Chapter 17. Synthesis

In this chapter I begin by describing three types of suppressor T cells called Ts1, Ts2, Ts3, two kinds of helper T cells called Th1 and Th2 cells, and an intriguing aspect of serum IgG antibodies. This leads to a more comprehensive co-selection model of regulation involving these components. More of the extensive data on I-J is then discussed in the context of this model. The model leads to a postulated role for serum IgG in the maintenance of self tolerance. The model is then further extended to include IgM secreting and IgG secreting B cells. I conclude by addressing the question of why HIV is not highly infectious compared with many other viruses. We begin with some phenomenology.

The suppressor T cells Ts1, Ts2 and Ts3

Evidence has been obtained for the existence of three kinds of suppressor T cell, that came to be known as Ts1, Ts2 and Ts3 cells. Some investigators gave them the names "suppressor inducer" (Ts1), "suppressor amplifier" (or "acceptor", Ts2), and "suppressor effector" (Ts3). Ts1 cells were antigen-specific and were found to induce the appearance of Ts2, and Ts2 induced the appearance of Ts3. Ts3 is typically a population that expresses the same idiotype as Ts1, but does not bind antigen.[275] This means that both Ts1 and Ts3 cells have specific receptors that bind to an antiidiotypic reagent. If the Ts3 cells bind antigen, they can be considered to be part of the Ts1 population by definition, and in some systems only Ts1 and Ts2 but not Ts3 have been described.[276] The presence of idiotypic and antiidiotypic Ts in this "cascade" is unambiguous evidence of idiotypic network regulation. Specific T cell factors are involved. The antigen acts on Ts1 cells, which make specific factors called TsF1, that act on (induce) Ts2, and these make specific factors called TsF2, that in turn act on (induce) Ts3. Ts1 and TsF1 typically express an idiotype that is present on antibodies produced in response to the antigen. Ts2 and TsF2 have a corresponding antiidiotype, and Ts3 and TsF3 express the same or a similar idiotype to that of Ts1 and TsF1. In some systems Ts1 cells do not express I-J, while Ts2 and Ts3 cells express I-J.

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[275] K. Okuda, M. Minai, S. Furusawa and M. E. Dorf (1981) Analysis of T cell hybridomas. 2. Comparisons among 3 distinct types of monoclonal suppressor factors. J. Exp. Med. 154, 1838-1851.

[276] M. S. Sy, A. Nisonoff, R. N. Germain, B. Benacerraf and M. I. Greene. (1981) Antigen- and receptor-driven regulatory mechanisms. VIII. Suppression of idiotype-negative, p-azobenzenearsonate-specific T cells results from the interaction of an anti-idiotypic second-order T suppressor cell with a cross-reactive-idiotype-positive, p-azobenzenearsonate-primed T cell target. J. Exp. Med. 153, 1415-1425, 1981.

Th1 and Th2 helper T cells

Tomio Tada and his collaborators found evidence for two types of helper T cells, one of which does not express I-J called Th1, and one that expresses I-J. They called the latter Th2.[277] These two kinds of helper T cells were defined in *in vivo* experiments, and as mentioned in chapter 7 are not to be confused with Th1 and Th2 cell lines that were later defined on the basis of the cytokines they produce.

The experiments of Tada et al. were done using a hapten-carrier system, in which the hapten was DNP (dinitrophenyl) and the carrier was keyhole limpet hemocyanin (KLH) or egg albumin (EA). Hapten primed B cells were combined with carrier primed T cells in vitro, and the anti-DNP IgG response to the hapten-carrier conjugate was measured. There are two kinds of response in such systems called "cognate interaction" and "non-cognate interaction." In the cognate interaction the hapten has to be attached to the carrier used in priming the T cells in order to obtain a response. In the non-cognate interaction the hapten can be coupled to a different carrier, and then both carriers have to be present as antigens to obtain the response. When the T cells are primed with KLH and the B cells are primed with DNP, the Th1 cells were able to help an anti-DNP response to DNP-KLH conjugates as the antigen in vitro (cognate help). The Th2 cells were able to help an anti-DNP IgG response to DNP-EA and KLH as the antigens (non-cognate help). Cognate help is considered to reflect the need for a B cell and a T cell to be in close proximity, while non-cognate help reflects a situation in which the help can be delivered less specifically via lymphokines that act over greater distances.

IgG dimers in pooled sera

When many human sera are pooled and then examined under an electron microscope, dimers of IgG molecules are observed.[278,279] The dimers can be seen in the electron microscope images to be bound to each other via V-V interactions. Very few such dimers are seen in IgG from a single serum. This finding fits with the symmetrical network theory. The IgG

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[277] Tada, T., Takemori, T., Okumura, K., Nonaka, M. & Tokuhisa, T. (1978) Two distinct types of helper T cells involved in the secondary antibody response: Independent and synergistic effect of Ia- and Ia+ helper T cells. J. Exp. Med. 147, 446-458.

[278] J. S. Finlayson, B. L. Armstrong and A. M. Young (1971) Reversibility of human immunoglobulin G dimerization. Acta Radiol. Suppl. 310, 114-123.

[279] D. L. Tankersley, M. S. Preston and J. S. Finlayson (1988) Immunoglobulin G dimer: an idiotype-anti-idiotype complex. Molec. Immunol. 25, 41-48.

specificities in a single serum include those for which the immune system is in the immune state. IgG molecules kill cells with high affinity complementary specificities, such that clones with complementary V regions with high affinity are effectively eliminated. When serum antibodies from one individual are combined with IgG from other sera, the IgG idiotypes in those other sera are different ones, and hence there are complementary clones that have not been eliminated. The more sera that are combined, the higher the fraction of IgGs that form dimers.

While a plasma sample from a single individual contains less than one percent of the IgG molecules as IgG-IgG (idiotype-antiidiotype) complexes, pools of IgG from many donors can contain as much as 40% of the IgG being present as such dimers. In one experiment Tankersley and colleagues discovered a striking linear relationship between the percent of IgG present as dimers and the logarithm of the number of donors. For the number of donors between 23 and 10,000 this relationship is shown in Figure 17-1.[280] From their data the relationship is

$$\text{percentage of dimers} = 8.6 \log_{10}(\text{number of donors}) - 9.3$$

to a good approximation. The formulation of a model that would quantitatively account for this linear relationship is an intriguing challenge. The percentage of dimers for a single individual does not lie on the straight line. When IgG from 23 donors were pooled only 2.91% of the IgG forms dimers, and in order to roughly double the percentage of dimers from 10% to 21% it was necessary to increase the number of donors in the pool by a factor of 20.

It is surprising that IgG from so many donors is needed to form the fraction of dimers shown in this figure. If serum IgG V regions satisfied the unpredictability axiom, meaning that they are generated by a random process, one might expect that pooling the IgG from even two donors would result in a higher fraction of dimers than 2.91%. For if each of the two donors made a million random antibodies, there would be 10^{12} possible V-V interactions, and each V region would have a million chances to find complementary V regions in the other donor's IgG. So such a pool of IgG from even just two donors would be expected to have a very large fraction of dimers, and the low fraction of dimers present in serum IgG pooled from a small number of donors is a paradox in the context of the unpredictability axiom.

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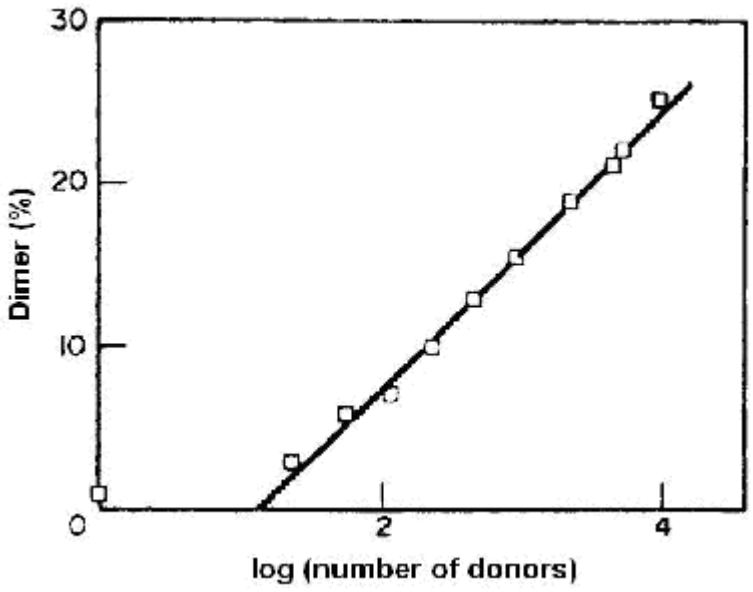
[280] From figure 2 in the previous reference by Tankersley et al.

Figure 17-1. The fraction of IgG dimers in pooled IgG from many donors, as a function of the logarithm of the number of donors. From a figure published in Molecular Immunology, volume 25, by D. L. Tankersley, M. S. Preston and J. S. Finlayson, "Immunoglobulin G dimer: an idiotype-anti-idiotype complex", pages 41-48, Copyright Elsevier (1988). The formulation of a model that would account for this linear relationship is a challenge for immune network theorists.



A model incorporating Ts1, Ts2, Ts3, Th1, Th2 and serum IgG

A co-selection model that incorporates Ts1, Ts2, Ts3, Th1, Th2 and B cells that secrete serum IgG is shown in Figure 17-2. Recall that co-selection means a combination of being selected by another population and contributing to the selection of that population. The Ts2 cells are still the "centre-pole" of the system. There is co-selection of Th1 cells and Ts2 cells as shown previously in the model of Figure 13-2. However, the co-selection of the Ts2 population also involves co-selection of Ts1 and Ts2 cells and co-selection of Ts2 and Ts3 cells. The Ts1 population is shown being selected also by interactions with MHC class II bearing cells, and being co-selected with Th2 cells and serum IgG. Ts3 cells are co-selected with Ts2 cells, Th2 cells and serum IgG. "IgG" in this diagram stands for both the serum IgG and IgG secreting B cells. The concept of "co-selection" applies strictly to the B cells, since IgG molecules cannot be stimulated to proliferate. Nevertheless serum IgG may be more important in stimulating Ts1 and Ts3 cells than the B cells, since IgG is typically present at a high concentration of about 10mg/ml in serum, and by being divalent is able to cross-link complementary receptors. B cells diffuse much more slowly than IgG, and in order to stimulate cells with complementary receptors would need to have cell-cell contact with such cells. Figure 17-2 is a steady state model that shows how the various populations are related to MHC class II. Within each of the cellular populations shown there are both antigen-specific and antiidiotypic cells, and the serum IgG includes both antigen-specific and antiidiotypic antibodies, for any antigen.

The interaction of Ts1 cells with MHC class II cells is consistent with the possibility that the Ts1 population is the same as a population that has more recently been called "regulatory T cells", and that have been ascribed a role in maintaining self tolerance.[281,282] Ts1 cells and these regulatory T cells both express CD4. Since CD4 has some complementarity to MHC class II, these cells would have a tendency to bind to accessory cells that express MHC class II. Then it is furthermore plausible that Ts1/regulatory T cells with

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[281] S. Sakaguchi, N. Sakaguchi, M. Asano, M. Itoh and M. Toda (1995) Immunologic self-tolerance maintained by activated T cells expressing IL-2 receptor α-chains (CD25). Breakdown of a single mechanism of self-tolerance causes various autoimmune diseases. J. Immunol. 155, 1151-1164.

[282] M. J. McGeachy, L. A. Stephens and S. M. Anderton. (2005) Natural recovery and protection from autoimmune encephalomyelitis: contribution of $CD4^+CD25^+$ regulatory cells within the central nervous system. J. Immunol. 175, 3025-3032.

specific receptors that have some complementarity to MHC class II are preferentially selected, just as is the case for CD4 expressing helper T cells.

In this model both Th2 and Ts2 cells are anti-anti-MHC class II, but Th2 cells differ from Ts2 in that they are co-selected by Ts1 and Ts3, while Ts2 cells are co-selected by Th1, Ts1 and Ts3. Since Ts2 cells are co-selected with three other populations, these are the most tightly regulated cells in the system. They are the centre-pole of the idiotypic network.

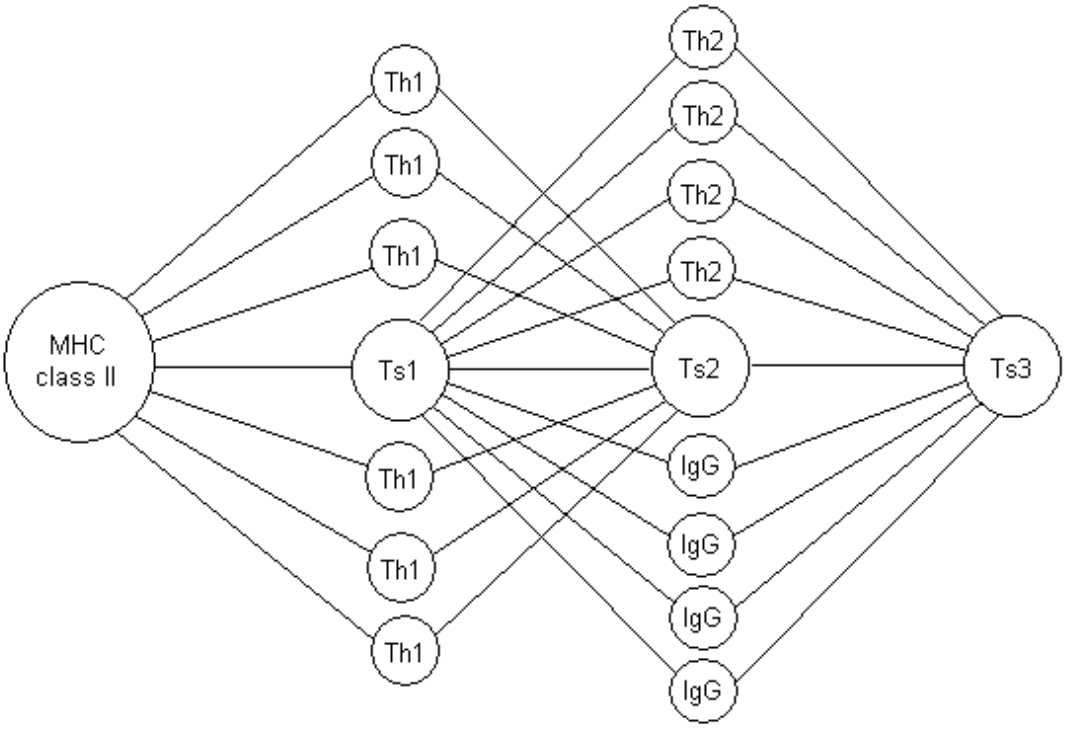
In the model the interactions of Th2 cells with both Ts1 and Ts3 means that Th2 cells are more tightly regulated than are Th1 cells. On the other hand, when Th2 cells are stimulated by an antigen, this constitutes a more profound perturbation close to the heart of the system, resulting in the release of more lymphokines that can provide help over a greater distance. This is consistent with activation of Th2 cells resulting in non-cognate help as described above in the experiment of Tada et al. Since Th2 cells are an internal image of MHC class II cells, but differ from the Ts2 centre-pole, stimulating them is analogous to stimulating the system with allogeneic MHC class II, which is known to be a method for providing non-specific help for B cell responses. Since the T cell receptors of both Ts2 and Th2 cells are internal images of MHC class II, it is not surprising that Th2 cells express I-J determinants, just as Ts2 cells do.

Multiple I-J determinants for a given haplotype have been described. In this model an I-J determinant on Ts2 cells, that we can call "I-J_1", emerges as the result of co-selection of Th1 cells and Ts2 cells. Another I-J determinant on Ts2 cells, say "I-J_2", emerges as the result of co-selection of Ts1 cells and Ts2 cells. A third I-J determinant on Ts2 cells, say "I-J_3", emerges as the result of co-selection of Ts2 and Ts3 cells. The Ts2 cells then have very high idiotypic connectivity, which is consistent with being centrally implicated in suppression. Since in the model Th2 cells and serum IgG are both co-selected with Ts1 and Ts3 cells, they are both predicted by the model to express I-J_2 and I-J_3.[283]

The model of Figure 17-2 involves the serum IgG repertoire being sharply constrained by interactions directly with Ts1 and Ts3, and indirectly with the other populations shown. Ts1 and Ts3 cells are in turn both reciprocally regulated by the Ts2 centre-pole. The result is that serum IgG is a tightly regulated quasi-species, and expresses idiotypic determinants similar to those of Ts2. This commonality means the V regions of serum IgG are then far from random; they are all both anti-Ts1 and anti-Ts3. This constraint means that serum IgG molecules are less diverse than normally imagined; it means that serum IgG is a quasi-species. This explains the surprising fact that IgG from a large number of donors has to be combined in order to obtain a large fraction of IgG dimers, as shown in Figure 17-1. The idea that serum IgG is a quasi-species is a stark departure from traditional thinking, since the

[283] Prediction

Figure 17-2. An idiotypic network model of immune system regulation that includes MHC class II, Th1 and Th2 helper T cells, Ts1, Ts2 and Ts3 suppressor T cells and serum IgG antibodies. For explanation see text.



clonal selection theory involves the ability of an individual to make antibodies with a practically unlimited range of specificities. However, the model of Figure 17-2 refers to the repertoire of serum IgG antibodies and of the B cells that are co-selected to secrete IgG. The B cells that contribute to the pool of secreted serum IgG are a subset of all the B cells. This subset does not include B cells that secrete IgM, that can be expected to have a different repertoire, and there may be some B cells that have switched from IgM to IgG production but are not actively secreting IgG. Hence we have a B cell repertoire that is a potential repertoire, and the IgG repertoire that is a steady state secreted repertoire. The concept that serum IgG antibodies have V regions with idiotypic determinants that resemble idiotypic determinants on Ts2 cells leads to the surprising prediction that immunization of a mouse with the IgG from another mouse, that differs only in its MHC genes, can result in the production of anti-I-J antibodies, and more specifically anti-I-J_2 and anti-I-J_3 antibodies as defined above.[284] MHC congenic strains of mice can be used to test this prediction.

The serum IgG repertoire

In the model the Ts2 centre-pole is also regulated by Th1 cells and indirectly by Th2 cells and serum IgG, and it is important that these interactions are symmetrical. A consequence of the symmetry is that changes in the serum IgG population are accompanied by changes in the Ts2 centre-pole. For each immunization that results in the transient production of serum IgG of a particular specificity, there is a transient shift in the Ts2 centre-pole in shape space. Such a shift is the basis of the preventive AIDS vaccine described in the previous chapter.

The repertoire of Th1 cells is influenced by the complete repertoire of self antigens, including especially MHC class II. The serum IgG repertoire is also indirectly influenced by Th1 and Th2 cells. The totality of the V regions of an individual's serum IgG antibodies is then also an internal image of MHC class II, together with the rest of the self antigens. Since the complete set of self antigens is postulated to be evolutionarily conserved, in order for the set of self antigens to remain a balanced set of shapes and complementary shapes, this provides a rationale for the IgG of different healthy individuals being remarkably similar to each other, and only a relatively small fraction of dimers being formed when a small number of plasma samples are pooled. Different individuals nevertheless have different sets of self antigens, which means their Ts2 centre-poles are not identical, and the corresponding IgG repertoires do

[284] Prediction

not overlap exactly. The IgG idiotypes corresponding to the non-overlapping part of the repertoires of the proteome of different humans are responsible for the formation of the dimers.

While in the model the IgG serum antibodies are positively selected, directly by Ts1 and Ts3 and indirectly by Ts2, Th2 and Th1, the selection process does not need to converge to just a few idiotypes. The IgG idiotypes have in common that they are images of self antigens, including MHC class II, from the perspective of the Ts1 population, but this still allows for a great deal of diversity.

Serum IgG antibodies are thus postulated in this model to have a strongly biased repertoire, namely a repertoire that is a reflection of what is happening at the T cell level. For young, healthy and especially immunologically naïve individuals the spectrum of T cell V regions is expected to be determined by the spectrum of all the self antigens, which are postulated to constitute a balanced set of shapes and complementary shapes, and hence be much the same for different strains and even different species. Superimposed on this is the influence of the polymorphic MHC antigens on the T cell repertoires, that have an impact on both T cell and serum IgG repertoires.

Killing and stimulation by serum IgG

Recall that if two IgG molecules are bound next to each other on the surface of a target cell, complement molecules can bind to the complex and initiate the complement mediated killing of the cell. Such killing played a key role in the description in chapters 10 and 11 of the immune state for a particular antigen, with the relevant molecules on target cells being specific receptors that are antiidiotypic to the IgG. Since IgG killing involves two IgG molecules bound next to each other on a cell's surface, this killing can be expected to occur when the square of the product of the affinity of interaction and the concentration of the IgG is above a certain threshold level.

At lower values of the product of affinity and concentration, individual molecules (as opposed to pairs) of serum IgG bind to the specific receptors of the antiidiotypic clones, and presumably can cause cross-linking and proliferation of the clones. Recall that a cornerstone of the symmetrical network theory is that the stimulation of lymphocytes involves the cross-linking of receptors. There is about 10 mg/ml of IgG in serum, and these antibodies are divalent molecules that are capable of cross-linking receptors on antiidiotypic lymphocytes. The lower affinity condition would apply to relatively large number of antiidiotypic clones, compared to the number for which the threshold for killing is reached. This is because there are plausibly a larger number of pairs of V regions that bind to each other with low affinity, relative to the number of pairs that bind to each other with high

affinity. The lower affinity interactions are envisaged to be important in the co-selection firstly of Ts1 cells and serum IgG, and secondly of Ts3 cells and IgG as shown in Figure 17-2.

Serum IgG may mediate self tolerance

MHC class II molecules certainly have a strong impact on the repertoire of helper T cells. Less is known about the impact that less polymorphic molecules may have, including for example the serum proteins fetuin (a protein present at a high concentration in serum early in development), albumin and complement components. The fact that some complement genes are encoded within the MHC suggests that complement proteins could also influence the T cell repertoire significantly. It is plausible that Th1 and Ts1 cells are more generally anti-self, rather than solely anti-MHC class II, and that the Ts2 cells, Th2 cells and serum IgG are then accordingly more generally anti-anti-self.

In the model of Figure 17-2 there is symmetry in the T cell repertoire in the sense that The Th1 and Ts1 cells are biased to be anti-self, while Th2 cells and Ts2 cells are anti-anti-self. On the other hand the selection of serum IgG molecules through their interactions with Ts1 and Ts3 cells results in the serum IgG having only anti-anti-self specificity and no anti-self specificity. This one-sidedness accounts for the low fraction of dimers that are formed when IgG from only a small number of donors is pooled. Consequently anti-anti-self serum IgG molecules kill cells that have receptors with a high affinity for self, that is, anti-self lymphocytes. Thus this model describes how the emergent, selected repertoire of serum IgG can delete self-specific clones, and can therefore be an important mediator of self tolerance.

I-J restriction in suppressor cell interactions

Suppressor factors and suppressor cells that interact to give suppression typically need to be of the same I-J haplotypes[285,286]. For example Ts2 cells or TsF2 factors from an H-2^b mouse, that has the I-J^b phenotype, activate I-J^b Ts3 cells, but cannot interact effectively with the I-J^k Ts3 cells of an I-J^k mouse. We say the interaction is "I-J restricted". Such restrictions firstly underline the fact that I-J is indeed central to the regulation of the immune system. The idiotypes of the Ts3 population are co-selected with the idiotypes

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[285] K. Okuda, S. Minami, S. Furusawa and M. E. Dorf (1981) Analysis of T cell hybridomas. II. Comparisons among three distinct types of monoclonal suppressor factors. J. Exp. Med. 154, 1838-1851.

[286] M. E. Dorf and B. Benacerraf (1985) I-J as a restriction element in the suppressor T cell system. Immunol. Rev. 83, 23-40.

of the Ts2 population, and the repertoire of the latter is influenced by the particular MHC class II haplotype. Since Ts2 cells in an I-J^b mouse differ from the Ts2 in an I-J^k mouse, the Ts3 cells in the I-J^b mouse are necessarily also different from the Ts3 in the I-J^k mouse. In each case the Ts3 cells are selected (both directly and indirectly) largely by the corresponding Ts2. The individual Ts repertoires that have been selected in the context of different MHC class II, and hence different centre-poles, do not fit together neatly as shown in Figure 17-2.

Igh restriction in suppressor cell interactions

In some systems the interactions of Ts cells and factors are restricted by antibody V region genes, namely the heavy chain locus called Igh.[287,288,289] This phenomenon is called Igh (immunoglobulin heavy chain) restriction. In the previously mentioned p-azobenzenearsonate system of Benacerraf and colleagues, the action of Ts1, Ts2 and Ts3 are all restricted by immunoglobulin heavy chain genes. For example, antigen-specific suppressor T cell factor from Balb/c mice, which of have the H-2^d, Igh-1^a genotype, can suppress T cell responses in Balb/c mice but not in C.AL-20 mice, that are H-2^d, Igh-1^d. Similarly, antigen-specific suppressor T cell factors from C.AL-20 mice can suppress T cell responses in C.AL-20 but not in Balb/c mice. In our model serum IgG exerts a stimulatory role on Ts1 and Ts3, and indirectly also on Ts2, and thus plays an important role in the selection of those repertoires. Then the Ts1 repertoire and the Ts3 repertoire influence also the Ts2 repertoire, and serum IgG indirectly influences also the Ts2 centre-pole repertoire. By first symmetry, these influences are reciprocal, so that the serum IgG repertoire is also profoundly influenced by the Ts1, Ts2 and Ts3 repertoires.

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287 K. Yamauchi, D. B. Murphy, H. Cantor and R. K. Gershon (1981) Analysis of antigen specific immunoglobulin restricted cell-free material made by I-J^+ Ly-1 cells that induces Ly-2^+ cells to express suppressive activity. Eur. J. Immunol., 11, 905-912.

288 M-S Sy and B. Benacerraf (1981) Suppressor T cells, immunoglobulin and Igh restriction. Immunol. Rev. 101, 134-148.

289 M. S. Sy, A. Lowy, K. HayGlass, C. A. Janeway Jr., M. Gurish, M. I. Greene and B. Benacerraf (1984) Chronic treatment with rabbit anti-mouse μ-chain antibody alters the characteristic immunoglobulin heavy-chain restriction of murine suppressor T-cell factors. Proc. Nat. Acad. Sci. USA **81**, 3846-3850.

Immune responses: interplay between T cell and B cell repertoires

The next step is to describe how the model of Figure 17-2 is consistent with the stable steady states for specific antigens described in chapter 10, together with the process of switching from a virgin state to an immune state or from a virgin state to a suppressed state for an antigen.

Figure 17-2 shows only one "principal" axis in shape space, that can be considered to be defined by the anti-MHC class II specificity of Th1 cells of an animal or person, and the anti-anti-MHC class II specificity of the corresponding Ts2 cells. I will call this the host αMHC class II/ααMHC class II shape space axis. When an immune response to an antigen X takes place there is a change in the system with respect to another shape space axis, namely an axis defined by the αX receptors of antigen-specific lymphocytes and the ααX receptors of corresponding antiidiotypic lymphocytes. As already mentioned, for the αX/ααX shape space axis there will be both αX and ααX lymphocytes and antibodies among each of the populations shown in Figure 17-2. The response to the antigen X is governed by the fact that the Th1 cells are the least tightly regulated and hence the most sensitive to stimulation by antigen, and antigen-specific cells are stimulated before the corresponding antiidiotypic cells. If the stimulus, say antigen X, results in the activation of non-specific accessory cells, and αX B cells differentiate to produce αX IgG, there is a change in the system with respect to the αX/ααX shape space axis associated with the antigen, and there is memory (immunity) associated with that change. The system then reverts to close to its original position with respect to the host αMHC class II/ααMHC class II shape space axis, while having a new position with respect to the αX/ααX shape space axis, including changes in the levels of antigen-specific B cells and antigen-specific IgG.

If the non-specific accessory cells are not activated, there can nevertheless be changes in the Ts populations, and antigen-specific tolerance may be induced, without any production of antigen-specific IgG antibodies. Memory can be associated not only with immunity, but also with antigen-specific tolerance. Recall from chapter 10 that the suppressed state of the symmetrical network theory is characterized by elevated and mutually stabilizing populations of antigen-specific and antiidiotypic T cells. Such a change in the T cell repertoires necessarily results in a change in the Ts2 centre-pole of the system. The change in the Ts2 population results in inevitable changes in the other populations, including the IgG repertoire. An increase in antigen-specific and antiidiotypic T cells (induction of the suppressed state) can be expected to correlate with a decrease in the level of antigen-specific serum IgG. The level can be expected to be lower than the

level for an immune system that is in the virgin state for the antigen, since the elevated Ts and TsF levels result in the inhibition of B cells that secret antigen-specific IgG.[290]

While the T cell V region repertoire of an individual influences the B cell V region repertoire,[291,292] and the influence is reciprocal,[293,294] the immune system is regulated primarily by T cells, that are more sensitive to antigen than are B cells.[295] In the model of Figure 17-2, the Th1 cells are ascribed lower network connectivity than the Ts2 cells, and are the least inhibited for proliferation in response to antigen.

The presence of serum IgG at the heart of the self-stabilized system is consistent with the concept that serum IgG is a quasi-species, that mimics the Ts2 central regulating element. It is also consistent with the concept that there is immunological memory for immune responses that exhibit changes in the serum IgG population and associated changes in the Ts2 repertoire.

We recall again that the two major classes of antibody in serum are IgM and IgG. Interaction matrices between IgM monoclonal antibodies derived from neonates have been measured[296,297] and found to have a connectance (fraction of non-zero terms) of about 0.2. IgM responses are not regulated by T cells to the same extent that IgG responses are, and there is no memory associated with immune responses that are solely IgM. We have seen that in

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[290] Prediction

[291] Weksler, M. E. Russo, C. & Siskind, G. W. 1989. Peripheral T cells select the B-cell repertoire in old mice. Immunol. Rev. 110, 174-185.

[292] Freitas, A. A. Lembezat, M.-P. and Rocha, B. 1989. Selection of antibody repertoires. Transfer of mature T lymphocytes modifies VH gene family usage in the actual and available B cell repertoires of athymic mice. Int. Immunol. **1**, 398-408.

[293] M-S Sy and B. Benacerraf (1981) Suppressor T cells, immunoglobulin and Igh restriction. Immunol. Rev. 101, 134-148.

[294] Martinez, C. Pereira, P. Toribio, M. L., Marcos, M. A., Bandeira, A., Hera, A., de la Marquez, C., Cazenave, P. A. & Coutinho, A. 1988. The participation of B cells and antibodies in the selection and maintenance of T cell repertoires. Immunol. Rev. 101, 191-215.

[295] Howard, J. G. & Mitchison, N. A. 1975. Immunological tolerance. Prog. Allergy 18, 43-96.

[296] Holmberg, D., Andersson Å., Carlsson, L. and Forsgren, S. 1989. Establishment and functional implications of B-cell connectivity. *Immunol. Rev.* **110**, 89-103.

[297] Kearney, J. F., Vakil, M. and Nicholson, N. 1987. Non-random VH gene expression and idiotype-antiidiotype expression on early B cells. In: "Evolution and Vertebrate Immunity: The Antigen Receptor and MHC Gene Families." Kelsoe, G. and Schulze, D. Eds., Texas University Press, Austin, pp. 175-190.

the symmetrical network theory IgM plays a role in the virgin state, which is a stable steady state involving many specificities and symmetrical killing between mutually specific clones. As described in chapter 11, mathematical modelling of the postulated IgM interactions has shown that for a given set of IgM secreting clones there is a unique stable steady state. The results obtained with that mathematical model are consistent with the finding that no memory is associated with immune responses that are solely IgM.

When however there is an αX IgG response to an antigen X, there is a fundamental change in the system. While mathematical modeling of the system shown in Figure 17-2 may be helpful, even without it we can envisage how the αX IgG response would change the system. The αX IgG antibodies would stimulate ααX T cell populations, and there would be co-selection of these with αααX T cells. The long-term result would be a shift in each of the populations, including the Ts2 central regulating element, with respect to the αX/ααX shape space axis. The selection and differentiation of IgG-secreting αX B cells can be regarded as a change in the repertoire of self antigens, that similarly impacts on all the T cell repertoires.

On I-J and contrasuppressor T cells

Contrasuppressor cells, as their name implies, inhibit suppression. An experiment demonstrating the phenomenon of contrasuppression is shown in Figure 6-7. The data on contrasuppression is much more limited than the data on suppression, and to my knowledge experiments that could link contrasuppression directly to idiotypic regulation are lacking. Hence a model to explain the phenomenon is more speculative than is the model for suppressor cells shown in Figure 17-2. Contrasuppression is most simply explained in the context of the symmetrical network theory as a process involving a competing mode of excitation of the network, that competes with the mode of excitation that leads to antigen-specific suppression. The idea is that each mode of activation involves a positive feedback loop, and two modes can compete, with one of them becoming dominant. The proposed mechanism of contrasuppression is then essentially the same as that proposed for antigenic competition (chapter 10), in which one mode of excitation of the network preempts another mode. The site of the competition is the A cell surface. If antigen-specific T cell factors and corresponding antiidiotypic factors on the A cell surface have the potential to catalyze the induction of the suppressed state, then specific factors of other specificities have the potential to inhibit that autocatalytic process.

Just as there are Ts1, Ts2 and Ts3 cells, there are three contrasuppressor cell types called Cs1 (“contrasuppressor inducers”), Cs2 (“contrasuppressor acceptors”) and Cs3 (“contrasuppressor effectors”). These contrasuppressor T

cells express an I-J determinant that is different from the I-J of Ts2 suppressor cells, as defined by certain anti-I-J monoclonal antibodies.[298] To be consistent with the rest of our model for I-J, the I-J on contrasuppressor cells must also be the result of a co-selection process, and the challenge is to determine which cells and self antigens play a role in that co-selection process. One possibility is that while the I-J expressed on Ts2 suppressor cells (let us call them collectively I-J^{suppressor}) are primarily an image of MHC class II in the context of CD4-expressing Th1 helper T cells, the I-J idiotypic determinants on contrasuppressor cells (I-J^{contrasuppressor}) are images of MHC class I in the context of CD8 cells. Then the activation of the system along the anti-MHC class I—I-J^{contrasuppressor} shape space axis could inhibit activation along the anti-MHC class II—I-J^{suppressor} axis. The site of competition between the two modes of activation would again be the A cell surface, just as described for the antigenic competition phenomenon.

Monoclonal anti-I-J antibodies specific for suppressor cells and others that are specific for contrasuppressor cells should be useful tools for testing this hypothesis. Anti-I-J antibody mediated activation of suppressor cells is predicted to inhibit anti-I-J activation of contrasuppressor cells and vice versa.[299]

The inverse relationship between antibody responses and DTH

The inverse relationship between antibody immune responses and delayed type hypersensitivity (DTH)[300] may be related to the competition between suppressor T cells and contrasuppressor T cells. If an antigen stimulates the system more along the anti-MHC class II—I-J^{suppressor} shape space axis than along the anti-MHC class I—I-J^{contrasuppressor} shape space axis, the result would be little or no antibody production together with a DTH response. Conversely, an antigenic stimulus that results in more activation along the anti-MHC class I—I-J^{contrasuppressor} axis than along the anti-MHC class II—I-J^{suppressor} shape space axis would result in a stronger antibody response and a weaker DTH response.

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[298] K. Yamauchi, M. Taniguchi, D. Green and R. K. Gershon (1982) The use of a monoclonal I-J-specific antibody to distinguish cells in the feedback suppression circuit from those in the contrasuppressor circuit. Immunogenetics 16, 551-558.

[299] Prediction

[300] C. R. Parish (1972) The relationship between humoral and cell-mediated immunity. Immunol. Rev. 13, 35-66.

A balance in self antigens between shapes and complementary shapes?

The immune system is a highly sensitive system that can be modulated by very small amounts of antigens and antibodies. We have seen that experiments in mice and rats show that the specific response of the system to a particular antigen can be significantly decreased by prior injections of antigen as low as picograms or even less.[301,302] A response consisting of antibodies with a particular idiotype can be suppressed by an injection of 10 to 100ng of antiidiotypic antibody.[303] The injection of nanogram amounts of monoclonal IgM antibody can induce the production of antibodies of the same specificity.[304] The genetic manipulation of adding a single heavy chain gene, that is a marker of a particular idiotype, to the genome of a mouse results in the production of antibodies with the same idiotype, but using other genes.[305] It would seem that such manipulations of the immune system can make a marked difference to the state of the system only if it is normally precisely balanced, such that very small perturbations can shift the state of the system significantly. This may be because a balance between each shape and other shapes that are complementary to it is a basic feature of the repertoire of self antigens that impact on the V regions of the immune system. We can call this the "balanced proteome hypothesis." This hypothetical balance in the proteome of self antigens may be enhanced by the response of the immune system to the repertoire of self antigens, with any imbalance in the self antigen repertoire being dynamically compensated by adjustments in V region repertoires.

There are many soluble self antigens that have complementary cell surface receptors to which they bind. These are examples of shapes and corresponding complementary shapes. The stimulation of the T cell V region

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[301]G. R. Shellam and G. J. V. Nossal (1968) The mechanism of induction of immunological paralysis. IV. The effects of ultra-low doses of flagellin. Immunology 14, 273-284.

[302] G. L. Ada and C. R. Parish (1968) Low zone tolerance to bacterial flagellin in adult rats: a possible role for antigen localized in lymphoid follicles. Proc. Nat. Acad. Sci. (USA) 61, 566-561.

[303] K. Eichmann (1974) Idiotype suppression. I. Influence of the dose and of the effector functions of anti-idiotype antibody on the production of an idiotype. Eur. J. Immunol. 4, 296-230.

[304] L. Forni, A. Coutinho, G. Köhler and N. K. Jerne (1980) IgM antibodies induce the production of antibodies of the same specificity. Proc. Nat. Acad. Sci. (USA) 77, 1125-1128.

[305] D. Weaver, H. Moema, M. H. Reis, C. Albanese, F. Costantini, D. Baltimore and T. Imanishi-Kari (1985) Altered repertoire of endogeneous immunoglobulin gene expression in transgenic mice containing a rearranged mu heavy chain gene. Cell, 45, 247-259.

repertoire by a soluble self antigen may be more or less balanced by stimulation exerted by stimulation by the corresponding cell surface receptor.

There is some cross-reactivity between mouse MHC class II molecules and human MHC class II molecules,[306,307] which can also be understood in this context. The MHC molecules are selected in the context of the complete set of all the self antigens, and according to the balanced proteome hypothesis, the environment for the selection of mouse MHC molecules is similar to the environment for the selection of human MHC molecules.

On a balanced set of self antigens and linkage disequilibrium

In chapter 15 we encountered the phenomenon of linkage disequilibrium for HLA (that is, human MHC) genes.**Error! Bookmark not defined.** This means that there is a tendency for particular MHC alleles to remain associated with each other. In the context of the idea that self antigens are a balanced set of shapes and corresponding complementary shapes, we can interpret HLA linkage disequilibrium in terms of some HLA genes combining with others to give more balanced stimulation of the T cell idiotypic network than other combinations would do. At another level, the set of V regions of CD4 helper T cells, that are stimulated and hence selected by a particular MHC class II protein, for example alleles "a", may have greater complementarity to the V regions of CD8 suppressor cells, that are stimulated and selected by a particular set of MHC class I alleles, for example alleles "b", than is the case for other MHC alleles. Then linkage between MHC class II alleles "a" and the MHC class I alleles "b" will tend to be maintained during evolution. There are many ways in which MHC class II can be roughly complementary to MHC class I, so this concept also provides an explanation for the high polymorphism of MHC class II and MHC class I molecules. The rough complementarity constraint is not a very restricting constraint, so there are many ways in which it can be satisfied.

Erosion of symmetry with aging

Every immune response that we make changes or "skews" the repertoire, but the dominant role of T cells, and the stabilizing effect of the complete set of self antigens on the centre-pole, can be expected to normally

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306 J. K. Lunney, D. L. Mann and D. H. Sachs (1979) Sharing Ia antigen between species III. Ia specification shared between mice and human beings Scand. J. Immunol. 10, 401-413.

307 M. Pierres, J. P. Rebouah, F. M. Kourilsky, M. Dosseto, P. Mercier, C. Mawas and B. Malissen (1981) Cross-reactions between mouse Ia and human HLA-D/DR antigens analysed with monoclonal alloantibodies. J. Immunol., 126, 2424-2429.

have the effect of restoring much of the symmetry to the system following an immune response. As aging occurs, with the occurance of many immune responses, one can envision that there is nevertheless a drift of the centre-pole from where it started at birth, with the symmetry of the system being gradually eroded. With aging immune responses are known to become weaker, and they increasingly have an autoimmune component.[308] This may be due to the system no longer being optimally balanced with respect to proteomic shapes and corresponding complementary shapes.

On I-J in mice and humans

Anti-I-J antibodies can be made by cross-immunizing strains that have the same sets of genes, including all the MHC genes, but, according to our model, different mutually stabilizing sets of helper and suppressor T cell clones[309,310] This is the case for the B10.A(3R) and B10.A(5R) strains. Most remarkably, anti-I-J reagents from the murine system (both antisera and monoclonals) also recognize determinants on CD8 T cells in humans.[311] (Recall that CD8 is a marker of regulatory T cells, that include some suppressor T cells and contrasuppressor cells.) This finding may be of fundamental importance. It may mean that there is a close relationship between the centre-poles of mice and humans. I-J was first defined using mice with no known genetic differences (but different I-J), and an antigenic determinant that is at least very similar is present also in humans. This phenomenon can plausibly be interpreted in terms of T cell repertoires in mice and humans being similar at some fundamental level. It may mean that the centre-pole is strongly conserved in evolution, and that I-J determinants are reflections of the repertoire of all the self antigens of the individual. This would again be consistent with a balance being maintained between shapes and

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[308] E. A. Goidl, M. A. Michelis, G. W. Siskind, and M. E. Weksler (1980) Effect of age on the induction of autoantibodies. Clin. Exp. Immunol. 44, 24-30.

[309] T. Tada, M. Taniguchi and C. S. David (1976) Properties of the antigen-specific suppressive T-cell factor in the regulation of antibody response of the mouse. IV. special subregion assignment of the gene that codes for the suppressive T-cell factor in the H-2 histocompatability complex. J. Exp. Med. 144, 713-725.

[310] D. B. Murphy, L. A. Herzenberg, K. Okumura, L. A. Herzenberg and H. O. McDevitt (1976) A new I sub-region (I-J) marked by a locus (Ia-4) controlling surface determinants on suppressor T lymphocytes. J. Exp. Med. 144, 699-712.

[311] T. Lehner, R. Brines, T. Jones, and J. Avery (1984) Detection of cross-reacting murine I-J like determinants on a human subset of $T8^+$ antigen binding, presenting and contrasuppressor cells. Clin. Exp. Immunol. 58, 410-419.

corresponding complementary shapes, not only for V regions, but also for the total set of self antigens that impinges on the immune system. The addition of a new gene to the genome would then create a viable organism only if there is not a significant disruption of a hypothetical balance between shapes and complementary shapes. That balance may involve changes in the spectrum of the V regions themselves, which are part of the set of self antigens. For example, adding a heavy chain gene with a particular specificity may cause the expansion of helper T cells with complementary specificities, with the result that other B cell genes with the same idiotype as that of the added heavy chain gene are expressed, as was observed in the experiment of Weaver et al.

The presence of I-J-like molecules on regulatory T cells in humans may also be related to the fact that there is some cross-reactivity between mouse MHC class II molecules and human MHC class II molecules.[312,313] On the other hand, if I-J were to be regarded solely as an image of MHC class II, I-J on human cells would be surprising, since there are many determinants that differ between mouse MHC class II and human MHC class II. One would then expect the image of MHC class II to be influenced by these differences, and hence to be significantly different in the two species. This puzzle can again be resolved by generalizing our perspective of I-J from being an image of MHC class II to it being an image of the entire set of self-antigens to which the immune system is exposed, with some self-antigens (including MHC class II) being more immunogenic and thus having a more dominant role than others. Other less polymorphic proteins such as fetuin, albumin and complement components would then also play a role in the selection of the shape that is I-J. I-J would then be an even more central element in the repertoire of shapes in the body, and its conservation during evolution can be related to the idea that the average shape of all the self antigens would not change much with time. At the same time the mapping of I-J to the MHC indicates that I-J is an emergent shape that arises by a co-selection process that involves helper T cells with some anti-MHC class II specificity.

On the subject of similarities in the V region repertoires of mice and humans, it is also noteworthy that many human fetal antibodies display

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312 J. K. Lunney, D. L. Mann and D. H. Sachs (1979) Sharing Ia antigen between species III. Ia specification shared between mice and human beings Scand. J. Immunol. 10, 401-413.

313 M. Pierres, J. P. Rebouah, F. M. Kourilsky, M. Dosseto, P. Mercier, C. Mawas and B. Malissen (1981) Cross-reactions between mouse Ia and human HLA-D/DR antigens analysed with monoclonal alloantibodies. J. Immunol., 126, 2424-2429.

homologies to the first heavy chain V gene expressed in mice.[314] The constraint of maintaining, during evolution, a set of self antigens that is a balanced set of shapes with corresponding complementary shapes could mean that the sum of the antigenic similarities between the mouse proteome and the human proteome is much greater than the sum of the differences. As an organism ages, this postulated balance may be gradually eroded.

A model with all the self antigens and IgG and IgM producing B cells

The model of Figure 17-2 can be extended to explicitly include all the self antigens, IgM producing B cells, denoted by B1, and IgG producing B cells, denoted by B2, as shown in Figure 17-3. Contrasuppressor T cells are not shown here, and may also be important as discussed above. The serum concentrations of IgM and IgG depend on the B1 and B2 repertoires and also the various T cell repertoires. Here MHC class II is replaced by all the self antigens, since we know that small changes in the repertoire of self antigens can result in significant changes in idiotypic repertoires. IgM secreting B1 cells are shown as being selected solely by Ts2 cells, and as a result they are not as tightly regulated as IgG secreting B2 cells.

While Figure 17-3 shows all self antigens impacting on the Th1 population, MHC class II plays a particularly important role in this respect.

Antigens that induce an immune response that is solely IgM are typically "T-independent" antigens, and are typically multivalent, flexible molecules that are efficient in being able to cross-link specific receptors on lymphocytes. A T-independent antigen stimulates a broad spectrum of diverse idiotypes with a low average affinity at the level of the binding of a single epitope to a receptor. The stimulated clones are so diverse that the antigen is eliminated by IgM before there much co-selection of antigen-specific and antiidiotypic T cells.

In the case of an IgG response on the other hand, the number of antigen-specific clones stimulated by the antigen is much lower, and co-selection of antigen-specific and antiidiotypic T cells plausibly leads to the emergence of an idiotypically homogeneous antiidiotypic population, that is at least as important as the antigen itself in stimulating antigen-specific B cells, leading the B cells to switch to making IgG. In this co-selection model of IgG responses there is network focusing involving diverse antigen-specific T cells and less diverse antiidiotypic T cells. The model provides an explanation for the Oudin-Cazenave phenomenon, in which antibodies to various

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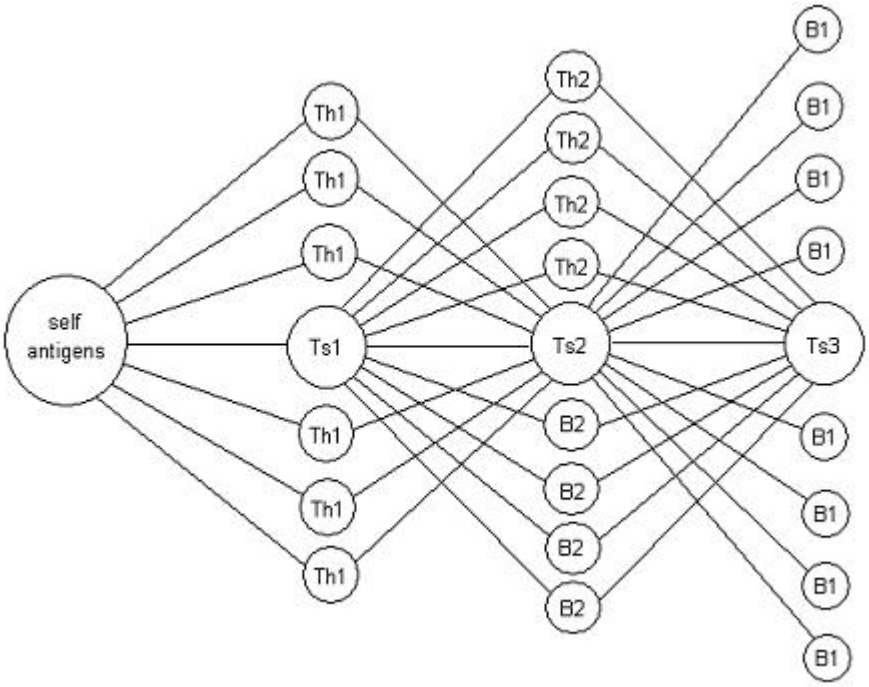
[314] H. W. Schroeder Jr, J. L. Hillson and R. M. Perlmutter (1987) Early restriction of the human antibody repertoire. Science 238, 791-793.

Figure 17-3 A model showing interactions between all of the self antigens and Th1, Th2, Ts1, Ts2, Ts3, B1 and B2 cells, where B1 cells secrete IgM antibodies and B2 cells secrete IgG antibodies. For explanation see the text.



determinants on an antigen express common idiotypic determinants.[315] Such antibodies share idiotypic determinants because they have been selected primarily by an emergent homogeneous antiidiotypic T cell population, rather than by the antigen itself.

In summary, the Ts2 population is seen in this model as the central regulating element of the immune system, and it is constrained to be a homogeneous population primarily via co-selection with Th1 cells, the repertoire of which is also influenced by the repertoire of all the self antigens. Figure 17-3 is furthermore a model that shows in some detail how the repertoire of self antigens may interact with Th1 and Ts1 populations, how these may interact with the Ts2, Th2 and B2 populations, and how they in turn may interact with B1 and Ts3 populations. The figure illustrates the set of interactions with respect to an anti-self/anti-anti-self shape space axis.

IgM and HIV

In our theory of HIV pathogenesis, HIV evolves in infected people to mimic the receptors of the Ts2 central regulating element of the immune system. People who become infected with HIV go through a phase of synthesizing large amounts of HIV, yet the amount of transmission of the virus to healthy uninfected individuals is low, compared for example with the infectivity of measles for people who have not been immunized. Figure 17-3 provides a rationale for this. In the model the IgM repertoire is selected to have complementarity to Ts2, and since HIV resembles Ts2, the IgM repertoire also has complementarity to HIV. Hence HIV is normally quickly cleared by IgM, without seroconversion to the production of anti-HIV IgG antibodies.

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[315] J. Oudin and P. A. Cazenave (1971) Similar idiotype specificities in immunoglobulin fractions with different antibody functions or even without detectable antibody function. Proc. Nat. Acad. Sci. (USA) 68, 2626-2620.