GENETICS OF THE IDIOTYPE OF BALB/c
MYELOMA S117: MULTIPLE CHROMOSOMAL LOCI FOR
VH GENES ENCODING SPECIFICITY
FOR GROUP A STREPTOCOCCAL CARBOHYDRATE*

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Idiotypic polymorphism has been demonstrated among inbred strains of mice using various antigen-antibody systems or antigen-binding myeloma proteins (reviewed in reference 1). Genetic analysis revealed that idiotype expression in inbred mice is inherited according to Mendelian rules, and is controlled by genes linked to the heavy chain constant region (C\text{\textsubscript{H}}) genes which determine the allotypes (2-5). Therefore, these genes are believed to be heavy chain variable region (V\text{\textsubscript{H}}) Genes. The chromosomal region which contains the C\text{\textsubscript{H}} and V\text{\textsubscript{H}} genes (the \text{Ig-1} complex) appears to be important in the control of specific antigen recognition not only by B cells but also by T-helper cells (6).

We have in recent years investigated the genetics of a V\text{\textsubscript{H}} gene controlling the idiotype of antibodies to Group A streptococcal carbohydrate (A-CHO)\textsuperscript{1} in strain A/J mice (2, 7). This gene has been termed A5A\textsuperscript{+} according to the lymphocyte clone A5A which secreted the original antibody to which anti-idiotypic antisera were first produced (8). In this paper we describe the genetic control of the idiotype of the A-CHO-binding BALB/c myeloma protein S117 (9), which provides a convenient V\text{\textsubscript{H}} gene marker for antibodies to A-CHO in this strain. In breeding experiments the S117 and A5A idiotypes segregate as if controlled by allelic genes. The distribution of both markers in various recombinant mice, however, suggests that they map at nonhomologous, pseudoallelic positions in the \text{Ig-1} complex.

Materials and Methods

Mice. BALB/c mice were obtained from Zentralinstitut für Versuchstierzucht, Hannover, Federal Republic of Germany. Inbred strains A/J, RF/J, DBA/1J, DBA/2J, C57L/J, 129/J, C57BL/
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6J, C3H/HeJ, CBA/J, and the AKXL and BXD lines were obtained from the Jackson Laboratory, Bar Harbor, Maine. AL/N mice were obtained from Dr. Michael Potter, NIH, Bethesda, Md., and BAB14 mice were obtained from Dr. Martin Weigert, Philadelphia, Pa. and from Dr. Olli Mäkelä, Helsinki, Finland. BB7 mice (formerly called BBkJ) were maintained in our animal facilities in Cologne.

Myeloma Tumors and Proteins. Plasmocytoma S117 was kindly given to us by Dr. Melvin Cohn, Salk Institute. S117 protein (IgA/K) was isolated from ascites by affinity chromatography on p-aminophenyl-N-acetyl-glucosamine coupled to Sepharose 2B, an immunoadsorbent which is also used to isolate induced antibodies to A-CHO, as previously described (8). Plasmocytomas MOPC315 and TEPC15, as well as ascites from mice bearing plasmocytoma J539 were obtained from Dr. Michael Potter.

Isolation of Antibody A5A. Antibody with A5A idiotype is isolated from the sera of irradiated A/J mice which have been reconstituted with 1 × 10⁷ pooled normal A/J spleen cells and subsequently immunized with Group A streptococcal vaccine (Strep.A) (8).

Anti-Idiotype Antibodies. Anti-idiotype antibodies to purified S117 were prepared in guinea pigs (xeno-ΔS117), and in AL/N mice (allo-ΔS117). The preparation of xeno-ΔS117 was done as previously described (9), except that the guinea pig antisera were absorbed on Sepharose 2B-coupled IgA/K myeloma protein J539. Allo-ΔS117 was prepared by the method of Potter and Lieberman (10) and also absorbed on Sepharose 2B-coupled J539.

Determination of Idiotype. The determination of idiotypic antibody employed a solid-phase radioimmune assay (11, 12). Polystyrol tubes (Greiner, Solingen, W. Germany) were coated with 0.5 ml of xeno-ΔS117 in a dilution previously determined to bind an optimal proportion of 25 ng purified radiolabeled S117 (~30%). After incubation for 90 min at 37°C the antiserum was replaced by 1:10 diluted normal rabbit serum (NRS) for 60 min at 37°C. The radioiodinated S117 was then added to the tube together with various inhibitors including anti-A-CHO antibodies in serial dilutions. The tubes were rocked in horizontal position overnight at 37°C, rinsed twice with 10% NRS, and the remaining radioactivity was counted.

Determination of Allotype. Anti-allotype antisera distinguishing Ig-1α and Ig-1β allotypes were prepared by cross-immunization between strains A/J and BALB/c (13). Allotypes of individual mice were determined by inhibition of passive hemagglutination. Allotype-casted sheep red blood cells (SRBC) were prepared by incubating SRBC for 1 h at 37°C with subagglutinating concentrations of anti-SRBC antisera of the appropriate strains. This was followed by 10 min incubation with 0.25% glutaraldehyde; a 1 min incubation with 1 M lysine, both in Hanks’ balanced salt solution; and three washes in phosphate-buffered saline containing 1% (wt/vol) bovine serum albumin. All other allotypes were taken from the literature (13, 14). The recent subdivision of the Ig-1β allotype into two groups (15) is accounted for by the symbols Ig-1β+ and Ig-1β-.

Previously Described Methods. The following methods, procedures, and materials have been previously described: The isolation of normal immunoglobulin from mouse serum (8, 16) or guinea pig serum (8, 16), the preparation of streptococcal vaccines from lyophilized streptococcal cultures (17) (gift from Dr. R. M. Krause, NIH, Bethesda, Md.) and the immunization of mice (8), the radioiodination of proteins and carbohydrates (8, 18), the determination of anti-A-CHO antibodies by a modified Farr assay (8, 19), and the determination of idiotype by an indirect radioprecipitin test using a rabbit anti-guinea pig IgG antiserum for precipitation (7).

Results

Strain Distribution of the S117 Idiotype. The BALB/c myeloma protein S117 has been shown to have specificity for terminal β-linked N-acetyl-glucosamine residues (9), which are the major antigenic determinants of A-CHO (20), and to which antibodies can be elicited by immunization with Strep.A (17). It was therefore not unreasonable to assume that idiotypic determinants would be shared between this myeloma protein and antibodies elicited with Strep.A in mice.

Using the solid-phase radioimmune assay, antibodies with idiotypic determinants of myeloma protein S117 could be clearly shown to exist in BALB/c mice immunized with Strep.A. As shown in Fig. 1, the binding of radioiodinated S117
to anti-idiotypic antibody raised in a guinea pig (xeno-$\alpha$S117) is inhibited most efficiently by cold S117 itself but clearly also by antisera from BALB/c mice immunized with Strep.A. The inhibitory effect of such antisera can be removed by absorption on $N$-acetyl-glucosamine-coupled Sepharose 2B, indicating that the antibody to A-CHO was the inhibitory component. The binding is not inhibited by BALB/c normal serum, by sera from BALB/c mice immunized with lactic dehydrogenase or with Group C streptococci, or by sera from BALB/c mice bearing myeloma tumor J539. Thus, inhibition of S117 idiotypic binding is restricted to antibodies with specificity for A-CHO.

The lower frame of Fig. 1 shows examples of inhibition curves obtained when antisera to A-CHO from various strains were used as inhibitors. Antisera from 129/J mice inhibit as well as do antisera from BALB/c mice. Weaker inhibition is seen with antisera from strain RF/J, whereas no inhibition is obtained with antisera from strain A/J. Thus, the appearance of antibodies with S117 idiotypic determinants is a strain-specific character.

Table I summarizes the inhibition data on a greater panel of inbred strains.
Table I
Strain-Specific Expression of S117 Idiotypic Determinants, as Detected by Xeno-αS117 and by Allo-αS117

| Strain     | Ig-1 | % Inhibition by 1 µg anti-A-CHO* | Xeno-αS117‡ | Allo-αS117§ |
|------------|------|---------------------------------|-------------|-------------|
| BALB/c     | a+   | 27,35,10,40,43,43,38             | 16,24,35    |             |
| C58/J      | a+   | 15,35,46,23,35,30,34             | 24          |             |
| C57L/J     | a+   | 40,20,44,37                      | 18          |             |
| 129/J      | a+   | 40,23,43,34                      | 21,17       |             |
| DBA/1J     | c    | 17,14,6,35,0                     | 8,32        |             |
| DBA/2J     | c    | 10,30,24,6,0                     | 15,19       |             |
| RF/J       | c    | 14,13,25,0,0                     | 11          |             |
| CBA/J      | a−   | 0,0,0,0                          | 0,0         |             |
| C3H/HeJ    | a−   | 3,7,0,9,3                        | 0,0         |             |
| C57BL/6J   | b    | 0,0,0,0                          | 0,0         |             |
| A/J        | e    | 0,0,0,0                          | 0,0,0       |             |
| AKR/J      | d    | 0,0,0,0                          | NT†         |             |
| AL/N       | d    | 0,0,0,0                          | NT          |             |

* At least three points were determined, and the inhibition by 1 µg antibody was extrapolated from the curve.
‡ Antisera from individual mice were tested.
§ Antisera from individual mice or pooled antisera were tested. These were not the same as those tested with xeno-αS117.
|| NT, not tested.

whose antibodies were analyzed for their capacity to inhibit the binding of radioiodinated S117 to xeno-αS117 and to allo-αS117. It is apparent that all strains bearing the Ig-1c haplotype showed strong inhibition, strains bearing Ig-1c haplotype showed weak inhibition whereas strains of the Ig-1 haplotypes a−, b, e, and d had no inhibitory capacity. The same strain-specific patterns are observed using anti-idiotypic antisera of allogeneic and xenogeneic origin. Other strains whose data are not shown in the table and which are negative for S117 idiotypic determinants are A.SW (Ig-1e), C57BL/10, B10.A, B10.D2, B10.BR, and B10.S(7R) (all Ig-1b). Data on these strains have been published in another context (6).

When the data in Table I are reconciled together with those previously obtained on the strain distribution of the A5A idiotype, five different idiotypic phenotypes of antibodies to A-CHO can be distinguished. The idiotypic characteristics of the antibodies of the reference strain for each of the phenotypes are represented by the inhibition data in Fig. 2. Each of the strains A/J, DBA/2J, and C57BL/6J represents a distinct Ig-1 allele or group of alleles with a characteristic idiotypic phenotype. Strains BALB/c and C57L/J both share the same Ig-1 allele yet are distinct by their idiotypic phenotypes. Idiotype phenotypes that possess the same inhibitory capacity as the reference strains A/J or BALB/c are referred to as A5A+ and S117+, respectively. Idiotype phenotypes with antibodies that possess an inhibitory capacity which is incomplete as compared to that of the reference strains are referred to as A5Acr and S117cr, respectively.
Linkage of the S117 Idiotype to Allotype. Linkage analysis was performed using two series of recombinant inbred (RI) lines and breeding experiments. One of the RI series, AKXL, is derived from crosses between strains AKR/J and C57L/J (21). The data of 17 different AKXL lines are summarized in the upper part of Table II. Three to six mice of each strain were analyzed after immunization with Strep.A for the expression of S117 and A5A idiotypic determinants, and it was found that each strain carrying the $Ig-1^a+$ allele of the progenitor strain C57L/J expressed the idiotypic phenotype which is characteristic for this strain, whereas each strain carrying the $Ig-1^d$ allele of the progenitor strain AKR/J was negative for both idiotypes.

The second series of RI strains, BXD, is derived from crosses between C57BL/6J and DBA/2J (22). Since the latter is only weakly cross-reactive for both idiotypes (see Fig. 2 and Table I) the results of typing these strains are somewhat less reliable than that of the AKXL lines. As shown in the lower part of Table II, 3 out of a total of 18 tested BXD strains showed unexpected phenotypes and the question of recombination in these strains is presently under investigation. Strain BXD-25 (three mice tested) had the $Ig-1^b$ allele of the parent C57BL/6J, yet had antibodies cross-reactive with both A5A and S117 like the other parent DBA/2J. Strain BXD-20 (three mice tested) and strain BXD-27 (five mice tested) had the $Ig-1^c$ allele of the DBA/2J parent and produced antibodies with the A5A$^c$ idiotype. Both strains, however, were negative for S117 idiotypic determinants like the other parental strain C57BL/6J. In addition, both strains expressed antibodies with the NIP-NP fine specificity marker.
**TABLE II**

**Linkage analysis in RI Lines**

| RI lines* (and progenitor strain) | Phenotype | Parental no. | Recombinant† no. |
|----------------------------------|-----------|--------------|------------------|
| (C57L/J, AKXL-4,6,11,13,14,16,18,19,-21,29,36) | a+ cr§ + | 11 |
| (AKR/J), AKXL-8,24,25,28,37,38 | d – – | 6 |
| (DBA/P2J), BXD-6,11,15,16,18,24,30 | c cr cr§ 7 |
| B × D-20,27 | c cr – 2 |
| (C57BL/6J), BXD-2,5,8,14,19,21,22,29 | b – – 8 |
| BXD-25 | b cr cr 1 |

Total 35 lines 32 3

* Three to six mice of each line tested.
† On the basis of the 3 recombinants among the 18 BXD RI lines the estimated distance between Ig-1 and the A5A cr idiotype locus is 0.0152, and between A5A cr and S117 cr is 0.0304. Inclusion of the AKXL RI negative data would approximately halve these distances. However, there is no assurance that the same structural elements are segregating in the two groups of RI lines.
§ Strain carries idiotypic determinants weakly cross-reactive with that of the reference strain of C57BL/6 parent (T. Imanishi, personal communication). These results strongly suggest that the Ig-1 complexes of strain BXD-20 and BXD-27 originate from recombinational events between VH genes of strains C57BL/6J and DBA/2J. In general, although recombinant phenotypes are observed, the analyses of the RI strains indicate the linkage of genes that control the idiotypic phenotypes of the strains AKR/J, C57L/J, C57BL/6J, and DBA/2J to the Ig-1 complex.

Linkage analysis also employed breeding experiments, but these were designed particularly to increase the chance of finding S117-positive recombinants. Allotype heterozygous offspring from a backcross (A/J × BALB/c)F1 × BALB/c were crossed with each other such that all chromosomes have had two changes of recombination. The data on these breeding experiments are summarized in Table III. It is clear from the data that in this strain combination the A5A + and S117 + markers segregate like alleles similar to the segregation of the allotypes to which they are linked. There is, however, quite a high frequency of recombinant phenotypes which is similar to that previously reported for the A5A idiotype in a conventional backcross experiment (1). The offspring of breeding pair no. 6 is particularly interesting since all the Ig-1 cr homozygotes had a recombinant phenotype. This is compatible with the occurrence of recombination at the first backcross generation in this family.

**Allocation of Genes Specifying the S117 and A5A Idiotypes to More than One Locus Within the Ig-1 Complex.** Multiple loci for VH genes encoding specificity for A-CHO are readily demonstrated by recombinational events between them. For the genes A5A + and S117 + there are two relevant recombinant lines known, one of which separated all thus far known VH genes from the Cg genes (BAB14) and the other separated the A5A + gene from all other known VH genes and from the Cg genes (BB7). Table IV summarizes the data from this and other laboratories on these two recombinant haplotypes and the parental haplotypes which
TABLE III

Linkage Analysis in Progeny from Intercrosses between Allotype-Heterozygous Offspring of a Backcross (A/J × BALB/c)F₁ × BALB/c

| Breeding pair | No. of offspring | Phenotype | Parental* | Recombinant† |
|---------------|-----------------|-----------|-----------|--------------|
|               |                 | Ig-1      | a/a       | e/a          | e/e          | a/a | e/e |
| A5A           |                 | (+)       | (+)       | (+)          | (+)          |     |     |
| Sl17          |                 | (+)       | (+)       | –            | (+)          |     |     |

1 38 7 22 8 1
2 29 9 16 4
3 24 1 15 7 1
4 21 8 8 5
5 18 2 10 5 1
6 12 4 5 1
7 10 1 7 1 1

Total 152 32 83 30 2 5

* Occasional mice which did not express an expected idiotype were grouped as parental since not all parental mice express idiotype.
† Only allotype homozygous mice which positively expressed an unexpected idiotype were grouped as recombinant. Thus, the number of recombinant opportunities (twice [number of families plus number of mice]) is 82 for A5A and 84 for Sl17. The recombinant frequency between Ig-1 and A5A is estimated to be 0.024 (2/82), and the corresponding estimate for Ig-1 and Sl17 is 0.036 (3/84). The family with three recombinants (breeding pair 6) is scored as a single crossover having occurred in the backcross generation.

TABLE IV

Recombinant Ig-1 Haplotypes Suggesting Nonhomologous Positions of the Sl17 and A5A Loci in Different Ig-1 Complexes

| Strain      | Ig-1 | T15 | J558 | ARS | Sl17 | A5A |
|-------------|------|-----|------|-----|------|------|
| BALB/c      | a    | +   | +    | –   | –    | –    |
| C57BL/Ka    | b    | –   | –    | –   | –    | –    |
| A/J         | e    | –   | –    | +   | –    | +    |
| BAB/14      | b    | +‡  | +    | –   | +‡   | –    |
| BB7         | a    | +‖  | +‡   | –   | +‡   | +    |

* Data in this column are from reference 4.
‡ This result was communicated to us by Dr. M. Potter. It is in contrast to previously published data (3).
§ Six BAB14 and six BB7 mice were tested and found positive for Sl17 idiotype.
‖ We thank Dr. Rose Lieberman, NIH, Bethesda, Md., for performing this analysis. The other data in this column are from reference 3.
¶ We thank Dr. Roy Riblet, Institute for Cancer Research, Philadelphia, Pa., for performing this analysis. The other data in this column are from reference 5.

Gave rise to them. BAB14, arisen from a cross between strains C57BL/Ka and BALB/c, possesses the Ig-1 gene from the former in combination with all thus far known V₃ genes from BALB/c. This includes the T15 gene, which was previously thought to be of C57BL/Ka type (M. Potter, personal communication). Strain BB7 arose from a cross between strain A/J and BALB/c and this strain possesses the A5A gene of A/J in combination with all other BALB/c
genes including $S_{17}^+$. According to formal genetic rules, and unless an unequal crossing over has occurred, this is only possible if $A_5A^+$ and $S_{17}^+$ are at nonhomologous positions.

As was mentioned above (see Table II), the results on the putative recombinant lines BXD-20 and BXD-27 also suggest that genes encoding A-CHO specificity may be at more than one locus in the $Ig-1$ complex. The $Ig-1^c$ haplotypes at these strains appear to have lost the $S_{17}^{cr}$ gene without losing the $A_5A^{cr}$ gene. This suggests that in the DBA/2 genotype the antibodies carrying $A_5A$ and $S_{17}$ idiotypic determinants are coded for by two different genes in the $Ig-1$ complex, which is in agreement with our unpublished observation that the two antibody populations are separate. Furthermore, and most striking, the BXD-20 and BXD-27 recombinants suggest an order for the $A_5A^{cr}$ and $S_{17}^{cr}$ loci which is the reverse of that of the $A_5A^+$ and $S_{17}^+$ genes in the BB7 recombinant. As the latter appears to indicate a location for the $S_{17}^+$ gene between the $Ig-1$ locus and the $A_5A^+$ gene, the former suggests the $A_5A^{cr}$ gene to be between $S_{17}^{cr}$ and $Ig-1$. Taken together, the results on the various recombinant lines suggest that genes specifying the idiotypic characteristics of antibodies to A-CHO may be present on at least four distinct loci within different allelic $Ig-1$ haplotypes.

Discussion

The present study adds a new $V_H$ genetic marker to the rather extended library of such markers known to date. In addition, the $S_{17}$ idiotypic system provides a unique and new type of information when reconciled together with the $A_5A$ system (1, 2, 7). Both idiotypic systems are associated with antibodies to the same haptenic group, N-acetyl-glucosamine, which can be elicited by immunization with Group A streptococci (8, 17). Yet neither idiotypic system cross-reacts with the other. Hence, using the two idiotypic systems, $V_H$ genes in various $Ig-1$ haplotypes encoding different anti-A-CHO antibodies can be identified. All of the previous studies on idiotypic polymorphism have been limited to the identification of genes in only one haplotype.

Using the two idiotypic systems, five different idiotypic phenotypes of antibodies to A-CHO can be clearly distinguished in inbred mice. Our data and results from other laboratories suggest that in general a given $Ig-1$ haplotype is associated with a single idiotypic phenotype such that all strains that carry the same $Ig-1$ complex express the same idiotypic phenotype regardless of their genetic background. We have, however, found the $Ig-1^{as}$ haplotype associated with two distinct idiotypic phenotypes such that strain C57L appears to differ from all other testing $Ig-1^{as}$ strains. This suggests that the degree of polymorphism of the $V_H$ genes is possibly greater than that of the $C_H$ genes.

In our linkage studies we found that each of the five idiotypic phenotypes is controlled by genes in the $Ig-1$ complex. Therefore, and because the idiotypic characteristics of an antibody reside in its variable region, it is assumed that genes encoding the structure of the $V_H$ region specify the idiotypic phenotypes of mouse antibodies.

In this as well as in previous studies it has been found that genes specifying idioype can genetically separate from genes specifying allotype (5) and also
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from genes specifying other idiotypes (23, 24). This has been interpreted as recombinational events between \( V_H \) and \( C_H \) genes or between \( V_H \) genes (5, 23, 24) and is in full agreement with a model of discontinuously arranged \( V \) and \( C \) genes in the \( \text{Ig-1} \) complex (1).

The present report augments these observations in suggesting that \( V \) genes which serve the same antigen-binding specificity may be at several different loci in different \( \text{Ig-1} \) haplotypes. The evidence for this is threefold: (a) The \( A5A^+ \) and \( S117^+ \) genes, associated with the \( \text{Ig-1}^+ \) and \( \text{Ig-1}^\ast \) allotypes, respectively, recombine onto one chromosome in strain BB7. (b) \( A5A^\ast \) and \( S117^\ast \) occur together in the \( \text{Ig-1}^c \) haplotype and appear to represent separate genes because only \( S117^\ast \) is lost in the BXD-20 and BXD-27 RI strains. (c) The BB7 recombinant suggests the order of genes to be \( \text{Ig-1}, S117^+, A5A^+ \), whereas the BXD-20 and BXD-27 recombinants suggest the partially reversed order \( \text{Ig-1}, A5A^\ast, S117^\ast \). Thus, each of the gene pairs \( A5A^+/S117^+, A5A^+/A5A^\ast, A5A^\ast/S117^\ast \), and \( S117^+/S117^\ast \) can be allocated to nonidentical loci in the \( \text{Ig-1} \) complex.

It is obvious that the nonidentical location of such genes allows their expression as "allotypes" as well as "isotypes" in individuals or strains carrying various forms of recombinant haplotypes. This is readily demonstrated by strain BB7 which expresses \( A5A^+ \) and \( S117^+ \) as isotypes, whereas the two parental strains BALB/c and A/J expressed the same genes as allotypes. A similar situation is observed in strains DBA/2 and RF/J which express the genes \( A5A^\ast \) and \( S117^\ast \) as isotypes, and it is conceivable that the \( \text{Ig-1} \) complexes of these strains originated from crossovers between two \( \text{Ig-1} \) complexes that carried these genes as pseudoalleles.

Nonhomologous and pseudoallelic \( \text{Ig-1} \) complexes could have either evolved in geographically separated mouse populations or could be the result of multiple unequal crossing overs due to frequent mismatching of chromosomes in the \( \text{Ig-1} \) complex. Mismatching could very well be a frequent event here because of the possibly extended repetitions of very similar genes in this chromosomal region. If this were the case, even originally homologous \( \text{Ig-1} \) complexes would rapidly evolve into nonhomologous ones and the \( \text{Ig-1} \) complexes of inbred strains would be rather unstable in spite of homozygocity. As we cannot discriminate between such different pathways of evolution, the contemporary situation appears to be the result of some unusual evolutionary history possibly unique to immunoglobulin genes. This is also in agreement with structural data on seemingly allelic immunoglobulin products whose numbers of amino acid differences are incompatible with simple allelic relationships (25).

Finally we like to stress the use of our pseudoallelic idiotypic markers for studying various aspects of the genetic control of immune recognition. In recent work, these genetic markers have been used to study the genetic control of antigen recognition by B and T cells, exploiting our discovery that both kinds of cells respond to anti-idiotypic antibody (6, 26, 27). Along the same line are experiments in progress that deal with the idiotypic properties of T-cell receptors and the use of our anti-idiotypic reagents for their identification. Finally, the S117 idiotypic system may be useful for studying the ontogeny of diversity in a defined antigen-antibody system, since a constant clonal constituent of a rather heterogenous response can be easily identified.
Summary

A small proportion of the antibodies to Group A streptococcal carbohydrate (A-CHO) elicited in BALB/c mice by immunization with Group A streptococci, has idiotypic determinants in common with the BALB/c myeloma protein Sl17 which has specificity for N-acetyl-glucosamine, the major antigenic determinant of A-CHO. The expression of these idiotypic determinants is under the control of a gene which is linked to the Ig-I*+ allotype locus in strain BALB/c and in other strains carrying the same Ig-I haplotype. This gene (S117+) segregates in breeding experiments as if it were an allele to the gene A5A+ which controls the expression of the A5A idiotype in association with antibodies to A-CHO in strain A/J and which is linked to the Ig-Ic allotype locus. Another possible allele, linked to the Ig-Ic allotype locus, controls the expression of both Sl17 and A5A cross-reactive determinants (S117cr, A5Acr). The distribution of these idiotypic determinants in various lines that carry recombinant Ig-I haplotypes suggests that the A5A and S117 loci are nonallelic and map at different positions in the Ig-I region. The data suggest complex pseudoallelic relationships between different Ig-I haplotypes that allow the expression of the same genes in allelic and in nonallelic fashion.

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