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Immunoglobulin-Receptors Revisited

A model for the differentiation of bone marrow–derived lymphocytes is described.

Ellen S. Vitetta and Jonathan W. Uhr

The concept of an immunoglobulin (Ig) receptor for antigen on precursors of antibody secreting cells was first clearly enunciated by Ehrlich (*1*). Burnet, in his clonal selection theory, postulated that each cell was unipotential: that is, all the antibody receptor molecules on a given cell have a similar specificity (*2*). During the last two decades, considerable information, stimulated primarily by the introduction of immunofluorescent techniques by Coons (*3*), has accumulated concerning such receptors on lymphocytes. The purpose of this article is to evaluate past studies of Ig receptors for antigen on lymphocytes, to discuss new information regarding cell surface immunoglobulin D (IgD), and to propose a model of B cell (bone marrow–derived lymphocyte) differentiation and "triggering." The major reason for formulating the model was to accommodate the recent findings regarding receptor IgD. However, in developing the model, it became apparent that current concepts of B cell differentiation and triggering could be simplified by the inclusion of several additional concepts regarding the function of Ig receptors for antigen: these include a mechanism for induction of tolerance, absence of certain receptor isotypes (that is, immunoglobulin classes as defined by the H chain) on B cells, and a molecular mechanism underlying their stimulation.

The major concepts that have emerged from past studies are as follows: (i) Each clone of B lymphocytes has a single homogeneous immunoglobulin on the surface of its cells, which acts as antigen-specific receptor; these cells can differentiate into plasma cells that will secrete an immunoglobulin of identical specificity (*4*). (ii) Immunoglobulin M (IgM) is the class of receptor on immunocompetent virgin B lymphocytes (*5–7*). (iii) Binding of ligand to receptor is usually insufficient for stimulation; a second signal is needed from an accessory cell such as the T cell (*8*). (iv) After stimulation of B lymphocytes by antigen and T cell (thymus-derived lymphocyte) signals, they "switch" from the synthesis of IgM to either IgG, IgA, or IgE (*9*), and these isotypes are the antigen-specific receptors on memory B cells. These memory cells are the precursors of the plasma cells secreting immunoglobulin of the same isotype and specificity (*9*). (v) In many species, such as man and guinea pig, IgG-bearing lymphocytes represent the major type of circulating B lymphocyte in adults (*10*). (vi) IgA-bearing lymphocytes and IgA-secreting plasma cells are the predominant ones in Peyer's patches and lamina propria of the intestines (*11–13*). (vii) IgD is a cell surface immunoglobulin in humans that appears earlier in ontogeny than IgM and therefore may be the primordial cell surface Ig (*14*).

The above concepts are not universally accepted, however. For example, Sercarz and co-workers (*15*) argue that murine B lymphocytes are multipotential, that is, a large proportion of single cells from unimmunized mice can bind two unrelated protein antigens. If verified, this finding would challenge the clonal selection hypothesis. There is also controversy concerning the aforementioned arguments that large populations of B cells have surface IgG or IgA (*4*). Finally, there is contention concerning the antigen dependence of the presumed switch from synthesis of IgM to other classes of immunoglobulin in lymphocytes. Thus, Cooper and his co-workers suggest that such a switch can occur in germ-free animals (*9*) and in mouse fetal liver cultured in vitro (*16*).

In evaluating these conflicting data, two important obstacles to studies of cell surface immunoglobulins should be mentioned. (i) Specificity of antiserum to immunoglobulins. Clearly, specificity is critical to the interpretation of all data. Immunologists are aware of this problem, and the manipulations to obtain monospecific antiserums have become increasingly sophisticated. The magnitude of the problem is not fully appreciated, however. Not only are there natural antibodies to cell surface structures in the majority of, if not all, heterologous serums, which are not easily eliminated by conventional absorption, but there may be unexpected cross reactivities; for example, a rabbit antiserum prepared against purified mouse γ chain reacts with a portion of mouse δ and μ chains even af-

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ter extensive absorption with light (L) chains (*17*). The cross reactivity is probably attributable to the polypeptide portion of the heavy (H) chain (*18*) but could be due to the carbohydrate moiety (*19*). (ii) Fc receptors on B lymphocytes. The binding of exogenous immunoglobulin can occur in vivo (homologous immunoglobulin) or in vitro when heterologous immunoglobulin is used for immunofluorescent staining. The latter can be obviated when the $F(ab)'_2$ fragment of antiserum to immunoglobulin is used as the staining reagent. We believe that these two problems account for virtually all the controversy regarding immunoglobulin on B cells.

Surface Iodination of Murine B Cells

Since the introduction several years ago of the enzymatic iodination technique, it has been possible to study immunoglobulin receptors biochemically. Early studies suggested that IgM in its monomeric form was the major surface immunoglobulin on splenocytes from young mice (*5*). Occasionally, traces of cell surface IgG were detected on these cells. Presumably, the extensive washing or iodination procedure or both had removed cytophilic IgG. The monomeric IgM is synthesized by the cells on which it resides (*20*).

Studies from our laboratory in collaboration with Melcher, McWilliams, Lamm, and Phillips-Quagliata (*17*), which were confirmed by Abney and Parkhouse (*21*), have described a second major class of immunoglobulin on murine lymphocytes, with the following properties: (i) It is a tetramer of approximately 170,000 daltons containing covalently bound H and L chains. (ii) It is immunoprecipitable with antiserum to κ chains but not with antiserums to μ, α, or γ chains. (iii) The H chain has a mass of about 65,000 daltons and has a carbohydrate content of approximately 15 percent (*22*). (iv) The molecule undergoes proteolysis easily (*17, 22*). All of these properties are similar to those described for human IgD (*23*), and, by analogy, we have called this new immunoglobulin, "IgD-like." For simplicity we call it IgD. Definitive identification of mouse IgD, however, awaits the demonstration of structural homology or immunologic cross reactivity with IgD.

Further studies have revealed the following biological features of murine IgD.

1) It appears after IgM during the differentiation of B lymphocytes. This conclusion is deduced from three distinct findings. (i) Splenocytes from newborn BALB/c mice have only IgM on their surfaces for the first 10 to 14 days after birth. Then, IgD appears and increases in amount until the animals reach about 3 months of age when it constitutes 60 to 70 percent of surface immunoglobulins that can be iodinated (*24*). (ii) Bone marrow cells from adults bear only IgM (*24*). [Thymus cells have no detectable immunoglobulin, as described previously (*25*).] (iii) The population of large cells in the spleen bears only IgM, whereas the population of small lymphocytes has both IgM and IgD (*26*). There is evidence that a stem cell from the bone marrow becomes a lymphoblast in the spleen, which then differentiates into a small lymphocyte (*27*). Taken together, the above evidence indicates that immature IgM-bearing bone marrow cells populate the spleen, divide, and give rise to more mature cells bearing both IgM and IgD.

2) The acquisition of surface IgD on splenocytes appears to be independent of both antigen and T cell influence (*24*). Examination of lymphoid cells from congenitally athymic mice and their heterozygous littermates indicates that the time of acquisition of IgD and the amounts present on their cells are virtually identical. It appears, therefore, that the development of IgD on B lymphocytes is T cell independent. Similar experiments carried out in germ-free mice indicated that lymphoid cells from both normal and germ-free animals of similar ages express similar amounts of IgD on the surface. Although the germ-free mouse is subjected to low levels of antigenic exposure via the gut, this exposure is insufficient to trigger the switch to IgG synthesis, indicating that antigenic stimulation has been markedly reduced. It can therefore be concluded that the acquisition of IgD requires less antigenic stimulation or T cell influence than the synthesis of IgG. The simplest explanation is that the appearance of IgD on virgin B cells is a phase of normal differentiation.

3) IgD is the major class of cell surface Ig on peripheral lymphocytes of adult mice in terms of cell surface Ig that can be iodinated; IgD ranges from 60 to 70 percent in the spleen (*24*) to 85 to 95 percent in Peyer's patches (*28*). IgM accounts for the remainder of radioactive surface Ig. These observations are not inconsistent with studies of others who report a small percentage of lymphocytes bearing IgG (*29*) or IgA (*7, 11, 12, 29, 30*) since our iodination techniques might not be sensitive enough to detect such small subpopulations. [We have detected a 0.25 percent subpopulation of Ig-bearing cells in a non-Ig–bearing cell population by increasing the number of cells and amount of radioactivity severalfold (*25*). In our experiments, however, this was not practical.]

4) IgD is easily proteolyzed. One reason for the failure to detect surface IgD in earlier studies was its lability, that is, after cell lysis IgD is readily degraded and thereby rendered nonantigenic unless precautions are taken to inhibit proteolytic enzymes. Surface IgM, however, remains intact under the same conditions. In an experimental model of proteolysis in which intact iodinated cells were treated with low concentrations of papain, virtually all of the Fd portion of IgD but very little of the IgM was removed from the cell (*31*). This susceptibility to proteolysis, which distinguishes surface IgD from IgM, may be functionally significant.

Immunofluorescence Studies of IgD in the Human

There are several findings in the human which are pertinent to understanding the role of IgD in B lymphocyte differentiation. Thus, by means of immunofluorescent techniques, it has been amply demonstrated that a large proportion of IgM-bearing lymphocytes also bear IgD (*14*). Reappearance of the two classes after "stripping" with trypsin (that is, the immunoglobulin is cleaved from the cell and subsequently reexpressed) (*14*) suggests that they were synthesized by the cell on which they reside. Most important, Fu *et al.* have shown (*32*) that, in a patient with chronic lymphocytic leukemia and macroglobulinemia, the idiotype of IgM and IgD found on the majority of peripheral B lymphocytes is the same. This finding suggests that the variable portion of the heavy chains of the two isotypes is identical in this patient. A similar conclusion was reached by Pernis *et al.* (*33*), who noted that, in another leukemia patient, both the IgD and the IgM on the same cell had specificity to aggregated human IgG. The inference is that IgM and IgD antibody molecules synthesized by the same cell have similar specificity for antigen. This situation would be predicted from the clonal selection hypothesis.

Model for B Cell Differentiation

The aforementioned results of enzymatic iodination of murine lymphocytes indicate that there is a marked dichotomy between the representation of isotypes in the serum and as receptors on B lymphocytes. Thus, IgG, by far the major isotype in the serum, is poorly represented, if at all, on lymphocytes, whereas IgD which is poorly represented, if at all, in the serum is a major, if not predominant, cell surface receptor. Recent immunofluorescence studies of human blood lymphocytes suggest that this dichotomy should be a fea-

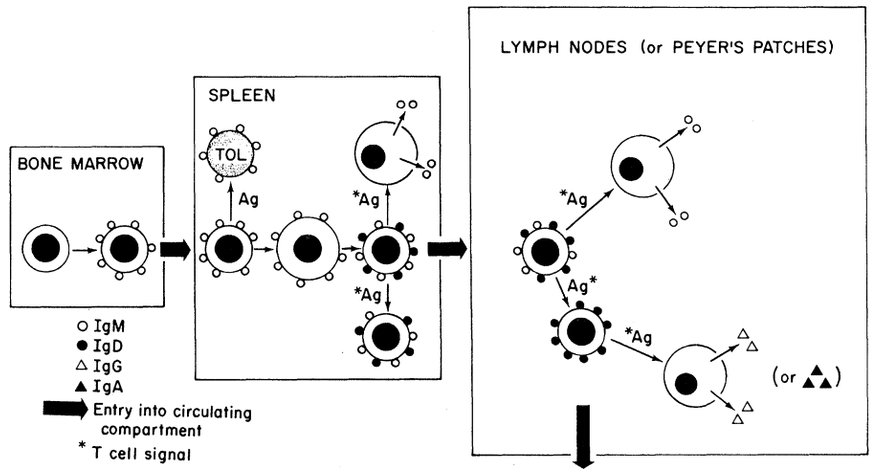

Fig. 1. A model for the differentiation of B lymphocytes.

ture of all higher mammals. Clearly, receptor IgD is not concerned with secretion of IgD. Rather, IgD may be a receptor that regulates antibody formation to other isotypes.

There are several major possibilities to consider for the regulatory role of receptor IgD: (i) Receptor IgD facilitates "triggering" of lymphocytes for replication and differentiation. (ii) IgD receptors arrest further differentiation of the cell, that is, IgD acts as a "brake." A cell bearing IgD encountering antigen either is not stimulated or replicates; the cell must lose IgD to differentiate. (iii) IgD determines the pathway of differentiation. For example, after interaction with antigen, cells bearing IgD receptors may give rise to memory cells only. Cells not bearing IgD may be capable of differentiating into plasma cells.

We favor the possibility that IgD is a "triggering" receptor. The major impetus is that IgD is acquired late in B cell differentiation and at a critical point in ontogeny when immunocompetence increases (*34*). We therefore propose a model (Fig. 1) that accommodates IgD and hypothesizes about its role in the development and "triggering" of B lymphocytes. The model is described below briefly and is subsequently discussed in more depth.

Antigen-independent events. In the bone marrow and fetal liver, stem cells acquire IgM and migrate to the spleen. In the adult spleen, such IgM-bearing cells differentiate into blast cells, whose progeny are small lymphocytes bearing both IgM and IgD. These cells migrate into the thoracic duct and blood, seeding peripheral lymphoid tissues, including Peyer's patches and the spleen (not shown in the model and probably a different anatomical compartment from that occupied by their precursors).

Antigen-dependent events. The interaction of antigen with IgM-bearing cells in the spleen results in tolerance. In contrast, interaction of antigen and T cell signals with spleen cells bearing both IgM and IgD results in either differentiation into IgM-secreting plasma cells or proliferation of more precursors (IgM- and IgD-bearing), that is, IgM memory cells. Interaction of antigen with double bearers in nonsplenic peripheral lymphoid tissue results in differentiation into IgD-bearing lymphocytes (that is, loss of cell surface IgM) or IgM-secreting plasma cells. The cells that bear only IgD are the precursors of the plasma cells secreting IgG (or IgA) after additional antigenic stimulation; that is, they switch synthesis of isotypes two times, μ to δ to γ (α, ϵ). These memory cells form part, if not all, of the recirculating pool of B lymphocytes. The IgD-bearing cells in the Peyer's patches will differentiate mainly into IgA-secreting plasma cells, whereas those in the lymph node become predominantly IgG-secreting plasma cells.

There are therefore a series of antigen-dependent differentiation steps between the lymphocytes bearing both IgM and IgD and plasma cells secreting IgG or IgA. Cooperation of T cells is probably important in many or all of the antigen-dependent steps for T-dependent antigens.

The critical features of the model are: (i) The accommodation of IgD into B cell maturation as a late event during both ontogeny and differentiation. (ii) The designation of circulating B lymphocytes as those that bear IgD (with or without IgM). (iii) The postulation that IgD is a "triggering" receptor. (iv) The postulation that switches in synthesis of immunoglobulin class occur both in the lymphocyte (μ to δ) and the plasma cell (δ to γ, α, or ϵ). (v) The relegation of cells bearing only receptor IgM to a tolerance-induction compartment and the absence of IgG or IgA receptor lymphocytes.

Are There Small Lymphocytes with IgG and IgA as Cell Surface Receptors?

Probably the most controversial aspect of our model is the omission of lymphocytes bearing IgG and IgA receptors. By receptor we mean cell surface immunoglobulin synthesized by the lymphocyte on which it resides and which plays a functional role through interaction with antigen. This definition excludes cytophilic immunoglobulin and immunoglobulin on cells actively secreting it. (The latter is probably immunoglobulin that is destined for secretion in cells previously stimulated by antigen.)

There are innumerable reports of IgG- and IgA-bearing lymphocytes in a variety of species including man (*9–12, 29, 30*). Because of the recent awareness of the problem presented by Fc receptors on B lymphocytes (*35*), however, investigators have begun to use the $F(ab)'_2$ fragments of antibodies to immunoglobulin as reagents for immunofluorescence studies. This maneuver has resulted in a dramatic reduction in the percentage of IgG- and IgA-bearing cells detected. For example, 0.2 percent or less of cells in human blood stain for IgG (*36*) compared to older figures which were as much as 100-fold higher. In addition, the use of proteolytic enzymes for stripping cell surface proteins coupled with subsequent incubation of the denuded cells to allow reexpression of those proteins synthesized by the cell has also helped to clarify the major contribution of cytophilic immunoglobulin to the earlier results (*12*). Additional relevent data are the findings in chronic lymphocytic leukemia in man (which is usually an expression of B cell neoplasia) and in established lymphoblastoid lines of IgG-bearing cells (*37*). In one laboratory, however, careful study by the same techniques discussed above found no IgG- or IgA-bearing cells in a series of approximately 50 such patients (*38*); all had IgM or IgD, or both. These data coupled with the iodination studies mentioned previously strongly suggest that if there are lymphocytes that have IgG or IgA receptors, their proportion in a given lymphoid tissue such as blood is very small, perhaps less than 1 percent. This minute proportion could be explained by the presence of specificities (in the antiserums) to other surface molecules as mentioned previously or the presence of transitional forms between lymphocytes and plasmablasts that have Ig on their surface that is destined for secretion. For these reasons, we consider the existence of lymphocytes with receptor IgG or IgA not proven. To keep our model of B cell differentiation as simple as possible, therefore, we have excluded such lymphocytes. There are therefore two

classes of receptors only—one that induces tolerance (IgM) and one that induces triggering (IgD).

A definitive decision about the existence of IgG and IgA receptor cells may be achieved through experiments involving the fluorescence-activated cell sorter (*39*). Cells with IgG (or IgA) receptors should give rise to progeny plasma cells which secrete immunoglobulin of the respective isotype. Therefore, if antiserum that stains such cells is specific to the isotype in question, one would expect to find a marked enrichment of formation of the corresponding isotype in a cell transfer experiment. The donor cells would have to be from an immune animal, the recipient would have to be challenged with the corresponding specific antigen, and the isotype of antibody would have to be determined to ensure that the function of transferred B lymphocytes is being measured rather than the transfer of cells on whose surface immunoglobulin is secreted while they continue to differentiate and secrete immunoglobulin in the recipient. A recent experiment of this type (*40*) suggests that there may be a small population of IgG receptor cells. If this finding should be substantiated, IgG (IgA) receptor cells could be incorporated into our proposed scheme of B cell differentiation as an alternative differentiative pathway for antigen-stimulated IgD-bearing lymphocytes. Such an alteration, however, would greatly complicate the simple concept of triggering of Ig-bearing cells (see below).

Genetic Implications

Recent studies in rabbits (*41*) indicate that, in a crossover, variable (V) and μ genes segregate from γ and α genes. The proposed sequence of isotypes in cell surface Ig does not, of course, necessarily imply genetic sequence. One could suppose, however, that the sequence is V, μ, δ and that commitment in small lymphocytes proceeds to activation of the δ gene. After stimulation of a δ-bearing small lymphocyte by antigen, there would be activation further down the gene complex with derepression of either γ, α, or ϵ in the developing plasma cell.

If there is a switch from μ to δ synthesis, then a translocation mechanism such as that suggested by Gally and Edelman (*42*) would satisfy the genetic requirements of the proposed scheme of differentiation. The possibility, however, that IgM and IgD synthesis may occur concomitantly in a single cell complicates in a profound manner the genetic control of synthesis of these two isotypes. In this regard, it would be important to determine whether a single cell can synthesize two isotypes with identical specificity simultaneously and for what duration of time. Proteolytic digestion of the two classes of immunoglobulins on the cell surface with their reappearance on the same cell would not be sufficient evidence for this critical point. Thus, the cell might have an intracellular pool of preformed immunoglobulin which had not yet been externalized as receptor. It would also be crucial to prove that the antigenic specificity of the two isotypes is identical. Two studies already cited point to this conclusion but definitive evidence is still needed. If the tentative interpretation of these experiments is confirmed, it will be necessary to consider underlying molecular mechanisms. For example, there could be joining of messenger RNA's transcribed from the V gene and either of the constant (C) genes. Another possibility is duplication of the particular V gene that had been activated by a clone.

If both isotypes can be synthesized simultaneously by the same cell, it will help to explain an otherwise awkward aspect of the model. Thus, we suggest that a blast cell that makes IgM and later IgD eventually can differentiate into an IgM-synthesizing plasma cell. If IgM synthesis can continue after IgD synthesis begins, then it is only necessary to postulate termination of IgD synthesis. If only one immunoglobulin can be synthesized at a time, then it is necessary to postulate a turnoff of IgM formation when IgD synthesis begins, followed by a second phase of IgM synthesis.

Induction of Tolerance

The impetus for suggesting that IgM is a tolerance-inducing receptor is conceptual rather than experimental. Thus, if there are only two isotypes that serve as receptors, they presumably serve different functions. Since IgD appears late in ontogeny, we suggest that it is a "triggering" receptor and, therefore, that IgM which appears early in ontogeny serves an opposite function. The hypothesis explains simply the signal discrimination between induction of tolerance and stimulation. The constant portion of the H chains of the two isotypes is different, thereby providing a structural basis for two different signals. For example, δ but not μ may have a binding site for another membrane protein; interaction of receptor IgD with antigen and T cell signals may result in the exposure of this binding site, and the resultant interaction with the membrane protein in question may initiate stimulation of the cell. This possibility is discussed in detail in a later section. Another significant difference between the two isotypes is that the IgM monomer may function univalently with large immunogens [see (*43*)], whereas IgD may function divalently. This could affect the extent of surface aggregation of receptors with antigen. Triggering versus tolerance could depend on the extent of aggregation.

Our model readily explains tolerance to self proteins in the embryo because a triggering isotype is not present. Our model does not explain tolerance in adults. Induction of immunological tolerance in adults may be a more complex phenomenon than in embryos. Thus, the contributions of irreversible B cell tolerance, receptor blockade, and suppressor T cells to induction and maintenance of tolerance in adults have not been defined [see (*44*)]. In our model, two types of cells are present, those that can be activated and those that can become tolerant. Thus, an additional mechanism (for example, T cell suppression) would have to be postulated to deal with specifically stimulated B cells arising during induction of tolerance.

Relationship of This Model to Other Hypotheses of B Cell Differentiation

The major idea of Cooper and coworkers (*9*) is that there is an antigen-independent switch from the synthesis of cell surface IgM to the synthesis of IgG and IgA that occurs at an early stage in the maturation of B lymphocytes—for example, in the liver of fetal mice (*16*) and in the bursa of Fabricius of chickens (*9*). Hence, in peripheral lymphoid organs, there are separate lineages for IgM, IgG, and IgA. Our model differs in that we postulate that in the mouse the acquisition of a non-IgM class of cell surface immunoglobulin occurs neonatally and in peripheral lymphoid tissue and the acquired Ig is IgD and not IgG.

Our hypothesis is also not in accord with those regarding the development of IgA-secreting cells. Thus, Williams and Gowans (*11*) believe that large and small lymphocytes bearing IgA receptors in the thoracic duct migrate to the lamina propria where they develop into IgA-secreting cells. A similar viewpoint derives from the observations of Jones *et al.* (*45*), who were unable to stain precursor cells with a heterologous antiserum to α, but they could with an antiserum to α allotype. There is evidence that the determinants that react with the antibodies to the allotype are on the Fd portion of the α chain while the heterologous antibody to α reacts with determinants that are hidden in the membrane.

We have no evidence to exclude the above interpretations which have common to them that the precursor of an IgA-se-

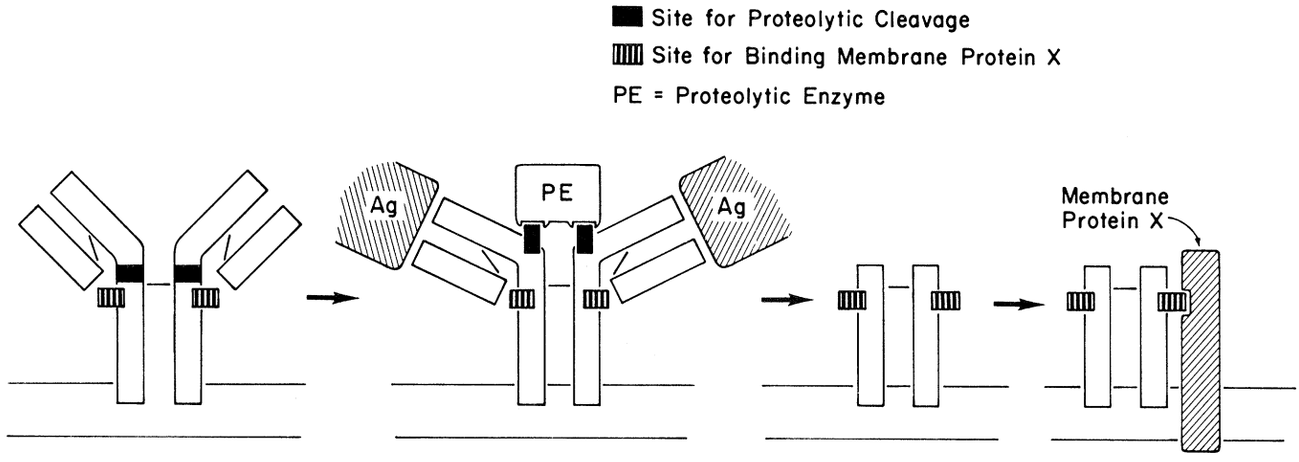

Fig. 2. A model for the triggering of B lymphocytes. After interaction of receptor IgD and specific antigen, a binding site on the hinge region for a proteolytic enzyme (*PE*) is exposed. The enzyme then binds to IgD and removes its Fab portions. This removal results in exposure of a second binding site which can interact with another membrane molecule. The latter interaction results in the transmission of a signal to the interior of the cell.

creting plasma cell is a small lymphocyte with IgA on its surface acting as a receptor. An alternative explanation for the above data (*11, 45*) is that the IgA-bearing cells are progeny of antigen-stimulated IgD-bearing lymphocytes that are differentiating into IgA-secreting plasma cells and therefore have surface IgA destined for secretion.

Function of IgD

As was mentioned above, surface IgD is particularly susceptible to proteolysis. We propose that proteolysis is an obligatory step for triggering.

A simple testable model that suggests a central role for proteolysis of IgD (*23, 46*) is illustrated in Fig. 2. IgD binds to its multivalent ligand, exposing a critical site in the hinge region for subsequent attack by a proteolytic enzyme. The proteolytic enzyme may be on the surface of the B cell itself and may be activated by the product of an accessory cell such as the macrophage or T cell. Alternatively, the product of the accessory cell may be a proteolytic enzyme. Proteolysis results in removal of the Fd portion. The remaining Fc portion has a binding site exposed that was previously inaccessible. This site interacts with another surface molecule leading to a signal which is then transmitted to the cell cytoplasm.

There is little evidence from studies of Ig in solution that binding of Fab segments by monovalent ligand induces changes in the conformation of the Fc portion (*43, 47*). However, binding by multivalent antigens which induce aggregation may result in conformational changes in the hinge region. Electron microscopic evidence suggests that the Fab arms of antibody can open wider in such aggregates (*43*), and the result could be exposure of a proteolytic binding site in the hinge region.

There is also precedence for postulating that removal of the Fab portion of the molecule could reveal a binding site that would allow new interactions. Thus, there is a receptor for the first component of complement (C1) on human IgG_4 (a subclass that does not fix C1) which is exposed when the Fab portions are removed by proteolysis (*48*).

General Comments

Our discussion of B cell differentiation is not meant to be all-encompassing. We have not discussed cooperation of B cells with T cells, B cell defects, homing of lymphocytes, the possible relationships within the IgA secreting system of Peyer's patches, lamina propria, and other sites of IgA secretion, and IgD plasma cells (which may be a later evolutionary event than membrane IgD). Rather, the main purpose of the model presented is to accommodate the startling finding that the predominant cell surface immunoglobulin in the mouse (and undoubtedly in all mammalian species) is an isotype not represented in the serum in significant amounts. The major ideas of this proposal are that IgD is the receptor on most if not all cells that will be stimulated by antigen (and T cell factors) and that IgD therefore is a receptor designed for triggering. We have suggested that proteolysis of IgD may be a critical step in this process. We also believe that we have focused attention on the question of whether there are IgG and IgA receptors. Our decision to eliminate such cells from the proposed model may prove to have been incorrect; regardless, critical reevaluation of the existence of these two types of receptors is needed. Some aspects of the model presented are derived from a solid foundation of experimental evidence. These data include the acquisition of IgD late in the development of B lymphocytes. There is also considerable but not compelling evidence that this acquisition is independent of both antigen and T cells and that in the human both IgM and IgD can be synthesized by the same cell at the same time. Interwoven with these features are highly speculative aspects of the model: IgM receptors postulated to induce tolerance, and proteolysis of IgD initiating triggering. The virtue of these ideas is that they simplify the model and are testable.

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The Need for an Ethnomedical Science

The study of medical systems comparatively has important implications for the social and biological sciences.

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Diseases and the disruptions that they occasion have long attracted the interests of scientists who study nonliterate people. Physical anthropologists have contributed information with regard to the basic characteristics of man. By means of cross-cultural epidemiologic studies, social scientists have added substantially to an understanding of the causes of disease. However, disease has not had any special appeal to anthropologists interested in culture theory. As an example, a comparative approach to disease has never gained any momentum in cultural anthropology (*1*). Ethnomedicine, the study of how members of different cultures think about disease and organize themselves toward medical treatment and the social organization of treatment itself, has been viewed as one of the various "domains" of culture. In actual practice, enthnomedicine as an area of inquiry has been either bypassed and neglected or handled indirectly.

There are many reasons for this neglect of ethnomedicine (*2*). The real problem has been that a truly social formulation of disease and its related phenomena has not been pursued. In order to make use of disease in a theory about social groups, a broad definition of disease that accommodates the many meanings people can give to disease is needed. Heretofore, a largely descriptive and relativistic course of action that emphasized cultural patterns has been pursued. At the same time, there has not been sufficient description of the medically relevant behaviors of sick persons nor of processes of treatment. Both of these facts have made difficult the development of useful concepts and generalizations in ethnomedicine. The inchoate state of ethnomedicine reflects and contributes to a lack of appreciation of the essential connection between ethnomedical questions and those that involve human evolution and social adaptation. Moreover, neglect of ethnomedical science has meant that the insights about disease and medical care that are available from comparative studies have not been fully used to examine contemporary problems in the practice of medicine in our own society.

The Special Logic of Biomedical Diseases

The study of different ways in which people orient to and cope with disease brings into sharp focus questions of epistemology and ontology as they pertain to disease and medical care. One is forced to ask, for example, what is a disease? What does this central medical term signify? In Western cultures, "disease" is what physicians and biologists study. The whole medical complex in Western nations, which includes knowledge, practices, organizations, and social roles, can be termed "biomedicine." Biomedicine thus constitutes our own culturally specific perspective about what disease is, and how medical treatment should be pursued; and like other medical systems, biomedicine is an interpretation which "makes sense" in light of cultural traditions and assumptions about reality (*3*).

Terms such as "diabetes," "rheumatoid arthritis," or "multiple sclerosis" seem deceptively simple. Careful analysis will disclose that they represent a complex set of physiologic, chemical, and structural facts. Furthermore, such diseases can implicate a host of social and psychological factors although, in a strict sense, they are not seen as necessary features of the disease. In biomedicine, disease signifies an abstract biological "thing" or condition that is, generally speaking, independent of social behavior (*3*). When examined logically, disease in biomedicine usually refers to undesirable deviations in a cluster of related physiological and chemical variables (for ex-

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