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Working principles in the immune system implied by the "peptidic self" model

(major histocompatibility complex/antigen/peptide/B cells/T cells)

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ABSTRACT **The hypothesis that self as well as foreign proteins are processed into peptides and presented by major histocompatibility complex antigens leads to a set of working principles that could govern cellular interactions in immune responses. In particular, "idiopeptides," derived from immunoglobulins and T-cell receptors and recognized by appropriate T cells, are expected to play an important regulatory role. We show here that these speculations fit into a consistent view of the immune system.**

In the past few years, a remarkable series of experiments has cast light on the function of class I and class II molecules of the major histocompatibility complex (MHC). A growing body of evidence enforces the view that class II MHC molecules bind peptides derived from "processed" (i.e., partially degraded) antigen and expose them on the cell surface (1–3). Importantly, recent experiments indicate that class I MHC molecules could do the same (4–6). The primary function of MHC molecules might thus be to present peptides derived from processed proteins.

Assigning a molecular function to MHC molecules is a major accomplishment because they play a pivotal role in regulatory interactions between cells of the immune system. It is well established that the activation and action of various types of T lymphocytes (T_H, helper; T_S, suppressor; CTL, cytolytic) requires recognition by T-cell receptors (TCR) of (processed) antigen in association with MHC molecules on the surface of antigen-presenting cells (APCs) or target cells.

Under the assumption that the actual function of MHC molecules relies on peptide presentation, we have proposed a logical generalization based on an interpretation of results by Townsend *et al.* (4, 5)—namely, that self, as well as foreign proteins, can yield peptides presented by MHC molecules (7, 8). Cells expressing MHC molecules would thus be permanently coated with a set of distinct peptides somehow reflecting their protein content. For example, somatic cells, most of which express class I MHC molecules, would display myriads of self peptides associated to the latter. APCs (i.e., macrophages, dendritic cells, B cells), which express both class I and class II MHC molecules, would be loaded with antigen-derived peptides in addition to self peptides. Finally, B cells producing a given antibody would expose peptides derived from it, called antibody idiopeptides (designated **Ab**), while T cells expressing TCR could expose TCR idiopeptides (designated **TCR**). Therefore, the generalization proposed under our initial peptidic self model (7, 8) leads to two major predictions: (*i*) the presentation of self peptides by MHC molecules, and (*ii*) the existence of idiopeptides, which, as discussed below, could constitute an important class of regulatory elements. Here, we delineate the implications arising from these premises and show that they lead to a consistent view of the immune system.

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WORKING PRINCIPLES

Presentation by MHC Molecules. So far, little is known about the mechanisms of antigen presentation, but they are likely to be very complex. It appears that processing of proteins usually (but probably not exclusively) takes place intracellularly. However, endogenous and endocytosed proteins could be processed differently. The amounts of class I and class II MHC molecules vary in different cell types. Both can be internalized and recycled, albeit differentially in various cell types. Thus, activated B cells spontaneously recycle their class II molecules and activated T cells recycle their class I molecules (9, 10). In the latter case, the endocytic pathway is similar to that followed by the transferrin receptor (10). Furthermore, the intracellular route followed by newly synthesized class II molecules crosses that of the recycling transferrin receptor (11). The exact way in which exocytic and endocytic pathways intersect is not fully understood but, in line with experiments by Morrisson *et al.* (12), it was suggested that endogenous proteins made intracellularly yield peptides preferentially presented by class I molecules, while ingested or internalized exogenous proteins would preferentially be dealt with by class II molecules (13). We also suggest that the co-internalization of a surface molecule with a MHC antigen could favor presentation of the latter by the former. Evidence is presently lacking to prove or disprove these assumptions, which, however, have important immunological implications (see below).

An Alternative Interpretation of MHC Restriction and Alloreactivity. In several instances, the specific presentation of synthetic peptides by certain MHC molecules and not others has been demonstrated (reviewed in ref. 14). MHC molecules thus appear as peptide receptors of loose specificity (8), each one being able to bind a limited number of peptides (15) in a selective fashion. Claverie and Kourilsky (8) and Wederlin (60) have proposed that TCRs could recognize the presented peptides and not necessarily the polymorphic part of MHC molecules. This concept, if correct, would resolve the disputes on the one- vs. two-TCR models, or on the various forms of the one-receptor model: MHC restriction would primarily reflect the selection of peptides exerted by individual MHC molecules (restricted presentation), rather than the direct recognition, by TCRs, of their polymorphic traits (as discussed in ref. 8). Alloreactivity would result from the presentation by cells displaying distinct MHC molecules of different sets of self peptides (including, perhaps, peptides derived from MHC molecules themselves) (6, 7). A TCR specific for a given peptide would thus be

Abbreviations: MHC, major histocompatibility complex; T_H, helper T cell(s); T_S, suppressor T cell(s); CTL, cytotoxic T lymphocyte(s); TCR, T-cell receptor; APC, antigen-presenting cell; Ab, antibody; V_H, variable-region heavy chain; V_L, variable-region light chain.

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offered the opportunity to cross-react with one of the thousands of distinct peptides present on the surface of the alloreactive target (8).

Possible Regulatory Roles of Idiopeptides. The predicted existence of idiopeptides playing a regulatory role in immune responses, although hypothetical, fits the conclusions of several reports. It seems that IgG2a allotypes require a presentation process to elicit a T-cell response (16). λ_2 light (L)-chain idiotopes and chemically synthesized peptides have a similar effect in a syngeneic T-cell response (17), and a MHC-linked gene control of helper T cells specific for variable-region heavy-chain (V_H) determinants has been demonstrated (18). On the other hand, one should question the existence of T cells responsive to idiopeptides. Synthetic peptides corresponding to V_H hypervariable regions are highly immunogenic in a xenogenic host (19). In a few instances, anti-idiotypic T_H cells have been convincingly demonstrated (20, 21). The immunoglobulin H-chain locus has been shown to influence the repertoire of CTLs (22). More generally, anti-idiotypic T cells are implied by, and thereby implicitly postulated in, the network theory (23). Certain anti-idiotypic T cells could thus respond to antibody idiopeptides rather than idiotopes as previously assumed (an idiotope possibly involving three-dimensional structures produced by nonconnex amino acid residues of the same or different chains of an antibody). In summary, the relevant evidence is scarce, but to our knowledge it is compatible with and does not rule out the existence of idiopeptides. Three conclusions would follow.

First, both chains of antibodies and TCRs could yield specific idiopeptides. Their regulatory effects could be synergistic but also affect cells making other heterodimers sharing one of the chain or some of the idiopeptides. [For example, the joint action of $T_H(V_HAb)$ and $T_H(V_LAb)$ could yield maximum stimulation of B(Ab) cells but $T_H(V_HAb)$ could also stimulate B(Ab') cells where Ab' shares the same V_H chain as Ab.] Recent data with transgenic mice carrying exogenous V_H genes could be interpreted in this way (24).

Second, regulatory phenomena involving idiopeptides should in general appear as MHC restricted. It should be noted, however, that some of the nonclassical class I MHC molecules (for example, those encoded in the mouse Qa-Tla complex), expressed on the surface of subsets of B cells and T cells, might serve to present idiopeptides. Since they are poorly polymorphic, MHC restriction could not be apparent in all situations. Other non-MHC-linked antigen-presenting molecules may be found in the future, and it may be recalled that exceptions to the rules of MHC restriction have been reported, including in T-cell/B-cell cooperation experiments (25).

Finally, if idiopeptides do mediate regulations specific to the immune system, they must be foreign to the somatic self. Accordingly, we draw a distinction between the "somatic self" (i.e., the set of peptides derived from self nonimmunological molecules, as selected by the MHC molecules of the organism) and the "immunological self" (i.e., the set of MHC-presented peptides derived from immunological molecules during the lifetime of the organism) (7).

Rules for Cellular Recognition. T_H cells are activated by contact with APCs presenting the processed antigen (i.e., peptides) in association with class II MHC molecules. CTL recognize (processed) antigen in association with class I MHC molecules on their targets, but sometimes with class II MHC molecules as well (12). For T_S cells, class II restriction has been mostly reported (26–28), but the involvement of class I molecules (as in CTL) remains possible.

In our interpretation of MHC restriction, TCRs *per se* (i.e., heterodimers of polymorphic chains) do not recognize the polymorphic parts of MHC molecules. If such is the case, they may also be blind to the presenting class I or class II MHC molecule (8). As suggested by Goverman *et al.* (25), the discrimination between class I- and class II-mediated presentation could be achieved by accessory molecules. It might also depend on the affinity of TCRs for their specific antigens, which, when plentiful, could make accessory molecules dispensable (29).

We mentioned above the possibility that internalized proteins are preferentially presented as peptides by actively recycling MHC molecules—that is, in general, class II in B cells, and class I in activated T cells (9, 10). According to this hypothesis, $T_H(\mathbf{X})$, $T_H(\mathbf{Ab})$, and $T_S(\mathbf{Ab})$ would be activated in a class II context and $T_S(\mathbf{TCR})$ in a class I context. This preference might not preclude peptide presentation by slowly recycling MHC molecules of the opposite class (I vs. II), which could be less intensive or delayed, but might also activate T cells [such as $T_S(\mathbf{X})$]. Degraded external proteins could directly bind class I or class II molecules. Internal proteins made intracellularly would be mostly associated to class I molecules (3, 13) and activate CTL(**X**).

IMPLICATIONS FOR IMMUNE RESPONSES

The Primary Antibody Response. (*i*) Upon immunization at immunogenic (not too low or too high) doses, a protein X is ingested by an APC, such as a macrophage. Peptide presentation by class II MHC molecules is favored (see above). T_H cells specific for one or several peptides [designated $T_H(\mathbf{X})$] are thus activated.

(*ii*) A resting B cell, with some 10^5 antibody molecules of the appropriate specificity, binds the X protein, internalizes it, processes it as any other APC, and presents **X** peptides associated with class II (and, in some cases, class I) MHC molecules. As strongly supported by the experiments of Lanzavecchia (30), the cooperation between $T_H(\mathbf{X})$ and B(Ab) cells involves not a protein bridge, but the peptide bridge illustrated in Fig. 1.

This scheme accounts for an important feature of the antibody response—namely, the selection of antibodies with relatively high affinity for the X antigen, since B cells bearing antibody with a high affinity for X have a better chance to be activated.

(*iii*) With time, the X antigen and $T_H(\mathbf{X})$ cells disappear. However, the antigen-driven antibody production may only be a component of the primary response (31, 32). Upon massive production of antibody, some of it (particularly the IgM and IgG isotypes) could be processed and presented as **Ab** by APCs, or by the activated B cells themselves, which internalize it and display enhanced class II expression. This would trigger $T_H(\mathbf{Ab})$ and restimulate B(Ab) cells (which expose **Ab**) (Fig. 2). Several reports show that the injection of a given antibody results in increased synthesis of antibodies with similar specificity and/or idiotypes (31, 33–36). These data have been taken in support of, or interpreted in the frame of, Jerne's network theory (23) (that is, in the usual terminology, reflecting Ab2-instructed antibody synthesis). In our interpretation, they could reveal a direct $T_H(\mathbf{Ab})$-mediated induction of B(Ab) cells by the antibody. An idiopeptidic relay could thus lengthen the X antigen-driven phase of the primary response. (Anti-idiopeptidic relays could also be included, but they may lead to closed regulatory loops: see figure 3 in ref. 7.)

Induction of Suppression During the Antibody Response. Suppression by T_S and/or CTL cells could occur in different ways. In several systems, the determinants responsible for suppression and help have been found to be separate (37, 38). Considering T_S cells only, it is thus possible that $T_S(\mathbf{X}')$ cells are activated by the presentation of **X'** peptides (distinct from **X**) by class I MHC molecules. Similarly, B(Ab) cells could present **Ab** and induce $T_S(\mathbf{Ab})$ or $T_S(\mathbf{X}')$ cells. These $T_S(\mathbf{X}')$ and/or $T_S(\mathbf{Ab})$ cells could thus act on B(Ab) cells, which expose **X'** and **Ab** peptides. But another kind of suppressive

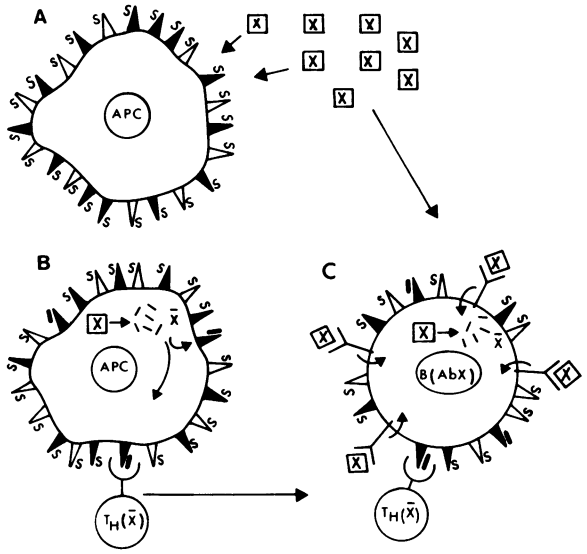

FIG. 1. Primary antibody response to antigen X. Class I (△) and class II (▲) MHC molecules, often coated with self peptides (S) also display X peptides, noted $\bar{X}$ in the figure, derived from the antigen ingested by the APC (*A*) or internalized by the B(AbX) cell (*C*). T_H(**X**) cells are activated (*B*) and stimulate B(AbX) cells (*C*). T_S(**X**) cells could be involved in a similar way, perhaps via **X′** peptides associated with MHC molecules.

mechanism could involve a direct interaction between T_S and T_H cells (39, 40). It is conceivable that, once activated, helper T cells expose their T_H-**TCR** in association with their actively recycling MHC molecules. Recently, in a human T cell, the existence of intracytoplasmic vesicles containing two membrane proteins as well as a TCR complex has been described (41). If foreign to the somatic self, these **TCR** could activate T_S(T_H-**TCR**) or CTL(T_H-**TCR**) directed against their cognate T_H cells, thereby causing suppression.

T_S cells readily fit into the above schemes of the primary antibody response with T_S(**X′**), T_S(**Ab**) down-regulating the activity of B(Ab) cells. The hypothetical T_S(**TCR**) would create a negative regulatory loop on T_H cells of the various specificities.

Immunological Memory. There are two ways in which memory cells (42) can be pictured: either as long-lasting quiescent cells, or as shorter-lived cells engaged in a cyclic process of stimulation and inhibition of growth, leading to

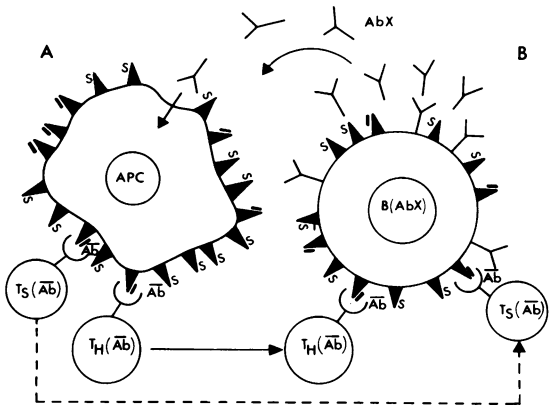

FIG. 2. Possible involvement of **Ab** idiopeptides, noted $\overline{Ab}$ in the figure, in the antibody response. (*A*) The AbX antibody released by B(AbX) cell is ingested by an APC leading to the activation of T_H(**Ab**) and T_S(**Ab**) cells acting on B-cell AbX. T_S cells are shown activated by **Ab** associated with MHC molecules (▲) as discussed in the text.

oscillations. Oscillations in antibody synthesis, also postulated in the network theory, have been observed (43, 44).

After immunization, once antigen has disappeared, idiopeptides appear as the possible substitutes that provide the necessary stimuli needed in any type of homeostatic immunological memory. At the end of the antibody response, B(Ab) cells might thus enter a cyclic process positively driven by T_H(**Ab**) cells (activated by the antibody itself) and negatively regulated by T_S(**Ab**) cells acting on B(Ab) cells, and/or T_S(T_H-**TCR**) cells [or even CTL (T_H-**TCR**) acting on T_H(**Ab**)]. Such homeostatic loops can maintain a low level of antibody synthesis. In this dynamic view, B-cell memory is dependent on T_H cell memory and vice versa. There is no autonomous T_H or T_S cell memory (i.e., independent of B cells) because the postulated T_H–T_S interactions lack a positive stimulus of T_H cells.

The Secondary Response. The success of the secondary response may require that the homeostatic loop described above is broken. T_H(**X**) cells induced by reinjection of X may be unable to stimulate B(Ab) cells. They might, however, activate those B(Ab*) cells that produce a mutated antibody (Ab*) still able to bind X, but such that **Ab*** escapes suppression by T_S(**Ab**). This selective pressure may account for the wider and wider occurrence of somatic mutations in antibodies and the use of distinct germ-line V genes upon repeated immunization (45). Somatic mutations would thus be largely irrelevant to an increase of affinity for antigen.

Response to Coupled Antigens. If peptide presentation by MHC molecules is as selective as we anticipate, it is no surprise that many peptides are poorly immunogenic except when polymerized or coupled to an immunogenic carrier. What happens upon immunization with a peptide (P) coupled to a carrier (X)? The P–X complex is taken up by APCs and processed into P and X. If P can be presented by class II MHC molecules, a B(AbP) cell response should normally follow (AbP represents anti-P antibody); coupling to the carrier served to promote peptide presentation, perhaps by helping uptake by APCs. However, if P is not presented, a B(AbP) cell response should still be obtained. This is because B(AbP) cells bind P–X, process it, and expose **X** peptides, allowing activation by T_H(**X**) cells, which are normally stimulated (Fig. 3*A*).

This rationale explains how antibodies are made against nonimmunogenic peptides, including self molecules such as peptidic hormones. It also accounts for epitopic suppression, in which immunization by the X carrier weakens the anti-P response elicited by subsequent immunization with X–P. In this instance, the activated T_H(**X**) cells, if limiting, will stimulate the numerous B(AbX) cells that are present, due to the first immunization, rather than the fewer B(AbP) cells that have never been activated and will thus be competed out (Fig. 3*B*). This agrees with the sizes of the B(AbX) and B(AbP) cell compartments as recently measured (46) (Fig. 3*B*). Allotype-specific suppression could be explained in a similar way (47).

Cellular Responses to Foreign Antigens. Most somatic cells express class I but not class II MHC molecules. In the peptidic self model (7), cells infected by a virus expose peptides derived from viral proteins in a class I context, amongst many self peptides derived from internal and surface proteins of the host cell. CTL reactions may thus be triggered by internal as well as external viral proteins (the former being, perhaps, favored by the intracellular routes leading to loading of peptides onto class I molecules).

Some of the minor transplantation antigens [as also suggested by Germain (13)] could reflect polymorphisms of intracellular proteins, or their presence vs. absence in certain individuals and not in others. This might explain why their recognition is MHC-restricted (48–50) and why their sero-

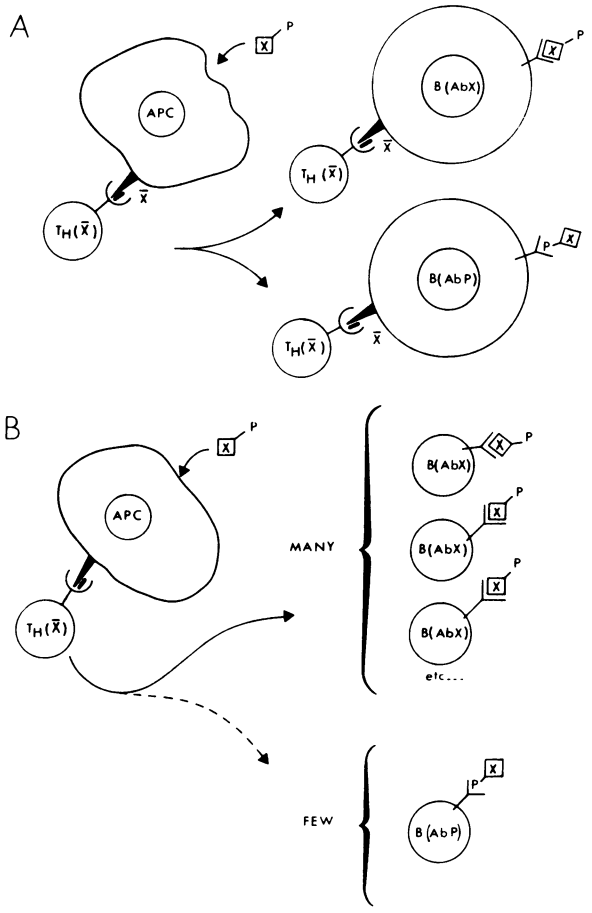

FIG. 3. Antibody response to a peptide (P) coupled to a carrier X upon primary immunization (*A*) or after immunization by the X carrier (*B*).

logical and biochemical characterization (e.g., H–Y) has been so difficult.

Internal Activity of the Immune System. The frequency of mutations in complex organisms and their potential consequences are often overlooked. In mammals, considering only spontaneous point mutations (occurring at a rate of $\approx 10^{-9}$), one or several point mutations must take place at each cellular division, yielding structural mutations in expressed proteins in one out of every hundred cells. Each cellular protein should, on the average, be mutated in 1 of 10^6 cells.

On this basis, we argued earlier that the somatic self may be placed under generalized immune surveillance (7, 8). The selection exerted by presenting MHC molecules (see above) implies that some but not all structural mutations are seen by the immune system. Interestingly, regulatory alterations could also be detected: rare proteins yielding too rare peptides to be presented do not belong to the somatic self. If synthesized in larger amounts (for example, in tumor cells), they might be presented, recognized as foreign, and trigger a CTL reaction. Resurgence of embryonic proteins would have a similar effect. Interferons and tumor necrosis factors, with presumed or demonstrated anti-tumoral activity, increase MHC gene expression (51, 52) and may thereby improve detection of alterations in the quality or amount of rare proteins.

In the schemes described above accounting for the stimulation of antibody synthesis, it is important that a distinction is made between the immunogenic peptide and the epitope of the native antigen recognized by the antibody. This explains tolerance-breaking experiments (reviewed and discussed in ref. 53) and leads to the concept that mutations producing altered self proteins may induce the synthesis of antibodies directed against self proteins themselves (Fig. 4).

The immune system, even in the absence of any external stimulus, produces large amounts of so-called "natural" antibodies (54), which often display auto- and multireactivity (i.e., they react against self proteins and several antigens) (55). We propose that at least some of these natural antibodies are raised by mutated self proteins. They could help in the clearance of proteins released by dead cells, which would favor their opsonization and restimulate their synthesis. The most abundant proteins would be more likely to induce an autoantibody response. Synthesis of polyreactive autoantibodies might be favored because their producing B cells might be polystimulated by several types of T_H cells. Various cascades, including those produced by the presentation of idiopeptides, might lead with time to the establishment of a connective network, a feature displayed by natural antibodies, at least in the newborn animal (55).

Ontogeny. The ontogeny of the immune system could then fit in a frame where the somatic self creates a "hole" in the developing T cells, while the immunological self and altered self generated by the uneluctable flow of mutations are driving forces in the expansion of the B-cell and T-cell repertoires. It is agreed that autoreactive T cells are depleted in the thymus, where self peptides are presumably presented in association with MHC molecules by a variety of cells. It should be noted that idiopeptides should not appear in the thymus and be seen as self because they are exposed on peripheral B and T cells (**TCR** being presented only by activated T cells). In this scheme, clonal deletion and/or inactivation of anti-self B cells is not compulsory, while, in fact, their existence is implied by the occurrence of natural antibodies.

The B-cell repertoire, however, could be internally activated by mutant self proteins and idiopeptides (as well as by foreign antigens). For example, it may be relevant that pre-B cells synthesize V_H chains devoid of constant region (56), possibly meaning that they expose V_H idiopeptides: activated $T_H(V_H)$ cells could then stimulate B cells expressing the corresponding idiopeptide. Thus, the B-cell repertoire, with its cortege of T cells, would develop under control of the latter with no systematic "hole" other than that imposed by T cells.

DISCUSSION

The above considerations ignore much of the known complexity of the immune system (for example, the role of lymphokines in the activation of effector cells), as well as the growing diversity of immunological molecules [in TCR, human CD1 molecules (57), mouse Qa-Tla antigens, etc.]. In

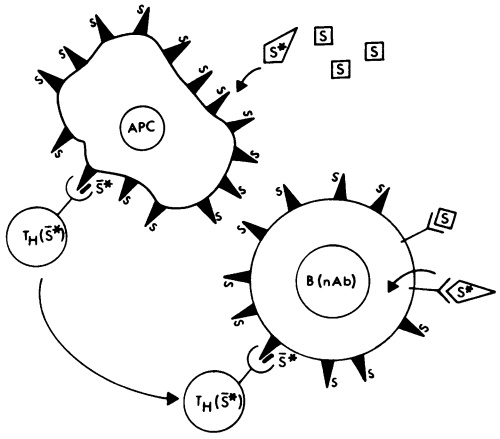

FIG. 4. Synthesis of natural antibodies (nAb). Self proteins are shown as S and their mutant counterparts are designated S*.

addition, our emphasis on peptide presentation does not preclude the possibility that denatured or native proteins that happen to expose the appropriate site are bound as such by MHC molecules. This would account for exceptions to the requirement for antigen processing and for examples of conformational-dependent recognition of certain antigens by T cells (58). In spite of these multiple oversimplifications, the edifice built with the above working principles is internally consistent and compatible with most of the available evidence. It also displays some explicative and predictive value in areas of high theoretical and practical importance, such as tolerance, synthetic vaccines, and autoimmunity. In the latter case, it is conceivable that mutations could generate undue coincidences between the somatic self and the immunological self. In addition, altered regulations leading to the presentation of rare self proteins (and, thereby, never seen by the immune system) could trigger autoimmune reactions against the deregulated cells or tissue.

In our view, the somatic and the immunological self are under mutual intense co-selection, because certain overlaps are forbidden. Presentation by MHC molecule is also open to selection (for example, one could argue that albumin is so abundant that it would compete out most antigen presentation by circulating APCs, unless it evolved in such a way as not to be taken up, processed, or presented).

Finally, we predict "idiopeptidic" regulatory loops rather different from the usual version of the intricate self-centered idiotypic network (23). The completeness and "openness" of the latter (59) could make it hardly "revealable." By involving idiopeptides rather than idiotopes, we picture the regulation of immune responses with a limited number of cellular interactions and simple regulatory loops, which need not be indefinitely extended in a recurrent fashion. Instead, the minimal loop (Fig. 2) displays the interesting property that antibodies induced by (Ab) mimic part of their antigenic stimulus (55) (providing a basis for a different understanding of "internal image").

As speculative as it stands, this extension of our initial "peptidic self" model leads to testable hypotheses. Not all may be true, but they may, hopefully, be useful in stimulating informative experiments.

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