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STRAIN-DEPENDENT IgG SUBCLASS RESPONSE PATTERNS[1]

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Previous studies have shown that antigens preferentially stimulate IgG subclasses. However, the immunologic processes responsible for the patterns of IgG subclasses stimulated by antigens are probably complex and are certainly unclear. To define some of the genetic controls of IgG subclass expression in mice, we have studied the patterns of IgG subclasses elicited by antigens in BALB/cAn, C57BL/6N, derived recombinant inbred strains, and derived Ig congenic strains. This study shows that both thymus-independent antigens and thymus-dependent antigens stimulate different patterns of IgG subclasses in BALB/cAn and C57BL/6N. Furthermore, analysis using recombinant inbred strains and Ig congenic strains shows that the patterns of IgG subclasses stimulated by all antigens are linked to Ig allotype. In contrast, only the IgG subclass patterns stimulated by thymus-dependent antigens are linked to major histocompatibility complex haplotype. This study also shows that the Ig allotype-linked controls of IgG subclass response patterns are located telomeric to a BAB14 intra-heavy chain variable region recombinant site. Therefore, this region of mouse chromosome 12 may contribute to the control of IgG subclass selection in the B cell.

Murine IgG subclasses are preferentially stimulated by antigens. Some thymus-dependent (TD)[2] antigens, such as trinitrophenyl-bovine serum albumin (TNP-BSA), preferentially stimulate IgG1 production; other TD antigens, such as TNP-*Brucella abortus* (BA), and the thymus-independent (TI) antigen TNP-lipopolysaccharide (LPS) preferentially stimulate IgG2b and IgG3 production; and many TI and TD antigens including the TI antigen TNP-Ficoll preferentially stimulate IgG3 production (1–4).

Such nonrandom expressions of IgG subclasses can be explained by contrasting schemes of B cell differentiation. On the one hand, B cells of distinct lineages may be precommitted to the making of certain IgG subclasses during early development (2, 5). Alternatively, equivalent uncommitted B cells may be restricted to the making of certain IgG subclasses by exogenous signals during the immune response (6–8). To better understand whether either of these B cell differentiation schemes has merit, it is important to define the immunologic processes that contribute to patterns of IgG subclass expression.

Patterns of IgG subclass expression are genetically controlled. CBA/N mice have a well characterized X chromosome-linked mutant gene (9, 10) that causes a selective IgG3 subclass immunodeficiency (2, 11), and additional genetic controls of IgG subclass expression may exist in BALB/cAn and C57BL/6N. The serum IgG of BALB/cAn, for instance, is predominantly IgG1, that of C57BL/6N, predominantly IgG2b (12–14). To more clearly define the genetic controls of IgG subclass expression, we have studied the patterns of IgG subclasses stimulated by antigens in BALB/cAn and C57BL/6N. This study shows that genes linked to Ig allotype and major histocompatibility complex haplotype can also control patterns of IgG subclass expression.

MATERIALS AND METHODS

Mice. BALB/cAn, C57BL/6N, Bailey recombinant inbred (RI) strains (15) and the immunoglobulin (Ig) congenic strains BC8, CB20, and BAB14 were obtained from Dr. Michael Potter, National Institutes of Health, under Litton Bionetics contract NO1-CB-25584 and are now maintained in the Indiana University School of Medicine breeding colony. The BC8 congenic strain represents a C57BL/ka mouse with the BALB/c Ig constant heavy chain locus (Igh) introduced over eight backcross generations before being made homozygous. BAB14, an intra-heavy chain variable region (V_H) recombinant (16–18), and CB20 were established by backcrossing the C57BL/ka Igh into BALB/cAn. C57BL/10J and H-2 congenic strains: B10.D2, B10.A, B10.AkM, B10.RIII, and B10.M were purchased from The Jackson Laboratory, Bar Harbor, ME.

Antigen preparation and immunizations. TNP-Ficoll with an average of 56 TNP groups per Ficoll molecule (m.w. 400,000; Pharmacia Fine Chemicals, Uppsala, Sweden) was made by the method of Inman (19). TNP-BA was prepared with BA obtained from the U.S. Department of Agriculture Animal and Plant Health Inspection Services, Ames, IA (20); and TNP-LPS (LPS from *Escherichia coli* 0111:B4, Difco Laboratories, Detroit, MI) was prepared as previously described (21). TNP-BSA was prepared with an average of 36 TNP groups per BSA molecule (22). Female mice in groups of four were immunized i.p. with 100 μg TNP-Ficoll, 100 μg TNP-LPS, or 10^9 TNP-BA organisms. Plaque-forming cell (PFC) responses were measured 7 days later. Female mice in groups of four were also immunized i.p. with 400 μg TNP-BSA in complete Freund's adjuvant (Difco), followed in 1 mo by 100 μg in Freund's incomplete adjuvant. PFC responses were measured 5 days later.

Isotype-Specific PFC Assays. Spleen cells secreting either BALB/cAn or C57BL/6N TNP-specific antibody of the IgM class and of the IgG1, IgG2a, IgG2b, and IgG3 subclasses were facilitated by isotype-specific antisera in a TNP-specific plaque assay (23). Facilitation of PFC producing these isotypes was verified with BALB/cAn and C57BL/6N hybridomas/plasmacytomas in reverse plaque assays (3, 14, 24) and in TNP-specific plaque assays. Antisera specific for and hybridomas/plasmacytomas making the BALB/cAn or C57BL/6N IgG subclasses were obtained from Dr. Michael Potter (see above), or were kind gifts from Dr. Mitchell Scott, Washington University School of Medicine, St. Louis, MO. All antisera were made isotype-specific by affinity chromatography, and all myeloma and hybridoma monoclonal Ig were purified by preparative isoelectric focusing. To detect only IgG-secreting spleen cells in the TNP-specific plaque

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[1] This work was supported by the United States Public Health Service Grant AM 35601, awarded by the National Institute of Arthritis, Diabetes, Digestive and Kidney Diseases.
[2] Abbreviations used in the paper: TD, thymus-dependent; TI, thymus-independent; Igh, immunoglobulin constant heavy chain locus; RI, recombinant inbred; V_H, heavy chain variable region; BA, *Brucella abortus*.

assay, direct (IgM) PFC were suppressed by anti-μ (goat anti-MOPC104E) included in the agarose.

RESULTS

BALB/cAn, C57BL/6N, and Bailey RI strain IgM and IgG subclass PFC responses to TD and TI antigens. The subclass patterns of IgG responses in BALB/cAn and in C57BL/6N were initially compared with those in derived Bailey RI strains. As shown in Figure 1, TNP-BSA stimulates 1,000 IgG1 PFC/10^6 spleen cells in BALB/cAn, but only 90 IgG1 PFC/10^6 spleen cells in C57BL/6N. PFC of the remaining IgG subclasses induced by TNP-BSA range from 120 to 190 PFC/10^6 spleen cells in BALB/cAn and from 40 to 60 PFC/10^6 spleen cells in C57BL/6N.

Figure 2 indicates that RI strains CXBG and CXBJ respond to TNP-BSA with similar amounts of IgG1, intermediate to the IgG1 amounts made by the parental strains; the same is true for RI strains CXBD and CXBH. RI strains CXBE, CXBI, and CXBK, however, all make IgG1 in an amount comparable to that made by the parental strain C57BL/6N. The RI strains that make similar amounts of IgG1 have the same Ig allotype and MHC haplotype. Thus, the IgG1 response to TNP-BSA is linked to Ig allotype and MHC haplotype. Similarly, Figure 2 shows that the IgG2b response to TNP-BSA is also linked to Ig allotype and MHC haplotype, whereas the IgG2a and IgG3 responses are linked only to MHC.

Like TNP-BSA, TNP-BA stimulates IgG1 and IgG2b responses (Fig. 1) that are linked to Ig allotype and MHC haplotype, and IgG2a and IgG3 responses that are linked only to MHC (Fig. 2). TNP-BA may be able to stimulate a better IgG2b response than TNP-BSA because the Ig allotype-linked control of the TNP-BSA response may be weaker than that of the TNP-BA response.

Like TNP-BSA, the TI antigen TNP-Ficoll stimulates a high IgG1 response in BALB/cAn. The other TI antigen, TNP-LPS, resembles TNP-BA by stimulating a high IgG2b response in C57BL/6N. The IgG1 response to TNP-Ficoll is linked to Ig allotype as is the IgG2b response to TNP-LPS. Both the controls of the IgG1 and IgG2b responses to TI antigens, and the controls of the IgG1 and IgG2b responses to TD antigens are allotype-linked. However, the TI antigens stimulate similar IgG2a and IgG3 responses in both BALB/cAn and in C57BL/6N, suggesting that only IgG subclass responses to TD antigens are controlled by MHC. Thus, controls of IgG subclass responses to all antigens may be linked only to Ig allotype.

Ig congenic strain IgG PFC responses to TNP-Ficoll and TNP-LPS. If controls of the IgG1 and IgG2b responses are linked to Ig allotype, the TI antigens TNP-Ficoll and TNP-LPS should produce the same IgG subclass patterns in the Ig congenic strain BC8 (BC8 has the BALB/cAn Ig allotype but C57BL/Ka background genes) as are seen in BALB/cAn, and the same IgG subclass patterns in the Ig congenic strain CB20 as are seen in C57BL/6N. As shown in Table I, TNP-Ficoll stimulates a high IgG1 response in

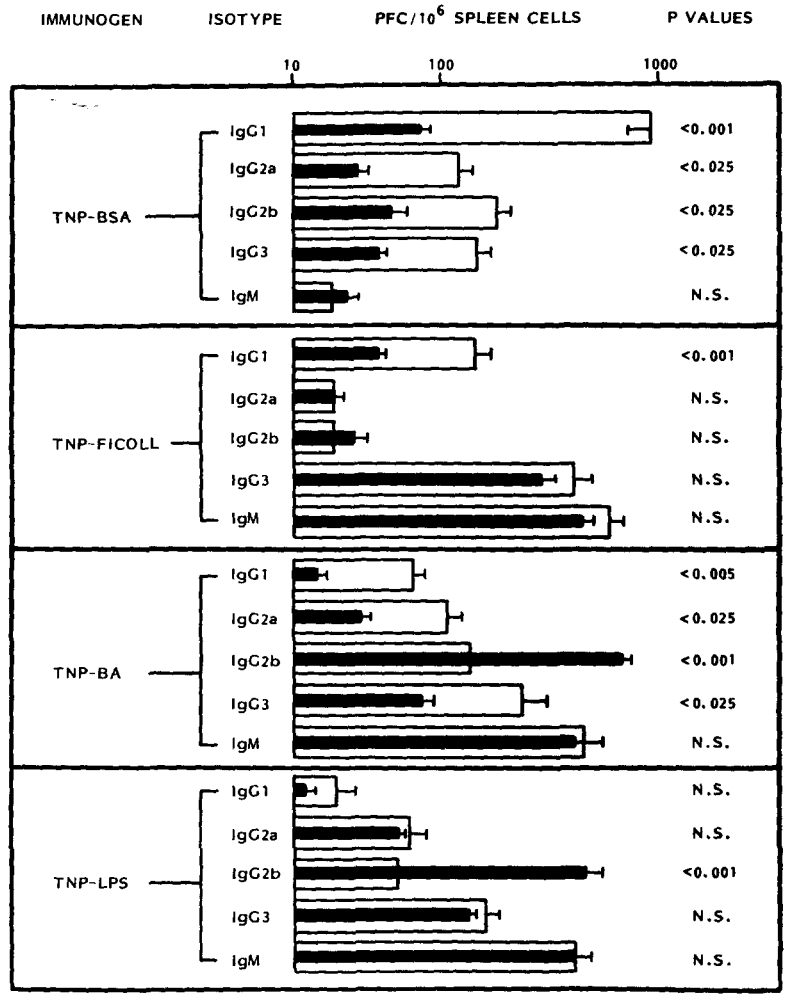

Figure 1. IgM and IgG TNP-specific spleen cells were numerated by antigen-specific plaque assay systems in groups of four immune mice 5 to 7 days after the final administration of antigen. Shown are geometric means and standard error bars. The Student's *t*-test was used to evaluate significance of differences between BALB/cAn and C57BL/6N mean PFC response values. p Values indicating 95% confidence limits were accepted as significant. BALB/cAn PFC values are indicated by *clear bars*, C57BL/6N values by *darkened lines*.

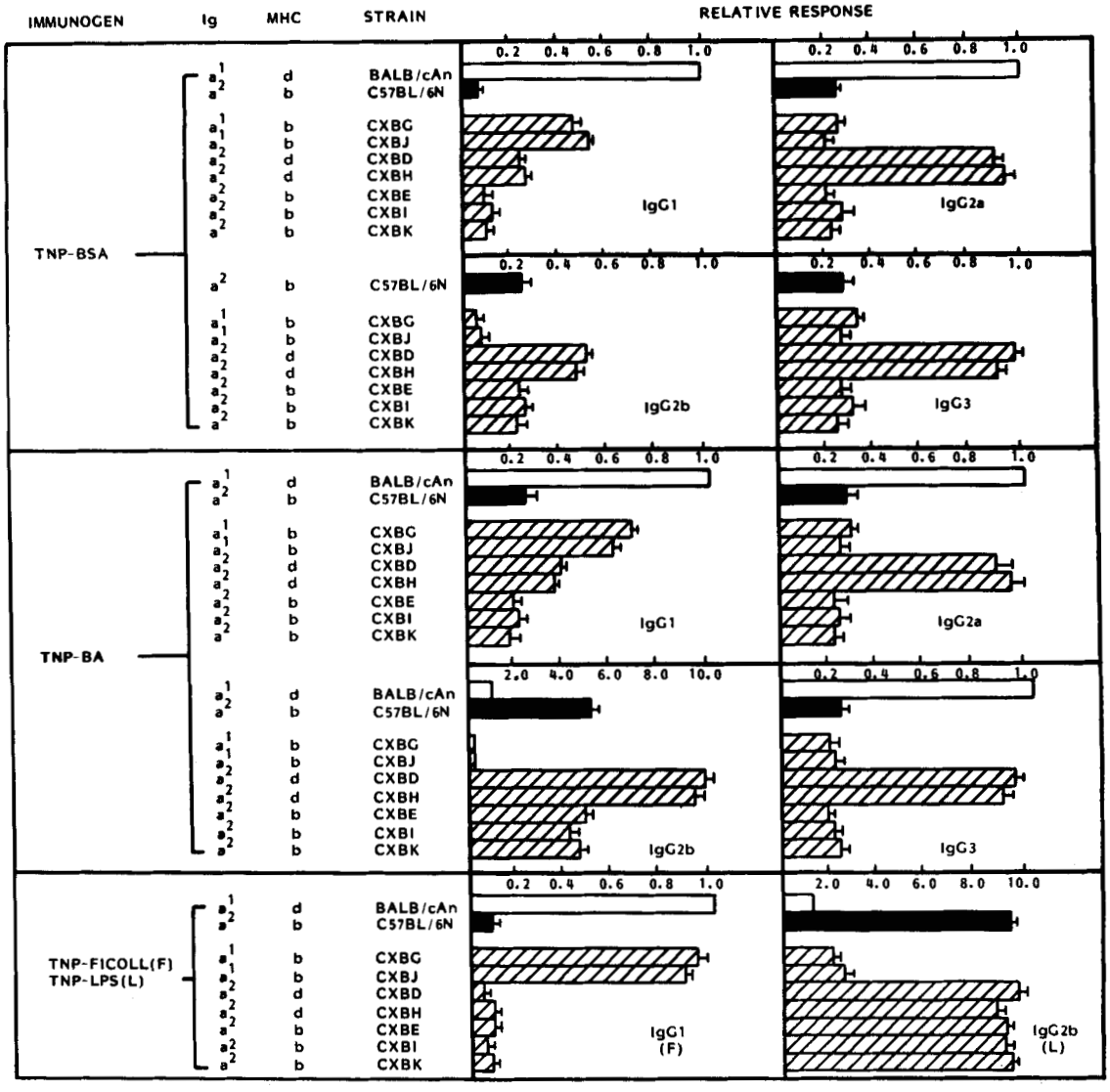

Figure 2. The IgG subclass patterns of the Bailey RI strains are displayed as response ratios (Bailey RI strain IgG PFC responses relative to those of BALB/cAn). As a reference point, the BALB/cAn standard ratio value of one is shown. Statistical significance of ratios was determined by the Student's *t*-test evaluation of respective means. The Bailey RI strains were made by randomly inbreeding BALB/cAn (with the a^1 Ig allotype and d MHC haplotype) and C57BL/6N (with the a^2 Ig allotype and b MHC haplotype) F_2 generation-mice.

TABLE I

IgG subclass PFC responses of Ig congenic strains[a]

Immunogen	Strain	Ig	V_H Dex[b]	PFC/10^6 Spleen Cells (SE Factors)		
				IgG1	IgG2	IgG3
TNP-Ficoll	BC8	a^1	+	325 (1.3)	47 (1.2)	545 (1.4)
	CB20	a^2	−	42 (1.2)	22 (1.4)	475 (1.2)
	BAB14	a^2	+	57 (1.1)	35 (1.2)	525 (1.3)
TNP-LPS	BC8	a^1	+	22 (1.4)	52 (1.3)	60 (1.3)
	CB20	a^2	−	12 (1.5)	545 (1.2)	35 (1.2)
	BAB14	a^2	+	15 (1.3)	625 (1.3)	55 (1.4)

[a] IgG subclass TNP-specific PFC were evaluated in the reciprocal Ig congenic strains BC8 and CB20 and the intra-V_H recombinant BAB14 after administration of TNP-Ficoll or TNP-LPS. The IgG2 values are sums of IgG2a- and IgG2b-secreting cell determinations. Shown are geometric means (standard error factors).

[b] V_H Dex is the region of mouse chromosome 12 that controls anti-dextran heavy chain idiotypes. BALB/cAn mice are V_H Dex positive, whereas C57BL/6N mice are V_H Dex negative.

BC8 but a low one in CB20, whereas TNP-LPS stimulates a high IgG2b response in CB20 but a low one in BC8. The high IgG1 and low IgG2b responses by BC8 are characteristic to BALB/cAn, but the low IgG1 and high IgG2b responses by CB20 are characteristic of C57BL/6N. These results confirm that controls of IgG1 and IgG2b responses are linked to Ig allotype. Furthermore, the responses of BAB14 to TNP-Ficoll and TNP-LPS resemble those of CB20 (Table I). This result associates these allotype-linked controls of IgG subclass responses with a region of chromosome 12 telomeric to V_H Dex.

IgG subclass distributions of TNP-BSA responses in MHC congenic strains. Since IgG1 and IgG2b but not IgG2a and IgG3 subclass responses are found in this study to be allotype-linked, the production of IgG subclasses may be preferentially linked to Ig allotype. In contrast, IgG subclass responses do not appear to be preferentially controlled by MHC, as indicated by the IgG subclass patterns induced by TNP-BSA in MHC congenic strains (Table II). As shown, TNP-BSA stimulates different amounts of total IgG but the same IgG subclass patterns in mice of different MHC haplotype, indicating that preferential production of IgG subclasses is not controlled by MHC haplotypes.

DISCUSSION

This study's major finding is that the patterns of IgG subclasses stimulated by antigens are controlled by MHC

TABLE II

IgG subclass distributions of TNP-BSA responses[a]

Strain	Ig	MHC	PFC/10^6 Spleen Cells (SE Factors)		% Total IgG		
			Direct	Indirect	IgG1	IgG2	IgG3
C57BL/6N	a^2	b	8 (1.4)	451 (1.2)	56	38	6
C57BL/10J	a^2	b	4 (1.2)	415 (1.1)	60	32	8
B10.D2	a^2	d	15 (1.5)	3,210 (1.3)	52	35	13
B10.A	a^2	a	5 (1.3)	625 (1.3)	53	40	7
B10.AKM	a^2	m	25 (1.3)	9,375 (1.2)	48	36	16
B10.RIII	a^2	r	6 (1.2)	550 (1.1)	51	42	7
B10.M	a^2	f	15 (1.1)	4,600 (1.2)	49	37	14

[a] IgG TNP-specific PFC were numerated in mice 5 days after the final administration of TNP-BSA. IgG subclass distributions were determined by normalizing values of IgG subclass producing lymphocytes with sum totals of all IgG subclasses.

and Ig allotype-linked genes. These controls were found to have different characteristics. MHC-linked genes were found to nonselectively control the IgG subclasses stimulated by TD antigens, whereas Ig allotype-linked genes preferentially controlled the IgG1 and Ig2b subclasses stimulated by all antigens. Ig allotype-linked genes but not MHC-linked genes cause antibodies of restricted IgG subclass.

Antibodies of restricted IgG subclass have been explained at the cellular level by contrasting schemes of B cell differentiation. On the one hand, uncommitted B cells may be induced to differentiate into cells making certain isotypes by interactions of exogenous antigen and helper T cells (6–8, 25–27). The discovery of the T cell derived-factor B cell stimulatory factor-1 supported the theory that isotypes were regulated by exogenous stimuli because this factor was initially reported to enhance IgG1 responses only (28). However, B cell stimulatory factor-1 now appears to stimulate antibodies restricted to subclasses other than IgG1 and thus may not inherently restrict B cell isotype expression (29, 30).

Antibodies of restricted IgG subclass may also be caused by mechanisms operating in the B cell alone. B cell subsets might be precommitted to making certain IgG subclasses and to expressing other cell surface activation components that might interact with exogenous stimuli to cause B cell differentiation and induction of IgG subclasses (1–5).

Processes of these contrasting schemes of B cell differentiation may be controlled by genes linked to either MHC or Ig allotype. Indeed, allotype-linked genes but not MHC-linked genes are found by this study to preferentially control IgG subclasses and thus may control processes of B cell differentiation that cause antibodies of restricted IgG subclass. Furthermore, B cell rather than T cell functions are likely to be controlled by Ig allotype-linked genes because IgG1 and IgG2b responses to both TD and TI antigens were found to be linked to Ig allotype. Therefore, this study suggests that B cell isotype precommitment processes may be linked to Ig allotype.

It is not surprising that nonrandom patterns of IgG subclass expression are controlled by Ig allotype-linked genes since controls of T cell and B cell functions are located in and near Igh. Genes located distal to Igh (31) and genes in close proximity to Igh (32) are known to control T cell functions. These genes, however, appear to control structures of antigen-specific T cell receptors and thus probably are not controlling helper T cells that restrict IgG subclass expression. Inherent controls of antibody expression such as switch site regions located adjacent to structural C_H genes, which may selectively influence isotype switch events (33), and controls of B cell Fc receptors located distal to Igh (34) may function early in development without T cell help to inherently induce isotype precommitment.

Allotype-linked genes must be polymorphic to cause strain-dependent patterns of IgG subclass expression. The IgG1 and IgG2b patterns of isotype expression detected in this study correlate with polymorphisms in switch site lengths. In BALB/cAn the longest switch site region is the $\gamma 1$ switch site. In C57BL/6N one of the longest switch sites is the $\gamma 2b$ switch site (35). This study found that high IgG1 but low IgG2b expression is linked to the BALB/cAn Ig allotype, whereas low IgG1 but high IgG2b expression is linked to the C57BL/6N Ig allotype. There may be no cause-and-effect relationship between such polymorphisms and the strain-dependent IgG subclass patterns found by this study. Even so, regions that may be critical to B cell isotype regulation are polymorphic in BALB/cAn and C57BL/6N. Such polymorphisms as found in switch site regions or in other regions of isotype control located near Igh might influence the development of lymphocytes precommitted to making certain isotypes, allowing antigens to stimulate allotype-linked IgG subclass patterns.

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