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# BASIC STRATEGIES OF THE IMMUNE SYSTEM IN THE REGULATION OF ANTIBODY RESPONSE

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The essence of the immune system is its highly refined regulation. Therefore, a comprehensive review of immunoregulation will eventually become a review on the immune system, and this communication will only focus on current concepts of basic strategies used by the immune system to regulate the antibody response.

In higher vertebrates, as noted by many immunologists [20, 48], the only system comparable to the immune system, for level of complexity and type of function performed, is the central nervous system. Critical characteristics highly developed only in the immune and nervous systems are the ability to respond to unexpected stimuli, to maintain flexibility in the repertoire of possible responses, to learn from the environment in order to give the most appropriate response, and to remember it.

These unique characteristics obviously call for very precise and sophisticated regulatory mechanisms, able to carefully modulate and control the interaction of every component of the immune system and their reactivity to foreign substances.

This review is divided into three sections representing major regulatory mechanisms operating in the control of antibody response: 1. antibody feedback, 2. T cell regulation and 3. idiotypic network.

## 1. ANTIBODY FEEDBACK

Twenty years ago cellular immunologists imagined, rather naïvely, the immune system as composed of only one type of lymphoid cell: the plasma cell. Accordingly, regulatory mechanisms were thought to be extremely simple: antigen selected B cell clones to produce antibodies and antibody feedback inhibited B cells. Within this

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conceptual framework the idea of antibody feedback, that is regulation of antibody response by actively produced or passively received antibody, developed as the first regulatory mechanism described in detail in the immune system.

Originally, the interpretation of antibody feedback was a peripheral one, relating suppressive activity to a diminution of the available immunogenic stimulus. In fact, UHR and MÖLLER [105] demonstrated that formation of antigen-antibody complexes can render antigen sterically unavailable to the immune machinery.

Subsequently, antibody feedback was found to be considerably more complex since, as it appears from tab. 1, many different mechanisms may be involved. The first indication of direct B cell suppression in antibody feedback was given by ROWLEY et al. [80] who demonstrated that passively transferred antibody decreases the number of antibody forming cells *in vivo*, without affecting the rate of proliferation.

PIERCE [76] obtained experimental evidence for a different mechanism in antibody feedback. In his system the primary *in vitro* anti-sheep red blood cell (SRBC) response was strongly suppressed by addition to cultures of hyperimmune anti-SRBC antibodies. Suppression was antigen specific and directly related to the amount of antibody added. Incubation of separated lymphoid cells with antibody did not impair their ability to develop an anti-SRBC response. However, if macrophages were incubated with antibody before culture the subsequent *in vitro* response was strongly suppressed. It was therefore concluded that antibody feedback can operate via neutralization of the antigenic stimulus at the macrophage-dependent phase of the response.

Activation of suppressor T cells by specific antibody as a mechanism for antibody feedback was postulated by GERSHON et al. [37]. This was indicated by experiments in which adult thymectomy was shown to completely eliminate the suppressive effects of passive antibodies, as judged by the ability of macrophages to bind specific tumor cells in the presence of cytophilic antibody.

BIRNBAUM et al. [12] described a model of tolerance induced in adult mice by a single injection of a moderate dose of hapten-carrier conjugate. The mechanism underlying this tolerant state was shown to be the production of small amounts of high affinity antibody in response to the tolerogenic antigen. This antibody can inhibit the response to a subsequent challenge by a mechanism comparable to passive antibody-mediated suppression.

| immunoregulatory mechanism | reference |
|---|---|
| reduction of antigenic immunogenicity | UHR and MÖLLER [105] |
| direct B cell inhibition | ROWLEY et al. [80] |
| macrophage inhibition | PIERCE [76]<br>RYDER and SCHWARTZ [81] |
| induction of suppressor T cells | GERSHON et al. [36] |
| induction of small amounts of tolerogenic high affinity antibodies | BIRNBAUM et al. [12] |
| T cell receptor blockade | KONTIAINEN [58] |
| inhibition of T-B cooperation | SINCLAIR [88] |

Tab. 1 - Antibody and antigen-antibody complexes mediated immunoregulation.

An alternative model of immunoregulation by antibody and antigen-antibody complexes has recently been proposed by SINCLAIR [88]. According to this author, the Fc portion of antibody is required for suppression of the antibody response and this suppression may directly affect B cells or involve T cells. In this case T cell involvement is not, as indicated by GERSHON et al. [37], activation of suppressor T cells, but may result in removal or dampening of an existing antibody feedback by helper T cells engaged in B cell activation.

Although immunologists have been recently relatively less interested than before in antibody feedback, its importance is clearly documented. As an example, recent work has demonstrated that the decline of plaque-forming cells (PFC) response *in vitro* after days 5 and 6 of culture is mediated, at least in part, by antibody feedback [1]. Direct evidence for the suppressive role of endogenous production of antibody *in vitro* has been obtained by the addition of *Staphylococcus aureus* to the reservoir of diffusion cultures in which macromolecular diffusion was allowed by the use of 0.2 μ Nuclepore membrane to separate inner and outer chamber. Continuous removal by this immunoadsorbent of antibody produced during *in vitro* culture markedly increased the PFC response.

The plethora of different mechanisms involved in antibody feedback probably reflects different experimental conditions, but it also offers an example of redundancy in the immune system. In other words, to perform such a fundamental task like suppression of the antibody response, the immune system has many options available which are selected and carried out through different functional pathways.

## 2. T CELL REGULATION

T cells have a fundamental role in the regulation of the immune system. In particular, the net antibody production is controlled by a delicate balance between helper T cells (surface phenotype: Thy $1^+$, Ly $1^+23^-$, $Ia^+$) and suppressor T cells (Thy $1^+$, Ly $1^-23^+$, I-$J^+$) [15, 32, 69, 70]. Many recent reviews examine in detail characteristics and functions of T cell subsets [16, 35, 75, 90].

We will consider three aspects of T cell regulation: I. regulatory interactions among T cell subsets; II. H-2 linked Ir gene control of T cell function; III. regulatory role of antigenic epitopes in T cell subsets induction.

### I. *Regulatory interactions among T cell subsets*

The delivery of a positive or a negative signal to B cells is mainly the result of complex regulatory interactions among T cell subpopulations. The first example of T-T cooperation was given by CANTOR and ASOFSKY [14] which demonstrated synergy between precursor and amplifier T cells in the generation of graft-versus-host reaction. Subsequently, negative T-T interactions, leading to suppression of the antibody response, have been demonstrated to take place between suppressor and helper T cells [36, 97]. Detailed analysis of T cell interactions in the regulation of antibody response has been carried out by TADA et al. [94-98]. Two distinct antigen specific T cell factors, one suppressing (TsF) and the other enhancing (TaF) the antibody response have been identified [98, 102]. The gene which codes for the TsF was mapped in the I-J subregion and that coding for TaF in the I-A subregion of the H-2 complex [96, 99]. Both molecules were found to be selectively expressed

on T cell subpopulations and were antigenically distinct from classical B cell Ia antigens. TsF is a product of Ly $23^+$ cells and TaF is produced by Ly $1^+$ T cells (see also tab. 3). The acceptor sites for both T cell factors were found to be on Ly $123^+$ T cells. Two distinct amplification loops have been suggested [93]. TsF acts on Ly $123^+$ cells to induce new suppressor T cells, whereas TaF will induce precursor cells of the same Ly $123^+$ pool to become helper T cells. Thus, antibody production is regulated by multiple T cell factors, some of which directly mediate T-B collaboration and others regulate the magnitude, duration and quality of the response.

Subsequently, two distinct types of carrier specific helper T cells were demonstrated to act independently and synergistically in the generation of a B cell activating signal [95]. The first type of helper T cell (Th1) can help the response of hapten-primed B cells only if the haptenic and carrier determinants are present on the same molecule (cognate interaction). The second type of helper T cell (Th2) can help the B cell response to an hapten coupled to heterologous carrier upon stimulation with unconjugated relevant carrier (polyclonal interaction). Therefore, at least two distinct pathways involving different subsets of carrier specific helper T cells are operating in T-B collaboration. Both Th1 and Th2 are Ly $1^+$ cells but Th2 bear also products controlled by the I-J subregion. Thus, the I-J subregion contains at least two distinct loci controlling different I-J molecules on suppressor and helper T cells [71, 94].

New fascinating complexities in immunoregulatory circuits among T cell subpopulations have been recently revealed. Members of the Ly $1^+$ set are divisible into more discrete populations according to differential expression of the Qa1 surface phenotype [91, 92]. Antigen-stimulated Ly $1^+$ cells, in addition to stimulating B cells to secrete antibody, can induce Ly $123^+Qa1^+$ T cells to exert feedback suppression activating the Ly $23^+$ system both *in vivo* [18] and *in vitro* [25]. In addition, it has been shown that signals from both Ly $1^+Qa1^+$ and Ly $1^+Qa1^-$ cells are required for optimal B cell induction [17].

## II. *H-2 linked Ir gene control of T cell function*

Immune recognition and cellular interactions to T-dependent antigens are controlled by the products of immune response (Ir) genes, located within the major histocompatibility complex, H-2 in the mouse. Ir genes are mapped in the I region, a segment of the 17th chromosome between the K and S regions of the H-2 complex [56, 86, 108]. Results obtained in a number of laboratories have permitted the delineation of Ir genes regulatory function [7, 8, 55, 63]. Analysis of Ir genes and their regulatory effects has been possible through the use of congenic and recombinant strains and of immunogens restricted in specificity and heterogeneity such as synthetic polypeptides with limited number of amino acid residues, alloantigens, and relatively small proteins with a limited number of antigenic epitopes. A representative list of H-2 associated immunoregulatory functions is given in tab. 2.

Antibody response to T-dependent antigens requires interactions among T cells, B cells and macrophages. (Throughout this review the word macrophage is used as a synonym for antigen-presenting accessory cell). The mechanisms by which H-2 linked Ir genes regulate interactions among these cell populations remain controversial. An up-to-date summary of the conflicting results and discordant interpretations of the genetic control of antibody response can be found in [8].

| function | reference |
|---|---|
| immune response to T-dependent antigens | McDevitt and Chinitz [64] |
| allogeneic effect | Hirst and Dutton [42] |
| T-B collaboration | Kindred and Shreffler [54] |
| complement activity | Demant et al. [23] |
| serologically detectable Ia antigens | David et al. [22] |
| cell-mediated immunity to viral antigens | Zinkernagel and Doherty [114] |
| cell-mediated immunity to bacterial antigens | Zinkernagel [113] |
| complement receptor expression | Gelfand et al. [33] |
| production of helper factor | Taussig and Munro [100] |
| production of T cell derived suppressor factor | Takemori and Tada [98] |
| T cell-mediated suppression | Kapp et al. [50] |
| Ir gene complementation | Vaz et al. [107] and Dorf et al. [24] |
| cell-mediated immunity to hapten-modified cells | Shearer et al. [85] |
| cell-mediated immunity to minor histocompatibility antigens | Bevan [10] |
| macrophage-T cell interaction | Erb and Feldmann [29] |
| development of delayed-type hypersensitivity | Miller et al. [66] |
| antigen-dependent T cell proliferation | Schwartz and Paul [83] |
| suppression of mixed lymphocyte reaction | Rich and Rich [77] |
| response to different peptides on the same molecule | Berzofsky et al. [9] |
| production of T amplifier factor | Tokuhisa et al. [102] |
| activation of helper or suppressor T cells by the same peptide | Adorini et al. [2] |

Tab. 2 - Partial list of H-2 associated immunoregulatory functions.

Initially, analysis of Ir genes function in the regulation of antibody response indicated a requirement for H-2 identity between helper T cells and B cells, and between macrophages and proliferating T cells [86]. Subsequently, it has been demonstrated that genotypic identity between helper T cells and B cells is not sufficient and not required for an effective T-B collaboration to occur. Therefore, the role of Ir genes in regulation of cell interactions could be viewed as a requirement for T cell recognition of H-2 determinants expressed on macrophages and/or B cells, rather than strict H-2 identity between T and B cells.

Erb and Feldmann [29] first demonstrated genetic restriction at the level of macrophage-T cell interaction in the *in vitro* generation of helper T cells. In fact, antigen-primed helper T cells are able to stimulate syngeneic unprimed B cells only if antigen-pulsed macrophages are syngeneic with helper cells at the I-A subregion [29].

In a recent study by Singer et al. [89] requirements for helper T cell recognition of H-2 determinants expressed on macrophages and/or B cells were examined using separated and purified cell populations. Complicating allogeneic effect, likely a major source of conflicting results in this area, were minimized or avoided by the use of helper T cells from normal $F_1$ hybrids, parent$\rightarrow F_1$ and $F_1\rightarrow$parent chimeras. Results of this study support the general notion that regulation of cell interactions by H-2 linked Ir genes is best understood as specific recognition, rather than

homology, of H-2 determinants expressed on the surface of the interacting cell populations. In particular, it appears that no requirement for H-2 recognition exists between helper T cells and B cells, and that helper T cells are only required to recognize H-2 determinants expressed by macrophages.

Ir gene expression on T cell subsets has been mainly studied by examining antigen-specific factors which bear I-region coded determinants [31, 52, 59, 68, 101, 109]. Representative examples of T cell factors are given in tab. 3.

These factors have several features in common: they are antigen specific, are extracted or released from immune T cells, lack immunoglobulin determinants, their molecular weight is about 50,000, and bear I-region controlled determinants. Recently, it has been demonstrated that azobenzenearsonate-specific suppressor factor bears idiotypic determinants, and that this suppressor factor contains a molecular complex composed of idiotypic determinants and H-2 linked products [34]. T cell factors and the closely linked T cell receptor are still imprecisely defined, but their final biochemical and functional characterization should soon be available through the analysis of T cell hybridoma products.

Although the vast body of data on T cell factors points to the expression of Ir genes in T cells, direct experimental evidence is still lacking. However, specific Ir gene function is clearly expressed in macrophages and B cells, as shown in various systems by the demonstration of non responder defect in one or the other cell populations. The prototype experiment to demonstrate the selective role of macrophages in T cell activation is to prime (responder x non responder) $F_1$ T cells with antigen on either of the parental macrophages. SHEVACH and ROSENTHAL [86] first demonstrated, in the guinea pig system, that antigen-pulsed macrophages from the non responder parent fail to activate $F_1$ proliferating cells, whereas macrophages from the responder parent induce strong T cell proliferation. More recently, MARRACK and KAPPLER [63] demonstrated that when (responder x non responder) $F_1$ T cells are titrated with various combinations of B cells and macrophages of either parental H-2 type, high responsiveness requires the presence of at least high responder B cells and, in one case, high responder macrophages in the cultures, indicating expression of Ir genes in both cell types.

A currently accepted model of Ir gene function postulates that Ir genes control expression of Ia molecules on macrophages and B cells. Therefore, macrophages bearing certain Ia determinants (e.g. I-A) may favour induction of helper T cells whereas macrophages presenting antigen in the context of K or D molecules could favour preferential stimulation of suppressor T cells. In addition, subsets of macro-

| function | source | target | H-2 restriction | reference |
|---|---|---|---|---|
| helper | Ly $1^+$ | B | — | MUNRO and TAUSSIG [68] |
| | Ly $1^+$ | macrophages (B?) | — | HOWIE and FELDMANN [45] |
| suppressor | Ly $23^+$ I-$J^+$ | Ly $123^+$ | + | TADA et al. [93, 96] |
| | Ly $23^+$ I-$J^+$ | ? | — | KAPP et al. [51, 52] |
| | Ly $23^+$ I-$J^+$ | Ly $1^+$ | — | KONTIAINEN and FELDMANN [59] |
| amplifier | Ly $1^+$ | Ly $123^+$ | + | TOKUHISA et al. [102] |

Tab. 3 - Antigen specific T cell factors as immunoregulatory molecules.

phages could handle antigen in different ways and through a process of intramolecular selection [79] present to the respective T cell subsets helper or suppressive antigenic epitopes [2]. The interaction through Ia determinants and antigenic epitopes [53] could create the immunogenic signal for T cell activation. This hypothesis has been verified and a genetically restricted factor (GRF) has been found in macrophage culture supernatants. GRF is composed of Ia and antigenic determinants and is able to induce antigen specific helper T cells [30].

The model also predicts that the same Ir gene products are expressed on B cells and macrophages. Interaction of Ia molecules with antigen bound to specific receptors on the B cell membrane could thus provide a target for products of GRF-activated T cells. Restrictions imposed by the GRF-helper T cell interaction could therefore explain the restriction observed in secondary antibody responses at the level of T-B collaboration [54, 89].

### III. *Regulatory role of antigenic epitopes in T cell subsets induction*

In every immunogenic molecule there are antigenic epitopes potentially able to induce suppressor or helper T cells [84]. The intramolecular selection of critical peptides by macrophages [79] can lead to preferential activation of functionally different T cell subpopulations [2], and what may be crucial is the complex of macrophage enzymes available to a strain which would eventually determine the size and nature of the peptides presented to T cells [65].

A comprehensive analysis of the regulatory role of antigenic epitopes has been carried out in the lysozyme system [85]. The antibody response to a set of closely related lysozymes is under H-2 linked Ir gene control [41]. C57BL/10 mice (H-$2^b$) are non responders to hen egg-white lysozyme (HEL), whereas the congenic B10.A (H-$2^a$) mice are responders. Both strains respond to the closely related ring-necked egg-white lysozyme (REL). HEL, but not REL, is able to induce suppressor T cells in non responder mice [4]. HEL and REL differ only at ten amino acid residues (out of 129) indicating that a limited region on the non immunogenic HEL, absent on REL, can account for the induction of suppressor T cells in H-$2^b$ non responder mice. The N-terminal, C-terminal peptide (N-C) obtained from HEL and representing 20% of the entire molecule, is able to induce antigen specific suppressor T cells in B10 and helper T cells in B10.A mice. The $L_{II}$ peptide, the remaining 80% of the HEL molecule, induces helper cells specific for HEL in both B10 and B10.A mice [2]. The genetic nonresponsiveness of B10 mice to HEL can therefore be attributed to the activation of suppressor T cells by a restricted portion of the molecule (N-C) which prevents the potential response directed against other epitopes on the same molecule ($L_{II}$). Therefore, one manifestation of Ir gene activity appears to be the intramolecular selection of different antigenic determinants leading to the activation of suppressor or helper T cells, as exemplified in the B10 strain by the N-C and $L_{II}$ peptides effect.

The existence of limited regions on antigenic molecules able to activate suppressor T cells to nullify the positive effect induced by helper T cells reactive with other epitopes present in the same molecule has been demonstrated in the response to β-galactosidase, where a single cyanogen bromide peptide of β-galactosidase induced T cell-mediated suppression specific for haptens coupled to the native enzyme [104]. Furthermore, a peptic fragment of BSA has been demonstrated to induce suppressor T cells able to suppress the primary anti-BSA IgE response [67].

The regulatory role of limited portions on a protein antigen in affecting the overall response to the entire molecule has also been reported in the myelin basic protein system [39]. Myelin basic protein, which can induce experimental allergic encephalomyelitis, can be cleaved into distinct regions, one of which causes encephalomyelitis whereas a different one induces specific suppressor T cells preventing the disease upon subsequent challenge with myelin basic protein. Induction of suppressor T cells able to counteract helper activity has also been indicated by the finding that a polypeptide of glutamic acid and alanine (GA), which is immunogenic in H-$2^s$ mice, can be converted into a non-immunogenic antigen by the addition of 4-10% tyrosil residues (GAT) [83].

Presentation of selected antigenic epitopes has therefore a relevant part in regulation of antibody response, and they probably play a decisive, although not always recognized, role in tipping the immune balance toward help or suppression.

## 3. IDIOTYPIC NETWORK

The term idiotype was originally coined to designate unique antigenic determinants present on immunoglobulin molecules of a certain animal responding to a given antigen [61, 72]. However, the discovery of extensive idiotypic cross-reaction rendered the original definition obsolete. Idiotypes are therefore currently defined as antigenic determinants present in the immunoglobulin chain variable domain. The structural and serological analyses of idiotypic determinants have been extensively reviewed [28, 44, 62, 110] and we will restrict our discussion to a recently developed area of idiotype research, the functional role in immunoregulation of idiotypic determinants of antigen specific receptors.

The concept of the immune system as a functional idiotypic network stemmed from a theory proposed by JERNE [47-49] to explain Oudin's results [72] and the Oudin-Cazenave phenomenon [73]. These observations, critical for the formulation of the network theory, are that a given idiotype may be associated with combining sites specific for different antigens. In addition, the same antigen specificity may be associated to different idiotypes. This led to the fundamental idea of the network theory: each combining site not only recognizes antigenic determinants but it is also recognized by anti-idiotypic determinants within the same immune system. Thus, a large number of idiotype-anti-idiotype connections are easily formed in a functional network of lymphocyte receptors and soluble molecules. The basic features of Jerne's network are depicted in fig. 1.

According to Jerne's theory the immune system is normally suppressed and when it is perturbed by immunogens there is a response in order to reestablish homeostasis.

The induction of the first set of idiotypes (1) is stimulated by an antigenic epitope (E) on an immunogenic molecule. A second, idiotypically complementary set (2) is activated when a certain threshold level is reached and will induce suppressive or enhancing events. In addition, two other sets were postulated: the 'internal image' (3) set bearing idiotypic determinants recognized by the first set, and thus similar to the antigenic epitope, and the 'parallel' set (4), similar in idiotypic determinants to (1) but with different antigenic specificity. This is an 'open' system, idiotype-anti-idiotype reactions will involve ever larger sets of lymphocytes and potentially the entire network of the immune system.

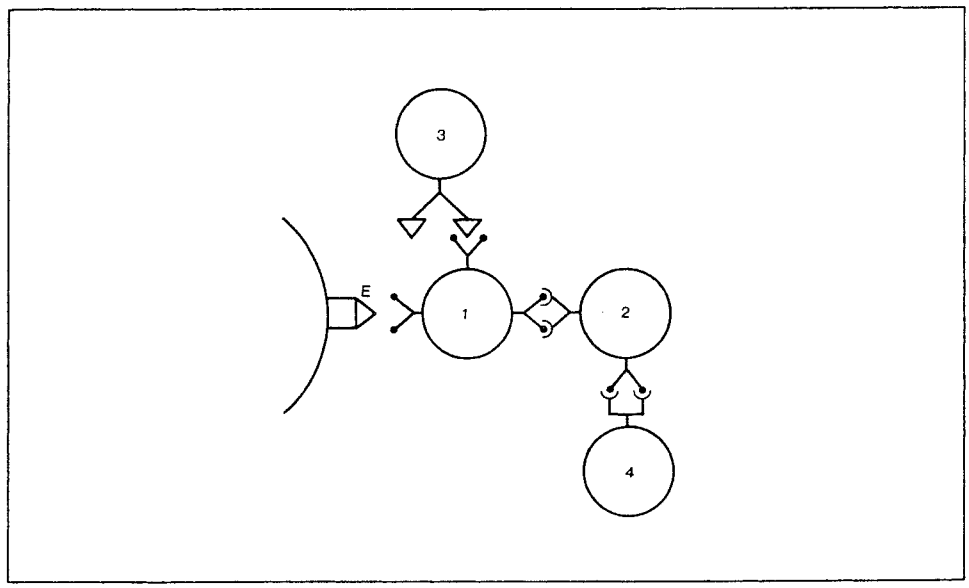


Fig. 1 - Schematic representation of Jerne's idiotypic network. E = antigenic epitope on an immunogenic molecule. 1 = epitope recognizing set; 2 = anti-idiotypic set; 3 = 'internal image' set; 4 = non antigen specific parallel set. See text for details.

The principles of the network theory were formulated in the early seventies when idiotypic analysis was merely descriptive and since then it has been considerably refined and extended [43, 78, 106], but it created the speculative framework of a radically different view not only of the regulation of the immune system, but of the immune system itself. This became an antigen-independent, self-regulated network of interaction in which all the components are in mutual equilibrium receiving positive and negative signals from within the system. Antigen introduction perturbs the network and its effects reverberate through the entire system until a new stable state is reached.

The basic requirement for an idiotypic network is therefore the mutual recognition of idiotypes and anti-idiotypes by B and T cells. A complete survey of all the systems in which idiotypic recognition has been demonstrated is beyond the scope of this review and only selected examples will be examined.

A clear example of recognition by B cells of B cell idiotype is obviously the production of anti-idiotypic antibodies. This has been demonstrated not only in syngeneic systems [21] but, more important, also in autologous systems [57].

Recognition of T cell idiotypes by B cells has been elegantly shown in an impressive series of experiments by Ramseier and Lindemann, and Binz and Wigzell, reviewed in [11]. The general protocol of these studies has been to elicit an anti-idiotypic response against T cell-bound receptor molecules by injecting into $F_1$ animals (mice or rats) cells from one parental strain. The conclusion reached is that idiotypic determinants on antibodies might be shared or identical to corresponding recognition structures on T lymphocytes. $V_H$ sharing between T and B cell antigen receptor was also suggested by BLACK et al. [13]. Guinea pig anti-idiotypic antibodies of the IgG1 class, directed to an A/J antibody against group A

streptococcal carbohydrate (A-CHO), or directed to a Balb/c myeloma protein that binds the same antigen, stimulate, when injected in mice, specific precursor B cells as well as helper T cells. Thus, the answer to the fundamental question: "Do T and B cell receptors share the same set of V genes?", seems to be positive at least for what concerns $V_H$ structures [60].

Recognition of B cell idiotypes by helper T cells has been demonstrated by JANEWAY et al. [46]. These authors have shown that T15 specific helper T cells generated in Balb/c mice (T15 is the idiotype characteristic of the phosphorylcholine-binding TEPC 15 myeloma protein of Balb/c origin) bear receptors which, like antibodies, have exquisite specificity and can discriminate among individual idiotypic determinants present on other isologous PC-binding myeloma proteins. WOODLAND and CANTOR [111] demonstrated that idiotype specific helper T cells bear anti-idiotypic receptors which recognize and interact directly with idiotype positive B cells. Induction of idiotype positive B memory cells after immunization of A/J mice with azophenylarsonate conjugated with keyhole-limpet hemocyanin (Ar-KLH) requires a signal from idiotype specific Ly $1^+$ cells in addition to a signal from carrier reactive Ly $1^+$ cells. Similarly, HETZELBERGER and EICHMANN [40] have demonstrated idiotypic restriction for T-B cooperation in the A5A system, the major idiotype obtained in A/J mice against group A streptococcal carbohydrate. Helper T cells primed *in vivo* with anti-idiotype specific for the A5A idiotype and therefore essentially A5A idiotype positive, cooperate only with the A5A idiotype positive B cells even when mixtures of idiotype positive and idiotype negative B cells are present.

Recognition of B cell idiotypes by suppressor T cells has been demonstrated for the anti-azobenzenearsonate idiotype [74]. A/J mice suppressed by injection of anti-idiotype and hyperimmunized develop suppressor T cells bearing anti-idiotypic determinants detected by rosette formation with mouse red blood cells coated with idiotypic Fab fragments. Shared idiotypic determinants have been detected on antibodies and T cell derived suppressor factor specific for the random terpolymer L-glutamic $acid^{60}$-L-$alanine^{30}$-L-$tyrosine^{10}$ (GAT) [34]. In these experiments, GAT specific T cell derived suppressor factor obtained from non responder mice was specifically absorbed by and eluted from immunoadsorbents prepared from a guinea pig anti-idiotype antiserum recognizing a cross-reactive idiotype found on most murine anti-GAT antibodies. These data provide suggestive evidence for sharing of V region structures between antibodies and T cell suppressor factor specific for an antigen (GAT) under H-2 linked Ir gene control. In addition, T cell derived suppressor factor specific for azobenzenearsonate was found to contain antigen-binding specificity, idiotypic determinants and H-2 gene products, all on the same molecular complex [6].

Direct evidence for sharing of idiotypic determinants between antibodies and suppressor T cells has been obtained in the lysozyme system in which HEL-induced suppressor T cells are eliminated by treatment with anti-idiotypic serum and complement [38]. All these experiments indicate that in different systems helper or suppressor T cells may bear idiotypic or anti-idiotypic determinants. Probably in a functional network both cell types, idiotype and anti-idiotype positive, are present and the predominant induction and/or detection of one of them may only reflect the use of different activating signals for the network: injection of antigen or anti-idiotype.

Recognition of T cell idiotypes by T cells was first suggested by BINZ and WIGZELL [11]. Purified T cells from $F_1$ mice immunized with parental T cells were transferred into irradiated $F_1$ recipients which became resistant to GVH reaction of the relevant parental lymphocytes but not those of the other parent. These results suggest that anti-idiotype bearing $F_1$ T cells can suppress the reactivity of GVH-reactive parental T cells via idiotypic recognition.

Idiotypic recognition within a functional network can result in suppression or enhancement of the idiotype specific B cell response depending whether clonally restricted suppressor T cells or helper T cells have been predominantly activated. Several examples of network activation leading to positive or negative effects by anti-idiotype injection have been reported.

Newborn Balb/c mice, when injected with anti-idiotype to the T15 idiotype, become cronically suppressed in the anti-phosphorylcholine (PC) response [5]. After several months some degree of anti-PC responsiveness is restored but this response is T15 idiotype negative whereas in control mice almost 100% of the anti-PC antibody population expresses the T15 idiotype. However, in this experimental system suppressor T cells have not been demonstrated. Therefore, if suppressor T cells, which could theoretically suppress T15 positive B cells or T15 specific helper T cells, are not involved, the most likely explanation for this case of idiotype suppression is direct blockade of B cell clones by anti-idiotypic antibody. Thus, we have come to a full circle, this form of suppression could very well be considered as a more precise definition of antibody feedback and, retrospectively, it is conceivable that most forms of antibody feedback represent indeed suppression by anti-idiotype.

In addition, EICHMANN [27] demonstrated that adult A/J mice injected with guinea pig IgG2 fraction of anti-A5A idiotype become specifically suppressed. This suppression has been shown to be caused by suppressor T cells able to induce unresponsiveness of A5A positive helper T cells. On the other hand, injection of IgG1 fraction of the same anti-idiotype induces enhancement of the response, presumably via direct activation of A5A positive helper T cells [26, 27].

Thus, perturbation of the network by administration of anti-idiotype can alter mechanisms of immunoregulation in different ways. However, injection of anti-idiotype does not permit an entirely satisfactory analysis of the network, because it can potentially turn on or off multiple cell subsets involved in immunoregulation. A distinct approach, which could allow more meaningful interpretations, is to inject antigen and then follow the expression of network components on the surface of the different cell types participating in the response.

Following this experimental approach, a model has recently been proposed relating idiotypic and antigenic specificity of helper T cells, suppressor T cells and B cells induced by HEL (see also section 2, part III). These studies have permitted to envisage a minimal network model implicating four different lymphocytes bearing complementary receptors, as shown in fig. 2. HEL immunization of B10 non responder mice induces suppressor T cells specific for the N-C region of the molecule. These suppressor T cells could interact through idiotypic complementarity with an idiotype specific helper T cell, or through antigen bridge with carrier specific helper T cells. The latter mechanism has been demonstrated in a T cell proliferative system [112] and the former is implied by the presence of idiotypes on suppressor T cells and of anti-idiotypic determinants on helper T cells [3]. Moreover, plate absorp-

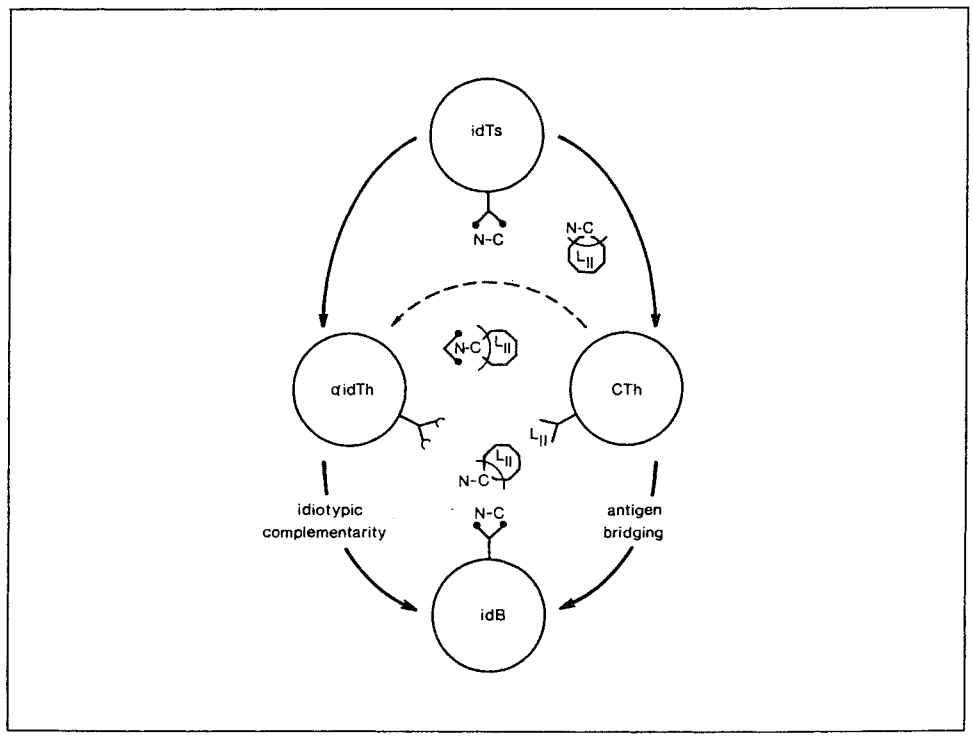


Fig. 2 - Cellular specificities and a possible network of interactions in the response to HEL. The octagon represents the HEL molecule, operationally divided into hapten (N-C) and carrier ($L_{II}$) specific determinants. Optimal activation of idiotype positive, hapten specific B cells (idB) is achieved through interaction with idiotype specific helper T cells (αidTh) and carrier specific helper T cells (CTh). A possible interaction between these two types of helper T cells is suggested by the broken arrow indicating presentation of idiotypic determinants by carrier specific helper cells to idiotype specific helper cells. Idiotype positive, hapten specific suppressor T cells (idTs) could interact via idiotypic complementarity with idiotype specific helper T cells, or via antigen bridge with carrier specific helper T cells.

tion experiments have demonstrated that idiotype positive, hapten (N-C) reactive B cells are optimally stimulated by two different signals, one coming from anti-idiotype positive helper T cells (idiotypic bridge) and the other from carrier ($L_{II}$) reactive helper T cells (antigen bridge) [3]. Therefore, carrier specific helper T cells involved in this network are directed against a different determinant on HEL than are suppressor T cells or B cells. This could explain the presence of complementary idiotypic determinants on helper T cell and B cell receptors. In other systems helper cells can bear idiotypes identical to the dominant B cell idiotype. Interestingly, this occurs when antigen is multivalent such as streptococcal carbohydrates [27,28] or phosphorylcholine [5], where helper T cells specific for the repeating epitope can present the same antigenic determinant to B cells. In the lysozyme system this type of relationship is obviated because HEL is monovalent for any given epitope. Moreover, the requirement for different antigenic specificity between helper T cells and B cells could lead to a functional helper population lacking the dominant B cell idiotype.

In summary, the antibody specificity in the response to HEL is restricted antigenically and idiotipically. Likewise, suppressor T cells raised in a non responder

mouse strain show a remarkably similar restriction to this same determinant. The presence of the same antigenic and idiotypic determinants on these two cell populations ensures communication between suppressor T cells and B cells via helper T cells with complementary idiotypic and epitopic receptors.

Thus, the two major specific communication systems among lymphocytes engaged in the antibody response, antigen bridge and idiotypic complementarity have been integrated and a possible regulatory circuit has been delineated.

## CONCLUSIONS

We have so far examined a number of models, for the most part limited to restricted areas of immunoregulation. While the ultimate model, encompassing all the aspects of immunoregulation is still elusive, we could perhaps try to imagine a possible *scenario* of antigen-triggered events in the antibody response.

1. *Before antigen*: the system is in equilibrium through a subthreshold level of mutually inhibitory, idiotypically complementary cell interactions.

2. *Antigen enters*: after a degree of macrophage processing antigenic epitopes with helper or suppressive properties are complexed to Ir gene products and stimulate helper or suppressor T cells. Intracellular communication can then take place among T cells over a bridge of native antigen or via idiotypic complementarity. Accordingly, clonally restricted B cells will be stimulated to proliferate and differentiate by antigenic and idiotypic signals. The immunodominance of certain epitopes, presumably the resultant of macrophage presentation and repertoire availability, will also influence the relative preponderance of suppressor or helper cells in the circuits. In this way antigen sets the framework in which the idiotypic network will operate.

3. *Antigen is eliminated*: after having conditioned the system into certain options (suppression or help), the antigen looses its primary, steering, regulatory function. The long-term overall regulation of the system is then mainly sustained by a self-contained, self-limited, 'closed' idiotypic network.

Obviously, this is not an absolute conclusion, but a provisional one.

## SUMMARY

Three major regulatory mechanisms operating in the control of antibody response have been examined: 1. antibody feedback; 2. T cell regulation (I. regulatory interactions among T cell subsets, II. H-2 linked Ir gene control of T cell function, III. regulatory role of antigenic epitopes in T cell subsets induction); 3. idiotypic network. Analysis of the results obtained in the lysozyme system together with available data in the literature have permitted the delineation of a model of antigen-triggered events involved in the regulation of antibody response. The basic feature of the proposed model is the integration of two major specific communication systems among lymphocytes engaged in the antibody response: antigen bridge and idiotypic complementarity.

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