INFLUENCE OF Igh-LINKED GENE PRODUCTS ON THE GENERATION OF T HELPER CELLS IN THE RESPONSE TO SHEEP ERYTHROCYTES*

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Since the cellular basis of antibody production was firmly established by Gowans et al. (1), we have come to appreciate the intricacy of the cell interactions involved in this process. Claman et al. (2), Davies et al. (3), and Miller and Mitchell (4) showed that thymus-derived (T) cells had a synergistic (helper) effect on the generation of antibody-secreting (B) cells. Mitchison (5) and Rajewsky and Rottlander (6) found that help that could be generated via T cells responding to one set of antigenic determinants while B cells were responding to others. These T cells will be designated T-helper carrier or (TH$_{car}$).[1]

More recently, a second type of T-helper cell has been found. In certain mouse strains, and under conditions in which production of an allotype had been suppressed, Herzenberg et al. (7) showed that there are some T-helper cells (TH) that are restricted to supplying help for the production of antibody of a particular isotype and allotype. Subsequently, Hetzelberger and Eichman (8) and Woodland and Cantor (9) were able to demonstrate the existence of TH with specificity for idiotype. Kishimoto and Ishizaka (10) found that help for IgE could be generated separately from help for IgG (10). Thus, TH with specificity for allotypes, idiotypes, and isotypes have all been demonstrated. Collectively these will be called TH$_{Ig}$.

What remains to be demonstrated is that TH$_{Ig}$ play an important role in the typical situation where the initial response is clearly heterogeneous.

To examine this question we tried to determine if TH$_{Ig}$ are important in the antibody response of CBA mice to sheep erythrocytes (SRBC). We also wanted to test the idea that clones of TH$_{Ig}$ are selectively stimulated by an Ig-containing product of an antigen-stimulated B cell. Finally, we wished to see if the production of antibody of different isotypes was equally dependent on TH$_{Ig}$.

We utilized a set of three congenic strains of mice that we have developed: CBA/Tufts, CBA.*nude*, and CBA.*Igh^b*. All three strains are H-2^k and Mls^d. The first two carry the Igh^j haplotype, whereas CBA.*Igh^b* mice carry the Igh^b haplotype from

[1] *Abbreviations used in this paper:* PBS, phosphate-buffered saline; sIg, surface immunoglobulin; SRBC, sheep erythrocytes; TH, helper T cells; TH$_{car}$, helper T cells specific for carrier determinants; TH$_{Ig}$, thymus-derived helper cells specific for immunoglobulin determinants.

C57BL/6 NIMR mice. The CBA.*nude* mice carry the nude gene and homozygous *nu/nu* mice lack a normal thymus.

In all of the experiments, the amount of help provided by T cells from Igh^j and Igh^b donors was compared. In essence, we asked if antigen-primed Igh^j B cells, but not Igh^b B cells, expand clones of TH$_{Ig}$ that help Igh^j B cells. The rationale for these experiments was that the Igh^j and Igh^b haplotypes are known to contain alternative alleles for the constant regions μ, δ, γ, γ_{2b}, γ_{2a}, and α (11). They also differ at some unknown number of V$_H$ loci (12). We reasoned that clones of TH$_{Ig}$ in mice of one strain should be selectively expanded by Ig-containing products produced by that strain. These expanded TH$_{Ig}$ clones should be able to help B cells that bear Ig molecules similar to those that expanded the clone. Therefore T cells primed by products of Igh^j B cells should be able to help B cells of Igh^j phenotype better than T cells primed by B cells of Igh^b haplotype.

Materials and Methods

Animals. CBA/Tufts, CBA.*Igh^b*, and CBA.*nude* mice were produced in our breeding colony at Tufts University School of Medicine, Boston, Mass. CBA/Tufts mice are derived from a cross between CBA/Ca NIMR and CBA/J mice. The congenic partner CBA.*nude* is in the 12th backcross generation. Nude mice and their phenotypically normal littermates were from the F$_9$ to F$_{12}$ generations. CBA.*Igh^b* mice are the product of 14 generations of backcrossing of the IgG$_{2a}$b allotype from C57BL/6 mice onto a CBA/Tufts background. Mice used in this study were from F$_{14}$ to F$_{18}$ generations. These mice are all H-2^k (J. Klein and H. H. Wortis, unpublished data) and Mls^d they do not provoke mixed lymphocyte responses (S. Tonkonogy, H. Winn, and H. H. Wortis, unpublished data). Skin grafts between CBA/Tufts and CBA.*nude* ($+/?$) mice are accepted in both directions. Grafts from CBA.*Igh^b* mice to CBA/Tufts or CBA.*nude* ($+/?$) mice are rejected slowly, indicating a weak histocompatibility barrier (H. Winn and H. H. Wortis, unpublished data). Grafts in the other direction are accepted. CBA.*Igh^b* mice bear the IgG$_{2a}$b and IgG$_1$b alleles. Their antibody to staphylococcal nuclease bears an Igh-Ns idiotype (13) produced by Igh-V^b mice but not by mice with other Igh-V haplotypes (D. Sachs and H. H. Wortis, unpublished data). Because these mice bear the IgG$_{2a}$b allele and Igh-Ns allele and these two loci mark the known extremes of the Igh linkage group (13, 14), we concluded that these mice bear the whole Igh^b haplotype rather than assume that a double recombination event took place during the derivation of the congenic strains.

Unless otherwise indicated, female mice 2–5 mo of age were used. Nude mice were maintained in sealed, sterilized cages with filter tops. They received sterile bedding, food, and acidified water at 2-wk intervals. They were handled in a laminer flow hood under sterile conditions. Under these conditions, nude mice live for $\geq$1 yr.

Antigens. SRBC for immunization were purchased from Mr. Don Gaulitz of Massachusetts General Hospital, Boston, Mass. SRBC were kept in Alsever's solution at 4°C and used when 1–3 wk old.

Immunization. Experimental animals were challenged on days 0 and 21 with 4 × 10^7 SRBC by intraperitoneal injection. As indicated, some T cell donor mice were immunized with 4 × 10^6 SRBC by intraperitoneal injection 1 wk before they were killed. T cells from these mice are referred to as primed T cells.

Cell Preparation and Transfer. Lymphoid organs were pressed through a wire mesh and the cells collected were suspended in Hanks' balanced salt solution (Grand Island Biological Co., Grand Island, N. Y.) supplemented with 2% fetal calf serum. Thymocytes were taken from 2-wk-old donors. Peripheral T cell-enriched preparations were made by removing surface Ig$^+$ (sIg$^+$) cells from lymph node suspensions by the panning technique (15, 16). Nonbinding cells were 2–5% sIg$^+$ as determined by fluorescein-coupled goat anti-mouse Fab prepared in this laboratory. They showed little mitogenic response to lipopolysaccharide (e.g., stimulation index = 6.5, Δcpm = 5,500 cpm) but did give a vigorous response to concanavalin A (e.g., stimulation

index = 253, Δcpm = 251,000). 1×10^7–2×10^7 Ig$^-$ (T) cells were injected i.v. into recipient nude mice as indicated. Recipient nude mice were tail bled on days 5 or 7 and day 12 or 13.

Antibody Assay. Serum antibodies to SRBC were measured in a radioimmunoassay developed by J. Haber and described in detail elsewhere (17). In brief 25 μl of serum diluted on 0.01 M phosphate-buffered saline (PBS) pH 7.5 was incubated with 25 μl of a 20% suspension of SRBC in round-bottomed microtiter plates (MIC-2000, Cooke Engineering Co., Alexandria, Va.) for 1 h at room temperature. The plates were spun at 180 g for 5 min. The supernates were removed, fresh PBS added, and the plates agitated. Washing was repeated three to four times. I^{125}-labeled goat anti mouse γ_1, γ_{2a}, γ_{2b}, γ_3, or, μ antibody was added to the antibody-coated, washed cells. After an overnight incubation at room temperature, the plates were centrifuged and the antibody-coated cells washed three times. The wells were cut with a hot wire and the number of bound counts determined in a Beckman gamma counter (Beckman Instruments, Inc., Spinco Div., Palo Alto, Calif.).

A serum pool from mice hyperimmunized with SRBC was used as a standard. Units of antibody in test bleeds were determined by comparison with the antibody content of the standard. Because no attempt was made to convert units into micrograms or moles of antibody, quantitative comparison of different isotypes can not be made.

Recent assays have utilized microtiter wells pretreated for 15 min at room temperature with 0.025 mg/ml poly-L-lysine hydrobromide (Miles Laboratories, Inc., Elkhart, Ind.). After coating, the wells were washed with PBS then incubated with 50 μl of 5% SRBC in 0.1 M PBS, pH 7.5, for 30 min. Excess cells were washed away. The assay then proceeded as above. This method of coating plates with SRBC has the advantage of permitting extensive washing without need for centrifugation, and gives results equivalent to those seen with the SRBC pellet method.

Goat Anti-Mouse Isotype. The preparation and characterization of the goat anti-mouse Ig reagents used in this study have been described in detail elsewhere.[2] Briefly, antisera raised in goats after immunization with appropriate BALB/c myeloma proteins were made isotype specific by absorption with heterologous myeloma proteins. Antiallotype antibodies have been found in goat anti-mouse Ig antisera (17, 18) and have been shown to introduce significant error in measurements of isotypes of different allotypes (18). Because antiallotype antibodies directed against Igh^a (BALB/c) specificities were present in the antisera reactive with IgG$_1$, IgG$_{2a}$, and IgG$_{2b}$, these reagents were prepared by acid elution from an immunoadsorbent carrying Igh^b (C57BL/6J) or Igh^e (A/J) Ig. This step resulted in the isolation of antibody reacting with isotypic specificities and possibly allotypic specificities common to Ig molecules of the Igh^a, Igh^b, and Igh^e phenotypes. The isotype specificity of these reagents was confirmed in a radioimmunoassay employing Sepharose beads to which myeloma proteins representative of each mouse Ig isotype (IgM, IgA, IgG$_1$, IgG$_{2a}$, IgG$_{2b}$, and IgG$_3$) had been coupled. Absorption studies showed that the anti-Ig reagents used in this study do not discriminate among Ig molecules from BALB/c (Igh^a), C57BL/6J (Igh^b) or A/J (Igh^e) mice and are therefore acceptable for comparative measurements of Ig molecules of the Igh^a, Igh^b, and Igh^e phenotypes. Because Igh^a and Igh^j allotypes differ only at C$_H$ alleles coding for IgG$_{2a}$, our reagents are suitable for comparative measurements of IgG$_1$, IgG$_3$, and IgG$_{2b}$ molecules from CBA/Tufts (Igh^j) and CBA.*Igh^b* mice. Furthermore, our anti-IgG$_{2a}$ reagent does not discriminate between Igh^j and Igh^b IgG$_{2a}$ molecules. On this basis, we conclude that our comparisons of the levels of anti-SRBC antibody present in sera from CBA/Tufts (Igh^j) and CBA.*Igh^b* mice are valid.

Results

To What Extent is the Response to SRBC T Dependent? On day 14 after a primary immunization, nude mice produced <10% of the normal amounts of γ_3, γ_1, γ_{2b}, and γ_{2a} anti-SRBC. They did produce ~25% of the normal IgM response (Fig. 1). Similar results (data not shown) were obtained on day 5 of a primary response and after multiple immunizations. Nude mice given 1×10^7–2×10^7 T cells produce normal
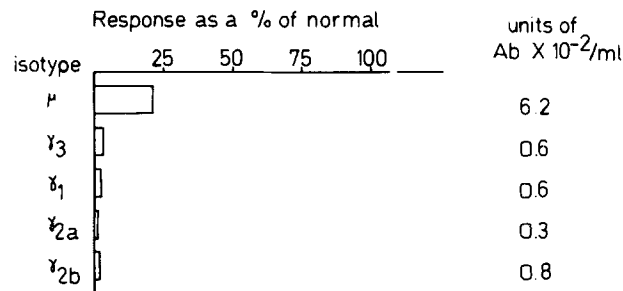
Fig. 1. Serum levels of anti-SRBC found in nude mice 14 d after a primary immunization with 4 × 10⁷ SRBC i.p. Values represent those found in sera pooled from six mice. A similar pool of sera from normal littermate mice was also analyzed. For details of the radioimmunoassay used to determine antibody (Ab) levels, see Materials and Methods.
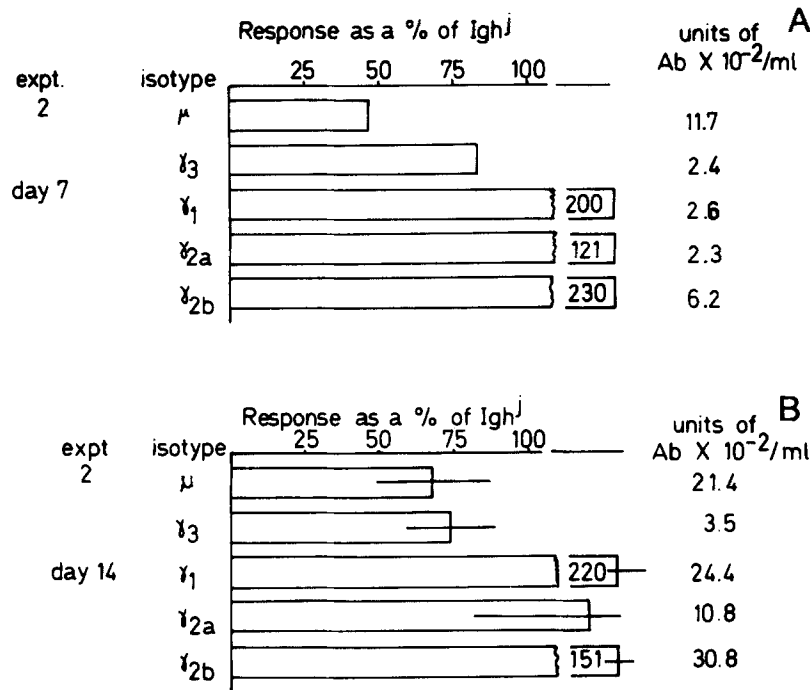

Fig. 2. Serum levels of anti-SRBC found in CBA.Igh^b mice 7 d after a primary (A) or secondary (B) immunization with 4 × 10⁷ SRBC i.p. Values represent those found in sera pooled from six mice. A similar pool of sera from age- and sex-matched CBA/Tufts (Igh^j) mice was also analyzed. Ab, antibody; (—) SEM.

responses to SRBC (Fig. 3 A, below). Thus for all five isotypes examined the majority of the anti-SRBC response is T dependent.

Do Igh^j and Igh^b Mice Produce Different Amounts of Anti-SRBC Antibody? Because we were interested in comparing the helper ability of T cells from Igh^j and Igh^b, mice it was important to establish that the donor strains do not have quantitatively different responses to SRBC. As shown in Fig. 2, after either a primary or a secondary immunization the mice from the two strains produced comparable amounts of anti-SRBC of each isotype. Therefore, there was no reason to believe that the presence of

TABLE I

T Cells from SRBC-primed Igh Allogeneic Mice Show No Evidence of Priming

	Igh^j T cells (syngeneic)				Igh^b T cells (allogeneic)			
Isotype	Unprimed	Primed	Δ*	Stimula-tion in-dex	Unprimed	Primed	Δ	Stimula-tion in-dex
μ	7.3 (1.1)‡	104.7 (1.8)	97	14	4.6 (1.2)	6.5 (1.7)	2	1.4
γ₃	9.3 (1.9)	42.7 (1.2)	33	5	11.5 (1.2)	8.7 (1.9)	−3	0.8
γ₁	8.8 (1.4)	38.0 (1.4)	29	4	8.9 (1.3)	3.6 (1.8)	−5	0.4
γ₂ₐ	9.1 (1.3)	30.2 (1.3)	21	3	6.3 (1.7)	3.3 (2.7)	−3	0.5
γ₂ᵦ	9.5 (1.0)	75.9 (1.1)	66	8	14.6 (1.5)	10.0 (1.8)	−5	0.7

* Units of anti-SRBC × 10^{-2}/ml; geometric mean ×/+ SEM; day 12/13; experiments 3-5, 8, 10-12.
‡ Δ, Units of antibody (primed) − (unprimed); stimulation index = units of antibody (primed)/(unprimed).

TABLE II

T Cells Become Primed If Challenged with SRBC While Residing with Host B Cells

	Igh^j T cells			Igh^b T cells		
Isotype	Day 12	Day 28	Stimulation index	Day 12	Day 28	Stimulation index
μ	6.3*	19.5	6	3.3	21.1	7
γ₃	3.8	13.9	3	8.7	82.4	10
γ₁	5.3	134.8	25	5.9	430.9	80
γ₂ₐ	6.3	62.0	10	2.9	114.8	38
γ₂ᵦ	10.0	20.5	2	8.0	8.0	1

* Units of anti-SRBC × 10^{-2}/ml; experiment 5.

either the Igh^j or the Igh^b haplotype in itself produced an enhanced anti-SRBC response.

Does the Igh^b Haplotype Restrict the Ability of T Cells to Generate Help for Igh^j B Cells in either a Primary or a Secondary Response? Peripheral T cells from unprimed donors, either Igh^j or Igh^b, were transferred to Igh^j nudes and the host animals immunized. The presence of T cells of both genotypes provided help for nude Igh^j B cells. For each isotype examined the amount of antibody found on day 12-13 was similar regardless of the T cell genotype. (Fig. 3 A). Therefore the presence of an Igh^b genotype (or the absence of the Igh^j genotype) does not prevent T cells from providing help for Igh^j B cells. This result was confirmed when the recipient animals were challenged on day 21 (Fig. 3 C).

Are T Cells from SRBC-immunized Igh^j and Igh^b Mice also Equivalent in Providing Help for Igh^j B Cells? In contrast to the previous results T cells from SRBC-primed Igh^b donors failed to provide as much help as Igh^j T cells (Fig. 3 C). On subsequent challenge, these Igh haplotype mismatched T cells were also less efficient than their matched counterparts in generating help (Fig. 3 D).

Is Priming of TH Influenced by the Igh Phenotype of the Environment? An examination of the amount of antibody produced in the course of a primary response to SRBC indicates that Igh^b T cells from both primed and unprimed donors provide as much help as unprimed Igh^j T cells but far less help than T cells from SRBC-primed Igh^j donors (Table I). That is, whereas Igh^b mice can provide helper T cells, they do not

Igh^b (allogeneic) T help: unprimed donors: primary response   **A**

Response as a % of Igh^j T help   units of Ab X 10^{-2}/ml

expts	isotype	25	50	75	100		units of Ab X 10^{-2}/ml
5,12	μ						4.6
	γ_3					┤124├→	11.5
day 12-13	γ_1					→	8.9
	γ_{2a}						6.3
	γ_{2b}					┤154├→	14.6

Igh^b (allogeneic) T help: primed donors: primary response   **B**

Response as a % of Igh^j T help   units of Ab X 10^{-2}/ml

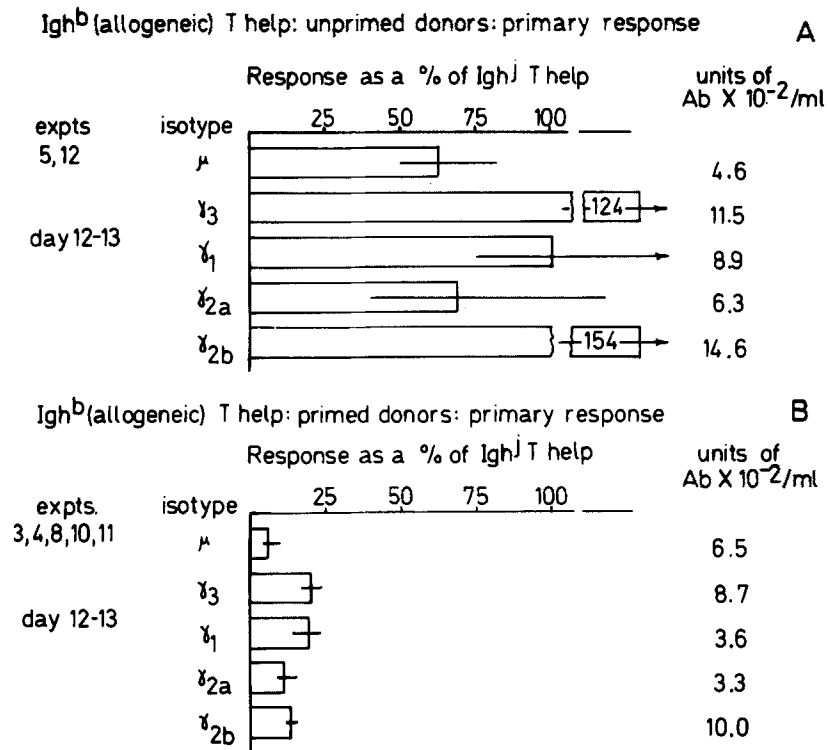| expts.	isotype	25	50	75	100		units of Ab X 10^{-2}/ml
3,4,8,10,11	μ						6.5
	γ_3						8.7
day 12-13	γ_1						3.6
	γ_{2a}						3.3
	γ_{2b}						10.0

Fig. 3A and B

Fig. 3.   Serum levels of anti-SRBC found in CBA.*nude* mice after receiving peripheral T cells and SRBC immunization. In each case, the amount of antibody (Ab) seen in mice given congenic CBA.*Igh^b* T cells is presented both as a percentage of that found in control nudes given CBA.Tufts (Igh^j) T cells (bar graph) and in units. T cells were from unprimed (A and B) or primed (C and D) donors and responses were measured during the primary (A and C) or secondary (B and D) response. Values represent the geometric mean of the indicated experiments. The SEM is also shown (—).

show any evidence that they can be primed by SRBC to provide augmented help for Igh^j B cells. This result contrasts with that seen with Igh^j donor mice where priming with 4 X 10^6 SRBC i.p. 6 d before T cell transfer resulted in a marked augmentation of help for all isotypes. This means that either contact with SRBC induced different levels of help in Igh^j and Igh^b T cells or that Igh^j- and Igh^b-linked genes produce a difference in the priming environment that effects the helper capability of T cells from the two strains.

The first conclusion is unlikely because (*a*) the primary and secondary responses of the two strains are similar (Fig. 2); and (*b*) the responses to a secondary immunization of Igh^j mice given either unprimed Igh^j or Igh^b T cells were equivalent (Fig. 3B). That is, T cells of the Igh^b genotype were primed to help Igh^j B cells provided that Igh^j-linked products were present at the time of SRBC immunization (Table II).

A more direct test of this last conclusion was possible using a double transfer of T cells. T cells of either Igh^j or Igh^b genotype were transferred to Igh^j nude mice which were then immunized with 4 X 10^6 SRBC. 6 d later, T cells from these primary recipients were recovered and transferred to second group of Igh^j nudes. Although Igh^b T cells from intact Igh^b SRBC-primed mice failed to provide any help when
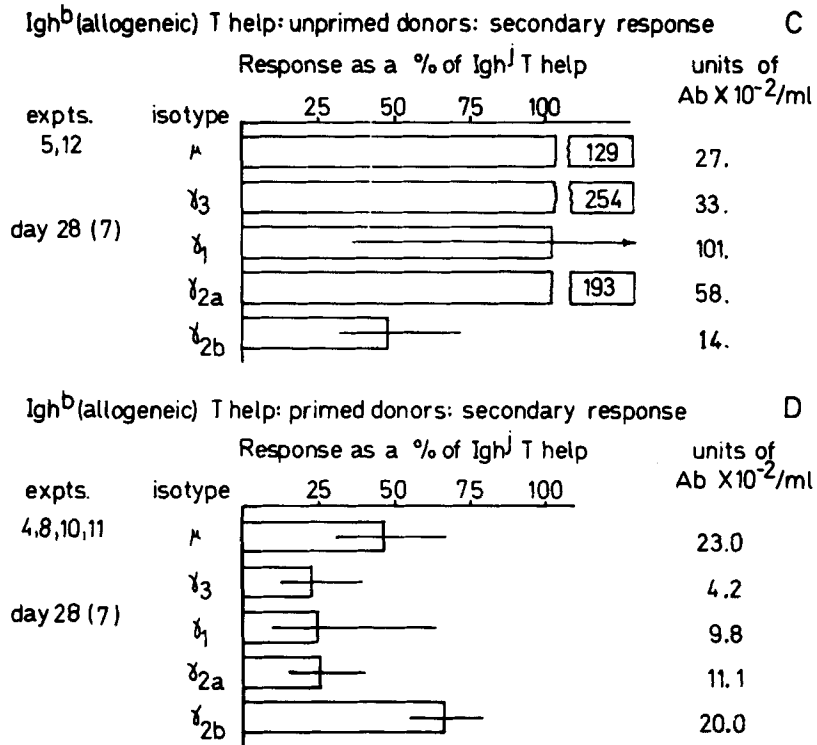
Igh^b(allogeneic) T help: unprimed donors: secondary response   C

Response as a % of Igh^j T help   units of Ab $\times 10^{-2}$/ml

expts.	isotype	25	50	75	100	units of Ab $\times 10^{-2}$/ml
5,12	μ				129	27.
	γ_3				254	33.
day 28 (7)	γ_1					101.
	γ_{2a}				193	58.
	γ_{2b}					14.

Igh^b(allogeneic) T help: primed donors: secondary response   D

Response as a % of Igh^j T help   units of Ab $\times 10^{-2}$/ml

expts.	isotype	25	50	75	100	units of Ab $\times 10^{-2}$/ml
4,8,10,11	μ					23.0
	γ_3					4.2
day 28 (7)	γ_1					9.8
	γ_{2a}					11.1
	γ_{2b}					20.0

FIG. 3C and D

transferred to Igh^j nudes, Igh^b T cells that were in an Igh^j environment at the time of SRBC priming provided help (Fig. 4).

Discussion

The central observation of these experiments is that the ability of T cells to help in the generation of an antibody response is strongly influenced by Igh-linked genes of the cellular environment. This observation rests on the demonstration that the majority of antibody to SRBC—IgM, IgG$_3$, IgG$_1$, IgG$_{2b}$, and IgG$_{2a}$—is T cell dependent as demonstrated by the weak responses of nude mice (Fig. 1) and the vigorous responses of T cell-restored nudes (Fig. 3). This confirms previous findings (19), as does our observation that IgG responses are more T dependent than IgM responses (20). That some antibody, mainly IgM but also IgG, appears in nude mice could mean either that there is a T-independent response to some determinants and/ or that there is sufficient (weak) T help in the nude (21) to permit these small responses.

We did not find any significant difference in the amounts of antibody produced by Igh^j and Igh^b mice. This could mean either that the T cells of the two strains provide equivalent amounts of help for their own B cells, or that the T cells of one strain provide less help but that their B cells make a more vigorous response. The first explanation is probably correct because when T cells from either strain were allowed to collaborate with Igh^j B cells, the amounts of antibody generated were equivalent (Fig. 3 A, and Table I). This equivalence continues through a second immunization
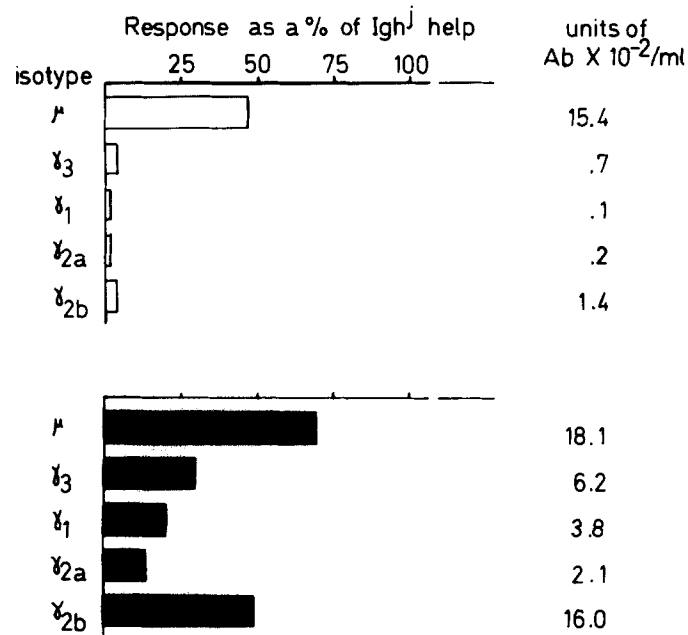
Fig. 4. Serum levels of anti-SRBC in nude mice after receiving Igh^b lymph node T cells primed in IgH^b mice (open bars) or in Igh^j nude mice (solid bars). The amount of antibody is shown as a percentage of that found with Igh^j T cells primed *in situ* (open bars) or in Igh^j nude mice (solid bars). Values given are those of pooled sera.

with SRBC, a finding indicating that T cells of both genotypes can provide help for B cell clonal expansion and triggering. This conclusion rests on the observation that both the establishment of B cell memory, and its expression requires interaction with T cells (22). In summary we can say that Igh^j- and Igh^b-linked genes do not limit the potential for T and B cells to collaborate.

In contrast, T cells introduced to SRBC in an environment that does not contain the products of Igh^j-linked genes are inefficient helpers for Igh^j B cells. (Figs. 3 C and D and Tables I and II). In terms used in other contexts, these T cells are restricted or adaptively differentiated with respect to the products of Igh-linked genes.

Our interpretation of this result is that B cells are triggered by antigen (SRBC) and produce SRBC-specific, Ig-containing products. These products serve to trigger a set of TH bearing receptors that are complementary to the Ig products. As a result of proliferation and differentiation, an expanded pool of Ig-specific memory T cells is produced. These primed cells then serve as effector T helper cells with specificity for B cells bearing molecules structurally similar to those produced by B cells that originally responded to SRBC.

Although we favor the idea that B cells are the source of the priming Ig product, we have not ruled out the possibility that other cells, e.g. cells of the T lineage (which would be present in nude mice [23–25]) are responsible. Direct evidence implicating B cells is provided by L'age-Stehr (26).

Because it requires antigen to generate a B cell product that is coded for by Igh-linked genes, it is reasonable to propose, as we do, that the B cell product contains the immunoglobulin heavy chain. However, we can not, with certainty, rule out the

possibility that the products of other loci, e.g., minor histocompatibility loci, are the relevant molecules. We favor the idea that there are Ig-specific helper cells because such cells have been shown to exist in three entirely different helper systems: isotype (10), allotype (7), and idiotype (8, 9). This means that two classes of TH have been demonstrated: carrier specific and Ig specific. Independent estimates of the number of interacting T cells have also suggested the evidence of two populations (27). In fact, there is some evidence at hand that one of these populations does depend on the presence of B cells with sIg (28). Proof of the Ig specificity of the helper T cell receptor requires a more direct test, such as the demonstration of the ability of these T cells to specifically bind (anti-SRBC) antibody.

Assuming that we are seeing help provided by T cells with anti-Ig specificity, we can not respond to the question as to whether these cells recognize V_H or C_H sequences. Resolution of this point requires experiments using V_H-C_H recombinant mice (26) and appropriate T cell-Ig-binding studies. Although the demonstration of allotype-, isotype-, and idiotype-specific help is consistent with the possibility that TH_{Ig} populations exist that have receptors for each of these three specificities, it is not a proof. The nonrandom association of V_H products with C_H products (29) would lead to allotype- or isotype-specific help even if TH_{Ig} had receptors only for V_H sequences.

If, indeed, there are TH_{Ig}, we do not know if they are specifically stimulated by free antibody, surface antibody, or antigen-antibody complexes. Nor do we know if the responding T cells must bind other molecules (e.g., antigen or H-2 product) to be effectively triggered. The possibility exists, for instance, that TH_{car} are Ia restricted with respect to antigen-presenting cells, whereas TH_{Ig} are (Ia?) restricted by the phenotype of the B cell.

Although T cells from SRBC-primed Igh^b mice were less helpful than syngeneic cells they did provide substantial help. Does this help represent TH_{Ig} and/or TH_{car} help? At this time we can not say. It is possible that all the allogeneic help is a result of TH_{car}. Alternatively, there could be some cross-reactivity between Igh^b and Igh^j determinants that are recognized by TH_{Ig}, or in the course of their residence in Igh^j nudes, the Igh^b TH_{Ig} are primed by B cell products from their hosts. The nature of the interaction between help provided by TH_{car} and TH_{Ig} awaits future exploration (9, 30, 31).

Summary

The role of Igh-linked loci in the generation and expression of T cell help for antibody responses to sheep erythrocytes (SRBC) was investigated. The production of IgM, IgG_3, IgG_1, IgG_{2b}, and IgG_{2a} antibody to SRBC was shown to be T cell dependent. The Igh-congenic mouse pair CBA/Tufts (Igh^j) and CBA.Igh^b gave equivalent responses to SRBC. CBA.*nude* mice (Igh^j) supplemented with peripheral T cells of either Igh^j or Igh^b genotype produced equivalent, high responses. Therefore, T cell-B cell mismatching for the Igh haplotype is not in itself a bar to the generation or expression of help. In contrast, T cells primed in an environment that lacks Igh^j-linked products are inefficient helpers for Igh^j B cells. These results suggest that antigen-primed B cells or their products prime a set of T cells that can help B cells that bear matching, Igh-linked gene products.

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