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REVIEW

Idiotypes and autoimmunity

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INTRODUCTION

When Jerne first proposed that antibodies and lymphocytes could interact with each other via their idiotypes, this marked the final rehabilitation of autoimmunity. Immunologists had come to see that autoimmunity did not necessarily produce autoimmune disease, and that autoimmune recognition was a corollary of self-tolerance. Now the network theory proposed that recognition of idiotypes on other lymphocytes was an integral part of immunoregulation. It is now fully established that idiotypic interactions do occur in the immune responses to external antigens and can modulate these reactions. It is also possible to manipulate immune responses by the use of idiotypes (Ids) and anti-idiotypes (anti-Ids), acting on B cells or any of the T cell subpopulations. Once the ground rules of network interactions were established by observing the responses to external antigens, attention turned to autoimmune responses. Investigations in this field have centred around three questions:

(1) Do particular idiotypes recur in particular autoimmune diseases, and if so, what does this say about the aetiology and pathogenesis of the disease?

(2) Do idiotypic interactions play a role in triggering or regulating autoimmunity?

(3) Is it possible to modulate autoimmune responses, either by perturbing an established regulatory network or by inducing novel regulatory interactions?

RECURRENT IDIOTYPES IN AUTOIMMUNE DISEASE

There are two main reasons for investigating whether particular Ids occur in different individuals with autoimmune disease. First, the recurrence of an Id suggests an association between the Id and autoantibody, and more pragmatically, idiotypic manipulation of autoimmune disease is more likely to succeed when the cognate Id is present on a large number of autoreactive lymphocytes, in different individuals. Essentially there are three possible explanations for recurrent idiotypes in the responses of different individuals to a single antigen. (a) If the level of a particular idiotype is small by comparison with the entire response to that antigen, then the presence of that Id may be coincidental, and unrelated to the autoimmunity. If however the Id constitutes a considerable proportion of the autoantibody response, then either (b) the individuals carry particular sets of immunoglobulin (Ig) variable domain genes which are preferentially selected during an autoimmune response, or (c) the nature of the epitope tends to induce antibodies with a particular grouping of amino acid residues in the paratope, and this is recognized by anti-Id. Since the antibody response to an antigen is determined both by the Ig repertoire available, and the antigen, both (b) and (c) may contribute towards an explanation of why some Ids recur in autoimmune disease.

These two explanations do however have different implications. If particular *V*, *D* or *J* genes are

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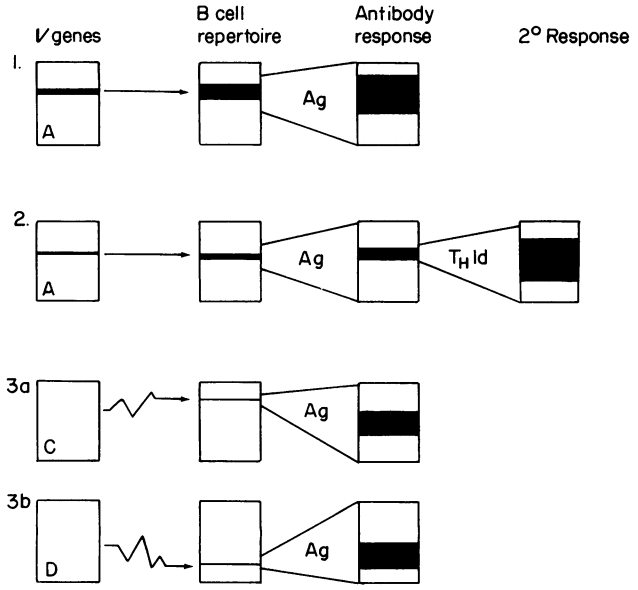

Fig. 1. Three explanations for the recurrence of particular Ids in immune responses to a single antigen. The idiotype bearing element is shaded black. (1) The individual's Ig *V* genes encode sequences which express the Id. This Id appears in the B cell repertoire and if antigen (Ag) stimulates that set of B cells, this Id will appear in the antibody response in different individuals of the same strain. (2) In some cases Id specific T helper cells (T_HId) can selectively expand Ids appearing in the primary response, so that they become dominant. (3) Individuals with different sets of Ig *V* genes (C and D) may generate antibodies with a common Id by the processes of somatic recombination and mutation. If the Id so generated binds the antigen, then the antigen will select the same Id from the repertoire in unrelated strains.

associated with autoantibodies, we must explain why they are retained in the germline. Idiotypes generated by germline *V* genes may be inside or outside the antibody paratope, but one would anticipate them to be restricted to strains or species with that set of genes. By contrast, if a particular paratope is associated with a specific autoantigen binding activity then the Id might recur in different strains or even different species (Fig. 1). Indeed one would expect the internal image anti-Id of a dominant autoantigenic epitope to bind to autoantibodies in many species (Jerne, Roland & Cazenave, 1982). With these considerations in mind, what happens in reality?

Anti-Ids have been raised both to the spontaneously occurring autoantibodies in human disease and their animal models, as well as to the antibodies induced in experimental autoallergic conditions (Roitt *et al.*, 1983, review). These studies have identified recurrent idiotypes in virtually all systems studied. The RIA and EIA techniques used to identify Ids in different individuals are usually based on the ability of sera to inhibit Id/anti-Id binding, and are very sensitive. Consequently the identification of a recurrent Id in the sera of different individuals does not mean that the Id is a dominant part of the autoantibody response. For example the idiotype D8 which recurs in CBA mice with EAT and is associated with auto-anti-thyroglobulin rarely constitutes more than 5% of the total autoantibody response (Male *et al.*, 1983). It is also tempting to assume that when an Id appears concommitantly with an autoantibody, the animal is expressing Id^+ autoantibody, but this may not be so. An example of this is the H130·Id expressed on a major proportion of anti-DNA antibodies of MRL-*lpr* mice. This Id appears in serum as the mice age, but levels of H130 do not correlate with anti-DNA or anti-cardiolipin titres, and most of the Id is on non-anti-DNA parallel sets (Rauch *et al.*, 1982). Sometimes the same Id can even occur on parallel sets of autoantibodies with different specificity (Lymberi *et al.*, 1985). These kinds of observation are consonant with immunoregulation of the parallel sets via a network.

ANTI-DNA

Another way of investigating recurrent Ids has been to generate monoclonals from different individuals and to see whether they share Ids, on the assumption that the spectrum of Ids generated in the experiment reflects that in the autoimmune response. This approach was first tried in NZB/W mice (Marion *et al.*, 1982) where 8/13 monoclonal anti-DNAs shared a common Id, but has since been extended to humans (Shoenfeld *et al.*, 1983; Zouali, Fine & Yquem, 1984; Rauch, Massicote & Tannenbaum, 1985). The first of these studies on patients showed that the majority of 60 anti-DNA monoclonals derived from seven systemic lupus erythematosus (SLE) patients expressed one or more recurrent idiotypes, while the second identified a single Id on all but one of 44 human myeloma antibodies checked for anti-DNA activity. One explanation for this remarkable incidence of recurrent idiotypes is that some particular set of germline genes is selected for the anti-DNA response in each patient. Evidence for this is seen in the recurrence of an Id on anti-DNA antibodies in normal relatives of SLE patients (Halpern *et al.*, 1985), but once again this Id is also found on other antibodies. In other experiments the finding of a single site associated Id on anti-DNA antibodies from NZB/Ws and in SLE sera (Eilat, Fischel & Zlotnick, 1985) suggests that some anti-DNA associated Ids are determined by the nature of the paratope rather than the individuals' genes, and this would also explain the high incidence of particular Ids in different individuals of the same species. It has been noticed that the spontaneous cationic anti-DNA molecules of different strains of mice share a public idiotype, which suggests that the unusual degree of idiotypic crossreactivity in these antibodies could be related to a peculiarity of the antigen (Hahn & Ebling, 1984). There is a similar finding in humans where a set of rheumatoid factors which react with DNA/histone share an idiotype (Agnello *et al.*, 1980). So, considering the recurrent Ids on anti-DNA, there is good evidence that intrastrain Ids associated with anti-DNA are probably related to the use of a limited set of germline genes for the anti-DNA, whereas the interstrain and interspecies recurrent Ids are selected by the antigen, which is highly charged and has a limited number of repeated epitopes.

The association of particular Id related Ig genes and autoantibodies, outlined above, touches on the *V* gene theory of autoimmune disease (Knight & Adams, 1982), but the relationship between the *V* genes, the Ids and autoimmunity is not causal. This has been demonstrated for example in NZB × C58 recombinant inbred mice (Bocchieri *et al.*, 1982). It is not that one set of Id related *V* genes produce autoimmunity, but that, when autoimmunity develops, those *V* genes which are used to generate particular autoantibodies are selectively expressed, along with their associated Ids.

ANTIGLOBULINS

Recurrent Ids have also been identified on antiglobulins. Here again the levels of the Ids varies greatly depending on the anti-Id used. Two of the first to be identified were the Wa and Po Ids of human IgM rheumatoid factors (RFs) (Kunkel *et al.*, 1973). The former is associated with the κ chain and is present on 60% of RFs, and on mitogen induced antiglobulins (Bonagura, Kunkel & Pernis, 1982), but is ordinarily only present at low levels in serum, and is not found on antibodies of other specificity. Although this Id was originally thought to be related to the J segment, a more recent study suggests that Wa is determined by HV2. A synthetic peptide corresponding to HV2 of the κ chain of a monoclonal IgM RF induced antibodies in rabbits reacting with 10/12 other RFs, but not with antibodies of other specificities (Chen *et al.*, 1985). These authors believed that since Wa was dependent on HV2, that it must be derived from a small set of germline genes. Another study which suggests the heritability of RF Ids was made by Pasquali and colleagues (1980), when they identified an Id in a rheumatoid patient, present on 90% of the RF and also present in all first degree relatives. This Id however was not present in 10/11 other RF preparations. These studies may be contrasted with others (e.g. Nelson, Nardella & Mannik, 1985) which identify private Ids. Apart from the differences between the anti-Ids and the technical difficulties related to work with RFs, one other factor makes it very difficult to compare studies in this field: in experiments where the detection of recurrent Id depends on the ability of the test material to block Id/anti-Id binding, what

constitutes significant inhibition? This problem is especially difficult when polyclonal (polyspecific?) anti-Ids are used. One study identified a large degree of crossreactivity among IgM and IgA RFs, but in no case did a RF bind to a heterologous anti-Id at levels approaching the homologous Id/anti-Id reaction (Gharavi *et al.*, 1985). One explanation of partial idiotypic crossreactivity is available when the anti-Id is polyclonal, i.e. the anti-Id serum recognizes several idiotopes, but only one is shared between the different Ids. Alternatively, one may say that the idiotope on the heterologous Id, is slightly different to the homologous Id, and therefore binds less well to the anti-Id. If several different Ids happen to share an identical idiotope, then they might be coordinately regulated as part of an idiotypic network (Hirai *et al.*, 1981). The function of regulatory idiotopes has been discussed by Paul and Bona (1982). The problem of how to determine whether two idiotypes are crossreactive also resurfaces when examining whether an anti-Id recognizes a site associated Id. This is usually checked by seeing whether antigen can displace anti-Id from the Id or vice versa. Often the experiment works one way round but not the other. This can sometimes be related to a difference in the affinity of the antigen and anti-Id for sites on the Id. The problem is particularly marked in the field of autoimmunity where the affinity of antigen for autoantibody is often low. An example of this was described by Nelson *et al.* (1985) who showed that whereas IgG bound to a particular RF (Id) at approximately 10^5/M an anti-Id bound to the same RF at 1,000-fold higher affinity. They also failed to find evidence for recurrent Ids on the small number of RFs tested.

To summarize the work on antiglobulins, there appear to be recurrent Ids which may represent a major proportion of the autoantibody response. In some cases these have been tracked back to germline genes. As with the anti-DNA antibodies Ids associated with antiglobulins can also appear on other antibodies. Other recurrent Ids have been identified with different anti-Ids but since the criteria for saying whether crossreaction between Ids is significant, varies between groups, it is difficult to say whether these other Ids constitute a large proportion of the autoantibody response, or whether they are just widely distributed throughout the rheumatoid population.

ANTI-THYROGLOBULIN

Both strain-related and interstrain recurrent Ids have been identified in the induced autoantibody response to thyroglobulin (Zanetti, De Baets & Rogers, 1983; Male *et al.*, 1983) as well as the spontaneous autoimmunity developing in Buffalo rats (Zanetti & Bigazzi, 1981) and patients with Hashimoto's thyroiditis (Matsuyama, Fukumori & Tanaka, 1983; Delves & Roitt, 1984). The recurrent Ids in these patients appear to be less common than in the systems above, as judged by the lower level of crossreactivity between different monoclonal anti-thyroglobulins, and the relatively low ability of patient serum to inhibit binding of different anti-Id/Id reactions. There are however a number of interesting features of thyroglobulin associated Ids. A study of one of the recurrent idiotypes which appears in experimental allergic thyroiditis in mice has shown that the Id can be readily induced by anti-Id, even though it normally constitutes a small proportion of the anti-thyroglobulin response. Induced idiotypes are spectrotypically similar in different animals of the same strain. Since the same autoantibody can appear in different mice this strongly implies that the autoantibody comes from a gene which readily generates anti-thyroglobulin, or even is a germline autoantibody (Male, Pryce & Roitt, 1985). Despite this the gene expression is evidently under some form of control otherwise one would anticipate that it would be a larger proportion of the response. Another interesting finding has been seen in BALB/c mice—in this case the Id can be identified on both the heavy and light chains of the autoantibody (Zanetti *et al.*, 1985). This is most unusual, but its physiological significance, if any, is still undetermined.

SIGNIFICANCE OF RECURRENT IDIOTYPES

Recurrent Ids have been found in many other autoantibody systems including red cell autoantibodies and anti-acetyl-choline-receptor antibody. These only lead to further speculation as to the significance of recurrent Ids in autoimmunity. The evidence that some germline genes tend to

produce autoantibodies is overwhelming. Why then have these genes not been selected out of the repertoire? One possible explanation is that they do in fact encode for some more useful antibody, and the crossreaction with autoantigen is coincidental. Perhaps only a single mutation in a germline antibody produces the autoantibody. In fact it is known that some autoantibodies to DNA in the MRL/Mp-*lpr*/*lpr* mouse are generated from an equivalent set of genes to that which generates anti-NP in C57BL/6 (Kofler *et al.*, 1985). In another study, a point mutation in a germline T15$^+$ anti-*PC* gene caused the expressed antibody to become self reactive (Diamond & Scharff, 1984).

An alternative explanation for the recurrence of particular Ids is that they are involved in the regulation of autoantibody responses. We have examples of recurrent Ids on different antibodies to external antigens, even on antibodies directed towards different epitopes (Metzger *et al.*, 1981), but there is no indication that such regulatory Ids modulate autoantibody responses. It has also been suggested that certain germline Ids are retained and required for the establishment of particular idiotypic immunoregulatory circuits. Since B cell Ids are required in some systems to establish the repertoire of idiotype specific T cells (Bottomley & Mosier, 1979), particular autoantibody Ids might stimulate Id specific T suppressors. Indeed Id administration can sometimes suppress the antibody response to the cognate external antigen, but only in a minority of cases is this due to suppressor T cell induction. Therefore the idea that germline autoreactive Ids establish autoimmune regulation, is still highly conjectural.

IDIOTYPE REGULATION OF AUTOIMMUNITY

Do idiotypic interactions modulate autoimmunity *in vivo*? Many studies of idiotype networks succeed in modulating immune responses by immunization with Id or anti-Id. There are far fewer instances where naturally occurring anti-Ids have been found during an immune response to antigen or autoantigen. In some studies it has been suggested that material in serum which interferes with Id/Ag reaction is anti-Id, but unless anti-Id is specifically isolated there are no grounds for saying that free antigen or immune complexes or other antibodies are not involved. It is possible to isolate naturally occurring anti-Ids to autoantibodies in some cases, for example anti-Id can be isolated from the sera of 40% of myasthenics, the Id in this instance being anti-acetyl-choline-receptor (Dwyer, Bradley & Urqhart, 1983). This study showed that the highest levels of anti-Id were in patients with the lowest levels of Id and vice versa. This finding is reminiscent of the study by Abdou *et al.* (1981) who showed that anti-Id to autologous anti-DNA was present in the sera of inactive SLE patients but was not found in active disease. The anti-Ids in these patients appeared to recognize private Ids on the patients own serum Ig only—although most studies on the control of autoimmunity have used recurrent Ids, there is no reason why physiologically efficient idiotype regulation within a single patient, should not involve Ids found only in that individual. These studies show that levels of Id and anti-Id may vary reciprocally in autoimmune responses, which is analogous to the waves of Id and anti-Id seen in the response to external antigens (Rose & Lambert, 1980). The possible protective action of anti-Id is also seen in healthy relatives of patients with myasthenia gravis (Lefvert, 1985).

In some instances then, anti-Id may be protective in an autoimmune individual, by blocking binding of autoantibody to its target. However some interesting and unusual effects can occur when anti-Ids to autoantibodies arise. For example, immunization of mice with insulin leads to the production of anti-insulin (Id) and anti-Id also. Anti-Id can also bind to the insulin receptor on fat cells, where it can partially mimic the action of insulin, but also blocks the binding of insulin itself. In this case the anti-Id acts as an internal image of insulin (Schechter *et al.*, 1982). A similar effect is seen in rabbits immunized with thyroid stimulating hormone (TSH). Anti-Id produced to the anti-TSH is maximal at 3 months after the final injection with TSH, which again suggests that Id and anti-Id do not vary synchronously. In these experiments the induced anti-Id mimicked the thyroid stimulating activity of TSH (Beall *et al.*, 1985).

The examples above consider the effects of anti-Id in an already established immune response, but some authors have proposed that idiotype network interactions may be instrumental in initiating autoimmunity (Cooke & Lydyard, 1981). The idea here is that Id directed to an external

antigen fortuitously carries idiotopes which are also present on autoantibodies. Consequently, if Id specific T cells are induced by the Id, then these cells can also stimulate idiotope bearing autoreactive B cells. This is analogous to bypass of T cell tolerance to self antigens when the immune system encounters an external antigen carrying determinants which crossreact with an autoantigen. In one instance the breakdown of self tolerance occurs by stimulation of antigen-specific T helper cells, and in the new hypothesis by stimulation of idiotype specific T cells. Both hypotheses are quite difficult to test for any one autoimmune disease, unless some particular organism or Id is strongly implicated, in the aetiology.

IDIOTYPE MANIPULATION OF AUTOIMMUNITY

The ultimate aim of many of the studies mentioned above is to find a way of suppressing autoimmunity by idiotypic manipulation (Roitt *et al.*, 1981) (Fig. 2). Even if recurrent Ids are

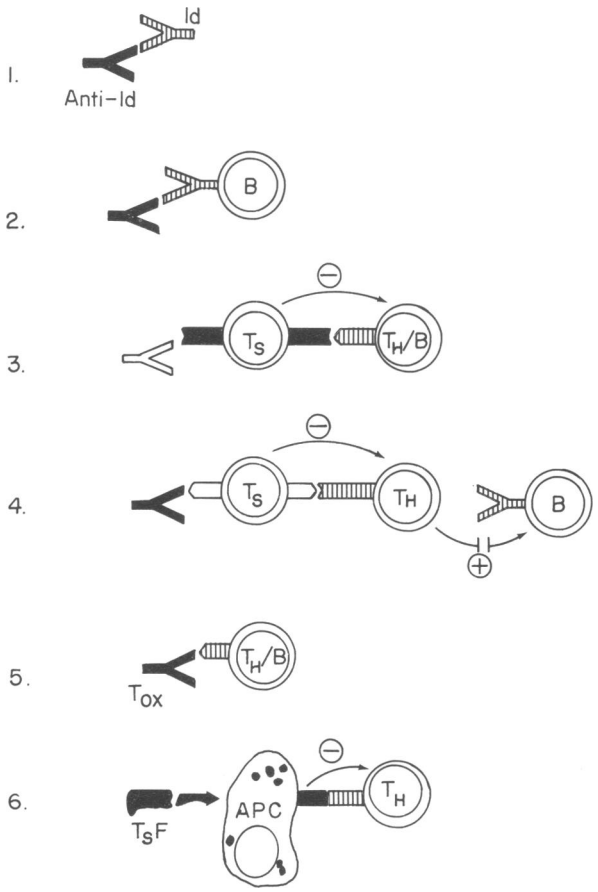

Fig. 2. Possible ways of manipulating autoimmunity with Ids and anti-Ids. Autoreactive receptors are cross-hatched. (1) Direct neutralization of autoantibody. (2) Tolerization of autoreactive B cells, by clonal abortion, clonal exhaustion or antibody-forming cell blockade. (3) Stimulation of Id-specific T suppressor by the use of Id, where suppressors are specific for Id bearing autoreactive T or B cells. (4) Use of anti-Id to stimulate Id-specific T suppressors which can act on antigen specific T helpers and thus prevent autoreactive B cells from receiving a second activation signal. (5) Use of anti-Id coupled to toxic (T_{ox}) molecules to directly eliminate autoreactive T or B cells. (6) Use of Id-specific T suppressor factors (T_sF) to inhibit T cells or B cells. Some of these factors are effective in the presence of antigen-presenting cells only (APC).

present which constitute a large proportion of an autoantibody response, suppression of these Ids may be insufficient to abrogate the autoimmune response, since there are many instances of silent Ids arising in Id suppressed animals to take the place of the dominant suppressed Id (Primi, Juy & Cazenave, 1981). In one attempt to suppress a dominant Id, Zanetti *et al.* (1981) injected spontaneously autoimmune buffalo rats with anti-Id to a recurrent anti-Tg Id. While they succeeded in reducing the circulating anti-Tg in the short term (14–47%), this reduction was temporary and did not markedly affect the outcome of the autoimmunity. This may reflect the appearance of previously silent Ids, but may also relate to the difficulties encountered in trying to suppress an established immune reaction. A possible problem associated with a direct counterattack on autoantibody Ids is the real possibility of producing immune complex formation and deposition (Goldman *et al.*, 1982). For these reasons it now appears that Id manipulation via regulatory T cells is more likely to succeed (Roitt *et al.*, 1983). In fact there are several instances where Id expressed on B cells is also present on T cells, so that the search for usable recurrent Ids has now been extended to look for Ids on autoimmune T cells. Ultimately it may be that Id-specific T cell suppressor factors (e.g. Moser, Kaufman & Abbas, 1985) will succeed in suppressing autoimmune reactions and conventional Ig anti-Ids fail.

At present a number of avenues of research look promising. One area has been the use of autoantigen specific T cell lines to immunize against autoimmunity. For example injection of a T cell line specific for myelin basic protein into mice protects against the subsequent induction of autoimmune encephalomyelitis (Ben-Nun, Werkerle & Cohen 1981), however selection of the right line is likely to be important, since other T cell lines can actually induce autoimmunity. A related approach has been to inject auto-anti-Tg Id into mice and to see the effect on the induction of experimental allergic thyroiditis (Male *et al.*, 1986). The Id in this case is a recurrent Id in the anti-Tg response and also appears to be present on Tg specific T cells. In a number of experiments injection of this Id produced a dramatic decrease (75–100%) in the titres of induced anti-Tg. One can explain Id induced suppression of an immune response, either by saying that the Id causes Fc mediated sequestration of antigen, and reduces its immunogenicity, or that Id induces Id specific T suppressor cells which act on Id bearing T helper cells. Since the Tg autoantigen in this experiment was injected after titres of Id had decayed to undetectable levels, the second explanation appears more likely. A further possibility is the use of anti-Ids to target toxic drugs to autoreactive lymphocytes, an approach which has been used to control Id bearing lymphomas. Although the scale of the problem is larger when attempting to control a whole set of autoreactive lymphocytes rather than a single neoplastic cell clone, in some ways control of lymphocytes by this means is theoretically easier. For example a problem associated with the control of neoplastic cells via their Ids occurs if the cells lose their surface receptor, but if autoreactive cells modulate, and become insusceptible to targetting by anti-Id they may also lose their autoreactivity.

From these remarks, one may conclude that there are many possible ways of manipulating autoimmunity via idiotype interactions. Some of these have been explored and look hopeful, but the greatest difficulty may well arise in attempts to reverse established autoimmune disease, rather than in just pre-empting the onset of autoimmunity.

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