 (1.19)         | <20|       |
|                  | TEPC-15/PnC (1) | 200 (1.62)            | 1 | ND    |
|                  | (10)           | 1,430 (1.20)          | 9 | <20   |
|                  | (100)          | 475 (1.26)            | 3 | ND    |

Mice from each strain were injected intraperitoneally with either 1 μg of PnC or with various concentrations of TEPC-15/PnC complexes as indicated. 5 d later, the number of direct PFC was determined using PnC-coated burro RBC as target cells. The results are expressed as the geometric mean of the number of PFC/spleen with the standard error factor in parentheses. The percentage of PFC secreting the T15 idiotope defined by the AB1-2 mAb was determined by plaque inhibition.

TABLE II

Responsiveness to TEPC-15/PnC Complexes Is Not Allotype Restricted

| Responder strain | Genetic loci | Immunogen | PnC-specific response* |
|------------------|--------------|-----------|------------------------|
|                  |              | PFC/spleen| T15 Id* PFC (%)        |
|                  | H-2 | Igh |        |                          |
| Exp. 1           | BALB/c | d | a | PnC | 11,755 (1.33) | 92  |
|                  |       |   |   | TEPC-15/PnC | 7,027 (1.06) | 99  |
| CB-20            | d | b | PnC | 56,426 (1.29) | 98  |
|                  |   |   | TEPC-15/PnC | 25,118 (1.54) | 98  |
| Exp. 2           | CB-20 | d | b | PnC | 39,423 (1.23) | 99  |
|                  |       |   |   | TEPC-15/PnC | 22,019 (1.37) | 99  |

* The number of direct PFC/spleen was determined as in Table I, 5 d after the injection of 1 μg of PnC or 10 μg of TEPC-15/PnC complexes. In each experiment, the response of CB-20 mice to TEPC-15/PnC complexes is not significantly different from their response to PnC using Student's t-test.

Thus, CB-20 mice (which are congenic with BALB/c at the Igh locus) were tested for responsiveness to PnC and to TEPC-15/PnC complexes. The results (Table II) demonstrate that the CB-20 mice responded almost as well to the complex as they did to free antigen. Thus, the response to the complex does not appear to be allotype-restricted. Interestingly, even though CB-20 mice are Ighb, their response to both PnC and TEPC-15/PnC complexes is dominated by the T15 (AB1-2) Id.

In further experiments, we wished to determine whether responsiveness to the complexes was controlled by I-region genes in the H-2 complex. Thus, we used two H-2 congenic strains on the C3H background, C3H.SW and C3H-OH. C3H mice are H-2k, whereas the C3H.SW strain is H-2b, and the I-region of the C3H-OH strain is of the d haplotype, the same as that of BALB/c mice. The results...
from Table III (Exps. 1 and 2) demonstrate that both congenic strains respond similarly to C3H mice; i.e. their response to TEPC-15/PnC complexes is about 10-fold less than their response to PnC alone. Based on these results, responsiveness to the complexes is apparently not determined by I-region genes, since BALB/c and C3H-OH mice share the same I-region, and yet the former are high and the latter are low responders to the complex. Interestingly, both C3H.SW and C3H-OH mice are T15 (AB1-2) Id⁺, suggesting a relationship between responsiveness to the complex and expression of the T15 (AB1-2) Id.

To determine whether responsiveness to TEPC-15/PnC complexes is controlled by other H-2 genes, BALB.K and BALB.B mice (which are congenic with BALB/c mice at the H-2 complex) were tested for their response to PnC and to TEPC-15/PnC complexes. The results (Table III, Exp. 3) show that the overall response to PnC appears to be under Ir gene control, since the response of BALB.K mice was ~10-fold higher than the response of BALB.B mice. However, mice from each strain responded as well to the immune complex as they did to free antigen, and in each case the response was dominated by the T15 (AB1-2) Id. Taken together, the results from Table III indicate that responsiveness to the TEPC-15/PnC complex is not controlled by genes in the H-2 complex.

Further genetic studies were performed to examine the serum IgM response to PnC and TEPC-15-PnC complexes. 13 strains comprising six allotypes were studied to determine their anti-PnC antibody response to immunization with either PnC or TEPC-15/PnC complexes. The results (Fig. 1) confirm the PFC data showing that responsiveness to the TEPC-15/PnC complex is not controlled by the H-2 gene complex. Thus, BALB.K mice are high responders, whereas

| Table III | Responsiveness to the TEPC-15/PnC Complex Is Not Controlled by Genes in the H-2 Complex |
|-----------|------------------------------------------------------------------------------------------|
| Strain    | H-2 haplotype | Immuneogen* | PnC/spleen | Percent of control | T15 (AB1-2) Id⁺ (%) |
| Exp. 1    | BALB/cByJ     | d d d d d d d d | PnC | 9.699 (1.89) | Control 92 |
|           | C3H/HeJ       | k k k k k k k k | PnC | 10.014 (1.23) | Control <20 |
|           | C3H.SW        | b b b b b b b b | PnC | 3,644 (2.45) | Control <20 |
| Exp. 2    | BALB/cByJ     | d d d d d d d d | PnC | 2.009 (2.73) | Control 93 |
|           | C3H/HeJ       | k k k k k k k k | PnC | 1,974 (1.31) | Control 98 |
|           | C3H-OH        | d d d d d d d d | PnC | 210 (1.49) | Control <20 |
| Exp. 3    | BALB.K        | k k k k k k k k | PnC | 38.562 (1.30) | Control 98 |
|           | BALB.B        | b b b b b b b b | PnC | 26.688 (1.37) | Control 97 |

* Mice from each strain were injected with either PnC or TEPC-15/PnC complexes, and the number of direct PFC/spleen was determined on day five as in Table I.
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C3H mice are low responders, even though both strains are H-2^k. Furthermore, the results demonstrate that the serum response to the TEPC-15/PnC complex is not allotype-restricted. Thus, CB-20 (Igh^b) and A/J (Igh^e) strains are high responders to complexes prepared using TEPC-15, a BALB/c (Igh^a) myeloma protein.

Although responsiveness to the complex is not allotype-restricted, the results suggest that the response may be controlled by genes linked to the Igh locus. Thus, strains that are Igh^c, Igh^d, and Igh^f tend to be low responders, whereas strains that are Igh^a, Igh^b, and Igh^e are high responders to the immune complex. (BALB/c × C3H)F1 mice gave an intermediate response to the complex. The C58 strain appears to be an exception, since it is Igh^a, yet tends to be a low responder; however the response of individual mice from this strain was variable, with some mice yielding a relatively high response, which was T15 (AB1-2)-positive (data not shown). The SEC strain also appears to be an exception since it has been classified as Igh^c (20); however, the allotype of this strain remains uncertain, since previous studies by Herzenberg et al. (21) indicated that the SEC strain is Igh^h.

When the results from Fig. 1 were analyzed in more detail, it became apparent that the high-responder strains (to immunization with TEPC-15/PnC complexes) expressed high levels of T15 (AB1-2) Id in their response to PnC, whereas low-responder strains produced relatively low levels of T15 in their response to PnC.
Indeed, as shown in Fig. 2, there is a very strong correlation between responsiveness to the TEPC-15/PnC complex and the level of T15 Id produced in the response of each strain to PnC. These results suggest that the genetic factors that control T15 Id expression also control responsiveness to the TEPC-15/PnC complex.

The results thus far are consistent with the concept that the response to TEPC-15/PnC complexes is Id-restricted. This suggests that BALB/c mice should be low responders to complexes formed using a T15-antibody. To address this question, we prepared a T15" PnC-specific mAb from C3H mice (which are low responders to the TEPC-15/PnC complex). This antibody (79-14G6) was used to form complexes with PnC to test for immunogenicity in BALB/c mice. The C3H antibody (79-14G6) is IgM; therefore, control complexes were prepared using a BALB/c IgM antibody (41-H11) rather than using TEPC-15, which is IgA. As shown in Table IV, BALB/c mice gave a good PnC-specific antibody response (8,290 PFC/spleen) to complexes formed with the BALB/c antibody, whereas they gave a low response (1,036 PFC/spleen) to complexes formed with the C3H antibody. There are no reported allelic differences between BALB/c

![Figure 2. Correlation between T15 Id expression and responsiveness to TEPC-15/PnC immune complexes.](image)
TABLE IV
Response of BALB/c Mice to Immune Complexes Formed with BALB/c (T15*) vs. C3H (T15*) Antibodies

| Immune complex | Idiotype | PnC-specific PFC/spleen |
|----------------|----------|-------------------------|
| 41-H11/PnC (BALB/c) | T15* | 8,290 (1.45) |
| 79-14G6/PnC (C3H) | T15' | 1,056 (1.39) |

BALB/c mice were injected intraperitoneally with 30 μg of either 41-H11/PnC or 79-14G6/PnC immune complexes formed at equivalence. 5 d later, the number of PnC-specific PFC/spleen was determined as in Table I.

and C3H IgM antibodies (both are Igh-6*); therefore, these results support our conclusion that the response to certain immune complexes is Id-restricted.

Discussion

The results of these studies indicate that the antigen-specific response of mice to TEPC-15/PnC immune complexes is genetically controlled, i.e., the response of certain strains to the complex is 10-fold less than their response to free antigen. Since the TEPC-15 myeloma was derived from BALB/c mice, and since BALB/c but not C3H mice were responders to the complex, we attempted to determine whether responsiveness was allotype-restricted by using CB-20 mice, which are congenic with BALB/c mice at the Igh locus. The results showed that CB-20 (Igh¹) mice responded as well or better than BALB/c (Igh*) mice. Thus, responsiveness to the complex does not appear to be restricted to strains expressing the same allotype as BALB/c. Furthermore, the antibody used to form the complex (TEPC-15) is IgA, whereas the response that we measured is IgM. Taken together, the results suggest that responsiveness to the TEPC-15/PnC complex is not determined by immunoglobulin heavy chain constant region gene products.

The response to many antigens is controlled by genes located in the I region of the MHC (16–18). Therefore, determination of whether the I region controlled the response to TEPC-15/PnC complexes seemed reasonable. Thus, we determined the response of H-2 congenic C3H mice to PnC and to TEPC-15/PnC complexes. The results showed that both C3H.SW (H-2b) and C3H-OH (which has the d haplotype in the I region) are similar to C3H (H-2k) mice in that they are low responders to the complex. In spite of sharing the same I region genes, C3H-OH mice are low responders whereas BALB/c mice are high responders to the TEPC-15/PnC complexes. Thus, the I region does not appear to control responsiveness to the complex.

In a reciprocal experiment, we tested the response of BALB.B and BALB.K mice (which are congenic with BALB/c at the H-2 complex) for their response to PnC and TEPC-15/PnC complexes. Interestingly, the results showed that BALB.K mice gave a response to free PnC that was ~10-fold higher than the response of BALB.B mice, whereas BALB/c mice yielded an intermediate response. Thus, the antibody response to PnC appears to be under Ir gene control. Nevertheless, in each strain, the response to the complex was approximately the same as the response to the free antigen, indicating that H-2 genes
were not controlling responsiveness to the immune complex. The antigen used in these studies (PnC) is a soluble extract from *S. pneumoniae* R36a; it differs from a vaccine prepared from whole bacteria, which is highly immunogenic in BALB.B mice (J. Cerny, personal communication).

Responsiveness to the antigen/antibody complex appears to correlate with the ability of a mouse strain to produce high levels of antibody that expresses the same idiotype as that used to form the complex. Thus, strains such as BALB/c and CB-20, which express high levels of the T15 (AB1-2) Id are high responders to TEPC-15/PnC complexes, whereas strains such as C3H, C3H.SW, and C3H-OH (which express low levels of the T15 [AB1-2] Id) are low responders to the complex. When the results from 13 strains were examined (Fig. 2), there was a very strong correlation between the level of response to the complex and the level of T15 (AB1-2) Id produced in response to PnC. These results suggest that the same genetic elements that control the expression of the T15 (AB1-2) Id may also control the response to TEPC-15/PnC complexes.

Claflin (19) has shown that mice from a large variety of strains express the T15 Id, as defined by an A/J (mouse) anti-T15 sera; however, three strains C3H/HeJ, CBA/J, and PL/J (which are all *Igh* 

In other studies, Sher and Cohn (22) examined the strain distribution of the S107 Id (which is identical to the T15 Id examined herein) using a conventional anti-Id antisera prepared in CE/J mice. Their results suggested that the expression of the S107 Id is controlled by multiple factors, including *Igh*-linked genes and genes of the H-2 complex. Our current results, found using the anti-T15 mAb AB1-2 (11), favor the conclusion that the expression of the T15 Id is controlled by allotype-linked genes. Thus, responsiveness to the complex (which is correlated with the expression of the T15 Id) also appears to be controlled by allotype-linked genes.

The apparent requirement for Id recognition in the response to TEPC-15/PnC complexes leads us to suggest that the response is dependent on Id-specific helper cells. Indeed, we have preliminary results demonstrating that athymic BALB/c nude mice are low responders to TEPC-15 PnC complexes (M. Caulfield and D. Isaak, unpublished observation), indicating that responsiveness to the complex is T-dependent. The putative Id-specific helper T cells could interact directly with B cells via the Id expressed on surface immunoglobulin molecules, resulting in the selective stimulation of an Id response. Alternatively, the immune complex could serve as a bridge to link Id-specific T cells with antigen-specific B cells. In the second case, the response to the complex could be composed of a mixture of Id and Id antibodies. Indeed, we have observed (Fig. 1) that the response of several strains to TEPC-15/PnC complexes is not completely dominated by the T15 (AB1-2) Id, suggesting that T15 B cells are being triggered. This second possibility suggests that Id-specific helper T cells could stimulate Id B cells when the two cells were linked by the appropriate antigen/antibody bridge. This would be analogous to the interaction of carrier-specific helper T cells with hapten-
specific B cells via a hapten-carrier conjugate (23) in which both Id+ and Id- antibodies would be induced. In support of the above argument, Klaus (24) has presented evidence for the activation of anti-Id antibody through the cooperation of antigen-specific T cells and Id-specific B cells mediated through immune complexes. Furthermore, we previously showed (9) that the T15 (AB1-2) Id is exposed in the TEPC-15/PnC complexes, since anti-Id antibody binds to the complexes. Presumably, the Id (in the complex) could also be recognized by Id-specific helper T cells.

The results shown here may have some relevance to the phenomenon of Id matching in the response to PC-KLH described by Bottomly et al. (25, 26). These investigators showed that carrier-primed T cells could induce an Id-dominated response in recipient mice only if both the T cell donors and the recipient mice were Id+. These results were interpreted to suggest the existence of a helper T cell population that recognizes both antigen and Id. Our results suggest a mechanism whereby two separate populations of helper T cells, one carrier-specific and the other Id-specific, could be responsible for the Id-matching phenomenon. Thus, we suggest that the PC-KLH antigen (employed by Bottomly et al.) could form complexes with Id+ antibody when injected into Id+ recipients, thereby allowing Id-specific helper cells to interact with Id+ B cells and carrier-specific T cells. Id- recipient mice could not form Id+ immune complexes, and therefore would not trigger an Id-dominated response. Support for this notion was provided by Woodland and Cantor (27), who showed that Id-specific helper T cells were required (in addition to carrier-specific helper cells) for optimal production of antibody to hapten-carrier conjugates.

Our finding that the antigen-specific response to the TEPC-15/PnC complex correlates with the relative dominance of the T15 (AB1-2) Id suggests that preexisting Id-specific regulatory mechanisms control the response to the immune complex. Thus, presentation of antigen in the context of Id (i.e., in the form of an immune complex) restricts the response to the antigen. Therefore, our results strongly indicate that the recognition of self-Id is important in controlling the immune response. This information adds further support to the network hypothesis (2).

Summary

The primary antigen-specific antibody response of various strains of mice to TEPC-15/PnC immune complexes has been examined. We found that both BALB/c and C3H mice were good responders to the PnC antigen; however, C3H mice were low responders, whereas BALB/c mice were high responders to the TEPC-15/PnC complexes. Using congenic strains on the C3H and BALB/c background, we have shown that the response to the complexes is not restricted by gene products of the H-2 complex or by the Igh (allotype) locus. However, responsiveness may be controlled by genes linked to the Igh locus, since we have shown that strains that are Igh1, Igh2, and Igh3 are low responders, whereas strains that are Igh4, Igh5, and Igh6 are high responders to the immune complex. Moreover, responsiveness correlates with the expression of the T15 Id as measured using the anti-T15 monoclonal antibody, AB1-2. Thus, strains such as BALB/c, BALB.B, BALB.K, and CB-20, which express high levels of T15 (AB1-2), are good responders to the TEPC-15/PnC immune complexes, whereas strains that are Igh1, Igh2, and Igh3 are low responders.
2) Id in their PFC response to PnC are relatively high responders to TEPC-15/PnC complexes, whereas C3H, C3H.SW, and C3H-OH, which express low levels of the T15 (AB1-2) Id, are low responders to the complexes. Finally, we found that BALB/c mice are high responders to complexes formed with T15* antibodies, whereas they are low responders to complexes formed using T15- antibodies. The results suggest that the antigen-specific response to these immune complexes is Id-restricted.

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