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Immunology

Shared idiotopes among antibodies encoded by heavy-chain variable region (V_H) gene members of the J558 V_H family as basis for cross-reactive regulation of clones with different antigen specificity

(cross-reactive idiotype/heavy-chain variable region framework regions/neonatal idiotype suppression)

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ABSTRACT **A wide idiotype cross-reactivity was observed among six groups of monoclonal antibodies specific for arsonate and nitrophenyl haptens, hemagglutinin of PR8 and X31 influenza viruses, dextran, A48-idiotype, and a set of six monoclonal antibodies with unknown antigenic specificity. All of these antibodies are encoded by heavy-chain variable region (V_H) genes belonging to the J558 V_H family. This idiotypic cross-reactivity was determined by studying the binding of these antibodies to a panel of six monoclonal anti-idiotype antibodies, each one raised against a member of the six groups of monoclonal antibodies. The administration at birth of two such monoclonal anti-idiotype antibodies induced a long-lasting suppression not only of the corresponding idiotype but also of V_H-related idiotypes with different antigenic specificities. These results suggest that the idiotypes encoded by V_H genes that belong to the same V_H gene family are interactive one with another. The possible physiological consequences of this immunochemical cross-reactivity are discussed.**

Not long after idiotypes were shown to be the phenotypic markers of variable region (*V*) genes, Oudin and Cazenave (1) demonstrated that antibodies with different antigenic specificities could share cross-reactive idiotopes. Such antibodies were designated by Jerne as "parallel sets" (2). During the course of our studies on idiotypy, we encountered several examples of parallel sets. They include the identification of the dominant E109 IdX and J558 IdI expressed on β2-1 fructosan- and dextran-binding antibodies, respectively, on immunoglobulins devoid of these antigen specificities in maternally idiotype suppressed mice (3, 4). We also found that idiotypes were shared among antibodies specific for various epitopes of the hemagglutinin (HA) of PR8 influenza virus (5), and even among antibodies specific for the HA of different strains of virus such as PR8 (H1N1) and X31 (H3N2) (6). Similarly, we found the 384-idiotype (Id), borne by MOPC384, a myeloma protein specific for a methyl β-galactoside—the immunodominant sugar of *Salmonella* tranaroa lipopolysaccharide—on various monoclonal antibodies specific for glucose and galactose immunodominant sugars of *Escherichia coli* 0113B lipopolysaccharide (7). Finally, cross-reactive idiotypes (CRI) expressed on anti-arsonate antibodies and β2-6 fructosan-binding proteins (A48-Id) were identified on monoclonal antibodies devoid of these antigenic specificities obtained from mice injected with the respective anti-Id antibodies (8, 9). We proposed several hypotheses to explain those occurrences (5, 7). In this paper, we tested the most plausible explanation—namely, that these CRI expressed on antibodies with such vastly different specificities result from the conservation of a region of DNA within the *V* genes that encoded these antibodies. To test this hypothesis, we studied the cross-reactive binding of anti-Id antibodies to monoclonal antibodies specific for dextran (10), arsonate (Ars), the HA of PR8 virus, and anti-A48-Id antibodies. All these monoclonal antibodies are encoded by heavy-chain variable region (V_H) genes that belong to the J558 V_H family. This assignment was based on DNA or amino acid sequence homology (11, 29), and in the absence of those data, by hybridization using RNA or Southern blotting techniques with germ-line gene probes derived from known members of the J558 V_H family (i.e., 36-65, B1-8) (4, 12–14). Some of these anti-Id antibodies administered at birth caused a long-lasting suppression of corresponding idiotype as well as of V_H-related idiotypes with different specificity.

MATERIALS AND METHODS

Mice. One-day-old C57BL/6 and BALB/c mice were obtained in our animal facilities by breeding adult mice obtained from The Jackson Laboratory.

Monoclonal Antibodies. The monoclonal antibodies used in this study are the following: anti-PR8 HA, PY211 (13); anti-X31 HA, PY206, XY102, XY108 (13); anti-Ars, 36-71, 31-62, 44-10, 45-248, 36-65, 307100 2-9, hV_H65-8, hV_H65-5, A6-51.2, A6-50-1, A6-56.2, A-6-13-1, A6-12-2, hV_H65-202, 2dX3-8, 3AH, 2dX3-8, A7-62.1.1, 2C2-1, 2Ab7-8-11, 45-273, 45-49 (12, 15); anti-NP, MS, B1.8, 15-1, 124-4, R8/6, 124/29.1, 28/16.8, B1.48, S43 (11, 16); anti-dextran, MOPC104E, J558, Hdex2, Hdex14 (17); unknown antigen specificity, NWSM 5-13, NWSM 18-6, LP32-14, LP32-24, MPC11, 1F-6 (4, 15, 17); A48-UPC 10Id, IDA 10, IDA 23, IDA 27, 150-9, 25-12 (14).

Monoclonal Anti-Id Antibodies. The monoclonal anti-Id antibodies used in this study are described in the text and were all affinity-purified from the corresponding idiotype-Sepharose column. A1DA 23-2 was kindly donated by P. Legrain (Pasteur Institute, Paris), and CD3-2 was donated by J. Kearney (University of Alabama, Birmingham).

Radioimmunoassays. The presence of CRI was determined by a sensitive sandwich assay as described (6). Briefly, the microtiter plates were coated for 1 hr at 37°C with the test monoclonal antibodies (5 μg/ml) in carbonate buffer (pH 9.2), washed three times, and then incubated at room temperature for 1 hr with 3% bovine serum albumin. After extensive washing, the plates were incubated overnight at 4°C with anti-Id antibodies (20 μg/ml), again washed exten-

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Abbreviations: Id, idiotype; CRI, cross-reactive idiotype; V_H, variable region of heavy chain; HA, hemagglutinin; Ars, arsonate; NP, 4-hydroxy-3-nitrophenyl.

sively, and then incubated for 2 hr at room temperature with ^{125}I-labeled idiotype-bearing antibodies.

The presence of anti-dextran and anti-4-hydroxy-3-nitrophenyl (NP) antibodies was determined in a sandwich assay by measuring the binding of ^{125}I-labeled rabbit anti-λ antibodies to microtiter plates coated with Type I bacterial dextran B1355S (30) or NP chicken immunoglobulin, whereas anti-bacterial levan was measured with ^{125}I-labeled monoclonal rat anti-k antibody on bacterial levan-coated plates. The concentrations of these antibodies were determined from the linear portion of standard curves obtained with purified proteins: J558 specific for dextran, 2-1-1 specific for levan, and B1-8 specific for NP, as described (18).

The presence of the J558 IdX, B1.8 IdX, and J606 IdX was determined by inhibition competition radioimmunoassays as described (18). The concentration of idiotype-bearing antibodies was determined from the linear portion of standard curves obtained with J558, B1.8, and J606.

Neonatal Idiotype Suppression. One-day-old BALB/c or C57BL/6 mice were injected on days 1, 3, and 5 with 100 μg of purified monoclonal anti-Id antibodies. After 6 weeks, the BALB/c mice were injected i.p. with 100 μg of dextran B1355S or with 20 μg of levan and the C57BL/6 mice were injected with 100 μg of NP-Ficoll and 20 μg of levan in saline. The mice were bled on day 7 after antigen challenge. The concentration of both antigen-specific antibodies as well as J558, B1.8, and J606 idiotype-bearing immunoglobulins was determined on the samples obtained from individual mice.

RESULTS

CRI Expressed on Monoclonal Antibodies Specific for a Variety of Antigens Encoded by V_H Genes Members of the J558 V_H Family. The expression of CRI by monoclonal antibodies with diverse specificities was studied by analyzing a panel of 28 monoclonal antibodies specific for Ars encoded by a single V_H gene (12), 10 monoclonal antibodies specific for NP and 4 specific for dextran classified in the J558 family based on sequence homology (11, 17), 3 monoclonal antibodies specific for the X31 influenza virus HA and one for the PR8 influenza virus HA encoded by V_H genes hybridizing with the J558 germ-line gene probe (13), 5 monoclonal antibodies devoid of dextran-binding activity encoded by V_H genes that belong to V_H J558 family (4, 17), and 5 monoclonal anti-A48-Id antibodies encoded by V_H genes that hybridize with V_H B1.8 (14).

The expression of six CRI was analyzed in this study and they were detected by the following six monoclonal anti-Id antibodies: syngeneic SN3-9A specific for the PY206 antibody (anti-X31 HA) (13), allogeneic CD3-2 specific for the J558 IdX (19), xenogeneic (rat) AD8 specific for the CRI of Ars antibodies (20), syngeneic AC146 and 14-4 specific for the B1.8 and MS idiotype, respectively, of anti-NP antibodies (16, 22), and A1DA 23-2, a syngeneic anti(anti-A48-Id) antibody specific for IDA23, which is an anti-A48-Id antibody (21).

As can be seen in Table 1, we analyzed the binding of each of these monoclonal anti-Id antibodies to the six prototypical Id-bearing monoclonal antibodies for the six CRI being studied. The SN3-9A anti-PY206-Id antibody bound at significant levels to all six monoclonal antibodies. CD3-2 anti-J558 IdX bound J558, 36-65, PY206, and weakly to IDA 23. AD8 anti-Ars CRI bound 36-65 and B1.8. 14-4 anti-MS idiotype bound to all but the 36-65 monoclonal antibody, while AC146, specific for B1.8 idiotype, bound to all, including T15, which is from the V_H S107 family and X24 from the V_H X24 family. Finally, A1DA 23-2 the anti-IDA23 anti(anti-A48-Id) bound to all the monoclonal antibodies, including J606 from the V_H J606 family and X24 from the V_H X24 family. In every case, where binding was observed to non-V_H J558 family members, the magnitude of this interaction never exceeded that of the weakest binding V_H J558 monoclonal antibody.

We next extended our studies on the cross-reactive binding of these six anti-Id to the panel of 59 monoclonal antibodies. The data presented in Table 2 show the fraction of monoclonal antibodies from each of six groups interacting with six monoclonal anti-Id antibodies. Id-positive antibodies were considered those that exhibited at least 5-fold higher binding than those monoclonal antibodies exhibiting a binding similar to background level (100–300 cpm).

These results suggested that some monoclonal antibodies with different specificities are serologically related to one another. The vast majority of these antibodies are encoded by V_H genes belonging to a single V_H family; however, these data do not preclude the possibility of idiotypic sharing between members of different V_H families.

The DNA or protein sequences for the V_H genes or V_H regions, respectively, of some of the antibodies included in our studies were compared to the J558 V_H sequence. The degree of homology existing between the CDRs and the framework segments is presented in Fig. 1. These results show that the highest degree of DNA or protein sequence homology was observed in the framework two or three segments of the V_H region.

At this point, it should be mentioned that Ars-BGG, NP-caproic acid, and A48 monoclonal antibody in a concentration range of 0.001–10 μg/ml, could not significantly

Table 1. Binding of anti-Id antibodies to prototype idiotype-bearing antibodies with various antigen specificities encoded by V_H genes belonging to V_H J558 family and to other antibodies belonging to various V_H families

	Anti-Id–Id system					
Microtiter plates coated with	SN3-9A PY206*	CD3-2 J558*	AD8 36-65*	A1DA-23-2 IDA23*	14-4 MS*	AC.146 B1.8*
PY206*	29,832 ± 2025	1,483 ± 171	191 ± 32	982 ± 303	1933 ± 197	2246 ± 671
36-65*	4,652 ± 1293	5,082 ± 62	2931 ± 649	1051 ± 145	125 ± 103	1374 ± 281
IDA23*	6,359 ± 350	651 ± 48	56 ± 12	4378 ± 128	3367 ± 208	864 ± 153
J558*	4,008 ± 334	22,683 ± 3,010	85 ± 10	3952 ± 299	3321 ± 45	2618 ± 387
B1.8*	8,216 ± 619	ND	1006 ± 34	2076 ± 173	3298 ± 566	2081 ± 329
MS*	13,734 ± 1376	ND	ND	435 ± 185	8699 ± 587	1772 ± 62
J606	71 ± 86	45 ± 53	199 ± 72	961 ± 451	460 ± 75	303 ± 2
T15	484 ± 494	247 ± 19	108 ± 46	342 ± 179	345 ± 106	794 ± 46
X24	121 ± 50	13 ± 1	265 ± 68	891 ± 89	185 ± 44	554 ± 64
MOPC460	35 ± 2	26 ± 14	3 ± 5	198 ± 38	466 ± 311	496 ± 12

J606 is from V_H 606 family; T15 is from V_H S107 family; X-24 is from V_HX-24 family; MOPC460 is from V_H 36-60 family; ND, not done.

*Antibodies of V_H subgroup III encoded by V_H genes belonging to V_H J558 family.

Table 2. Fraction of monoclonal antibodies with various antigen specificities encoded by V_H gene members of V_H J558 family exhibiting CRI specificity

Anti-Id antibody	Idiotype	Specificity of monoclonal antibodies					
		Arsonate	Influenza virus HA	Dextran	NP	A48-Id	Unknown
I4-4	MS (NP)	44-10	PY206, PY211 XY102	Hedex 2, J558	28/16-8, B1.48 MS	IDA23, IDA10 150-9 IDA-17	NWSM 5-13 MPC11
		(1/28)	(3/4)	(2/4)	(3/9)	(4/5)	(2/6)
AC146	B1.8 (NP)	44-10	PY206	Hedex14, MOPC104 J558	124/4 R8/6, 124.29.1 B1.48, B1.8, MS	IDA10, 150-9 25-12	LP32-14 NWSM 18-16 LP32-24
		(1/28)	(1/4)	(3/4)	(6/9)	(3/5)	(3/6)
SN3-9A	PY206 (X31 HA)	36-71, 31-62 44-10, 36-65	PY206, PY211 XY102, XY108	Hedex14, J558 Hedex2	15.1, 543, 124-40 R8/6, 124.29.1 28/16.8, B1.48 B1.8 MS	IDA10, 150-9 25-12, IDA17 IDA23	LP32-14, LP32-24 NWSM 5-13 MPC11
		(4/28)	(4/4)	(3/4)	(9/9)	(5/5)	(4/6)
AD8	36-65 V_H (Ars)	31-62, 45-248 36-65, 45-223 307-1002-9 hVH65-5, hVH65-8 hVH65-17, A6 12-1 32.2872, A613-1 A612.2, A651.8 36-71			S43, 124.29.1 B1.48, B1.8	IDA10	1F6 NWSM 18-6
		(14/28)	(0/5)	(0/5)	(4/9)	(1/5)	(2/6)
CD3-2	J558 (Dextran)	36-71, 31-62 45-208, 36-65 45-223, 45-49 2c2.1, 2ab 7-8	PY206, PY211 XY108	Hedex14, J558 Hedex2, MOPC104	15-1, R8/6 129.29.1, B1.8		1F6 MPC11
		(8/28)	(3/4)	(4/4)	(4/9)	(0/5)	(2/6)
A1DA23-2	IDA23 (Anti-A48-Id)	44-10, 36-65	PY211	Hedex14, MOPC104 Hedex2, J558	124.4, 543 28, 116.8, B1.48 B1.8	IDA23, IDA10 150-9, 25-12	LP32-14 NWSM 18-16 NWSM 5-13 MPC 11
		(2/28)	(1/4)	(4/4)	(5/9)	(4/5)	(4/6)

In this experiment, EB7.2, a monoclonal antibody specific for J558 IdI, bound to only J558. Numbers in parentheses represent fraction of antibodies in each group displaying at least 5-fold higher activity compared to background (100–300 cpm). In this experiment, we also detected binding of only the CD3-2 and A1DA23-2 antibodies to normal BALB/c immunoglobulins at levels of 2.5 μg/ml and 1.0 μg/ml, respectively.

inhibit the cross-reactive binding of the AD8, 14-4, AC146, and A1DA 23-3 monoclonal antibodies, respectively, to any of the antibodies exhibiting an antigen specificity not associated with the homologous idiotype system (data not shown).

Neonatal Suppression of Anti-Dextran and Anti-NP Antibody Responses Induced with Anti-Id Antibodies. In an attempt to determine whether this broad immunochemical idiotypic cross-reactivity observed with these anti-Id antibodies had any functional significance, we used them in a protocol to induce neonatal idiotypic suppression of the B1355S dextran response and the anti-NP response. The data presented in Table 3 show the results of this study. BALB/c mice that were immunized with either dextran or bacterial levan showed a strong specific inhibition of only their anti-dextran response and the corresponding J558 IdX when the animals were treated at birth with CD3-2 and SN3-9A monoclonal anti-Id antibodies or a partial inhibition in animals treated with AC146.

The strong suppressive effect of neonatal treatment with SN3-9A could be related to the strong binding of this anti-Id antibody to idiotypes shared by dextran and NP-binding antibodies. The data of competitive inhibition RIA illustrated in Fig. 2 show that the binding of PY206 to SN3-9A was strongly inhibited by NWSM5-13 and MS and was partially inhibited by Hedex 14, MPC11.

The partial inhibition of the anti-bacterial levan response observed in BALB/c mice treated with A1DA23-3 can be attributed to the suppression of the A48-Id$^+$ component of this immune response by the activation of anti-A48-Id clones. A1DA23-3 antibodies have been previously shown to elicit the production of antibodies against A48 regulatory idiotopes (23).

In C57BL/6 mice that were immunized with NP-Ficoll or bacterial levan, no significant differences were observed between the magnitudes of the anti-NP and anti-levan responses among the various groups of animals.

By contrast, a strong inhibition of the B1.8 idiotype was observed in animals treated at birth with AC146 and a weaker but significant inhibition with CD3-2 and SN3-9A monoclonal antibodies. No J606 IdX antibodies were detected in these mice, which is in agreement with a previous observation made by Lieberman *et al.* (24), who demonstrated the linkage of IdX G, B, and A to the C^a_H haplotype.

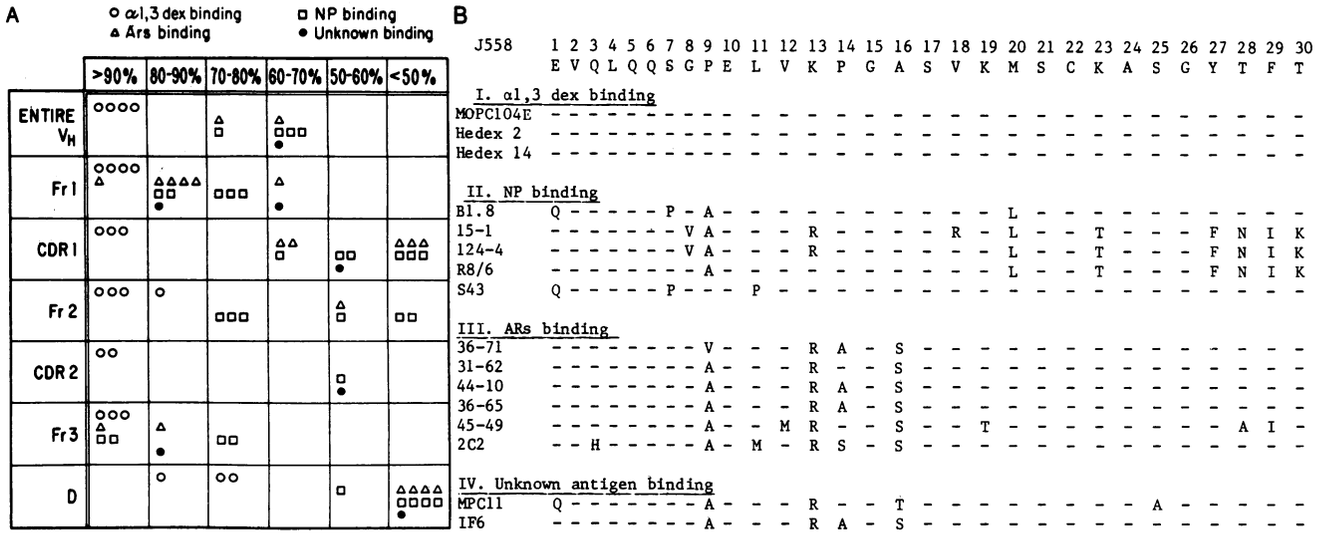

FIG. 1. Homology V_H sequences of antibodies with various antigen specificities encoded by V_H gene members of V_H J558 family. (*A*) Comparison with V_H J558 protein sequence. (*B*) A sample comparison of the sequences of framework (amino acids 1–30) and monoclonal antibodies with various J558 specificities. Amino acids are identified by the single-letter code.

DISCUSSION

The results presented in this communication demonstrate a wide idiotype cross-reactivity among antibodies with different antigen specificities. The strongest cross-reactivity was noted between antibodies encoded by V_H gene members of the V_H J558 gene family. In addition, the parenteral administration after birth of anti-Id antibodies, which demonstrate a cross-reactive binding to idiotypes expressed on antibodies with various antigen specificities, caused a long-lasting suppression of the antibody response against dextran in BALB/c mice as well as the corresponding J558 IdX. In C57BL/6 mice, the same administration after birth of anti-Id antibodies altered only the expression of the B1.8-IdX but not the magnitude of the anti-NP response.

The results raise three fundamental problems:

***(i)* CRI Shared by Antibodies with Various Antigen Specificities Appear as Antigenic Determinants Borne by the Framework Segments of the V_H Region.** The CRI detected by our set of monoclonal anti-Id antibodies are located on the V_H region of the immunoglobulin molecules and do not require the contribution of light-chain variable region (V_L) segments. Indeed, the anti-Id antibodies specific for J558 and B1.8 monoclonal proteins, which both use $V_L\lambda$ sequences, bound to the Ars-specific antibody 36-35, which uses V_k10 sequences, and to PR8 HA-specific PY211, which uses V_k21 light chain (13, 17). The converse was also true: the antibodies specific for PY206, IDA23, and 36-65 monoclonal proteins using V_L^k bound to anti-dextran and anti-NP antibodies using $V_L\lambda$ chain.

These data are in agreement with previous observations demonstrating that AD8 recognizes idiotypic determinants that do not depend on D, J_H, or V_L regions (25).

A comparison of the sequence of the J558 protein with sequences of the monoclonal proteins with different antigen specificities that bear these CRI suggests that these proteins exhibit the highest degree of homology in the framework II and III V_H regions. Furthermore, the structural basis for these CRI appears to be three-dimensional antigenic determinants rather than primary amino acid sequences because our sequence comparisons did not yield a common structural correlate accounting for these CRI.

***(ii)* Lack of Antigen and Idiotype Binding Dichotomy in the Paratope Universe of Immunoglobulin.** The serological definition of idiotypes by anti-Id antibodies led to the idea that immunocompetent cells are divided into two parallel repertoires, one devoted to the recognition of foreign antigens and the other to idiotypic recognition (or other antigenic deter-

Table 3. Effect of neonatal administration of anti-Id antibodies

Mouse strain	Antibody injected at birth	*N*	Antibody response, μg/ml		Idiotype response, μg/ml	
			α1-3 dextran	β2-6,β2-1 fructosan	J558-IdX	J606-IdX
BALB/c	nil	9	94.5 ± 39.4	118.6 ± 34.0	47.3 ± 5.1	20.7 ± 14.5
	AC146	3	34.0 ± 13.7	89.3 ± 20.7	7.3 ± 3.8	16.3 ± 8.9
	A1DA23-2	3	100.5 ± 18.3	40 ± 12.5	47.5 ± 11.8	18.0 ± 5.3
	SN3-9A	4	1.0 (3)	126.0 ± 31.7	2.5 (3)	43 ± 27
	CD3-2	3	<1	89.7 ± 37.6	<0.1	15.3 ± 6.8
	Anti-E109 IdX	6	77 ± 2.6 (4)	27.4 ± 44.4 (4)	84.8 ± 35.6	3.0 ± 1.4 (4)
			NP	β2-6,β2-1 fructosan		B1.8-IdX
C57BL/6	Saline	5	244.8 ± 48.3	93.4 ± 45.2		28.4 ± 6.2
	AC146	7	227.5 ± 67.5	83.2 ± 43.7		<0.3
	A1DA23-2	6	116.3 ± 17.1	89.0 ± 20.1		35.8 ± 5.3
	SN3-9A	7	192.0 ± 41.6	94 ± 33		13.9 ± 10.2
	CD3-2	3	177.3 ± 31.8	141.6 ± 20.1		10.6 ± 4.5

N, number of mice injected. Numbers in parentheses represent number of mice exhibiting complete suppression. Values shown are mean ± SEM.

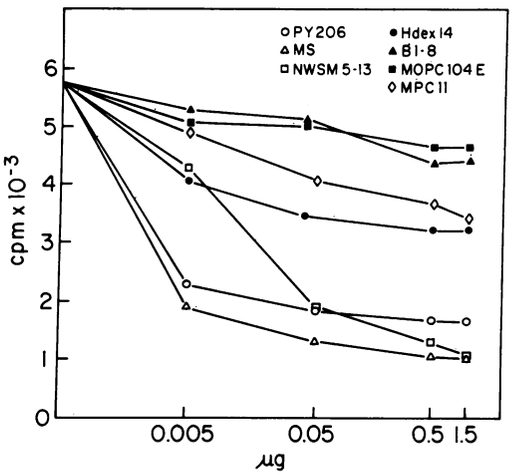

FIG. 2. Inhibition of binding of ^{125}I-labeled PY206 to SN3-9A monoclonal anti-PY206-Id antibodies by α1-3 dextran and NP-binding proteins as well as other J558 V_H-derived antibodies.

minants of immunoglobulin molecules). Utilizing IEF techniques, a clonotypic analysis was performed on the syngeneic anti-J558 antibodies produced by a large population of J558 immune BALB/c mice. In the antisera of individual mice, anti-Id clonotypes were observed that correspond to the expression of five to six clones. A careful comparison of the spectra of distinct clonotypes observed with many such mice revealed that within the BALB/c strain at least 100 clones are capable of producing anti-J558-Id antibodies (26). These data suggest that the anti-Id repertoire is as large as the antigenic repertoire. By contrast, our data clearly demonstrate the lack of this dichotomy in the antibody repertoire since the paratope of an immunoglobulin receptor cannot distinguish between three-dimensional structures of idiotopes and antigens that exhibit a certain degree of similarity, despite the fact that the affinity for one or another can differ. Indeed, we found that anti-Id antibodies specific for idiotypes borne by dextran-, NP-, or HA-specific antibodies bound to anti-A48-Id antibodies, which are encoded by V_H genes that are members of the J558 family. Furthermore, our anti(anti-Id antibody) (Ab3) specific for idiotopes of anti-A48-Id antibodies (Ab2) also bound to antibodies specific for various antigens (Ab1). The most likely explanation for this observation lies in a probable similarity in the sequence of the region of DNA encoding the idiotopes of anti-A48-Id Ab2s as well as antibodies specific for influenza virus HA, dextran, Ars, or NP (Ab1). Thus, a paratope of a given variable region can recognize a foreign or self-antigen and itself can be recognized by another paratope.

***(iii)* Cross-Reactive Regulation.** The existence of a self- and nonself-recognition by the same immune receptor implies that cross-reactive recognition could play an important role in the regulation of clonal expression. The findings presented in this communication demonstrate that the parenteral administration of anti-Id antibodies against antibodies with various specificities can profoundly alter the anti-dextran response in BALB/c mice. This coregulation was specific for clones bearing a CRI encoded by V_H genes from the J558 V_H gene family because the anti-fructosan antibody response was not affected. It is known that the antibody response to fructosans is encoded by genes that belong to the J606 (for β2-1 fructosans) and X24 (for β2-6 fructosan) V_H gene families. The idiotype neonatal suppression observed is probably related to a direct interaction of anti-Id antibodies with the immunoglobulin receptor of B-cell clones as we demonstrated previously by an inability to transfer the suppression with T cells (27) and by the fact that the suppression was also obtained by using nude mice (28). Our data demonstrate that idiotype-mediated cross-reactive regulation leads to cross-reactive inhibition of clones with different antigen specificities and that these CRI function as regulatory idiotopes (23).

Idiotype suppression obtained with some but not all anti-Id antibodies (i.e., SN3-9A for J558 IdX and CD3-2 for B1.8 IdX) could be related to the affinity of these anti-Id antibodies for CRI or, alternatively, these antibodies recognize germline encoded idiotopes.

The ability to induce cross-reactive regulation of clones with different antigen specificity represents an interesting finding for the understanding of hyperglobulinemia, which accompanies infectious diseases, and furthermore could provide a new insight in the studies of the pathogenesis of autoimmune diseases.

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