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Protective role of anti-idiotypic antibodies in autoimmunity – Lessons for type 1 diabetes

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Abstract

Circulating autoantibodies to beta cell antigens are present in the majority of patients with Type 1 diabetes. These autoantibodies can be detected before and at time of clinical diagnosis of disease. Although the role of autoantibodies in the pathogenesis of the disease is debated, their presence indicates a dysregulation of the humoral immune response. Mechanisms regulating autoantibodies in Type 1 diabetes are not well understood. In contrast, in other autoimmune diseases there is acceptance that autoantibodies are regulated not only by antigen but also by other antibodies that bind to the antigen-binding site of these autoantibodies (anti-idiotypic antibodies). The proposed purpose of this network is to maintain an equilibrium between autoantibodies and their anti-idiotypic antibodies, preventing autoimmunity, while allowing a robust response to exogenous antigen. Anti-idiotypic antibodies regulate both autoantibody binding and their levels by a) neutralizing autoantibodies, and b) inhibiting the secretion of autoantibodies. Because it has been proposed that the B lymphocytes that produce autoantibodies function as autoantigen presenting cells, inhibiting their binding to autoantigen by anti-idiotypic antibodies may prevent development of autoimmune disease. This hypothesis is supported by the presence of anti-idiotypic antibodies in healthy individuals and in patients in remission from autoimmune diseases, and by the lack of anti-idiotypic antibodies during active disease. We recently reported the presence of autoantibodies to glutamate decarboxylase in the majority of healthy individuals, where their binding to autoantigen is prevented by anti-idiotypic antibodies. These anti-idiotypic antibodies are absent at clinical diagnosis of Type 1 diabetes, revealing the presence of autoantibodies. Type 1 diabetes (T1D) is an autoimmune disease characterized by the dysfunction and destruction of insulin-producing beta cells by autoreactive T cells. Although much progress has been made towards understanding the respective roles of effector and regulatory T cells in this beta cell destruction, the development of autoantibodies to beta cell proteins is widely considered simply a by-product of the autoimmune destruction of the beta cells, rather than having an active role in the pathogenesis. This view is starting to change based on increasing recognition that autoantibodies can have defined roles in other autoimmune diseases, and the emergence of new data on their role in T1D. This exploration of the role of autoantibodies in autoimmune disease has been spurred, in part, by increasing recognition that development of autoimmune diseases is influenced by regulatory antibodies (anti-idiotypic antibodies) directed against the unique binding site of

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autoantibodies. This review provides an overview of the development and function of these anti-idiotypic antibodies, and present evidence supporting their role in the development of autoimmune diseases. Finally, we conclude this review with a model of the events that may cause loss of anti-idiotypic antibodies and the implications for the development of T1D.

Keywords

autoimmune disease; autoantibodies; type 1 diabetes; glutamate decarboxylase; Idiotypic Network Hypothesis

The specific antigen binding sites of an antibody are located in the three-dimensional structure created by the variable regions of the antibody's two light and two heavy chains. This part of the antibody is referred to as the idiotypic determinant [1]. This antigen-specific "idiotype" of each antibody determines its unique recognition of its antigen. However, the idiotype itself can serve as an antigen and is recognized by anti-idiotypic antibodies (anti-Id), which can function as a critical part of a regulatory network.

The concept of anti-Id as regulatory factors was first formulated by Niels Jerne in the Network Hypothesis nearly 40 years ago [2–4]. He postulated that this unique ability of antibodies both to recognize an antigen and be recognized by other antibodies as an antigen creates a balanced network that acts to regulate the humoral arm of the immune system. Anti-Id are proposed to maintain the homeostasis of the adaptive humoral immune responses by neutralizing idiotypic antibodies and regulating idiotypic antibody secretion (for reviews see [5,6]).

Although this Network Hypothesis dominated the immunological field for over a decade, interest subsequently waned in part because of its seeming contradiction with aspects of the clonal selection theory, especially the concept of self-tolerance. Today, however, there is increasing recognition that low levels of autoimmunity are a common phenomenon in healthy individuals. These low levels of autoantibodies and autoreactive T cells have been found in many healthy cohorts used as controls for patients with clinical autoimmune disease. This natural autoimmunity is held in check by regulatory mechanisms [6].

Moreover, the apparent conflict of the Network Hypothesis with the clonal selection theory has largely been resolved with the recognition that the process of affinity maturation introduces significant amino acid changes in the idiotype – thus creating an antigen to which self-tolerance does not apply (see below). For these reasons, interest in the Idiotypic Network has re-emerged during the last decade, especially in the field of autoimmune disease [7–9].

Development of an immune response to antibodies

(A) Diversity of the variable region of antibodies develops during affinity maturation. When B lymphocytes encounter an antigen, they begin rapidly to proliferate and enter the proliferative compartment – the dark zone – of the germinal center (GC) of the lymph nodes. It is during this rapid proliferation phase

that B lymphocytes undergo somatic mutation at a very high rate (somatic hypermutation), a process critical for the generation of antibodies with high affinity towards a specific antigen. As the B lymphocytes move towards the light zone of the GC, only those B lymphocytes that express antibodies with increased affinity are selected to survive and exit the GC as antibody producing plasma cells or memory cells (for details see [10]) (Figure 1).

The somatic hypermutations occur predominately in the hypervariable region of the antibody and on average 15 amino acid substitutions occur per antibody during this process [11], causing substantial differences in the antigenic determinants of the idiotype (Id). The antibodies generated during affinity maturation not only have improved antigen-binding abilities, but also differ significantly from the germline sequences. While the immune response in general is tolerant towards the germline sequences presented on naïve antibodies (for review see [12]), the immune system is not tolerant to the amino acid changes in the idiotypic region. Thus Id-specific antibodies (anti-Id) are stimulated during this change of idiotype [13–15]. The new idiotype of the antibody is indeed “foreign” to the body and will therefore not be recognized as “self” by the immune system. Therefore B cells reactive to the idiotype of this antibody will not be eliminated through the usual mechanisms applying to peripheral tolerance.

Anti-Id (also termed Ab2) can be directed to different epitopes of an antibody (Ab1). Depending on the binding sites they are classified as Ab2-α or Ab2-β. Ab2-α bind outside the antigen-binding site of Ab1, while Ab2-β bind to the complementarity determining region (CDR) of Ab1. Ab2-β can represent the internal image of antigen and compete with the binding of Ab1 to antigen, thus participating in the regulatory network [16] (Figure 2). These characteristics of anti-Id have important implications in their therapeutic use, as are discussed later.

(B) T cell responses to antibodies after affinity maturation. The original Idiotypic Network Hypothesis considered predominantly the humoral aspects of the Network. However, the observation that T cell-deficient animals do not develop anti-Id when immunized with antibody [17,18], demonstrated that T cells are an essential part of the Network. Therefore, below we provide an updated view of the Idiotypic Network by discussing the role of T lymphocytes within the Network.

The first step in the development of anti-Id is the presentation of the idiotypic antibody. Idiotypes are endocytosed by antigen-presenting cells (APC), such as macrophages, dendritic cells and B lymphocytes, and subsequently presented to T cells on MHC class II molecules [19]. B lymphocytes continuously present their endogenous Id-peptides on their MHC class II molecules [19,20] (Figure 3). Presentation of these Id peptides is essential for the generation of anti-Id. The presentation of idiotypic peptides on MHC class II stimulates T cells, which in turn provide signals for the B lymphocytes to differentiate into antibody-producing plasma cells and secrete anti-Id [15,21,22].

Furthermore, B lymphocytes internalize anti-Id that bind to their B cell receptor (BCR). Consequently anti-Id peptides are presented on MHC class II molecules (conventional T-B collaboration) [23] (Figure 3). These interactions between T and B cells create an antigen-

independent cooperation between T cells and B cells called Id-driven T-B cell collaboration, permitting continuous activation of both Tand B cells even in the absence of antigen [19,24–27]. This antigen-independent cooperation is an essential part of the “Relay Hypothesis” a mechanism proposed to account for the maintenance of the immunological memory in the absence of antigen [28,29].

Anti-Id in the Idiotypic Network

As discussed previously, B lymphocytes present peptides derived from anti-Id. Low concentrations of anti-Id stimulate T cells, which in turn stimulate idiotypic antibody secretion, resulting in a equilibrium between complementary B and T cells – the Idiotypic Network.

Antigen stimulation transiently disturbs this network. Antigen is taken up, presented to antigen-specific T cells, which stimulate B lymphocyte to secrete antigen-specific antibodies. This increase of idiotypic antibody titer induces the secretion of anti-Id, which firstly neutralizes the antibody, and secondly down-regulates the secretion of the antibody as discussed below (Figure 4). This series of events was demonstrated in individuals receiving tetanus toxoid vaccination [30].

Serum samples from vaccinated individuals were evaluated for tetanus toxoid specific antibodies and their anti-Id. The initial injection of vaccine antigen triggered an increase in tetanus toxoid antibody titer. This increase of idiotypic antibody titer was followed by an increase in anti-Id and a subsequent decrease in the titer of free tetanus toxoid antibody. This apparent decrease of tetanus toxoid antibody titer was caused by competition of anti-Id for the tetanus toxoid binding site on the idiotypic antibody. There is also a real decrease of tetanus toxoid antibody, which was caused by the anti-Id-induced inhibition of secretion of idiotypic antibody (for mechanism see below).

In addition to neutralizing secreted antibody, anti-Id can also down-regulate the secretion of the idiotypic antibody [31,32]. This effect is only observed at high concentrations of anti-Id. It has been demonstrated *in vitro* where anti-Id suppressed the synthesis of antibodies by human B lymphocytes [33–35]. This down-regulation of antibody secretion by anti-Id is due to the simultaneous binding of anti-Id to both the BCR and the Fc receptor (FcR) on B lymphocytes (Figure 5).

B lymphocytes express only one subtype of FcR: the FcγRIIB. This FcR is an inhibitory receptor and if in close proximity to the BCR (e.g., through anti-Id mediated co-ligation), the activated FcγRIIB abrogates the BCR initiated signal [36,37] and – if maintained long enough - results in B cell apoptosis [38,39]. Because FcγRIIB is a low affinity receptor, this inhibitory pathway is activated only at high anti-Id levels. As the threshold for the FcγRIIB is reached, anti-Id will inhibit secretion of the antibody, causing antibody levels to decrease.

The importance of the FcγRIIB-mediated regulatory mechanism in the maintenance of a balanced immune response was first proven in FcγRIIB-deficient mice. These animals developed uncontrolled antibody secretion and exacerbated autoimmunity [40–42]. Autoantibody levels are influenced by FcγRIIB also in human autoimmune diseases since

reduced levels of FcγRIIB are found in patients with active systemic lupus erythematosus and those with untreated multiple sclerosis [43,44], two autoimmune diseases characterized by increased levels of autoantibodies.

Function and uses of anti-Id

The ability of anti-Id to neutralize potentially pathogenic antibodies is thought to be one of the major mechanisms by which administration of Intravenous Immunoglobulin (IVIg) exerts its therapeutic benefit in the treatment of several autoimmune diseases, as outlined below [45,46].

IVIg preparations consist of pooled IgG fractions from over 10,000 donors and exert their therapeutic effects through different modes of action [47]. Among these is the binding of pathogenic autoantibodies by anti-Id present in the IVIg, which include anti-Id that neutralize or bind to autoantibodies directed to anti-Factor VIII, anti-thyroglobulin, anti-DNA, anti-intrinsic factor, anti-platelet GPIIb/IIIa, and antigens in the cytoplasm of neutrophil granulocytes [48–52]. That anti-Id are the mediator of the therapeutic effect of IVIg is demonstrated by the elimination of the therapeutic action of IVIg after removal of anti-Id and confirmed by the demonstration that the isolated anti-Id fractions restore the therapeutic activity of IVIg [53].

The role of anti-Id in IVIg treatment has been best studied in hemophilia patients. Replacement therapy of hemophilia A patients with coagulation factor VIII (FVIII) can elicit the development of antibodies that neutralize FVIII. These anti-FVIII antibodies are a serious obstacle to the chronic treatment of hemophilia patients. Anti-FVIII autoantibodies can also develop spontaneously in acquired hemophilia [54]. Hemophilia patients are treated successfully with IVIg, which contain anti-Id to anti-FVIII antibodies [55], and anti-Id have been demonstrated to completely neutralize the inhibiting activity of polyclonal anti-FVIII antibodies from hemophilia A patients [56].

Other examples of anti-Id-mediated neutralization of autoantibodies occur in Myasthenia Gravis, Lambert-Eaton syndrome, Immune thrombocytopenic purpura, patients with primary and secondary Sjögren's syndrome and scleroderma [57–59] and antibody-mediated neuropathies [60–63]. The observation that IVIg contains anti-Id to so many different autoantibodies illustrates how common they are in healthy individuals. The wide prevalence of anti-Id also explains the efficacy of IVIg in the treatment of different autoimmune diseases [47,64].

Anti-Id in autoimmune diseases

Support for the proposed role of anti-Id as regulators in the immune response comes from studies of auto-immune diseases. A protective role of anti-Id against autoimmune diseases is based on two major observations:

- **a.** anti-Id specific to autoantibodies are present in patients during remission and/or in healthy individuals,
- **b.** anti-Id are absent during periods of active disease.

This negative correlation between anti-Id and autoimmune disease has been studied in great detail in different forms of systemic lupus erythematosus and autoimmune thyroid diseases. Similar, but less extensive associations have been found in other autoimmune diseases (Table I).

Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by the presence of autoantibodies directed against nuclear antigens (nucleosomes, DNA, histones) and phospholipids. Available evidence strongly suggests a protective role for anti-Id directed against these autoantibodies.

The most frequently detected autoantibodies in SLE are those against double-stranded DNA (dsDNA). Naturally occurring anti-Id to anti-DNA antibodies can be detected in relatives of patients with SLE [65], individuals who were in contact with such patients [66], and even in healthy controls [67–69]. In marked contrast, these anti-Id are not present in most patients with active SLE [70,71]. However, patients in remission from SLE do show a resurgence of anti-Id. Thus in SLE anti-Id levels are inversely correlated with disease activity [69,72].

Immunization of a mouse model of SLE with the mouse anti-dsDNA monoclonal antibody 3E10 induced the development of anti-Id and was associated with inhibition of anti-dsDNA antibodies and suppression of lupus nephritis [73]. Vaccination of nine humans with SLE with the same antibody in a phase 1 trial induced the development of anti-Id in five patients, who remained disease free for the 2-year follow-up period [74].

The human anti-ssDNA monoclonal antibody 16/6 Id was found to correlate with levels of SLE disease activity, being elevated during active disease [75,76]. Passive administration of anti-Id to 16/6 Id suppressed production of the anti-ssDNA antibody in mice and temporarily attenuated SLE [77].

Another major autoantibody found in patients with SLE is directed against ribosomal P phosphoproteins. These autoantibodies are highly specific for SLE and correlate with disease activity. Stafford *et al.* discovered concealed autoantibodies to ribosomal P phosphoproteins in healthy individuals and in those SLE patients who had tested negative for autoantibodies in conventional antibody assays [78–80]. These autoantibodies were in complexes with specific anti-Id and were detectable only after the removal of the latter [78].

These findings further support the notion that autoantibodies are present in healthy individuals but concealed by the presence of anti-Id. Thus, although most healthy controls appear to be autoantibody-negative using conventional antibody assays, more sophisticated assays show that they in fact have autoantibodies that are masked by anti-Id (discussed in more detail later).

Neonatal lupus syndrome

Neonatal lupus syndrome (NLS) is a rare systemic autoimmune disease caused by the transplacental passage of maternal autoantibodies to the fetus. These maternal autoantibodies are directed against Ro/SSA, La/SSB, and/or U1-ribonucleoprotein. The

mothers often have no symptoms at the time of birth. The affected child shows cardiac and dermatologic symptoms, which have been attributed to Ro/SSA and La/SSB autoantibodies, respectively. Sera from mothers of healthy children exhibit higher anti-Id levels towards anti-La/SSB autoantibodies compared to mothers giving birth to a child with NLS, suggesting that the anti-Id to La/SSB autoantibodies may protect the fetus by blocking the pathogenic maternal autoantibody [81].

Autoimmune thyroid diseases

Autoantibodies present in sera of patients suffering from autoimmune thyroid diseases, such as Graves' disease and Hashimoto's thyroditis, are directed to three major autoantigens; thyroid-stimulating hormone receptor (TSHR), thyroid peroxidase, and thyroglobulin. Naturally occurring anti-Id to these autoantibodies have been characterized [82,83] and anti-Id to anti-TSHR are associated with remission in Graves' disease [84]. Anti-Id to anti-TSHR are also present in 8–30% of untreated patients [85,86] and presence of anti-Id has been linked to a better response of patients with Graves' disease to anti-thyroid drugs [86]. These findings suggest that an idiotypic network also exists in autoimmune thyroid diseases.

Technical considerations in the detection of anti-Id in sera

The intrinsic capacity of anti-Id to bind to autoantibodies often prevents the detection of the anti-Id, particularly in healthy individuals where both antibodies are present in immune complexes. Thus, in these sera, the bound anti-Id need to be "unmasked" before they can be detected. Likewise, the autoantibodies present in the sera of healthy individuals are usually missed when measured by conventional assays. The reason autoantibodies are routinely detected in patients with autoimmune disease is precisely due to the paucity of anti-Id in these individuals. Several methods are used to "unmask" anti-Id: absorption of autoantibodies to a large excess of immobilized antigen [79], blocking of anti-Id using peptides that present the antigenic determinants of the autoantibody (complementary peptides) [72,81,87], or absorption of anti-Id to immobilized autoantibodies [88]. The removal of inhibitory anti-Id from the serum reveals the presence of autoantibodies in seemingly autoantibody-negative samples [81,87,88]. The presence of anti-Id can be confirmed by the re-addition of the isolated anti-Id to the autoantibody, resulting in the inhibition of autoantibody binding to the antigen [66,78].

The function of these concealed autoantibodies is currently unclear. However, what is becoming increasingly clear is that when a serum is found to be autoantibody negative in conventional autoantibody ligand binding assays, this can be due to the absence of autoantibodies or the presence of anti-Id in complex with autoantibodies.

Anti-Id in Type 1 diabetes

Work suggesting a protective role of anti-Id in Type 1 Diabetes (T1D) is beginning to emerge, consistent with the more extensive data on the role for anti-Id in SLE and the inverse correlation of anti-Id with clinical disease in other autoimmune diseases, detailed above and in Table I. Progression to T1D is characterized by the presence of circulating autoantibodies directed against several beta cell autoantigens: insulin, the smaller isoform of

glutamate decarboxylase (GAD65), Insulinoma 2-associated protein, and the Zinc Transporter 8 protein (for review see [89]). Although the pathological role of these autoantibodies has not been established, the notion that autoantibodies may be involved in the pathogenesis of T1D has received recent support from the findings that GAD65 autoantibodies (GAD65Ab) enhance presentation of GAD65-derived peptides and can promote cytotoxic T cell responses [90–92].

IVIg treatment of T1D was attempted with mixed results depending on the duration of disease and duration of IVIg treatment [93–97]. However, all studies had at least one subgroup of patients who showed some benefit from IVIg treatment, with higher rates and longer durations of remission and preserved c-peptide release, indicative of improved beta cell function [98].

In T1D, anti-Id against insulin autoantibodies were first described in both humans [99] and the BB rat model [100]. The presence of GAD65Ab-specific anti-Id was initially suggested by the observation of an immunoglobulin inhibiting the binding of GAD65Ab to GAD65 in human sera. However, the lack of appropriate monoclonal antibodies prevented further identification of this inhibitor [101]. We subsequently observed that NOD mice injected with a human GAD65Ab monoclonal antibody develop high titers of anti-Id [102]. Since these animals did not develop diabetes and had reduced levels of insulitis, the induction of anti-Id was linked to prevention of T1D in this animal model.

To determine whether a GAD65Ab specific Idiotypic Network is present in humans, we tested a large cohort of healthy individuals and found that their sera contained both anti-Id and GAD65Ab in complexes [88], although dissociation of the complexes was necessary for the detection of both. This finding suggests that GAD65Ab are present in the majority of healthy individuals, rather than being restricted to T1D, and that anti-Id normally bind GAD65Ab and, as discussed above, mask their detection. By extension, these findings suggest that loss of anti-Id may be associated with the development of T1D. This latter hypothesis has received further support from our finding that anti-Id specific to GAD65Ab are low or missing in T1D patients [88] and that anti-Id levels increase in T1D patients who experienced a temporary remission after diagnosis of disease (honeymoon period). In contrast, those patients who did not undergo a remission phase did not show an increase of anti-Id levels [103]. This correlation of increased anti-Id with improved beta cell function has also been found in Latent Autoimmune Diabetes in Adults (LADA) patients who received alum-GAD vaccination [103]. In this instance, patients who experienced an improvement in beta-cell function also showed an increase in anti-Id levels, while patients in the placebo groups or patients who did not respond to the vaccination, did not demonstrate such an increase. Although these findings do not establish causality, they support the hypothesis that anti-Id protect against the development and progression of T1D. These studies are critically needed to test this hypothesis to identify the mechanism by which such protection occurs.

Moreover, it is likely that the by us described GAD65-specific Idiotypic Network is not the only network present in T1D. Because of the scarcity of human monoclonal autoantibodies to other major autoantigens in T1D – insulin, Insulinoma 2-associated protein, and the Zinc

Transporter 8 protein – we have not yet tested whether also these autoantibodies and their anti-Id are present in healthy individuals. Until these reagents become available, we propose GAD65 and its Idiotypic Network as a model system for the study of the mechanisms by which anti-Id may be involved in the immune system.

As briefly mentioned here and reviewed in detail elsewhere [104], prevention and intervention therapy of T1D in humans still faces difficulties. Existing therapies are either only marginally successful, or cause side effects that may outweigh the benefits. Further work establishing a possible protective function of anti-Id in T1D is therefore warranted.

Model for the failure of the Idiotypic Network in T1D

Our model of a GAD65Ab-specific Idiotypic Network in T1D incorporates our hypothesis of how loss of anti-Id occurs and its possible consequences. In the healthy immune system GAD65Ab, anti-Id, and T cells are in equilibrium. According to the Network Hypothesis, introduction of antigen, GAD65, stimulates the production of GAD65Ab. GAD65Ab in turn trigger an increase in anti-Id, thus restoring the equilibrium. (Figure 6 left panel). Indeed, vaccination with GAD65 has been shown to induce a temporary increase in GAD65Ab [105,106]. Whether the subsequent decrease in GAD65Ab titer is caused by an increase in anti-Id is an important, but unanswered, question. Prolonged release of GAD65, e.g., during destruction of pancreatic beta cells and release of islet cell autoantigens, is predicted to continuously stimulate GAD65Ab secretion (Figure 6 right panel).

In addition, GAD65 itself competes with anti-Id for binding to membrane-bound GAD65Ab, thus preventing both co-ligation of the BCR with FcγRIIB by anti-Id and downregulation of GAD65Ab secretion. Therefore, when the autoantigen is present continuously, the GAD65Ab-specific B lymphocytes will receive a net stimulatory signal. At the same time anti-Id specific B lymphocytes receive a net inhibitory signal as detailed below, resulting in down-regulated anti-Id secretion. Based on observations in other systems, continuous suppression of anti-Id secretion will eventually lead to the apoptosis of anti-Id specific B lymphocytes [38,39]. Loss of anti-Id will then permanently remove the inhibition of GAD65 binding to GAD65Ab [88] and allow GAD65Ab-mediated antigen presentation and prolonged stimulation of autoreactive T cells.

Future directions

Further studies are needed to prove that GAD65Ab-specific anti-Id protect individuals from developing T1D.

In addition, to determine the specific steps leading to the development of GAD65Ab-specific anti-Id, it will be necessary to analyze GAD65Ab and anti-Id levels in longitudinal samples obtained from individuals who go on to develop T1D. We expect that such an analysis will reveal that during progression to T1D GAD65Ab levels increase as anti-Id levels decrease.

To support our hypothesis that anti-Id develop as a consequence of increased GAD65Ab levels, it will be necessary to investigate anti-Id levels in individuals who were vaccinated with GAD65 and show a transient rise in GAD65Ab levels. We predict that this temporary

rise in GAD65Ab levels will be followed by an increase in anti-Id levels and is responsible for the later masking of GAD65Ab.

Finally, it is essential to demonstrate that anti-Id protect against the development of T1D. Injection of NOD mice with GAD65Ab-specific anti-Id before and after development of T1D followed by a careful analysis of the different components of the immune response, such as T cells and infiltrating lymphocytes should establish whether anti-Id can prevent T1D or cause its remission in this animal model. Such studies evaluating the efficacy of monoclonal anti-Id specific to GAD65Ab to prevent T1D in animals are currently underway. Positive outcomes of these experiments may lead to the development of a new therapeutic tool for the prevention of human T1D.

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Nomenclature

Idiotype (Id)
Antigenic determinants of an antibody directed to a particular antigen; found only in the variable region

Anti-Idiotypic antibody (anti-Id)
Antibody directed towards the idiotype of an antibody.

Hypervariable regions:
Portions of the light and heavy immunoglobulin chains with highly variable amino acid sequences, that constitute the antigen-binding site of the antibody.

MHC class II
Complex expressed on antigen presenting cells, that present antigen to CD4 + T cells.

Fragment of antibody (Fab)
Fragment of antibody that contains the antigen-binding site.

Intravenous immunoglobulin (IVIg)
Pooled IgG from > 1000 blood donors, used for the treatment for autoimmune diseases.

Affinity maturation:
Affinity-selected differentiation of activated B cells, which increases the affinity of the antibody for the antigen.

Plasma cell
B lymphocyte specialized in producing antibodies.

Memory cells
B lymphocytes with prolonged life span that enable the immune system to respond faster to a second exposure.

B-cell antigen receptor (BCR)

Membrane bound antibody expressed on B lymphocytes.

FcγRIIB

Inhibitory receptor. Only IgG receptor expressed on B-lymphocytes.

Internal image

The part of an anti-Id that is structurally complementary to the idiotype.

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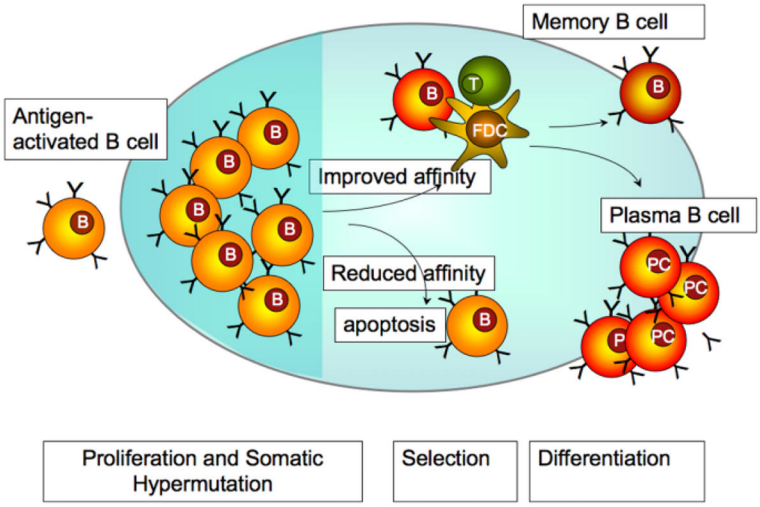

Figure 1.

Affinity maturation of antigen-stimulated B lymphocytes. Upon binding to antigen the B lymphocytes enter germinal centers (GC) and undergo rapid proliferation and somatic hypermutation (in the dark zone). The somatic hypermutations cause random changes in the affinity of the antibody to the original antigen. B lymphocytes with higher affinity to the antigen, can interact successfully with GC T cells and follicular dendritic cells (FDCs) and receive survival signals from them (selection in the light zone). These B lymphocytes eventually differentiate into antibody secreting plasma B cells or memory B cells (Figure adapted from [120]).

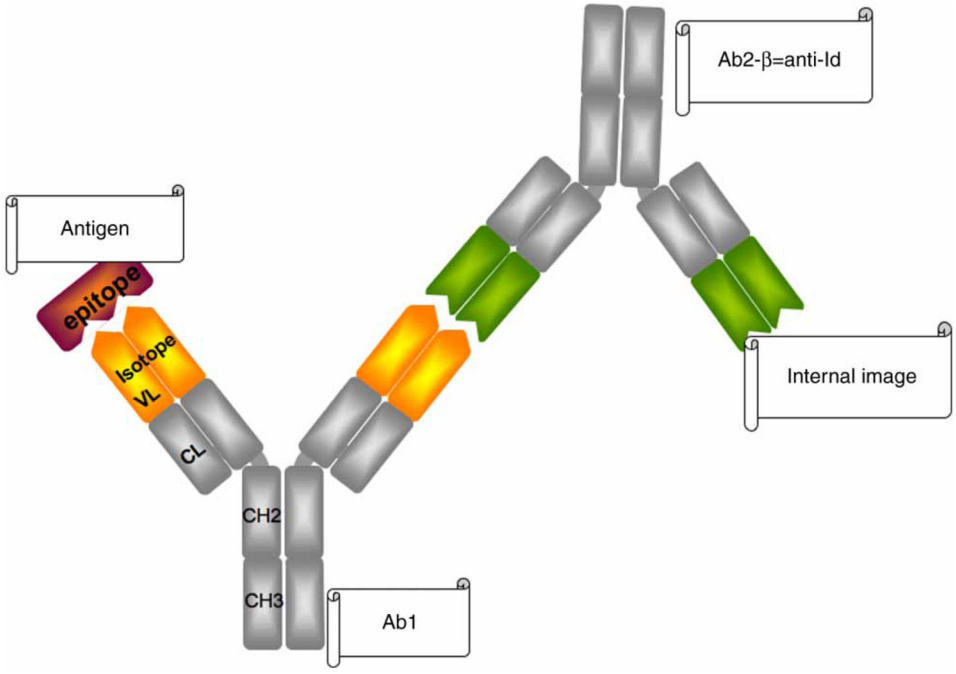

Figure 2.

Anti-Id presenting the internal image of the antigen. The epitope of an antigen is bound by Ab1. Ab2-β (anti-Id) has an idiotype that is structurally similar to the epitope presented by the antigen. It therefore binds to the antigen-binding site of Ab1 and competes with the antigen for binding to Ab1, thus regulating antibody function.

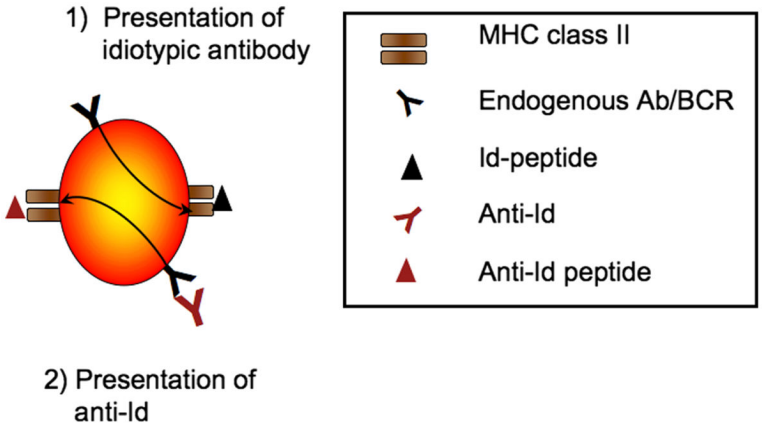

Figure 3.

Presentation of idiotypic peptides by B lymphocytes. B lymphocytes present peptides derived from their endogenous antibodies on MHC class II molecules (1). They also endocytose anti-Id that bind to the cells' B cell receptor and subsequently present the anti-Id-peptides on MHC class II molecules.

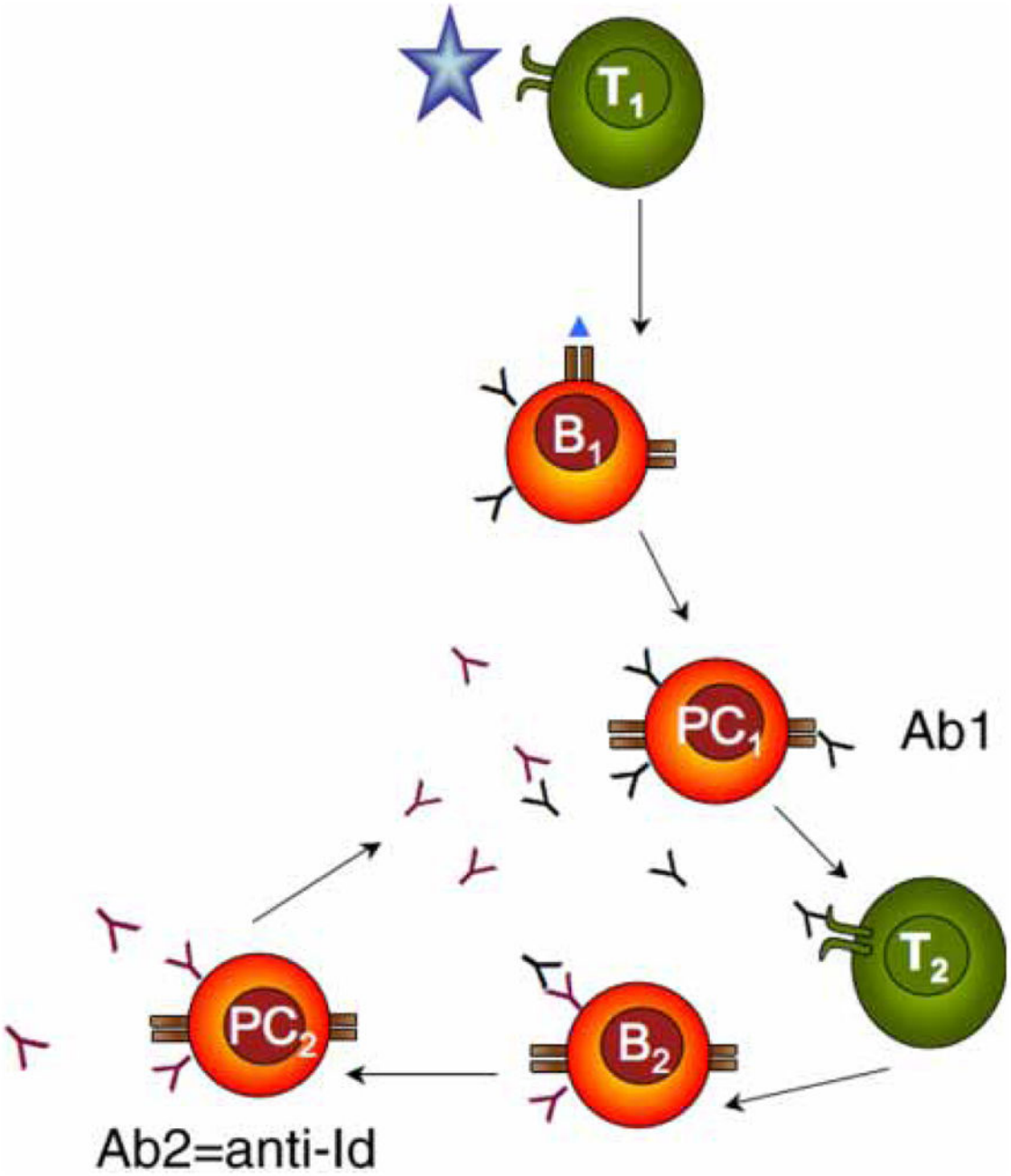

Figure 4.

Re-establishment of the homeostasis after antigen stimulation. Antigen is presented to T cells (T1) that stimulate B lymphocytes (B1) to differentiate to plasma cells (PC1). PC1 secrete antibody (Ab1). Ab1 is recognized by T cells (T2), that stimulate B lymphocytes (B2) capable of recognizing the idiotypic determinant of Ab1. B2 lymphocytes differentiate to plasma cells (PC2) secreting Ab2, a.k.a. anti-Id, which neutralize Ab1.

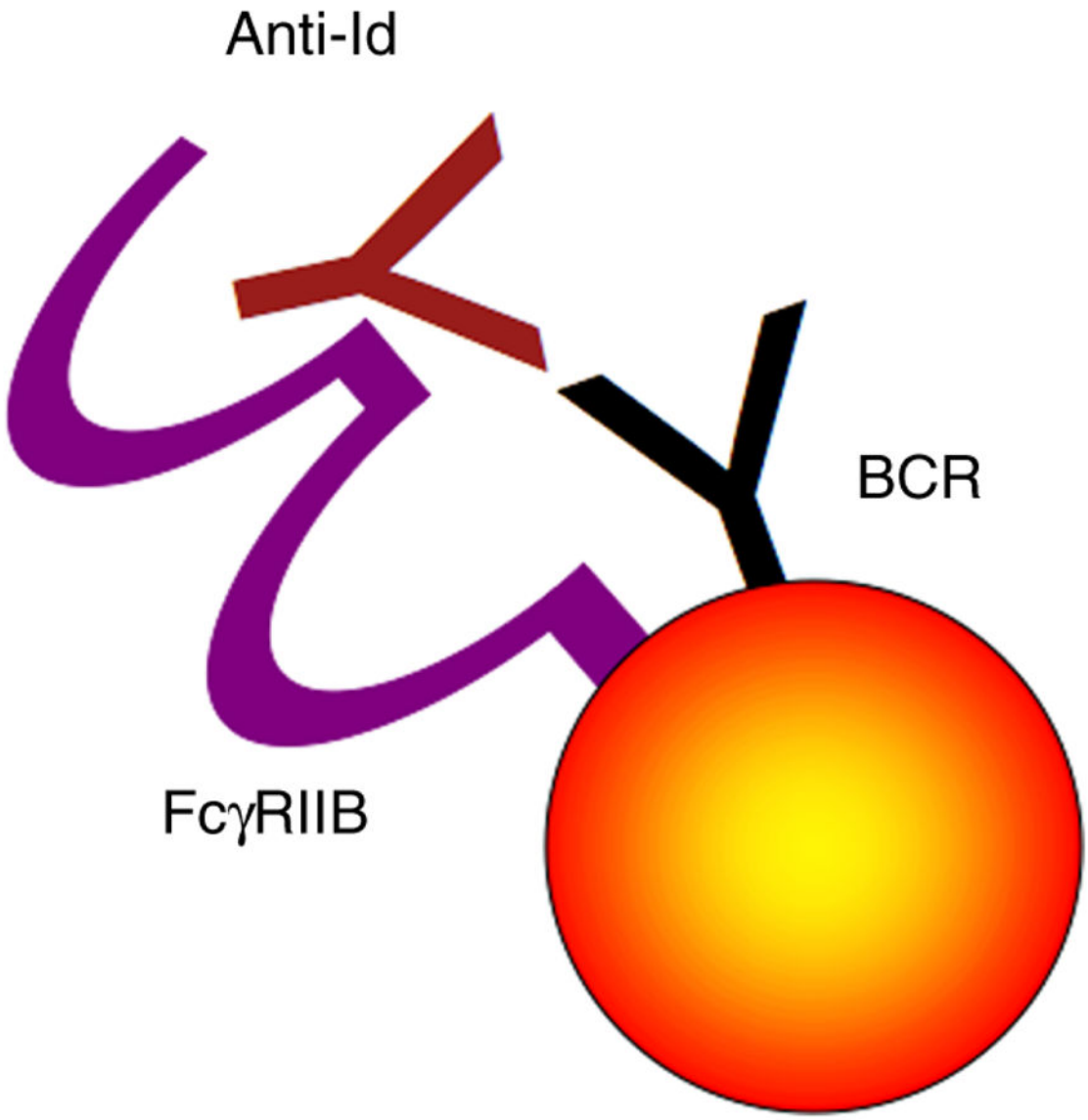

Figure 5.

Co-ligation of FcγRIIB with the BCR. The Fc portion of anti-Id binds to the B lymphocyte's FcγRIIB. Simultaneously the Fab portion of anti-Id binds to the BCR, thereby co-ligating these two membrane proteins. Co-ligation of the FcγRIIB to the BCR abolishes the BCR-induced stimulation of antibody secretion.

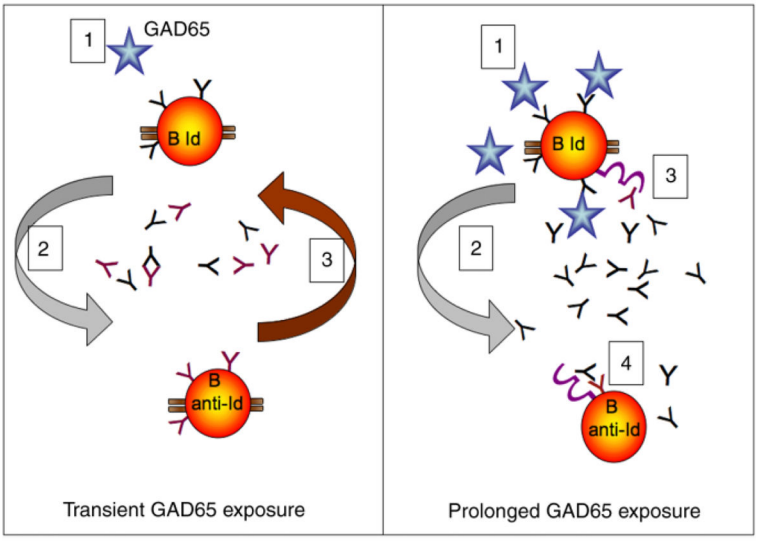

Figure 6.

Model for the Failure of the Idiotypic Network in T1D during prolonged GAD65 exposure. Left panel: In the healthy individual, transient introduction of GAD65 (1) will cause a temporary disturbance of the Network's equilibrium. GAD65 will stimulate the secretion of GAD65Ab, which will in turn stimulate the secretion of anti-Id from specific B lymphocytes (2), restoring the equilibrium (3). Right panel: The continuous presence of GAD65 (beta cell injury/death) will destroy the Network. As before, GAD65 stimulates secretion of GAD65Ab (1), which initially will trigger the production of anti-Id (2). However, GAD65 itself binds to the BCR on GAD65Ab-specific B lymphocytes, both stimulating these specific B lymphocytes and preventing the anti-Id from co-ligating the BCR with the FcγRIIB (3). With increasing GAD65Ab levels, co-ligation of the BCR with the FcγRIIB on anti-Id specific B lymphocytes (4) will generate a net inhibitory signal, resulting first in the inhibition of anti-Id secretion and eventually in the apoptosis of anti-Id specific B lymphocytes.

Table I

Autoantibodies and anti-Id in autoimmune diseases other than those discussed in this review.

Disease	Target of autoantibodies	Anti-Id	Anti-Id absent during acute disease	Anti-Id present during remission	Possible mechanism	Reference
Membranoproliferative glomerulonephritis	Alternative pathway C3/C5 convertase	Yes	Yes	Yes	Suppression of autoantibody secretion	[107–109]
Idiopathic thrombo-cytopenic purpura	Platelets	Yes	Yes	Yes	Suppression of autoantibody secretion	[110–112]
ANCA-associated vasculitides	Anti-neutrophil cytoplasmic antibodies (ANCA)	Yes	Yes	Yes	Neutralization of autoantibody	[48,113–116]
Sjogren's Syndrome	Ribonucleoproteins = La/Ro RNP	Yes	Not tested	Not tested	Neutralization of autoantibody	[72]
Primary biliary cirrhosis	E2 subunit of pyruvate dehydrogenase complex	Yes	Not tested	Not tested	Neutralization of autoantibody	[117]
Myasthenia Gravis	Acetylcholine Receptor	Yes	Not tested	Not tested	Neutralization of autoantibody	[118,119]