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Antigenic complementarity in the induction of autoimmunity: A general theory and review☆

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Abstract

The mechanism by which tolerance is broken in the induction of autoimmunity is unknown. Simple, well-characterized antigens suggest that molecular complementarity may play a key role in breaking tolerance. Experimental allergic encephalomyelitis can be induced using myelin basic protein combined with muramyl dipeptide. These molecules bind specifically to each other. Insulin antibodies can be induced when insulin is combined with glucagon, to which it binds. These cases suggest that molecular complementarity may alter the processing of "self" proteins. Antigenic complementary yields molecularly complementary immune responses (i.e., idiotypic–anti-idiotypic), undermining immune system regulation. In addition, complementarity insures that the antibodies (or T cells) directed against one antigen will molecularly mimic the other antigen, and vice versa, so that "self" and "nonself" will be confused. If at least one complementary antigen mimics a "self" protein, then an unregulated, self-sustaining immune response against tissue results. This testable theory of antigenic complementarity in autoimmunity is reviewed.
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Keywords: Idiotype; Anti-idiotype; Autoimmunity; Complementary; Epitopes; Anti-epitopes; Complementarity; Antibodies; Antigens; T cells; Induction; Tolerance; Jerne; Immune networks; Antisense peptides

Contents

1. Antigenic complementarity theory . . . 0
2. Evidence for antigenic complementarity . . . 0
3. Tests of the theory . . . 0
4. Are antisense proteins antigenic complements? . . . 0
Take-home messages . . . 0
References . . . 0

1. Antigenic complementarity theory

I have proposed that everything in a functional living system is highly integrated using molecular complementarity as its basis. [1] It follows that "self" is whatever has

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molecularly matching complementary pairs within such a system (i.e., is functionally and structurally integrated). "Nonself" is anything that is non-paired (i.e., has no molecular complement and is non-functional and non-integrated).

I have proposed further [2] that the immune system evolved to deal with unpaired material that poses a threat to the integrity of living systems. One may think of such unpaired material as presenting the same threat to a living system as a wrench would if thrown into a piece of complicated machinery. The immune system responds to "nonself" materials ("antigens") either by excluding or destroying the material (e.g., proteolytic digestion by lysozyme, or other innate immune mechanisms) or by producing molecularly complementary pairs (antibodies, T cell receptors) that neutralize the ability of the unpaired material to interact destructively with the organismal system.

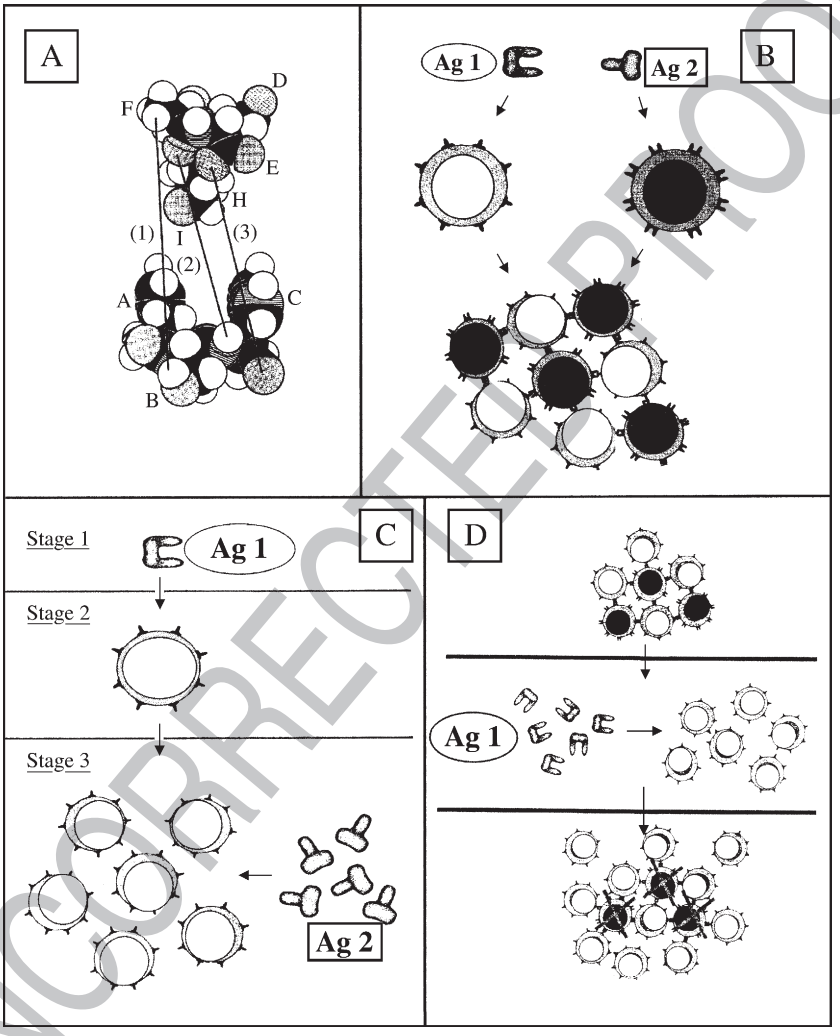

Fig. 1. A. Structural schematic of two complementary antigens (based on NMR study of the tryptophan peptide of myelin basic protein binding to muramyl dipeptide [Root-Bernstein and Westall.]. B. Each antigen in A will induce its own immune response, which will be molecularly complementary to it (illustrated via a T cell response) and the resulting complementary cells will aggregate (as is seen in perivascular cuffing, for example). C. Prevention or vaccination against autoimmunity can be explained by antigenic complementarity because the prior inoculation of one antigen will produce a cellular (or antibody) response that is complementary, and this complementary immune response will mimic the complementary antigen, causing it to be viewed as "self". D. Treatment of an existing autoimmune disease can also be explained by antigenic complementarity: induction of autoimmunity using complementary antigens requires a balance between the immune responses to the two antigens; if a large dose of one antigen is inoculated into the host after autoimmunity starts, then the immune response to this inoculated antigen will be increased significantly and overwhelm the competing T cell or antibody response. Note that the theory predicts that such a treatment will result in the elimination of one immune response, but not the other, yet this will resolve the "self–nonself" confusion, and therefore resolve the autoimmune problem.

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In the theory I have proposed, the origins of autoimmunity follow from an "Achilles heal" that results from the production of molecular complements to unpaired antigens. *Pairs* of molecularly complementary antigens will fool the immune system into creating complementary *pairs* of antibodies or T cells [2–8]. These antibodies or T cells will not only pair with antigens, but with each other, resulting in confusion within the immune system between "self" and "nonself": the response to one member of a pair of complementary antigens is also an attack on the complementary immune response to the other antigen in the pair (Fig. 1, A and B).

Autoimmune diseases are therefore primarily targeted by the immune system *at itself*, and in all cases, immune system disregulation results from this intra-immunological confusion. Consider the series of events that will follow immunological processing of a pair of complementary antigens. Each antigen elicits its appropriate T cell response or antibody (Figure). The resulting immune responses will be complementary to each other, therefore resulting in binding of T cells to T cells (e.g., perivascular cuffing) or of antibodies to antibodies (circulating immune complexes). More problematic for the immune system, each antibody or T cell response will mimic one of the antigenic pair, so that the distinction between "self" and "nonself" will be abrogated (Fig. 1, A and B). The immune system will be triggered to attack not only the initiating antigens, but also its own responses to those antigens, resulting in a chronic immunological civil war. The specific nature of any autoimmune disease then follows from the nature of the specific antigens that trigger the intra-immunological disruption. If the molecularly complementary antigens mimic one or more "self" proteins, then the disregulated immune response will also target tissues or organs in the host.

My theory integrates two of the major competing theories of autoimmunity: the antigen-mimicry theories [e.g. 9] and the anti-idiotype antibody theories [e.g., 10–16] proposed by previous investigators. Antigenic mimicry will lead to cross-reactivity between antibodies or T cells and host tissues. The necessity of complementary (or epitope–anti-epitope) antigens will result in pairs of antibodies or T cells that act like anti-idiotypes towards each other. In this way, all of the existing data concerning the roles of both antigenic mimicry and of anti-idiotype antibodies in autoimmunity can be accounted for within the current theory.

What the current theory explains that previous theories do not is what induces the breakdown of tolerance in the host. In a sense, the current theory proposes that there is no breakdown of tolerance. Each antigen is processed normally. Autoimmunity occurs only through an unusual confluence of antigens that have a specific molecular relationship being processed simultaneously. The theory therefore also suggests that it should be possible to vaccinate against any autoimmune disease by inducing an immune response to one of a pair of complementary antigens significantly prior to the exposing the host to the pair (Fig. 1, C). And it should be possible to cure an existing autoimmune disease by inoculating an animal with a large dose of one of the antigens that induced the disease (Fig. 1, D).

While the complementary antigen theory is not dependent upon Jerne's network theory of immune regulation [17], it is compatible with it, so that one can restate the problem posed by complementary pairs of antigens. Such antigens will induce pairs of antibodies (or T cells) that are each idiotypic, but which will function as if they were idiotype–anti-idiotype pairs. According to Jerne's theory, such a situation would result in loss of network regulation of the antibody or T cell response. One would therefore want to speak of antigenic epitopes and anti-epitopes.

2. Evidence for antigenic complementarity

All of the steps outlined above have been observed. It has been demonstrated that the minimal antigens required to induce experimental allergic encephalomyelitis in guinea pigs (the tryptophan peptide from myelin basic protein and muramyl dipeptide) bind to each other with high affinity (Fig. 1, A) [18–20]; that insulin and glucagon bind to each other to create a hyperantigenic complex leading to anti-insulin antibodies [21]; and that cPR-3 (105–201) protein is complementary to human autoantigen proteinase-3 in autoimmune vasculitis associated with Wegener granulomatosis [22]. Experimental evidence for complementarity in both perivascular cuffing (Fig. 1, B) [2] and circulating immune complexes [23] exists. Artificial circulating immune complexes have been created using specific pairs of complementary idiotypic antibodies and these combinations are highly associated with specific human autoimmune diseases, particularly those associated with AIDS [7,24–28]. Vaccinating animals against one antigen does prevent onset of autoimmunity when they are subsequently challenged with the autoimmunogenic pair (Fig. 1, C) [reviewed in Refs.2,3,29]. And inoculating animals with a large dose of a single purified antigen can cure an existing autoimmune disease induced by a complex mixture (Fig. 1, D) [reviewed in Refs. 2,3,30–32].

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3. Tests of the theory

1) The antigenic complementarity theory predicts that the complex and often molecularly undefined antigen–adjuvant combinations commonly used to induce autoimmunity in animal models will be found to contain minimal, active *pairs* of complementary antigens.
2) The theory predicts that autoimmune diseases will occur at much higher rates in multiply-infected individuals than in singly-infected individuals. One would therefore expect to find increased rates of autoimmune diseases in immunosuppressed individuals such as transplant patients, people on chronic steroids, and people with AIDS who are characterized by multiple, concurrent infections. This is, in fact, the case: these groups have an incidence of autoimmune diseases hundreds of times higher than the general population [reviewed in Refs. 7,24–28].
3) The specific sets of infections that occur in multiply-infected individuals who develop autoimmune complications can provide crucial clues as to the nature of the particular agents necessary to trigger an autoimmune response. I have demonstrated that a combination of active herpes virus infections and mycobacterial infections are highly correlated with demyelinating autoimmune processes in people with AIDS and in transplant patients [7] A similar set of infections (Streptococcus type A and herpes viruses) appears to precede the onset of autoimmune thrombocytopenia purpura [8].
4) Testing the current theory will require modification of Koch's postulates [2,7,8]. All current theories of autoimmunity assume that the cause of disease is monofactorial, and therefore that it is possible to isolate a single, purified agent that is sufficient to induce the disease in a naive host [e.g., 9,10,16]. If, however, the complementary antigen theory is correct, then it will not be possible to find a single causative agent for any autoimmune disease. Instead, two or more agents will be found to be highly correlated with onset of autoimmune diseases; none of the agents individually will be able to induce the disease in naive hosts; but combinations of two or more of the correlated agents will be able to induce autoimmunity. Concomitantly, no single antibody or T cell clone will be sufficient to transfer

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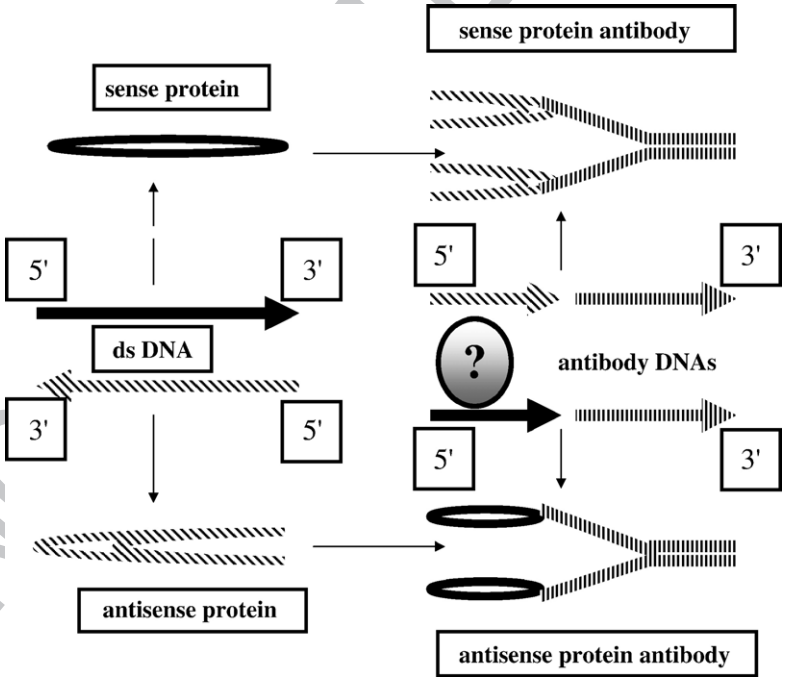

Fig. 2. Pendergraft, et al. have proposed that antigenic complementarity is based on antisense proteins. Antisense proteins are those that or would be produced if the sense and antisense strands of DNA were both translated. Blalock has proposed that such proteins will themselves be complementary. It would follow that antibodies to each of these antisense proteins would be complementary to each other. What Pendergraft, et al. and others have not realized is that there should be an antisense genetic relationship between the hypervariable regions of the complementary antibodies as well (denoted by the question mark in the figure), but in this case the relationship will not be antiparallel as in the two antigens, but parallel. This prediction is a crucial test of the antisense antigen theory.

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autoimmunity; a combination of either antibody (or T cell) with antigen, or of pairs of antibodies or T cells will be required to transfer autoimmunity.

4. Are antisense proteins antigenic complements?

One complication needs to be addressed in concluding this brief review of antigenic complementarity in autoimmunity and that involves the definition of complementarity. The term complementarity as used here refers to any pair of compounds that can bind stereospecifically to each other. Since such compounds must be antigenic to induce autoimmunity, it would be more accurate to speak of complementarity involving any pair of antigenic epitope–anti-epitopes.

A very different definition of antigenic complementarity has been proposed by Pendergraft, et al. [22,33]. Pendergraft bases his theory of antigenic complementarity on Blalock's theory of antisense proteins [34,35]. Antisense proteins are those that would be encoded by the sense and antisense strands of DNA, if both chains of a gene were translated (Fig. 2). Pendergraft, et al. claim to have found at least one case in which the initiating antigen of a human autoimmune disease is an antisense protein for the protein that is targeted by the immune system in that disease [19]. McGuire and Holmes have suggested that such antisense relationships may exist in a broader class of autoimmune diseases [36]. What neither Pendergraft nor McGuire and Holmes have pointed out is that, if the antisense protein scheme is applicable to understanding autoimmunity, then it follows that the hypervariable regions of idiotype–anti-idiotype antibodies must be antisense sequences for each other, but in a parallel, rather than antiparallel, genetic encoding (Fig. 2, question mark). This unlikely prediction provides a test for the antisense theory.

An additional issue is the generality of Pendergraft's theory compared with mine. While my definition of stereospecific binding incorporates the genetically-based cases of antigenic complementarity, the antisense theory does not incorporate non-genetically encoded forms of antigenic complementarity such as tryptophan peptide-muramyl dipeptide binding, or insulin–glucagon complexation. Moreover, extensive physicochemical tests of the Blalock antisense theory fail to demonstrate that antisense proteins bind to each other [37–39]. The simple fact that two proteins are encoded by complementary strands of a gene does not, apparently, assure that the proteins are themselves molecularly complementary or that they will be antigenically complementary. But if antigenic complementarity should provide usefully insights into the origins of autoimmunity, this issue of what constitutes complementarity will become crucial.

Take-home messages

- Autoimmune diseases are primarily targeted by the immune system *at itself*, and in all cases, immune system disregulation results from this intra-immunological confusion.
- Pairs of molecularly complementary (epitope–anti-epitope) antigens induce pairs of complementary antibodies or T cells (idiotype–anti-idiotype) such that each antibody or T cell mimics one of the antigens, resulting in loss of the self–nonself distinction.
- Molecular mimicry of one or both antigens results in the dysregulated immune response being targeted at host tisssues.
- Both idiotypic and anti-idiotypic immune responses play equal roles in autoimmunity.
- Complementary antigens bind to each other physicochemically; complementary antibodies produce circulating immune complexes; and complementary T cells produce lymphocyte aggregates such as perivascular cuffs.
- Experimental and clinical studies provide evidence for all aspects of the complementary antigen theory.
- Testing the theory of antigenic complementarity requires modification of Koch's postulates because only specific *pairs* of purified molecularly complementary antigens will suffice to induce autoimmunity.
- The application of antisense peptide theory to autoimmunity is problematic evidentially and conceptually but is testable.

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