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# Idiotypic Network Dysregulation

*A Common Etiopathogenesis of Diverse Autoimmune Diseases*

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## Abstract

The pathogenesis of autoimmune disease is still an enigma. Whereas the diverse clinical manifestations of many autoimmune diseases cannot be explained by the existence of autoantibodies, idiotypic dysregulation may provide an alternative explanation. Experimental models, serum level changes of pathogenic idiotypes during exacerbation and remission, and the increased expression of pathogenic idiotypes following common infections all support this notion. In this article we review experimental models of autoimmune disease induction (systemic lupus erythematosus, antiphospholipid syndrome, Goodpasture's syndrome, autoimmune thyroiditis, and vasculitis) by manipulation of the idiotypic network, and discuss the utilization of idiotypes for the immunotherapy of autoimmune diseases and other conditions that involve the immune system (e.g., atherosclerosis).

**Index Entries:** Autoimmunity; idiotypes; systemic lupus erythematosus.

## Introduction

Antibodies can be characterized by the antigens with which they bind and by the isotypic variation of their constant regions. Nonetheless, the variable regions of the antibodies are immunogenic, and can thus be used to generate a set of autoantibodies that recognize them. The antigenic constitution of the variable region of an antibody is known as its idiotype, and it is recognized by antiidiotypic antibodies *(1)*. The idiotypes may be composed of amino-acid sequences located on either light or heavy chains alone, or in combination (conformational idiotypes). They can also be located within the antigen binding-hypervariable segments, or within the intervening framework sequences. Private idiotypes are those that react only with the immunizing immunoglobulin, and define idiotypes specific for the individual antibody clone. Conversely, idiotypes that are shared

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between separate antibody clones from different individuals are termed common or cross-reactive idiotypes *(2)*. These are believed to result either from inheritance of antibody genes among related individuals, or from preservation and sharing of certain germline genes by unrelated individuals within a species.

Whereas the diverse clinical manifestations of many autoimmune diseases cannot be explained by the existence of autoantibodies, idiotypic dysregulation may provide an alternative explanation. Experimental models, serum-level changes of pathogenic idiotypes during exacerbation and remission, and the increased expression of pathogenic idiotypes following common infections all support this notion. In this article, we review experimental models of autoimmune-disease induction by manipulation of the idiotypic network, and discuss the utilization of idiotypes for the immunotherapy of autoimmune diseases and other conditions in which the immune system is involved (e.g., atherosclerosis).

## Idiotypes in Autoimmune Diseases

The role of idiotypes in autoimmunity has been described at length in our book: *Idiotypes In Medicine: Autoimmunity, Infection And Cancer (3)*. Some examples are described herein. With respect to anti-DNA antibodies, over 30 idiotypes of these antibodies have been described [reviewed in *(4)*]. Most of them were described on human hybridoma-derived monoclonal antibodies (MAbs) from the peripheral blood lymphocytes of lupus or leprosy patients, while some were identified on monoclonal anti-DNA antibodies drawn from normal individuals. There are two general classes of anti-DNA antibodies: germline-gene segments encode one group, while the other is encoded by genes that have undergone somatic mutations *(5–6)*. Examples for some of these idiotypes include WRI 176β that was derived from the spleen cells of a patient with systemic lupus erythematosus (SLE) *(7)*. This common idiotype, that was located on the heavy chain of an IgM MAb and reacting with ssDNA and dsDNA, was found in 44% of SLE patients with no correlation to the activity of the disease, and in some healthy first-degree relatives of SLE patients *(7)*. Other examples of anti-DNA idiotypes include B3, D5-R, D5-M, RT-6, RT-72, and RT-84 *(8–10)*. These are found in elevated levels in 20–30% of SLE patients, and sometimes in other autoimmune diseases as well. The latter two idiotypes were found in 18 and 45%, respectively, of immunofluorescence staining of SLE renal sections compared with none in the control group *(10)*. In addition, the B3 idiotype was found in association with arthritis rather than other manifestations of SLE (42 vs 9%, respectively).

The importance of idiotypes in the pathogenesis of autoimmune diseases can also be exemplified by the effect of therapeutic intervention on disease course. SNF1 mice provide an experimental model for immune-complex glomerulonephritis (similar to human SLE) in which there is a pathogenic role for LNF1 idiotypes *(11)*. When these mice were injected

with specific antiidiotypes, there was a suppression of production of antibodies carrying these idiotypes, decreases in the percentage of B cells expressing LNF1 idiotypes and CD4 T cells specific for these idiotypes *(11–12)*. These were associated with increased survival and delayed onset of glomerulonephritis in the mice. Another autoimmune disease whose pathogenesis may be related to the idiotypic network is insulin-dependent diabetes mellitus, as idiotypes found on insulin autoantibodies are also found in the sera of patients with rheumatoid arthritis and autoimmune thyroid disease *(13)*.

## Induction of Experimental Autoimmune Diseases by Immunization with Antibodies Carrying Idiotypes

The pathogenic role of idiotypes in autoimmunity is best exemplified by animal models of idiotypic network manipulation. In short, immunization of naive mice with a specific autoantibody (Ab1) leads to the generation of antiantibody (e.g., antiidiotype = Ab2) directed against the idiotype on the immunizing antibody. A follow-up of the mice for a longer period reveals the de novo generation of anti-antiantibodies (Ab3) by the mice, which may simulate the original autoantibody in its binding characteristics. The phenomenon of naive mice producing specific autoantibodies might be associated with the emergence of the full-blown serological, immunohistochemical, and clinical manifestations of the respective disease.

### *Systemic Lupus Erythematosus*

Even though the level of anti-dsDNA antibodies correlates with SLE activity, the infusion of these antibodies (passive induction) fails to induce the disease in experimental models. Nevertheless, immunization of mice with monoclonal or polyclonal human or murine anti-DNA antibodies in an adjuvant (active induction) *(14–18)* led to the appearance of SLE in the mice with characteristic autoantibodies (anti-DNA, SS-A, histones, and Sm) and clinical presentations (proteinuria, alopecia, increased erythrocyte sedimentation rate, paralysis, immune complexes in kidneys, and short survival time). Furthermore, infusion of antiidiotypes to the 4B4 idiotype could inhibit from 20–68% of the binding of antibodies carrying 4B4 to Sm and dsDNA *(18)*. However, the presence of pathogenic idiotype or antiidiotype on an autoantibody is not the only factor to determine its capability for the induction of autoimmunity. The anti-16/6 idiotype could induce experimental SLE in naive mice when it was carried on the MAb 1A3-2, whereas the MAb 3F7-8 that also contains anti-16/6 idiotype failed to do so *(19)*.

### *Antiphospholipid Syndrome*

The antiphospholipid syndrome is characterized by various clinical manifestations—primarily with repeated thromboembolic phenomena,

thrombocytopenia, and various obstetric and reproductive disorders associated with the presence of lupus anticoagulant or antiphospholipid antibodies *(20)*. The antiphospholipid syndrome can be either primary or secondary (associated with other autoimmune disease), mainly to SLE. Animal models of antiphospholipid syndrome include spontaneous developed disease in lupus-prone mice, and induction of the disease in naive mice *(21)*; the latter can be done either by passive induction *(22)* (as opposed to SLE) or by active induction through manipulation of the idiotypic network. Thus, following immunization with autoantibodies carrying a specific idiotype (Ab1), anti-antiidiotypic antibodies (Ab3) with binding characteristics similar to the idiotype on the injected autoantibodies emerged, and this was associated with the clinical manifestations of experimental antiphospholipid syndrome: low pregnancy rate, decreased embryos and placental weights, fetal resorptions, implantation failure, and cognitive defects *(23–26)*.

### *Goodpasture's Syndrome*

Goodpasture's syndrome is characterized by glomerulonephritis with hematuria and pulmonary hemorrhage, associated with antiglomerular basement membrane antibodies, which are considered pathogenic. One of the therapeutic interventions in this condition is plasma exchange. An attempt to induce this disease through idiotypic manipulation resulted in the emergence of murine antibodies to the noncollagenous domain of type IV collagen (anti-NC1), and of proteinuria or erythrocyturia in the mice *(27)*.

### *Autoimmune Thyroiditis*

Experimental autoimmune thyroiditis is characterized by the presence of antithyroglobulin antibodies. Immunization of mice with these antibodies has led to production of mouse antihuman thyroglobulin antibodies, with subsequent decreased levels of thyroid hormones *(28)*.

### *Vasculitis*

Vasculitis involves vessel inflammation. Some of the autoimmune vasculitides are associated with the presence of autoantibodies, and their pathogenic role remains controversial. One such group is antineutrophil cytoplasmic antibodies (ANCA), which are mainly present in Wegener's granulomatosis, Churg–Strauss syndrome, and microscopic polyangiitis. After immunization of naive mice with human C-ANCA-enriched IgG, the mice subsequently developed anti-antiantibodies (Ab3) that exhibited the binding characteristics of the injected ANCA, concomitantly with the appearance of lung vasculitis and mononuclear infiltrate, and glomerular deposition of immunoglobulins in a granular pattern *(29,30)*. These clinical and histological findings partially resemble Wegener's granulomatosis. Similarly, active immunization of BALB/c mice with purified human antiendothelial cell antibodies has led to the emergence of these antibod-

ies in the mice, followed by deposition of immunoglobulins at the outer part of the blood vessels of the kidneys and lungs, and lymphocyte infiltration around arterioles and venules *(31)*. Recently, antiendothelial cell antibodies produced by idiotypic manipulation have been characterized *(32)*. Three MAbs purified from the induced vasculitis model described above showed specific binding to human umbilical vein endothelial cells. In addition, one of these antibodies—BGM antibody—was able to induce endothelial cells to secrete high amounts of interleukin-6, and to induce significant levels of antibody-dependent cell cytotoxicity *(32)*, thus providing insight into the pathogenesis of antiendothelial cell antibodies in vasculitis.

## The Idiotypic Network and Atherosclerosis

The immune system plays an important role in both prevention and acceleration of atherosclerosis through its response to several antigens such as heat-shock proteins, β2-glycoprotein-I, and oxidized low-density lipoprotein (LDL) *(33)*. Immunization of LDL-receptor knockout mice with anticardiolipin antibodies (Ab1) has led to the production of high levels of anticardiolipin antibodies (Ab3) by the mice. The immunized mice showed a significantly higher degree of fatty streaks at the aortic sinus, compared with the control group *(34)*. Furthermore, immunization of mice with β2-glycoprotein-I—the probable target of autoimmune anticardiolipin antibodies—resulted in the production of high titers of mouse antibodies against human and mouse β2-glycoprotein-I, and also in the enhancement of atherosclerosis compared with the control groups *(35)*. By contrast, immunization of apo-E-deficient mice with homologous malondialdehyde LDL resulted in the production of high titers of antibodies to this LDL, and suppression of the extent of atherosclerosis compared with the control group *(36)*. Thus, atherosclerosis is similar to well-established autoimmune diseases in its ability to modulate it through antigenic/idiotypic stimulation. In this respect, both anticardiolipin antibodies and β2-glycoprotein-I can be regarded as carrying pathogenic idiotypes that activate the immune system to accelerate atherosclerosis, whereas immunization with homologous malondialdehyde LDL results in the opposite effect.

## Conclusion

The animal models presented—as well as the increased prevalence of certain idiotypes in patients with autoimmune diseases and their clinical association—all support the theory of idiotypic network dysregulation in autoimmune diseases. Under normal conditions, antiidiotypes bound to idiotypes in an amount sufficient to practically prevent the detrimental effects of the latter. This explains the presence of very low levels of autoantibodies in many individuals. Thus, it is possible that autoimmune diseases—which are usually characterized with the presence of autoantibodies—stem from increased levels of pathogenic idiotypes, and thus the natural neu-

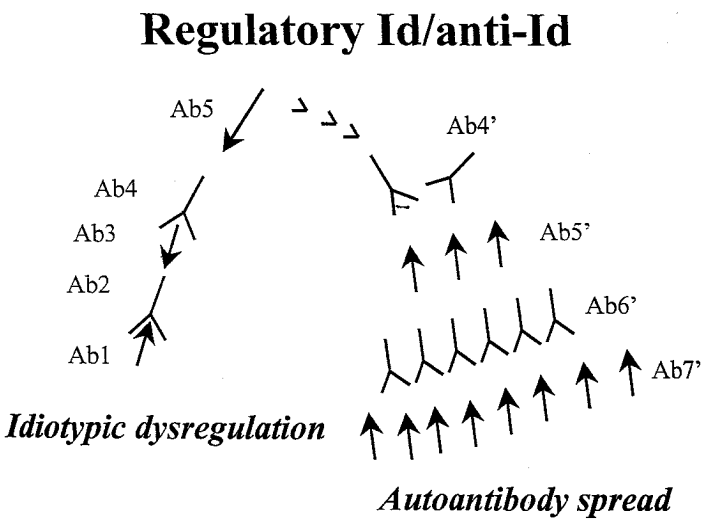


Fig. 1. Induction of autoimmune diseases by idiotypic manipulation: autoantibodies spread in systemic lupus erythematosus. Following immunization with anti-DNA antibodies carrying pathogenic idiotypes (Ab1), antiidiotypes (Ab2) are generated, followed by anti-antiidiotypes (Ab3), the latter having binding characteristics similar to Ab1. In a certain generation of idiotypes or antiidiotype production (Ab5 in this illustration), regulatory antibodies might be secreted, followed by autoantibody spread (Ab4′-Ab7′): the production of a larger network of autoantibodies not restricted to only one idiotype, but to a larger number of antigens (DNA, Ro, La, cardiolipin, Sm, Histones).

tralizing antiidiotypes are not enough. Following an exposure to an environmental antigen carrying a sequence identical to a pathogenic idiotype (such as one carried on a bacterium or a virus) in a genetically susceptible individual, the balance between idiotypes and antiidiotypes might be lost, and subsequent antiidiotypes and anti-antiidiotypes would be generated *(37)*. In a certain generation of idiotypes or antiidiotype production, regulatory antibodies may be secreted. Following that, a larger network of autoantibodies not restricted to only one idiotype, but to a larger number of antigens, would be generated. This explains the spread of autoantibodies observed in many models of experimental autoimmune diseases induced by idiotypic manipulation: the production of many autoantibodies that characterize an autoimmune disease following immunization with only one autoantibody, as in SLE (*see* Fig. 1).

If autoimmune diseases can be considered as resulting from increased levels of idiotypes compared with antiidiotypic, infusion of antiidiotypes from healthy donors to patients with autoimmune diseases might restore this deficiency, since in healthy patients there is no such antiidiotypes deficiency. In fact, this theoretic therapeutic option is being carried out daily in the treatment of many autoimmune diseases by infusion of intravenous immunoglobulin, which are plasma concentrates from numerous donors. These preparations contain antiidiotypes to many autoantibodies found

in autoimmune diseases, and were shown to inhibit these idiotypes in vitro *(38)*. Future research aims would be the development of more disease- and patient-specific medications not containing polyclonal immunoglobulins, but more specific antiidiotypes.

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## Discussion

*Unidentified*: Are the T cells specific for the idiotope or some other component of the antibody? Where do you think that T-cell help comes from?

*Shoenfeld*: I should have mentioned that it is very important to immunize interdermally in the experimental model. This promotes T-cell help, most probably because of prolonged handling of the autoantigen and exposure to the immune system. It is not isotype-related. It is mostly idiotype-related. We have generated a T-cell line against idiotopes, and we were able to transfer the disease in mice with cell line.