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MINIREVIEW

Internal Antigen and Immune Network[1]

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The concept of an immunological network proposed first by Jerne (1) and Lindemann (2) 10 years ago has gained general acceptance by immunologists and created great interest in related biological fields (see for review, Rowley *et al.* (3) or Bona (4)). The greatest impact of the network concept has come in an indirect way, since the network hypothesis has changed the thinking of immunologists and their perception of data. The question, however, remains to understand the physiological and pathological implications of idiotype determined regulation.

In this review we will focus on a particular feature of the network concept which appears to be the most difficult one to understand. The topic of this review is the "Internal" antigen as it exists in the immune network. Immunologists have worked for many years without taking notice of these internal antigenic structures and only recently interest has arisen in "Internal Antigens." Idiotopes which cross-react with foreign epitopes are the internal images of antigen. It is an obvious conclusion that the internal antigens play an equally important role in the network as external antigens.

The representation of antigen in the network via idiotopes offers opportunities for exploitation. It is, however, unlikely that idiotope antigens one day would replace conventional vaccines, but it is a safe prediction that idiotope vaccines will offer in certain situations greater effectiveness and lower risk of side effects.

Besides the importance for practical implications of internal antigens, the connections between different biological systems, such as endocrine system, nervous system, and the immune system, can be better understood using the internal mimicry concept. Furthermore, the presence of internal antigens in the immune system anticipates encounters with antigen and thereby ensures a speedy and effective immune response to life threatening infections.

Definition. An internal image is defined by anti-Id antibodies (Ab2) which cross-react with a foreign antigen (epitope) This Ab2 is able to behave like the antigen itself by mimicking the antigen structure. It is important to note that not every anti-idiotope antibody (Ab2) is an internal antigen. Niels Jerne (5) has recently classified the Ab2s into two subsets: The Ab2-α is the classical anti-idiotype antibody which recognizes an idiotope; the Ab2-β displays an idiotopic structure which looks like an antigen. This distinction is somewhat artificial and entirely dependent on the vectorial view of Ab1 $\rightarrow$ Ab2 $\rightarrow$ Ab, etc.

Examples for internal antigen. Several experimental data exist which demonstrate the existence of internal idiotope antigens, from which we present the most intriguing examples here. Sege and Peterson (6) demonstrated that anti-idiotype antibodies produced in rabbits against rat anti-bovine insulin antibodies bind to the cellular receptor for insulin. The binding of this Ab2 to insulin receptor was able to partially mimic the function of insulin. Schreiber *et al.* (7) have shown that rabbit antibodies produced against a potent adrenergic antagonist bind to cellular adrenergic receptor (i.e., turkey erythrocytes). The binding of these anti-Id antibodies to turkey

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erythrocytes stimulates basal adenylate cyclase activity. The binding of anti-Id antibodies to the cell receptor mimicked the binding of catecholamine to the adrenergic receptor. Neurath *et al.* (8) synthesized a peptide with the sequence of the first 26 amino acids from the amino terminal methionine corresponding to the 55-residue amino terminal portion (coded for by the pre-S region of Hepatitis B virus (HBV) DNA) of the HBV minor envelope component which could be recognized by human antibodies to HBV. They elicited antibodies against this peptide in rabbits which can be utilized for diagnostic tests. Anti-idiotypic antibodies directed against the group specific A determinant confer protective immunity against the HBV (9). Rabbit anti-idiotypic antibody to human rheumatoid factor autoantibodies isolated by affinity chromatography on rabbit anti-human IgG-FC Sepharose 4B bore the "internal image" of the antigen, human IgG (10). These antibodies reacted with multiple human monoclonal and polyclonal IgM-rheumatoid factors (RF), independent of any particular light- and heavy-chain amino acid sequence and not with IgM or IgG without rheumatoid factor specificity. The addition of this anti-idiotypic antibody to peripheral blood mononuclear cell cultures from patients with rheumatoid arthritis induces lymphocyte proliferation, but not RF synthesis. No proliferation in mononuclear cell cultures from normal individuals could be induced. Moreover, when B cells were preincubated with the anti-idiotype antibody before coculturing them with autologous pokeweed mitogen T cells, the secretion of IgM-RF was suppressed, i.e., these anti-idiotypic antibodies carrying the internal image of antigen are able to interact with respective B-cell receptors. There are several examples indicating that anti-Id antibodies can elicit an immune response or can prime the antibody forming cells instead of the antigen. Thus, Rubinstein *et al.* (11) found a monoclonal antibody specific for A48 Id borne by ABAC48 or β2-6 fructosan binding protein able to elicit an anti-β2-6 fructosan response in BALB/c mice. Strong antiviral antibody responses were also obtained in mice by injection of rabbit anti-Id antibodies against monoclonal antibodies specific for HBV (12) or rabies (13).

Anti-idiotype antibodies have protective immunity against African trypanosomiasis in mice (14). Genetic restrictions, however, were placed on the protection to trypanosomiasis. These authors showed that the one protective allogeneic anti-idiotypic antibody raised against protective monoclonal antibodies specific for the variant surface antigen of a clone of *Trypanosoma rhodiense,* which was effective in immunizing BALB/c mice against homologous challenge, was restricted to mice bearing genes linked to Igh-Ca. Similarly, Stein *et al.* demonstrated that the set of anti-Id at birth followed by immunization with polysaccharide vaccine can protect the mice against 10 LD_{50} of *Escherichia coli* K 13 (15).

Autoanti-idiotypic antibodies may modulate autoantibody production in myasthenia gravis (16) and systemic lupus erythematosus (SLE) (17, 18). The question arises whether suppression of autoimmune tubolointerstitiae nephritis, myasthenia gravis, and spontaneous autoimmune thyreoditis by the addition of exogenous anti-idiotypic antibodies can be effective, in case the disease involves multiple pathogenic idiotypes. Teitelbaum *et al.* (19) studied the influence of the production of autoantibodies with a high-frequency idiotype of MRL-lpr/lpr (H130) mice by administration of corresponding anti-idiotypic antibodies. They found that these anti-idiotypic antibodies induced antibodies with H130 idiotype. In the case of administering F $(ab')_2$ fragments of anti-idiotypic antibodies, a rise of anti-DNA antibodies could be observed.

Therefore it appears that treatment of autoimmune diseases with anti-Id antibodies may have the undesired effect of augmenting the production of autoantibodies.

The Mechanism of Internal Antigen Presentation and Effects. Images of external antigens are part of the network concept right from the beginning of its formulation. Lindenmann (2) in 1973 has created the term "homobody" to describe idiotypes which mimic antigenic structure and Jerne in 1974 (1) has introduced "internal antigen" into his parallel set of anti-idiotypes. These ideas, however, lay dormant for several years until

the first experimental evidence was produced by a nonimmunologist (6). It was only recently in 1982 that a clearer classification of idiotypic determinants was introduced by Jerne (5). According to Jerne two types of idiotypes must be distinguished: Ab2α anti-idiotype antibodies are specific for idiotopes associated with the framework determinants of immunoglobulin molecules. The binding of Ab2 to Ab1 does not alter the antigen binding of Ab1. In the so-called β Ab2 binding to Ab1 the paratope of Ab1 "sees" the idiotypic determinant on Ab2 like an antigen. Thus, this binding mimics the binding of antibody to antigen. The notion of the internal antigen image comes as a statistical necessity of the idiotypic diversity within the network. The binding of both categories of anti-Id antibodies to distinct idiotype structures on Ig receptors can deliver similar transmembrane signals which can either turn off or induce the expression of structural genes responsible for the synthesis of specific antibodies.

The interaction of the paratope of Ab2β to the idiotope of Ab1 can be envisaged as an idiotype–paratope binding as well as an interaction of two active sites. Because the chemical structure of the paratope and idiotope is generally very different from the structure of antigens we have to conclude that similar three-dimensional structures of AB2β and epitope are responsible for these interactions.

A subdivision of idiotypes within the Ab2 class was recently proposed by us (20). With this subdivision of Ab2 types we wanted to pay attention to a special case of Ab2 binding to a determinant very close to the paratope of Ab2. This type of binding creates very similar reactions in assays which are indistinguishable from the Ab1–Ab2β type. Both, the Ab1–Ab2γ and the Ab1–Ab2β are inhibited by hapten or antigen. However, with respect to network considerations, Ab2γ is very different from Ab2β since Ab2β does not mimic an antigenic structure which fits the paratope of Ab1.

Antigen images are as much part of the network as paratopes. The paratope–Ab2 relationship predicts that external antigen can take the place of the Ab2β. Using hybridoma technique the Ab2 can be isolated and used instead of antigen to induce Ab1. During the spontaneous anti-anti-idiotypic response Ab2β is made. So, "homobodies" or "internal antigens" by definition resemble epitopes, which lead to physiological mimicry of the external antigens as shown in the examples above. Like antigen, and antibody carrying internal image competes for binding to receptor on B, T, or other somatic cells. *In vitro* assays have been developed and used to screen for Ab2β. While the hapten inhibits the homologous reaction between idiotype and Ab2γ, the Ab2β in the insulin system inhibits the binding of insulin to the coresponding receptor expressed on fat cells or thymocytes regardless of species origin (6). In other words, the competition of internal image with antigen is demonstrable with cell types for different species and is not restricted to a particular idiotype–anti-idiotype interaction. When comparing the affinity of interaction of hormones to their receptors, the interaction between internal image and the coresponding receptor should be of relatively low affinity. Indeed, the highest observed affinity for antibody (e.g., 10^{-8} M) never reaches the values of hormone receptors. However, no measurements of affinity of Ab2β were reported.

An interesting proposal was made by Nisonoff and Lamoyi (21) which suggested that the induced antibodies of Ab2β type should recognize hapten inhibitable idiotopes on Ab1 which was used to induce their synthesis. This model suggest the very interesting possibility of "narcistic" idiotypes which carry "positive" and "negative" shapes at the same time. Whether this occurs and what the biological significance of this situation might be is unknown.

Holmberg *et al.* (22) speculate on the importance of idiotypic mimicry with major histocompatibility complex determinants, for both the selection of natural antibody repertoires and the evolution of antibody genes. In an attempt to test this possibility, they derived a collection of immunoglobulin-secreting hybridomas from nonimmune newborn BALB/c mice, which they assume rep-

resent natural antibody specificites, and screened this collection for IgM molecules specifically reacting with anti-MHC antibodies. An IgM antibody was found to react with the monoclonal anti-Ia.7 antibody 14-4-4S. The characterization of this clone (BA.N4:4,57) revealed its antitrinitrophenyl specificity and demonstrated specific binding to five different monoclonal anti-Ia.7 antibodies but not to other anti-H-2 antibodies. Since the idiotypic selection operating in the normal immune system in the absence of external antigens appears to determine the choice of the expressed clones after immunization, it would not be surprising if the conventional families of recurrent, germ line-encoded idiotypes would display MHC relatedness. This has profound implications on theoretical perspectives of which B-cell and T-cell repertoires are evolutionarily and functionally related.

Structural Considerations. An internal antigen which has some measurable biological activity might be expected to mimic not only the physiological function of the antigen, but, also as a necessary requirement its steric outline. This is not easy to perceive, since it is unlikely that a biologically active molecule exerts its action via exactly the same topochemical contour that characterizes its epitopes.

For instance, conceptual difficulties arise from the classical experiment of Sege and Peterson on the mimicry of insulin by an antibody. The idiotope which resembles insulin, is a part of a bulky immunoglobulin molecule, while insulin is a relatively small ligand. Some very recent and some older data on the flexibility in the fitting of antibody to antigen are helpful for our understanding. In a classical experiment, Rotman and Celada (23) showed that inactive mutants of β-galactosidase became enzymatically active when allowed to react with antisera to the wild-type enzyme. Since the mutant enzymes bind to substrates as well as the wild type, the effect of antibody is in restoring catalytic activity. Mutant enzymes are considered to exist in two conformations, inactive and active, the former being favored normally, but the presence of wild-type antibody shifts the equilibrium toward the active wild-type conformation (24). That the antibody combining site actually induces conformational change is clearly illustrated by changes in the optical rotatory dispersion or circular dichroism. A similar effect of an induction of a conformational change of a cellular receptor by the internal antigen site on the immunoglobulin molecule mimicking the activating ligand could be considered. The structural correlates of idiotypes have been sought in several well-defined antibody systems (25–27). However, the precise molecular basis of idiotypes are exceedingly difficult to define. Noticeably, in the murine anti-Dextran system, one private idiotype and one public idiotype were assigned, respectively, to the third and second hypervariable region of the heavy chain (28). However, in most other cases, it was difficult to associate a particular idiotypic determinant with a specific amino acid sequence.

Chen *et al.* (29) used an approach of inducing antibodies of predetermined specificity by immunizing with a synthetic peptide corresponding to a hypervariable region on a monoclonal human rheumatoid factor. The results demonstrated that specific anti-idiotypic antibody of predefined specificity can be induced by a hypervariable region peptide. Protein antigenic determinants are dependent from its primary structure, i.e., amino acid sequence; Hopp and Wood (30) presented a method of predicting antigenic determinants from amino acid sequences by determining the point of greatest local hydrophilicity out of analysis of the amino acid sequence. According to the authors, not all antigenic determinants are correlated with hydrophilicity, but it may be possible to improve prediction success by using available methods for predicting secondary structure, particularly β bends. Once an antigenic determinant has been predicted, it should be possible to verify its existence by synthesizing the indicated region chemically and testing its activity in appropriate immune assays, such as binding of the induced antibodies to the intact Ig molecule and its isolated heavy or light chains and the capability of the synthetic peptide to inhibit that binding. However, no structural data are yet available for anti-idiotypic Ab2.

Three-Dimensional Structure. From X-ray crystallographic studies, the three-dimensional interaction of hapten and the combining site of antibody molecules is known for a few antibody molecules. Equivalent studies for internal images are not yet done and in the absence of these critical data we can only speculate about the topographical regions of Ab2β. Complete chemical identity between antigen and polypeptide sequence of internal image idiotopes can be ruled out since Ab2s were reported which mimic polysaccharide, catecholamine, and viral envelope protein antigens. Most likely, the level of mimicking is stereochemical. Thus, the shape of antigen or of an internal image idiotope can be similar enough to be recognized by the cellular receptor. It is safe to say that idiotopes carrying internal image can only be "infidele" copies of antigens.

A potentially useful approach to identify the Ab2β is the study of the interactions between Id and anti-Id at the EM level. Recently, Roux and Metzger (31) have produced immunoelectromicroscopic pictures of anti-allotypic and anti-idiotypic (Roux and Kohler, unpublished) antibodies attached to idiotypes. The resolution of this analysis is high enough to identify the general surface region of Ab1 to which Ab2 is binding.

Outlook. Idiotopes mimicking antigens have potentials as vaccine for protection against infectious diseases and in tumor therapy (21, 32, 33). Internal images are a portion of the anti-idiotypic response (Ab2β) and they can be pulled out and amplified by the hybridoma technique. Thus, it might be possible to prepare large amounts of internal images monoclonal antibodies bearing the foreign antigens and to use these antibodies as idiotype vaccines. The data so far published on anti-idiotypic antibodies as vaccines are still preliminary, i.e., the use as vaccine is still in experimental stage and no epidemiological studies on human subjects have been performed yet.

As mentioned, Sacks and Sher (14) have found a protective effect of idiotypic antibodies to antibodies specific for *Trypanosoma rhodiense* which was genetically restricted in mice. This might critically limit the use for corresponding anti-idiotype antibody vaccines to humans since humans represent a genetically outbred population. However, there are indications that antibodies carry the internal image of the antigen in autoimmune diseases which may be an important hint in the route of treatment of these diseases. Teitelbaum *et al.* (19) found that in case of an auto-antibody producing mouse strain with high frequency of idiotype specific for H130 monoclonal antibodies to which corresponding anti-idiotypic antibodies were administered a parallel increase of levels of anti-DNA antibodies could be observed. Therefore it appears that treatment of autoimmune diseases with anti-Id antibodies may have the undesired effect of augmenting the production of autoantibodies. Nevertheless, it could be shown that auto-anti-idiotypic antibodies can inhibit autoantibody production in autoimmune diseases.

In one study (33) patients with gastrointestinal adenocarcinoma were inoculated with mouse monoclonal antibodies specific for human gastrointestinal cancer cells. This resulted in the production of anti-idiotypic antibody which reacts with the binding site of the monoclonal antibody. The anti-idiotypic antibody isolated from sera of three patients showed cross-reactivity. Patients who developed the anti-idiotype antibody improved clinically and had long remission from their disease. These data open new approaches to the control of tumor growth.

In a recent experiment one of us has induced effective immunity against a lethal dose of *Streptococcus pneumoniae* in mice (34) using a monoclonal anti-idiotope antibody. Interestingly, the monoclonal antibody in its unaltered form did not induce anti-streptococcal immunity nor any significant increase in the effective antibody idiotype. The internal idiotope antigen had to be coupled first to a large protein carrier before it could induce protection. This finding might indicate a general rule for internal antigens which would predict that internal antigens per se are poor antigens. That this has to be so, can be deduced from the network theory which requires a homeostasis between suppression and stimulation. Obviously,

strong internal antigens would unbalance this equilibrium.

Summary. The network hypothesis postulates the existence of internal idiotopic structures which mimic nominal antigens. Experimental evidence for idiotope internal antigen is presented and its implication for the Network hypothesis is discussed. The exploitation of the internal idiotope antigens (or preparation of vaccines) is a realistic possibility.

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