Leading article: Idiotypes and anti-idiotypes: What are they trying to tell us?

A cardinal feature of the immune system is its ability to generate an enormous number of different antibodies (approximately 100 million in the mouse).\textsuperscript{1} Antibodies are classically identified by their antigen binding properties. A second method of describing antibodies serologically is by an analysis of their idiotypes. The variable (V) region of the immunoglobulin molecule was first shown to be antigenic by the injection of V region polypeptides into experimental animals.\textsuperscript{2} These antigenic determinants are known as idiotopes and collectively comprise the idiotype. The three dimensional shape of the idiotype may involve structures on either the heavy or light chains or both. Idiotypes can be divided into two main types based on their precise location within the variable region: (a) those located at the antigen binding site (known as paratopes) and (b) those adjacent to it (known as framework determinants). Antibodies (anti-idiotypes) may be raised against idiotypes in either the same or different species by suitable immunisation. Furthermore, it is evident that the immune system may provide its own anti-idiotypes. Anti-idiotypic binding to the paratope will inhibit binding of the antigen to antibodies bearing the homologous idiotype, whereas those against framework determinants will not usually do so. Idiotypes may be restricted to a particular immunoglobulin molecule—a private idiotype, or appear on antibodies of different antigen binding specificity—a common or public idiotype. Idiotypes represent the phenotypic products of variable (V) region genes, and analysis of idiotypes permits study of the genetic relation between antibodies.

Consideration of idotype-anti-idiotypic interactions led Jerne to propose the network theory.\textsuperscript{3} Stimulation of the immune system by antigen results in a cascade with formation of antibody 1 (Ab1), which in turn induces formation of anti-idiotypic antibody 2 (Ab2), which has its own anti-idiotypic antibody Ab3. These three antibodies and antigen can form a simple circuit because Ab1 and Ab3 may have structural similarity. In the mouse immunisation with the synthetic random polymer (Glu\textsuperscript{60} Ala\textsuperscript{30} Tyr\textsuperscript{10})(GAT) induces formation of the idiotype cascade Ab1 (anti-GAT), Ab2 (anti-idiotypic), and Ab3 (anti-anti-idiotypic). It has been shown by isolation and sequencing of immunoglobulin V\textsubscript{H} genes in the GAT system that a single V\textsubscript{H} germline gene accounts for the expressed V\textsubscript{H} sequences of Ab1 and Ab3 antibodies and that immunisation with Ab2 preferentially stimulates direct expression of V\textsubscript{H} germline genes.\textsuperscript{4} Furthermore, Ab2 may bear structural similarity to the stimulating antigen because the combining site of Ab1 will be complementary to a structure on the antigen and the combining site on Ab2 will be complementary to that on Ab1. The amino acid sequence of reovirus haemagglutinin (antigen) has a region of sequence homology with the light chain of anti-anti-haemagglutinin (anti-idiotypic Ab2).\textsuperscript{5} The immune system may therefore have within the idiotype network an internal image of potential antigens available before meeting an antigen for the first time. This notion is being extensively investigated to determine whether anti-idiotypes may have a role as vaccines. In particular, this approach is being explored as a possible method of vaccination against human immunodeficiency virus (HIV) infection. Monoclonal anti-CD4 (the CD4 antigen is an essential component of the cell surface receptor for HIV\textsuperscript{6}) is used to induce an anti-idiotypic which mimics the molecular structure of the CD4 molecule and thereby neutralises HIV.\textsuperscript{7} The potential advantages of this approach include the ability of anti-idiotypes to act as surrogate antigens without attendant infection or adjuvant risk problems. Anti-idiotypes could also in theory be manufactured easily in large amounts. There are additional theoretical reasons for thinking that anti-idiotypes may stimulate a more effective cytotoxic T cell response than inactivated virus.

As idiotypes, composed of several idiotopes, are present on the surface of B cells, T helper and T suppressor cells, a mechanism for regulation of the immune system is evident. Both enhancement and suppression of idiotypes in response to anti-idiotypic have been demonstrated (reviewed in ref 8). Reciprocal changes in idiotype and anti-idiotypic have been demonstrated in man after booster immunisation with tetanus toxoid,\textsuperscript{9} and there is some evidence that idiotype-anti-idiotypic interaction may play a part in maternal suppression of fetal rejection.\textsuperscript{10} In a single patient with systemic lupus erythematous (SLE) reciprocal changes in levels of anti-DNA antibodies and anti-idiotypic antibodies have been shown to occur, with the anti-idiotypic appearing as the patient went into remission.\textsuperscript{11} Abdou et al also demonstrated in vitro suppression of serum anti-DNA antibody binding to DNA by anti-idiotypic in
SLE. Similarly, anti-idiotypic activity to rheumatoid factor (RF) and RF levels have been shown to be reciprocally related in a patient with a monoclonal IgM gammopathy with RF activity and pneumococcal pneumonia.13

Cross reactive idiotypes have been reported on many human autoantibodies (reviewed in ref 14), including anti-DNA autoantibodies,15 anti-Sm antibodies,16 antiacetylcholine receptor antibodies,17 and antithyroglobulin antibodies.18 Furthermore, amino acid sequence homology has been found between the light chains of human hybridoma derived lupus antibodies bearing a public 16/6 idiotype and a Waldenstrom IgM protein that binds to the klebsiella K30 antigen.19 Such cross reactivity suggests a mechanism for initiation of autoimmunity through perturbation of the idiotype network. In the rabbit experimental myasthenia gravis and anti-acetylcholine receptor antibodies can be induced by immunisation with a synthetic ligand of the receptor.20 Viruses21 and bacteria have both been proposed as initiators of an idiotypic cascade resulting in autoimmunity.

Spontaneous autoanti-idiotypic have been described in both organ specific and non-organ specific autoimmune diseases, including mixed cryoglobulinaemia,22 IgA deficiency (anti-anticasein antibodies),23 myasthenia gravis (anti-acetylcholine receptor antibodies),24 rye sensitivity (anti-rye 1 antibodies),25 and insulin dependent diabetes mellitus (anti-anti-insulin receptor antibodies).26 The widespread existence of autoanti-idiotypic suggests that they are important in terms of immunoregulation and that they may be involved in the pathogenesis of autoimmunity.

Further evidence that perturbation of the idiotype network can have deleterious effects has been provided by Mendlovic et al, who injected C3H.SW female mice (a non-autoimmune prone strain) with human monoclonal antibodies bearing the public 16/6 idiotype.27 High levels of murine anti-16/6 and anti-anti-16/6 antibodies (resembling anti-DNA antibodies) were detected in the sera of the immunised mice. High titres of antibodies to DNA, Sm, RNP, Ro, and cardiolipin were noted, as were immune complexes in the kidneys which contained the 16/6 idiotype. Injection of a common idiotype thus appears to have induced a lupus-like disease.27

The existence of cross reactive idiotypes on autoantibodies from unrelated people and on antibodies binding foreign antigens suggests that highly conserved germline genes may be involved and that they arise from a restricted number of V genes. Datta et al have shown that the cross reactive idiotype 16/6, originally described on a human monoclonal anti-DNA antibody, is present in normal individuals.28 Fong and coworkers showed that most RF light chains from patients with rheumatoid arthritis possess a cross reactive idiotype (designated PSL2) but not two other cross reactive idiotypes (PSL3 and 17–109).29 In contrast, elderly people and patients with Sjögren’s syndrome bore all three, and they suggested that this represents somatic diversification of a common RF light chain Vk gene(s) or, alternatively, use of multiple possibly related Vk gene segments.29 Sequence analysis of anti-DNA antibodies derived from hybridomas from patients with SLE and leprosy has shown that those bearing the 16/6 idiotype are products of the VH germline gene VH26 (a member of the VHIII gene family), whereas those bearing another idiotype, 21/28, are products of a different VH germline gene.30 Thus unmutated germline genes can encode autoantibodies. Similar results have been reported for human RF.31 32 It seems increasingly likely that far from ‘horror-autoxicus’ autoantibodies are products of the normal human immunoglobulin repertoire and often detectable in healthy subjects. The stimulation leading to their expansion and their precise role in immunopathology are unknown.

Modulation of the immune system with idiotypes or anti-idiotypes has been proposed as a therapeutic approach in the management of SLE. In lupus prone mice anti-idiotype administration has been shown to suppress both production of anti-DNA antibodies and nephritis. The effect was transient, however, and anti-DNA antibodies appeared that did not bear the idiotype.33 Zouali et al inoculated mice with syngeneic anti-DNA IgG and muramyl dipeptide (an immunoadjuvant) and found that anti-DNA antibody levels were suppressed and that an anti-idiotyptide antibody specific for the injected IgG appeared.34 Conjugation of anti-idiotyptide to a cytotoxic agent (neocarzinostatin) has been shown to eliminate anti-DNA antibody producing cells in vivo.35 Similar results have been obtained in vitro using conjugates of the A chain of ricin and antiidiotype to inhibit antibody response to acetylcholine receptor.36 Down regulation of a group of public idiotypes, such as those recently identified on anti-DNA, anti-Ro, and anti-Sm antibodies,37 may be an effective means of down regulating autoantibody production. This response may provide the fine tuning needed by the immune system to rid itself of unwanted autoantibodies and provide a therapeutic approach without the dangers of conventional intensive immunosuppressive therapy. Perhaps plasma exchange coupled with passage of plasma over anti-idiotypic columns could one day be a feasible proposition.

In conclusion, analysis of idiotypes and anti-idiotypes is casting light on the genetic origins of
autoimmunity and the interrelations of antibodies of various specificities, and may through manipulation of these interactions lead to new treatments.

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