ASSOCIATION OF H-2 TYPES WITH GENETIC CONTROL OF IMMUNE RESPONSIVENESS TO IgG (γ2a) ALLOTYPES IN THE MOUSE

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Immune responses of mice and guinea pigs to several antigens are under the control of immune response (Ir) genes linked to the major histocompatibility locus of the species (specifically to the H-2 in the mouse) (1-12).

We have recently described one such gene (*Ir-IgA*) which controls the immune response of mice to allotypic and idiotypic determinants on IgA myeloma proteins derived from BALB/c mice (1). Analysis of inbred, congenic, and recombinant mice suggests that *Ir-IgA* is associated with K region specificities of the H-2 locus and thus resembles *Ir-1*, the gene described by McDevitt and Chinitz (10) controlling the immune response to a series of branched-chain amino acid polymers.

As was described previously (13) the immune response to the allotypic and idiotypic determinants of BALB/c myeloma proteins is only detected in strains of mice whose immunoglobulins do not share all the allotypic determinants of BALB/c. The allotypic determinants are located in the constant region of the heavy chain and the genes controlling these determinants constitute a linked series for each of the immunoglobulin heavy chains for which allelic variants have been described.

Thus the action of the Ir genes controlling the immune response to γA could only be observed in mice of different allotype linkage groups than the BALB/c.

In this paper we will show the immune response to γG (γ2a) myeloma proteins of the BALB/c mouse is also dependent on an H-2-linked Ir gene. This gene (*Ir-IgG*) is linked to different H-2 specificities than is the *Ir-IgA*. The immune response to γG is similar to γA inasmuch as there is a dual control involving the H-2 linked Ir gene and the gene for the allotypic determinants. This was demonstrated by the analysis of the immune response to BALB/c γG myeloma proteins (MOPC 173 and LPC 1) of mice of various H-2 types from five different immunoglobulin linkage groups.

Materials and Methods

BALB/c Myeloma Proteins Used for Immunization.—IgG (γ2a) myeloma proteins MOPC 173 (M173) and LPC 1 and IgA myeloma proteins MOPC 467 (M467) and MOPC 406 (M406), all of BALB/c origin, were obtained from Dr. Michael Potter, NIH. The IgG myeloma proteins have heavy-chain constant region (C_H) allotypic determinants $G^{1, 6, 7, 8}$ as well as idiotypic determinants on the Fab piece. The idiotypic determinants are myeloma specific. The M467 carry C_H allotypic determinants $A^{12, 13, 14}$ in addition to the (Fab) idiotype.

Preparation of Myeloma Proteins Used for Immunization.—The preparation of myeloma

proteins has been previously described for the IgA (1) and was essentially the same for IgG myeloma proteins M173 and LPC 1.

Inbred and Congenic Mouse Strains.—The inbred strains were obtained from Animal Production Section, NIH, and Jackson Laboratory, Bar Harbor, Maine. H-2 congenic strains were obtained from the Jackson Laboratory except for B10.P strains, which were obtained from Dr. Jack Stimpfling, McLaughlin Research Institute, Columbus Hospital, Great Falls, Mont. All F_1 progeny were bred in this laboratory.

32 strains of mice from five different linkage groups of immunoglobulin heavy chains were immunized separately with the myeloma proteins M173 and M467 where indicated. In the mouse, C_H allotypic determinants have been identified on four different immunoglobulin classes: IgG (γ2a), IgH (γ2b), IgF (γ1), and IgA (13). The C_H determinants are controlled by closely linked genes in a single chromosome region. Alleles of each of these genes have been found and characteristic sets of C_H genes make up the five linkage groups indicated in Table I.

The mice immunized with BALB/c M173 myeloma protein either had all the allotypic determinants ($G^{1,6,7,8}$), three determinants ($G^{6,7,8}$), two determinants ($G^{7,8}$), one determinant (G^{8}), or no determinants (G^{-}) similar to those present on the myeloma protein.

Immunization.—The method of immunization has been described (1) and was the same for

TABLE I

Immunoglobulin Heavy-Chain Linkage Groups of Inbred Strains

Prototype inbred strains	Immunoglobulin heavy-chain linkage group*	Abbreviation of heavy-chain group
BALB/c	$G^{1,6,7,8}H^{9,11}F^{f}A^{12,13,14}$	a1
C57BL/6	$^{2}G\text{-}H^{9,16}F^{s}A^{15}$	a2
DBA/2	$G^{3,8}H^{9,11}F^{f}A^{-}$	a3
A/He	$^{4}G^{6,7,8}H\text{-}F^{f}A^{13}$	a4
NH	$G^{5,7,8,}H^{9,11}F^{f}A^{14}$	a5

* Genes G, H, F, and A control C_H specificities on γG (γ2a), γH (γ2b), γF (γ1), and γA, respectively.

all the strains used. Each mouse received four subcutaneous injections each containing 75 μg of the specific myeloma protein at 3- to 4-day intervals distributed over six sites; two footpads, two axillary areas, and two inguinal areas. The same sites were used for all subsequent injections. The first injection was given in complete Freund's adjuvant, second in incomplete Freund's adjuvant, and all subsequent injections were administered in saline. Sera were collected from individual mice (infraorbital sinus) 1 wk after the fourth injection and tested for antibody. If no antibody was found, additional injections of the myeloma protein were administered at weekly intervals. The sera were tested for antibody 1 wk after each injection. A total dose of 600 μg of myeloma proteins (eight injections of 75 μg each) was given over a period of 2 months before immunization was discontinued.

Antibody Assay.—Each antiserum was tested for antibody to allotypic and idiotypic specificities by passive hemagglutination (14) and by precipitation in double agar-gel diffusion plates. Antisera reacted to the immunogen (IgG-M173 or IgA-M467, respectively) may identify allotypic and idiotypic determinants. Antisera reacted to a different myeloma of the same class (IgG-LPC 1 or IgA-M406) identifies only the allotypic determinants.

RESULTS

The immune responsiveness of mice was determined by examining their immune sera for antibodies to allotypic constant region heavy-chain deter-

minants and myeloma-specific (Fab) idiotypic determinants. Antisera were reacted to the specific immunogen (M173) and also to a different myeloma protein (LPC1) of the same immunoglobulin class. Anti-M173 antisera reacted to M173 may identify both allotypic and idiotypic determinants, whereas when reacted to LPC1 only the allotypic determinants may be identified (13).

TABLE II

Immune Responsiveness to BALB/c γG (γ2a) Myeloma Proteins (M173 and LPC 1) in Mice of Various H-2 Types Sharing All or Some Allotypic Determinants With the BALB/c Immunizing Myeloma Protein (M173)

Ig heavy-chain linkage group	IgG-C_H determinants	H-2	Strain	No. of mice	Number with precipitating antibody		Log 2 HA titer	
					M173	LPC1	M173	LPC1
a1	$G^{1,6,7,8}$	b	129/SN	20	0	0	0	0
"	"	d	BALB/c	20	0	0	0	0
"	"	k	C57BR/cd	20	0	0	0	0
a4	$G^{6,7,8}$	a	A/J	10	0	0	1.1	0.6
"	"	a	A/HeN	16	0	0	0.8	0.5
"	"	b	A.By	14	0	0	13.0	1.3
"	"	d	NZW	5	0	0	0.5	0.3
"	"	k	AKR	10	0	0	1.7	1.4
"	"	s	A.SW	10	10	1	14.2	3.6
a5	$G^{7,8}$	k	CE	8	0	0	0	0
"	"	?	DE	8	0	0	0	0
a3	G^{8}	b	D1.LP	17	4	0	8.40	6.5
"	"	d	DBA/2	9	0	0	0.66	0.33
"	"	k	RF	8	0	0	0	0
"	"	q	DBA/1	18	0	0	0	0
"	"	q	SWR	9	0	0	2.9	0.77
"	"	r	RIII	8	1	0	7.8	8.37

Antisera reacted to the M173 immunogen may identify both (C_H) allotypic and (Fab) idiotypic determinants. Antisera reacted to LPC1 identifies only the allotypic determinants.

Immune Responsiveness of Inbred and Congenic Strains of Mice of Different H-2 Types Having All or Some IgG C_H Allotypic Determinants Similar to the BALB/c Myeloma Protein Used for Immunization.—In mice of the a1 linkage group of immunoglobulin heavy chains, the C_H allotypic determinants of the donor myeloma protein (BALB/c) and the recipient mice immunized are similar. The H-2 types of the two strains other than BALB/c were $H\text{-}2^b$ and $H\text{-}2^k$, and neither gave a measurable response. No antibody was produced to the Fab idiotypic specificities on the IgG myeloma protein used for immunization (M173) (Table II, group a1).

Six strains of the a4 immunoglobulin heavy-chain linkage group comprising 65 mice of H-2 types a, b, d, k, and s were tested. The mice have $G^{6, 7, 8}$ determinants similar to those present on the BALB/c myeloma protein used for immunization. The high responders A.By ($H\text{-}2^b$) and A.Sw ($H\text{-}2^s$) produced high titers of hemagglutinating antibody (13.0 and 14.2 [log 2], respectively) directed mainly to the idiotypic specificity. Only the A.Sw mice made precipitating antibody and this was directed to the idiotype. A low response was obtained in mice with H-2 types a, d, and k.

In mice of the a5 immunoglobulin heavy-chain linkage group three strains have been identified. The H-2 type of only one strain CE ($H\text{-}2^k$) is known. The two strains available for testing CE ($H\text{-}2^k$) and DE ($H\text{-}2^?$) have $G^{7, 8}$ Ig C_H determinants similar to those on the immunizing myeloma protein. No antibody to either the C_H allotypic or Fab idiotypic determinants was produced.

In the six strains of the a3 immunoglobulin heavy-chain linkage group of H-2 types b, d, k, q, and r and comprising 69 mice, only the G^8 allotypic determinant was shared by the BALB/c myeloma protein used for immunization. A high response was found in $H\text{-}2^b$ and $H\text{-}2^r$ types; a low response was found in d, k, and q. The high responders D1.LP ($H\text{-}2^b$) and RIII ($H\text{-}2^r$) produced hemagglutinating antibody to idiotypes and allotypes (Table II). Some D1.LP also produced precipitating antibody to the idiotype.

Immune Response of Inbred and Congenic Mice of Different H-2 Types That Have None of the IgG C_H Allotypic Determinants That Are Present on the BALB/c Myeloma Protein Used for Immunization.—14 inbred and congenic strains comprising 140 mice of H-2 types a, b, bc, d, k, p, r, s, and v were examined for antibody to idiotypes and allotypes on BALB/c IgG myeloma proteins (M173 and LPC1) (Table III). All the strains were from the a2 immunoglobulin heavy-chain linkage group and shared no IgG-C_H determinants in common with the immunizing BALB/c myeloma protein. A high response was associated with H-2 alleles b, bc, p, r, s, and v; a low response was associated with a, d, and k. The high responders, B10, B6, LP, B10.129 (6M), B10.P, B10.y, LP.RIII, SJL, and SM, produced hemagglutinating antibody to allotypes and idiotypes. The range of HA titers, however, varied considerably among some strains with the same H-2 allele. For example, among strains with $H\text{-}2^b$ allele B/Ka gave a fairly low response (3.6), B10 a higher response (7.28), and LP a very high response (12.83).

Precipitating antibody was only found in selected strains and was always accompanied by high titers of hemagglutinating antibody. However frequently hemagglutinating antibody was obtained with little precipitating antibody as in B10 and B10.y strains. Within selected strains the number of mice producing precipitating antibody was high. These included LP (19/19), B10.P (5/6), LP.RIII (10/15), SJL (8/8), and SM (3/5). In other responsive strains fewer mice produced precipitating antibody; these included B10 (1/15), B6 (5/18),

B10.129 (6M) 4/10, and B10.y (1/5). Antibodies produced by the latter group only identified the idiotype.

Thus in the presence of favorable H-2 types: (*a*) no anti-idiotype antibody was produced when allotypic determinants were the same for the strain immunized and the myeloma protein used for immunization; and (*b*) alternatively, anti-idiotype antibody was produced when differences existed in allotypic determinants. For anti-allotype antibody production, however, differences in

TABLE III

Immune Responsiveness to BALB/c IgG Myeloma Proteins (M173 and LPC 1) in Mice of Various H-2 Types Sharing No Allotypic Determinants with the Immunizing Myeloma Protein (M173)

H-2	Strain	No. of mice	Number with precipitating antibody		Log 2 HA titer	
			M173	LPC1	M173	LPC1
a	B10.A	9	0	0	2.88	2.77
b	B10	15	1	0	7.28	6.83
b	B6	18	5	1	6.50	5.12
b	B/Ka	10	0	0	3.60	3.40
b	LP	19	19	17	12.83	10.0
bc	B10.129 (6M)	10	4	1	9.12	6.75
d	NBL	8	2	0	3.87	3.87
d	B10.D2	10	0	0	1.20	1.20
k	B10.BR	8	0	0	2.0	2.0
p	B10.P	6	5	2	11.33	8.66
p	B10.y/J	5	1	0	7.60	6.80
r	LP.RIII	15	10	8	9.0	8.50
s	SJL	8	8	8	10.87	10.25
v	SM	5	3	0	8.83	8.16

All mice were of the a2 heavy-chain linkage group of immunoglobulins and shared no IgG allotypic determinants with the myeloma proteins used for immunization. Antisera reacted to the M173 immunogen may identify both (C_H) allotypic and (Fab) idiotypic determinants. Antisera reacted to LPC1 identifies only the allotypic determinants.

at least three allotypic specificities between the recipient strain and the immunizing myeloma protein were required.

H-2 Alleles Associated with Ir-IgG and Ir-IgA Genes.—The H-2 alleles associated with the *Ir-IgG* and *Ir-IgA* genes controlling immune responsiveness to IgG and IgA BALB/c myeloma proteins respectively, are shown (Table IV). The H-2 alleles linked to the *Ir-IgA* have been previously reported (1) with some new data presented here. The H-2 type of the strains are indicated in the table. Mice were all of the a2 linkage group of immunoglobulin heavy chains which have no IgG or IgA allotypic determinants in common with the BALB/c IgG and IgA myeloma proteins used for immunization.

The *Ir-IgG* gene is associated with H-2 types b, bc, p, r, s, and v.

The *Ir-IgA* gene is associated with H-2 types a, k, m, p, r, and s.

Progeny Tests of Ir-IgG for Autosomal Dominance.—Immune responsiveness to BALB/c IgG myeloma protein M173 was tested in progeny of four different crosses of high and low responder strains (Table V).

In the first cross (B10.A × LP), the B10.A is a poor responder to γG, whereas the LP is a good responder. Neither parental strain shared any allotypic determinants with the BALB/c myeloma protein used for immunization. The progeny of this cross (B10.A × LP) gave a high response (Table V) indi-

TABLE IV

H-2 Alleles Associated with Ir-IgG and Ir-IgA Genes Controlling Immune Responsiveness to IgG and IgA Allotypes, Respectively

H2	IgG		IgA	
	M173	LPC1	M467	M406
a	L*	L	H	H
b	H	H	L	L
bc	H	H	L	L
d	L	L	L	L
k	L	L	H	H
m	NT	NT	M	L
p	H	H	H	M
q	L	L	L	L
r	H	H	H	H
s	H	H	H	M
v	H	H	L	L

* L = low; H = high; M = medium; NT, not tested.

Antisera reacted to the M173 immunogen may identify both (C_H) allotypic and (Fab) idiotypic determinants. Antisera reacted to LPC1 identifies only the allotypic determinants. Antisera reacted to M467 immunogen may identify both allotypic and idiotypic determinants, whereas when reacted to M406 only may identify allotypic determinants.

TABLE V

Immune Response to BALB/c IgG Myeloma Proteins (M173 and LPC 1) of F_1 Progeny from Crosses between High and Low Responder Mice

Female		Male	Ir-IgG	H-2 types	IgG determinants	No. of progeny	HA Titers (log 2)	
							M173	LPC1
B10.A	×	LP	L × H	a × b	$G^- \times G^-$	17	15.3	10.2
C57BL/6	×	A	H × L	b × a	$G^- \times G^{6,7,8}$	10	4.3	0.6
LP	×	A	H × L	b × a	$G^- \times G^{6,7,8}$	6	3.3	2.1
SJL	×	A	H × L	s × a	$G^- \times G^{6,7,8}$	10	3.6	0.4

Antisera reacted to the M173 immunogen may identify both (C_H) allotypic and (Fab) idiotypic determinants. Antisera reacted to LPC1 identifies only the allotypic determinants.

cating that the *Ir-IgG* was a dominant autosomal gene. Antibody directed to both idiotypic and allotypic determinants was produced.

In the three other crosses (B6 × A), (LP × A), and (SJL × A), the paternal strain in each cross contributed $G^{6,7,8}$ allotypic determinants to the progeny. The γG BALB/c myeloma protein used for immunization carries allotypic $G^{1,6,7,8}$ determinants. The only difference therefore between the IgG allotypic determinants of the progeny of these three crosses and the immunizing myeloma protein was the G^1 determinant. The immune response of all these progeny was low and it appeared that the introduction of the $IgG^{6,7,8}$ allotypic determinants into the F_1 mice markedly diminished the immune response.

DISCUSSION

The immune responsiveness to IgG allotypes (BALB/c myeloma proteins) was shown to be under the control of an *Ir-IgG* gene associated with specific H-2 types. H-2 types b, bc, p, r, s, and v were high responders; a, d, k, and q were low responders. The congenic B10 strains were particularly useful in demonstrating the association of H-2 and *Ir-IgG* genes. B10 ($H\text{-}2^b$), B10.129 (6M) ($H\text{-}2^{b,e}$), and B10.P ($H\text{-}2^p$) were high responders; B10.A ($H\text{-}2^a$), B10.D2 ($H\text{-}2^d$), and B10.Br ($H\text{-}2^k$) were low responders. All these strains are of the same Ig genotype and share no IgG-C_H determinants with BALB/c.

Production of homologous antisera to mouse immunoglobulin allotypes is dependent not only on the H-2 type of the recipient but also on differences in genes that control heavy-chain determinants between the donor (BALB/c IgG myeloma proteins) and the recipient strains. BALB/c IgG myeloma proteins carry myeloma specific Fab idiotypic determinants in addition to C_H allotypic determinants. When C_H allotypic determinants were the same for the myeloma protein immunogen and the strain immunized, no antibody was produced to the (Fab) idiotype. When two to three allotypic determinants were similar to those present on the BALB/c myeloma proteins used for immunization, antibody specificities were directed only to the idiotype. However, when only one or no C_H allotypic determinants were similar to the immunizing BALB/c myeloma protein, antibody was directed to both the allotypic and idiotypic specificities.

In mice of $H\text{-}2^b$ type where no IgG C_H determinants were similar to BALB/c, the immune response varied over a broad range. LP gave a very high response, B10 and B6 a more moderate response, and B/Ka a fairly low response (Table III). These findings suggest that additional factors (genetic or nongenetic) other than the H-2 are involved in the degree of immune responsiveness.

Another interesting observation was the ability of selected strains to produce precipitating antibody. All LP mice produced precipitating antibody to the allotype and idiotype. B10 mice rarely produced precipitating but did make hemagglutinating antibody to the allotype and idiotype. Both strains are $H\text{-}2^b$ types and are of the same immunoglobulin genotype. Precipitating anti-

body was accompanied by high titers of hemagglutinating antibody. Frequently, however, high titers of hemagglutinating antibody were detected without precipitating antibody. The specificities of both these antisera appeared to be similar (data not shown). The possibility that some of these differences may be due to different classes of antibodies is being investigated.

No antiserum prepared with myeloma proteins has been found that identified allotypic determinants without also identifying idiotypic determinants. Frequently, however, antisera may identify idiotypic determinants alone. The latter was especially apparent in the congenic strains. Examples are the A.Sw and A.By strains which produced antibodies essentially to only the idiotype. All the A.Sw mice also made precipitating antibody which on immunoelectrophoresis showed mobility characteristic of 7S immunoglobulins.

The *Ir-IgG* gene was shown to be a dominant autosomal gene. A high response was obtained in (B10.A × LP)F_1 progeny from a cross of low (B10.A) and high (LP) responder strains. The progeny from three other crosses, (B6 × A), (LP × A), and (SJL × A), gave low immune responses. In each cross the $G^{6,7,8}$ allotypic determinants were contributed by the paternal strain immunoglobulin. The BALB/c IgG myeloma protein used for immunization carries $G^{1,6,7,8}$ allotypic determinants and the only difference between the immunoglobulins of the progeny immunized and the immunizing myeloma protein was the G^1 allotypic determinant. However, the presence of three shared allotypic determinants between the F_1 progeny and the immunizing myeloma protein appeared to greatly diminish the immune response. With continuing immunization following the prescribed eight doses, a moderate immune response was finally obtained in the progeny of these three crosses (data not shown).

SUMMARY AND CONCLUSION

Immune responsiveness to IgG allotypes in the mouse was found to be controlled by an immune response gene *Ir-IgG* linked to the H-2 locus. This was demonstrated by the analysis of the immune response to BALB/c IgG (γ2a) myeloma proteins in mice of various H-2 types from five different linkage groups of immunoglobulin heavy chains. Antisera were examined for antibodies to idiotypic (Fab) and allotypic (Fc) specificities. No immune response to BALB/c IgG myeloma proteins was found in mice with the same heavy-chain immunoglobulin linkage group as BALB/c but of different H-2 types. In mice with immunoglobulin heavy chains that are different than BALB/c, a high immune response to IgG myeloma proteins was found in H-2 types b, bc, p, r, s, and v; a low response in a, d, k, and q. The *Ir-IgG* gene is controlled by a dominant autosomal gene.

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