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Perpetuation of immunological memory: a relay hypothesis

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SUMMARY

A mechanism is proposed which explains the perpetuation of B-cell immunological memory indefinitely without requiring the presence of long-living memory cells or persisting antigen. The salient feature of this model is that immunological memory can be perpetuated indefinitely through the mutual interaction of idiotypic and anti-idiotypic B cells. These cells mutually stimulate and clonally expand with either specific or bystander T-cell help. Because B cells can present antigen, they present 'apparently foreign' idiopeptides to T cells. The idiopeptides of *de novo* synthesized antibody is presented to $CD8^+$ T cells that recognize the idiopeptide-presenting cell as targets and regulate their population. The recycling of immunoglobulins from surface to endosomal compartment of B cells leads to the presentation of idiopeptides by major histocompatibility complex (MHC) class II to $CD4^+$ T cells. Even if the majority of the clonally expanded cells die because of lack of stimulation, cytotoxic T lymphocyte (CTL) lysis or for other reasons, the surviving cells will be able to carry forward the memory. This mechanism also provides a means for affinity maturation through idiotypic selection of somatically mutated high affinity cells or those from the naïve pool. We have termed these two types of complementary B cells as Burnet B cells: those which recognize the antigen or antigen mimic, and Jerne B cells, which can recognize the idiotypes of antibody and carry antigen mimics. The proposed hypothesis can explain differential duration of memory for different antigens, the shelf space paradox, affinity maturation, repertoire shift, etc.

INTRODUCTION

Immunological memory is an intrinsic property of the immune system. The mechanism governing the generation and perpetuation of immunological memory has been the subject of many investigations and yet has not brought out any clear-cut and definite mechanism for its perpetuation. Four possible mechanisms, not mutually exclusive, have been proposed to account for immunological memory recently reviewed by Zinkernagel *et al.*[1] (1) Memory is the result of increased numbers of specific resting B and T cells maintained in an antigen-independent fashion.[2] (2) Memory represents a special quality of specific lymphocytes, which have a lifespan considerably longer than virgin cells as well as the effector cells in the population.[3] (3) Memory represents elevated frequencies of activated, specific lymphocytes; the elevated frequencies being maintained by the triggering of recurrent infections involving persisting or cross-reactive antigens, resulting in an equilibrated level of induction of specific effector cells. (4) Memory reflects 'regulatory' influences exerted by immune networks. The widely accepted mechanism that immunological memory is perpetuated by long-living memory cells has come under severe scrutiny. It fails to explain many phenomena associated with immunological memory and raises additional questions. Some of the questions are as follows. (1) If memory cells are continuously stored, it leads to a corresponding continuous decrease in the shelf space, which finally limits new cells from being accommodated. A natural consequence of this would be a reduction in the ability to acquire immunological memory for new antigens in ageing individuals. (2) The B memory cells against different antigens are otherwise very similar except for the specific membrane-bound antibody they carry on their cell surface, which only differ in their idiotypic determinants. Therefore, the life span of these memory cells for different antigens are likely to be very similar. Thus, the duration of memory is expected to be similar for all antigens, since the memory would have to be maintained through very similar or almost identical memory cells (except for the differences in the idiotypic determinant). However, the duration of immunological memory is different for different antigens.[4] (3) The affinity maturation is not necessarily

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Abbreviations: Id, idiotypic; FDC, follicular dendritic cell.

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explained by the mere presence of somatic mutations in the memory cells unless it is accompanied by selective proliferation of high affinity cells. The somatic mutation is expected to broaden the affinity, as mutation is not directional. In practice, because of somatic mutation, a given memory cell has less chance of increasing the affinity (with favourable mutation) but more chance to accumulate unfavourable mutations. In a population of memory cells, mutation being random, the affinity would shift in either direction, but more towards lower affinity. Affinity maturation would occur only if the high affinity memory cells were being selected with concomitant cell proliferation and/or death of lower affinity cells.[5] This concomitant selection mechanism is not built-in in the long-living memory cell model and there is no mechanism for the selective elimination of low affinity memory cells. The persistence of antigen is invoked to explain the selective proliferation of memory cells. (4) Existing theories of immune memory fail to explain cytotoxic T lymphocyte (CTL) memory for exogenous antigens including protein antigens except under very special situations leading to the presentation of exogenous antigens by major histocompatibility complex (MHC) class I[6] or CD1 molecules.[7]

A theoretical, all comprehensive, 'peptidic self' model has been proposed for the working of the immune system, in which immunological memory forms a subset.[8] According to this model, 'cross-talk' between various types of cells involved in the immune system governs primary, secondary, autoimmune as well as memory responses. However, experimental proof for many of the assumptions in this hypothesis is not available yet. UytdeHaag *et al.*[9] have proposed an interesting model for maintenance of immunological memory through anti-idiotypic antibody V region of $CD5^+$ B cells serving as surrogate antigen. Even though anti-idiotypic $CD5^+$ B cells may stimulate the antigen-specific memory B cells leading to their clonal expansion, the mechanism by which these cells can keep long-lived resting cells alive is not clear. Recently, Maruyama *et al.*[10] using a genetic switch mediated by Cre recombinase have shown that there is no requirement for persisting antigen for the memory cells and argue that the memory B cells are long living. This experiment however, does not rule out the possibility of idiotypic–anti-idiotypic interactions in genetically switched mice.

We propose a mechanism to explain the generation, maintenance and the regulation of immunological memory, which does not require the presence of long-living memory cells or persisting antigen. The hypothesis combines the essential features of Burnet's clonal selection theory[11] and Jerne's network hypothesis.[12] It provides a framework for generation and maintenance of immunological memory, which is self perpetuating, autoregulating and terminable. The salient features of the hypothesis are described below.

BURNET AND JERNE CELLS

The antigen provides the initial trigger for generation of antigen-specific clones through clonal selection and initiation of immunological memory. After the antigen has been eliminated from the system, the antigen-specific B cells select from the naive pool, those complementary lymphocytes with anti-idiotypic specificity, which recognize the idiotypic determinant on these B cells. For clarity, we would like to refer to the antigen recognizing cells and their clonal derivatives as Burnet B cells. The Burnet B cells select from naïve pool complementary B cells that can react with the idiotypes of Burnet cells. We refer to these second set of complementary B cells as Jerne cells. These cells are pictorially depicted in Fig. 1.

The Burnet B cells, which can be triggered by the antigen, can in turn trigger Jerne B cells whose idiotopes are the antigen mimics. Thus, when Burnet B cells and Jerne B cells interact, clonal expansion of these complementary cells takes place. It may be noted that the clonally derived cells from both Jerne and Burnet B cells would also mutually interact through complementary idiotypic and anti-idiotypic determinants. The activation of B cells through the cell surface idiotype–anti-idiotype interaction results in clonal expansion and recruitment of additional B cells with higher affinity. Thus, B-cell memory is a function propagated by the interaction of a series of complementary B cells belonging to Burnet and Jerne series, where B, B″, B″″, etc. are Burnet cells and B′, B‴, etc. are Jerne cells. These cells with the ability to mutually interact may occupy the same anatomical location, because once one of the cells is anchored to a substratum, the complementary cells are also captured when they are encountered. It is assumed that germinal centre cells may contain both Burnet and Jerne cells. After the disappearance of the antigen, the idiotopes of the surface-bound antibodies of Jerne B cells function as surrogate antigens perhaps along with idiopeptides present on antibodies secreted by Jerne B cells. The selection mechanisms for memory cells proposed so far have been the continuous presentation of antigen by follicular dendritic cells (FDC)[13] and stimulation with the cross-reactive antigens.[14]

B cells can present antigens in the context of both MHC class I and class II.[15] This property of B cells ensures that it can present idiopeptides of internally synthesized antibody by class I pathway, the regurgitated idiopeptides by class II MHC as well as the peptides of foreign antigens (Fig. 2). Thus, both specific and bystander T cell help is available to interacting Burnet and Jerne cells. The Burnet cells and their clonal derivatives are 'memory cells' of the original antigen which are not naïve and not fully differentiated into plasma cells.

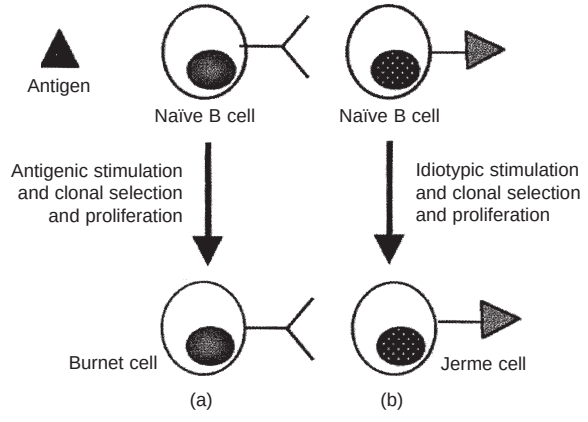

Figure 1. Pictorial depiction of Burnet and Jerne cells carrying antigen receptors that are complementary to each other.

INITIATION OF MEMORY

The naive B cells after coming into contact with the antigen undergo clonal selection and expansion. These clonally expanding cells, which are midway through differentiation and which express antibody of any isotype on their surface, are henceforth referred to as 'Burnet cells'. All Burnet cells, irrespective of their antigen specificity are identical with each other except for the immunoglobulin variable region and the consequent idiotype on the membrane. The cells selected by the idiotypes of the Burnet cells, carrying complementary anti-idiotypes are termed as 'Jerne cells'. The Jerne cells now undergo clonal expansion and in turn can select other Burnet cells or can 'Burnetize' naive B cells, that is select naive B cells of original antigenic specificity which now undergo clonal proliferation. Thus, due to reciprocal interactions between Burnet cells and Jerne B cells, the proliferation of these two types of cells can continue indefinitely initiating a dynamic cascade of memory B cells in the lymphocyte pool (Fig. 3).

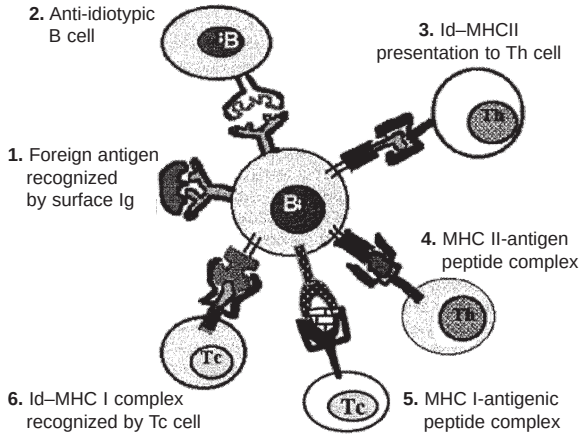

Figure 2. Multifunctional capability of B cells for free or cell-bound antigen recognition and antigenic peptide presentation to T helper (Th) and cytotoxic T cells (Tc) cells in contact with MHC class I and class II. Ig, immunoglobulin; Id, idiotype.

T-CELL HELP FOR JERNE–BURNET INTERACTIONS

Burnet cells and Jerne cells, being B cells, can present antigen as well as the idiotypic determinants of the antibody molecules in the context of class II MHC by way of internalizing the surface-expressed antibody, degrading it and presenting it to helper T cells with T-cell receptor (TCR) specificity for idiotypic determinants. If one imagines a situation as shown in Fig. 4, then the cognate T helper cell should also be able to selectively and specifically activate the proximate anti-idiotypic B cells by secreting paracrine cytokines such as interleukin IL-2 and IL-4. At the same time such T cells also are activated due to autocrine stimulation. Thus, specific help to both Jerne and Burnet B cells in a bi-, tri- or multicellular complex is available, triggering all interacting cells for proliferation (Fig. 4).

AFFINITY MATURATION THROUGH IDIOTYPIC SELECTION

In a resting cell, the somatic mutation can only be introduced during DNA repair processes or due to cytosine deamination followed by excision of uracil and repair.[16] However, if the cells are undergoing active DNA synthesis, the introduction of mutation is more efficient. The high affinity cells (both Burnet and Jerne cells) enjoy the advantage for selection and proliferation.

In the proposed mechanism, the higher the affinity of the antibody-producing cells for the antigen or the antigen mimic, the greater its chance of selection. In the long-living memory cell model,[17] antigen is the selector of the somatically mutated cells whereas in the present model both Burnet and Jerne cells

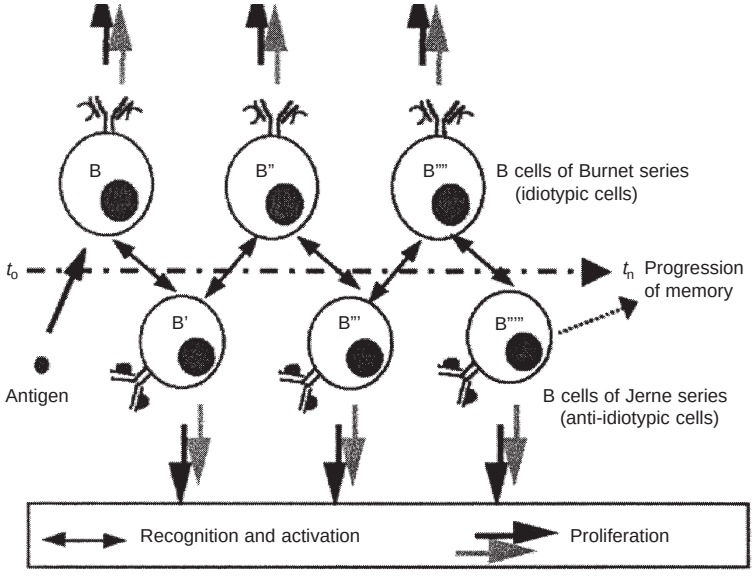

Figure 3. Generation of B-cell memory by idiotypic anti–idiotypic interactions and its propagation. t_0 indicates initial antigenic stimulation and t_n indicates any time at which memory response is seen. Between $t_{0\text{ and }}$ t_n both Burnet cells and Jerne cells have gone through several rounds of proliferation.

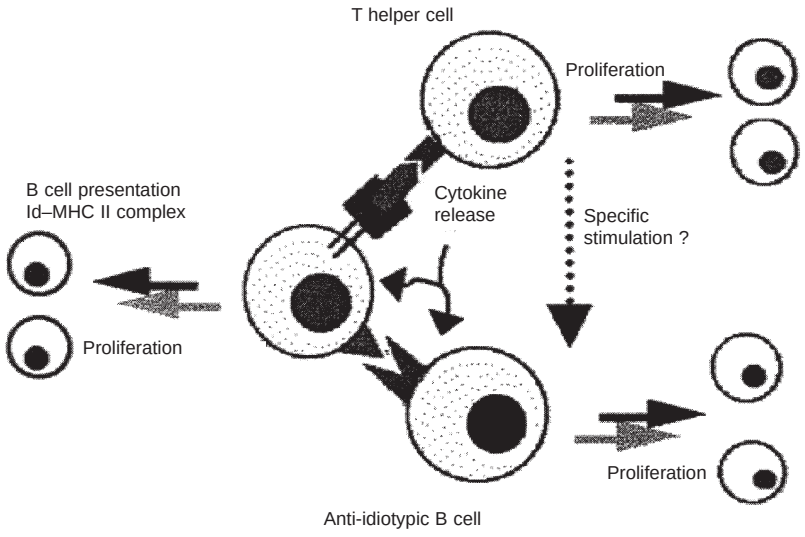

Figure 4. Selective and specific activation of anti-idiotypic B cells by T helper cells. Besides bystander help B cells can get specific T-cell help when Jerne cells, Burnet cells and Th cells recognizing idiopeptides of Jerne or Burnet cells are present in tri-molecular complex as shown or as multicellular complexes involving more antigen-specifc Th cells.

are selectors of high affinity Jerne and Burnet cells, respectively. Affinity maturation takes place if there is selection of high affinity cells generated by somatic mutations within the rearranged immunoglobulin gene. It is assumed that both Burnet and Jerne lymphocytes are in constant cycles of proliferation and quiescence, as they receive continuous activating stimulus provided by the receptor binding and T-cell help through presentation of idiopeptides by B cells. This selection of high affinity cells is a continuous process, the low affinity cells are eliminated in the course of time and the high-affinity cells are enriched. Thus, this mechanism represents true affinity maturation, which is an integral property of self-perpetuating immunological memory.

REGULATION OF CELL PROLIFERATION

The proliferation of Burnet and Jerne cells leads to the untenable situation of uncontrolled growth of these B cell populations, resembling malignancy-like situation. This hypothesis also provides a mechanism for the regulation of the clonally expanded B- and T-cell populations if a continuous cascade of cell–cell interactions, activation and proliferation were taking place saturating the available shelf space. The following are some of the mechanisms regulating the population of Jerne and Burnet cells.

(1) The low affinity cells, which are not idiotypically or otherwise selected and stimulated, are destined to undergo apoptosis after a definite life span.
(2) Burnet and Jerne cells interact with each other through antigen–antibody (idiotypic–anti-idiotypic) reactions. The antigen–antibody interaction involving cells can be subjected to complement-mediated lysis.[18] Therefore, binding of complement to Burnet–Jerne cellular complex is likely to destroy both cell types. This is potentially a mechanism to bring down the cell numbers and maintain homeostasis.
(3) One of the major ways in which the population of interacting Burnet–Jerne cells can be kept under check is through the CTL response. The activated T cytotoxic cells are capable of killing the B cells presenting the apparently 'non-self' peptides of the idiotypic determinants in the context of MHC class I molecules and regulate the B-cell population (Fig. 5). These B cells are capable of presenting the *in vivo* synthesized idiotypic determinants in the context of class I MHC molecules. These idiotypic epitopes, although self, will be treated by the immune system as foreign, thus generating specific CTL responses. Thus, the populations of Burnet cells and Jerne cells can be regulated through CTL killing of these cells.

T-CELL MEMORY AS A BY-PRODUCT OF B-CELL MEMORY

B cells can activate T cells by either MHC class I-idiotypic peptide or MHC class II-idiotypic peptide presentation. Thus a mechanism for T-cell memory is obvious wherein T-cell memory is generated as and when B cells present the antigen mimic idiopeptides (Fig. 5). Earlier work has shown that idiopeptides can evoke both $CD4^+$ and $CD8^+$ T cells and exist not only as the integral components of a bona fide antigen-binding receptor but also as distinct molecular entities in the processed forms on the cell surface of B lymphocytes.[19–21]

Two groups have shown through adoptive transfer of $CD8^+$ cells against lymphocytic choriomeningitis virus (LCMV) that continuous presence of antigen is not necessary for maintenance of $CD8^+$ memory.[2,3] However, it is not clear from these studies whether $CD8^+$ memory T cells were the originally transferred cells or cells which arose from the transferred cells through stimulation and resultant proliferation of these cells. LCMV-specific T-cell memory has been reported in B-cell deficient mice.[22] However, in such situations, the presentation of the TCR idiopeptides may take over the degenerate function of maintaining the T-cell memory for the antigen due to the TCR idiopeptide presentation through the MHC I and MHC II molecules present on T cells. Recently

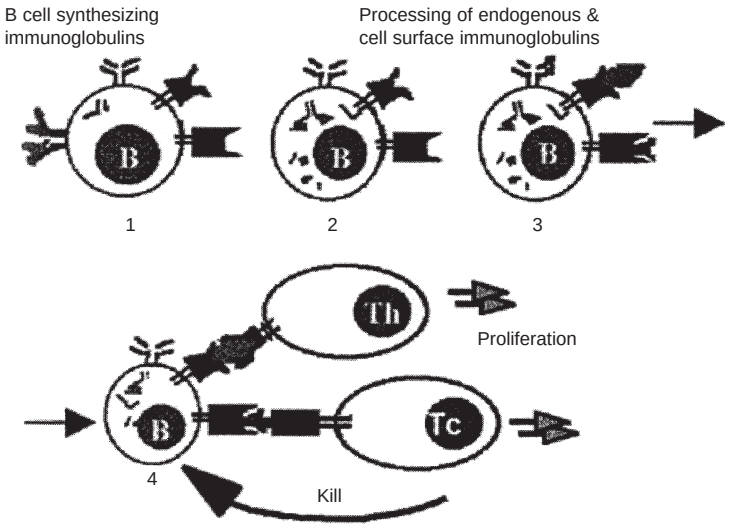

Figure 5. Regulation of B-cell populations and propagation of T-cell memory. T-cell memory is started every time Jerne cells present idiopeptide antigen mimics to T cells. The T cell numbers go up and some of these T cells may react with original antigenic peptide when it is encountered during an interaction. Cytotoxic T cells downregulate B-cell populations while Th cells upregulate B-cell populations. Upregulation of the B-cell population would be followed by the upregulation of T-cell population.

reported studies[23,24] prove the generation and maintenance of T-cell memory in MHC I- and MHC II-deficient mice indicating that MHC-dependent interactions were dispensable for T cell memory. However, it still does not rule out the possibility of B–T interaction through class II in MHC class I-deficient mice and through class I in the MHC II-deficient mice, respectively. Besides, Ciurea *et al.* have actually reported that very low levels of LCMV remain undetected in the mice as determined by conventional methods after infection, presenting a very low but nevertheless a continuous source of persisting antigen.[25]

A regulatory mode for the expanded clonal T-cell populations is automatically foreseen by the circuits of B, T helper and T cytotoxic T cells operating within their normal cellular life spans and therefore should die in the absence of any activating stimulus from idiotype-presenting B cells.

CONNECTIVITY BETWEEN B-CELL MEMORY AND T-CELL MEMORY

The antigen-presenting ability of B cells[15] confers on them the unique property of presenting the idiopeptides through class I as well as class II MHC molecules. Every time a B cell makes an antibody, the idiopeptide is treated as non-self and if presented correctly in the context of MHC I molecules, it can generate T cytotoxic responses. This antigen presentation can keep alive cytotoxic T-cell memory by triggering clonal expansion of these cells (Fig. 5).

Of the T cells the T helper cells are specific for the given B-cell populations and therefore perpetuate specific T helper memory at every cycle of proliferating B cells producing specific antibody. Thus, T helper memory appears to be a by-product of B-cell memory.

However, the CTL memory may not be as straightforward. While idiotypic–anti-idiotypic interactions are governed by complementarity, the same may not necessarily be true for T cells. The idiopeptides generated from antibody molecules have to bear structural identity with the antigenic peptide. It has been reported that immunoglobulin heavy chains have about 60% antigen-binding capacity of that of the complete antibody.[26] It is possible that the heavy chain idiopeptides may function as antigen mimics, which clearly needs experimental confirmation. B cells presenting idiopeptide could generate a CTL response, as mentioned earlier. The nature of this CTL response is such that it could lead to the regulation of B-cell populations. However, the idiopeptide of the antibody loaded onto the MHC class I, if similar to the antigen-derived peptide, will generate T-cell memory by keeping $CD8^+$ cells at elevated frequencies with cycles of proliferation. Recently, it has been shown that CDR3 regions of anti antibody have a stretch of amino acids which are similar to the antigen.[27,28] It may be noted here that $CD8^+$ T-cell and B-cell populations will exhibit an inverse relationship similar to a predator–prey relationship found in an ecosystem.

DISSIMILAR DURATION OF IMMUNOLOGICAL MEMORY FOR DIFFERENT ANTIGENS

If the phenomenon of immunological memory is to follow the mechanisms envisaged above one may also explain how different antigens elicit memory for different durations, as the choice of a long-term or a short-term memory is dictated by both the quantity and the quality of the selection pressure arising out of the antigen load, the number of lymphocytes participating in the primary response, and the nature of the T and B cells selected and committed to memory. The duration of the immune response is hypothesized to be governed by several factors.

(1) The strength of interaction between antigen–antigen mimic with the corresponding antibody present on the Burnet and Jerne cells determine the duration of memory. A weak interaction may not lead to cell selection while too strong

interaction may lead to failure of the cells to dissociate and/or proliferate prior to destruction of the interacting Jerne–Burnet complex by complement.

(2) The presentation of idiotypic peptide by B cells to T helper cells may be qualitatively or quantitatively variable in different B cells, therefore leading to differential cell proliferation.

(3) The number of Jerne and Burnet cells generated can determine how frequently the Jerne and Burnet cells come to contact with each other to trigger cross-proliferation. The higher the numbers, the greater is the encounter and longer the memory.

(4) The presentation of the idiotypic determinant on class I MHC to CTL limits or abrogates the memory response by killing either Burnet cells, Jerne cells or both depending on generation of CTLs. Once either Burnet or Jerne cells are destroyed, the memory response gets aborted for the said antigen (epitope).

DISCUSSION

It is proposed that immunological memory is maintained by the presence of sinusoidal waves of antigen-specific antibody expression and anti-idiotypic antibody expressing complementary B cells, which are generated by antigenic stimulus followed by idiotypic stimulus (Fig. 6). The waves are maintained because B cells can present antigen as well as idiotypic determinants in the context of both MHC class I and class II molecules which ensures their propagation by recruiting T-cell help for proliferation and attracting CTL response for regulation of its population. The presence of these two types of cells postulated by Jerne's idiotypic network hypothesis have been amply seen, and in fact the molecular mimicry between anti idiotypic antibody and the antigen has been demonstrated.[28] Our hypothesis can explain how in the absence of long-living memory cells or persisting antigens, immunological memory can be maintained. Besides, it provides a mechanism for affinity maturation through idiotypic selection. Since it is a dynamic mechanism, it provides a means for explaining differential memory for different antigens. For example, if the idiopeptides generated from the antibody and anti-antibody are poorly presented by MHC to T cells, then this antigen is likely to generate poor memory response even though it may be a good antigen by itself. Likewise, if the idiopeptide presentation is skewed in favour of $CD8^+$ T cells, the antigen may prove to generate poor immune response. Similarly, if the idiopeptide presentation is in favour of $CD4^+$ T cells then the antigen may generate good memory response even when the antigen may be a poor immunogen. This hypothesis intends to provide a few working principles for experimentation, which can provide evidence for the generation, maintenance and regulation of immunological memory.

The proposal attempts to provide a theoretical basis for the linkage of B, T helper and T cytotoxic memory, which are driven by the presentation of idiotypic determinants by B lymphocytes. On a more practical level, there has been a great emphasis in developing subunit vaccines, especially recombinant vaccines for immunization. However, the theoretical basis behind the use of the exogenous proteins as vaccines is not understood. Particularly, one does not know how these proteins are able to elicit good CTL responses, because these proteins are not endogenous in nature and therefore, not expected to be presented effectively by MHC class I molecules to CTL.

The present hypothesis may be termed as relay hypothesis, as the immunological memory is postulated to be carried by relay of two types complementary B cells, referred to here as Burnet and Jerne cells. This relay hypothesis is developed by linking the observed facts, like the presence of complementary idiotypic and anti-idiotypic B cells, antigen presenting ability of B cells,[15] presentation of self peptides,[19] generation of self peptides by cells through protein processing and degradation,[29–31] generation of antigen mimics by anti-idiotypic B cells[27,28], etc. A cardinal feature of memory response, namely affinity maturation, is easily explained by our relay hypothesis, which is not explained by the long living memory cell model.

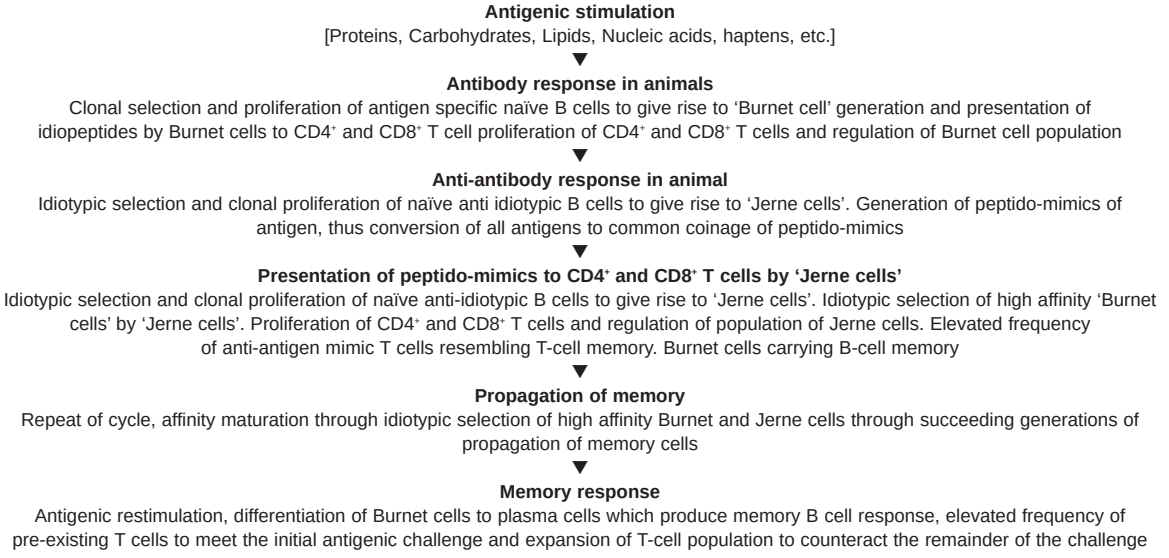

Figure 6. Proposed mechanism for immunological memory. Flow chart showing events involved in propagation of immunological memory.

The antigen held by FDC[32] to provide recurrent simulation can only be valid for some antigens but not for all antigens. The relay hypothesis provides an intrinsic built-in mechanism to handle all antigens, and immunological memory becomes a *fait accompli* given the presence of mutually complementary B cells (Burnet and Jerne cells), and their antigen-presenting ability.

UytdeHagg *et al*.[9] have invoked the possible role of $CD5^+$ B cells with anti-idiotypic specificity interacting with antigen-specific memory B cells and maintaining the B-cell population either through selection and proliferation of antigen-specific B cells or maintaining them in a long-lived resting state. This surely is a plausible mechanism of maintenance of memory. Though the first part is evidently an accepted phenomenon, keeping long-lived memory cells in an indefinite resting state would require a very special mechanism. Again the population of $CD5^+$ cells should be quite high with very similar repertoire as seen for antigen-specific B cells. Our hypothesis on the contrary does not require any special requirement for the overall B-cell population and the relay mechanism would provide necessary conditions for maintenance of immunological memory throughout the life span of an individual.

It is commonly observed that the duration of immunological memory is not the same for all vaccines. For some, a single immunization is sufficient to produce life-long immunity whereas for some others, revaccination at various time intervals is required. If the memory cells are long living, then there is no way of explaining differential duration of immunological memory for different antigens. The memory B cells are otherwise similar except their antigen receptors that only differ in the complementarity-determining region. This difference has no bearing on the life span of the cell. One of the major postulates on which the present hypothesis is based is that antigens are converted into their peptido-mimics in Jerne cells. The presentation of idiopeptides by Burnet cells and peptidic mimics by Jerne cells to T cells drives the memory response. If the idiopeptides and the peptido-mimics are not presented by the B cells, the B cells do not receive T-cell help, therefore the relay terminates as these B cells do not proliferate. Similarly if the peptidic mimics are very good epitopes for T cytotoxic cells, the B cells will serve as targets for the CTL and thus the memory response will be abrogated. The best memory response therefore will be one where the presentation of peptidic mimics or idiopeptides to T helper cells and T cytotoxic cells are well balanced, neither leading to the excessive generation of Burnet or Jerne cells, nor leading to their excessive killing. One may argue that the differential duration of memory may be explained by recurrent stimulation provided by antigens held by FDC, one will find memory against those antigens that are retained by FDC. Though it is quite plausible that selective memory can be brought about by antigen depots within the FDC, it will not explain different duration for different antigens unless one assume that FDC hold different antigens for different durations.

Affinity maturation is a cardinal feature of memory response. The relay hypothesis provides a mechanism for affinity maturation through continuous selection of high-affinity cells. The long-living memory cell model has only two occasions for selection of high affinity cells. First, during the primary response when antigens are still present in the system and second when the B cells, which have become quiescent, begin cell division during memory response, by a similar mechanism. The selection of high affinity cells is done in these cases by antigens.

Antigens retained by FDC can theoretically provide a means for selection of high-affinity cells. However if FDC also present antigen to T cells, then the antigen, in this case protein antigen, cannot survive in FDC as they have to be converted into peptides for presentation by MHC molecules. The high-affinity cells thus have to depend for their proliferation on bystander T-cell help. For these reasons we believe the relay hypothesis provides a better explanation for affinity maturation. Affinity maturation of T cells is neither foreseen nor ruled out by relay mechanism as the T-cell response may not be the result of selection. In any case, there is no strong evidence for affinity maturation in literature for T cells.[33]

There is evidence for the requirement of B- and T-cell interactions for memory.[34] Implicit in these studies is that the primary response can be generated in these animals but not secondary response. This means that there is substitute for T-cell help in the primary B-cell response in these animals. These animals are not T-cell null animals and perhaps the residual or substitute help available is sufficient to drive the memory response as well, but perhaps less vigorously. The T-cell memory in B-cell deficient animals can be explained by the possible presence of persisting antigen, which can be presented by professional antigen-presenting cells, and persisting antigen can carry forward the immunological memory.

The shelf space problem is one of the factors that argues against having long-living memory cells as carrier of immunological memory. The immune system comes in contact with large numbers of antigens and therefore, would generate memory cells that are many times more than the antigens. All these have to be stored by the limited space available in the body. One of the consequences arising out of this will be that memory cells for antigens encountered later in life will not be stored. This clearly is not the case as an individual can be immunized against any antigen at any time in life. The alternate possibility is that newer ones may replace the old memory cells. That will mean that the earlier immunizations will be ineffective if an individual is immunized with other antigens later, which is not the case. Therefore, it would stand to reason to believe that long-living memory cells are not the answers to immunological memory. The relay hypothesis presented here seems to suggest at first glance that two sets of cells instead of one set of memory cells need to be stored. However, not all memory cells for all antigens are required to be stored. Only a small number of cells need to be retained to carry forward immunological memory as they have been endowed with the ability for self-sustaining reactions. Besides, many of the antigens may not produce viable memory response, if the idiopeptides and peptido-mimics of the antigens are not presented to T helper cells. Thus, an outcome, according to relay hypothesis, will be that all antigens, even if they are immunogenic, need not generate a good memory response. A systematic study using multiple antigens and sequential immunizations may answer this question. The relay hypothesis thus does not find shelf space as a real problem since memory response is regulatable, terminable and can distinguish between antigens as memory-genic or non-memory-genic depending on the kind of idiopeptides and antigen mimics they generate.

Repertoire shift is a phenomenon observed in memory response.[35,36] The presence of dominant B cells of primary

response, which are not found in the secondary response because of repertoire shift, can be explained by the proposed hypothesis. It is argued that the antigens that produce best primary response are not necessarily the ones that automatically generate good memory response. We have discussed previously that these antigens which produce idiopeptides and peptido-mimics that are presented efficiently to T cells only carry forward the memory. During repertoire shift it is quite possible that the dominant B cells are lost because they produce idiopeptides which are poorly presented to T helper cells or the Jerne cells they select have peptido-mimics that are poorly presented to T helper cells. Thus, these dominant cells are not carried through and are not found during memory response. The alternate possibility that is built in the hypothesis is that if the B cells produce idiopeptides that are very efficiently presented to cytotoxic T cells, these cells are killed and therefore are also not propagated.

We assume that the antigen mimics generated in Jerne cells, and idiopeptides of Burnet cells, in spite of being self antigens, are treated by the immune system as foreign or apparently non-self, as the system has not encountered these antigens in the naïve state at concentrations seen after immune response. The routine cell–cell interactions thus result in maintenance of memory in a dynamic equilibrium. In the model proposed here there is no need for persistent antigen or the long-living memory lymphocytes though their presence could be an added reinforcement of the memory response. The presence of Burnet cells and complementary Jerne cells establish a memory-regenerating system through the idiotypic–anti-idiotypic interactions of their surface immunoglobulins, which is self-perpetuating. The function of original antigen is to trigger immunological chain reactions involving succeeding generations of complementary B cells and T cells that are stimulated due to the presentation of idiopeptides or peptido-mimics by Burnet and Jerne cells, respectively.

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